Women's Sexual Desire and Arousal Disorders

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ABSTRACT

Introduction. A committee of five was convened to update the chapter on women's sexual dysfunctions from the perspective of diagnostic issues, pathophysiology, assessment, and treatment.
Aim. To review the literature since 2003 and provide recommendations based on evidence.
Methods. Research databases, conference proceedings, and articles in press were read for relevant new data on these topics for hypoactive sexual desire disorder (HSDD), female sexual arousal disorder (FSAD), female orgasmic disorder (FOD), and persistent genital arousal disorder (PGAD).
Main Outcome Measures. Recommendations by five experts from five countries were formulated with associated grades.
Results. The definitions of HSDD, FSAD, and FOD in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text-Revised are imperfect and have been criticized over the last decade. Proposed new criteria that take into account empirical findings and the diversity across women are recommended. There has been a flurry of new epidemiological studies on women's sexual dysfunction; studies also assessing distress consistenly find a much lower prevalence of dysfunction if distress is considered. Assessment of sexual difficulties is best achieved through a biopsychosocial clinical interview of the woman and her partner (if possible); though laboratory investigations, a physical examination, psychophysiological measurement, and self-report questionnaires can often supplement the interview information. There are currently no approved pharmacological treatments for women's sexual dysfunction in North America, though a number of promising agents have been studied. Evidence for the efficacy of psychological treatments is based on limited studies. There is an urgent need for more data on the assessment, etiology, and treatment of PGAD.
Conclusions. Specific recommendations for the assessment and treatment of women's desire, arousal, and orgasm disorders are forwarded; however, more research into these domains is needed. **Brotto LA, Bitzer J, Laan E, Leiblum S, and Luria M. Women's sexual desire and arousal disorders. J Sex Med 2010;7:586–614.**

Key Words. Female Sexual Dysfunction; Hypoactive Sexual Desire Disorder; Female Sexual Arousal Disorder; Female Orgasmic Disorder; Persistent Genital Arousal Disorder; Assessment; Pathophysiology; Treatment; Diagnosis

Part I: Diagnostic Issues

Women's sexual desire, arousal, and orgasm disorders have traditionally been conceptualized, studied, assessed, and often treated from a perspective which compartmentalizes them. However, despite the common finding in recent population-based epidemiological studies in which low sexual desire is the most prevalent of concerns relating to women's sexual functioning, women's sexual complaints are rarely experienced as discreet entities. The four Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) categories pertaining to lack of desire, arousal, orgasm problems or to sexual pain, are not independent, and in clinical practice, classification is

Table 1 Diagnostic criteria for women's sexual dysfunctions according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text-Revised (DSM-IV-TR) [10] and American Urological Association Foundation (AUAF) [11]

	DSM-IV-TR	AUAF
Desire	Hypoactive sexual desire disorder: Persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity. The disturbance causes marked distress or interpersonal difficulty	Sexual interest/desire disorder: Absent or diminished feelings of sexual interest or desire, absent sexual thoughts or fantasies, and a lack of responsive desire. Motivations (here defined as reasons/incentives) for attempting to become sexually aroused are scarce or absent. The lack of interest is considered to be beyond a normative lessening with life cycle and relationship duration.
Arousal	Female sexual arousal disorder: Persistent or recurrent inability to attain, or maintain until completion of the sexual activity, an adequate lubrication-swelling response of sexual excitement. The disturbance causes marked distress or interpersonal difficulty. The sexual dysfunction in not better accounted for by another Axis I disorder (except another sexual dysfunction) and is not due exclusively to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.	Subjective sexual arousal disorder: Absent or markedly diminished feelings of sexual arousal (sexual excitement or sexual pleasure) from any type of sexual stimulation. Vaginal lubrication or other signs of physical response still occur. Genital sexual arousal disorder: Absent or impaired genital sexual arousal. Self-report may include minimal vulval swelling or vaginal lubrication from any type of sexual stimulation and reduced sexual sensations from caressing genitalia. Subjective sexual excitement still occurs from nongenital sexual stimuli. Combined genital and subjective arousal disorder: Absent or markedly diminished feelings of sexual arousal (sexual excitement or sexual pleasure) from any type of sexual stimulation as well as complaints of absent or impaired genital sexual arousal (vulval swelling, lubrication).
Orgasm	Female orgasmic disorder: Persistent or recurrent delay in, or absence of, orgasm following a normal sexual excitement phase. Women exhibit wide variability in the type or intensity of stimulation that triggers orgasm. The diagnosis of female orgasmic disorder should be based on the clinician's judgment that the woman's orgasmic capacity is less than would be reasonable for her age, sexual experience, and the adequacy of sexual stimulation she receives. The disturbance causes marked distress or interpersonal difficulty. The orgasmic dysfunction is not better accounted for by another Axis I disorder (except another sexual dysfunction) and is not due exclusively to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.	Women's orgasmic disorder: Despite the self-report of high sexual arousal/excitement, there is either a lack of orgasm, markedly diminished intensity of orgasmic sensations, or marked delay of orgasm from any kind of stimulation.

often based on the way in which complaints are presented [1]. Studies find comorbidity between desire and arousal [2–5]. In part, this may be because women express difficulties differentiating desire from subjective arousal [5–7]. Also, some women report their experience of desire to precede arousal whereas for other women, desire appears to follow arousal [6], as women do not seem to follow one universal sexual response cycle [8]. As such, there has been notable criticism of the DSM-IV-Text-Revised (TR) classification of sexual dysfunctions in women [7–9].

Definition of Hypoactive Sexual Desire Disorder (HSDD)

A critical look at existing definitions of the female sexual dysfunctions is warranted given that they have a direct and profound impact on instrument development, epidemiological studies, treatment protocols, etc. The DSM-IV-TR [10] diagnosis of HSDD focuses on "persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity" which causes marked distress or interpersonal difficulty (Table 1). This definition has been criticized as overpathologizing women on the basis that women themselves may not necessarily consider sexual fantasies and desire for sexual *activity* to be an index of their sexual desire [5] and that some women may deliberately evoke fantasy as a way of boosting their sexual arousal. Moreover, in two large recent prevalence studies of older women, 70% reported desiring sex less than once a week but the majority (86–89%) were at least moderately to extremely emotionally sexually satisfied [12]; and in the second study, the majority (71.2%) of women with low desire were happy with the relationship [13]. There is also desyn-

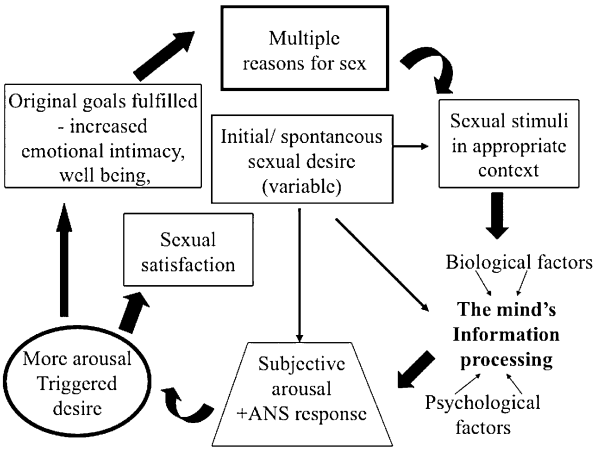

Figure 1 Model of women's sexual response (copied with permission from American Psychiatric Publishing Inc. [24]). ANS = autonomic nervous system.

chrony between sexual satisfaction and frequency of sexual activity [14]. Collectively, these studies suggest that women may experience a satisfying sexual life with a partner without the outright desire for sexual activity.

Also complicating this issue is the finding that clinicians and researchers may differ from patients in how they define sexual desire [15] where among women with an ICD-10 diagnosis of low desire who also self-reported having a sexual problem, the percent agreement was only 18%. The prevalence dropped further to 6% if women received the diagnosis, acknowledged it, and reported distress.

Mounting evidence suggests that all sexual desire is responsive [16–20]. There are a large number of cues that provoke sexual desire and sexual activity in women [21–27]. Engaging in sexual activity in the absence of an identifiable external trigger (e.g., "because the opportunity presented itself," "because I was in the mood") was an unlikely reason women provided for having sex. These findings are in accordance with the conceptualization of a new sexual response cycle [23] (Figure 1) which proposes that women initiate sexual activity for any number of reasons or incentives, and that "feeling" sexual desire is not a usual trigger. Moreover, the model emphasizes that sexual desire emerges in response to the experience of sexual excitement. There is great heterogeneity among women in the sexual response models they identify with [8]; however, both women with and without sexual dysfunction were equally likely to adopt this model of responsive sexual desire [25].

Recommendation

The current accepted definition of HSDD in women is highly problematic and the emphasis on sexual fantasies and desire for sexual activity is not applicable to all women. We recommend that desire be regarded as the result of an incentive (sexually competent stimulus) which activates the sexual system, of which the subjectively perceived desire is one of many components. **Grade C**

Definition of Female Sexual Arousal Disorder (FSAD)

In the DSM-IV-TR, FSAD is defined as the "peristent or recurrent inability to attain, or to maintain until completion of the sexual activity, an adequate lubrication-swelling response of sexual excitement," coupled with "marked distress or interpersonal difficulty." In contrast to earlier editions of DSM, subjective sexual experience is not part of the definition [10].

There are a number of problems with these criteria. Lubrication problems are not necessarily distressing for women [26,27]. In a closer exploration of personal vs. interpersonal distress associated with lubrication problems [28], 31.2% of the sample complained of lubrication difficulties but only 7.3% reported "marked distress" about the relationship and 6.5% personal distress. Lack of lubrication is often a poor predictor of distress, except among postmenopausal women. In the clinical setting, complaints of "genital deadness" or absent/impaired subjective sexual arousal are far more common.

Another difficulty in making the diagnosis relates to the determination by the clinician that the women have received an adequate amount of sexual stimulation. The precise definition of "adequate" arousal may vary across women; for some, adequate sexual arousal involves physical as well as "psychological" and "situational" stimulation [29]. Also, in the case of stimuli no longer being effective, is this indeed FSAD or a case of habituation? The clinician has to evaluate what is normal, based on age, life circumstances, and sexual experience. There is a great variety in the ease with which women can become sexually aroused and in which types of stimulation are required [1].

Finally, there is strong evidence that, especially for women, genital response does not coincide with subjective experience [19,30]. Instead, women's subjective experience of sexual arousal appears to be based more on their appraisal of the situation [31]. Thus, it is highly problematic that

the current definition of FSAD neglects the most important aspect; namely, that of subjective sexual arousal.

