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Sexual Function Across Aging

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Abstract Women experience multiple changes in social and reproductive statuses across the life span which can affect sexual functioning. Various phases of the sexual response cycle may be impacted and can lead to sexual dysfunction. Screening for sexual problems and consideration of contributing factors such as neurobiology, reproductive life events, medical problems, medication use, and depression can help guide appropriate treatment and thereby improve the sexual functioning and quality of life of affected women. Treatment options include psychotropic medications, hormone therapy, and psychotherapy.

Keywords Female sexual dysfunction · Neurobiology · Depression · Hormones · Pharmacotherapy · Life span

Introduction

Across the life span, women experience changes in environment, partners, roles, lifestyle, and biological and reproductive statuses, all of which can impact upon sexual functioning. In this article, we will review general issues that may impact women and their sexual functioning as well as the variation in factors affecting women. Important factors for clinicians to consider include the psychosocial impact of healthy sexual function and effect on general health, barriers/taboos/obstacles to sexual health in an aging population, neurobiology, reproductive/endocrine status, definitions and identification of sexual problems, partner influences, medical problems and medication use, and depression.

The biopsychosocial model of female sexual response incorporates biology, psychology, sociocultural, and interpersonal factors as influencing various aspects of female sexual functioning [1]. Any of these factors has the potential to enhance or impair some components of the desire, arousal, or orgasm phases of the sexual response cycle.

The desire phase includes physiologic, cognitive, and behavioral components; sexual thoughts and fantasies; the wish to participate in sexual activity; and initiation of sexual activity or receptivity to partner approach. Sociocultural factors related to a woman's upbringing or sociocultural norms and expectations can directly affect the desire phase of the sexual response cycle. Psychosocial factors such as gender expectations and religious beliefs may influence the expectations and roles of partners and become a source of relationship conflict or internal conflict about the expression of sexual desire and sexual conduct. Such conflicts may contribute to sexual problems. Cultural practices, too, can affect sexual satisfaction; for example, in some eastern societies, sexual activity is focused on reproduction and is associated with less sexual satisfaction. Societies that are partner-centered, rather than focused on reproduction efforts, have higher levels of sexual satisfaction. Technology may also impact sexual desire and function; i.e., easy access to online pornography or advertising campaigns that market products purported to enhance sexual activity may enhance sexual excitement or lead individuals to believe that they (or their partners) are comparatively lacking in sexual desirability and activity.

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The second phase of the sexual response cycle, the arousal phase, involves cognitive and physical sexual arousal with pelvic vasocongestion, vaginal lubrication, and swelling of the external genitalia. This phase may be affected, as well, by interpersonal factors such as psychological or relationship issues, partner availability and aging, pregnancy or infertility concerns, STI, and history of sexual abuse or trauma. Partner conflict and partner sexual dysfunction (SD) due to medical illness, age, and side effects of medication may also impact a woman's sexual functioning.

Finally, the orgasm phase of the sexual response cycle is the physiological release of sexual tension with rhythmic contractions of perineal tissues and associated cardiovascular and respiratory changes. This phase can be directly affected by biological factors, medication, illness, alcohol or illicit drug use, poor partner technique, or sociocultural prohibitions.

A circular model of sexual functioning has been described that illustrates how interpersonal emotional intimacy is interrelated with biological and psychological factors and can prompt a woman's desire to initiate or her motivation to be receptive to sexual activity initiated by a partner [2]. Conversely, disruption at any point in this circular process can lead to sexual problems.

The World Health Organization has set sexual health, defined as "a state of physical, emotional, mental, and social well-being related to sexuality," as a goal for all; it is not just the absence of sexual dysfunction [3]. Assessment for sexual problems is important across the life span as sexual dysfunctions and disorders may negatively affect quality of life by the impact they have on relationships and self-esteem and may influence adherence to prescribed pharmacotherapy that is associated with sexual problems. In the 1992 National Health and Social Life Survey (NHSLS), sexual complaints were voiced by 43 % of 1749 US women interviewed who had been sexually active in the previous year [4]. The most common concerns were low sexual desire (33 %), difficulty achieving orgasm (24 %), and problems with lubrication (19 %).

