Current Perspectives on the Clinical Assessment and Diagnosis of Female Sexual Dysfunction and Clinical Studies of Potential Therapies: A Statement of Concern

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ABSTRACT

Introduction. The assessment and diagnosis of female sexual dysfunction (FSD) are in a state of transition because of evolving concepts of female sexuality and suggested changes to the FSD diagnostic framework.

Aim. To review the problems with current FSD diagnosis.

Methods. Multidisciplinary experts from five countries were assembled to convene a "Postmenopausal FSD Roundtable on specific topics related to FSD."

Main Outcome Measure. Expert opinion was based on a review of evidence-based medical literature, presentation, and internal discussion.

Results. Current FSD diagnosis is challenging because of poorly defined distinctions between normal and abnormal, a limited ability to integrate subjective and objective findings and an inability to incorporate contextual factors that play a significant role in sexual behavior. The availability of self-administered questionnaires (SAQs) that assess various domains of female sexual function, as well as those developed specifically for postmenopausal women, suggests that a more structured approach to assessment and diagnosis may be possible. Several SAQs reflecting proposed changes to the FSD diagnostic framework by the American Foundation for Urologic Disease (AFUD), including the Sexual Function Questionnaire (SFQ) and the Female Sexual Distress Scale (FSDS), have been introduced and recently incorporated into a Structured Diagnostic Method (SDM). Recent regulatory decisions and events affecting the development of FSD interventions have highlighted the lack of consensus with regard to clinically meaningful FSD outcomes, as well as shortcomings in a U.S. Food and Drug Administration draft document that provides the primary guidance for conducting FSD clinical studies in the United States.

Conclusions. Given the high cost and inherent risk of clinical studies, continued development efforts toward FSD therapies are unlikely to proceed in the absence of significant changes in regulatory guidance that reflect the current understanding of FSD and incorporate validated assessment tools. **Althof SE, Dean J, Derogatis LR, Rosen RC, and Sisson M. Current perspectives on the clinical assessment and diagnosis of female sexual dysfunction and clinical studies of potential therapies: a statement of concern. J Sex Med 2005;2(suppl 3):146–153.**

Key Words. Female Sexual Dysfunction; Sexual Desire Disorders; Sexual Arousal Disorders; Assessment; Diagnosis

Introduction

Assessment can be utilized both for the purpose of diagnosis and for the assessment of change in specific parameters over time. The ability to accurately and reliably assess female sexual dysfunction (FSD) is not only the basis for diagnosis and treatment of the individual patient but is also central to studies of epidemiology (FSD incidence and prevalence), the longitudinal course of sexual disorders, and the efficacy and outcome of interventions to treat various forms of FSD. In a very real sense, assessment is the key to understanding patterns of sexual function and dysfunction, pre-

scribing the most effective FSD treatments, and providing patients with an understanding of both disorders and likely outcomes.

The consideration of FSD assessment is particularly timely given the rapidly shifting concepts of FSD classification and etiology [1], some of which are addressed in the accompanying article by Dennerstein and Hayes [2]. In addition, the results from recent clinical trials of pharmacological agents designed to treat FSD have, in a very public way, highlighted the issue of consistency in assessment with regard to the standards established for treatment efficacy. In this article, we address the interrelationships between assessment and diagnosis, and briefly describe some aspects of current assessment instruments and diagnostic tools. We then discuss the impact of these considerations on evaluation of the efficacy and outcomes of treatments for FSD, especially in light of the current regulatory environment.

Interrelationship Between Assessment and Diagnosis

In general, the term *assessment* refers to the evaluation of behaviors, parameters, signs, or symptoms exhibited or experienced by a given person (including, but not limited to, physical, neurological, hormonal, psychological, emotional, relational, contextual, and behavioral parameters). Assessment implies the use of some type of framework that guides the examination of the patient. Physical assessment, for example, involves measurement of height, weight, and vital signs, while endocrinological assessment involves both an evaluation of signs and symptoms and the withdrawal of a blood sample to be analyzed for the presence and level of a predefined set of hormones.

Diagnosis, the assignment of a given medical or psychological condition (which can include no diagnosis) that describes the patient's situation, is one, but by no means the only, goal of assessment. Diagnosis is by its nature categorical; a given diagnosis is defined by a set of parameters that must be satisfied for it to be applied to the patient. For that reason, although diagnosis is but one goal of assessment, the criteria for a diagnosis or set of diagnoses tend to be the most important drivers of the approach to assessment.