Definition of Female Orgasmic Disorder (FOD)

Because women have difficulty perceiving genital changes associated with sexual arousal [19], and because women who report lack of orgasm may in fact be insufficiently sexually aroused, the distinction between FSAD and FOD is unclear. FOD is defined as the persistent or recurrent delay in, or absence of, orgasm following a normal sexual excitement phase [10] (although it does not stipulate whether it is normal subjective or physiological arousal being referred to). In cases where the clinician does not have access to a psychophysiological test, it cannot be established that her deficient orgasmic response occurs despite a normal sexual excitement phase, *unless* she reports feelings of sexual arousal.

The success of directed masturbation for anorgasmia [32] suggests that lack of adequate sexual stimulation is an important etiological factor underlying lifelong, and probably also acquired, FOD. Consequently, if the clinician would strictly adhere to the DSM-IV criteria, neither the diagnosis of FSAD, nor FOD, would be appropriate, because the problem can be reversed by adequate sexual stimulation.

Recommendation

The focus on "lubrication/swelling response" in the DSM-IV-TR definition of FSAD is highly problematic given that this is rarely a complaint motivating treatment seeking. Moreover, there is minimal, if any, correlation between subjective and genital sexual arousal. Given the importance of "adequate sexual stimuli" for sexual arousal and desire, this should be assessed clinically when evaluating whether an arousal or orgasm disorder is present. **Grade C**

Alternative Classifications for Sexual Dysfunction in Women

Because of these criticisms, there have been attempts to offer revised definitions of the female sexual dysfunctions (Table 1) [11]. The emphasis of the revised definition of "Sexual Interest/Desire Disorder" was that the experience of sexual desire could take place after arousal. There have also been proposed criteria for DSM-V to replace HSDD [9]. Disorders of sexual arousal were expanded into three that focused on whether the impairment was entirely subjective, entirely genital, or experienced as a combination of the two. The latter was argued to be the most common clinical presentation (i.e., *Combined genital and subjective arousal disorder*). To date, there have been a few empirical tests of these revised definitions [33]; however, further validation of these groups in large-scale studies is needed. Moreover, there will be a new edition of the DSM-V published in 2012 and proposed criteria for a new sexual interest/arousal disorder have been offered [34]. The addition of "reduced orgasmic intensity" in FOD has also been proposed for DSM-V [35], field trials of proposed DSM-V criteria are underway.

Recommendation

The available evidence suggests that there are problems in existing definitions of sexual desire, arousal, and orgasmic disorders in women. Given the upcoming publication of the DSM-V in 2012, it is likely that the current diagnostic criteria for these disorders may change. The proposed definitions that were sponsored by the American Urological Association Foundation (AUAF) in 2003 present alternative criteria for these disorders that are currently recommended for the clinical setting. **Grade B**

Prevalence of Sexual Desire and Arousal Dysfunction in Women

There has been a recent surge in epidemiological studies estimating the prevalence of sexual desire, arousal, and orgasm complaints in women. Although different assessment tools have been employed and in differing formats (e.g., face-to-face interview vs. questionnaire vs. computer-assisted interviewing), in general these studies find convergence on the frequency of reported low desire in women to be approximately 20–30% (Table 2). However, when the complaint of sexual distress is also included, the prevalence of desire difficulties drops usually by half. In addition, the age-associated decline in sexual desire that is found somewhat consistently is not found when low desire plus distress are taken into account [44]. Studies that have specifically explored predictors of sexual distress have found that age, negative mental state, physical health, having undergone a bilateral salpingo-oophorectomy (BSO), having a sexual partner, sexual dissatisfaction, use of hormonal therapy, and history of urinary incontinence are some of the identified

Table 2 Prevalence of sexual desire and arousal difficulties in cross-sectional representative studies

Study	Sample characteristics	Age	In a sexual relationship	Distress measured	Prevalence of desire difficulties	Prevalence of arousal difficulties
Laumann et al. [36]	1,749 American women (NHSLS)	18–59	Had to be sexually active over the past 12 months	No	27–32% Critical symptom for diagnosis had to be present in the past 12 months	20.6% trouble lubricating
Fugl-Meyer and Fugl-Meyer [37]	1,335 Swedish women	18–74	Not necessary	Indirectly with the question: "Has this been a problem in your sexual life during the last year?"	Sexual disability was defined as having low desire quite often/nearly all the time/all the time = 34%. Among these, 43% viewed it as a problem. Symptom had to have occurred in the past 12 months	Sexual disability was defined as having insufficient vaginal lubrication during intercourse quite often/nearly all the time/ all the time = 12%. Among these, 63% viewed it as a problem.
Mercer et al. [38]	11,161 British men and women (NATSAL)	16–44	Must have had at least one partner in past year	No	Low desire lasting 1 month: 40%; lasting 6 months: 10%	Lubrication problems lasting 1 month: 9.2%; lasting 6 months: 2.6%
Bancroft et al. [28]	987 American women; half were African-American	20–65	Not necessary	Assessed distress over the relationship and distress to one's own sexuality	Low desire: 7.2% Sexual experiences over the preceding month were assessed	Lubrication problems: 31.2%; Impaired arousal: 12.2%
Oberg et al. [26]	1,056 Swedish women recruited in 1996	19–65	Must have had sexual intercourse once in past year	Manifest distress: experienced quite often, nearly all the time, or all of the time	Low desire: Manifest—29%; Mild—60% Symptoms were assessed over the previous 12 months	Insufficient lubrication: Manifest—12%; Mild—50%
Laumann et al. [39]	13,882 women recruited internationally. Analyses based on 9,000 sexually active women (GSSAB)	40–80	Must have had sexual intercourse once in past year	No	26–43% across countries reported a lack of interest in sex lasting for a period of 2 months or more	16.1–37.9% across countries
Leiblum et al. [40]	952 American surgically or naturally women (WISHeS)	20–70	Currently sexually active	Personal Distress Scale	24–36% depending on age and menopausal status. Among those who also had distress, rates of HSDD ranged from 9% to 26%. Symptoms occurring in the past 30 days were assessed	n/a
Dennerstein et al. [41]	2,467 European women from France, Germany, Italy, UK, and United States (WISHeS)	20–70	Currently sexually active	Personal Distress Scale	16–46% depending on age and menopausal status. Among those who also had distress, rates of HSDD ranged from 7% to 16%. Symptoms occurring in the past 30 days were assessed	n/a
West et al. [42]	755 American premenopausal, 552 naturally menopausal, and 637 surgically menopausal women	30–70	In stable relationships for at least 3 months	Personal Distress Scale	Overall rate of low desire 36.2%. Overall rate of HSDD 8.3%. Symptoms in the past 30 days were assessed	n/a
Witting et al. [43]	5,463 Finnish women	18–49	Must have engaged in sexual activity with a partner over the past 4 weeks.	Female Sexual Distress Scale (FSDS)	Using FSFI cut-off score of 3.16, 55% had low desire. Using FSDS cut-off score of 8.75, 23% had low desire and distress. Symptoms were assessed in the past 4 weeks	Using FSFI cut-off score of 4.31, 10.9% had lubrication difficulties. Using FSDS cut-off score, 7% had lubrication problem plus distress.
Shifren et al. [27]	13,581 women	United States	18–102	Not necessary	Sexual desire assessed with one question: "How often do you desire to engage in sexual activity?" Distress assessed by FSDS	34% had low desire, overall 10% had low desire and distress

NHSLS = National Health and Social Life Survey; NATSAL = National Survey of Sexual Attitudes and Lifestyle; n/a = not applicable; GSSAB = Global Study of Sexual Attitudes and Behaviors; WISHeS = Women's International Study of Health and Sexuality; HSDD = hypoactive sexual desire disorder.

variables associated with significant distress [13,28,40–42]. In the assessment of arousal difficulties, most studies have used lack of "lubrication-swelling response" [34] as the study end point. The prevalence of FSAD is listed in Table 2, with an overall range between 10.9% and 31.2%. Unfortunately, the prevalence of other aspects of arousal impairment (e.g., subjective sexual arousal difficulties) is largely unknown exept for one study which found a prevalence of approximately 17% [45]. Like desire complaints, when distress is also considered, the prevalence of arousal impairment drops markedly [43].

Sexual Satisfaction and the Association with Desire and Arousal

Sexual satisfaction is an important component of contemporary models of women's sexual response [46–47], and it is recognized to have personal and relational domains [48,49]. One's level of sexual satisfaction depends on one's frame of reference (e.g., expectations and past experiences) [50]. For instance, a woman who does not expect to experience orgasm during sexual encounters with her partner may be more sexually satisfied than a woman who expects to, but occasionally does not experience orgasm. Interestingly, several recent population-based studies of sexual difficulties find that a proportion of women report sexual satisfaction despite the presence of sexual symptoms or infrequent sexual activity [12,14,28] and other studies find that a proportion of women without sexual symptoms will still report dissatisfaction [15,26,28,39,51].

Conclusions and Recommendations

Overall, the prevalence of desire complaints ranges from 10% to 40% and for arousal difficulties from 10% to 30%, depending on the study methodology, participants, and geographic location. Moreover, when the assessment of distress is included, the prevalence of these complaints drops to approximately half. Given these disparate rates, we recommend that distress or some other measure of severity always be included in future epidemiological trials and that clear operational definitions of the sexual domain be given, along with a duration of complaints of at least 3–6 months for denoting difficulty. Sexual satisfaction is rarely correlated with sexual frequency and is not consistently associated with sexual symptoms; thus, sexual satisfaction must be assessed clinically. Future research is needed on the definition of sexual satisfaction, on the correlates of sexual satisfaction in women, and how these correlates may differ for men. **Grade C**

Part II: Etiological Factors in Desire and Arousal Difficulties

Biological Aspects of Low Sexual Desire and Low Subjective Arousal

From the perspective of Emotion Theory, sexual desire may be conceived of as being connected to other basic emotional systems like fear–anxiety, in that it is a highly adaptive response to an emotionally competent stimulus [52]. In this perspective, the subjective experience of desire may be the conscious awareness of the automatically generated bodily responses to the stimulus (i.e., arousal) that produces the sensation of "wanting" [53]. The subjectively experienced state of desire may thus be the final result of a complex interplay of driving and inhibiting forces [54]. The biological factors mentioned below may hamper responses to "sexually competent stimuli."

