Update on female sexual function

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In this review, we briefly discuss recently published data on female sexual desire, arousal, orgasm and pain, and on medical/iatrogenic factors associated with female sexual function. The studies reviewed highlight a number of important methodological and etiological issues in the study of female sexual function. Researchers are urged to use standardized methods for defining sexual disorders and for selecting patient samples. Placebo-controlled studies are essential for examining the pharmacological aspects of female sexual dysfunction. Evidence suggests that free testosterone levels may be associated with sexual desire in women. Sildenafil citrate increases genital blood flow but may not impact on subjective reports of arousal. Past research implicated the serotonin 5-hydroxytryptamine 2 and 5-hydroxytryptamine 1A receptors in female sexual function, while recent data suggest a role for the 5-hydroxytryptamine 3 receptor. Increasing attention is being paid to medical/health conditions that impact sexual function (e.g. neurological conditions, cancer, hysterectomy, and cardiovascular disease). Curr Opin Urol 11:603–609.

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Abbreviations

DSM	Diagnostic and Statistical Manual of Mental Disorders
FSAD	female sexual arousal disorder
FSFI	Female Sexual Function Index
HRT	hormone replacement therapy
HSDD	hypoactive sexual desire disorder
5-HT	5-hydroxytryptamine
SNS	sympathetic nervous system
SSRI	selective serotonin re-uptake inhibitor

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Introduction

The aim of this review is to discuss briefly recently published data on female sexual function as they relate to past relevant research, and to offer suggestions for future investigations. We begin with a short discussion of issues in the classification and diagnosis of female sexual dysfunction, and then summarize the current research on sexual desire, arousal, orgasm and pain, and on medical and iatrogenic factors relating to female sexual function.

The classification and diagnosis of female sexual dysfunction

Research on female sexuality has rapidly increased over the past few years, and this has brought to light the need for an empirically grounded classification system and for the development of validated measures for assessing female sexual dysfunction. The Diagnostic and Statistical Manual of Mental Disorders (DSM), 4th edition [1] delineates sexual problems into disorders of desire (hypoactive sexual desire, sexual aversion), arousal, orgasm, and pain (dyspareunia and vaginismus). This classification system represents an improvement over earlier DSM editions, in that attention is paid to psychological factors such as interpersonal distress. It remains open to criticism, however, in that it lacks objective criteria and is ambiguous with regard to the degree of impairment necessary to warrant clinical diagnosis. Moreover, it conceptualizes sexual desire, arousal, and orgasm as distinct sexual phases, when in actual clinical practice these difficulties often coexist. In 1998, an interdisciplinary consensus conference panel of 19 experts in female sexual dysfunction was formed to revisit the existing classification system. The panel's recommendations were published in the *Journal of Urology* 2000 [2••] and were reprinted, together with invited expert comments, in a special edition of the *Journal of Sex and Marital Therapy* 2001 [3••]. Although modifications were made to the DSM-IV system, we agree with the position of Bancroft *et al.* [4] that, from a clinical perspective, the current system still lacks both therapeutic and prognostic significance, and from a research perspective, it is atheoretical with regard to the determinants of female sexual function.

Despite the difficulties inherent in the DSM-IV classification system, it remains the most widely utilized and recognized system, and offers some standardization for subject classification. Too often in sexuality research, investigators create their own definition of what constitutes a sexual disorder, and this leads to confusion and inconsistent findings across studies. For example,

Simons and Carey [5••] reviewed the past 10 years of literature on prevalence estimates for female sexual dysfunction, and noted widely discrepant results across studies. Rates for hypoactive sexual desire disorder (HSDD) ranged between 5 and 46%, and for female orgasmic disorder from 4 to 42%, depending on the diagnostic criteria used and the population sampled [5••]. Researchers interested in assessing female sexual arousal disorder (FSAD) may consider using the Female Sexual Function Index (FSFI) [6••]. This newly validated 19-item self-report measure of female sexual function provides scores on six domains derived using factor analyses: desire, arousal, lubrication, orgasm, satisfaction, and pain. The FSFI was developed and normed on 128 women who met DSM-IV criteria for FSAD (age range 21–69 years) and a sample of age-matched controls.