The current diagnostic framework for sexual dysfunctions, including several forms of FSD, was developed by the American Psychiatric Association and is published in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (*DSM-IV-TR*) [3]. The sexual diagnoses delineated in *DSM-IV-TR* (and the dysfunctions that apply to women's sexual health) are classified as sexual desire disorders (hypoactive sexual desire disorder and sexual aversion disorder); sexual arousal disorder (female sexual arousal disorder); orgasmic disorder (female orgasmic disorder), and sexual pain disorders (dyspareunia and vaginismus). All of these (including sexual pain disorders) include "marked personal distress or interpersonal difficulty" as an essential criterion for diagnosis. They are further specified by the addition of subtype classifications: lifelong vs. acquired, generalized vs. situational and due to exclusively psychological factors vs. combined factors [3].

Diagnosis of FSD under *DMS-IV-TR* is based on a diagnostic interview conducted by a clinician whose field of expertise is FSD. Although there is no standardized assessment procedure, most clinicians have developed an interview approach with sufficient structure to facilitate consistent diagnosis. However, diagnosis of FSD is rendered problematic by several factors. The *DSM-IV-TR* provides no clear delineation of "normal" and "abnormal" states of desire or arousal, nor any algorithm to guide the integration of subjective and objective information. In addition, there is limited ability to incorporate contextual factors that appear to play a significant role in sexual behavior, especially in women [4]. On a practical level, the limited number of available FSD experts can also make access to diagnosis and care problematic for many patients.

Moreover, the *DSM-IV-TR* classifications are under review and possible revision as the result of the efforts of the International Consensus Committee on Definitions of Women's Sexual Dysfunctions convened under the auspices of the American Foundation for Urologic Disease (AFUD). The most recently suggested AFUD revisions (2003) reflect a nonlinear, contextual model for female sexual response, and are described more fully in the accompanying article on epidemiology [1,2,4].

The original version of the AFUD revisions (2000) retained the "distress" component as a criterion for diagnosis [4]. However, this decision has been questioned, in part because it is felt that the disorders exist as clear entities with or without the presence of distress, and in part because distress is a nearly universal component of most FSD and affords no additional diagnostic value [1,5]. More recently (2003), the AFUD committee has suggested that the degree of distress (along with

"interpersonal difficulties") be specified as a descriptor of the primary diagnosis [1].

Assessment Tools

Although FSD diagnosis currently relies on a non-standardized expert interview, a number of assessment instruments have been developed over the past quarter-century that permit the evaluation of several dimensions of sexual function and sexual satisfaction, as well as changes in those dimensions over time. Although a comprehensive review of these instruments is beyond the scope of this article, it is worth considering some theoretical aspects of assessment. Two of the most critical considerations in any assessment are reliability (consistency of measurement) and validity (ability to measure a specific construct under study).

Other important characteristics of an assessment instrument are sensitivity—the ability to detect the presence or level of a specific attribute, and specificity—the ability to discriminate between those individuals who have a particular condition and those who do not. For example, a diagnostic instrument should be able to discern the presence of characteristics that indicate a specific diagnosis (sensitivity) but should not indicate a diagnosis where it is not appropriate (specificity) [6].

Sexual function involves psychological factors and behaviors that for the most part are not amenable to direct observation. Therefore, two basic modes are available for assessment of sexual function parameters: self-report (through questionnaires or diaries) and clinician interviews. Both modes have their advantages and drawbacks: the accuracy of self-report depends on the willingness of the subject to provide truthful responses, while interview can be subject to clinician bias. Although proponents of one mode point out errors inherent in the other, the magnitude of error may be comparable for each [6].

In the context of a discussion about assessment during clinical studies, Derogatis (2001) has characterized the subject attributes that may add variability to results (Table 1) [6]. Although presented as factors that could reduce sensitivity to treatment effects, this list can also be taken as potential sources of error in the assessment of FSD. The list of patient characteristics strongly suggests that an assessment tool specific to postmenopausal women be used to assess postmenopausal FSD, despite the potential confounding effects of age. The ability of nosological precision (or lack

Table 1 Subject-specific attributes that may increase assessment error

Patient characteristics
Gender
Age
Health status
Menopausal status
Personality
Partner variables
Quality of relationship
Comorbid sexual dysfunction
Features of sexual dysfunction
Etiology of disorder
Chronicity
General vs. situational
Nosological precision

Adapted from Derogatis, 2001 [6].

thereof) to affect diagnoses makes it imperative that the diagnostic framework truly describe the disorder or disorders.

