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REVIEW

Women's sexual function and dysfunction: current uncertainties, future directions

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There is increasing evidence that women at the outset of sexual activity do not need to have sexual desire, as in 'drive', and that many do not distinguish desire from arousal. Multiple modes of investigation confirm poor correlation between women's subjective arousal and measured genital congestion. Suggested revisions to the DSM-IV definitions of sexual disorder have been published: there is now need to align interview assessments and screening questionnaires with contemporary understanding of women's sexual response. Whereas the psychological factors associated with women's sexual function and resilience to biological insults and external stressors are well documented, the role of biological factors is less clear. Variations in the rate of decline of adrenal and ovarian pro-hormones, activity of converting enzymes in peripheral cells, sensitivity of androgen and estrogen receptors and cerebral production of sex steroids may all be involved. Thus there is great complexity underlying the question of sex hormone supplementation, and in particular, little clarity as to which women have decreased brain and/or peripheral androgen activity. When psychosexual etiological factors appear to be minimal and investigational testosterone supplementation is considered, it would be appropriate to target women with disordered arousal and desire in keeping with the recently recommended revised definitions.
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Introduction

Clinical, empirical, psychophysiological, cultural, brain imaging and hormonal research data allow us now in 2008 to identify some of the complexities of women's sexual function and dysfunction. As we move away from older linear models of sexual response, and from concepts more typical of men's sexuality, many questions emerge. This manuscript will focus on some of those questions: specifically what constitutes sexual disorder, whether women distinguish between desire and arousal and what motivates women to be sexually active over and beyond 'sexual desire'—thereby questioning the current focus on desire in most therapeutic trials. Why, despite universally marked reductions in sex hormones with menopause and age, only some women develop sexual dysfunction will also be addressed from both psychological and biological perspectives. The current status of hormonal therapy for dysfunction will be highlighted: reasons for concern about the lack of safety data for long-term systemic estrogen and testosterone supplementation being a major focus. Finally, other areas of needed research will be identified.

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What is normal: what is disordered?

Sexual motivation, including sexual desire

Recent data allow us to conceptualize women's sexual response as highly variable for the individual woman—depending on the context and stage of her life, as well as among different women, and between women of different cultures. Thus, the challenge is to determine whether a woman's sexual symptoms are reflective of normal change, adaptation to current circumstances or of disorder of her sex response system.

Although frequent in new relationships,[1] sexual desire experienced ahead of sexual activity may be rare for sexually content women in longer-term

relationships.[2] Studying mostly younger women, empirical data show that reasons for sex are numerous and have been divided into the domains of 'emotional reasons' including love and commitment; 'physical reasons' including stress reduction and pleasure; 'goal-attainment reasons' including resources, social status and revenge; and 'insecurity reasons' including boosting of self-esteem, duty/pressure and mate guarding.[3] Studying 1500 undergraduate psychology students, the majority of both men and women were motivated mostly by reasons related to attraction, pleasure, affection, love, romance, emotional closeness and the desire to please but women exceeded men in reporting emotional motivations.[3] Further empirical data confirm that women's sexual desire is commonly triggered rather than spontaneous. Data from 125 women aged 20–70 years showed that both pre and postmenopausal women with and without sexual dysfunction report triggers of sexual desire in the domains of emotional bonding, erotica, romance and physical proximity.[4] The Study of Women Across the Nation focusing on 3250 multiethnic mid-aged women in North America, indicated that the vast majority are moderately or extremely satisfied with their physical sexual pleasure and yet, some 42% never or very infrequently sensed desire, with even higher figures for Chinese and Japanese women (61.4 and 67.8%).[2] Anticipatory sexual desire is more common among women early in relationships when it may be a major reason for sexual engagement. According to one cross-sectional study that phase may only last 1 year.[5] Therefore, a willingness to become aroused and to sense desire 'soon', appears to be a very common initial phase.[6,7] Unfortunately, validated questionnaires for assessment of sexual function are based upon older models of women's sexual response, where desire was assumed to be needed at the outset of a sexual experience.[8] Consequently women, who mostly recognize a triggered rather than spontaneous desire, are at risk of being inappropriately labeled as dysfunctional when these questionnaires are used.[9]

Sexual arousal

Women's experience of arousal is complex. Qualitative research indicates that most women cannot clearly distinguish between desire and arousal.[10] Although nearly all women may speak of desire in terms of thoughts and emotions, some 80% may also include nongenital physical sensations and some 75% include genital sensations.[11] Defining disordered arousal is therefore difficult. Data from many sources identify further levels of complexity such that the genital neurovascular response of swelling and lubrication is now understood to be a prompt automatic reflex entity that can be completely disconnected from any subjective arousal (Table 1).