Neurobiology

Neurotransmitters and Sex Steroids

Neurobiology and neuroendocrine function are of central importance in sexual functioning and behavior and involve neurotransmitters, sex steroids, and specific genetic loci which impact central nervous system and peripheral (e.g., genital) targets [5, 6]. These systems are also directly impacted by the major reproductive events that occur across a woman's life span.

The neurotransmitters that regulate sexual functioning are the same systems that are implicated in depression and its treatment, which are also affected by sex steroids which modulate neurotransmitter deficiencies, synthesis, metabolism, and receptor activity. The sex steroids, particularly in women, are variably secreted due to hormone cyclicity and reproductive events (e.g., menstrual cycles, pregnancy, and menopause) that occur at various stages across the life span. Prior to puberty, there is a matched incidence of depressive disorders among genders; however, following puberty, and lasting until after the menopause, women have twice the prevalence of mood disorders as men. This increased risk coincides with the years of reproductive hormone fluctuation (i.e., estradiol and progesterone), as compared to the prepuberty and postmenopausal years in which reproductive hormone levels remain static. These hormonal changes and potential subsequent mood changes are also relevant to sexual functioning and may impact components of a woman's desire and sexual response.

In women, estradiol appears to be important in sexual desire and is particularly important in arousal. With the onset of puberty, in the early reproductive stage, estradiol begins a cyclical secretion pattern, which may be erratic at first and include anovulatory cycles.

Then, in the peak and late reproductive stages, hormone secretion patterns, and therefore menstrual cycles, exhibit a regular pattern. During early perimenopause, variable menstrual cycle length and hormonal fluctuations ultimately progress into the late perimenopause when there are longer periods of lower estradiol secretion and withdrawal. The lower levels of estradiol associated with the menopausal transition and postmenopausal state may lead to vaginal atrophy, irritation, urinary incontinence and discomfort, and difficulty with vasocongestion and lubrication. These changes may also lead to diminished sexual interest, arousal, and orgasm due to the resulting discomfort during sexual activity.

Testosterone is the sex steroid that primarily influences desire and is involved in initiation of sexual activity. Testosterone is modulated by the neurotransmitters dopamine and serotonin in the hypothalamus and limbic system and is also aromatized to estrogen in peripheral tissues.

Symptoms of androgen insufficiency may present as diminished sense of well-being or dysphoric mood, persistent and unexplained fatigue, and sexual function changes, including diminished libido, reduced sexual receptivity, and diminished sexual pleasure. Excessive levels of testosterone such as in polycystic ovarian syndrome (PCOS) are also associated with menstrual cycle irregularities, anovulatory cycles, infertility, and sexual dysfunction [7].

Testosterone levels that are correlated with sexual desire decline gradually as a normal part of aging as the ovaries secrete less androgen over time [8•]. Androstenedione, a testosterone precursor of both adrenal as well as gonadal sources, is also correlated with women's sexual desire presumably through conversion to testosterone and action on the androgen receptor, and these levels also decline with aging. However, if

a woman undergoes surgical oophorectomy, medically induced menopause, or some types of premature ovarian failure, there may be an abrupt cessation of testosterone release.

Prolactin interferes with arousal and subsequent phases of sexual functioning. Lactation and breastfeeding cause increased release of prolactin which may interfere with the sexual response cycle. Oxytocin may enhance sexual interest and receptivity, sexual activity, and satisfaction and increases at the time of orgasm with associated perineal contractions and increased systolic blood pressure. Oxytocin is secreted variably across the menstrual cycle and may play a role in increased sexual interest and function around ovulation.

Dopamine exerts central effects on sexual functioning by enhancing sexual desire, motivating sexual behavior, increasing pleasure, and building the cognitive experience of excitement.

Dopamine also enhances the ability to focus on sexual activity once it has been initiated.