Several brief assessment tools, suitable for office-based use, that are specific to or inclusive of female sexual function have been introduced since 1980. Several that have demonstrated good reliability and validity (listed in order of introduction) include:

- The Golombok Rust Inventory of Sexual Satisfaction (GRISS; 1987), a 28-item questionnaire that includes five domains specific to women (anorgasmia, vaginismus, female avoidance, female nonsensuality, and female dissatisfaction) [7].
- The Brief Index of Sexual Functioning for Women (BISF-W; 1994), a 22-item questionnaire; a new scoring algorithm provides composite scores and domain scores for thoughts/desires, arousal, frequency of sexual activity, receptivity/initiation, pleasure/orgasm, relationship satisfaction, and problems affecting sexual function [8,9].
- The Sexual Desire Inventory (SDI; 1996), a 14-item questionnaire that measures domains of dyadic sexual desire and solitary sexual desire [10].
- The Derogatis Interview for Sexual Functioning (DISF/DISF-SR; 1997), a 25-item gender-keyed questionnaire suitable for men and women that includes five domains (cognition, arousal, behavior, orgasm, and drive/relationship) and a total score [11].
- The Female Sexual Function Index (FSFI; 2000), a 19-item questionnaire specific to women that comprises six domains (desire, subjective arousal, lubrication, orgasm, satisfaction, and pain). Recently, the FSFI has been cross-

validated in women with mixed sexual dysfunctions, and cutoff scores have been developed to define dysfunction and nondysfunction [12,13].

- The Menopausal Sexual Interest Questionnaire (MSIQ; 2004), a 10-item instrument that assesses three domains of sexual function (desire, responsiveness, and satisfaction), and is specifically designed for use in menopausal women [14].

Recent Additions: Assessment Instruments for Clinical Studies

The potential for effective pharmacological treatment of FSD, fueled by the successful treatment of erectile dysfunction (ED) in men using phosphodiesterase type 5 (PDE5) inhibitors, has led to the development of several instruments specifically orientated toward clinical pharmacological studies. The Sexual Function Questionnaire (SFQ), introduced in 2002, was developed to assess multiple dimensions of female sexual function and sexual satisfaction for women involved in trials of pharmacological interventions for FSD. In addition, the 34-item SFQ is one of the first instruments explicitly based on the originally suggested AFUD (2000) diagnostic revisions [3], measuring attributes of sexual function across eight domains: desire, physical arousal/sensation, physical arousal/lubrication, enjoyment, orgasm, pain, partner relationship, and cognition. The distinction between the two domains of physical arousal reflects the distinction between subjective and physiological (genital) aspects of arousal disorder [2,15].

The Profile of Female Sexual Function (PFSF), introduced in 2004, is a proprietary instrument specifically developed to assess sexual function and response to treatment in menopausal women; initially developed for clinical trials in women who had undergone bilateral oophorectomy, it is now validated for naturally menopausal women. The PFSF is a 37-item self-administered questionnaire (SAQ) that comprises seven domains: sexual desire, arousal, orgasm, sexual pleasure, sexual concerns, sexual responsiveness, and sexual self-image. The desire domain of the PFSF has demonstrated the ability to identify women with clinically diagnosed hypoactive sexual desire disorder (HSDD) with both high sensitivity (0.94) and high specificity (0.86). If the PFSF is at some point made available for nonproprietary use, it may be useful in the assessment of desire disorders [16].

The development of the Female Sexual Distress Scale (FSDS), introduced in 2002, was based in part on the AFUD-suggested revisions (2000) and in part on a draft guidance document issued by the U.S. Food and Drug Administration (FDA) that recommended inclusion of a distress component in clinical studies of FSD treatments [17]. The FSDS is a 12-item assessment that results in a total distress score; a cutoff score of ≥ 15 is proposed as satisfying the criterion for personal distress [18].

A novel instrument, the Structured Diagnostic Method (SDM), has been developed to establish a diagnosis of FSD subtypes for use in clinical studies. The SDM is based on the AFUD (2000) revisions and consists of four SAQs followed by a structured face-to-face interview. The first SAQ is the Life Satisfaction Checklist, with nine items that assess overall quality of life, including a question specific to sexual function; the next component is a subset of questions regarding sexual function from the Medical History Questionnaire; while the third and fourth components are the above-mentioned SFQ and FSDS [19,20].