In view of the data in Table 1 confirming the poor correlation between subjective arousal and the measures of congenital congestion, plus the fact that in marked contrast to men's assessment of erection, women's assessment of the degree of congenital congestion is inaccurate, women's arousal cannot be assessed by their 'report of genital swelling lubrication response.'[17] Including subjective arousal in definitions of disorder is advocated.[18,19]

An absence of genital response may be reported even though appropriate genital congestion may be occurring. When neither subjective nor genital response is perceived the preferred term is 'combined sexual arousal disorder'. However, a related but different clinical construct is 'genital deadness' despite retained ability to be aroused from nongenital and nonphysical stimuli. Such loss of genital sexual

Table 1 Data identifying poor correlation between subjective sexual arousal and measurements relating to the neurovascular genital response[12–16]

Data source	*Findings*
Brain imaging while viewing visual erotica[12,13a]	Activation of complex brain circuitry including cortical, limbic and paralimbic areas involved in cognition, motivation, emotions as well as hypothalamic areas modulating autonomic nervous system. Activation in hypothalamus to increase genital congestion correlates poorly with subjective arousal[b]
VVP in women with and without problematic desire, arousal, orgasm, dyspareunia and viewing erotica[14]	Minimal correlation between subjective arousal and measures of increased vasocongestion
Genital MRI while viewing erotica[15a]	Measures of increases in genital blood flow correlate poorly with subjective arousal
VPP during the viewing of biologically sexual but not erotic stimuli (primates mating)[16a]	Prompt increases in vasocongestion despite absence of subjective arousal[b]

Abbreviations: MRI, magnetic resonance imaging; VVP, vaginal photoplethysmography.
[a]Sexually healthy subjects.
[b]These findings are in contrast to those in men.

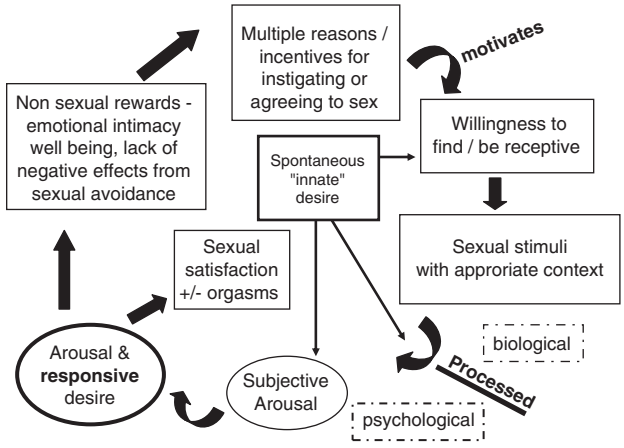

Figure 1 Circular response cycle of overlapping phases: desire may not be present initially but triggered during experience. The sexual and nonsexual outcome influences future sexual motivation. Copied with permission from Lippincott Williams & Wilkins from Figure 2: Basson R. Female sexual response: the role of drugs in the management of sexual dysfunction. *Am Coll Obstet Gynecol* 2001;98:350–352.

sensitivity has been recently termed genital sexual arousal disorder.[18] Both retained neuronal sexual sensitivity and vascular response of the extensive sinusoidal tissue in the vulva including the clitoral head, body, rami, bulbs and periurethral tissue seems to be necessary to allow subsequent physical stimulation to be sexually pleasurable and exciting. When reduction of this response causes dryness and dyspareunia from reduced lubrication, a diagnosis of dyspareunia and not 'arousal disorder' is recommended.[18]

Sex response model

An increasingly used model of women's sexual response reflects the overlap of phases and their varied order to allow patient and clinician to identify sites of weakness in, or interruptions of the cycle.[20] Figure 1 shows that a women's attention to appropriate sexual stimulation and her ability to stay focused on the moment, will encourage her subjective arousal—and that arousal is variably correlated with prompt reflexive genital congestion. If this complex state of arousal with mental excitement and various physical responses is accompanied by positive emotions and thoughts, then sexual desire, along with further arousal, is experienced. Orgasms may or may not be necessary for sexual satisfaction. More intense arousal can follow the first orgasm(s). High arousal can allow the woman to be receptive to more erotic types of stimulation that she previously declined or was unable to acknowledge given her sexually unaroused mind. Thus, with time, more erotic stimuli can allow higher arousal. The circle shown in Figure 1 may be cycled many times during one sexual encounter. Positive sexual experiences provide further motivation to be sexual again—adding to the woman's future list of reasons to deliberately allow stimuli to move her from a neutral to a sexually aroused state. The overlap and cyclicity predicts the known comorbidities of dysfunction.[21–23]

Many have noted the challenge in defining 'normal' or 'disordered' sexual response.[8,24] The difficulty only increases when the variability associated with life cycle, culture, life contexts and current relationship, are taken into account. Frequently, for women with sexual 'dysfunction' there is no evidence of innate dysfunction of sexual response, rather, a paucity of reasons to begin, or problematic stimuli and/or context explain the reported dysfunctional episodes of sexual engagement.[25] Thus, to assist a woman experiencing sexual dysfunction, we must assess the context of her life and relationship, as well as the details of sexual interactions. The inclusion of etiological descriptors—current context, developmental history or medical factors, alongside any diagnosis of sexual disorder—has recently been recommended.[18] Management may well be other than directly to her sexual response with investigational medication or sex hormone supplementation. Women themselves rate relationship difficulties as a major perceived cause of sexual dysfunction.[24] When the sex response system itself appears disordered, means to attend to the sexual stimuli such as the meditative technique of mindfulness are now being studied.[26] Increased empirical study of clinically well-established Cognitive Behavioral Therapy (CBT) techniques to alter negative thoughts and emotions, precluding or generated by the sexual arousal has frequently been encouraged.