Norepinephrine is also involved in the arousal phase, centrally and peripherally. The combined effects of dopamine and norepinephrine on sexual functioning, however, can both be diminished by increasing serotonergic neurotransmission. Estradiol, testosterone, and progesterone released by the ovaries or the adrenals can influence bioavailability and function of each other. For example, increasing levels of estradiol lead to increased sex hormone-binding globulin (SHBG) with subsequent binding of testosterone, thus lowering bioavailable or free testosterone. In addition, progestin can reduce estradiol levels. A spike in testosterone secretion at mid-cycle may contribute to increased sexual interest at the time of ovulation, followed in the luteal phase by diminished desire, decreased frequency of sexual activity, reduced ability to achieve orgasm, and lack of satisfaction in women with premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD) [9].

Genetic Factors

Burri et al. found that two genetic factors influence female sexual dysfunction (FSD) and account for about 30 % of the variance [10]. A single genetic locus impacts all the following four phases of the sexual response cycle: desire, arousal, lubrication, and orgasm. The other locus impacts only three of these phases, e.g., arousal, lubrication, and orgasm, but does not impact desire.

Environmental factors account for the remaining 70 % of variance. These environmental factors are varied and affect different phases of the sexual response cycle. Environmental factors modify the expression of the genotype resulting in the expressed phenotype. This explains the heterogeneity of FSD. There are multiple genetic loci that may increase the risk of sexual dysfunction in patients receiving pharmacologic treatment for depression. From a research perspective, the benefit of this information is that we could potentially test for specific genetic markers that would indicate someone is at risk for sexual dysfunction in the context of treatment of depression with a specific type of antidepressant. One such locus was re1128503, which interacts with P-glycoprotein substrates (such as the antidepressant drugs, citalopram, paroxetine, and sertraline) to cause sexual dysfunction [11]. Based on Changes in Sexual Functioning Questionnaire (CSFQ) scores in women with the rs1128503 TT, CT, or CC genotypes, it was recommended that in women who have the TT genotype, use of a non-P-glycoprotein substrate, such as fluoxetine, may help to reduce the potential to experience sexual dysfunction as a side effect from antidepressant use. Identification of women who are T allele carriers might help in antidepressant selection and promote close monitoring and early clinical management of sexual dysfunction.

Another study by Bishop et al. (2006) found that the 5HT2A-1438 GG was associated with a 3.5-fold increase in the rates of sexual dysfunction as compared to GA or AA genotypes in subjects taking a selective serotonin reuptake inhibitor (SSRI) [12]. The GG genotype was also associated with lower levels of sexual arousal, primarily in female participants. A secondary analysis of the large, multicenter effectiveness trial of antidepressant treatment response for depression, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, found several genes within the glutamate system to be associated with SSRI-induced sexual dysfunction but failed to identify such genes within the serotonergic system. A decrease in libido was reported by 54 % of the 1473 participants, while 36 % reported difficulty achieving orgasm; among the 574 men, 37 % reported erectile dysfunction. The genetic locus associated with erectile dysfunction was GRIN3A, and the three single-nucleotide polymorphisms (SNPs) with the greatest association had a 50–60 % increased overall risk for sexual dysfunction. For low libido, the GRIK2 gene had three SNPs that were linked, resulting in a 20–30 % greater risk for carriers. Difficulty with orgasm was associated with the GRIA1 gene, and overall odds of difficulty with orgasm for carriers of the risk allele were increased 40–50 % [13].

Neuroimaging

Relevant neurobiology considerations for the link between depression and sexual dysfunction also include the relationship of the network of neural pathways found to be affected in these conditions. Metzger et al. (2013) have conducted neuroimaging studies in men that reveal alterations in the typical responses of the amygdala, ACC, mid-brain, and LOC regions during sexual processing in patients who have sexual dysfunction due to SSRI (paroxetine) treatment [14, 15]. Specific areas of the mid-brain were altered in patients who reported decreased ability to achieve orgasm. In contrast, reduced sexual arousal was correlated with alterations in response of the anterior insular region. These images demonstrate how antidepressant treatment can affect specific areas of the brain differently.

