Pharmacological Management of Sexual Dysfunction in Females

Aditya Somani, Ashish Sharma

Department of Psychiatry, Adesh Medical College and Hospital, Shahbad (M), Kurukshetra, Haryana, India

ABSTRACT

Human sexuality has multiple facets and dimensions. Treatment of sexual dysfunctions and been attempted since ages. However, there has been limited progress in management of sexual dysfunctions in females. Flibanserin is a recently approved molecule for treatment of hypoactive sexual desire disorder (HSDD) in females. It is a 5-HT_{1A} receptor agonist and 5-HT_{2A} receptor antagonist. Other treatment modalities include local and systemic hormonal agents including estrogen, progesterone, testosterone, ospemifene and tibolone. Combination treatments are also being investigated. To provide holistic care to the patient, one must always include psychological treatments in the management plan of the patient.

KEYWORDS: Female sexual dysfunction, Flibanserin, Ospemifene

INTRODUCTION

Since ages, people have been trying their best to understand human sexuality and have been working to improve sexual experiences. Sexual dysfunctions and their remedies have been described even in ancient medical practices like Ayurveda [1]. However, human sexuality has been difficult to understand because of its complex and multi-dimensional nature. It involves biological, psychological, social and possibly spiritual dimensions of life [2]. Healthy sexual functioning is one of the indispensable keys to harmonious marital life. Poor sexual health leads to frustration, low self-esteem and affects day to day functioning of a person [3] . It was the pioneering work of Masters and Johnson that lead to beginning of behavioral/psychotherapeutic management of sexual disorders [2]. Medical management of sexual disorders had its true beginning with the advent of sildenafil, a phosphodiesterase type-5 (PDE-5) inhibitor. Sildenfil was tried in women too but it did not bring the same response as it did for males [2]. For a long time, there were no specific drugs for treatment of sexual dysfunction in females, and they could be offered either some of the psychotropics or hormonal treatment in few of the cases [2,3]. The arena is likely to change soon with advent of new drugs like flibanserin.

Nosology, classification and approach to female sexual dysfunction (FSD) has been discussed in detail

elsewhere in this publication. This article shall focus on available pharmacotherapies for treatment of sexual dysfunction in females. For the purpose of this article, the diagnostic labels Hypoactive Sexual Desire Disorder (HSDD) and Female Sexual Interest/Arousal Disorder (FSDD) shall be used interchangeably. The discussion shall focus on flibanserin, hormonal therapies, psychotropics and combination treatments.

FLIBANSERIN

Flibanserin is a 5-hydroxytryptamine 5-HT$_{1A}$ receptor agonist and 5-HT$_{2A}$ receptor antagonist, with additional moderate antagonistic$_4$ 5- HT$_{2C}$, 5-HT$_{2B}$ and dopamine D$_4$ receptors. As one can notice, it inhibits the 'anti-sexual' effects of serotonin and enhances 'pro-sexual' effect of dopamine. In total, flibanserin has a mixed mechanism of action and results in modulation of CNS neurotransmitters that leads to enhanced libido. Trials of this drug have revealed that it brings statistically and clinically significant improvement in number of satisfactory sexual events (SSE), level of desire and reduced distress [5]. The rate of serious adverse events with flibanserin is <1% [5-7]. Mean half-life of flibanserin is 11 hours and is primarily metabolized by CYP3A4 and to a minor extent by CYP2C19 [8] . Common side effects include fatigue, somnolence and syncope but most patients are likely to develop tolerance to the same. It is contraindicated in patients with hepatic failure and those taking alcohol. It is believed that combination of flibanserin with alcohol increases risk of severe hypotension and syncope [5,6,8] . The US-FDA has approved the use of flibanserin for treatment of acquired generalized HSDD in premenopausal women and the dose is 100 mg daily in the night [2].

One needs to note that the road to approval of flibanserin for use in HSDD and has been full of hurdles. There has been numerous discussion on various aspects of the drug as well as the medical condition for which it is being recommended. There have been intense discussions and controversies regarding the validity of diagnosis of HSDD, medicalization of a normal human function as sexuality, problems with needed end points, lack of clear guidelines regarding conduct of clinical trial in this arena, and finally, the concerns about true efficacy and safety of the drug itself. The drug has been in market since its approval on 18th August 2015, it is yet to pass the test of time [2,4,5,6,8].

HORMONAL THERAPIES

There is no doubt about role of hormones in sexual functioning of men and women, and it is a well-known fact that the major milestones in the sexual life of a lady viz. menarche, pregnancy and menopause are all marked by cascade of hormonal changes. Hormones not only bring about age related changes in genitalia but also modulate response to internal and external

cues. In other words, hormones have a major role to play in preparing a lady physically as well as mentally for sexual activity [9] . Despite advances in research about hormones, their receptors, synthesis, intracrine pathways, etc. there has not been any clear understanding about measurement of levels of hormones and their utility in clinical therapies [10] . It is important to note that hormonal therapies have been studied mostly in postmenopausal women and the studies of the same in premenopausal women are inadequate [11]. Few of the available hormonal treatment for FSD are reviewed here in the following section.