Following administration of the four SAQs, a trained interviewer (whose field of expertise is not necessarily FSD) conducts a structured interview based on a guide to diagnostic assignment. In a validation study, the SDM was the first standardized diagnostic instrument for FSD to demonstrate a high degree of convergent validity and inter-rater reliability when compared with the available gold standard (i.e., expert diagnosis) [20]. Although its length and the need for interviewer training preclude the routine office-based use of the SDM in a primary care setting, it has recently been qualified as a screening instrument and may be amenable to use by a broader range of practitioners than are currently considered qualified to diagnose FSD as outlined in the *DSM-IV-TR* and the AFUD (2000) revisions [21]. Moreover, it may help provide an element of rigor to the diagnostic categories in the AFUD-proposed revisions.

Female Sexual Dysfunction Intervention and Assessment

As noted above, the ability to effectively treat male ED has spurred interest in the possibility of providing analogous pharmacological intervention for FSD, and has resulted in the initiation of several clinical development programs targeting this goal. There are two important ways in which assessment plays a key role in the clinical development process. First, assessment can and should be used to firmly establish a baseline diagnosis of FSD prior to the initiation of any treatment. The

assignment of study subjects to specific diagnostic categories affords the opportunity to differentiate treatment effects on patients within those categories.

Second, some form of assessment should form the basis for establishing efficacy (or lack of it). In order to accomplish this, the assessment instrument must be sensitive enough to provide a picture of clinically meaningful change over time. The statistical power of a given assessment instrument in detecting these changes is directly proportional to the sample size and the mean effect of a given treatment, and is inversely proportional to inherent measurement errors and to variation within the group being tested [6]. An accurate baseline diagnostic instrument helps minimize within-group variation, thus increasing statistical power.

The assessment of treatment efficacy in FSD is challenging on a number of fronts: the shifting diagnostic landscape; the subjective nature of several aspects of FSD (especially desire); the contextual nature of female sexual function (which may overwhelm treatment effects); and, perhaps most important, the difficulty involved in defining measurable, and clinically meaningful, end points in terms of patient outcomes. In addition, as with many conditions that comprise strong psychological and emotional components, a considerable placebo response in clinical studies of FSD may make it difficult to detect a "true" treatment signal [6,21].

For purely physical disorders, efficacy is usually determined using well-defined end points that reflect the presence, absence, or severity of a particular disease state. In the treatment of hypertension, for example, the clinical end points are typically defined in terms of reduction in systolic blood pressure and the number of patients whose blood pressure reaches ranges associated with lower risk for hypertension-related sequelae. Outcomes of antihypertensive drug studies may include the risk for cardiovascular disease and/or events, as well as long-term survival. In any case, both end points and outcomes are measurable using widely accepted definitions and guidelines.

The complexity of female sexual response, and the strong impact of contextual factors, make the definition of end points and outcomes far more challenging than in the studies that demonstrated efficacy of PDE5 inhibitors in ED. The sexual response pattern of men, especially younger men, seems far more linear, more objective, and less contextual than that of women; moreover, the

assessment of efficacy, in terms of ability to attain erection and improvements in erection quality, is more obvious and straightforward.

Assessment and the Regulatory Landscape

The FDA draft guidance document suggests that clinical trial end points "should be based on the number of successful and satisfactory sexual events or encounters over time" [17]. Although the document clarifies that the definition of "*successful and satisfactory*" lies with the woman and not her partner, it defines sexual events or encounters as including [17]:

- satisfactory sexual intercourse;
- sexual intercourse resulting in orgasm;
- oral sex resulting in orgasm;
- partner-initiated or self-masturbation resulting in orgasm.

These proposed end points have been criticized on a number of grounds. The emphasis on the *number* of sexual events as the primary end point constitutes a "one item/multiple concept" measurement that can be influenced by a range of factors (e.g., partner availability, relationship issues) that have no connection to either the primary disorder or the efficacy, if any, of the applied treatment. Sexual events are a measure of behavior, rather than of biological or psychological change; in addition, the concept of satisfactory sexual encounters is obviously highly subjective, and may be partly or completely unrelated to the disorders defined by the diagnosis, such as arousal or desire [21].

