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Evaluation and treatment of female sexual disorders

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Abstract Prevalence data suggest that more than 40% of women experience sexual problems and that 12% of these women are distressed by the problem. In the 1960s, Masters and Johnson introduced what is now considered the classic linear model of female sexual response based on a physiologic foundation. Recently, Rosemary Basson introduced a nonlinear interconnected model which emphasizes the importance of emotional intimacy and satisfaction as integral components of the female sexual response cycle. According to the Diagnostic and Statistical Manual (DSM-IV TR), there are six female sexual disorders: hypoactive sexual desire disorder, aversion disorder, sexual arousal disorder, female orgasmic disorder, vaginismus, and dyspareunia. Despite the high prevalence, few healthcare professionals take the time or feel adequately trained to assess and treat these sexual problems. Sexuality questionnaires play an integral role in the diagnosis and treatment of male and female sexual dysfunctions. They are used to (1) identify/diagnose individuals with a particular dysfunction, (2) assess the severity of the dysfunction, (3) measure improvement or satisfaction with treatment, (4) examine the impact of the dysfunction on the individual's quality of life (relationship satisfaction, mood, sexual confidence), and (5) study the impact of the dysfunction on the partner and his or her quality of life. Patient-reported outcomes (PRO) are increasingly important in both clinical practice and research settings. The instruments reviewed have played a significant role in furthering our understanding of the impact of female sexual function on the patient and partner and its treatment. It is important for the clinician and researcher to familiarize themselves with the best available measures for identifying specific dysfunctions, measuring distress due to the sexual dysfunction, assessing treatment efficacy, and objectively evaluating the quality of life issues of women with these dysfunctions. However, even the best PRO cannot replace the clinician–patient interview and the careful gathering of the patient's sexual history. PROs should always be interpreted and integrated with the woman's history.

Keywords Sexual disorder · Patient-reported outcomes · Distress

Data presented at the IUGA Roundtable on Sexual Dysfunction in Women, June 2008.

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Introduction

Although sexual problems have become more widely discussed in recent years, more often than not, healthcare providers and their patients circumvent the topic in clinical visits. This stands in stark contrast to the fact that sexual disorders in women are highly prevalent [1–4] and clear evidence that healthy sexual functioning is an important contributor to a woman's sense of well-being and quality of life [5]. Yet women are uncomfortable initiating discussions with their doctors about sexual concerns, apparently concerned that time constraints, lack of effective treatments,

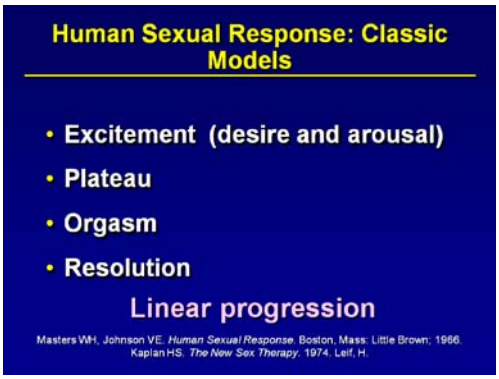

Fig. 1 Classic model of human sexual response

or their own embarrassment might be too high a barrier to result in any satisfactory resolution to their distress [6].

The patient timidity in this dynamic would indicate that clinicians can best serve their patients by *routinely* initiating discussions about sexual function during office visits. If physicians can appreciate the distress patients might be experiencing with sexual problems and therefore make an assessment of sexual function a priority, even time-constrained visits can include a brief inquiry about sexual concerns. Although many women experience sexual difficulties, an essential criterion to merit a diagnostic label is the inclusion of the woman's or her partner's distress as a function of the sexual problem. In this article, we provide an overview of the female sexual dysfunctions, their treatment, and an in-depth discussion of patient-related outcome measures for screening and assessing efficacy of any treatment intervention.

Historical perspective

Female sexuality has historically been given little attention. Kinsey's research in the 1950s on the sexual practices of American men and women helped to dispel the misperception that women are not interested in sex, but it has taken our culture a long time to accept the notion that women have a right to their sexuality [7]. The struggle for sexual equality continues today as may be evident by the fact that research on female sexuality lags behind research on males and the difficulty our culture has in accepting that female sexual problems are as disruptive to a woman's quality of life as male sexual problems are to men.

There are a number of reasons why research has focused more on male sexual problems than female sexual problems. First is the difficulty in measuring appropriate end points in clinical trials. For example, until recently, there have been few valid scales for assessing female sexual desire. In contrast, assessment of male arousal is relatively uncomplicated. Second, current models for conceptualizing the female sexual response reveal how complicated and multifactorial it is. The traditional linear models of Masters and Johnson [8], Kaplan [9], and Leif [10] suggested that the sexual response is invariant, the same for both males and females, and in which desire always precedes arousal (Fig. 1).