Table 2 lists definitions of disorder as per the American Psychiatric Association's *Diagnostic and Statistical Manual*, 4th edn (DSM-IV-R),[17] an international consensus committee organized by the American Urology Association Foundation deliberating over 2 years and published in 2003[18] plus recent suggested revisions by three psychiatric sexual medicine colleagues.[19] There is some urgency to decide on 'official definitions' which all can use and to develop instruments reflective of the new understanding of disorder for use in clinical trials.[8] The major recommendations are:

(1) To acknowledge desire limited to 'responsive' or 'triggered' desire is a normal variant.
(2) To address loss of subjective arousal.
(3) To include the entity of genital sexual arousal disorder—loss of genital sexual sensitivity such that arousal, pleasure, orgasms from that mode of stimulation are minimal. These symptoms may or may not be accompanied by measurably decreased vasocongestion as would be expected for example after non-nerve sparing radical hysterectomy or in the context of generalized vascular disease.[27]

Table 2 Changing definitions of women's sexual dysfunctions[17–19,28]

DSM-IV[17]	*Revised definition from AFUD/AUAF International Consensus Committee, 2003*[18]	*Revisions suggested by Segraves et al*[19]	*Comments*
Hypoactive sexual desire disorder: Persistent or recurrently deficient (or absent) sexual fantasies and desire for sexual activity. The judgment of deficiency is made by the clinician taking into account factors that affect sexual functioning such as age and context of the person's life	*Sexual desire/interest disorder*: Absent or diminished feelings of sexual interest or desire, absent sexual thoughts or fantasies and a lack of responsive desire. Motivations (here defined as reasons/ incentives), for attempting to become sexually aroused are scarce or absent. The lack of interest is beyond a normative lessening with life cycle and relationship duration	*Hypoactive sexual desire disorder*: Persistent lack of desire for sexual activity and/*or* lack of responsive desire. This is beyond normative lessening with relationship duration or aging	The evidence is that minimal spontaneous sexual thinking or desiring of sex ahead of sexual experiences does not necessarily constitute disorder (given the data on women in sexually satisfactory established relationships). Lack of desire triggered during the sexual encounter, that is 'responsive' desire, is integral to the revised diagnosis. Segraves *et al*. note in their manuscript that 'many women do not report the presence of spontaneous desire'. Thus, 'or' (lack of responsive desire) seems incorrect
There is no DSM-IV definition addressing lack of subjective arousal	*Combined arousal disorder*: Absent or markedly reduced feelings of sexual arousal (sexual excitement and sexual pleasure) from any type of stimulation and absent or impaired genital sexual arousal (vulval swelling and lubrication)	*Female sexual arousal disorder*: Persistent or recurrent lack of sense of building sexual excitement and pleasure during sexual activity and/or inability to attain and maintain the lubrication/swelling response until completion of sexual activity	In the two revised versions there is no sexual excitement (in the mind) and no awareness of reflexive genital vasocongestion
There is no DSM-IV definition addressing lack of subjective arousal	*Subjective arousal disorder*: Absent or markedly reduced feelings of sexual arousal (sexual excitement and sexual pleasure) from any type of stimulation. Vaginal lubrication and other signs of physical response still occur	There was no recommendation to separate the different types of arousal that might be lost	In the AUAF/AFUD definition there is no sexual excitement (in the mind) but awareness of adequate lubrication
Female sexual arousal disorder: Persistent or recurrent inability to attain or to maintain an adequate lubrication/swelling response of sexual excitement until completion of the sexual activity	*Genital arousal disorder*: Absent or impaired genital sexual arousal—minimal vulval swelling or vaginal lubrication from any type of sexual stimulation and reduced sexual sensations from caressing genitalia. Subjective sexual excitement still occurs from nongenital sexual stimuli	There was no recommendation to separate different types of arousal that may be lost	The presence of subjective arousal (sexual excitement) from nongenital stimuli (for example erotica, stimulating the partner, receiving breast stimulation, kissing) is key to the revised AUAF/AFUD diagnosis. When the concern is limited to dryness/ dyspareunia then the diagnostic term is dyspareunia
	Persistent genital arousal disorder: Spontaneous, intrusive and unwanted genital arousal (tingling and throbbing) when sexual interest or desire is absent. Awareness of subjective arousal is infrequent but mostly unpleasant. The arousal is unrelieved by orgasms and the feelings persist for hours or days		This condition is poorly understood. Hypervigilance toward genital sensations and increasing anxiety that the symptoms are highly abnormal is a clinical finding.[27] Reliable treatment has not been found
Female orgasmic disorder: Persistent or recurrent delay or absence of orgasm following a normal sexual excitement phase	*Female orgasmic disorder*: Despite the self-report of high sexual arousal/ excitement, there is either lack of orgasm, markedly diminished intensity of orgasmic sensations or marked delay of orgasm from any kind of stimulation	*Female orgasmic disorder*: Persistent or recurrent delay in, or absence of orgasm following a normal sexual excitement phase	Women with arousal disorders frequently do not experience orgasm. Their correct diagnosis is one of the arousal disorders. The AUAF/AFUD version specifically includes only women unable to orgasm under any circumstances

