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# Therapeutic options for postmenopausal female sexual dysfunction

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## ABSTRACT

*Background* Female sexual dysfunction (FSD) is a multidimensional problem combining biological, psychological and interpersonal elements of multiple etiologies. Menopause-related sexual dysfunction may not be reversible without therapy. Hormonal deficiency does not usually decrease in severity over time. Many options are available for the successful treatment of postmenopausal FSD.

*Objective* To review the pharmacological and non-pharmacological therapies available for postmenopausal FSD, focusing on practical recommendations for managing postmenopausal women with sexual complaints, through a literature review of the most relevant publications in this field.

*Psychosocial therapy* This type of therapy (basic counselling, physiotherapy and psychosexual intervention) is considered an adaptable step-by-step approach for diagnostic and therapeutic strategies, normally combined with biomedical interventions to provide optimal outcomes.

*Pharmacological therapy* For postmenopausal FSD, many interventional options are now available, including hormonal therapies such as estrogens, testosterone, combined estrogen/testosterone, tibolone and dehydroepiandrosterone.

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*Conclusions* Menopause and its transition represent significant risk factors for the development of sexual dysfunction. FSD impacts greatly on a patient's quality of life. Consequently, it is receiving more attention thanks to the development of effective treatments. Non-pharmacological approaches should be used first, focusing on lifestyle and psychosexual therapy. If required, proven effective hormonal and non-hormonal therapeutic options are available.



## INTRODUCTION

Female sexuality encompasses sexual identity, sexual function and sexual relationships and is modulated throughout life by a number of factors, including life events, reproduction-related events, health, relationships and sociocultural variables[1]. Sexuality as a part of human behavior is a complex phenomenon that involves physiological and psychological influences. For this reason, the definition, prevalence assessment and evaluation of its disorders have been traditionally difficult[2]. Several investigators have proposed models of the female sexual response cycle. Most recently, Basson suggested in 2001 a non-linear model of female sexual response, incorporating intimacy-based motivation, sexual stimuli, co-influencing biological and psychological factors and satisfaction[3].

Female sexual dysfunction (FSD) can occur at any age but is most common around middle age. Two important overlapping factors that affect female sexuality are the aging process and the menopause[4]. Sexual problems can be a particularly important facet of the menopause transition and are more likely to be a cause of concern if hormone deficiency is ultimately responsible[5–7]. The accompanying decrease in estrogen production with the menopause leads to epithelial thinning as well as reduced vasocongestion and lubrication of the genitalia during sexual arousal, which turns into vaginal dryness and dyspareunia[8]. Some of the distressing manifestations of the menopause, especially decreased libido, fatigue and decreased sexual activity, can be attributed to the decline in testosterone levels that begins in a woman's twenties. By the time a woman reaches the age of 45, her testosterone levels may have fallen by 50%[9–13].

The consequences of menopause-related sexual dysfunction may not be reversible unless therapy is initiated. Hormonal deficiency in particular is not a condition that tends to decrease in severity over time[14–16].

As postmenopausal sexual dysfunction is a complex condition, treatments must be employed in a way that is sympathetic to the multifactorial etiology of this condition. Around menopause, there are numerous medical conditions associated with sexual dysfunction, such as diabetes mellitus, cardiovascular disease, hypertriglyceridemia, hypertension, neurological disease, genitourinary disease and psychiatric disorders, that must be evaluated[17]. Even in circumstances where the etiology transpires to be relatively simple, such as hormone insufficiency, the condition may have been prevalent for so long as to impinge on the patient's psychological well-being, thus requiring a more holistic approach.

Many therapeutic options are now available to the physician for the successful treatment of menopause-associated sexual dysfunction. These can be broadly divided into psychosocial (body awareness, individual psychotherapy, couple therapy, social interventions), physical (lubricants, physiotherapy, vaginal dilator training set, vacuum therapy) and pharmacological (estrogen therapy, testosterone therapy, tibolone, pain medication, anti-depressants, vasodilators) therapies.

This paper reviews the most relevant publications in the field of FSD with emphasis on classification, diagnosis and therapeutic options available to the physician. By no means is it either a systematic review or a meta-analysis of all the available evidence in this complex field; it merely reflects the expert opinion of the authors on addressing the various facets of postmenopausal sexual dysfunction and their appropriate application on a patient-by-patient basis.

## CLASSIFICATION OF SEXUAL DISORDERS

A woman's expression of her sexuality is unique to her and likely to change over time. Thus, defining a female sexual dysfunction can be very difficult. Nevertheless, FSD is a highly prevalent problem and is often underestimated in the

general population[18]. There are two classical, widely recognized medical sources that provide definitions and classifications of FSD: the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV TR)[19], which is published by the American Psychiatric Association and widely used in North America, and the World Health Organization International Classification of Diseases (ICD-10)[20], which is used by the rest of the world. Table 1 shows a comparison of both classifications.

The DSM-IV specifically emphasizes the emotional and psychological factors involved in female sexual dysfunctions, referring to the disorders as 'disturbances in sexual desire and psychophysiologic changes that characterize the sexual response cycle and cause marked distress and interpersonal difficulty'. The categories defined by the DSM-IV are hypoactive sexual desire disorder, sexual aversion disorder, female arousal disorder, female orgasmic disorder, dyspareunia, and vaginismus.

The ICD-10 focuses on physical factors that influence sexual response. Sexual disorders are defined as 'the various ways in which an individual is unable to participate in a sexual relationship as he or she would wish'. Classifications of sexual dysfunction include lack or loss of sexual desire, sexual aversion, failure of genital response, orgasmic dysfunction, non-organic vaginismus, non-organic dyspareunia, and excessive sexual drive.

New definitions and classifications are constantly being developed or modified to take into account new clinical findings[21]. The most current classification is that prepared by an international consensus committee made up of 19 experts in FSD from five countries organized by the American Foundation of Urological Disease (AFUD). This committee deliberated over 2 years and published a statement in 2000[22]. The categories outlined in the DSM-IV were retained and, as in the DSM-IV, the AFUD classification also includes personal distress as a diagnostic criterion. According to this revised definition from the AFUD International Consensus Committee, female sexual disorders can be categorized into four different groups. There is, however, considerable overlap of the four groups in description and symptoms (Figure 1).

**Table 1** DSM-IV and ICD-10 classifications of female sexual disorders

| *DSM-IV* | *ICD-10* |
|---|---|
| Hypoactive sexual desire | Lack or loss of sexual desire |
| Sexual aversion | Sexual aversion and lack of sexual enjoyment |
| Female arousal disorder | Failure of genital response |
| Female orgasmic disorder | Orgasmic dysfunction |
| Dyspareunia | Non-organic dyspareunia |
| Vaginismus | Non-organic vaginismus |
| | Excessive sexual drive |

DSM-IV, Diagnostic and Statistical Manual of Mental Disorders; ICD-10, International Classification of Diseases

## Sexual desire disorders

Several subsets of sexual desire disorders have been identified. Hypoactive sexual desire disorder (HSDD) is a persistent or recurrent deficiency (or absence) of sexual fantasies/thoughts, and/or desire for or receptivity to sexual activity, causing personal distress[22]. Sexual aversion disorder is defined as the persistent or recurrent phobic aversion to and avoidance of sexual contact with a sexual partner, causing personal distress[22].

## Sexual arousal disorder

Sexual arousal disorder is the persistent or recurrent inability to attain or maintain sufficient sexual excitement, causing personal distress, which may be expressed as a lack of subjective excitement, or genital (lubrication/swelling) or other somatic responses[22].

## Orgasmic disorder

Orgasmic disorder is the persistent or recurrent difficulty, delay in or absence of attaining orgasm following sufficient sexual stimulation and arousal, causing personal distress[22].