More recently, Basson [11] developed a new nonlinear model of female sexual response that integrates emotional intimacy, sexual stimuli, and relationship satisfaction (Fig. 2). This model recognizes that female sexual functioning (1) is more complex and is less linear than male sexual functioning and (2) many women initially begin a sexual encounter from a point of *sexual neutrality.* The decision to be sexual may

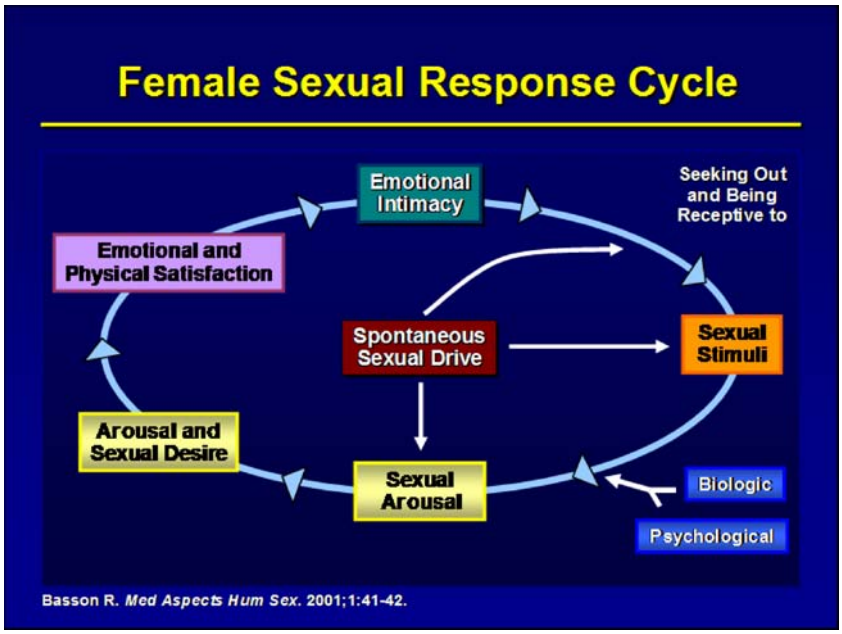

Fig. 2 Female sexual response cycle

come from a conscious wish for emotional closeness or as a result of seduction or suggestion from a partner. Women have many reasons for engaging in sexual activity other than simply sexual drive. Sexual neutrality or being receptive to, rather than initiating sexual activity, is considered a normal variation of female sexual functioning. In addition, it is often the case that women's arousal will precede desire.

The female sexual disorders: an overview of classification

According to the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM)-IV TR [12] which is based on the linear model of sexual response posed by Masters and Johnson, there are six sexual disorders which encompass dysfunctions across the sexual response cycle.

Hypoactive sexual desire disorder

Hypoactive sexual desire disorder (HSDD) is defined in the DSM-IV TR as persistent or recurrent deficient or absent sexual fantasies/thoughts and/or desire for or receptivity to sexual activity. The judgment of *deficiency* is subjective and made by a clinician only after taking into account factors that affect sexual functioning such as age, physical condition, and the context of a person's life. As with all of the sexual disorders, prevalence is difficult to determine. Although there have been a number of population surveys within the USA and worldwide, the prevalence estimates vary. Hayes et al. [13] and Segraves and Woodard [14] point to differences among studies in the definition of hypoactive desire, methods of data collection, age groups studied, and other defined criteria as the reason for such discrepancies. Segraves and Woodard [14] suggest that the prevalence of HSDD varies between 5.4% and 13.6%. Most recently, West et al. [15] reported an 8.3% prevalence of HSDD based on a nationally representative sample of almost 2,000 American women.

Women often present with the complaint of loss of desire but with very little awareness of how, when, or why this problem occurred. One reason that desire disorders remain elusive is that desire is a relatively complex concept that requires delineating the components for the patient and the clinician. Levine [16] suggests that desire comprised three discrete but interrelated components.

The first component is *drive*, the biological component based on neuroendocrine mechanisms and evidenced by spontaneous sexual interest. Patients recognize this as feeling "horny".

Unprompted sexual thoughts, fantasies, dreams, or sensations such as genital tingling are signs of drive. The amount of drive one has is relative, but it normally declines with age in both men and women. The second component is *cognitive*, which reflects a person's expectations, beliefs, and values related to sex. The third component of desire is the emotional or interpersonal component of desire and characterized by the willingness of a person to engage in sexual activity and is labeled as *motivation.* This is often the most important and is impacted by the quality of a relationship, psychological functioning, and worries about health, children, and other psychosocial factors.

This distinction between drive and desire is vital for any physician assessing or treating sexual problems because treatment is vastly different based on which component or components of desire have been impaired. For example, a woman might have a very strong sexual drive but if she is not motivated to be sexual, for instance if she is no longer happy with her partner, dealing with a stressful work problems, or suffering from depression, she will not act on the drive. Conversely, if a woman has lost some of her drive but remains motivated to be close and intimate with her partner, then despite having little physical cues or interest, she still enjoys the sexual experience.