Table 2 (Continued)

DSM-IV[17]	*Revised definition from AFUD/AUAF International Consensus Committee, 2003*[18]	*Revisions suggested by Segraves et al*[19]	*Comments*
Dyspareunia: Recurrent or persistent genital pain associated with sexual intercourse	*Dyspareunia*: Persistent or recurrent pain with attempted or complete vaginal entry or penile–vaginal intercourse	*Dyspareunia*: Recurrent or persistent pain associated with vaginal penetration or attempted vaginal penetration	There are many causes, including vestibulodynia, vulvovaginal atrophy, hypertonicity of pelvic muscles, interstitial cystitis, endometriosis and lack of sexual arousal
Vaginismus: Recurrent or persistent involuntary spasm of the musculature of the outer third of the vagina that interferes with sexual intercourse	*Vaginismus*: Persistent or recurrent difficulties in allowing vaginal entry of the penis, finger or any object, despite the woman's expressed wish to do so. There is often phobic avoidance, anticipation, fear or experience of pain and variable involuntary contraction of pelvic muscles. Structural or other physical abnormalities must be ruled out or addressed	*Vaginismus*: Recurrent or persistent inability to allow vaginal entry in spite of expressed wish to have vaginal intercourse	The diagnosis is initially presumptive as confirmation must follow therapy sufficient to allow a careful introital and vaginal examination. There is need to exclude abnormality additional to reflex muscle tightening. There is little qevidence of 'spasm'. The definition needs to include lesbian women

Abbreviations: AFUD/AUAF, American Urology Association Foundation formerly American Foundation of Urologic Disease; DSM-IV, American Psychiatric Association's *Diagnostic and Statistical Manual*, 4th edn.

Risk factors for sexual dysfunction

Despite universally marked reductions in sex hormones with menopause and age there is no universal sexual decline. Studying a nationally representative probability sample of 815 women in the United States in intimate relationships, of those aged 57–64 years, 80–90% were sexually active (the lower percentage were those reporting poor health), and of those, 76% reported sex as pleasurable, and 65% reported sufficient lubrication and ability to climax. Of those aged 65–74 years, 50–70% were active, with 78% of those reporting pleasure, 57% reporting sufficient lubrication and 76% the ability to climax.[29]

Psychological factors that increase the risk of sexual dysfunction

Poor mental health is consistently found to be a major risk factor in cross-sectional and longitudinal research.[1,30,31] Even when current mood and medications were factored in, of the 914 mid-aged women in the SWAN (Study of Women's Health Across the Nation) study, those with past history of major depressive illness reported less arousal, physical pleasure and emotional satisfaction in their present relationship.[32] Of 445 women with major depression, close to 80% had sexual dysfunction identified on a validated self questionnaire which improved with successful antidepressant therapy but worsened if depression continued.[33] When clinical depression is excluded, women complaining of low desire are still shown to have lower self-esteem, more mood variability and more anxious and depressed thoughts, than control women.[23] Anxiety disorders can preclude women's ability to attend to sexual stimuli and to be lost in the moment. For women with diabetes,[34] renal failure[35] or multiple sclerosis,[36] it is the comorbid depression that is associated with higher prevalence of sexual dysfunction compared to control women.

Positive past sexual experiences and positive feelings for the current partner are strongly correlated with women's sexual satisfaction and desire and may protect them from dysfunction associated with sex hormone loss.[1] Empirical data confirm that love and emotional bonding serves as a major cue or trigger for sexual desire.[3] Women's feelings for their partners, or a recent change of partner, were two of the three major determinants of women's desire and responsivity in the longitudinal study for women transitioning menopause[1] and were major determinants in cross-sectional studies.[30,37,38] Positive feelings for partners generally and specifically at the time of sexual interaction, were major factors affording protection against sexual distress.[31] Important predictors of sexual satisfaction among breast cancer survivors included mental health and

a better quality of relationship.[39] Also included was an absence of partner-sexual dysfunction, confirmed in many other studies of women without breast cancer.[40,41]

Less studied is the means by which women personally adapt to biological changes such that sexual experiences change over time but without perception of problem. Are factors such as ability to 'be present' for the longer duration of sexual stimulation that is now needed, or a more positive self-image or attitude to aging important?