## Sexual pain disorders

Dyspareunia is defined as recurrent or persistent genital pain associated with sexual intercourse, causing personal distress[22]. Vaginismus is the recurrent or persistent involuntary spasm of the musculature of the outer third of the vagina, which interferes with vaginal penetration, causing personal distress[22]. Non-coital sexual pain disorder is recurrent or persistent genital pain even without sexual intercourse[22].

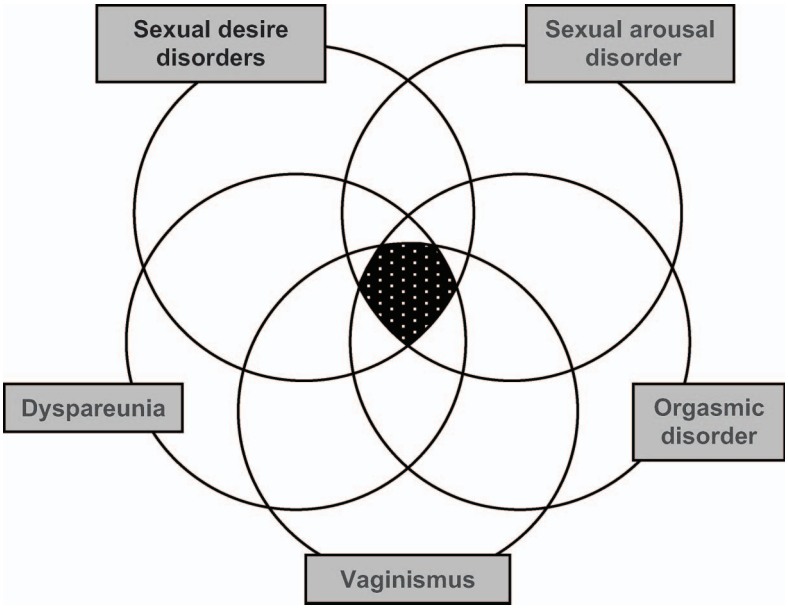


**Figure 1** Schematic representation of the types of female sexual disorder and how they overlap



## PREVALENCE OF FSD

It is difficult to provide accurate data on the prevalence of the different sexual dysfunctions. Laumann and colleagues[23] demonstrated the extent of the problem by assessing both the prevalence and the risk of sexual dysfunction using data from the National Health and Social Life Survey in the US. The authors found that sexual dysfunction was more prevalent in women (43%) than in men (31%) and was associated with various demographic characteristics, including age and educational attainment. Many reasons can explain the different prevalence figures found in the published literature: more than one accepted classification system, different methodologies and study designs, the multifactorial etiology of FSD involving biological, psychological and interpersonal factors, different populations (community-based vs. clinic-based settings), low response rates, no inclusion of sexual distress as a qualifier for the sexual disorder, etc. A thorough review of all the published prevalence data is beyond the scope of the present paper and the interested reader is referred to a recent publication reviewing prevalence studies on female sexual difficulty and dysfunction[24]. The authors found that the prevalence of sexual difficulty/dysfunction varied widely: desire, 2.5–54.8%, arousal, 2.6–31.2%, orgasm, 3.1–28.6%, and sexual pain, 3.1–20.3%. Despite this heterogeneity in the prevalence figures, the same authors showed that sexual desire difficulties were the most common disorder, followed by orgasm and arousal disorders[24]. Similarly, in a more recent study, Lindau and colleagues[25] showed that low desire was the most prevalent sexual problem (43%), followed by difficulty with vaginal lubrication (39%) and inability to climax (34%), among female respondents in a survey conducted in a US nationally representative probability sample of community-dwelling persons 57–85 years of age.

The prevalence of desire disorders (HSDD) in women from Europe (France, Germany, Italy, the UK) and the US was investigated in the Women's International Survey on Health and Sexuality (WISHeS) study[26,27]. WISHeS was a cross-sectional study conducted in 1999–2000 with the participation of over 4517 women aged 20–70 years resident in the countries cited above and identified from a market research database. Women were recruited by reproductive status and were grouped as follows: younger surgically menopausal women (20–49 years), older surgically menopausal women (50–70 years), premenopausal women (20–49 years), and naturally menopausal women (50–70 years). In the European cohort, the prevalence of HSDD ranged from 7% in younger premenopausal women to 16% in younger surgically menopausal women, with figures for older naturally and surgically menopausal women lying in between (9% and 12%, respectively)[26]. In the US cohort, the prevalence of HSDD ranged from 9% in naturally

postmenopausal women to 26% in younger surgically postmenopausal women, while the prevalence in the other two groups (premenopausal and older surgically postmenopausal women) was 14% each[27]. In both cohorts, HSDD was shown to be prevalent among women at all reproductive stages, with surgically menopausal women (especially at younger ages) at an increased risk. There were marked differences in the prevalence between countries for certain physical and psychological symptoms of FSD, suggesting that cultural and context-dependent factors may modulate the prevalence of FSD among countries[28,29].

More recently, West and colleagues[30] assessed the prevalence of HSDD, using a similar methodology to the WISHeS study, in a national probability sample of US households. In a cross-sectional study conducted in 2004–2005, 2207 women aged 30–70 years were interviewed. Women were stratified based on oophorectomy status and age (age groups 30–39, 40–49, 50–59, and 60–70 years). The prevalence of HSDD ranged from 6.6% in naturally menopausal women to 19.8% in younger surgically postmenopausal women, thus showing the highest prevalence of HSDD among surgically menopausal women, as in the WISHeS study.

## PSYCHOSOCIAL THERAPIES

Psychosocial interventions are excellent tools for addressing FSD and it is usual practice that biomedical and psychosocial interventions are combined to provide an optimal outcome. This type of therapy is best considered as a step-by-step approach, with continuous adaptation of diagnosis and therapeutic strategies. One of the barriers to this type of approach is what is known as treatment resistance. Sexual symptoms may be conditioned and maintained as an unconscious coping strategy for other underlying problems.

The first stage (psychosocial interventions) of a treatment regimen is to define the objectives of therapy, which can be identified using the following questions. What is the leading complaint? Is there any relevant medical co-morbidity (general or specific to the menopausal status)? What should be changed? What should remain as it is? How important is change? Are there any concerns about change? How confident is the patient that her sexuality and the couple's quality of intimacy can change? Is there any male factor (sexual dysfunction and/or general health problem) that may contribute to, precipitate or maintain the sexual dysfunction of complaint? How is the quality of the relationship?

Psychosocial interventions include basic counselling, physiotherapy and psychosexual intervention. Basic sexual counselling is an integral part of medical consultation. An initial session can involve the practitioner providing the patient with information on anatomy, physiology and, if needed, sexual development and function, sexuality in different life phases, the spectrum of human sexual behavior and cultural norms, and communication of sexual needs. This information is intended to elicit understanding and encourage questions, with the hope of increasing the patient's knowledge of and self-confidence in her sexuality and the possibility of maintaining the couple's erotic intimacy, if desired, throughout the menopause and beyond.

Body awareness education is a key part of psychosexual intervention and can involve a patient taking time to look at her naked body, preferably in a full-length mirror[31]. The patient can also explore her own genitals using a smaller mirror and investigate the most sensitive areas. Some patients may consider the suggestion to take time to explore their body as unusual, but many women, especially those with some manner of dysfunction, are surprisingly ignorant of their body in terms of how they look, their attractive features and what discrete areas feel good when stimulated[31].

Cognitive therapy is a key element of individual psychotherapy. It focuses on individual thoughts, feelings and behavior, encourages the patient to become aware of irrational beliefs and dysfunctional thoughts and, in doing so, helps to change their way of thinking. Psychodynamic focal therapy, which focuses on conflict and conflict resolution, is another regularly used tool in individual psychotherapy. For example, it may involve trying to resolve the conflict between instinctive wishes, norms and obligations or between the real sexual 'self' and the ideal sexual 'self'. It is often specifically used to address the aftermath of abuse and post-traumatic stress disorder.