The most important neurotransmitters involved in desire and subjective arousal identified so far are norepinephrine, dopamine, melanocortins, oxytocin, serotonin acting via 5 HT_{1A} and 5 HT_{2C} receptors—being prosexual, and prolactin, GABA and serotonin acting via other receptors—being inhibitory or negative. The actions of these substances are modified and influenced by the endocrine milieu provided by estrogen, progesterone, and testosterone (T). Extensive research has shown the impact of chronic medical illness, childbirth [55], and oral contraceptives [56,57] on sexual desire and arousal.

Psychological Aspects of Low Sexual Desire and Subjective Sexual Arousal Disorder

Psychological factors may contribute to desire and subjective arousal in manifold ways, including motivational and cognitive pathways. The motivation to engage in sexual activity may be the wish to be emotionally close to the partner, to satisfy the partner, to feel feminine, to feel powerful and accepted [22]. Cognitive pathways refer to the meaning given to the sexual activity which implies previous experiences provided by episodic memory [58]. There are many factors that may have a negative impact on motivation and cognition; however, the observations about facilitating and impeding factors for the development of

Table 3 Psychological factors associated with sexual desire/arousal impairments in women

Domain	Major findings	Reference
Sexual abuse and emotional neglect in childhood	Variable midterm and long-term effects on the female adult's sexuality after childhood abuse and neglect. One of the possible sequelae is low desire and sexual aversion.	[59–65]
Traumatic experiences during puberty	First negative sexual experiences and especially humiliation and offense may have long-term consequences for the internal sexual script which determines positive and negative attributions to one's sexual life.	[66]
Perceived stress	Psychosocial stress in general may reduce the motivation to become sexually active. Apart from cognitive processes, there may be an incremental effect of a stress-induced cortisol secretion. In one controlled study, chronic stress did not affect the level of subjective sexual arousal.	[27,67,68]
Distraction/Attention	Distraction has been shown to be detrimental to female sexual arousal, especially subjective arousal and desire.	[69–71]
Self-focused attention	Self-focused attention may negatively impact genital and subjective sexual arousal.	[72]
Anxiety	There is a large array of sexual concerns (worries about pleasing her partner, fear of partner rejection, fear of pregnancy and STI, unease related to the ability to reach orgasm) that may interrupt her experience of sexual desire. The role of anxiety as a key etiological agent in the genesis of sexual disorders has been highlighted in a number of clinical research studies.	[73–79]
Depression	A strong and clear relationship exists between depressed mood and sexual dysfunction in women. However, the literature on sexual function of depressed individuals is complicated by the influence of antidepressant medications. However, in a detailed review of the literature, it was concluded that loss of desire is a consistent consequence of major depression, regardless of antidepressant use.	[80]
Personality variables	From the available literature, it is apparent that personality features of low/fragile self-regulation and self-esteem, as well as histrionic personality relate to impaired sexual desire. Women with histrionic personality disorder were compared with nonhistrionic women and were found to have significantly lower sexual assertiveness, greater erotophobic attitudes toward sex, lower self-esteem, and greater marital dissatisfaction.	[81]
Body image self-consciousness	Body image self-consciousness has negative effects on female sexual function, above and beyond actual body size or general body image dissatisfaction.	[82]

STI = sexually transmitted infection.

sexual health are mainly theoretical, clinical, and anecdotal. The most frequent applied research methodologies in this field are correlational and ecological studies. Table 3 summarizes some of the psychological domains that have been associated with sexual desire/arousal impairment.

Recommendation

Screening for and treatment of anxiety disorders is recommended. Overall, the empirical results provide evidence of a significant relationship between anxiety and sexual difficulties. Sexual disorders including impaired arousal, desire, and satisfaction are common complications of various anxiety disorders. A strong and clear relationship exists between depressed mood and sexual dysfunction in women, although it is difficult to determine the order of causality. Given that personality factors (i.e., trait of an individual) are much less amenable to change than psychological reactions (i.e., state of an individual), assessment of personality as it might influence sexual health is important but there may be limits to what the clinician can do in terms of improving these aspects of the woman's personality disposition. Body concerns are found to have negative effects on sexual function in women and should be assessed. **Grade C**

Relationship Factors Influencing Low Sexual Desire and Subjective Sexual Arousal

Evidence-based research about relationship factors contributing to desire and arousal concerns is scant, but clinical experience and correlational studies show a close link between relationship and sexual satisfaction, although there is not a strict interdependence (both domains can operate independently meaning that couples with a good quality of their relationship may have severe sexual problems and couples with marital difficulties may function sexually in a positive way).

A considerable number of studies have shown that sexual dysfunction of the male partner, especially erectile dysfunction and premature ejaculation have a negative impact on the female partner's sexual desire [83] and successfully addressing the former restores the woman's sexual quality of life [84]. Some community surveys have shown that the duration of relationship is inversely correlated to sexual desire and arousal [85]. Compared to women without HSDD, women with HSDD report poorer dyadic adjustment, greater dissatisfaction with conflict resolution in their relationship, and less attraction to and emotional closeness with their partners. Difficulties expressing sexual needs, wishes, and

Table 4 Etiological factors that should be evaluated when assessing desire and arousal complaints in women

	Predisposing considerations	Precipitating considerations	Maintaining considerations
Biological	Endocrine factors, menstrual cycle disorders, history of surgery or medical illness, drug treatments affecting hormones or menstrual cycle, benign diseases	Change in hormonal status as a result of menopause, cancer, use of medications or drugs, current medical conditions	Drug treatment, metabolic/ malignant disorders, other chronic medical conditions, hormone treatment
Psychosexual	Past sexual history (both positive and negative), unwanted sexual experiences, history of rape, violence, coercion, body image concerns/issues, personality traits and temperament (extroverted vs. introverted, inhibiton vs. excitation), attachment history (past and present), coping resources, social/ professional roles and responsibilities	Current relationship satisfaction, affective disorders (anxiety, depression), loss of loving feelings toward partner as a result of discovery of affair, deception, etc.	Anxiety, tension, communication problems
Contextual	Ethnic/religious/cultural messages, expectations, constraints; socioeconomic status/access to medical care and information, social support network	Relationship discord, life-stage stressors (divorce, separation), loss or death of close fiends or family members, lack of access to medical/psychosocial treatment, economic difficulties, worries.	Cultural myths

fears between partners are frequently an immediate and direct factor which impacts negatively on the woman's desire to engage in sexual activity.

Recommendation

The above-mentioned biological and psychosocial factors have been described as separate entities. In clinical practice they usually interact in the individual patient with HSDD and FSAD and it is the task of the clinician to disentangle these factors, assess their pathogenetic importance and their accessibility to change. A biopsychosocial approach, advocated by many experts, is recommended. In this approach (see Table 4), the factors are grouped into biological, psychosexual, and contextual, and are subdivided along a timeline in predisposing, precipitating, and maintaining considerations. A comprehensive diagnostic workup using this model is likely to help clinicians to come to a fuller understanding of the patient's desire and arousal difficulties. **Grade C**

Etiological Factors Specific to Sexual Arousal

One of the most important but difficult tasks is to assess whether inadequate sexual stimulation is underlying sexual arousal problems, which requires detailed probing of (a variety of) sexual activities, conditions under which sexual activity takes place, prior sexual functioning, and sexual and emotional feelings for the partner. The initial clinical interview should help the clinician in formulating the problem and in deciding what treatment is indicated. If psychophysiological tools are available, observation of the genital arousal response to adequate stimulation by means of audiovisual, cognitive (fantasy), and/or vibrotactile stimuli may be useful. However, it is important to note that this often does not correlate with the woman's subjective report of (impaired) sexual arousal. Such a test may be crucial in establishing the etiology of FSAD for two reasons. A recent study by Laan and colleagues demonstrated how difficult it is to rule out that sexual arousal problems are not caused by a lack of adequate sexual stimulation [86]. In addition, they showed that impaired genital response cannot be assessed on the basis of an anamnestic interview. Women with sexual arousal disorder may be less aware of their own genital changes, with which they lack adequate proprioceptive feedback that may further increase their arousal. If a genital response is possible, even when other investigations indicate the existence of a variable that might compromise physical responses, an organic contribution to the arousal problem of the individual women is clinically irrelevant.

As reviewed earlier, the use of self-report measures (e.g., [87]) and a careful focused pelvic exam may be helpful in clarifying the correlates of the impaired arousal response.

Recommendation

A thorough assessment of FSAD must include an in-depth personal interview during which adequacy of sexual stimuli is assessed. Psychophysiological tools may be helpful though, at present, are reserved primarily for the research setting. Self-report measures may corroborate

information obtained from an interview. A carefully focused genital/pelvic examination is necessary when there are complaints of loss of genital sensitivity or pain or vaginistic reactions. **Grade C**

Part III: Assessment

The Biopsychosocial Interview

The most common approach to diagnosing sexual difficulties is via a comprehensive clinical interview of both the identified patient and her partner if possible. Such an interview includes discussion of the presenting problem and the predisposing, precipitating, and maintaining factors that govern its appearance and intensity [88]. Table 4 provides an overview of the contributory factors that may be etiologically
relevant in such a biopsychosocial interview [88]. Among these factors are life stage stressors such as childbirth, infertility, divorce or partner loss, unemployment, extra-relationship affairs, humiliating or traumatic sexual experiences, partner sexual inadequacy or clumsiness, and most significantly, relationship discord.

Althought it may be difficult to differentiate predisposing from precipitating and/or maintaining factors, it is helpful to attempt to determine what the immediate triggers or precipitating factors are for the appearance of a recent sexual complaint as these are likely to be important areas to address in the early stages of treatment. Assessment of perpetuating or maintaining factors includes the current contextual factors that affect sexual expression such as relationship satisfaction, privacy issues, current health of self and partner, medical or psychiatric issues, use of medications or recreational drugs/alcohol that may affect sexual expression, and current stressors.

Self-Report Assessment Tools

Standardized self-report questionnaires can be helpful in terms of saving time, identifying problems, and providing direction or greater focus for follow-up interview and evaluation. The assessment tools listed in Table 5 have demonstrated good reliability and validity and can identify problems with the various components of female sexual response, many of which overlap. Some focus on a particular symptom (e.g., low desire). Caution in using these self-report questionnaires and the tradition of focusing on (sexual event) quantity as opposed to quality are criticisms of existing measures that must be taken into account [102].