Biological factors that might increase the risk of sexual dysfunction

Although psychological factors might account for much of the risk of dysfunction, it remains possible that biological factors further modulate this risk. Are some women more vulnerable to the inevitable reduction in sex hormone activity on a biological basis? The roles of estrogen and testosterone in maintaining women's sexual health are not clearly understood. Although the vast majority of women discontinuing postmenopausal estrogen supplementation develop signs of vulvovaginal atrophy,[42] most epidemiological studies show little increase in dyspareunia with age.[29,41,43] Although surgical menopause has been chosen as an example of an androgen deplete state, the prevalence of subsequent sexual dysfunction is unknown. Indeed three recent studies showed that women choosing (as opposed to just consenting to), bilateral oophorectomy with their simple hysterectomy required for benign reasons, do not develop sexual dysfunction over the next 1–3 years.[44–46]

Despite reduction with age and with menopause, sex hormone production continues, but final hormonal activity may be modulated by various biological factors (Table 3). Before menopause, testosterone is produced by both the ovaries and adrenals: these organs also produce precursor sex hormones, including prasterone (known as dehydroepiandrosterone, DHEA) and androstenedione. In addition, the adrenals produce prasterone sulfate (known as DHEAS), androstene-5-ene-3β and 17β-diol. These precursor sex hormones or 'prohormones' can be converted to estrogen and/or testosterone in peripheral cells, including those of the brain, breast, bone and genitalia. From the age of mid 30s to early 60s adrenal production reduces by some two-thirds. Postmenopause, ovarian production of estrogen ceases and only intracellular production remains.[47] The situation for androgens is more complex in that ovarian production continues to a variable degree. Prohormones that can potentially become androgens continue to be produced but in increasingly smaller quantities from both adrenal glands and ovaries. Moreover, women with bilateral oophorectomy lose all ovarian production of testosterone and sex hormone precursors. In addition, sometimes premature ovarian failure involves all ovarian hormones and prohormones.

Table 3 Biological factors that may modulate sex hormone activity[47–49,55–57]

Rate of decline of adrenal pro hormones[47]
Rate of decline of ovarian prohormones and ovarian testosterone[46]
Activity of converting enzymes in peripheral cells[48]
Numbers and activity of co-regulators[54]
Sensitivity of AR and ERα and ERβ
Cerebral production and activity of sex steroids from cholesterol[55]
Activity of enzymes including aromatase[55]
Numbers of sex steroid receptors[55]
Activity of regulatory proteins[56]

Abbreviations: AR, androgen receptor; ER, estrogen receptor.

In some areas of medicine, serum levels of hormones or other chemicals are clinically useful even if they do not necessarily match intracellular levels: for instance, serum levels of potassium. However, the situation for mid-aged and older women is that the major production of the entity in question (testosterone and estrogen) is within the peripheral cells in which the hormones exert their action, and in the case particularly of testosterone, only a small portion leaks back into the blood stream to be measured.[48] Thus, it is by no means clear that any serum level of testosterone is a useful entity.[49] It is currently thought that measurement of intracellular production of hormones, as well as those of gonadal and adrenal original, is important.[48–50] Such measurement of global androgen activity might clarify an association between sexual function and sexual hormones. Two large recent studies failed to find correlation of sexual function with serum androgen levels measured as total testosterone and free androgen index in 2900 pre and perimenopausal multiethnic North American women,[51] and as free and total testosterone in 1021 Australian women aged 18–75 years.[52] Even in 81 women with premature ovarian failure, little correlation was found recently between sexual function and testosterone levels.[53] That there is no consistent relationship between sexual function and any of the prohormones has been well documented.[51,52] Total androgen activity is currently thought to be best reflected by the measurement of serum androgen glucuronides, most notably androsterone glucuronide (ADT-G).[48,49] These metabolite levels reflect both availability of substrate and activity of the steroidogenic hormones in the peripheral cells. These steroidogenic enzymes include P450 C17 (17, 20 lyase), 3β-hydroxysteroid dehydrogenase (HSD), 17β-HSD, as well as aromatase and 5α-hydroxylase. In the case of vulnerability to vasomotor symptoms rather than sexual symptoms (the latter not studied), women in the SWAN study who had two alleles for the polymorphism CYP19 11r (CYP19 being an aromatase enzyme converting

androstenedione and testosterone to estrone and estradiol), had more frequent and more severe flushes.[54]

But, measurement of metabolites (which have been studied far more from androgens than estrogens) may not be the whole answer (Table 3).

How well the sex hormone produced within a cell can activate its receptor to ultimately cause protein production depends on a number of factors including the numbers and activities of co-regulators. Once the testosterone (or estrogen) binds to the receptor, there is conformational change in the receptor such that it can recruit co-activators or co-repressors. It is this complex of sex hormone, sex hormone receptor and co-regulators that binds to the specific DNA response elements. At present there is no way of measuring numbers or activity of co-regulators in the human. Polymorphisms of the androgen receptor gene may be a further confound. Future studies may evaluate risk of sexual dysfunction with various androgen receptor polymorphisms.

Perhaps an even more important confound is the fact that the brain can synthesize sex steroids *de novo*, such that those entering from the peripheral circulation may be less relevant than has been assumed.[55] The evidence to date suggests that synthesis can directly start from cholesterol and is a generalized process within the central nervous system: of note, androgen receptors are prominent in the forebrain as well as in the well-characterized areas of the hypothalamus and limbic regions. Adaptive changes occur in the brain to reductions in serum levels of sex hormones associated with age and with menopause: in women, there is upregulation of steroidogenic enzymes[56] and of sex receptors.[56] Regulatory proteins such as those allowing the first step in steroid production, that is, movement of cholesterol from the outer to the inner mitochondrial membrane may also show increased activity, as in rodent models.[57] However, the whole area of biological adaptation to reduced amounts of sex hormones is only just the beginning.

