

Are there any Pharmaceutical Agents Available for the Improvement of Female Sexual Dysfunction (FSD)?

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Editorial

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Editorial

Women may not follow a linear model of sexual response (as previously defined by Masters and Johnson). In fact, women seem to respond to sexual cues in a more complex way than men. In her circular model, Basson introduced a new concept of emotional intimacy and emphasized the influence of biopsychosocial factors in women's sexuality. Although the contribution of spontaneous sexual desire in this model is not overlooked, Basson stresses emotional and physical intimacy derived from sexual stimuli and its reinforcing effect on sexual desire and arousal and ultimately in the couple's wellbeing. Thus, Basson's circular model illustrates the multifactorial nature of female sexual response allowing a more comprehensive and effective approach to female sexual dysfunction (FSD).

Framework of Sexual Complaints

Female sexual complaints are common and the prevalence of FSD is about 30% [1]. Throughout the last decades, there have been many changes in the definition and categorization of FSD but one thing remains: low sexual desire is the most prevalent dysfunction among women [1]. Although in DSM-V there is no distinction between sexual interest disorder and arousal disorder, most clinical trials still use the previous classification (DSM-IV-TR) which classifies FSD into four categories: sexual desire disorders, sexual arousal disorders, orgasmic disorders and pain disorders. However, these

four main categories are not exclusive, and women often complain of more than one difficulty. This poses a demanding challenge to the clinician/therapist when it comes to treat sexual dysfunctions or problems.

Treatment: General Considerations

There are various treatment options which can include: education, psychotherapy, pelvic floor physiotherapy, alternative treatment elements (such as lubricants, erotica, vibrators, Eros clitoral therapy device), surgery (in selected cases of vulvodynia where vestibulectomy is indicated) and pharmacological treatments. Health care professionals should be aware that not all female sexual complaints are psychological and there are possible pharmacological options, although they still have scarce practical implementation. However, treatment should always be tailored to each woman's particular needs, following the principles of a multidisciplinary and biopsychosocial approach.

Sexual Interest/Arousal Disorders

When it comes to sexual interest/arousal disorders, several pharmacological agents have been investigated as possible treatment options, and many are used off-label. Testosterone is one of the most commonly studied pharmacological interventions in desire but has not been approved by the Food and Drug Administration (FDA) for

the treatment of hypoactive sexual desire disorder (HSDD), being commonly prescribed off-label. The use of testosterone demands caution as long-term risks include breast cancer, insulin resistance and metabolic syndrome. Testosterone supplementation requires concomitant use of estrogens to prevent high testosterone/estrogen ratio which can be an important cardiovascular risk factor. Transdermal and topical formulations are preferable due to low hepatic metabolism. The use of transdermal testosterone patches (in a daily dose of 300mcg) in postmenopausal women with HSDD has had positive results with benefits in desire, responsiveness, orgasm and satisfaction, with good safety profile [2-5]. These clinical trials were specifically designed for women who are receiving concomitant oestrogen therapy and for oestrogen-replete surgically and naturally postmenopausal women [6,7]. Therefore, transdermal testosterone patches (300mcg/day) are approved by the European Medicines Agency (EMA) since 2006 for the treatment of low sexual desire after surgical menopause in women receiving simultaneous oestrogen therapy. In the future, a recommendation for the use of testosterone in low sexual desire in the context of natural menopause or without oestrogen association is a possibility. Local and systemic oestrogen therapy has also been submitted to clinical trials but official recommendation is lacking in desire disorders [8]. Recent reviews on oestrogen replacement in postmenopausal women have shown benefits on sexual function [9]. Tibolone, an androgenic, progestagenic and estrogenic synthetic hormone, has been used for the treatment of menopausal symptoms, with some evidence showing sexual desire and arousal improvement [10-12]. However, it has not been approved for FSD treatment. Dehydroepiandrosterone (DHEA), the so-called "youth hormone" commonly acquired as a nutritional supplement, has shown positive effects on sexual function in some studies, but the evidence is scarce and even contradictory, therefore, it has not been approved for the treatment of FSD [13,14]. Vasoactive drugs such as sildenafil or alprostadil were submitted to trials on the treatment of FSD but results are inconsistent and approval for the generalized use in clinical practice is lacking. However, sildenafil has shown some positive results in selective serotonin-reuptake inhibitors (SSRI) antidepressants-induced FSD in premenopausal women, in diabetes and multiple sclerosis [15-18]. Bupropion a dopaminergic antidepressant, has shown efficacy either in nondepressed women with HSDD and in women with SSRI-associated sexual dysfunction when used concomitantly [19,20]. In this case, bupropion has been associated with a significant increase in self-reported feelings of sexual desire and sexual activity. In recent

years, another psychotropic agent has been increasingly used: flibanserin, a 5-HT_{1A} agonist and 5-HT_{2A} antagonist, has received FDA approval for low sexual desire treatment in premenopausal women. However, its clinical efficacy is not completely established as the results seem to vary among different patients [21,22]. Altogether, increase in sexual desire and increase in the number of satisfying sexual encounters seems to be modest [23,24]. Bremelanotide a melanocortin receptor agonist has been recently approved by the FDA for HSDD treatment with an efficacy superior to placebo [25,26].

Pain/Penetration Disorders

Several pharmacological modalities have been used to treat genital pain and penetration disorders. Topical medications have been used alone or in combination with systemic drugs [27]. Topical agents include lidocaine, estradiol, nitroglycerin and amitriptyline or anticonvulsants in topical solutions. Antidepressants as amitriptyline and other tricyclic antidepressants, duloxetine or venlafaxine, and anticonvulsants as gabapentin, pregabalin, topiramate or lamotrigine have been used orally. Some patients have benefited from injectable administration of lidocaine. The majority of treatment options for genital pain and penetration disorders are not evidence-based and have limited success [28]. Some patients experience symptomatic relief but not complete resolution of their complaints.

Orgasmic Disorders

For the treatment of female orgasmic disorder (FOD) there are no FDA approved drugs. In cases of secondary FOD, the underlying cause should be targeted, sometimes by a specific pharmacological intervention. In most cases, there are no pharmacological options targeting orgasm disorders. Some argue that the pharmacological interventions for the treatment of other sexual disorders (such as desire and arousal disorders) can be relevant in FOD amelioration. Bupropion has already been tested for the treatment of FOD [29].

Final Considerations

Women's sexual complaints have a complex and multifactorial etiology that poses a demanding challenge in approach and treatment. Therefore, FSD amelioration requires evaluation from different specialists: gynaecologists, psychiatrists, psychologists, endocrinologists, urologists and physical therapists especially trained in sexual medicine. Some

pharmacological options are available for FSD treatment and might be useful in selected patients. Scientific evidence exists for the pharmacological treatment of low sexual desire in women after surgical menopause (transdermal testosterone associated with oestrogen replacement) and for SSRI-induced FSD (association with bupropion). The absence of established pharmacological options for FSD treatment arises as an opportunity to discuss non-pharmacological options with patients and to promote further basic and clinical research in this field.

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