Alongside psychotherapy tailored to the individual is couple therapy, which can be divided into communication training, psychodynamic therapy and sensate focus. The first of these involves gaining a basic understanding of the different levels of human communication. Listening is a key part of the communication between two individuals, as is the ability to be unambiguous when saying 'yes' or 'no'. Communicating effectively

with a degree of empathy is also important, especially if the topic in question has the potential to hurt the partner's feelings. The ability to provide feedback in a constructive and sensitive manner is also important in the communication between two people in a sexual context, as is the ability to negotiate.

Psychodynamic therapy allows a constructive platform for the discussion and resolution of subconscious conflicts that hinder sexual intimacy, such as gender roles, a third person, giving and taking, money, family loyalties and education of children.

Sensate focus can also be employed in couple therapy and integrates behavioral therapy, cognitive therapy, psychodynamic therapy and systemic therapy. Behavioral therapy can include exercises that can be conducted at home to reduce anxiety. Cognitive therapy trains the patient to become aware of thoughts and feelings that accompany sexual behavior. Psychodynamic therapy works towards overcoming resistance to change, and the objective of systemic therapy is to change existing patterns of communication and interaction. Sensate focus for couple therapy involves a range of exercises that can be carried out at home (Table 2).

Psychosocial interventions, when needed, are usually carried out by a certified psychotherapist in sexual medicine, working in the menopausal team. With FSD, physicians usually focus more on the medical diagnosis and treatment with which they are most familiar and refer to the psychotherapist/sexologist when psychosocial intervention is indicated.

## PHARMACOLOGICAL THERAPIES FOR FSD

### Hormone therapy

Hormone therapy encompasses treatment with estrogens, combined estrogen and testosterone, tibolone and dehydroepiandrosterone (DHEA). Sex hormones increase the sensitivity of an individual towards sexual stimuli[5,32,33]. Estrogens, androgens and progestins modify the 'motivational' state towards or against sexual activity. The distinct effects of estrogens and androgens on desire are still not completely understood. However, the interplay between these hormones appears to be important. The role of the androgen testosterone is relatively well understood; it seems to play a crucial role in sexual desire, arousal and receptivity towards sexual stimuli[34].

#### *Estrogens*

Estrogens are important for the maintenance and function of the vaginal epithelium, stromal cells, smooth muscles and nerve trophism. Genital sexual symptoms are more frequent in women with estradiol levels $< 50$ pg/ml[35]. Estrogens have vasodilatory effects and increase vaginal, clitoral and urethral blood flow via nitric oxide synthase (NOS) and vasoactive intestinal polypeptide (VIP) pathways, leading to genital congestion and vaginal lubrication. Estrogens also modulate sensory thresholds.

There are several randomized, controlled trials that show a positive effect of systemic estrogen on sexual function in naturally menopausal women.

**Table 2** Couple therapy – sensate focus

| *Step* | *Exercises at home* | *Discussion and reflection* |
|---|---|---|
| 1 | Caressing the body, excluding the genital regions; changing active and passive roles – 2 times per week for 45 min | What feels good? What feels bad or irritating or uncomfortable? How to talk about it? Negative feelings are important to report, they help to understand |
| 2 | Caressing the body, including the genital regions; changing active and passive roles – 2 times per week for 45 min | Exploring without the objective of stimulation; feelings and communication about the experience; feeling safe |
| 3 | Manual stimulation with changing roles. Build up excitation | How does it feel to play with stimulation, to build up and let it subside? How is each partner able to direct excitation? The joy of teasing |
| 4 | The man lies back and the woman sits on him, introducing the penis into the vagina | New experiences are possible; feeling close; the emotional significance of penetration; the woman has control |
| 5 | Movement and position experimentation | Body movements and body expression as sexual stimulation can be experienced and shared |

Sherwin and co-workers investigated the effects of various doses of estrogen and progestin on the psychological functioning and sexual behavior of 48 healthy, naturally menopausal women[36]. In all treatment groups, there was an increase in sexual desire and arousal[36]. In a double-blind, placebo-controlled study by Wiklund and colleagues, the quality of life of postmenopausal women on a regimen of transdermal estradiol therapy was investigated. Health-related quality of life and well-being both improved significantly in those patients receiving transdermal estradiol compared with placebo. Transdermal estradiol treatment was also associated with significant improvements in sexual problems and sexual dysfunction[37].

The effect of transdermal estradiol on sex life was also investigated in 242 postmenopausal women by Nathorst-Boos and co-workers[38]. Satisfaction with frequency of sexual activity, sexual fantasies, degree of enjoyment, vaginal lubrication and pain during intercourse were positively influenced in the group who received estradiol compared to the placebo group. The frequency of orgasm and sexual arousal were not enhanced by estradiol treatment[38].

Therefore, a recent review on the role of estrogen therapies in women's sexual functioning concluded that systemic estrogen treatments are associated with significant benefits in some domains of menopausal sexual function, especially when estradiol is delivered transdermally, whereas local estrogens (tablets, suppositories, creams, etc.) are effective in preventing urogenital aging[39].

### *Estrogen/androgen combination therapy*

It is well known that androgens play an important role in sexual desire, arousal, orgasm and satisfaction by interacting with receptors in the hypothalamus and priming the dopaminergic pathway that modulates the seeking-appetitive-lust system[40]. Combining androgens and estrogens appears to enhance female sexual function, evidence of which was obtained from studies in estrogen-replete patients.

Testosterone implants are available in some European countries, where they are licensed for hypogonadism in men. Despite this licensed indication, there are relatively little published data on the use of testosterone implants in postmenopausal women. Early observational studies suggested a positive effect of testosterone implants added to estrogen replacement therapy in postmenopausal women complaining of loss of libido. Studd and colleagues[41] showed that 136 out of 300 women (43.5%) attending a menopause clinic complained of loss of libido as one of their three primary problems. Women with persistent loss of libido (76), despite being given oral estrogens (conjugated equine estrogens 1.25 mg/day), were treated with a hormonal implant (50 mg estradiol and 100 mg testosterone) and were followed for 3 months. A significant improvement in libido was reported in 80% of these women, with many reporting that sexual response was better than or as good as before the menopause. Cardozo and colleagues[42] described the effects of subcutaneous hormone implants in a group of 120 pre- and postmenopausal women attending a menopause clinic. A total of 67 postmenopausal women received 286 implants (estradiol 50 mg and testosterone 100 mg at 4- to 12-monthly intervals) over a period of up to 4 years. Complete relief of loss of libido was reported by 67% of women with loss of libido present before the start of the treatment. In a comparative study, Dow and co-workers[43] evaluated a testosterone implant (100 mg) with estradiol implant therapy (50 mg) compared with treatment with estradiol implants alone in postmenopausal women who were experiencing a decline in sexual interest. No significant differences in sexual interest and responsiveness were found between the groups. Burger and colleagues[44] compared the efficacy of implants combining 100 mg testosterone and 40 mg estradiol against those containing 40 mg estradiol alone in postmenopausal women (either spontaneous or surgically induced) who had severe loss of libido while taking oral estrogen and progestogen therapy. At 6 weeks, significant improvements in libido and sexual enjoyment were noted in testosterone-treated women, and these improvements persisted for up to 18 weeks. In a 2-year trial, Davis and colleagues[45] evaluated the effect of adding subcutaneous 50 mg testosterone implants to estradiol implants (50 mg) in 34 postmenopausal women. Testosterone recipients had significantly greater improvements in sexual activity, satisfaction, pleasure, and frequency of orgasm compared with women receiving estradiol alone.