The interplay between sex hormones and brain amines including serotonin, dopamine and noradrenaline has yet to be clarified. Neurotransmitters such as dopamine can activate the androgen receptor. When an oophorectomized mouse is given estrogen and then primed with progesterone, she becomes sexually proceptive. Giving her dopamine without either sex hormone causes the same behavior.[58] Some women given dopaminergic drugs, such as bupropion, report increased sexual response[59] and some women with Parkinson's disease when given dopamine agonists report increased desire and responsivity such that sex becomes compulsive.[60]

It is clear also that the environment can trigger circuits typically triggered by sex hormones. Again, this can be established in the laboratory in the rodent: instead of giving the oophorectomized female rodent either sex hormones or dopamine, simply placing her adjacent to a cage holding an attractive male mouse or placing her in a cage associated with past sexual encounters will result in the same behavior.[61] In women, sexual desire and satisfaction is strongly correlated with change in partner and with positive past sexual experiences.[1] That none of this is simple is endorsed by a recent albeit preliminary study of surgically menopausal women receiving no hormone therapy, but who were sexually functional as tested by the BISF-W questionnaire. Viewing erotica failed to show the brain activation typical of premenopausal women and typical of themselves when treated with both testosterone and androgen—yet they reported sexual arousal from the erotic videos without as well as with hormonal supplementation.[62]

Hormonal treatment of dysfunction

Local estrogen

There is consensus that any of the approved local formulations of local estrogen are useful to reduce symptoms of dyspareunia and improve genital sexual sensitivity.

Given the (albeit minimal) systemic absorption, individualized advice is given to women having estrogen dependent cancer.[63]

Selective estrogen receptor modulators

Available molecules that bind to the estrogen receptor with agonistic action in some tissues and antagonism in others, do not ameliorate the genital sexual symptoms of estrogen lack—these symptoms being more frequent from raloxifene than tamoxifen.[64] Investigational lasofoxifene appears promising.[65]

Tibolone

Tibolone, a molecule possessing androgenic, progestogenic and estrogenic activity, reduces vulval atrophy in women recruited for reasons other than sexual dysfunction, and has comparable sexual benefit to transdermal norerthisterone acetate plus estradiol in women with sexual dysfunction.[66] Available in Europe, tibolone was found 'not approvable' by the Food and Drug Administration in June 2006.[67] There is concern regarding possible higher risks of breast cancer from tibolone compared to estrogen only, as shown in women in the million women study.[68] Furthermore, there was a doubled incidence of stroke compared to placebo in the Long-Term Intervention on Fractures with Tibolone trial.[69]

Systemic estrogen

Effective for sexual symptoms of estrogen deficiency, systemic estrogen is also a prerequisite for

benefit from systemic testosterone. Prescribing only testosterone would create a highly nonphysiological state. Within a context of needed estrogen deficiency, for example women with past histories of breast cancer, no observed benefit to sexual desire was seen from testosterone supplementation.[70] Long-term safety data for sexually symptomatic perimenopausal women given systemic estrogen, are not known with any certainty. Data from the (mostly asymptomatic) younger women in the Women's Health Initiative study and data from the observational Nurses study, suggest that such early initiation of estrogen therapy is advantageous to cardiovascular health[71] even if combined with progesterone—however, a small increase risk of breast cancer probably remains.[72]

Long-term systemic supplementation of testosterone (and estrogen)

There are limitations in our understanding of the consequences of systemic sex hormone therapy given for the duration of a woman's sexual lifetime—usually an indefinite period dependent to marked extent on the availability of a sexually functional partner.

Recent randomized controlled trials (RCTs) have focused on estrogenized surgically menopausal women who report less desire and less frequent sex since oophorectomy. Sexual benefit beyond placebo has been demonstrated from 300 μg, but not from 450 μg, transdermal testosterone daily.[73–76] Benefit was modest and varied across studies, all of which used similar protocols. In most studies, the frequency of 'sexually satisfying events' increased with active drug—from approximately 3, to 5 per month. Pooling the data showed that women receiving testosterone reported 1.9 more such events per month than at baseline whereas women receiving placebo reported 0.9 more. Increased scores in the desire domain of the psychometrically validated (but unpublished) questionnaire were seen in all trials. In some but not all trials, scores in the arousal, pleasure, orgasm, responsivity domains were increased, and distress scores were decreased. Needed now are trials recruiting women having sexual disorder according to contemporary understanding of women's sexual response and the current recommended definitions of disorder.[18] Such studies would focus on women who are still motivated to sexually engage for reasons other than desire, but who since bilateral oophorectomy, report that their minds and/or bodies fail to arouse or respond to past sexual triggers so that their baseline number of sexually satisfying events is set near zero. Recruitment criteria would comprise acquired sexual arousal disorder (combined, subjective or genital), plus sexual desire interest disorder.[18]