Sexual desire

The high prevalence of HSDD combined with the fact that there are currently no empirically validated treatments for HSDD in women [7] point to the strong need for research in this area of female sexuality. Increasing evidence points to the involvement of androgens in the female sexual drive, although past studies of this nature paint an unclear picture. Many women with hypoactive sexual desire have normal testosterone levels, some women with low testosterone levels have normal sexual drive, and high testosterone levels are not always associated with high libido [8••]. Whereas exogenous testosterone treatment has proved effective for treating a subset of women with low sex drive, most of this research to date has focused on surgically menopausal women [9••]. Most commonly, studies have included women who have undergone oophorectomy with or without hysterectomy, but Rako [10] brought to our attention how hysterectomy may lead to testosterone deficiency, even when the ovaries are spared as a result of the interruption of blood supply from the uterine artery.

Shiffrin *et al.* [11••] conducted perhaps the most vigorous study to date of replacement testosterone on sexual responses in 75 women who had undergone oophorectomy and hysterectomy. Using a double-blind, randomized, placebo-controlled, crossover design, the authors examined the effects of 150 and 300 μg of testosterone per day combined with oral estrogen on measures of sexual and overall well-being. Serum free testosterone levels were substantially increased at both treatment levels. Compared with a robust placebo response, measures of sexual desire, orgasm pleasure, and general well-being significantly increased with 300 but not 150 μg testosterone.

Methodological issues pertaining to how testosterone is measured and how the subject population is defined may help to explain some of the discrepancies noted in the past literature on testosterone and female sexual desire. Cognisant of these issues, Riley and Riley [12•] examined mid-cycle blood samples from 15 premenopausal women with lifelong absence of sexual drive and from 15 control women. The authors found that the women with lifelong HSDD had significantly lower levels of free testosterone than the control group, but no significant differences in measures of serum total testosterone or sex hormone-binding globulin were noted between the groups. Several researchers have suggested that there may be a threshold level of circulating testosterone above which additional testosterone would have no impact on sexual desire. In order to understand fully the relationship between testosterone and female sexual desire, there is a strong need for studies aimed at elucidating exactly where this threshold lies. To this end, studies that use multiple blood sampling for hormonal assays throughout the menstrual cycle in a sample of carefully diagnosed women with and without HSDD are needed. The findings from Riley and Riley [12•] and Shiffrin *et al.* [11••] suggest that free testosterone may be the blood assay most integral to this understanding. With regard to future studies, a review published in the past year on hormone receptors deserves mention [13]. Although DeCherney [13] presents only inferential evidence based on observational studies and deductive reasoning, he points to the possibility of testosterone receptors in the brain that are linked to the sex drive. Human research to date has focused on the peripheral influence of testosterone on sexual drive; the role of testosterone-mediated central events deserves scientific investigation.

Sexual arousal

The enormous success of using sildenafil citrate (Viagra) for treating male erectile disorder has brought increasing attention to the possibility that drugs that affect nitric oxide systems might also be effective in treating FSAD. Partly as a result of this pharmacological enquiry, in the past few years our knowledge of the mechanisms involved in female sexual arousal has increased substantially. Briefly, nitric oxide and phosphodiesterase type V (the enzyme responsible for cyclic 3′,5′-guanosine monophosphate degradation and nitric oxide production) have been identified in human clitoral and cavernosal smooth muscle [14••]. Published in the past year was an organ bath study [15•] showing that sildenafil, a potent phosphodiesterase type V inhibitor, caused a dose-dependent relaxation of female rabbit clitoral corpus cavernosum. These findings suggest that sildenafil plays a similar role in facilitating blood flow to the clitoral and penile corpus cavernosum and, from this perspective, may be useful for treating FSAD.

To our knowledge, no published controlled studies have examined the effects of sildenafil on sexual arousal in

human females. At the 2000 meeting of the International Academy of Sex Research, Laan *et al.* [16] reported the preliminary results from a double-blind, placebo-controlled, two-way crossover study of 50 mg sildenafil on vaginal and subjective sexual responses in 12 sexually functional women. Sildenafil significantly increased vaginal pulse amplitude responses, but had no impact on subjective perceptions of sexual arousal. Meston [17•] discussed the issue of desynchrony between genital and self-reported measures of female sexual arousal commonly noted in laboratory studies of this nature. Whether this sex-specific desynchrony is caused by an inability to detect subtle changes in genital blood flow, a confound of contrived laboratory settings, or the fact that women may attend more to contextual than physiological cues when estimating their degree of sexual arousal, this perplexing issue has significant implications for developing effective treatments for FSAD. Many of the drugs currently under investigation act as vasodilators with the end goal of increasing blood flow into the genitals. Even if the drugs are successful in doing so, the question is whether this will necessarily improve a woman's sexual experience. There is a great need for studies that examine the cause of this desynchrony and that aim at a better understanding of the myriad key factors that contribute to a woman's psychological experience of feeling sexually aroused.