Menopause is often assumed to result in HSDD. However, this assumption has been challenged by recent longitudinal studies that suggest that age has a stronger impact on sexual desire than does menopause alone [17]. Nevertheless, menopause, particularly surgical menopause, may negatively effect sexual desire in some women primarily due to the significant and often sudden (with surgical or chemical menopause) decline in testosterone levels. Testosterone is necessary for a normal sex drive in both men and women, playing a role in motivation, desire, and sexual sensation. Women achieve peak androgen production in their mid-20s and, beginning in their early 30s, gradually lose testosterone in an age-related fashion. By the time most women reach their 50s, their testosterone levels are half of what they were in their 20s [18]. Treatments include individual and/or couples psychotherapy/sex therapy, hormone therapy (e.g., exogenous testosterone replacement or Tibolone, a synthetic steroid with selective estrogenic, androgenic, and progestenic properties for postmenopausal women), and centrally acting pharmacologic agents that may have a positive impact on sexual function inhibiting serotonergic activity, facilitating dopaminergic activity, or binding to melanocyte receptors. To date, there are no pharmacologic treatments that are Food and Drug Administration (FDA)-approved for the treatment of any female sexual disorder. However, a number of treatments are currently in clinical trials; the testosterone patch (Intrinsa; Proctor & Gamble) has been approved and used in Europe.

Sexual aversion disorder

DSM-IV TR criteria for sexual aversion include persistent or recurrent aversive response to any genital contact with a

sexual partner and emphasize the role of avoidance. The incidence and prevalence of sexual aversion disorders are unknown. Sexual aversion disorder is sometimes conceptualized as sexual phobia, yet aversion implies the element of abhorrence and disgust, while phobia does not. Sexual aversion is routinely characterized by women as including elements of revulsion and disgust in ways that phobias rarely are. The DSM-IV TR criteria, however, do not require the physiologic responses that are often associated with aversion. While sexual aversion typically encompasses these responses (i.e., nausea, revulsion, shortness of breath), aversion can also be expressed as persistent avoidance of partnered sexual behavior and a situational-specific panic response. For an individual, whatever painful or traumatic event gave rise to the association of sexual behavior with aversion, the disorder can be conceptualized as maintained by ongoing avoidance of sexual behavior.

Sexual aversions can be general or quite specific and may develop in response to any sexual stimulus, overt or covert, such that a patient may present with a circumscribed aversion to a highly specific sexual thought or behavior or may exhibit more global revulsion to sexual behavior.

Assessment emphasizes careful sexual history, emphasizing the distinction between events that may have initiated aversion and current behavior that may continue to reinforce the aversive response. Behavioral treatment follows from the conceptualization. Since avoidance of sexual behavior is reinforcing aversion, a graduated exposure paradigm is employed in which patients pair relaxation exercises with a graded and patient-controlled reintroduction of sexual behavior. This strategy is often facilitated by the use of a selective serotonin reuptake inhibitor (SSRI).

Female sexual arousal disorder

Female sexual arousal disorder (FSAD) is defined as the inability to complete sexual activity with adequate lubrication. Absent or impaired genital responsiveness to sexual stimulation is the essential DSM-IV TR diagnostic criterion. These symptoms must cause personal or relationship distress.

More recent considerations of FSAD suggest that this disorder may now be better understood by using the subtypes of combined arousal disorder (no subjective or physiologic arousal), missed arousal disorder (physiologic arousal but no subjective arousal), and genital arousal disorder (subjective arousal but no physiologic arousal) [19, 20]. It may be difficult to adequately distinguish between arousal and orgasmic disorder due to the significant overlap. A thorough sexual history is particularly important for making an accurate diagnosis. Although there has been little evidence-based research on treatment for female sexual arousal disorder, treatment generally follows the work of Masters and Johnson [21] who taught patients to attend adequately to sexual sensations (sensate focus) using masturbation training while working to improve communication with their partners. Success rates using these strategies are reportedly quite good. More recently, physiologic strategies have also been introduced. Clinical trials of sildenafil were conducted to address the lack of vasocongestion. However, while vaginal engorgement in the presence of sexual stimuli was demonstrated, subjective experience of arousal was not reliably achieved, and ultimately, clinical trials of sildenafil were abandoned [22]. Estrogen therapy, systemic or local, is often an effective treatment for arousal disorder that is acquired after menopause and can improve vaginal blood flow and lubrication. Over-the-counter lubricants and/or long-acting vaginal moisturizers may also be helpful when lubrication has been diminished. Other topical pharmacologic treatments that are being studied include the use of androgens, alprostadil, L-arginine, and Zestra.

