Flibanserin: A Miracle Drug in Management of Hypoactive Sexual Desire Disorder in Female

Jeetendra Kumar Gupta[1], Ahsas Goyal[1] , Kajal Thareja[2], Bhavini Saraf[2]

[1]Assistant Professor, Pharmacology Division, [2]Scholar, Institute of Pharmaceutical Research, GLA University Mathura, Uttar Pradesh, India

Abstract

Female sensuality encircles wide range of behaviours and activities, including female sexual identity and etiquette. Many dimensions of female sexuality have been addressed by various societies and religions of the world, pertaining to biological sex, orientations and attitudes. A sufficient sexual appetite and libido in adults are essential for continuation of race. It also nurtures psychological health and immune functions. In case of hypoactive sexual desire, there will be recurrent deficiency or absence of interest and receptivity to sexual activities which causes distress and many interpersonal difficulties in fledged adult life. Flibanserin is the latest approved drug for the treatment of hypoactive sexual desire disorder in female. It generally functions on the activity and the role of neurotransmitters affecting mood and drives. Flibanserin has affinity with serotonin autoreceptor (5-HT_{1A}) and dopamine receptor (D_4). It is a full-fledged agonist of 5-HT_{1A} in prefrontal cortex region and partial agonist in the CA3 region of hippocampus. It also acts as partial agonist of dopamine receptor (D_4) but it has poor antagonist property with 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} receptors. Flibanserin declines neuronal firing rate generally in the cells of hippocampus, dorsal raphe and cortex region of brain. Hence, it can assist to improve the brain activation pattern and drives of hypoactive women.

Keywords: *Flibanserin, Hypoactive women, Autoreceptor agonist, Libido, Drive disorder.*

Introduction

Issues related to women's health are widening day-by-day. According to World Health Organization (WHO), women are more prone to hormonal imbalance, while males have a great tendency to resist the change[1]. The physiology of female is quite dependent on her cyclic menstrual and shows severe fluctuations in case of any interference with exogenous factors such as environmental toxins, poor-diet and impaired life style[2]. It can also be impeded during chemotherapy, hysterectomy and after prolonged use of xenoestrogens. Xenoestrogens are the chemicals that are found in every-day usable items, such as certain food products, cosmetics and preservatives. Excessive use of those items has dreadful tendency to imbalance many hormones, such as estrogens and progesterone[3].

Women's well-being and their unique health issues are usually related to the hormonal essence in their body. Such issues include pregnancy, menopause and ambiance of female organs. Due to the sociocultural factors, discrimination among sex is also a major cause that affects women's health and well-being. Depression, anxiety as well as hormonal misbalancing diseases are more likely to affect the women health as well as their libido[4]. Libido generally regarded as a person's drive for sexual activity. It is the force that is responsible for the intimate contact between a man and a woman but if the person loses the drive then this condition may lead to hyposexuality which is also referred as hypoactive sexual desire disorder (HSDD). Many systems of the human body are involved in sexual drive such as nervous system, vascular system, endocrine system and other structures that are auxiliary in intercourse[5]. For the modulation of women's sexual craving steroids are implicated such as testosterone and estradiol. Chief neurotransmitters

Corresponding author:
Dr. Jeetendra Kumar Gupta
Assistant Professor, Pharmacology Division
Institute of Pharmaceutical Research
GLA University Mathura, Uttar Pradesh - 281406
E-mail: jkgupta81@rediffmail.com

responsible for the regulation of libido in humans are dopamine as well as oxytocin. Stress, illness, pregnancy and many other factors collectively affect the human sex desires. Women's sexual problems are due to the mental and physiological reasons[6]. In present scenario, women are gradually loosing their drives because of their disturbed life style and ill food-drink habits. Many other factors have also been seen. Libido could also be affected due to social issues, such as work and family. It could also be disturbed due to certain medical conditions and puberty. Non-sexual diseases such as diabetes, blood pressure, neurological diseases could also affect the sex desire[7]. Hormonal alterations are the main and leading cause of loss of libido. Stunted libido can also lead to disquiets, such as dyspareunia, vaginal dryness, failure of orgasm, vaginismus and awful sex[8].