A number of recent case reports and small open studies have reported on the success of using sildenafil for reversing antidepressant-induced sexual side-effects in women. In the past year, Salerian *et al.* [18] reported significant improvements in psychotropic-induced sexual dysfunction among 31 women treated with sildenafil. Whereas the sample size used was considerably larger than previous reports of this nature, the lack of a placebo control severely limits the interpretation of these findings. Michelson *et al.* [19••] examined the comparative effects of 8 weeks' treatment with buspirone, amantadine, or placebo on fluoxetine-induced sexual dysfunction in women. The authors reported that neither busprione nor amantadine was more effective than placebo in restoring sexual function. That study [19••] was the first placebo-controlled examination of an antidote for antidepressant-induced sexual dysfunction. The null results reported stand in sharp contrast with findings from non-placebo-controlled drug studies published between 1986 and 1998, of which 20 out of 21 reported success in alleviating antidepressant-induced sexual dysfunction [20]. The studies by Michelson *et al.* [19••] and Shiffrin *et al.* [11••] published in the past year clearly highlight the importance of using placebo-controlled trials when examining the effects of pharmacological intervention on sexual dysfunction in women. Non-specific effects, such as expectancies of improvement, talking to a professional about one's sexual difficulties, increasing communication between sexual partners, and monitoring one's sexual responses, can have a substantial impact on sexual function and must be controlled for in studies of this nature.

Autonomic innervation of the vagina originates from the hypogastric and sacral plexus, which give rise to the uterovaginal nerves that contain both parasympathetic and sympathetic nervous system (SNS) fibers [14••]. Largely on the basis of analogies drawn from men, it has been assumed that SNS activation impairs genital blood flow in women. Meston [21] reviewed a series of studies using acute exercise and ephedrine to enhance SNS activity, and clonidine to decrease SNS activity, and argued for a potential facilitatory role of SNS activation on vaginal blood flow measures. In the first study to assess the effects of testosterone administration on vaginal blood flow measures, Tuiten *et al.* [22•] reported a significant increase in vaginal measures of blood flow and also subjective reports of arousal at approximately 4 h post-testosterone administration.

Sommer *et al.* [23] described a new device for measuring vaginal and labial blood flow during sexual arousal and orgasm. The device measures transcutaneous oxygen partial pressure, and consists of a thermistor-controlled heating element that measures the amount of electrical power needed to maintain a set temperature. It is unclear how this device differs from the heated oxygen electrode that was introduced by Levin and Wagner in 1976 [24]. Advantages of using this device over a vaginal photoplethysmograph (the most frequently used method for monitoring vaginal blood flow) are that it is relatively free from movement artifacts (hence can be used during orgasm) and can be calibrated in terms of absolute blood flow (for review of female psychophysiological assessment techniques, see Meston [17•]).

Orgasm

Unlike other areas of female sexual dysfunction, efficacious treatments for both primary (lifelong, global) and secondary (situational or acquired) anorgasmia have been demonstrated. Sensate focus, systematic desensitization, and directed masturbation training have shown high rates of improvement in orgasmic function in a number of controlled treatment outcome studies [7]. Pierce [25] provided a review of studies that support the use of a basic physiological alignment technique (coital alignment technique) that provides consistent and effective stimulation to the clitoris and vagina, in facilitating female orgasm. Modell *et al.* [26] reported significant improvements in orgasmic ability beyond placebo with 150 and 300 mg per day buproprion in a sample of non-depressed women.

Sexual pain

Pukall *et al.* [27•] provided a convincing argument for using a pain syndrome framework rather than sexual dysfunction framework when describing dyspareunia and vaginismus. Canavan and Heckman [28] offered physicians practical suggestions for enhancing patient–physician communication about dyspareunia.

Medical and iatrogenic factors influencing sexual function

Numerous medical problems are associated with sexual dysfunction, but it is often difficult to differentiate between predisposing, precipitating, and maintaining factors. The sexual problem may arise as a result of disease, surgery, medication, or psychological factors, and depending upon the age of the patient, may be confounded with normal age-related declines in sexual functioning [29•]. It is important that studies examining the relationship between medical conditions and sexual functioning consider all these potential factors and employ study designs that will help tease them apart.