Female orgasmic disorder

Female orgasmic disorder is the persistent or recurrent delay in or absence of orgasm following a normal excitement phase, as defined in the DSM-IV TR. However, it is difficult to determine the specific incidence of orgasmic difficulties due to the lack of well-controlled studies and the variability of definitions and criteria used for orgasmic disorder. Results from the National Health and Social Life Survey [2] indicate that 24% of the 1,749 American women (aged 18–59 years) had experienced a lack of orgasm in the past year.

Orgasm is simply a transient peak sensation of intense pleasure [23] and might best be viewed as a reflex with rhythmic contractions of the perineal, bulbocavernosus, and pubococcygeus muscles. Similar to reflex centers serving other functions, the orgasmic reflex center is subject to multiple inhibitory and facilitory influences from direct sensory input and higher neural centers.

It may be helpful to view orgasmic attainment in women as a normal distribution. This distribution reflects women who have no physical problems that might interfere with achieving orgasm. On one side are women who have never experienced orgasm, while on the other end of the curve are those fortunate women who can experience orgasm under almost any circumstance including fantasy without any physical stimulation. The rest of the population falls somewhere in between.

A large percentage of women are *situationally* orgasmic. These women can achieve orgasm readily and reliably with some specific forms of stimulation. For example, women are often reliably orgasmic with manual stimulation or cunnilingus, but not with intercourse. In fact, it is important to be aware that intercourse is not a particularly reliable method for many women to achieve an orgasm.

The cause of orgasmic difficulties is likely multifactorial and can be different for each woman. Many women develop performance anxiety around having an orgasm with a partner. If they start to worry that they are taking too long or will embarrass themselves by how they look or sound when they do orgasm, anxiety and distraction increase and desire and arousal are diminished. A number of psychosocial factors including age, social class, personality, and relationship status have been most commonly related to orgasmic ability. Religiosity has also been found to be negatively correlated with orgasmic ability due to excessive guilt about participating in sexual activity [23].

The most effective treatment is a cognitive-behavioral approach in which a woman learns to be comfortable with her body and then her own sexuality by altering negative attitudes and decreasing anxiety. The behavioral treatments include directed masturbation, sensate focus exercises, and systematic desensitization [23]. Homework assignments that women can do in the privacy of their own homes are given with the goal of helping them to discover what stimulation is pleasing and effective. Debunking myths that masturbation is bad is also a common theme in treatment. Masturbation is an extremely effective way for the woman who has never achieved orgasm to experience her first climax. In privacy, without the pressure of performing for, or pleasing a partner, the woman is free to explore her own body and responsiveness. Another effective component of treatment is permission-giving by a clinician.

Dyspareunia

Dyspareunia is defined as persistent, recurrent urogenital pain occurring before, during, or after sexual intercourse that is not caused exclusively by lack of lubrication or by vaginismus.

Although dyspareunia has long been considered to be psychogenic, biological factors often contribute to the presentation. Recent perspectives have characterized dyspareunia as a pain disorder that interferes with sexuality rather than as a sexual disorder characterized by pain [24]. Therefore, dyspareunia is seen as a specific pain disorder with interdependent psychological and biological contributions and context-dependent etiologies. Identification of the initiating and maintaining factors is fundamental to the diagnostic process. The differential diagnoses include vaginismus, atrophy, inadequate lubrication, and vulvodynia. Urethral disorders, cystitis, and interstitial cystitis can also present with painful intercourse. Less common etiologies are adhesions, infections, endometriosis, and pelvic congestion.

Dyspareunia can be described as involving pain on entry or deep pain. Painful entry is most typical of vulvodynia, inadequate lubrication, and vaginismus. A physical examination often reproduces the pain when the vagina is touched with a cotton swab or insertion of a finger. Palpation of the walls of the vagina, uterus, and urethral structures can help identify physiologic contributions.

Even if the dyspareunia is found to have a primarily organic etiology, there still must be an appreciation of the concurrent psychological or behavioral contributions. These factors, such as trauma or unpleasant experiences with intercourse, can be identified by taking a careful sexual history. Maintaining factors such as avoidance of intercourse which can contribute to anticipatory anxiety, fear and phobic response to sexual intimacy and negative sexual expectations, and negative expectations and attitudes may all perpetuate the pain cycle. Loss of desire and arousal disorders associated with dyspareunia may contribute to the worsening of coital pain over time, which is further magnified by the distress experienced by the patient as well as the partner. The psychobiology of sexual pain should be addressed with a comprehensive, integrated, and patient-centered perspective.

Vaginismus

Vaginismus is defined as involuntary, recurrent, and persistent spasm of the outer third of the vaginal musculature that interferes with vaginal penetration. However, there has been much criticism of this definition including whether the musculature actually does spasm. In July 2003, at the 2nd International Consultation on Erectile and Sexual Dysfunction, a committee of experts in female sexual function proposed an alternate definition as "The persistent or recurrent difficulties of the woman to allow vaginal entry of a penis, a finger, and /or any object, despite the woman's expressed wish to do so. There is often (phobic) avoidance and anticipation/fear of pain. Structural or physical abnormalities must be ruled out/addressed" [25]. This committee also reported prevalence rates to range between 1% and 6%. Although categorized under pain disorders, vaginismus is not necessarily a pain disorder since women may not feel any pain, although vaginismus essentially occurs as a result of the anticipation of pain. Women can still enjoy sexual activity and be orgasmic despite having vaginismus, only penetration is not possible.