Those areas of the brain are linked through a network, so it is possible that sexual dysfunction may be impacted from disruption of this network at numerous sites. In addition, there may be overlapping or shared pathways between the network processing sexual functioning and the network of relevant sites affected in depression. This may further contribute to the bidirectional relationship of depression and sexual dysfunction as the onset of one condition may enhance or trigger neurobiological pathways leading to onset of the other condition.

Reproductive Endocrine Events

In women, the fluctuations in levels of sex steroids that occur with aging as well as in context of discreet reproductive events (i.e., the menstrual cycle, pregnancy, peripartum, and the perimenopause) can influence both sexual functioning and mood. Most women tolerate such hormonal transitions during these reproductive events without serious adverse affects.

However, there is a subset of women who are vulnerable to the hormonal fluctuations during these reproductive periods and may develop new onset depression or voice sexual complaints during these transitions.

Reproductive Years

With the onset of puberty and the development of menstrual cycles in women (monthly fluctuations in estrogen, progesterone, and testosterone), there also occurs a rise in testosterone levels which are linked to increasing sexual desire. This is also a transition time when a young woman is further developing a sexual self-image, e.g., as a "woman" [16].

During the peak reproductive years, hormonal patterns become established and regular ovulatory and menstrual cycles occur. These physiological events appear to be influenced by sexual activity; e.g., sexual activity that occurs more frequently than once per week is associated with regular menstrual cycles and reduced anovulatory cycles [16]. In addition, psychological stresses such as fear of or desire for pregnancy and infertility concerns can negatively affect sexual experiences. Women seeking to avoid pregnancy frequently use oral contraceptives, which may increase SHBG and lower free testosterone levels, inadvertantly affecting sexual desire. However, triphasic oral contraceptives have been found to be associated with more sexual thoughts, fantasies, and sexual interest than monophasic oral contraceptives [17]; other data suggest little difference in the effects of different formulations of hormonal contraceptives (e.g., oral, transvaginal, and injectable) on sexual functioning.

Pregnancy and Postpartum

Pregnancy may be associated with dramatic changes in desire, pain on intercourse, structural impediments (e.g., growing fetus might prevent use of missionary position with intercourse), or decreased ability or fear of achieving orgasm (e.g., orgasm might cause miscarriage). Pregnancy is a time of dramatic bodily changes, during which a woman may experience body image concerns that affect sexual functioning, as well as a time of dramatic hormone change with levels of estradiol and progesterone that progressively increase throughout the pregnancy and could be potentially disruptive to or enhancing of sexual functioning.

Following delivery, resumption of sexual activity occurs in relationship to restoration of ovarian hormone cycling. If a woman breastfeeds, continued suppression of normal hormonal cycling and menstrual periods may occur and therefore may prolong the time to resumption of normal sexual activity. Postpartum low libido may occur, in part due to the plummeting levels of ovarian hormones, and long-standing discomfort with intercourse may persist in some women with vaginal deliveries. A woman's subjective experience of discomfort/pain and satisfaction with sexual activity may be adversely affected by perineal trauma from childbirth, such as from lacerations or episiotomy, which depending on the severity and the duration of the healing process, may delay and interfere with satisfying sexual experiences. The type of delivery is also associated with effects on sexual functioning, with deliveries requiring instrumentation resulting in the highest rate of sexual dysfunction, including low desire, and planned cesarean sections resulting in the lowest rate of sexual dysfunction [18, 19•].

Lowered levels of estradiol following delivery may cause vaginal dryness which can be a cause of dyspareunia. Estradiol levels may be continually suppressed during active breastfeeding, and the resulting vaginal dryness may persist for the duration of lactation. Other causes of sexual dysfunction and dissatisfaction include postpartum depression, fatigue due to thyroid disorder or anemia, and inadequate privacy for intimacy. Women who have not re-initiated sexual activity at 12 weeks postpartum are more likely to experience sexual dissatisfaction at 1 year postpartum [20]. However, the number of total deliveries or type of delivery are not predictors of long-term sexual quality of life; rather, women's desire and satisfaction are more influenced by age, general health, race, and partner factors [19•]. Women may be experiencing changes in body image, roles with work, roles within their families as new mothers, and in relationship with partners, all of which may be a source of stress and can potentially impact relationships and sexual functioning. Psychotherapy or support groups may provide benefit as they adapt to these changes. This is the time when many women may experience the onset of hypoactive sexual desire disorder (HSDD).