A number of studies have been published examining sexual functioning after surgery: hysterectomy [30•], vulvectomy [31], surgery for urinary incontinence [32,33], pelvic organ prolapse [33], and renal replacement therapy [34]. Retrospective studies may lack accurate recall, and prospective studies must consider the possibility that the pre-surgery levels of sexual function may be artificially lowered as a result of, for example, pre-surgery anticipatory anxiety or depression. Several authors have suggested that a validated measure of surgery-related sexual functioning is needed [31,32], and that it must be brief enough not to limit subject participation [34]. Confounding factors, such as anxiety, depression, and relationship functioning should also be assessed, as it is feasible that pre-surgical conditions will be most predictive of post-surgical sexual functioning. Green *et al.* [31] found that pre-surgery depression levels predicted post-surgical sexual adjustment. Diemont *et al.* [34] examined sexual functioning in patients receiving dialysis versus those with a renal transplant, and found that sexual dysfunction rates were lower among those with a transplant. Had the study included prospective measures of sexual functioning and potential confounding factors, it may have been possible to identify those factors most predictive of positive and negative outcomes.

A distinction should also be made between the types of surgery, and the degree to which they may physically alter the internal or external genitalia. Sexual functioning may be impaired as a direct result of physical damage to important tissues, as has been hypothesized with hysterectomy [30•], or as an indirect result of psychological factors, such as body image problems after vulvectomy [31]. It is also possible that some surgical techniques may be more or less likely to impair sexual functioning than others. Weber *et al.* [33] found that patients receiving posterior colporrhaphy alone or with Burch colposuspension were more likely to experience dyspareunia after surgery than women receiving anterior colporrhaphy, vaginal vault suspension, abdominal sacral colpopexy, and vaginal hysterectomy.

It is well established that cardiovascular disease [35•] and diabetes [36] often lead to sexual dysfunction, but increasing recognition is being given to other medical conditions, such as neurological conditions [37••,38•] and cancer [39••]. With some types of medical conditions (e.g. spinal cord injury) sexual activity or treatments for sexual dysfunction (e.g. sildenafil) may help improve the quality of life [40•], whereas for others, such as cardiovascular disease, it may be contraindicated [35•]. Those interested in learning more about drug treatments for female sexual dysfunction are encouraged to read Everaerd and Laan [41].

During pregnancy and the postpartum period, all women experience profound physical changes (e.g. fluctuating hormones) that are likely to affect sexual functioning, but other factors that existed before pregnancy (e.g. depression, anxiety, sexual dysfunction, relationship stress, co-morbid medical conditions) may exacerbate these changes. Bitzer and Alder [42•] noted that sexual desire and the frequency of intercourse steadily declines throughout pregnancy, and that sexual problems after pregnancy are the norm, rather than the exception. Many of the articles reviewed, however, were published over 10 years ago. Two articles published this year, one examining sexuality during pregnancy [43], and one examining sexuality during the postpartum period [44], noted similar results. Also worth noting was the finding that only 29% of women discussed sexual issues with their physician, and of those who did not, 76% indicated that they would have liked to (for review of pregnancy-related sexual dysfunction, see Bitzer and Alder [42•]).

As the population continues to age, increasing numbers of women will transition through the menopause. The challenge in menopause research is to differentiate menopausal symptoms and postmenopausal changes from normal aging-related changes and medical problems, as well as lifestyle and psychosocial factors. Ideally, menopausal research should be conducted using prospective, population-based longitudinal studies that follow women from premenopause through to the postmenopause period, as exemplified by Dennerstein *et al.* [45••]. Although these types of studies are costly and time consuming, they are useful in differentiating between non-menopausal and menopausal factors. In addition, as increasing varieties of hormone replacement

therapy (HRT) become available, large population-based clinical trials are needed to examine which regimen is most effective and safe for use with various pre-existing conditions, such as breast cancer and cardiovascular disease [46•]. Care should be taken before generalizing findings from one country to another, given the wide variation across countries in health risk factors (e.g. smoking and obesity), health surveillance (e.g. screening for breast and cervical cancer), HRT use, as well as non-specific cultural factors such as attitudes about menopause [46•]. Ideas and knowledge about menopause may have a profound impact on how it is experienced; for example, Dennerstein *et al.* [45••] noted that a common menopausal complaint among Australian women, vaginal dryness, was less severe among women with advanced education.