It is also important to note that for some women, vaginismus is limited to sexual activity and therefore have little difficulty during pelvic exams. Similarly, some women have no difficulty with intercourse but experience vaginismus due to the fear of pelvic exams.

The most effective treatment is a combination of cognitive and behavioral psychotherapeutic approaches. The goal is to desensitize a woman to her panic and help achieve a sense of control over a sexual encounter or a pelvic exam and an understanding that she is in no danger of experiencing pain, thereby feeling safe and calm. In response, her body can then learn to relax and the vaginal muscle contractions will no longer be a necessary automatic

defense; essentially, she will feel in more control of her muscles. One of the most commonly used treatment techniques is systematic desensitization. In this case, women are first taught deep muscle relaxation and then to very gradually insert objects (usually dilators) of increasing diameter into the vagina.

Assessment of sexual problems

The following section describes what to include in both a brief and a detailed sexual history. There are a number of communication strategies that will enhance the efficiency and effectiveness of the assessment.

Create a conducive environment

Establishing a rapport and putting patients at ease helps to make the environment conducive for discussion of sexual problems. If a physician is comfortable with sexual terminology, patients are more likely in turn to feel comfortable reporting their sexual concerns. Physicians may benefit by practicing the use of explicit sexual terminology in order to reduce embarrassment, hesitation in delivery, or other signs of discomfort. A balance can be found between terminology that is so formal as to be distancing and so informal as to be offensive or inappropriate.

When to take a sexual history/assessment

Taking even a brief sexual history during a new patient visit is very effective and indicates to the patient that the discussion of sexual concerns is appropriate and is a routine component of an office visit. Many health-related conditions, life events, or developmental milestones put patients at higher risk for sexual problems and provide opportunity to inquire about associated changes in sexual function. Urological surgeries or problems, menopause and depression, for example, are risks for the development of sexual problems, and physicians can normalize the frequency with which women find that medical issues give rise to sexual issues.

How to take a sexual history and assess current sexual function

The brief assessment (2–3 min)

Assessment of sexual function can be a part of the review of systems and should take place in a private setting in which confidentiality is assured. The patient should be clothed to eliminate the anxiety and sense of vulnerability that are commonly experienced when sitting in an examination gown [26, 27].

All practitioners can address sexual function in their patients. Even time-constrained visits can include basic assessment of sexual function which can be limited to a few specific questions. Reminding patients of the importance of assessing sexual function and that it is part of a normal history and physical for *all* patients may help put patients at ease. The questions listed in Fig. 3 are adequate for the initial assessment [26].

It is imperative that physicians not assume the gender of sexual partners, nor that the woman's sexual behavior is

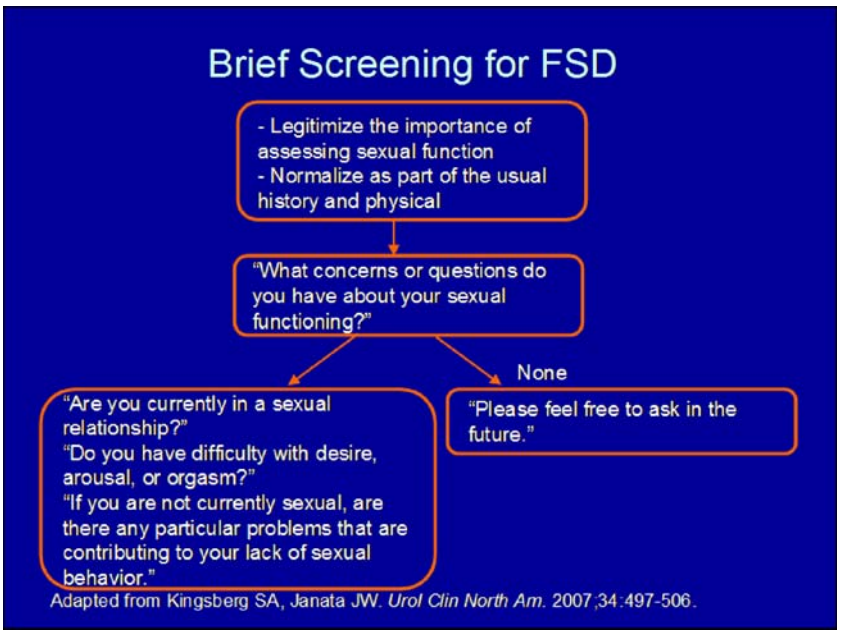

Fig. 3 Brief screening for female sexual dysfunction

limited to an identified partner or spouse. The implication that the physician does not hold pre-conceived notions may give patients the courage to discuss a sexual concern at a later time. It can be helpful to link a woman's current reproductive stage or presenting issue to her sexual function. For example, "Following surgery, many women experience discomfort with sexual intercourse or decreased sexual desire. Have you noticed any such problems yourself?" may allow the woman to understand that other women have similar issues and may make her more comfortable to prompt discussion [6].