Menopausal Transition

In mid-life women, the menopause, which occurs in US women on average at age 51 years, is preceded by a phase of

hormonal transition, the perimenopause, which may continue for 2 to 15 years. The menopausal transition involves a variable decline in the reproductive hormone estradiol, progesterone, and testosterone which culminate in static, low levels of these hormones after menopause. The risk of depression is increased two to fourfold in the perimenopause vs. reproductive age women [21, 22]. Periods of hypoestrogenic states or lowered testosterone levels may also contribute to sexual dysfunction. Hypoestrogenic states are often associated with vaginal atrophy, irritation, and reduced vaginal lubrication which may make sexual activity uncomfortable or even painful. In addition, some changes associated with the menopausal transition (i.e., lowered voice, facial hair growth, and hot flushes that may cause embarrassment) can affect a woman's self-perception of sexual attractiveness and self-esteem.

In fact, cross-sectional data from the Study of Women's Health Across the Nation (SWAN) found that during the menopause transition, 5 % of women endorsed a triad of symptoms including sleep disturbance, depressed mood, and sexual problems, most commonly following surgical menopause or in the late perimenopause [23•].

With aging, women in mid-life may begin to experience the onset of new physical symptoms or chronic medical conditions as well as changing health conditions in their partners, which can disrupt sexual functioning. Multiple other changes in roles such as assuming more responsibilities as part of the "sandwich generation," caring for children and caring for ill or aging parents, can affect relationships and sexual functioning [24–26].

Postmenopause

Elderly women may experience negative impacts on sexual functioning due to an overall decline in general health, new or worsening medical conditions, and medication use that may have sexual side effects. In addition, there may be emotional or physical changes in her partner, including sexual dysfunction or lack of or loss of partner [27].

In a survey of 606 adults 50–99 years of age and who had a partner, over 80 % reported engaging in sexual activity within the past year, 70 % reported engaging in sexual activity at least weekly, and more than 60 % rated themselves as somewhat or very satisfied with their sex lives.

Depressive symptoms were more likely to be associated with worse sexual functioning, than age, physical function, or anxiety or stress [28].

Definitions

To date, the majority of studies for female sexual disorders have been based on the Diagnostic and Statistical Manual of Mental Disorders-4th edition, text revision (DSM IV-TR) sexual disorder diagnostic categories and their criteria. The DSM-IV desire disorders include HSDD, or distressing low sexual desire, and sexual aversion disorder (e.g., phobia of sex). The DSM-IV also includes female sexual arousal disorder (FSAD) or distressing inadequate genital lubrication, female orgasmic disorder, and the sexual pain disorders of dyspareunia (vaginal pain on penile penetration) and vaginismus (the involuntary contraction of perineal muscles with attempted penetration) [29]. The DSM-5 has sex-specific sexual dysfunctions with diagnostic changes affecting women only. For women, desire and arousal disorders have been combined into female interest/arousal disorder, and dyspareunia and vaginismus have been combined into genitopelvic pain/penetration disorder [30]. Sexual aversion disorder was deleted. The diagnostic criteria, except for the substance/medication-induced sexual dysfunction category, require a duration of >6 months plus distress. In addition, subtypes include lifelong vs. acquired and generalized vs. situational. No data to validate the specific diagnostic criteria, ease of use or epidemiological/prevalence rates, have been published to date. Thus, epidemiologic and treatment data presented here will be based on DSM-IV diagnoses.