Moreover, it is not at all clear that the suggested end point reflects in any meaningful way the aim of the patient in seeking treatment for FSD, or the successful resolution of FSD symptoms. The focus on quantity (rather than quality) of sexual experiences notably differs from the efficacy measures in ED studies, which focused primarily on erection quality and ability to initiate and complete intercourse—the number of times intercourse was completed was only considered as a fraction of attempts. It is also worth noting that the influence of contextual factors was reduced in ED studies by including only men in stable relationships (this has also occurred in some studies of FSD) [22,23].

In addition, women may have intercourse for a range of contextual reasons (relationship issues, bonding) that do not indicate improvement in domains of desire or arousal [1]. The insistence on orgasm as an essential component of a successful and satisfactory sexual experience is also puzzling

(except when the treatment under study is being applied to female orgasmic disorder).

The FDA's guidance document has also been criticized on methodological grounds for elevating end points based on events recorded in daily diaries to primary status and relegating end points based on SAQs and health-related quality of life (HRQOL) to secondary status. In particular, diaries are demonstrably prone to error (caused in part by "backfilling") and are far more difficult to validate. In contrast, several well-validated SAQs exist for the assessment of various FSD domains, and provide both statistical and conceptual validity with regard to the domains being treated [21,24].

Unfortunately, these concerns have not been addressed to date. The FDA has yet to issue a final guidance document, nor has it published any superceding guidance or recommendations; thus, the draft guidance document remains the primary statement influencing the design and conduct of U.S. clinical studies in FSD. Recently, an FDA panel rejected fast-track approval for a transdermal testosterone preparation (Intrinsa®, Procter & Gamble) for treatment of FSD in surgically menopausal women. According to members of the panel, the decision was based on concerns about safety, especially in light of the adverse effects of long-term estrogen treatment (which is currently required as concomitant therapy while using Intrinsa®) revealed in the Women's Health Initiative. However, the panel may also have been influenced by a reluctance to approve a female "lifestyle" drug (considering the controversy over the approval of PDE5 inhibitors), or even a "dismissal of the modest benefits" demonstrated in clinical studies [25]. The Intrinsa® rejection followed the 2004 decision, by Pfizer Inc., to discontinue clinical studies of sildenafil for treatment of FSD [26].

Clinical studies on potential FSD therapies currently appear to be a risky proposition, given the Intrinsa® decision, the rapidly changing nosological and diagnostic landscape for FSD, the lack of consensus on clinically meaningful treatment end points, and the possibility that treatment effects may be subtle and similar in magnitude to placebo response. These factors are, of course, in addition to the risks already inherent in the development of pharmacological treatments for disorders with a substantial psychosocial component.

We are concerned that pharmaceutical companies will be dissuaded from pursuing clinical studies in FSD, given their high cost and extended time frame, especially in the absence of significant modifications to the FDA's guidance with regard to such studies. Many women are significantly distressed by their sexual symptoms; discontinuation of research into pharmacological treatment would diminish the hope that relief will soon be available to them.

Looking Toward the Future

The recent developments on the regulatory and clinical study front call into question our ability to demonstrate the effectiveness of treatments for postmenopausal FSD, and to make those treatments available to the large population of affected women who desire treatment. For those who have observed the personal and relationship costs associated with FSD, and the desire for treatment among affected patients, the current stasis is both disappointing and frustrating. We believe it is essential for the involved constituencies, specifically the clinical and academic communities, the pharmaceutical industry, and regulatory agencies, to work separately and together to create an environment more conducive to the development of FSD treatments.

The clinical and academic communities should be especially aware of their need to serve as advocates for the patient population, for whom self-advocacy is difficult. The current lack of diagnostic clarity needs to be resolved as soon as possible, accompanied by the development of assessment tools that reflect the ultimate diagnostic framework. Assuming that the changes proposed by the AFUD committee are broadly accepted, existing instruments may need to be refined to accommodate new definitions, as well as any additional modifications to the diagnostic framework as it is established. As patient advocates, clinicians and academic specialists should provide the primary voice with regard to validation and appropriate use of assessment and diagnostic instruments, as well as defining clinically meaningful treatment end points and outcomes for use by both industry and regulatory agencies.

In addition, the development of screening and diagnostic instruments suitable for use at the primary care level would be an enormous step forward. Analogous to the experience with ED, the ability to assess FSD rapidly in an office-based environment will help sensitize clinicians, pharmaceutical companies, and regulatory bodies to the prevalence and severity of FSD (in both premenopausal and postmenopausal women), thus

increasing the perceived need for effective medical and psychological interventions.