When a sexual problem is identified during initial screening, it should be determined whether (a) the concern can be addressed during the current appointment, (b) a follow-up visit is needed to allow more time to address the concern adequately, or (c) the sexual problem is beyond the physician's scope of training and the patient should be referred to a specialist. It is always helpful to legitimize the sexual problem and to attend to patient discomfort by deferring sensitive questions to a subsequent visit or by supplying alternative terminology for patients who seem too embarrassed to provide explicit sexual details [28].

Essentials of a complete sexual history

A thorough sexual history should include medical, reproductive, surgical, psychiatric, social, and sexual information [29–32]. Relevant content would include a past medical history, current health status, reproductive history, endocrine system review, thyroid conditions, and psychiatric illness.

The current use of medicines, including prescription drugs, over-the-counter medications, and alternative medicines should also be identified. Table 1 lists some commonly prescribed medications associated with sexual side effects.

A patient's history may not be sufficient to assess sexual function, and a physical examination and/or laboratory testing may help to determine the physiologic factors involved in a sexual complaint.

Elements of a complete sexual assessment

Table 2 lists questions that will help to identify the essential components of a sexual complaint. These questions help to elicit the patient's perceptions of the problem, determine its timeline, and current health problems that might be affecting sexual function. These questions also help identify which components of the sexual response (desire, arousal, orgasm) or pain are compromised. This information can help determine etiology and provide the basis for treatment considerations (i.e., education, psychotherapy, medication).

Referrals

The decision to refer a patient with sexual dysfunction will depend on the physician's comfort and level of expertise and the complexity of the dysfunction. Some sexual problems are best treated by specialists such as a sex or marital therapist, alone or in the context of a multidisciplinary approach. Referrals are more likely to be accepted by patients when the physician normalizes both the nature of the patient's problem and the process of referral to a specialist [6].

Scales, questionnaires, and patient-reported outcomes

Sexuality questionnaires play an integral role in the diagnosis and treatment of male and female sexual dysfunctions. They are used to (1) identify/diagnose individuals with a particular dysfunction, (2) assess the severity of the dysfunction, (3) measure improvement or satisfaction with treatment, (4) examine the impact of the dysfunction on the individual's quality of life (e.g., relationship satisfaction, mood, sexual confidence), and (5) study the impact of the dysfunction on the partner and his or her quality of life [36].

The development of new sexuality questionnaires and diaries, alternatively known as patient-reported outcomes

Table 1 Medications known to cause sexual side effects [31–35]

Psychotropic medications
Antidepressants and mood stabilizers
Selective serotonin reuptake inhibitors (SSRIs), Serotonin–norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, monoamine oxidase inhibitors (MAOI's)
Antipsychotics
Benzodiazepines
Antiepileptics
Antihypertensives
Beta-blockers
Alpha-blockers
Diuretics
Cardiovascular agents
Lipid-lowering agents
Digoxin
Histamine H2-receptor blockers
Hormones
Oral contraceptives, estrogens, progestins, antiandrogens, GnRH agonists
Narcotics
Amphetamines
Anticonvulsants
Steroids

Table 2 Essential questions to include in a sexual assessment [29]

How does the patient describe the problem?
How long has the problem been present?
Was the onset sudden or gradual?
Is the problem specific to a situation/partner or is it generalized?
Were there likely precipitating events (biologic or situational)?
Are there problems in the woman's primary sexual relationship (or any relationship in which the sexual problem is occurring)?
Are there current life stressors that might be contributing to sexual problems?
Is there guilt, depression or anger that is not being directly acknowledged?
Are there physical problems such as pain ?
Are there problems in desire, arousal or orgasm?
Is there a history of physical, emotional or sexual abuse?
Does the partner have any sexual problems?

(PROs), has been stimulated by the burgeoning sexual health pharmaceutical programs and guidance from regulatory agencies, such as the US FDA. For instance, the three phosphodiesterase type 5 inhibitors (Sildenafil™, Tadalafil™, and Vardenafil™) were approved, in part, because each compound demonstrated significant improvement on the erectile function domain of the International Index of Erectile Function [37, 38], a 15-item validated PRO that assesses severity of erectile dysfunction.

This article will identify and discuss the principal female sexuality questionnaires used in both clinical and research settings (Table 3). Some PROs assess all phases of sexual function (e.g., Female Sexual Function Index), while others focus on specific dysfunctions such as female HSDD, and FSAD. Prior to discussing the PROs, we will review the process and relevance of questionnaire validation.