Epidemiology of Sexual Dysfunction

The Prevalence of Female Sexual Problems Associated with Distress and Determinants of Treatment Seeking or PRESIDE study illustrates the prevalence of sexual problems in the general population and related distress in women and identifies important associated SD risk factors. This cross-sectional, population-based survey of adult women in the USA surveyed 50,001 women with 31,581 women (63 %) responding. The women who participated were, on average, 49 years old (ages ranged from 18 to 102 years old), primarily white (81 %), educated beyond high school (58 %), employed (54 %), had a partner (70 %), and were premenopausal (62 %). Many (27 %) had some symptoms of depression, and some (13 %) were taking antidepressants. Most (72 %) had a chronic medical condition other than depression (i.e., hypertension, arthritis, anxiety, thyroid problems, asthma, heart disease, and diabetes). Validated instruments were used including the CSFQ to assess sexual function, the Female Sexual Distress Scale (FSDS) to evaluate sexually related distress, and the Patient Health Questionnaire (PHQ-9) to document symptoms of depression.

The most common sexual problem was low desire (unadjusted prevalence 38.7 %), then low arousal (26.1 %), and orgasm difficulties (20.5 %) with the overall prevalence of any sexual problem of 44.2 % [31]. Sexually related personal distress was reported by 22.8 % of these women. The prevalence of all three sexual problems increased with older age; only 27.2 % of younger women (18–44 years old) reported any of the three problems, compared with 44.6 % of middle-aged women and 80.1 % of elderly women. However, personal distress caused by the sexual problems was lowest in elderly

women (12.6 %) and present in 25 % of middle-aged and younger women. Adjusting for age, the prevalence of any distressing sexual problem was highest in women aged 45–64 years (14.8 %), lowest in women 65 years or older (8.9 %), and intermediate in women aged 18–44 years (10.8 %). This difference is important to note, since although there are more reported sexual problems as women age, the related level of distress decreases with aging. This decline in the level of distress with aging is, at least in part, related to the reduction in the amount of stress placed on this problem by a partner. As women age, so do their partners, who may also develop their own sexual problems or physical activity restrictions and therefore do not choose to engage in sexual activity. The lack of availability of a partner may also occur due to divorce, separation, or death. A similar age pattern was seen for distressing desire and arousal problems, but not for orgasm problems, in which the prevalence was similar in middle-aged and older women. These 31,581 women were also assessed for a diagnosis of depression, depressive symptoms, and treatment with antidepressant medications [32]. About 40 % of the women with distressing sexual problems (met screening criteria for a sexual disorder) also had concurrent depression as defined by PHQ-9 self-reported symptoms and/or antidepressant treatment or prior major depressive disorder (MDD) diagnosis. In addition, the patients who were receiving treatment for MDD had less SD than the patients with depressive symptoms who were untreated, further illustrating the bidirectionality of both conditions.

Medical Problems, Medication Use, and Influence on Sexual Function

Medical conditions and indicated pharmacotherapy may both impose adverse effects on sexual functioning. Two important examples of medical conditions that may affect vascular and endocrine systems, and therefore potentially affect sexual functioning, are cardiovascular disease (CVD) and diabetes mellitus (DM), which are increasingly common with aging. In addition, many of the treatments commonly prescribed for cardiovascular disease and diabetes can further impair sexual functioning.

Patients with diabetes have two to threefold higher incidence of depression which may in part be related to the involvement of stress hormones. Patients with depression who have diabetes have worse glycemic control, and there is an association with increased complications including renal failure, blindness, gastroparesis, and amputations. The same patients with depression and diabetes may have less physical activity, increased smoking, poor diets, and poor ability to self monitor resulting in additional cardiovascular risk. This worsening of self-care and diabetes could further increase the risk for sexual dysfunction. Moreover, depression disrupts normal endocrine function and triggers an inflammatory response which could lead to an increased risk of type 2 diabetes and sexual dysfunction. Sexual dysfunction may be a direct result of medical conditions such as neurological disorders, pelvic disease, and other endocrine dysfunctions. Neurological disorders may include traumatic brain injury, multiple sclerosis, spinal cord injury, and Parkinson's disease. Pelvic disease considerations include overactive bladder, pregnancy, pelvic surgeries, and cancer treatments. Other endocrine dysfunctions can include metabolic syndrome, hyperprolactinemia, thyroid disease, and androgen deficiency. In addition, treatments for these comorbidities such as antihypertensives, beta-blockers, alpha-blockers, diuretics, lipid-lowering agents, digoxin, oral contraceptives, estrogens, progestins, antiandrogens, Gn-RH agonists, histamine H2-receptor blockers, narcotics, and NSAIDs may cause or contribute to SD.