The pharmaceutical industry, or at least those companies interested in developing treatments for FSD, should recognize the need to support the clinical and academic communities in establishing a diagnostic and assessment infrastructure robust enough to support further clinical studies. This infrastructure must maintain its patient-centered focus, and industry support should not be construed as an opportunity to bias end point and outcome definitions to favor specific agents, classes, or approaches.

In particular, pharmaceutical companies should endorse and support the development and use of nonproprietary assessment instruments. The use of proprietary instruments in clinical studies immediately raises questions of design and validation bias, and limits the ability of the wider clinical community to evaluate study results, the validity of the methods by which they were obtained, and their relevance to clinical practice. The decision to develop and utilize proprietary assessment tools is typically based on a desire to protect R&D investment and competitive advantage. However, in considering FSD, in which the need for treatment and even the reality of the disease state has been challenged, we believe these considerations must be subordinated to establishing the legitimacy of treatment approaches. The ED experience is again instructive in this regard: the use of the nonproprietary International Index of Erectile Function (IIEF) provided statistically robust assessment of erectile performance, and clinically meaningful improvement that was broadly accepted by the clinical community and regulatory agencies [27]. This in turn facilitated the acceptance of clinical study end points based on the IIEF as compelling evidence in support of agent approval.

The pharmaceutical industry should work with the FDA to establish clinical study end points that reflect the emerging understanding of differences between female and male sexual response, which are likely to be manifested in higher placebo rates and more subtle effects of possible FSD treatments. Although the influence of psychosocial factors on the development and maintenance of FSD makes it likely that pharmacological approaches will need to be accompanied by nonpharmacological therapy to achieve substantial improvement in a subset of FSD patients, this does not invalidate the potential usefulness of pharmacological intervention.

Finally, regulatory agencies must ensure that their review of potential FSD treatments is conducted in a setting appropriate to consideration of women's sexual health, by professionals who are both thoroughly familiar with sexual health disorders and committed to unbiased evaluation of efficacy and safety. In conjunction with clinical and academic specialists, the FDA should revisit and revise its draft guidance document, to provide a consistent and stable environment for clinical studies and evaluation of potential treatments. Consistent with the approach to other disease states, guidance to industry should take the form of general principles and criteria, rather than predefining specific efficacy criteria; such principles might include:

- patient-centered definitions of treatment end points and outcomes;
- use of validated, nonproprietary assessment instruments and other broadly accepted tools to establish efficacy;
- rigorous definition of disorders for which treatment is provided, and use of well-defined subject populations in clinical studies;
- extensive safety evaluations based on known attributes and potential side-effects of treatment agents under investigation;
- following agent approval, ongoing commitment to effective postmarketing surveillance.

The current difficulties surrounding development of FSD interventions are not insurmountable, but for the field to progress it is essential for the involved parties to address areas of potential conflict, building from areas of common ground such as the goal of improved patient outcomes. Although the above suggestions are by no means comprehensive, we believe they provide at least a starting point for further discussion and action.

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References

1 Basson R, Leiblum S, Brotto L, Derogatis L, Fourcroy J, Fugl-Meyer K, Graziottin A, Heiman JR,

Laan E, Meston C, Schover L, van Lankveld J, Schultz WW. Definitions of women's sexual dysfunction reconsidered: Advocating expansion and revision. J Psychosom Obstet Gynaecol 2003; 24:221–9.

2 Dennerstein L, Hayes RD. Confronting the challenges: Epidemiological study of female sexual dysfunction and the menopause. J Sex Med 2005; 2(suppl 3):118–32.

3 American Psychiatric Association. Diagnostic and statistical manual of mental disorders, fourth edition, text revision. Washington, DC: American Psychiatric Association; 2000.

4 Basson R, Berman J, Burnett A, Derogatis L, Ferguson D, Fourcroy J, Goldstein I, Graziottin A, Heiman J, Laan E, Leiblum S, Padma-Nathan H, Rosen R, Segraves K, Segraves RT, Shabsigh R, Sipski M, Wagner G, Whipple B. Report of the international consensus development conference on female sexual dysfunction: Definitions and classifications. J Urol 2000;163:888–93.