Psychometric properties of patient-reported outcomes

Psychometric properties of patient-reported outcomes are determined by multiple stepwise statistical procedures to ensure that the questionnaire meets or exceeds established psychometric principles. It is essential that PROs demonstrate reliability, validity, and sensitivity to detect changes in a specified population. Reliability insures that the questionnaire's measurement is stable or reproducible, that it is without any outside changes, such as a treatment intervention, and that the score will remain essentially the same.

Table 3 Various patient reporting outcomes assessing sexual function

Name of PRO	Number of questions	Domain names	Developed in accordance with FDA guidance	Primary goal of PRO
Female Sexual Function Index (FSFI)	19	Sexual desire, arousal, lubrication, orgasm, satisfaction, pain	No	Self-administered questionnaire assessing key dimensions of sexual function in women
Profile of Female Sexual Function (PFSF)	37	Desire, arousal, orgasm pleasure, sexual concerns, responsiveness and sexual self-image	Yes	Self-administered questionnaire measuring loss of sexual desire and related aspects of sexual function in oophorectomized women
Brief Version of the Profile of Female Sexual Function (B-PFSF)	7	No domains	Not relevant	Self-assessment tool for use by women who are experiencing low sexual desire to assist them in seeking help
Sexual Interest and Desire Inventory-Female (SIDI-F)	13	No domains	No	Clinician administered tool to quantify the severity of symptoms in women diagnosed with HSDD
Sexual Quality of Life Questionnaire (SQoL)	18		No	Self-administered questionnaire to assess the impact of FSD on a woman's sexual quality of life and to evaluate the benefits of therapeutic intervention
McCoy Female Sexuality Questionnaire (MFSQ)	19	No domains	No	Self-administered questionnaire to assess aspects of female sexual function in post-menopausal women
Female Sexual Distress Scale-Revised (FSDS-R)	13	No domains	No	Self-administered questionnaire that assess distress associated with female sexual dysfunction

There are several types of validity, face, known groups, construct, convergent, and divergent; however, the various forms of validity all insure that one is measuring what you believe you are measuring (e.g., the patient has female hypoactive sexual desire disorder). Sensitivity and specificity refer to the true positive and true negative rates, respectively. Finally, if the PRO contains domains, the items within these domains and the relation between the domain and total score must also meet established psychometric standards. This is generally accomplished by factor analysis and correlation analysis. Developing a PRO in this manner ensures that the clinician or investigator has a valuable tool for diagnosis and/or detection of change.

Regulatory requirements for patient-reported outcomes

New PROs that are being developed for use in clinical trial programs, which may lead to US labeling claims, need to satisfy the requirements of the FDA draft guidance for industry, PRO measures: use in medical product development to support labeling claims [39]. This document sets forth a process and the necessary psychometric tests and properties that need to be demonstrated for a new PRO to be considered valid. The FDA draft guidance also stipulates that the content of the tool be developed by interviewing patients and that the language used in the PRO reflect the experience of patients. Additionally, the guidance suggests that an end point model be developed to support why particular end points under investigation have been chosen. Any changes to a PRO, inclusive of medium of administration, or change in population would require revalidation.

FDA guidance for female sexual dysfunction clinical trials

The FDA has published another document, "Female Sexual Dysfunction: Clinical Development of Drug Products for Treatment" [40] that sets forth the suggested primary and secondary end points for female sexual dysfunction clinical trials. In brief, the FDA recommends the use of daily diary measures as primary end points and self-administered as secondary end points.

Specifically, the guidance states, "Primary endpoints for trials of drug products to treat FSD should be clinically meaningful and specifically related to the component or components of FSD being studies in the trials. These endpoints should be based on the number of satisfactory sexual experiences or encounters over time. The determination of satisfactory and successful should be made by the woman participating in the trial, as opposed to her partner." The FDA's emphasis on satisfying sexual experiences rather than improvement in a specific component of sexual function, such as sexual desire, and the emphasis of daily diaries rather than more psychometrically sophisticated self-administered questionnaires remain controversial. Several authors have criticized the guidance as being flawed on psychometric, scientific, and clinically meaningful grounds [41, 42].

Female hypoactive sexual desire and arousal disorders

This section will examine PROs that: (1) are useful for the diagnosis of HSDD and FSAD; (2) measure improvement in both dysfunctions; and (3) assess the important issues of distress/bother and quality of life concerns of women with these conditions (Table 3).

The Female Sexual Function Index (FSFI) is a brief, multidimensional self-report instrument for assessing key dimensions of sexual function in women [43, 44]. The scale consists of 19 items that measure sexual function over the past 4 weeks and provides domain scores in six areas: sexual desire, arousal, lubrication, orgasm, satisfaction, and pain. The FSFI possesses high level psychometric properties. Since its development in 2000, the FSFI has undergone further psychometric study which has confirmed the initial factor structure and its reliability and validity. A recent study proposed that subjects scoring ≤26 on the total FSFI score should be considered at risk for sexual dysfunction and be further evaluated [45]. The FSFI is frequently used in clinical trials and is becoming the gold standard for the evaluation of women with sexual problems.