Depression and Sexual Dysfunction

Sexual dysfunction and depression can both cause significant distress and impact multiple aspects of a person's well-being and functioning. Depression is well known to be a leading cause of disease burden, costing the USA alone billions of dollars yearly in treatment costs and reduced productivity. Sexual dysfunction also carries a significant burden, in that it contributes to indirect health care services and costs and can significantly impair relationships and thus negatively impact families.

Because of the multiple overlapping symptoms and risk factors shared by both depression and sexual dysfunction that may predispose an individual to develop either condition, Atlantis and Sullivan conducted a meta-analysis to further evaluate these components as potential causal or precipitating factors. In this analysis, six prospective cohort studies that evaluated the risk of sexual dysfunction in depressed patients and six studies that assessed the risk of major depressive disorder in patients with sexual dysfunction were ultimately included. A bidirectional association between depression and sexual dysfunction was found with a 50–70 % increased risk of sexual dysfunction in subjects with depression and a 130–210 % risk of depression in people with sexual dysfunction [33]. This meta-analysis did not address the severity of sexual dysfunction which could be a factor in depression risk.

Due to the complex and multifaceted bidirectional relationship of depression and sexual dysfunction, it is advised to screen for depression in patients presenting with complaints of sexual dysfunction and to screen for sexual dysfunction in patients presenting with complaints of depression.

Screening and Treatment Recommendations

Screening for depression associated with reproductive life events, evaluation for undiagnosed or ineffectively treated

medical and psychiatric conditions, and assessment of negative effects on sexual functioning by medications are recommended. Medical evaluation of the patient's partner and psychotherapy to address relationship conflicts may be helpful.

However, adequate randomized trials of psychotherapy that demonstrate an independent benefit on sexual dysfunction are limited.

Interventions for Treatment-Emergent Sexual Dysfunction with Antidepressants

Appropriate treatment of depression and anxiety symptoms is recommended; this includes both psychotherapy and pharmacotherapy. Classes of psychotropic medications used in the treatment of depression include SSRIs, serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), mood stabilizers, antipsychotics, benzodiazepines, and antiepileptic drugs, all of which may cause sexual dysfunction. Consideration may be given to use of bupropion or buspirone as adjunctive agents for antidepressant-induced sexual dysfunction or as primary pharmacotherapy for anxiety or depression, if appropriate, to help minimize or avoid development of sexual dysfunction. Vortioxetine [34] and vilazodone [35, 36] are newer antidepressants that appear to have a lower incidence of sexual dysfunction associated with use and should be considered in treating patients with depression and anxiety who have experienced sexual dysfunction with other antidepressant medications.

Hormone therapy may be considered to help treat new mood symptoms and symptoms of low libido, and may also improve vaginal dryness and atrophy (may improve with local estrogen alone), that may be associated with perimenopause or postmenopause. Recent approval of ospemiphene, a selective estrogen receptor modulator (SERM) for the treatment of dyspareunia in postmenopausal women, may be helpful while avoiding the use of sex steroids in at-risk individuals. Eighteen years after sildenafil was FDA approved for erectile dysfunction, the FDA approved the first non-hormonal product to treat FSD in August 2015. Flibanserin is a once daily, 5-HT1A agonist and 5-HT 2A antagonist for generalized, acquired HSDD in premenopausal women [37].