Hormone Replacement Therapy

Hormone replacement therapy (HRT) can be used in the form estrogen plus progesterone in postmenopausal women with intact uterus or only estrogen in women who have undergone hysterectomy [12]. This treatment is likely to bring small to moderate improvement in pain symptoms of postmenopausal women. It is more useful in women who are also suffering from other postmenopausal symptoms or when used in early postmenopausal years [13]. However, HRT has to be given only by a trained specialist either a gynecologist or endocrinologist, as per the latest recommendations and guidelines.

Tibolone

Tibolone is a synthetic steroid which has selective tissue estrogenic regulator activity. It has many metabolites and together, they possess activities of estrogen, progesterone and androgens. In addition to its use to treat postmenopausal symptoms, it has been found to increase vaginal blood flow, and has been shown to improve sexual desire and responsiveness to partner initiated sexual activity [14,15].

Androgens

Testosterone has been investigated for use in FSD mostly in postmenopausal women. While it is not recommended to use testosterone preparations for general use in FSD, it can be used in conditions where low levels of testosterone have been documented [16]. Preparations of testosterone include transdermal patches, creams and gel. They can be administered systemically or locally. Specific information regarding use of vaginal testosterone preparations are available for patients of breast cancer who are also receiving aromatase inhibitors. Use in such patients has resulted in decreased pain and improved desire [16]. Some authorities have also recommended use of testosterone preparations in addition to HRT being administered for postmenopausal symptoms [17].

Local Estrogen Therapy

Menopause may sometimes lead only to local symptoms by way of vulvo-vaginal atrophy (VVA). Local estrogen therapy (LET) is the first line treatment for the same [11]. Low dose intra-vaginal estrogen in form of ring, cream, tablet, gel

or suppository may be used. This modality has been found to reasonably safe and effective in studies done up to one year [11]. Major concern is rise in systemic estrogen levels. Recently, very low LET is also being investigated for VVA [18].

Ospemifene

Ospemifene is a selective estrogen receptor modulator, which is approved by US-FDA for systemic treatment of dyspareunia associated with postmenopausal vulvovaginal atrophy [19]. Ospemifene selectively binds to estrogen receptor (ER)-α and ER-β. It is highly selective in its action on vaginal epithelium. It has been found to be reasonably safe as far as estrogenic action on breast and endometrium is concerned. Dose of ospemifene is 60 mg/day. Relief in dyspareunia and vaginal dryness is expected by 4 weeks and generally leads to significant improvement in all domains of sexual activity by 12 weeks [19]. Overall acceptability of this drug is good among patients and drop-out rates are low [4,19,20].

PSYCHOTROPICS AND OTHER CENTRALLY ACTING AGENTS

FSD, when it is present in background of depression or other psychiatric illnesses, it is known to improve with treatment of the baseline illness. For independent FSD, there has only been a limited utility of psychotropics. Bupropion and trazodone have been tried for this purpose but the results are not encouraging [21]. Other compounds like apomorphine and investigative drugs like bremelanotide have also been tried but without any reasonable success [22].

COMBINED PHARMACOTHERAPY ON DEMAND

On demand treatment with PDE-5 inhibitors has been a huge success in males but these drugs have not yielded similar results in females. Till date, there are no approved on-demand treatments for FSD. However, research is under progress to find an answer to this problem. The combinations that have been tried are sublingual testosterone with sildenafil, and sublingual testosterone with buspirone [23,24]. Both physiological and subjective measures of sexual functioning have shown significant improvement and have paved way for future trials [23,24]. On demand treatments have their own potential benefits of avoiding concerns related to chronic pharmacotherapy. It could also pave way the way for more personalized treatment, instead of the classical 'one size fits all' approach.

CONCLUSION

Pharmacotherapy for FSD is largely an upcoming field and a lot is yet to be revealed. Experts have agreed that sexual desire is difficult to quantify, and perfect end points have yet not been discovered or

validated . At the same time, there is no escaping from the fact that unaddressed FSDs are a huge unmet need in clinical practice. While in quest of pharmacological treatment of FSD, one must not undermine the psychological aspects sexual relationships and the same must always form part and parcel of holistic care of the patient.