5 Althof SE. My personal distress over the inclusion of personal distress. J Sex Marital Ther 2001; 27:123–5.

6 Derogatis LR. Sexual function and quality of life: Endpoints and outcomes. J Gend Specif Med 2001;4:35–42.

7 Rust J, Golombok S. The GRISS: A psychometric instrument for the assessment of sexual dysfunction. Arch Sex Behav 1986;15:157–65.

8 Taylor JF, Rosen RC, Leiblum SR. Self-report assessment of female sexual function: Psychometric evaluation of the Brief Index for Sexual Functioning for Women. Arch Sex Behav 1994;23:627–43.

9 Mazer NA, Leiblum SR, Rosen RC. The brief index of sexual functioning for women (BISF-W): A new scoring algorithm and comparison of normative and surgically menopausal populations. Menopause 2000;7:350–63.

10 Spector IP, Carey MP, Steinberg L. The sexual desire inventory: Development, factor structure, and evidence of reliability. J Sex Marital Ther 1996;22:175–90.

11 Derogatis LR. The Derogatis Interview for Sexual Functioning (DISF/DISF-SR): An introductory report. J Sex Marital Ther 1997;23:291–304.

12 Rosen R, Brown C, Heiman J, Leiblum S, Meston C, Shabsigh R, Ferguson D, D'Agostino R Jr. The Female Sexual Function Index (FSFI): A multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther 2000;26:191–208.

13 Wiegel M, Meston C, Rosen R. The Female Sexual Function Index (FSFI): Cross-validation and development of clinical cutoff scores. J Sex Marital Ther 2005;31:1–20.

14 Rosen RC, Lobo RA, Block BA, Yang H-M, Zipfel LM. Menopausal Sexual Interest Questionnaire (MSIQ): A unidimensional scale for the assessment of sexual interest in postmenopausal women. J Sex Marital Ther 2004;30:1–16.

15 Quirk FH, Heiman JR, Rosen RC, Laan E, Smith MD, Boolell M. Development of a sexual function questionnaire for clinical trials of female sexual dysfunction. J Women's Health Gend Based Med 2002;11:277–89.

16 Derogatis L, Rust J, Golombok S, Bouchard C, Nachtigall L, Rodenberg C, Kuznicki J, McHorney CA. Validation of the profile of female sexual function (PFSF) in surgically and naturally menopausal women. J Sex Marital Ther 2004;30:25–36.

17 FDA Guidance Document, Guidance for Industry. Female sexual dysfunction: Clinical development of drug products for treatment (2000). Available at: http://www.fda.gov/cder/guidance/3312dft.htm.

18 Derogatis LR, Rosen R, Leiblum S, Burnett A, Heiman J. The Female Sexual Distress Scale (FSDS): Initial validation of a standardized scale for assessment of sexually related personal distress in women. J Sex Marital Ther 2002;28:317–30.

19 Fugl-Meyer AR, Lodnert G, Branholm IB, Fugl-Meyer KS. On life satisfaction in male erectile dysfunction. Int J Impot Res 1997;9:141–8.

20 Utian W, MacLean DB, Symonds T, Symons J, Somayaji V, Sisson M. A methodology study to validate a structured diagnostic method used to diagnose female sexual dysfunction and its subtypes in postmenopausal women. J Sex Marital Ther 2005;31:271–83.

21 Althof SE, Rosen RC, Derogatis L, Corty E, Quirk F, Symonds T. Outcome measurement in female sexual dysfunction clinical trials: Review and recommendations. J Sex Marital Ther 2005;31:153–66.

22 Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA. Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. N Engl J Med 1998;338:1397–404.

23 Hellstrom WJ, Gittelman M, Karlin G, Segerson T, Thibonnier M, Taylor T, Padma-Nathan H. Vardenafil for treatment of men with erectile dysfunction: Efficacy and safety in a randomized, double-blind, placebo-controlled trial. J Androl 2002;23:763–71.

24 Quirk F, Haughie S, Symonds T. The use of the Sexual Functioning Questionnaire as a screening tool for women with sexual dysfunction. J Sex Med 2005;2:469–77.

25 Spark RF. Intrinsa fails to impress FDA advisory panel. Int J Impot Res 2005;17:283–4.

26 Harris G. Pfizer gives up testing Viagra on women. New York Times, February 28, 2004.

27 Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): A multidimensional scale for assessment of erectile dysfunction. Urology 1997;49:822–30.