Adjunctive testosterone, although off-label in women in the USA, has also been used in some patients to treat sexual dysfunction, particularly in perimenopause and postmenopausal patients, as androgen levels progressively decline with age and risk of pregnancy and fetal exposure is minimal [38]. Testosterone assays in women are not indicated in the diagnosis of sexual dysfunction but may be used to monitor levels with supplementation. Testosterone supplementation also carries risks of hirsutism and hyperlipidemia, and these risks would need to be weighed against benefits for individual patients when considering this treatment option.

Positive studies that have shown benefit to women's sexual functioning from testosterone supplementation include a study by Davis et al. of 814 postmenopausal women with HSDD who were given transdermal testosterone 300 μg daily, 150 μg daily, or placebo.

Subsequent improvement in frequency of satisfying sexual experiences was seen in the group receiving 300-μg testosterone compared to the placebo group, and both groups receiving testosterone supplementation had significant improvement in desire and less distress vs. placebo [39]. In another study, the ADORE study, 272 postmenopausal women, the majority of whom were not receiving hormone replacement, were randomized to transdermal testosterone 300 μg daily or placebo for 6 months. The group receiving testosterone reported increased satisfying sexual episodes, improvements in sexual desire, and reduction of distress compared with placebo at the study end point [40]. A group of surgically postmenopausal women with a diagnosis of HSDD were given either 150, 300, or 450 μg daily transdermal testosterone for 24 weeks in addition to estradiol replacement, and the women receiving the two higher doses of testosterone had improvement in sexual desire and frequency of sexual activity compared with the placebo group [41]. The group receiving 150 μg testosterone daily did not show significant improvement in symptoms.

In a study of testosterone supplementation in premenopausal women, 34 women with low libido were given topical 1 % testosterone cream 10 mg per day or placebo daily. The women given testosterone had higher levels of sexual interest, satisfaction, pleasure, fantasy, sexual activity, and orgasm compared to those receiving placebo for a 12-week period [42]. In a 16-week trial of testosterone supplementation in premenopausal women, women were given transdermal testosterone in two 90-μl sprays, one 90-μl spray, one 56-μl spray, or placebo spray; positive sexual effects were significantly higher in the group receiving the one 90-μl spray than the placebo group.

Some investigations of intramuscular testosterone have shown positive effects on sexual functioning. In a study by Sherwin et al., 54 surgically postmenopausal women were given testosterone 220-mg injections or estrogen 10 mg or a combination of testosterone 150 mg with estrogen 8.5 mg or placebo monthly for 3 months; the groups receiving testosterone supplementation had significantly increased desire, arousal, and fantasies compared to the groups not receiving testosterone [43, 44].

The North American Menopause Society published a position statement in 2005 for androgen therapy in

women stating that there is limited data to support testosterone, in addition to estradiol supplementation may improve sexual functioning, particularly sexual desire [45]. The Endocrine Society published a clinical practice guideline in 2006 about androgen therapy in women which advised against the broad use of testosterone by women because data were inadequate and evidence of safety in long-term studies was lacking [46].

Finally, The British Society for Sexual Medicine (BSSM) published recommendations in 2010 that treatment of women with sexual desire and arousal problems should be individually tailored and may include psychosexual therapy, estrogen, testosterone, or tibilone [47].

Systemic estradiol and progesterone therapies may also carry significant risks such as blood clots, some types of cancers, and potential cardiovascular problems, and dementia when initiated in older women [48].

Conclusions

In conclusion, sexual functioning affects general health and well-being, and problems with sexual functioning may be experienced as a source of distress. Women, in particular, are affected by multiple biological, psychological, and social factors that may impact sexual functioning and which are directly affected during the course of reproductive events across a woman's life span. Women will benefit from clinicians' inquiry about sexual functioning and assessment and treatment of sexual problems, which may not be volunteered by the patient, as well as thoughtful consideration of the factors that may be affecting various phases of the sexual response cycle including social, psychological, and cultural obstacles to sexual health, partner influences, aging, medical conditions and treatments, neurobiology and neuroendocrine function, the context of reproductive endocrine events, definitions and identification of sexual problems, and depression.

Compliance with Ethical Standards

Conflict of Interest Veronica Harsh declares that she has no conflict of interest.

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