Recommendation

Although instruments may be helpful in guiding diagnosis or treatment, given their potential therapeutic value, none is a substitute for a thoughtful and sympathetic clinical interview that includes the woman and her partner (if possible and applicable). **Grade C**

The Physical Examination

A physical examination is recommended for reasons of good medical care and for education and reassurance. The examination is also a setting to explore perceptions, beliefs, and attitudes about a woman's own anatomy and encourage a patient's positive approach to her genitals and body.

The examination is particularly important for ruling out or identifying medical factors when concomitant complaints such as loss of sensitivity or sexual pain exist. A gynecological examination should include an evaluation of the level of voluntary control of the pelvic floor muscles, pelvic floor muscle tonus, presence of vaginal wall prolapse, signs of vaginal atrophy, size of introitus, presence of discharge, or evidence of infection (acute or chronic), epithelial disorders, and/or pain. In some disease conditions (e.g., multiple sclerosis or pituitary disease), there may be specific symptoms of vulvar sensory loss, atrophy, or hypertrophy.

Recommendation

A gynecological examination is recommended in the assessment of women with desire and arousal complaints to assess and rule out medical/physical contributors. **Grade C**

Psychophysiological Tools

Over three decades, several techniques have been developed to assess genital physiological changes in response to sexual stimuli. The most widely used of such psychophysiological tools is the vaginal photoplethysmograph [103]. Although its use has been of great value for indicating the arousal status of the vagina per se, it is still unclear exactly what vaginal pulse amplitude (VPA) actually represents [104]. This may, in part, be explained by its lack of an absolute scale. VPA is measured on an ordinal scale rather than an inter-

Table 5 Scales useful for the evaluation of sexual desire and arousal problems in women

Golombok–Rust Inventory of Sexual Satisfaction (GRISS) [89]	A 28-item questionnaire designed to assess the existence and severity of sexual problems across five domains relevant to women: anorgasmia, vaginismus, avoidance, nonsensuality, and dissatisfaction. Items are presented with a five-point response format ranging from never to always. Interpretation of the data is based on patterns across the different subscales and Rust and Golombok note that "this leads to indications for therapy, rather than to a diagnosis." The GRISS was standardized on couples receiving sex therapy. Split-half reliability is 0.94 and test–retest reliability is 0.65 for women. It was validated in those with a known sexual dysfunction vs. a control group and found to have good discriminant validity.
Brief Index of Sexual Functioning for Women (BISF-W) [90]	A 22-item questionnaire that provides domain and total scores on the following aspects of sexual function: desire, arousal, frequency of sexual activity, receptivity/initiation, pleasure/orgasm, relationship satisfaction and problems affecting sexual function. A principal components analysis resulted in three discrete factors: sexual interest/desire, sexual satisfaction, and sexual activity. BISF-W was also shown to possess a high degree of concurrent validity with the DSFI, displaying a Pearson correlation of 0.69. BISF-W, however, is much easier to administer than the DSFI and results in a more detailed evaluation of current sexual functioning.
Sexual Desire Inventory (SDI) [91]	A 14-item questionnaire that measures dyadic and solitary sexual desire on the basis of factor analysis. Using Cronbach's alpha, SDI exhibited high internal consistency estimates with coefficients of 0.86 for dyadic sexual desire and 0.96 for solitary sexual desire, suggesting excellent reliability.
Derogatis Interview for Sexual Functioning (DISF) [92]	A 25-item questionnaire that includes five domains: cognition, arousal, behavior, orgasm, and drive/relationship as well as a total score. The DISF/DISF-SR appears to fulfill fundamental psychometric criteria. High reliability scores and a nearly ideal subtest-total score relationship have been found. The hypothesized internal structure as well as the discriminative capacity of the scale have also been firmly established.
Female Sexual Function Index (FSFI) [87]	A 19-item questionnaire specific to women that assesses six domains (desire, subjective arousal, lubrication, orgasm, satisfaction, and pain). FSFI was shown to possess excellent test–retest reliability for each domain with a range of reliability coefficients from 0.79 to 0.96. High internal consistency was also determined using Cronbach's alpha which yielded values of 0.82 and higher. More importantly, greatly significant mean difference scores between women with Female Sexual Arousal Disorder and controls attest to the scale's construct validity ($P < 0.001$). Suggestions for improved scoring of the FSFI so it does not penalize women who are not currently sexually active have been offered [93,94].
Sexual Function Questionnaire (SFQ) [95]	A 31-item relatively new instrument designed to assess eight domains of women's sexuality: desire, physical arousal/sensation, physical arousal/lubrication, enjoyment, orgasm, pain, partner relationship, and cognition. This scale features good internal consistency, respectable reliability, excellent discriminant validity, and sensitivity. Specifically, internal consistency of the domains was found to range from 0.65 and 0.91, and test–retest reliability was noted to be between 0.21 and 0.71 for Cohen's weighted kappa and 0.42 and 0.78 for Pearson's correlation coefficient. In terms of validity, there was a significant difference between the baseline mean SFQ domain scores of female patients with sexual dysfunctions and scores of controls. Additionally, SFQ scores at the end of the study also significantly diverged between patients who reported improvement in their sexual functioning and those who did not.
Female Sexual Distress Scale (FSDS) [96]	A 12-item instrument for determining the amount of current distress experienced by a woman who reports sexual difficulties. A cut-off score of 15 or greater is believed to indicate personal distress. Using Cronbach's alpha, a high level of internal consistency was established for FSDS with a range from 0.86 in an early study to the low 0.90s in later clinical trials. Test–retest reliability has also been found to be respectable. In regards to discriminative ability, FSDS was found to successfully distinguish women with and without sexual dysfunctions.
Sexual Interest and Desire Inventory (SIDI) [97]	A 13-item clinician-administered measure of sexual interest, desire, and arousability. It assesses spontaneous and responsive sexual desire, receptivity and initiation of sexual activity, satisfaction with desire and arousal, and desire for nonsexual affection. The SIDI displays a high level of reliability and validity as a tool of assessing the severity of HSDD. It has a Cronbach's alpha of 0.9 for internal consistency and a moderate-to-good item-total correlation for all its items except the Orgasm measure. With respect to discriminant validity, the SIDI scores from women with HSDD were found to be significantly lower than those from women without sexual dysfunctions.
HSDD Screener [98]	A brief screening tool developed to diagnose HSDD in postmenopausal women. The measure consists of four self-report questions and a concise confirmatory physician interview. Self-report questions are rated on a 5-point Likert scale ranging from 0 (no difficulty at all) to 4 (a very great deal of difficulty), with a total cut-off score of 7 suggestive of HSDD. This measure has adequate sensitivity (0.82), specificity (0.99), and likelihood ratio (58.3), and there is good agreement between the cut-score alone diagnoses and cut-score in combination with physician interview (kappa of 0.669 and 0.562 respectively).
Female Sexual Distress Scale-Revised (FSDS-R) [99]	The most recent validation of the FSDS which was undertaken to enhance the sensitivity of the instrument for patients experiencing HSDD. The FSDS-R is identical to the FSDS except for the addition of one question that asks women to rate their level of distress related to low sexual desire: "Are you bothered by low sexual desire?" The respondent circles never (0), rarely (1), occasionally (2), frequently (3), or always (4). For both FSDS and FSDS-R, a Cronbach's alpha of >0.86 demonstrates that these tests possess high internal consistency and an intraclass correlation coefficient of >0.74 also show their good test–retest reliability. Furthermore, mean total FSDS, FSDS total, and FSDS-R item 13 scores were noted to be significantly higher ($P < 0.001$) in women with sexual dysfunctions or HSDD than controls, indicating that both tests and FSDS-R item 13 alone possess discriminant validity.
Decreased Sexual Desire Screener (DSDS) [100]	A measure developed to provide clinicians who are neither trained nor specialized in Female Sexual Dysfunction with a brief diagnostic procedure for diagnosis of generalized acquired HSDD in pre-, peri-, and postmenopausal women. The respondent indicates "yes" or "no" to five questions, and indicates which of the factors listed (e.g., medication, pregnancy, stress) may be contributing to her decreased desire or interest. The clinician then follows a brief set of instructions to determine whether the respondent's answers qualify her for a diagnosis of HSDD. This measure has high sensitivity and specificity (with point estimates of 0.84 and 0.88, respectively), and agreement between the DSDS and an extensive diagnostic interview was 97%.
Womens' Sexual Interest Diagnostic Interview (WSID) [101]	The WSID is a 39-item self-report measure designed to diagnose Female Sexual Dysfunction, and includes an interviewer worksheet to allow diagnosis of HSDD, FSAD, FOD, sexual pain disorder, and the presence of depressive symptomatology. This measure has been shown to diagnose HSDD with a high sensitivity of 82.1% and a specificity of 100%, with a kappa coefficient of 0.85. Agreement coefficients for FSAD and FOD were also in the acceptable range however there is some difficulty in diagnosing sexual pain disorders with this instrument.

DSFI = Derogatis Sexual Functioning Inventory; HSDD = hypoactive sexual desire disorder; FSAD = female sexual arousal disorder; FOD = female orgasmic disorder.

val or ratio scale, hampering the development of this measure as an individual diagnostic method of genital responsiveness.

Studies comparing women with and without sexual difficulties or dysfunction have failed to find significant group differences in VPA [69,86,105–111, but see 33]. When using a different definition of "Genital Sexual Arousal Disorder" that focused on lack of genital sensation, one study found that VPA differed significantly from women with impairments in only the subjective aspects of sexual arousal [33]. These findings suggest that genital responsiveness in somatically healthy women, at least as it is defined by the DSM-IV [10], may not play an important role in women's sexual problems. Summarizing these findings and the brief literature showing that in select subgroups of women with medical disease VPA may be impaired, Laan and colleagues concluded that it is not the presence of sexual arousal problems but presence of a somatic condition that influences genital response [86].

Several alternative, albeit to date less well-researched, methods for measuring genital response in women have been developed and these are summarized in Table 6.