Material and Method

Flibanserin is a new drug approved by US FDA for the treatment of hypoactive sexual desire disorder in premenopausal women. Interpretation of the importance of the drug has been accomplished on the basis of existing literatures and researches. The concerned articles have been assessed through various electronic searches such as Pubmed, Scopus, Medline and Google scholar using different key words. Various inclusion and exclusion criteria such as age, gender and disease-stage have also been followed while assessing the literatures through the electronic databases.

Female Sex Hormone And Behaviour

The two major hormones which are responsible for the sexual activity in females are estrogen and progesterone but testosterone is also produced in small amount in women although it is a male sex hormone. Placenta also produces the estrogen amid the gestation period. When the stimuli reaches the brain and strikes the hypothalamic region it generates gonadotropin-releasing hormone (GnRH) at puberty and arouse the pituitary to produce Follicle stimulating hormone (FSH) and Luteinizing hormone (LH). FSH and LH are the two hormones indirectly responsible for the synthesis of estrogen (mainly estradiol) as well as androgens. The main hormone that is responsible for the maturation of follicles is FSH. When the level of estrogen gets elevated it stimulate the endometrial proliferation and leads to the deluge of LH. The LH rush is responsible for ovulation[9].

Puberty, menstruation, pregnancy as well as menopause are generally governed through estradiol. Progesterone is responsible for the preparation of uterus lining for the fertilized egg and it also supports pregnancy. Testosterone is generally produced in very small amount in females from the adrenal glands and ovaries and it is also responsible for the sexual desire, regulation of menstrual cycle as well as muscle and bone strength. An elevated levels of different sex hormones in female result in the growth of pubic and armpit hairs, breast budding, increase in stout of thighs and hips as well as maturation generally of uterus, vaginal and ovaries that may lead to the onset of menstruation[10]. If there is hormonal imbalance in the female body it may cause certain critical conditions such as polycystic ovarian syndrome (PCOS), hot flashes and many behavioural changes[11]. Hence, hormones do influence behaviour of women, especially desire and drives are copiously affected. The commonest categories of woman's sexual dysfunctions are impaired desire and orgasmic dysfunction[12].

Sexual fragility in women

There are several factors that are responsible for women's sexual response that includes contextual, personal psychological and biological factors. According to the American Psychiatric Association's Diagnostic and Statistical Manual (DSM-IV-TR) women's sexual dysfunction is usually due to the absenteeism of sexual convictions or fantasies before the sexual activity[13]. Sexual difficulties are more prevalent in women. About 40% of premenopausal women lack engrossment in sexual drives because of certain physiological, psychotic or drug induced factors[14]. The main focus of sexual dysfunctioning lies on the genital staging and lubrication to the fulfilment and resolution. Women's sexual stimulation or desire is more complicated as their fantasies and emotional contact towards this feeling is complex. A woman requires increased level of emotional intimacy while stimulating for sexual adventure and amusement. Women's sexual dysfunction may be a result of sexual response that is due to the impaired perceptions, fantasies and desires[15]contextual, personal psychological and biological factors has led to recently published recommendations for revision of definitions of women's sexual disorders found in the American Psychiatric Association's Diagnostic and Statistical Manual (DSM-IV-TR. There are many factors that affect women's sensualities and drive (Figure 1).