Oral and buccal preparations are available that are licensed for use in males. Oral preparations are swallowable tablets. Buccal preparations are designed to be dissolved on or under the tongue or via the gum. These routes of administration result in rapid absorption and turnover and are associated with a greater risk of adverse effects on lipids and liver function as a result of first-pass hepatic metabolism than products that

are delivered via the skin – testosterone administered transdermally does not go through first-pass hepatic metabolism. Methyltestosterone, an alkylated derivative of testosterone suitable for oral administration, is available in the US but not in most European countries, where it was withdrawn from the market because of the potential risk of significant liver toxicity[46].

Sarrel and co-workers[47] randomized 20 women with natural or surgically induced menopause to either oral esterified estrogens (1.25 mg) or esterified estrogens plus oral methyltestosterone therapy (2.5 mg). All women were using estrogen therapy at baseline. At 8 weeks, methyltestosterone recipients had significantly improved combined sexual sensation and desire scores; those receiving esterified estrogen alone did not have a significant improvement from baseline (Figure 2). In a randomized, double-blind study, Lobo and colleagues[48] investigated the effect of adding oral methyltestosterone (1.25 mg) to oral esterified estrogens (0.625 mg) for 4 months in postmenopausal women with HSDD. Both spontaneous and surgically induced postmenopausal women were included. Testosterone recipients gave significantly greater scores for sexual interest/desire and the frequency of sexual interest/desire compared with women receiving estrogen alone. In a placebo-controlled, cross-over trial, Floter and colleagues[49] investigated oral testosterone undecanoate (40 mg/day) plus oral estradiol valerate (2 mg/day) therapy vs. estradiol valerate alone in 50 postmenopausal women (mean age, 54 years) whose menopause was surgically induced. The cross-over occurred after 24 weeks of therapy and continued for a further 24 weeks. Compared with women receiving estrogen alone, those receiving both testosterone and estrogen had significantly improved overall sexual function as shown by scores for enjoyment of sex, satisfaction with frequency of sexual activity and interest in sex. More recently, Blümel and co-workers[50] assessed the effects of oral methyltestosterone (1.25 mg/day) combined with oral hormonal replacement therapy (conjugated estrogens, 0.626 mg/day and micronized progesterone, 100 mg/day) on quality of life and sexuality in a randomized, placebo-controlled, double-blind, double-dummy clinical trial. Forty-seven healthy postmenopausal women (women with surgical menopause were not included) were evaluated at baseline using the Female Sexual Function Index (FSFI) and the Menopause-specific Quality-of-Life questionnaire (MENQOL). Forty of those diagnosed with sexual dysfunction were randomized to receive daily methyltestosterone and oral hormonal replacement therapy or placebo for 3 months. Compared with women receiving placebo, women receiving hormonal replacement therapy plus androgen had a significant improvement in quality-of-life symptom scores (vasomotor, psychical, physical and sexuality-related symptoms) measured using MENQOL and in sexual dysfunction scores measured with FSFI. According to FSFI final scores, all women in the placebo group had scores suggesting sexual dysfunction, whereas 69% of women in the active treatment group resolved this condition.

Intramuscular testosterone preparations are also licensed only for use in men. One study

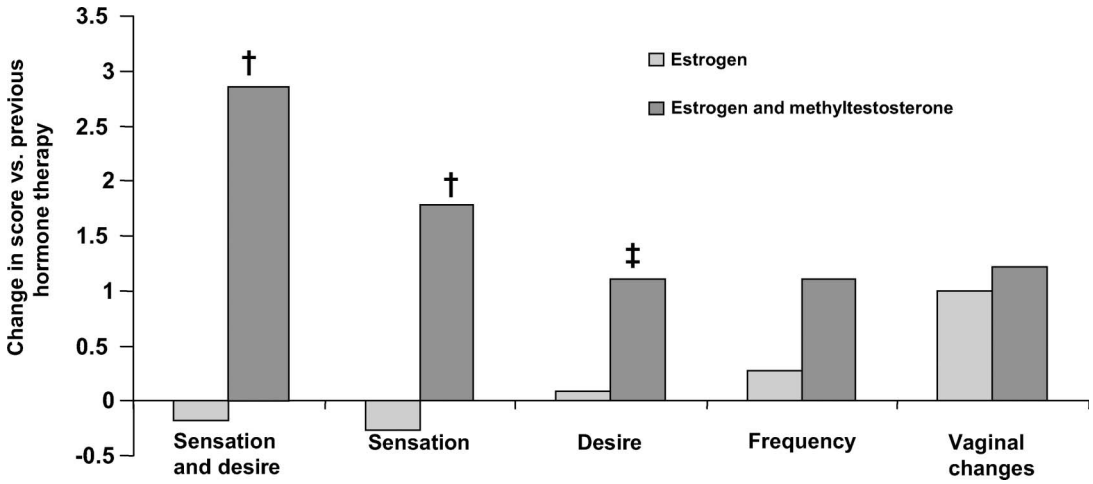


**Figure 2** Improving the effect of estrogen on female sexual function with the combination of testosterone[47]. †, $p < 0.01$; ‡, $p \leq 0.05$

investigating intramuscular testosterone and sexual functioning in 53 women after surgical menopause has been reported. Sherwin and colleagues[51] randomized women at the time of surgery to one of five groups: testosterone plus estrogen, estrogen alone, testosterone alone, placebo, or a hysterectomized-only control group. All drug treatments and placebo were intramuscular injections. The cross-over design had two 3-month active-treatment phases plus a 1-month placebo washout between the phases. In the treatment phases, adding testosterone significantly enhanced intensity of sexual desire, sexual arousal, and frequency of sexual fantasies compared with estrogen alone or placebo.

There are little published data on the use of men's testosterone gels in women, although gel is the most widely preferred administration method for off-label testosterone use. Nathorst-Boos and colleagues[52] reported on treatment with 10 mg testosterone per day delivered via a gel for postmenopausal women who were already on hormone treatment (HT). In a 3-month plus 3-month, double-blind, randomized, cross-over study, they found that, compared with placebo, testosterone gel significantly improved scores for 'frequency of sexual activity, orgasm and intercourse', 'sexual arousal, fantasies and enjoyment', 'satisfaction with orgasms', and 'interest in sex'.

To investigate further the utility of adding androgens to estrogen therapy, Somboonporn and co-workers reviewed the available literature on this subject and assessed 23 trials involving 1957 patients[53]. A pooled estimate from the studies suggests that the addition of testosterone to HT regimens improved sexual function scores for postmenopausal women. The authors of this review concluded that, although there are benefits of combining androgens with estrogen in terms of sexual function, the meta-analysis combined studies that used different testosterone regimens, making it difficult to estimate the effect of testosterone on sexual function in association with any individual HT regimen[53].

### *Transdermal testosterone specifically for women*

The treatment of the various elements of FSD with testosterone has been limited for a long time by the lack of testosterone preparations designed specifically for use in women, whose therapeutic requirements are less than one-tenth of those for hypogonadal men. Many of the earlier studies described above employed different doses of testosterone preparations that could result in supraphysiological androgen levels. In recent years, a transdermal testosterone patch designed specifically for women that delivers 300 $\mu$g/day testosterone has been investigated in a number of studies. Two separate phase III trials known as INTIMATE SM1 and INTIMATE SM2 involving 562 and 532 women, respectively, were conducted to assess the efficacy/safety of transdermal testosterone in surgically menopausal women with HSDD on concomitant oral or transdermal estrogen[54,55]. Both these trials reported significant improvements in total satisfying sexual activity (Figure 3) and in sexual desire and distress. In these trials, the effect of transdermal testosterone treatment on sexual function was quantified using the Profile of Female Sexual Function (PFSF),