Recommendations

To date, psychophysiological techniques have been reserved largely for the research setting and are not a standard component of the clinical assessment or treatment in women, due in part to its invasive nature. Although vaginal photoplethysmography, the best researched measure to date, is a sensitive tool, it is not useful diagnostically because it cannot be calibrated. More research is needed using one of the newer psychophysiological techniques to explore whether these methods hold utility in discriminating clinical subgroups. Findings from psychophysiological studies to date suggest that in somatically healthy women, the potential to become genitally aroused is not disrupted. **Grade B**

Laboratory Investigations

The possibility that laboratory testing will identify causes of sexual dysfunction is low. Estrogen deficiency is best detected by taking a history and performing a physical examination [138]. Measurements of estradiol and follicle stimulating hormone are indicated in amenorrheic young women or in women with irregular menstrual patterns or to evaluate menopausal status in hysterectomized women without a clear symptom history. Most studies have failed to find a correlation between low sexual desire and serum T levels in women [139–145]. In women with symptoms or signs of thyroid disease or hyperprolactinemia (galactorrhea, irregular menses, and/or infertility), diagnostic assays should be taken.

Recommendation

In women with symptoms or signs of thyroid disease or hyperprolactinemia (galactorrhea, irregular menses and/or infertility), diagnostic assays should be taken. **Grade C**

Estrogen and Sexual Response

The most abundant and potent estrogen before menopause is 17β-estradiol (or estradiol). Estriol and estrone are present at much lower levels and display less activity on estrogen receptors [146]. The primary source of estradiol in premenopausal women is the granulosa cells of the ovaries. After menopause, estrogen is produced in extragonadal intracellular sites from dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulphate (DHEAS), and androstenedione (A4). The major estrogen in serum of postmenopausal women is E1 which is not measured by clinically available assays.

Several clinical studies have shown that an adequate estradiol level is important for maintaining vaginal lubrication and avoiding dyspareunia [147–150]. However, this is not to say that low estrogen levels invariably cause dyspareunia. A weak correlation between lower levels of estradiol and decreased sexual desire has been found by some [150–152], but not by others [153–155], and differences may relate to methodological variability. Table 7 summarizes recent population-based studies that have explored the association between estrogens and women's sexual response.

Effects of menopause and hypoestrogenism on genital sensitivity are not well known but there are some nonhuman animal and human data linking improved sensitivity to estrogenized tissue [157–159].

Recommendations

Lack of estrogen has been found related to dyspareunia and vaginal dryness. However, many hypoestrogenic women do not have dyspareunia. When sufficiently sexually stimulated, low estrogen may be less important. An association between reduced estrogen and decreased sexual desire has

Table 6 Psychophysiological tools other than vaginal photoplethysmography used in the assessment of women's sexual arousal

Method	Details	Findings	Comment
Heated oxygen electrode	Fitted into a suction cup that could be applied to the vaginal wall and held there by a partial vacuum. The amount of electrical power needed to keep the disc at a constant temperature is monitored. Heat is lost from the disc mainly by conduction through the tissue and tissue fluid to the blood. Increased blood perfusion under the electrode will increase its heat loss and thus a greater power output will be needed to maintain the electrode at the set temperature. The changes in power (in milliwatts) thus becomes an indirect measure of the changes in blood flow under the electrode, reflecting the pooling of blood in the vascular bed. The electrode also records the amount of oxygen that diffuses across the skin, reflecting transient changes in blood flow. The greater the blood flow beneath the disk, the greater the apparent oxygenation of the flow will be as it gradually approaches that of the saturation of the arterial blood.	Subjects usually applied clitoral self-stimulation as a means to induce sexual arousal. Both techniques are sensitive to sexual arousal and orgasm [112–114].	Advantages: Combines two measures of blood flow; is relatively free of movement artifacts because it is attached to the surface of the vagina, [115]; the reliability of the signal is not compromised by masturbation and clitoral vibration; both measures can be calibrated in terms of absolute blood flow. Disadvantages: Expensive; the electrode should not be applied for very long periods of recording to protect the vaginal mucosa from heat damage; needs to be attached by the experimenter. A general disadvantage of temperature methods is that subjects require relatively long resting periods to show temperature stability, and after high sexual arousal the measures do not return to baseline easily [115,116].
Labial thermistor	A thermistor placed on a small clip that is attached to the labia minora [117,118]	Is more strongly correlated with self-reported sexual arousal than VPA [119]. When worn simultaneously with the vaginal photoplethysmograph, the labial thermistor discriminated sexual from nonsexual stimuli and was sensitive to different levels of sexual arousal [120].	Advantages: Unlike VPA, the units of change are measured on an interval scale (degrees Celsius), allowing direct comparisons across participants; is unaffected by orgasm [121]. Disadvantages: Menstrual cycle effects reported for labial temperature change [3,117]. Onset of change in labial temperature is slower than VPA and temperature takes longer to return to baseline.
Labial photoplethysmograph	A small plastic clip which can be attached to the labia majora, originally designed to measure blood flow in the ear lobe	In a small study, the labial photoplethysmograph was compared with VPA while participants viewed neutral, sexual, sexually threatening, and threatening film clips. Both instruments were specific to sexual content [122].	Advantages: Exhibited fewer movement artifacts than the vaginal photoplethysmograph; correlates with subjective sexual arousal Disadvantages: Somewhat more difficult to place and less comfortable than the vaginal photoplethysmograph
Clitoral photoplethysmograph	Attached to the silicon tube of the vaginal plethysmograph, along with a silicon placement device holding the clitoral photoplethysmograph in the correct anatomical position. The shape of the clitoral probe follows the anatomical curves of the area surrounding the urethral opening up to the clitoris, between the labia minora and just above the introitus.	Clitoral photoplethysmography, but not VPA, appeared sensitive to a sudden interruption of the visual stimulus. No differences between women with and without sexual problems found for either measure [123].	Advantages: Subjects are able to insert the probe and attach the clitoral device without supervision.
Measurement of vaginal pH	Vaginal pH increases with increasing sexual arousal [123].	Vaginal pH was measured at six separate surface sites under direct observation during basal conditions and after sexual arousal to orgasm. On some sites, there could be a large increase in pH (at least 1 unit) while at others there was very little or even an occasional decrease.	Disavantages: Requires potentially disruptive experimenter involvement, and pH seems to vary nonsystematically across different areas of the vagina [122].
Clitoral color Doppler ultrasonography	Non-invasive, reproducible, low-cost, and quantitative technique allows for ultrasonographic identification of the clitoris and for color Doppler assessment of clitoral blood flow [124].	Not successful in differentiating sexual arousal from a humor control condition [125]. Women with diabetes did have a lower pulsatility index, peak systolic velocity, and end-diastolic velocity values compared with controls [126].	Disadvantages: Requires a technician to hold the probe
Thermal imaging	Infrared thermography detects natural thermal radiation from the body and is able to produce an image representing temperature distribution of body areas. During sexual arousal, there is increased blood flow to the genialia, resulting in vasocongestion and a rise in temperature.	Discriminated between a sexually arousing, humor, and neutral clip, in a student sample [127] and between a sexually arousing, humor, anxiety and neutral clip in an older sample [128], using between-subject designs. In the latter study, within-subjects correlations between temperature change and subjective continuous arousal were variable with significantly positive correlations in 4 of 10 women who were measured in the sexual arousal condition.	Advantage: Highly correlated with subjective sexual arousal Disadvantage: Expensive
Magnetic resonance imaging of the pelvic area	During sexual arousal, the crura and body of the clitoris as well as the vestibular bulbs demonstrate a very prominent increase in size and signal intensity [129]. Initially required a contrast agent to observe dynamic changes in blood flow [126] but more recent techniques without contrast agent proved to be equally sensitive [130].	Measurement of other structures (e.g., vaginal mucosa, vaginal wall thickness, changes in labia) proved either unsuccessful or less reproducible than the clitoral volume measurement. No differences between pre- and postmenopausal women observed [131]. Unaroused clitoral volume (not including vestibular bulbs) of premenopausal women did not differ from postmenopausal women [132].	Disadvantage: A limitation of the noncontrast magnetic resonance technique is that it is not possible to obtain quantitative regional blood volume measurement, but because this is less robust than three-dimensional, anatomical clitoral volume measurements [133], this is not a significant limitation.

Table 6 Continued

Method	Details	Findings	Comment
Dynamic sonography	Functional 3D sonograpy requires a sonography probe placed on top of the vulva with a coronal, transversal, orientation to obtain coronal and transversal planes and the probe placed sagittally on the majora labia to obtain a sagittal scan. An echo-scan provides a fine anatomy of the clitoris and visualizes the displacement of structures during movement or perineal contractions in real-time.	The clitoris viewed as a 3-plane (cross-section, sagittal section, and coronal section) organ, with the clitoral bulbs reaching as far posteriorly as the perineal body [134–136]. Magnitude of clitoral bodies in sexually aroused state is close to the distal anterior vaginal wall [135].	Advantages: The proximity of the measured structures may explain the particular sensitivity of the anterior vaginal wall [137].

VPA = vaginal pulse amplitude.

been only described clinically. There is some limited evidence to affirm that there is an association between reduced vulvar sensitivity to pressure/touch and estrogen deficiency. **Grade B**

Androgens and Sexual Response

The androgens include T, DHEA, DHEAS, A4, and 5 α-dihydrotestosterone (DHT) [160,161]. Of the androgenic steroids, T and DHT have the most potent biological activity. DHEA, DHEAS, and A4 are adrenal and ovarian precursor steroids that can be metabolized into T, DHT, and estrogen in peripheral tissues [162,163].

Androgens circulate in the body bound by a variety of proteins, including albumin, cortisol-binding globulin, α2-glycoprotein, and most importantly, sex hormone-binding globulin (SHBG). Androgens bound to SHBG are essentially not bioavailable; in contrast, androgens complexed to albumin are rather available because of their lower affinity. Androgen levels peak when women are in their 20s and drop gradually with age, so that women in their 40s have approximately half the level of circulating total T as women in their 20s. T levels do not decline consistently during or after menopause [164,165]. Androgens are known to act on multiple tissue and receptor sites throughout the body [161].

In 2002, a Consensus Conference on androgens agreed that androgen insufficiency in women with adequate estrogen levels could lead to a diminished sense of well-being and energy, fatigue, and decreased sexual desire [161]. More recent guidelines from the Endocrine Society recommended against making a diagnosis of "androgen insufficiency," because of the lack of a well-defined clinical syndrome and normative data on T levels across the lifespan that can be used to define such a disorder [166]. However, a panel of sexual medicine clinicians challenged the conclusions from the Endocrine Society Guidelines as ignoring some of the available data in support of androgen therapy [167].

The lack of accuracy in current assays to measure T is a well-known limitation [168]. Tandem mass spectrometry methods in combination with gas chromatography or liquid chromatography have been developed for T and are the methods of choice for the precise measurement of the low levels [169] but are not yet widely available in clinical settings.