Clinicians in various countries are prescribing systemic testosterone using either recently approved patches or other formulations—adapting those approved for men or using compounded creams and gels. A recent RCT confirmed benefit from a 300 μg patch in naturally menopausal women.[77] Another showed marginal benefit from one of three doses of transdermal testosterone in premenopausal women with early morning serum free testosterone of less than or equal to 1.1 pg/ml.[78] The highest of the three doses, aimed to raise free testosterone levels to at least the 75th percentile failed to show benefit beyond placebo as did the smallest (one-third) dose. The one-half dosage allowed 0.7 more sexually satisfactory events per month than placebo, but outcome as measured by the Sabbatsberg Sexual Self-rating Scale was similar to placebo. It is very important that the limits of long-term safety of testosterone supplementation are explained to our patients and to colleagues entering the field of sexual medicine. Recent reviews have acknowledged that prospective studies of physiologic testosterone administration have been limited to 2 years or less and that prospectively collected long-term safety studies are needed.[79,80] *In vitro* and *in vivo* studies have reported both proliferative and antiproliferative effects on growth of breast cancer cells brought about by testosterone. Epidemiological review has suggested that endogenous androgen levels are positively correlated with breast cancer

Table 4 Aims of future research

- Further clarification of what is a sexual disorder: when is the woman's sex response system dysfunctional and when is it simply adaptive to problematic stimuli, context and outcome?
- Identification of markers of low androgen activity: these might include serum levels, for example of androgen metabolites as well as the woman's androgen receptor polymorphism
- Investigation of any correlation between such marker and sexual dysfunction
- RCTs of testosterone and estrogen supplementation in women unable to have any sexually satisfying experiences
- Tailoring of any testosterone substitution based on androgen receptor polymorphism
- Clarification of the role of *de novo* synthesis of sex steroids in the brain throughout a woman's life and its modulation by supplementation of exogenous sex steroids
- Development of drugs that effectively and safely increase women's sexual arousal and desire once they are sexually engaged
- SERMS to allow genital congestion in estrogen-deficient states but with desirable profile on estrogen receptors elsewhere
- ARMS for possible benefit to lost genital sexual sensitivity and lost arousal to nongenital stimuli
- RCTs of topical testosterone for possible benefit to lost genital sexual sensitivity
- Further development of nerve-sparing techniques for surgery for pelvic cancer, continence and, prolapse
- Further empirical data on psychosexual therapy including mindfulness, CBT, sex therapy—both with and without pharmacological adjuncts

Abbreviations: ARMS, androgen receptor modulators; CBT, cognitive behavioral therapy; RCTs, randomized controlled trials; SERMS, selective estrogen receptor modulators.

Table 5 Investigational drugs[89–100]

Drug type/name	*Rationale/comments*	*Published trials*
Bremelanotide: Synthetic peptide: α-melanocyte-stimulating hormone analogue-agonist at MCR1, MC3R and MC4R receptors	α-MSH implicated in male and female sexual responses in rodents probably by MCR4. Of note, MC4R also involved in satiety for food, stress response and nocioception. Possible limitation of benefit from melanocortins is due to agouti-related protein (a naturally occurring inverse agonist known to inhibit G-protein-coupled receptor activity), which not only blocks MCR signaling but also reduces the amount of MCR molecules accessible to melanocortins at the cell surface	No significant differences in psychophysiological or questionnaire responses to viewing erotic videos 15 min after intranasal drug but increased arousal during subsequent activity in eight women compared to the seven women given placebo.[89] Recent small RCT showed benefit for women's arousal disorder with in home use of nasal drug 45 min before sex[90]
Flibanserin: 5HT1A agonist and 5HT2A antagonist, weak partial agonist D4[91]	Serotonin acting on 5HT1A receptors has prosexual effects in rodents	None
Selective D3 dopamine agonists	Adverse effects of nonselective dopamine agonists thought to be D2 receptor related. Selective D3 agonist investigated for erectile dysfunction[92]	None
Bupropion: blocks noradrenaline and dopamine reuptake	Less likely to cause medication-associated dysfunction when used as an antidepressant and may ameliorate SSRI-induced dysfunction[93]	One small 4-month study, in nondepressed premenopausal women showed increased arousability and sexual response, no increase in initial desire[94]
Phosphodiesterase inhibitors: sildenafil	NO is a major neurotransmitter involved in vasodilatation of the clitoral structures and is also present in vagina. However, most women with arousal disorders have normal genital congestion	Increased genital congestion benefited women with diabetes[95] and multiple sclerosis[96] in small RCTs. Large multisite RCTs of women with arousal and desire disorders showed no benefit[95]
NEP inhibitors[98]	NEP degrades VIP—a major neurotransmitter allowing vasodilatation in the vagina. However, most women with arousal disorders have normal genital congestion	None
Dual NEP and SEP inhibitors	SEP also involved in VIP degradation	None
L-Arginine: arginmax	Arginine is a substrate for NO. However, most women with arousal disorders have normal genital vasocongestion	One RCT has shown some benefit in sexual dysfunction in pre and perimenopausal but not postmenopausal women[99]