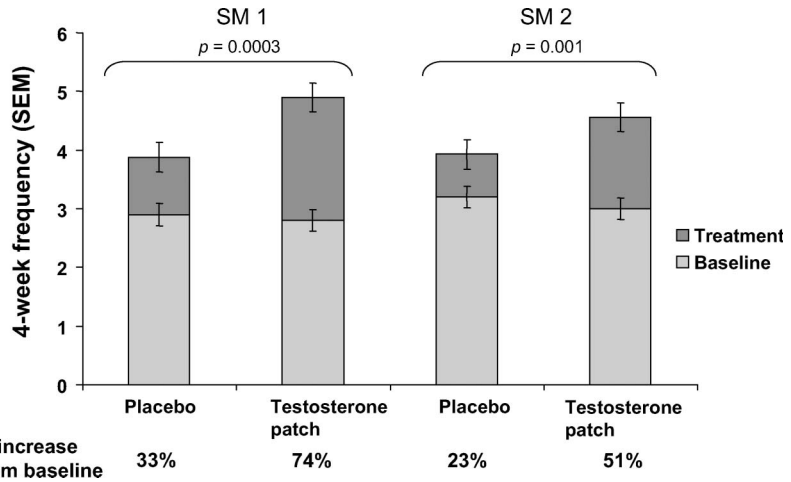


**Figure 3** Improvements in total satisfying sexual activity following treatment with transdermal testosterone in women with surgical menopause in INTIMATE SM1 and INTIMATE SM2 studies[54,55]

which is divided into various domains, including arousal, orgasm, pleasure, reduced concerns, responsiveness and body image. In both studies and across all the domains, transdermal testosterone treatment yielded significant improvements over placebo. In terms of safety and tolerability, the treatment and placebo groups were similar, although, in SM2, the incidence of androgenic adverse events was slightly higher among the treatment patients compared with the placebo patients. Of the adverse events reported, 91–96% of androgenic adverse events were mild[54,55].

If androgens have a positive effect on sexual function in surgically menopausal women, and given the fact that women exhibit progressively lower androgen levels as they age, then testosterone could also be helpful in improving sexual function in naturally menopausal women. Shifren and colleagues investigated this hypothesis in a large ($n = 549$), placebo-controlled, phase III trial (INTIMATE NM1) in naturally menopausal women with HSDD[56]. Women in this trial were also receiving a stable dose of oral estrogen with or without progestin. Women were randomly assigned to receive the 300 $\mu$g/day testosterone transdermal patch or placebo patches twice weekly for 24 weeks. Similar to the results of the INTIMATE studies in surgically menopausal women, significant improvements in total satisfying sexual activity and in sexual desire and distress (Figure 4) were seen in the testosterone group compared to the placebo group. Significant improvements were also observed in the testosterone group with respect to all secondary efficacy measures, including arousal, orgasm, pleasure, reduced concerns, responsiveness and body image. The incidence of androgenic side-effects was higher with testosterone treatment, but about 95% of androgenic adverse events were scored as mild.

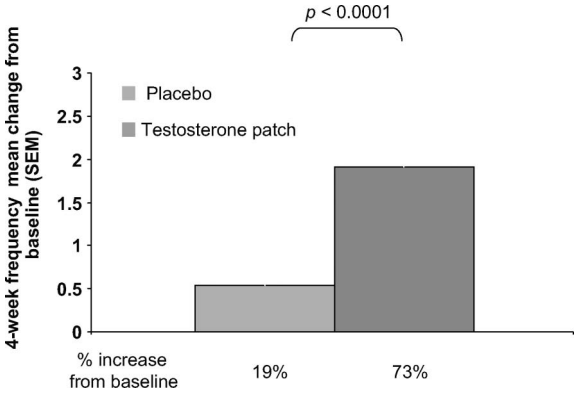


**Figure 4** Improvements in total satisfying sexual activity following treatment with transdermal testosterone in women with natural menopause[56]

The next question arising from the results of the clinical trials in surgically and naturally postmenopausal women discussed above is whether testosterone is also efficacious and safe in postmenopausal women with HSDD who are not on concomitant estrogen therapy. This is an issue that is highly relevant from a clinical point of view, as routine long-term use of estrogens with or without progestins is not recommended. This question was addressed by Davis and colleagues[57] in a phase III, placebo-controlled trial (APHRODITE) involving 814 women with HSDD. Women were randomly assigned to receive a testosterone patch delivering 150 $\mu$g or 300 $\mu$g of testosterone per day or placebo over 52 weeks. At 24 weeks, the increase in satisfying sexual episodes was significantly greater in the group receiving 300 $\mu$g of testosterone per day than in the placebo group, while the improvement in the group receiving 150 $\mu$g/day was not significant. Both doses of testosterone were associated with significant increases in desire and decreases in distress when compared with placebo. Similar to the results of the INTIMATE-SM and -NM trials, a significant improvement was also documented for all other secondary efficacy measures, including arousal, orgasm, pleasure, reduced concerns, responsiveness and self-image. The overall incidences of adverse events over a period of 52 weeks were similar among the study groups, and most events were mild and reported by the site investigators as being not clearly linked to treatment. Few serious adverse events were reported, and rates of these events were similar among the groups. As this was the first study to use the transdermal testosterone patch in women with an intact uterus without the concomitant use of an estrogen/progestin combination, special attention was paid to endometrial adverse effects. In the group receiving 300 $\mu$g testosterone per day, more women who had not undergone hysterectomy (10.6%) reported vaginal bleeding than in the other groups (placebo, 2.6%; 150 $\mu$g of testosterone per day, 2.7%). All women with vaginal bleeding underwent a biopsy, transvaginal ultrasonography, or both. No cases of endometrial hyperplasia or carcinoma were diagnosed.

### *Dehydroepiandrosterone*

DHEA is an androgen and is classed as a prohormone because it can be converted into a

variety of biologically active steroids. The specific action and safety of the final metabolites have not yet been clarified and conflicting data exist on the specific role of DHEA in sexual function. DHEA is a non-licensed substance; however, it can be purchased as an over-the-counter health supplement in many countries and, unfortunately, quality control is not always adequate in terms of origin and dosage. Therefore, caution should be exercised. DHEA can be converted into both testosterone and estrogen via the androgenic pathway. As with all androgens, it has been well documented that DHEA production steadily declines with age. However, there is conflicting evidence over the efficacy of DHEA in sexual functioning. In a double-blind, randomized, placebo-controlled trial of 24 women who had adrenal insufficiency, treatment with 50 mg/day DHEA produced a significant improvement in frequency of sexual thoughts, sexual interest and satisfaction[58]. However, no effect of DHEA on sexual function was observed in two similarly designed studies[59,60]. A placebo-controlled trial of DHEA in women aged 40–70 years also showed no improvement in sexual function[61].

## Synthetic steroids

Tibolone is a synthetic steroid with estrogenic, androgenic and progestogenic properties. It is indicated for the relief of climacteric symptoms in postmenopausal women. Studies have shown that tibolone treatment yields significant improvements in sexual fantasies, arousability, desire for sex with a steady partner and vaginal arousal after erotic stimulation (Table 3)[62,63].

In a study published in 2000, Castelo-Branco and colleagues examined the comparative effects of estrogens plus androgens and tibolone on bone, lipid pattern and sexuality in 120 surgically postmenopausal women[62]. Sexuality improved significantly with therapy; however, tibolone and androgens increased scores to a greater extent than estrogen replacement therapy. Sexuality was defined by frequency of sexual interest, frequency of orgasm, frequency of sexual responsiveness, frequency of general sexual satisfaction and frequency of dyspareunia[62].

A further study comparing tibolone and continuous estradiol/norethisterone acetate showed that the former resulted in improvements in frequency of sexual activity, sexual enjoyment and satisfaction compared with the latter[64]. Treatment with tibolone has demonstrated good overall tolerability with a low incidence of vaginal bleeding and breast tenderness; however, current available data on breast and endometrial cancer risk are inconclusive.