An additional complication relates to the intracrinology of sex hormones. Intracellular production is a major source of T and DHT, and is known to reduce by 80% through adult life. Active androgens, whether produced in a peripheral cell or stemming from the ovaries, are inactivated to glucuronide derivatives before their diffusion from the intracellular compartment into the general circulation (plasma), where they can be measured as androgen metabolities. Measurement of such metabolites (currently only a research tool) might identify cases of true androgen deficiency and differentiate women who will benefit from therapy from those who will not.

Over the last two decades, it has become clear that the brain is a steroidogenic organ. Current evidence in animals points to important roles for neurosteroids in behaviors that strongly influence sexual interest and motivation [170]. Sex steroid production and action within the brain may be more relevant to women's sexual desire and function than peripheral androgens.

The great variability in the responsiveness of women to treatment with androgens is another confounding factor. This may relate to polymorphic variations of the androgen receptor (AR) gene. Further elucidation of the genetic determinants for serum androgen activity and its significance on sexual function is warranted. A related although separate complication is that some women are more sensitive to androgens than others [171] (see Table 7).

Table 7 Population-based studies relating androgen levels to female sexual function

Citation	n	Design and inclusion criteria	Hormonal assessment	Sexual assessment	Significant findings
Cawood and Bancroft [139]	141	Prospective study over 5 weeks; healthy community volunteers, aged 40–60 years	Four weekly blood samples (midcycle samples excluded), averaged 4 samples; measured T, SHBG, A, DHEA, DHEA-S, E2,E1, P, FSH, LH, FAI.	Five structured interviews over 5 weeks; Frenken Sexual Experience Scale.	Hormones and menopausal status not significantly correlated with sexual function. Sexual function better if adequate vaginal lubrication, good relationship, higher socioeconomic status, lower BMI, and normal mood.
Gracia et al. [143]	326	Prospective study over 4 years; random population women aged 35–47, intact uterus and at least one ovary, premenopausal at baseline.	Blood sample on days 1–6 every 8 months; T, DHEAS, E2, FSH, LH. Used RIA.	One question on "decreased libido" in last month and one on vaginal dryness.	Twenty-seven percent of women had low desire. No difference in their mean hormone levels, but had greater fluctuation of total T over time. Low desire related to depression, vaginal dryness, and having children at home.
Dennerstein et al. [141,142]	336	Prospective study over 8 years; random population sampling of women aged 45–55 years, menstruating at baseline. The Melbourne Women's Midlife Health Project.	Yearly fasting morning blood sample days 4–8 of menstrual cycle or after 3 months of amenorrhea; FSH, E2, T, SHBG, DHEA-S, inhibin, FAI. Used RIA.	Personal Experiences Questionnaire validated for Australian women; Sexual response score included desire, arousal, pleasure, and orgasm.	Androgens had no impact on sexual function. Most important factors were previous sexual function, losing a partner (negative) or getting a new partner (positive), and satisfaction with current relationship. E2 level impacted sexual desire/arousal and dyspareunia.
Davis et al. [140]	1,021	Cross-sectional study in Australia; random selection from community, aged 18–75 years; 9% response rate.	One fasting morning blood sample; if premenopausal after cycle day 8 and before onset of menses (to avoid the early follicular phase testosterone nadir); T (direct RIA), FAI, DHEA-S, and SHBG (immunometric assays); A_4 (direct RAI); FSH, TSH, LH, and prolactin using automated machines.	Profile of Female Sexual Function, validated questionnaire (7 domains of desire, arousal, orgasm, pleasure, sexual concerns, responsiveness, and self image).	No significant relationship between androgen levels and sexual function, most women with low DHEAS did not report sexual problems.
Santoro et al. [145]	2,961	Longitudinal study, report of cross-sectional measurements at baseline. Multiethnic community-based sample of women aged 42–52 years, menstruating at baseline. The study of women's health across the nation (SWAN).	Blood drawn after 10-hour fast on days 2–7 of follicular phase. Serum E2 (automated analyzer immunoassay). T (polyclonal anti-T antibody binding), SHBG and DHEAS (chemiluminescent assays). FAI calculated. Assays were calibrated for low levels of T in women.	Questionnaire designed for the study asked about frequency of desire for sex and about arousal during sex.	Androgen levels weakly associated, if at all, with sexual desire, sexual arousal, or mood but were associated with having the metabolic syndrome.
Gracia et al. [144]	313	Penn Ovarian Aging Study; 3-year prospective data of equal samples of African-American and Caucasian women aged 35–47 years at baseline, menstruating.	Blood sample on days 1–6 of menstrual cycle in two consecutive cycles once a year; E2, FSH, LH, SHBG, DHEAS, total T. Radioimmunoassay commercial kits.	Female Sexual Function Index.	Sexual dysfunction did worsen as menopause progressed. Although low DHEAS was correlated with vaginal dryness, pain, and orgasmic dysfunction, much stronger relationship of sexual dysfunction was found with lack of a partner and with high anxiety.
Gerber et al. [156]	23	5-year longitudinal study, community-based including premenopausal (at baseline) women aged 45–55 years.	Free T measured by enzyme immunoassay. T levels obtained twice, 4 years apart.	Questionnaire designed for the study asked about desire, sexual initiative, sexual satisfaction.	No significant relationship between androgen levels and sexual function. Exercise improves sexual function.

A = androstenedione; DHEA = dehydroepiandrosterone; DHEAS = dehydroepiandrosterone sulphate; T = testosterone; E1 = estrone; E2 = estradiol; P = progesterone; FSH = follicle-stimulating hormone; LH = luteinizing hormone; RIA = radioimmunoassay; SHBG = sex-hormone-binding globulin; FAI = Free Androgen Index; BMI = body mass index.

Recommendation

Most of the evidence fails to find a significant correlation between sexual desire and response and T levels in women. There are significant limitations in this research: (i) the lack of standardized assays which are suitable for detecting androgens in the female range; (ii) the inability to quantify neurosteroid production and action; (iii) the current lack of understanding of the role of the AR gene polymorphism in the extent of serum androgen activity; (iv) the current lack of a clear definition of sexual desire and consensus about what constitutes sexual desire problems; and (v) possible individual differences in sensitivity to T. T level measurements in women cannot be recommended until more accurate measures of androgenic activity emerge. **Grade B**

Sex Hormones and Neurotransmitters

Neurotransmitters and steroid hormones appear to have a modulatory function on each other, and changes in one system may have a dramatic effect on the other [172]. For instance, recent longitudinal data suggest that the transition to menopause is strongly associated with new onset depressed mood among women with no history of depression [173]. Clinical and experimental data in addition to new imaging techniques such as positron-emission tomography, single photon emission computed tomography, spectroscopy, and functional and structural magnetic resonance imaging have confirmed a large part of earlier animal studies: the major neurochemical systems involved in sexual behavior consist of pathways involving neurotransmitters and hormones including dopamine, serotonin, norepinephrine, prolactin, oxytocin, melanocortins, and endogenous opioids. Some of these substances are substantially influenced by gonadal steroid hormones and/or interact among each other [172,174].

Age vs. Menopause in Predicting Sexual Problems

When exploring the influence of menopause on sexual response, separating age-related effects from hormonal changes can be difficult though it is essential. In the Melbourne Women's Midlife Health Project, comparison between age-matched premenopausal and postmenopausal women showed that sexual desire and lubrication are affected by both menopause and aging, independently [150,151]. In a longitudinal study of 1,525 British women aged 47–54, independent effects of menopause and aging on sexual functioning were also found [175].

Recommendation

Teasing apart age-associated vs. menopause-associated contributions can be difficult although practitioners should make an effort to do so. Age and menopause are both significantly associated with desire and arousal problems in women; however, the presence of distress appears not to be. Whereas sexual complaints increase with age, the associated distress appears to diminish. Psychosocial aspects of aging and menopause contribute more to difficulties than hormonal contributions and should therefore be the focus of assessment and treatment. **Grade B**

Surgical Menopause in Predicting Sexual Problems

The contribution of surgical (via BSO), as opposed to natural menopause, has been extensively studied but with inconsistent findings. The WISHeS study recruited 4,517 women from France, Germany, Italy, the United Kingdom, and the United States [40,41] and found that a greater proportion of surgically menopausal women had low sexual desire compared with age-matched premenopausal or naturally menopausal women. In another recent cross-sectional study of low sexual desire with and without distress in 2,207 U.S. women aged 30–70 [42], the highest prevalence of low sexual desire was found in naturally menopausal women (52.4%) rather than surgically menopausal women (39.7%) when compared with premenopausal women (26.7%). Low desire plus distress (HSDD) was found to be nearly twice as prevalent among surgically menopausal women (12.5%) than in premenopausal women (6.6%), especially if women were younger than 45. Women receiving exogenous hormones were less likely to complain about low desire but had slightly more distress than women not using hormones.

Prospective studies have not confirmed sexual dysfunction subsequent to surgical menopause for benign disease in three recent large trials [176–178].

Recommendation

Because distress associated with low desire, but not low desire per se, is the most prevalent among surgically as opposed to naturally menopausal women, sexual distress should always be assessed when there are complaints of low desire. **Grade B**

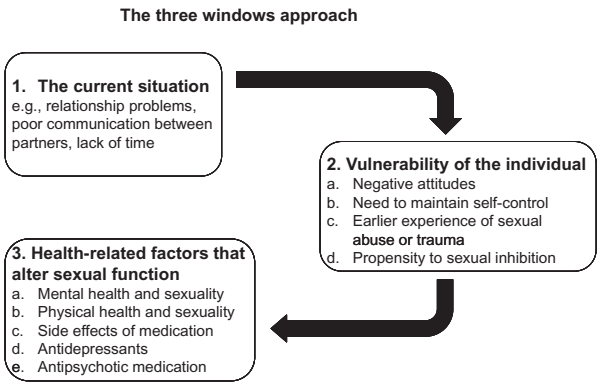

Figure 2 The three windows approach to understanding women's sexuality. Adapted from Graham and Bancroft (2009) [179].