The Profile of Female Sexual Function (PFSF) [46] is a self-administered questionnaire for the measurement of loss of sexual desire and related aspects of sexual function in oophorectomized women with HSDD. It was carefully developed in accordance with the FDA guidance beginning with individual and group interviews of women who were surgically post-menopausal, reported a meaningful loss in desire, decrease in sexual activity and distress after menopause, and a group of age-matched (by decade) women without HSDD. From an initial pool of 400 items, the measure was reduced to 37 items consisting of seven domains. The domains include: desire, arousal, orgasm, pleasure, sexual concerns, responsiveness, and sexual self-image. The PFSF has good reliability, content, and known group validity and is an excellent measure to assess change in a post-menopausal population.

There is also a brief version of the PFSF that is designed as a self-assessment tool for use by women who are experiencing low sexual desire that is concerning to them to help them decide whether or not to consult a physician [47]. The B-PFSF is a seven-item self-administered questionnaire that employs a 2- to 3-month recall period rather than the 30-day recall period of the PFSF. Using a cutoff score of ≤20, 85% of the women were correctly classified based up their responses to the initial screening criteria. The B-PFSF may be a useful screening tool for women concerned with

their sexual function, but is not an adequate substitute for more comprehensive assessment of the efficacy of a clinical or pharmaceutical intervention with a post-menopausal population (Table 3).

The Sexual Interest and Desire Inventory-Female (SIDI-F) is a 13-item scale developed as a clinician-administered assessment tool to quantify the severity of symptoms in women diagnosed with HSDD [48]. The SIDI-F exhibits excellent internal consistency and validity. It is an important and useful addition to the FSFI or PFSF. The Sexual Quality-of-Life Questionnaire (SQoL) was developed to specifically assess the impact of FSD on a woman's sexual quality of life and to evaluate the benefits of therapeutic intervention, complementing the evaluation of the more physical aspects of sexual function using either the FSFI or Female Sexual Function Questionnaire (FSQ) [49]. The SQoL contains 18 items that are responded to on a six-point Likert scale. Psychometrically, it has good reliability and validity. It is a valid instrument to detect the impact of FSD on sexual quality of life and is a useful adjunct in evaluating female sexual function in clinical trials. Another measure that can be utilized with a post-menopausal population is the McCoy Female Sexuality Questionnaire (MFSQ) [50]. The MFSQ was developed from the questionnaire used in a longitudinal study of the menopausal transition and designed to measure aspects of female sexuality likely to be affected by changing sex hormone levels. The self-administered questionnaire contains 18 questions answered on a seven-point Likert scale and one question that asks about frequency of sexual intercourse during the past 4 weeks. There have been several versions of the original 19-item questionnaire that include seven, nine, ten, or 17 questions. The 19 version questionnaire has good reliability and adequate face, content, and construct validity. The MFSQ was developed prior to the FDA guidance and is best suited for non FDA clinical trial menopausal research.

Although controversial, distress/bother is a central and necessary component in the diagnosis of FSD. The best PRO to assess distress is the Female Sexual Distress Scale-Revised (FSDS-R) [51]. It is a 13-item self-administered questionnaire that asks women to respond to a five-point Likert scale asking about their experiences over the past 7 days. A cutoff score of ≥11 indicates that the woman is distressed. The FSDS-R demonstrated good discriminant validity, high test–retest reliability, and a high degree of internal consistency in measuring sexually related personal distress in women with HSDD.

Summary

Patient-reported outcomes are increasingly important in both clinical practice and research settings. The instruments reviewed have played a significant role in furthering our understanding of the impact of female sexual dysfunction on the patient and partner and its treatment. It is important for the clinician and researcher to familiarize themselves with the best available measures for identifying specific dysfunctions, measuring distress due to the sexual dysfunction, assessing treatment efficacy, and objectively evaluating the quality of life issues of women with these dysfunctions. It is important to recognize that even the best PRO cannot replace the clinician–patient interview and the careful gathering of the patient's sexual history. PROs should always be interpreted and integrated with the woman's history.

Obviously, there are excellent sexual dysfunction measures that could not be reviewed in this article. We presented the measures we believe to be the most frequently used as well as the most researched and psychometrically sound.

Conflicts of interest Sheryl Kingsberg: Paid consultant: Boehringer Ingelheim, Procter and Gamble, Wyeth; speakers' bureau: Eli Lilly; Speaker/advisory board: Johnson & Johnson; clinical trials investigator: Boehringer Ingelheim, Procter and Gamble, BioSante. Stanley E. Althof: None.

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