## Non-hormonal therapy

Several non-hormonal therapies have been investigated or are under clinical development. Although preliminary findings with sildenafil demonstrated positive effects in sexual arousal in a subset of women with specific arousal disorders, placebo-controlled clinical trials yielded inconclusive results.

Dopaminergic drugs (bupropion, quinerolane), melanocyte-stimulating hormone analogs, α-adrenoceptor antagonists (phentolamine) and prostaglandins (alprostadil) have all also produced promising preliminary results, but no consistent efficacy has been shown in placebo-controlled clinical studies[2].

# TREATING THE TYPES OF FSD

## Hypoactive sexual desire disorder

As the etiology of HSDD is multifactorial, its treatment may draw on basic sexual counselling, lifestyle changes and hormone therapy in women with sex hormone deficiency using androgen/estrogen combination therapy, estrogen or tibolone. Co-morbid depression should also be addressed, as should the adjustment of certain types of medication, i.e. psychotropic drugs. The use of psychosexual therapy, either individual or couple-based, is also an option. Additional counselling of the partner is highly recommended (Figures 5 and 6).

**Table 3** Effects of tibolone on vaginal blood flow, sexual desire and arousability in postmenopausal women

| *Sexual function diary data* | *n* | *Tibolone* | *Placebo* | *p Value* |
|---|---|---|---|---|
| Sexual fantasy (frequency/week) | 37 | 2.78 | 1.68 | $<0.03$ |
| Arousability (frequency/week) | 37 | 12.08 | 9.05 | $<0.01$ |
| Desire for sex with steady partner | 25 | 2.80 | 2.24 | $<0.09$ |
| Vaginal lubrication after erotic stimulation | 37 | 7.13 | 5.92 | $<0.001$ |

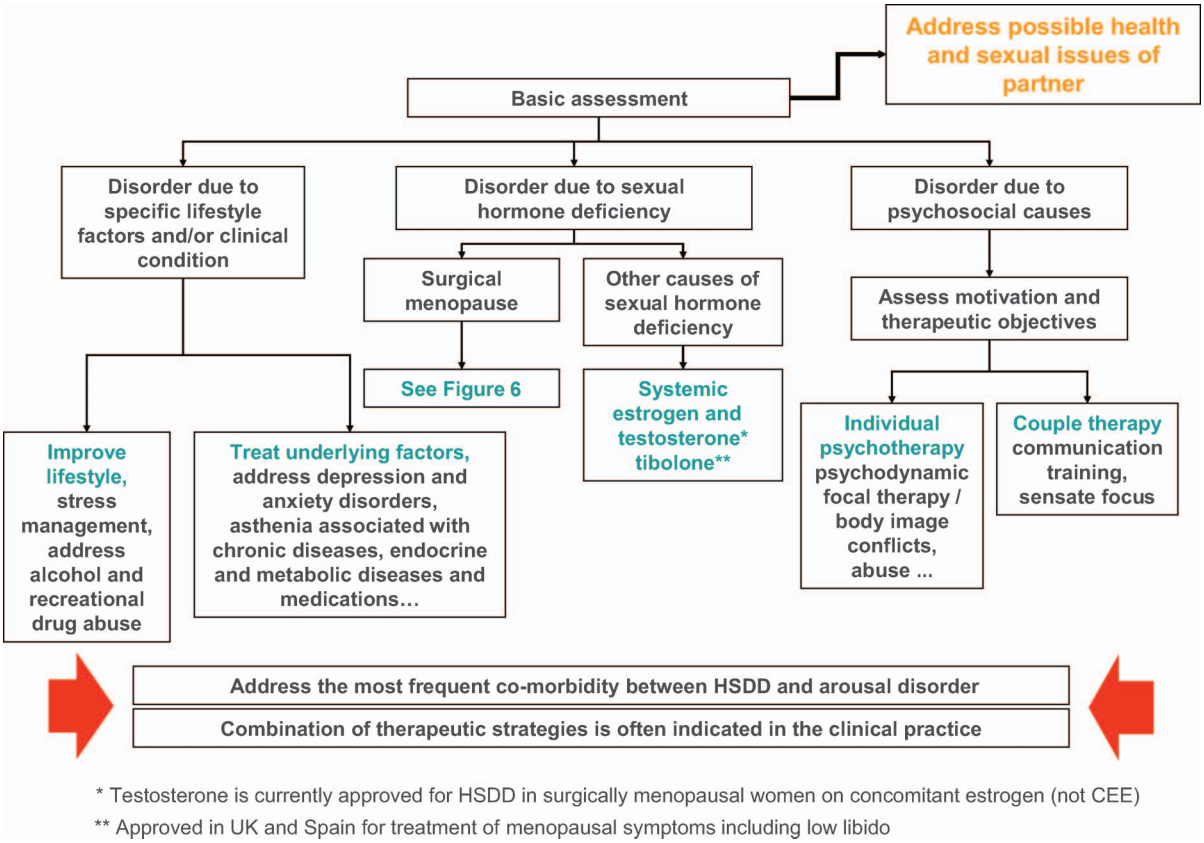


**Figure 5** Treatment of hypoactive sexual desire disorder (HSDD)

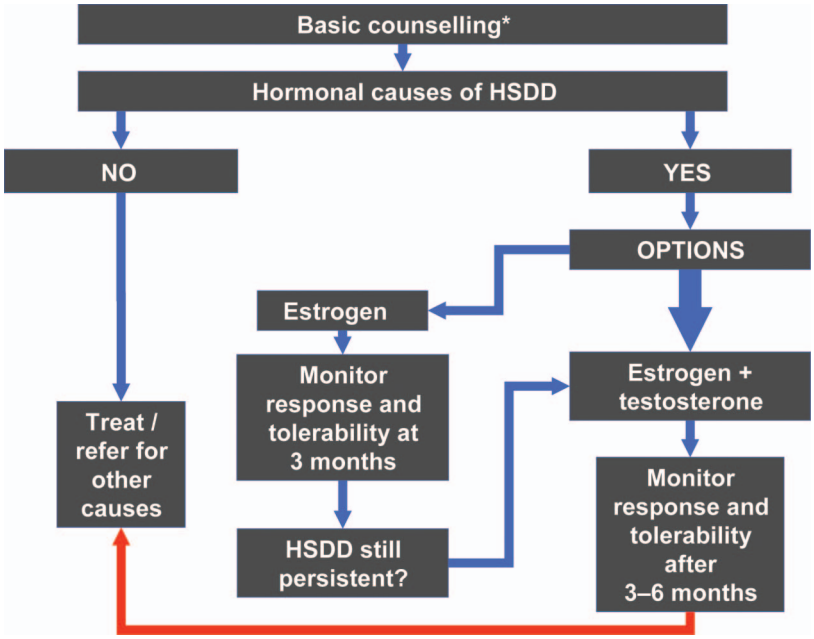


**Figure 6** Algorithm of treatment for hypoactive sexual desire disorder (HSDD) in surgically menopausal women

## Sexual arousal disorder

Treatment of sexual arousal disorder can involve hormonal therapy, blood vessel dilators, clitoral therapy devices, physiotherapy of the pelvic floor, lifestyle changes and psychosexual therapy. Transdermal testosterone treatment significantly improved arousal, as indicated in the secondary

endpoints of controlled trials in HSDD[54–57]. Additional counselling of the patient (and partner) is also recommended. Currently, there is no specifically approved medication for arousal disorder (Figure 7).

Various clinical trials investigating the treatment of sexual arousal disorder have reported contentious results. In some studies of women with sexual dysfunction and/or arousal or desire disorder using 10–100 mg/day sildenafil over a 12-week treatment period, no effect could be shown[65,66]. However, if only genital arousal disorder was present, sildenafil showed some positive effects on arousal[65–68]. Several blood vessel dilators are also under investigation for the treatment of sexual arousal disorder. A topical formulation containing a synthetic version of prostaglandin E1 (a vasodilatory agent) is under investigation, as is phentolamine, a competitive, non-selective α-adrenergic receptor antagonist promoting vasodilation; however, more data are needed on the efficacy and safety of an oral preparation[69].