Diagnosis and Formulation

On the basis of a thorough biopsychosocial assessment, of partners individually and together (when available and possible), and the relevant physical, physiological, or hormonal assessments, the clinician determines a diagnosis and formulation of a woman's sexual problem(s). Graham and Bancroft describe a "three windows" approach helpful for contextualizing factors influencing the sexual complaint [179] (Figure 2). The first window describes aspects of the woman's current situation, e.g., are poor communication, relationship difficulties, fatigue, or lack of privacy responsible for the desire or arousal concerns? The woman plagued with fatigue might benefit from a course of sleep hygiene therapy prior to (or instead of) sex therapy. In the second window, Graham and Bancroft suggest looking at individual vulnerability factors influencing the presentation of complaints. Does the woman display persistently negative attitudes about herself and her body? Does she have a high need to maintain control in all life and sexual situations? Is there a past history of sexual abuse or trauma such that flashbacks to the prior abuse are frequent and intrusive when she is attempting to be sexual? If such individual vulnerability factors are present, she may benefit from a cognitive behavioral therapy (CBT) treatment focused on that vulnerability factor (e.g., Cognitive Processing therapy for sexual assault, CBT for perfectionism, etc). The third window invites the clinician to consider health-related factors influencing the sexual response. One aspect of this domain would include mental health, such as depression or anxiety. This window also explores physical health-related factors, such as problems in the neural control of desire and arousal, problems in vascular supply to the genitals, endocrine dysfunction, and metabolic problems. The presence of any of these physical health-related factors significantly impacts the formulation of the sexual complaint (as being a result of a general medical condition). An important aspect of this third window includes the influence of both over-the-counter and prescription medications on sexual response.

It has been recommended that only problems lasting for a minimum of 6 months' duration be considered for diagnosis [9,34,35,180,181]. This time duration was chosen given the finding of the NATSAL survey [38] that lack of interest in sex for the past 1 month was significantly more common (40.6%) than lack of interest lasting for 6 months (10.2%). Short-term complaints that might be attributable to transient changes in the woman's health or relationship should not be diagnosed as a sexual dysfunction. Whether the problem is lifelong or acquired and generalized vs. situational can be coded as specifiers if one uses the traditional DSM-IV-TR classification scheme. However, a sexually distressing problem that is only situational should not be diagnosed as a dysfunction, although treatment of that problem might still take place.

Recommendation

A formulation of the diagnoses is recommended. The formulation integrates all information obtained from (sometimes a series of) assessments of the woman with and without a partner, and any relevant physical examinations, blood analyses, and self-report questionnaires completed. On the basis of the formulation, a diagnosis is applied, typically using both the DSM-IV-TR as well as the AUAF systems. The clinician also continues to modify the formulation as information emerges during treatment. The "three windows" approach can be very helpful for considering the many biopsychosocial factors that influence the woman's sexual complaints. An effort should be made to determine the duration and severity of symptoms. **Grade C**

Part IV: Treatment Ingredients Relevant to All Sexual Problems in Women

General issues related to improved well-being, such as diet, exercise, possible alcohol and chemical substance abuse, and sleep should be addressed in all women. Advising on all prescription and nonprescription medications, vitamins and herbal

supplements, and recreational drugs is important as well. Providing women relevant information on improving general health related to each of these domains may also be a component of care, and referral to appropriate medical or specialty providers may be necessary. The early stage of treatment might also include providing information on basic genital anatomy and physiology, and a discussion of sexual stimulation and sexual activities other than intercourse. Women should be encouraged to use techniques that enhance arousal, including enhancing the context and the stimuli she receives. **Grade C**

Part V: Treatment Issues Specific to Low Desire

Psychosexual Treatments for Low Desire

Unfortunately, there have been very few psychological outcome studies of treatments focusing specifically on low desire. When the low desire is better accounted for by depression, poor body image, sexual assault sequelae, or other more general personality or relationship factors, then those factors must be addressed either in conjunction or before the low desire itself is targeted.

Group CBT improves sexual desire disorder in 74% of couples and this effect was maintained in 64% at 1 year [182]. A modified Masters and Johnson sex therapy was also found to improve sexual function in 57% of women with sexual desire disorder [183]. Among the very limited available empirical literature testing sensate focus and traditional sex therapy techniques, one study showed that 65% of 365 married couples improved by clinical judgment at the end of therapy [184]. In one noncontrolled trial, a mindfulness-based CBT administered to women with mixed HSDD and FSAD in group format resulted in significant improvements in sexual desire and many other domains of sexual response and mood [185].

Recommendation

Psychological approaches to low desire have a long history and have been found to be effective immediately after treatment with sustained improvements over time. Moreover, they are without adverse side effects. Newer cognitive-behavioral treatments which integrate mindfulness meditation have shown excellent promise for sexual desire problems but await randomized controlled testing. There is also evidence that brief cognitive behavioral interventions are helpful for improving desire. Overall, there is an urgent need for more randomized controlled investigations of psychological therapy for low desire in women. **Grade C**

Hormonal Treatments for Low Desire

T has been used in the treatment of low sexual desire since the 1930s; however, systematic study of it is only relatively recent. Studies in surgically menopausal estrogen-replete women who reported a decline in their desire for sex since BSO have found a benefit of T administered via a 300 μg/day patch, but no significant beneficial effect of either 150 μg/day or 450 μg/day compared with placebo [186–188]. Similar effects were found among naturally menopausal, estrogen replete women [189]. A review of T trials among estrogen-replete surgically and naturally menopausal women found that those women receiving the 300 μg/day patch reported an increase in sexually satisfying events of 1.9 per month. Interestingly, a significant benefit was also found across placebo groups of approximately 0.9 events per month [190]. Among 814 naturally and surgically postmenopausal women with HSDD and not receiving estrogen, there was a significant beneficial effect of 300 μg/day patch, but not of 150 μg/day patch on sexually satisfying events. When natural vs. surgical menopausal women were compared, this beneficial effect was only seen in the naturally menopausal women. Both T doses produced a significant increase in desire for sex, above placebo. Of the T group, 30% experienced androgenic side effects, and there were four new cases of breast cancer in the T but not placebo group [191].

Despite its lack of approval, many women seek out T therapy for problematic low desire. In such instances, the clinician and patient should engage in a careful discussion of the benefits and hazards of such treatment.

The androgenic, progestogenic, and estrogenic synthetic hormone, tibolone, is available in Europe. One study found a significant increase in scores on the Female Sexual Function Index (FSFI) following 24 weeks of use [192]. An earlier placebo-controlled cross-over study also found significant increases in sexual desire, and the frequency of arousability and sexual fantasies compared with placebo [193]. In studies of arousal, tibolone significantly improved vaginal lubrication and baseline VPA levels and VPA response to sexual fantasy.

Recommendation

T therapy is effective for estrogen-replete naturally menopausal women, and marginally effective for premenopausal women, though it produces supraphysiological levels in the latter. Among estrogen-depleted women, there are conflicting data with no effect among cancer survivors with HSDD but a positive effect among menopausal women without cancer. The long-term risks of T therapy on breast cancer, insulin resistance, and metabolic syndrome are unknown, so a careful discussion with patients evaluating the potential hazards must take place before any T supplementation is considered. Because positive studies of T have required women to be engaging in sexually satisfying events 2–3 times per month, the efficacy of T on women in the larger population of treatment seekers is unknown. Future research should aim to use stricter inclusion criteria for low desire. **Grade B**

Nonhormonal Medications for Low Desire

Nonhormonal medications that have been investigated for low sexual desire have typically had a mechanism of action that was centrally acting. In nondepressed women with HSDD, the antidepressant buproprion, which blocks norepinephrine and dopamine reuptake, was found to significantly improve sexual arousal and orgasm, but not sexual desire [194]. In women with selective serotonin reuptake inhibitor (SSRI)-associated mixed sexual symptoms, 4 weeks of treatment with the addition of bupropion led to a significant increase in self-reported feelings of desire and sexual activity [195]. The most recently investigated of the centrally acting agents for HSDD has been flibanserin. Flibanserin's mechanism of action is not yet fully understood but it acts as a 5-HT1A serotonin receptor agonist and 5-HT2A serotonin receptor antagonist. At present, no peer-reviewed publications concerning efficacy of flibanserin on women's sexual desire are available, but results of the three large US and European RCTS with flibanserin 100 mg taken daily were made public at the European Society of Sexual Medicine annual meeting in November 2009 and summarized at the Boehringer Ingelheim website [196]. Of note, Boehringer Ingelheim categorizes HSDD as a medical disease, but unclear is how it was established that the complaints were of medical etiology and not resulting from other sources. The primary endpoint was frequency of satisfying sexual events (SSE) following 24 weeks of treatment, or the number of sexual events (defined as sexual intercourse, oral sex, masturbation or genital stimulation by the partner) which were satisfying for the woman (i.e., gratifying, fulfilling, satisfactory and/or successful), irrespective of whether women had an orgasm or whether the event was satisfying for the partner. The pooled analysis of 1,378 premenopausal US women showed a statistically significant increase in the frequency of SSEs in women taking flibanserin (from 2.8 at baseline to 4.5), versus placebo (2.7 at baseline increasing to 3.7), an increase in the FSFI total score and a reduction in FSDS-R sexual distress. An analysis of the 634 pre-menopausal European women showed women taking flibanserin 100 mg had statistically significant improvements in their level of sexual desure as measured by the eDiary and a reduction in FSDS-R sexual distress but no significant change in SSEs. Most adverse drug reactions in flibanserin 100 mg were mild to moderate and included dizziness, nausea, fatigue, somnolence and insomnia. Given that flibanserin's mechanism of action is not understood, it is as yet unclear which women, in the long run, may or may not benefit from its use, whether long-term use will prove to be safe, and whether, on a long-term basis, flibanserin is the best treatment for women with no/low sexual desire.

Recommendation

Centrally acting agents show promise for targeting low desire in women but published randomized controlled trials (RCTs) are required and an evaluation of their safety remains to be studied. **Grade A**

Part VI: Treatment Issues Specific to Low Arousal

Psychological Treatments

Psychological treatment of sexual arousal problems generally consists of sensate focus exercises and masturbation training, with the emphasis on becoming more self-focused and assertive [197]. A lack of meaningful treatment goals for women, the difficulty in obtaining adequate control groups, and the lack of clear treatment protocols, may explain the paucity of well-controlled randomized trials of psychological therapy. There are no RCTs of psychological treatments for FSAD.