Abbreviations: MCR, melanocortin receptor; MSH, melanocyte stimulating hormone; NEP, neutral endopeptidase; NO, nitric oxide; RCT, randomized controlled trial; SEP, soluble endopeptidase; SSRI, selective serotonin reuptake inhibitors; VIP, vasoactive intestinal polypeptide.

risk.[81] However, recent research has shown testosterone's reduction of the typical proliferative effects of postmenopausal estrogen and progesterone therapy.[82] The risk of cardiovascular disease (CVD) from supplementing androgens is unknown. A link between higher androgens and CVD continues to be debated. Evaluation of 600 healthy postmenopausal women in the SWAN study suggested that central obesity was associated with lower sex hormone-binding globulin (SHBG), higher free androgen levels, and insulin resistance, and that androgens are associated with hemostatic and inflammatory factors at midlife.[51] Other investigators have suggested that SHBG, not androgen production, is the primary marker of insulin resistance, and that the SHBG level has independent predictive power for cardiovascular risk for women.[83] Both of these studies were cross-sectional but prospective studies, including a nested case-controlled study, showed weak trends toward increased risk of CVD among women having higher androgen/estrogen ratios: among postmenopausal women not taking any hormone therapy, women with lower SHBG or with high free androgen indexes were at increased risk of CVD events.[84] Basic science[85] and clinical[86] data suggest that exogenous testosterone administration to women may promote abdominal fat deposition.

The North American Endocrine Society Clinical Practice Guideline recommends against the generalized use of testosterone by women because the indications are inadequate and evidence of long-term safety is lacking—this recommendation came about in the knowledge that there is evidence for short-term efficacy of testosterone in selective populations such as surgically menopausal women.[87] Guidelines from the North American Menopause Society are less restrictive but somewhat

confusing suggesting treatment must be 'administered at the lowest dose for the shortest time that meets treatment goals'.[88] There is no evidence that testosterone-related sexual symptoms are short term (for instance, analogous to estrogen related vasomotor symptoms).

Future research

An increasing acknowledgement of women's sexuality as a legitimate health concern may allow some of the aims listed in Table 4 to be realized.

Investigational drugs

Contrary to the unwanted sexual side effects of some antidepressants, the activation of sex receptors by certain amines has encouraged the development of molecules having actions on dopamine, serotonin, melanocortin and noradrenaline receptors that are likely to be prosexual as summarized in Table 5.

There has been interest in treating deficient genital congestion with various drugs including phosphodiesterase inhibitors, α-blockers, selective estrogen receptor modulators (SERMS) and peptidase inhibitors. However, the documented lack of correlation between women's sexual symptoms and any measurable deficit in genital congestion limits this approach. Focusing on women with expected deficient congestion due for instance to non-nerve sparing radical hysterectomies, would be useful.

Understanding the molecular actions of estrogen in restoring vaginal health is increasing and may allow development of nonhormonal therapies targeted at vaginal atrophy (VA). Changes in gene expression after estrogen treatment of VA include genes involved in several signaling pathways that promote tissue repair, remodeling, vascularization and defense against microbes in the vagina.[101]

Holistic therapy

Psychological therapy including CBT, sex therapy, psychoeducation, couple communication and more recently, mindfulness, has been the mainstay of therapy for women's sexual dysfunctions. However, well-designed, controlled studies on these nonpharmalogic treatment modalities are few—for review, see Brotto.[102] There is even less published research on combined medical and psychological approaches[103] which perpetuates the mistaken notion that sexual dysfunction is either psychological or biological and the corollary that either psychological or biological help is needed. Examples of how the mind can alter physical parameters include the measured decrease in vaginal congestion in response to erotica when a false feedback about their vaginal response is given to women with sexual arousal disorders, even though their subjective arousal was heightened by this feedback.[104] Hypnosis can be associated with remission of the neurological inflammation of vulvar vestibulitis syndrome (VVS)—typically considered a 'biological' entity.[105] The marked placebo response to drugs for sexual dysfunction notable in older women and in women in longer-term relationships[106] merits further research: what is its neurochemical basis?

Conclusion

Current evidence-based conceptualization of women's sexual response has led to various recommendations for revised definitions of disorder. Specifically, it is now advocated that desire disorder be defined as the absence of both any initial desire and any desire triggered along with arousal during the attempted sexual experience. Definitions of arousal disorder must recognize the importance of subjective arousal (excitement). The past focus on lubrication and swelling is no longer tenable given it is not the means by which women judge their arousal, is not accurately assessed by women, and when the increases in genital vasocongestion are measured, they correlate minimally with subjective arousal. Although the psychosexual factors protecting women from sexual dysfunction subsequent to dramatic changes in sex hormones with life cycle are well established, biological factors are less clear. Thus, which women might benefit from supplemental testosterone, has not been established—neither by biological nor by clinical parameters. It is recommended that hormonal or pharmacological approaches focus on women whose response is deemed disordered using currently recommended definitions.

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