A vacuum-based, clitoral therapy device has also been investigated in an original study and a follow-up study, both of which yielded some interesting results, including significant improvements in sensation and satisfaction[70,71].

## Orgasmic disorder

Currently, there is no specifically approved medication for orgasmic disorder, but there are numerous other therapeutic options at the disposal of the physician, including optimization of prescribed hormones, adjustment or cessation of orgasm-inhibiting medications such as selective serotonin reuptake inhibitor antidepressants, physiotherapy of the pelvic floor, lifestyle changes and psychosexual therapy. Transdermal testosterone treatment significantly improved orgasm, as indicated in the secondary endpoints of controlled trials in HSDD[54–57]. Again, additional counselling of the patient (and partner) is highly recommended (Figure 8).

## Sexual pain disorders

Sexual pain disorders can be broadly classed as dyspareunia or vaginismus. For the former, there

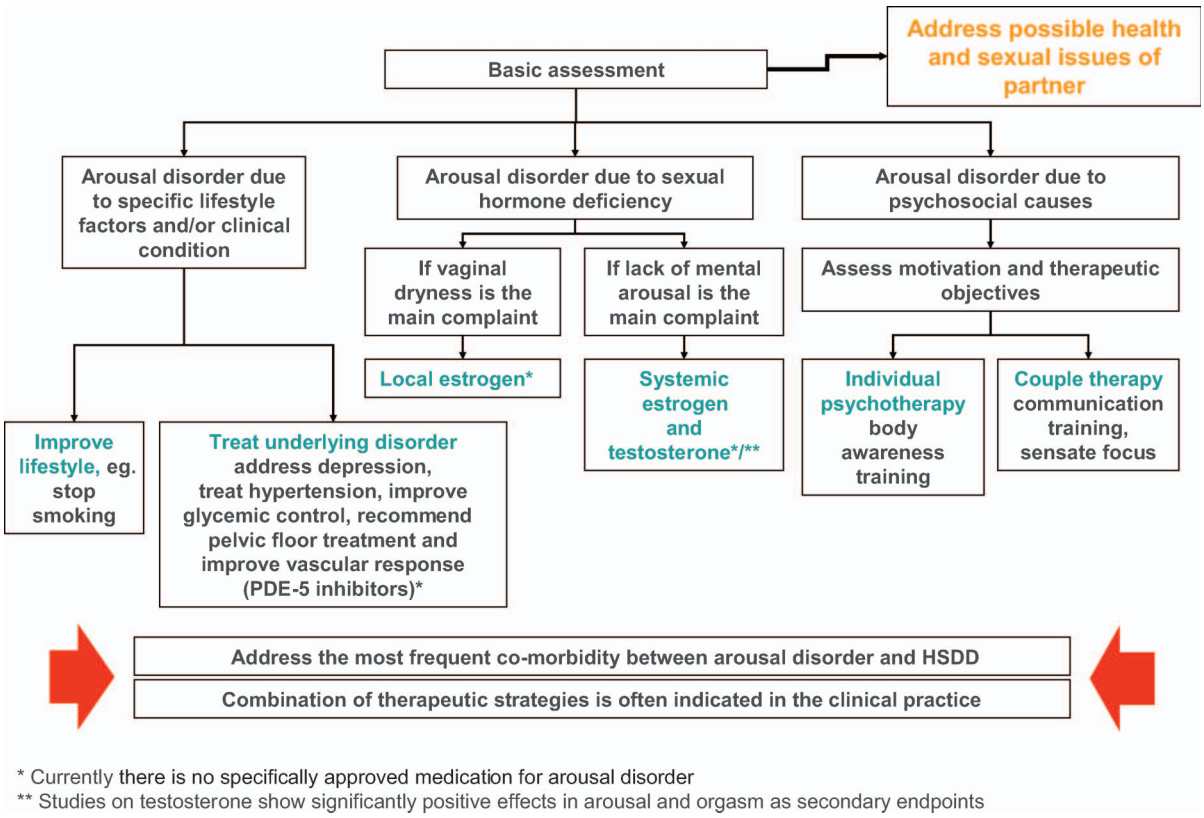


**Figure 7** Treatment of sexual arousal disorder

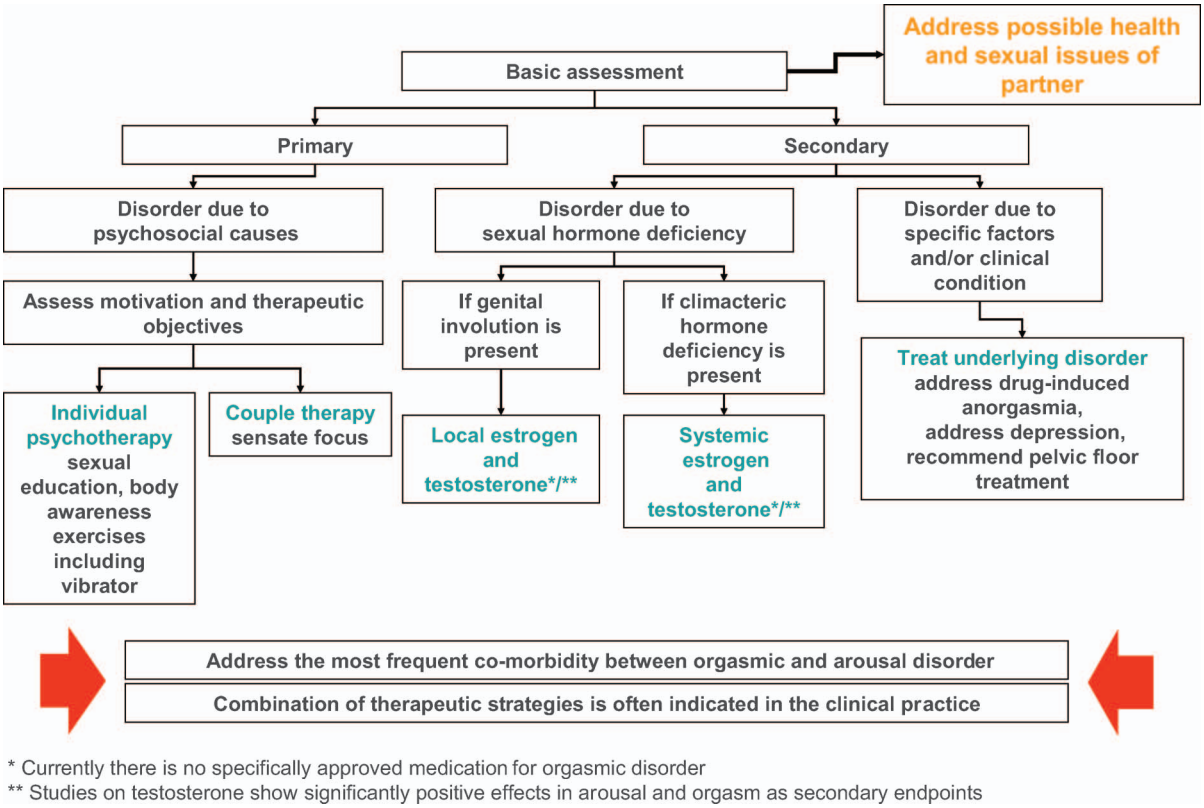


**Figure 8** Treatment of orgasmic disorder

are numerous treatment options available. Normalization of vulvar/vaginal trophism and pH is an important consideration in postmenopausal women and may include hormonal therapy with topical or systemic estrogen. Concurrent diseases, such as infections and dermatological conditions such as lichen sclerosus, should also be treated. The use of lubricants offers a simple, although minimalistic, means of addressing sexual pain. Physiotherapy is aimed at relaxing the pelvic floor when it is primarily (lifelong) hyperactive, or when hyperactivity is acquired in response to repeated introital pain at intercourse. When vulvodynia is the leading component of dyspareunia even in postmenopausal women, the physical pain of this condition can be treated systemically with analgesic drugs or locally with electro-analgesia or ganglion impar block. In severe cases of sexual pain disorder, surgical intervention such as laparoscopic uterosacral nerve ablation is an option.