Antidepressant medications

Several reviews have documented a high prevalence of sexual side-effects secondary to almost all the antidepressant drugs currently being prescribed [47,48]. In a randomized, double-blind, 14-center study of 248 depressed patients, Segraves *et al.* [49] found buproprion (enhances dopaminergic or noradrenergic function) use was associated with significantly lower rates sexual dysfunction than sertraline (a selective serotonin reuptake inhibitor; SSRI) use. Kennedy *et al.* [50] found that moclobemide, a reversible monoamine oxidase inhibitor, produced fewer sexual side-effects than venlafaxine, sertraline and paroxetine.

It is not known why SSRI produce sexual side-effects, but some evidence suggests that activation of the 5-hydroxytryptamine $(5\text{-HT})_2$ receptor impairs sexual functioning, and stimulation of the 5-HT_{1A} receptor facilitates sexual functioning [8••]. Cyproheptadine acts as a histamine and serotonin (5-HT_2) antagonist, and has been reported to reduce antidepressant-induced sexual side-effects. Nefazodone, a 5-HT_2 antagonist that causes an upregulation of 5-HT_{1A} receptors, reportedly causes fewer sexual side-effects compared with traditional SSRI. Some evidence suggests that the 5-HT_{1A} agonist, buspirone, may be useful in reversing SSRI-induced sexual dysfunction, although findings from the study by Michelson *et al.* [19••] noted earlier showed that it was no more effective than placebo. Gelenberg *et al.* [51] reported positive effects of mirtazapine, a new antidepressant that acts as an antagonist at the alpha2 adrenergic, 5-HT_2 and 5-HT_3 receptors, for reversing SSRI-induced sexual dysfunction, and Berk *et al.* [52•] found that granisetron, a 5-HT_3 antagonist, but not sumatriptan, a 5-HT_D agonist, significantly improved antidepressant-induced sexual dysfunction. The findings from these recent studies implicated the 5-HT_3 receptor in female sexual responding, but placebo-controlled studies are essential before confident assumptions can be made. Frohlich and Meston [53•] reviewed literature that suggested that some sexual side-effects of SSRI may result from the actions of serotonin in the periphery of the body rather than the central nervous system. Approximately 95% of serotonin receptors are located in the periphery of the body, and peripheral serotonin acts on the smooth muscles of the vascular system to produce vasodilation and vasoconstriction, acts on the smooth muscles in the genitals, and is active in peripheral nerve functions, including those of the sexual organs.

With regard to improving patient care, two articles published in the past year deserve mention. Phillips and Slaughter [54] offered physicians suggestions and guidelines to help minimize adverse treatment effects associated with depression, and Kornstein and McEnany [55] discussed issues specific to the assessment and treatment of female patients experiencing depression (e.g. menstrual cycle, pregnancy, menopause).

Conclusion

The studies reviewed highlight a number of important methodological and etiological issues in the study of female sexual dysfunction. Researchers are urged to use standardized methods for defining sexual disorders, measuring treatment effects, and for selecting patient samples. As is evident from the review by Simons and Carey [5••] of prevalence statistics, the failure to do so renders comparisons across studies extremely difficult. For studies examining FSAD, the first instrument validated on a clinical sample of women with FSAD is now available (the FSFI [6••]). As seen in the studies by Michelson *et al.* [19••] and Shiffrin *et al.* [11••], non-specific factors can dramatically impact treatment outcome effects, and it is essential that pharmacological studies on female sexual dysfunction include a placebo control group. Except to formulate new testable hypotheses, non placebo-controlled studies are misleading and of questionable utility. Studies on medical problems associated with sexual dysfunction must consider the independent contributing factors of disease, surgery, medication, and psychology.

Increasing evidence points to the role of androgens in HSDD, and the studies reviewed indicated that measuring free testosterone levels may be integral to a better understanding of this relationship. Studies suggest that sildenafil may be effective in facilitating blood flow to the clitoral corpus cavernosum, but it is unclear whether this will improve a woman's subjective sexual experience. The link between psychological and physiological aspects of female sexual arousal remain poorly understood. Adding to the past literature that implicates the 5-HT_2 and 5-HT_{1A} serotonin receptors, there is now reason to speculate that the 5-HT_3 receptor may be

involved in female sexual function. When exploring sexual disorders we often focus on peripheral mechanisms at the exclusion of central events, and vice versa. Consideration must be given to the potential role of both peripherally and centrally mediated events and to the complex interplay between the two.

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