Recommendation

Despite our support for evidence-based practice, care for people with sexual problems, according to

the rules of "good clinical practice," must continue, even without solid proof of efficacy. There clearly is a great need for controlled efficacy studies in this area. From our review that the majority of sexual arousal problems in healthy women are not related to impaired genital responsiveness, it follows that we recommend psychological treatments for FSAD. **Grade C**

Hormonal Pharmacotherapy for FSAD

A limited number of studies have investigated potential beneficial effects of T on sexual arousal. In a placebo-controlled study in hypogonadotropic hypogonadal women, treatment with T undecanoate, 40 mg orally per day during an 8-week period, enhanced genital arousal as measured by VPA [198].

There is evidence that treatment with local and systemic estrogen benefits vulvo–vaginal atrophy and relieves vaginal dryness and dyspareunia [199,200].

Tibolone treatment to postmenopausal women in a randomized, double-blind, cross-over study resulted in a significant increase in VPA in response to erotic fantasy but not during erotic film stimulation. Tibolone was associated with significant increases in sexual desire, and the frequency of arousability and of sexual fantasies compared with those with placebo. Vaginal lubrication was significantly improved on tibolone [193]. In another study, tibolone showed similar benefits on sexual function, where women receiving tibolone had significantly higher sexual desire, sexual excitement, intercourse frequency, and vaginal dryness scores [201].

A recent phase III prospective RCT studied the effect of the vaginal application of DHEA on vaginal atrophy in 216 postmenopausal women. All three doses induced a rapid beneficial change in the maturation of the vaginal epithelial cells and vaginal pH [202]. In addition, there were positive effects on sexual desire/interest, sexual arousal, orgasm, and pain as measured by validated sexual function questionnaires [203].

Nonhormonal Pharmacotherapy for FSAD

In the relatively short time span (compared with psychological treatments) that pharmacological treatments have become available for men in 1998, the effect of pharmacological treatments in women with sexual arousal problems has been investigated in several controlled and uncontrolled studies. To date, none of the treatments that are listed in Table 8 have been approved.

Recommendations

Although T showed a beneficial effect on sexual arousal as measured with a vaginal photoplethysmograph, these are supraphysiological levels with an unknown long-term safety profile. There is no evidence for increased subjective excitement or pleasure. Currently, no recommendation for pharmacotherapy for FSAD can be made because of lack of efficacy and/or unwanted side effects. Women with various medical conditions rather than medically healthy women may have an impaired genital response and may therefore gain from peripheral, genital arousal enhancing agents. **Grade C**

Part VII: Treatment Issues Specific to Difficulties with Orgasm

An extensive review of the literature has been published following the previous 2003 International Consultation on Sexual Dysfunctions [218] and at present, there are no significant new data on the subject except preliminary data showing significant heritability in orgasmic function either alone or with a partner [219]. Directed Masturbation in conjunction with sex education, anxiety reduction techniques, and CBT remain the main therapeutic tools for anorgasmia. One trial of sildenafil in women with SSRI-induced FOD who were recruited over 4 years across seven American treatment centers, those in the treatment group, had significantly fewer negative sexual side effects [220].

Recommendations

There are no significant new data on FOD since the 2003 International Consultation meeting. There is some preliminary genetic research from twin registries showing a significant heritability factor with orgasmic problems with intercourse and masturbation. There is one published RCT of sildenafil showing positive effects on orgasmic disorder in a highly selective sample of women with SSRI-induced FOD. **Grade C**

Part VIII: The Placebo Response

It has become increasingly apparent in pharmaceutically sponsored RCTs that there is a notable placebo response among women randomized to the placebo arm of a drug trial [191,205,221,222].

Table 8 Pharmacotherapy trials for women with FSAD

Agent	Findings
Sildenafil in 12 healthy premenopausal women [204]	Women randomized to 50 mg sildenafil or placebo across two sessions. Significant increase in vaginal engorgement (VPA) during erotic stimulus conditions but no effect on subjective sexual arousal.
Sildenafil in 557 estrogenized and 204 estrogen deplete pre- and postmenopausal women with mixed sexual dysfunctions [205]	Women randomized to 10–100 mg sildenafil for at-home use. No significant improvement on subjective sexual arousal and subjective perception of genital arousal, as assessed by several different measures
Sildenafil in women with FSAD and no complaints of desire disorder [206]	Significant benefit of sildenafil beyond placebo
Sildenafil in premenopausal women with FSAD [207]	Signficant improvement in subjective sexual arousal, pleasure, orgasm, and frequency of orgasm. However, unvalidated questionnaires were used.
Sildenafil in 34 postmenopausal women with genital FSAD and/or FOD [208]	Only those women with impaired genital arousal, as assessed with a vaginal photoplethysmograph, showed a significant benefit of 50 mg sildenafil.
Sildenafil in women with spinal cord injury and FSAD [209]	Significant beneficial effect of sildenafil on genital (VPA) and subjective sexual arousal. The beneficial effects of sildenafil over placebo were most evident in the strongest stimulus condition of both visual and manual stimulation.
Sildenafil in 30 women with diabetes Type 1 [210]	Sildenafil significantly improved subjective indices of arousal, and improved orgasm, sexual enjoyment, and dyspareunia compared with placebo. Clitoral blood flow (using clitoral Doppler ultrasonography) was higher with sildenafil compared with placebo and compared with baseline.
Alprostadil in a single-blind trial in women with FSAD [211]	No significant difference beyond placebo. A comparison of the lowest with the highest dose did show some effects in the expected direction, but these effects were estimated by visual inspection by an MD. It is unknown whether that MD was also blinded to treatment.
Alprostadil in postmenopausal women [212]	Significant benefit over placebo on genital sensation, subjective sexual arousal, and sexual satisfaction
Phentolamine administered orally in postmenopausal women with FSAD [213]	Significant positive effect on subjective and genital sexual arousal (VPA)
Phentolamine in a placebo-controlled trial administered both orally and vaginally to estrogenized and nonestrogenized postmenopausal women [214]	Subjective sexual arousal was significantly higher than placebo with the highest doses of both applications of phentolamine (in estrogenized women only)
Levodopa in a placebo-controlled study of sexually healthy men and women [215]	No significant enhancement of Achilles tendon reflex in men (a measure of somatic motor preparation)
Apomorphine administered daily to premenopausal women with HSDD and FSAD [216]	Significant improvement in sexual function
Bremelanotide administered to postmenopausal women with FSAD [217]	Significant increase in desire but not arousal

VPA = vaginal pulse amplitude; HSDD = hypoactive sexual desire disorder; FSAD = female sexual arousal disorder; FOD = female orgasmic disorder.

To explore this further, Bradford and Meston reviewed 16 placebo-controlled pharmacological trials in women's sexual dysfunction [223]. The placebo response was more prevalent in retrospective studies, those in postmenopausal women, and studies that focused on sexual desire (as opposed to sexual arousal).

In another study [224], age, length of relationship at baseline, and changes in relationship adjustment were all significantly correlated with the placebo response whereas psychological symptoms, baseline sexual function, and baseline relationship adjustment scores were not.

In speculating about the potential mechanisms by which the placebo response occurs, Bradford and Meston [223] reasoned that expectancies may partially explain this effect (e.g., expecting an enhanced sexual response). However, it is also possible that other mechanisms, such as desirable responding, regression to the mean, and effects of repeated measurement may have underlined this effect.

Recommendation

Clearly, statistical significance is not a sufficient indicator for determining treatment response between placebo and active treatment arms of a particular trial. Instead, the magnitude of placebo effects is important to consider as well as the clinical meaningfulness of the group differences. In the future, the magnitude of placebo effects and the correlates of the placebo response may also be used to guide thinking about a particular sexual dysfunction's etiology. **Grade B**

Part IX: Persistent Genital Arousal Disorder (PGAD)

PGAD is a perplexing condition characterized by high levels of genital arousal occurring in the absence of subjective sexual interest or desire. The diagnosis of PGAD is made based on the presence of all five of the following features: (i) the physiological responses characteristic of sexual arousal (genital vasocongestion and sensitivity) persist for an extended period of time (hours to days) and do not subside completely on their own; (ii) the genital arousal does not resolve completely despite one or more orgasms; (iii) the persistent genital arousal is experienced as unbidden, intrusive, and unwanted; (iv) the persistent genital arousal may be triggered not only by sexual activity but also by nonsexual stimuli as well (e.g. vibrations from a car) or triggers may not even be apparent; and most importantly, (v) there is at least a moderate or greater feeling of distress associated with the experience [225].

Because of shame and embarrassment attached to the symptoms, the phenomenon has been relatively unrecognized and under-reported. As a result, there are currently no reliable figures on the prevalence of PGAD, although it may not be as rare as initially described.

At this time, there is little consensus regarding the etiology of PGAD. Based on individual case reports or small series of cases, Goldstein et al. [226] have suggested the following major etiological possibilities: (i) central neurological changes (e.g., post-injury, specific brain lesion anomaly); (ii) peripheral neurological changes (e.g., pelvic nerve hypersensitivity or entrapment); (iii) vascular changes (e.g., pelvic congestion); (iv) mechanical pressure against genital structures; (v) medication-induced changes; and (vi) psychological changes (stress) or some combination of all of the above. From a psychological perspective, Leiblum and Chivers [227] have postulated that women with PGAD may be more vigilant in monitoring small changes in their physical well-being than women who simply report unsolicited but untroubling genital arousal.

While there is no generally accepted treatment for PGAD, current interventions [228,229] focus largely on symptom management.

Recommendation

PGAD is a distressing intrusive condition that is relatively new to the sexual dysfunction lexicon. Data on prevalence, pathophysiology, and treatments are very scant and there are no RCTs on any available treatment method. Psychoeducation and support are important in the early stages of intervention. There may be relief with medications (e.g., mood stabilizers, serotonin-norepinephrine reuptake inhibitors), anesthetizing medications, pelvic floor physiotherapy, psychological therapy, and mindfulness may be helpful for the condition and may be tried alone and/or in combination with one another. **Grade C**

Part X: Overall Recommendations and Conclusions

1. Our study and understanding of women's sexuality occurs through an ethnocentric lens more attention, therefore, to cultural factors in research and treatment is essential.
2. Desire and arousal/orgasm are two sides of the same "sexual coin."
3. Sexual stimulation must be assessed.
4. In healthy women, the potential to beome aroused is not the problem, but the contextual/relational factors usually are. Women with somatic conditions may benefit from drugs that enhance genital response.
5. Good methodological trials on psychological treatments are needed.
6. Placebo effects are valid, may underscore contextual factors, and should be further studied.
7. Subjective excitement, pleasure, and relationship satisfaction should be targeted end points in all future RCTS.

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