REFERENCES

1. Padhi MM. Male sexual disorders in Indian traditional medicine - a historical review. Anc Sci Life 1989;9 (2) : 90-4.
2. Reddy MS, Vijay MS. Pharmacological Advances in the Management of Sexual Dysfunction. Indian J Psychol Med 2017;39(3):219-22.
3. Avasthi A, Biswas P. Pharmacotherapy of sexual dysfunctions : current status. Indian J Psychiatry 2004;46(3):213-20.
4. Nappi RE, Cucinella L. Advances in pharmacotherapy for treating female sexual dysfunction. Expert Opin Pharmacother 2015;16(6):875-87.
5. Aftab A, Chen C, McBride J. Flibanserin and its discontents. Arch Womens Ment Health 2017;20(2):243-7.6. Dooley EM, Miller MK, Clayton AH. Flibanserin: From Bench to Bedside. Sex Med Rev 2017;5(4):461-9.
7. Simon JA, Kingsberg SA, Shumel B, Hanes V, Garcia M, Jr., Sand M. Efficacy and safety of flibanserin in postmenopausal women with hypoactive sexual desire disorder: results of the SNOWDROP trial. Menopause 2014;21(6):633-40.
8. Reviriego C. Flibanserin for female sexual dysfunction. Drugs Today (Barc) 2014;50(8):549-56.
9. Nappi RE, Polatti F. The use of estrogen therapy in women's sexual functioning (CME). J Sex Med 2009;6(3):603-16; quiz 18-9.
10. Pfaus JG. Pathways of sexual desire. J Sex Med 2009;6(6):1506-33.
11. Nappi RE, Davis SR. The use of hormone therapy for the maintenance of urogynecological and sexual health post WHI. Climacteric 2012;15(3):267-74.
12. De Villiers TJ, Pines A, Panay N, Gambacciani M, Archer DF, Baber RJ, et al. Updated 2013 International Menopause Society recommendations on menopausal hormone therapy and preventive strategies for midlife health. Climacteric 2013;16(3):316-37.
13. Alexander JL, Kotz K, Dennerstein L, Kutner SJ, Wallen K, Notelovitz M. The effects of postmenopausal hormone therapies on female sexual functioning: a review of double-blind, randomized controlled trials. Menopause 2004;11(6 Pt 2):749-65.
14. Biglia N, Maffei S, Lello S, Nappi

RE. Tibolone in postmenopausal women: a review based on recent randomised controlled clinical trials. Gynecol Endocrinol 2010;26(11):804-14.
15. Davis SR. The effects of tibolone on mood and libido. Menopause 2002;9(3):162-70.
16. Wierman ME, Arlt W, Basson R, Davis SR, Miller KK, Murad MH, et al. Androgen therapy in women: a reappraisal: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2014;99(10):3489-510.
17. Kingsberg S, Shifren J, Wekselman K, Rodenberg C, Koochaki P, Derogatis L. Evaluation of the clinical relevance of benefits associated with transdermal testosterone treatment in postmenopausal women with hypoactive sexual desire disorder. J Sex Med 2007;4(4 Pt 1):1001-8.
18. Bachmann G, Lobo RA, Gut R, Nachtigall L, Notelovitz M. Efficacy of low-dose estradiol vaginal tablets in the treatment of atrophic vaginitis: a randomized controlled trial. Obstet Gynecol 2008;111(1):67-76.
19. DeGregorio MW, Zerbe RL, Wurz GT. Ospemifene: a first-in-class, non-hormonal selective estrogen receptor modulator approved for the treatment of dyspareunia associated with vulvar and vaginal atrophy. Steroids 2014;90:82-93.
20. Lara L, Scalco SCP, Troncon JK, Lopes GP. A Model for the Management of Female Sexual Dysfunctions. Rev Bras Ginecol Obstet 2017;39(4):184-94.
21. Safarinejad MR, Hosseini SY, Asgari MA, Dadkhah F, Taghva A. A randomized, double-blind, placebo-controlled study of the efficacy and safety of bupropion for treating hypoactive sexual desire disorder in ovulating women. BJU Int 2010;106(6):832-9.
22. Caruso S, Agnello C, Intelisano G, Farina M, Di Mari L, Cianci A. Placebo-controlled study on efficacy and safety of daily apomorphine SL intake in premenopausal women affected by hypoactive sexual desire disorder and sexual arousal disorder. Urology 2004;63(5):955-9.
23. Poels S, Bloemers J, Van Rooij K, Goldstein I, Gerritsen J, Van Ham D, et al. Toward personalized sexual medicine (part 2): testosterone combined with a PDE5 inhibitor increases sexual satisfaction in women with HSDD and FSAD, and a low sensitive system for sexual cues. J Sex Med 2013;10(3):810-23.
24. Tuiten A, Van Honk J, Verbaten R, Laan E, Everaerd W, Stam H. Can sublingual testosterone increasesubjective and physiological measures of laboratory-induced sexual arousal? Arch Gen Psychiatry 2002;59(5):465-6.