Pain has a considerable psychological element; therefore, psychosexual therapy has a significant role to play in the treatment of sexual pain disorders. Individual and couple therapy and lifestyle changes are also important in the treatment of sexual pain disorders (Figure 9). The treatment of vaginismus is summarized in Figure 10.

## CONCLUSIONS

Menopause and the process of transition to menopause represent significant risk factors for the appearance or accentuation of sex-related problems. Sexual dysfunctions can affect one or more stages of human sexual response, including desire, excitement and orgasm. It is increasingly important to address sexual issues in clinical practice. Confidence in dealing with sexual issues increases with practice, and assessment and counselling can be learned. Female sexual disorders are receiving more attention thanks to the development of effective treatments for male erectile dysfunction. The therapeutic approach to female problems, however, is not and cannot be the same as for men; their management is different and more knowledge of the subject is required. Besides the known psychological factors associated with FSD, others should also be considered, such as the wide range of biological factors, including anatomical, hormonal, vascular and neurological factors.

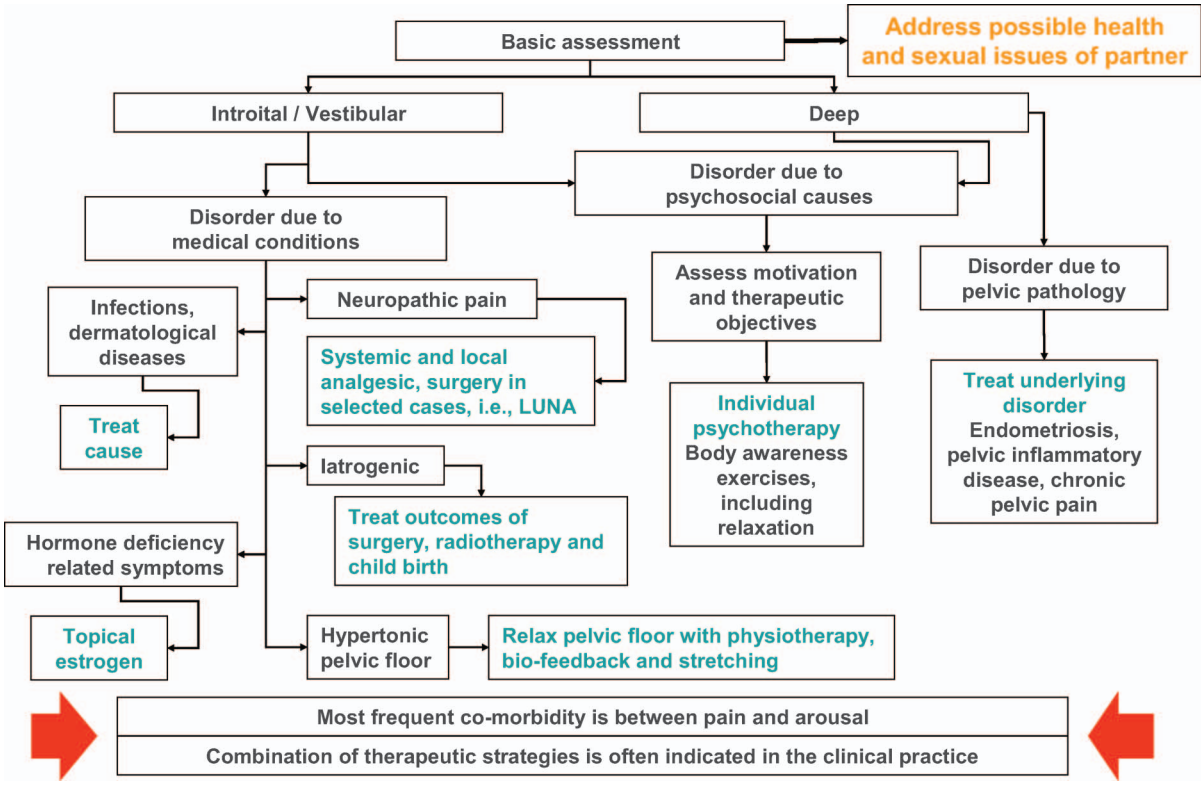


**Figure 9** Treatment of pain disorders – dyspareunia (introital and deep)

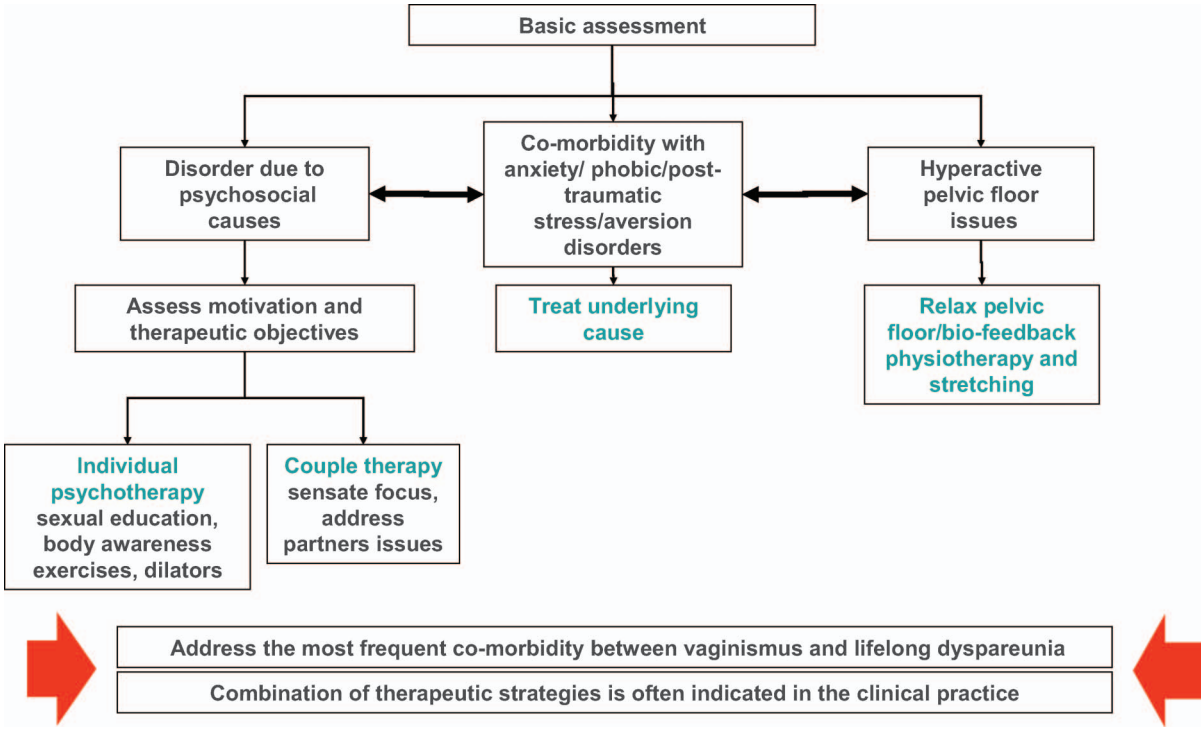


**Figure 10** Treatment of pain disorders – vaginismus

Treatment should begin by focusing on lifestyle and psychosexual therapy. Different pharmacological therapeutic options, both hormonal and non-hormonal, which have proven to be effective, are available.

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