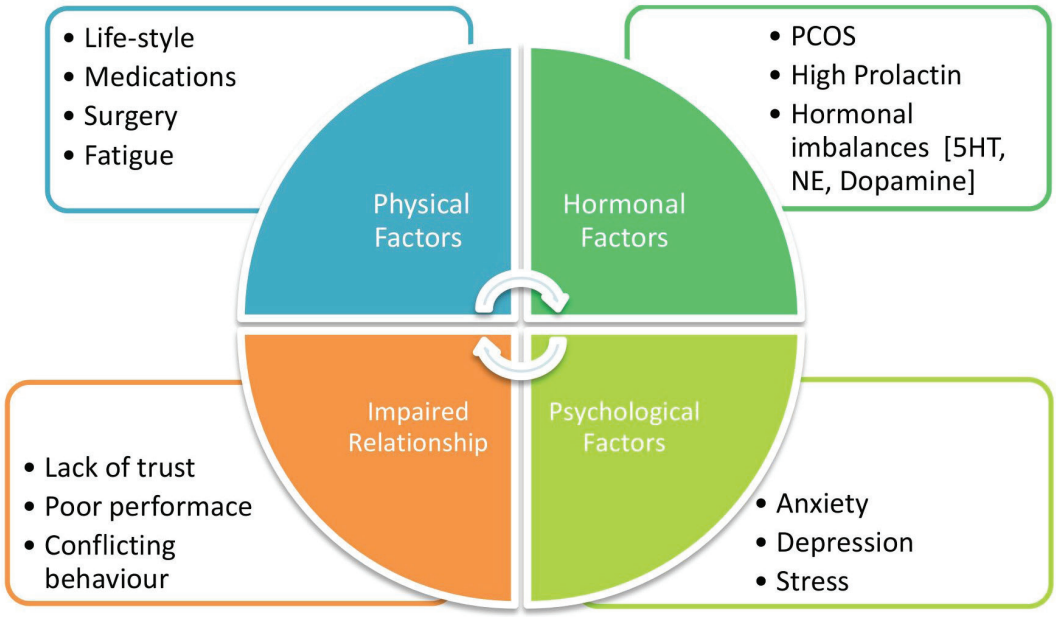

Figure 1: Factors affecting women's sensuality and drive

Impairment in the drive is also due to the elevated level of prolactin as it is seen in case of polycystic ovarian syndrome[16]. The symptoms of enhanced prolactin in premenopausal women may lead to amenorrhea and galactorrhea. Prolactin generally inhibits the Gonadotropin releasing hormone. The stimulatory effect of prolactin is on the mammary cells that results in lactation. Ingurgitation of alcohol elevates the women's sexual arousal transiently but shows negative effect after persistent use. Encephalonic arousal in the pre-frontal limbic system and amygdala elevate the feeling of love and enhances the responsiveness to ecstasy[17]with female orgasm solely from sexual intercourse often regarded as a unique feature of human sexuality. However, orgasm from sexual intercourse occurs more reliably in men than in women, likely reflecting the different types of physical stimulation men and women require for orgasm. In men, orgasms are under strong selective pressure as orgasms are coupled with ejaculation and thus contribute to male reproductive success. By contrast, women's orgasms in intercourse are highly variable and are under little selective pressure as they are not a reproductive necessity. The proximal mechanisms producing variability in women's orgasms are little understood. In 1924 Marie Bonaparte proposed that a shorter distance between a woman's clitoris and her urethral meatus (CUMD. Amygdala has dual role i.e. in sexual behaviour as well as in maternal care and extensively involved in building emotional competence, but in postpartum women amygdala is greatly responsible for maternal behaviour. Impairment in oxytocin release is also a noteworthy factor. It is an orgasmic hormone well-known by many names, such as 'trust hormone' or 'lust hormone'. Oxytocin is also responsible for inhibition of fear in amygdala. Sexual dysfunction is the common issue in the perimenopausal women. The chief reason for the sexual dysfunctioning is hormonal imbalance.

Factors Responsible For Impaired Libido

Sexual drive disorders: Disorders of sex drive are basically classified in two types namely Hypoactive sexual drive disorder (HSDD) and Sexual aversion disorder (SAD). The induction of HSDD is caused by persistently deficient sexual reveries and desires for long time due to certain emotional factors, such as persistent anxiety and depression that may cause marked interpersonal difficulty also. It is also caused by certain

physical factors like diabetes and extreme tiredness. SAD is developed as a result of persistent avoidance of all genital sexual contacts with a sexual partner due to some specific phobia[18].

Effect of medicines: Decreased level of sexual desires have been seen in case of long term medications, such as anti-hypertensive medications, anti-psychotic medications, anticoagulants, monoamine-oxidase (MAO) inhibitors, sedatives and also in case of fat lowering medicines[19].

Interpersonal and contextual factors: It includes the emotional intimacy of the women with her partner during sexual as well as the general activities. Deepening of emotional concerns are essential for intimate relationship. In case of fable relationship, boredom may happen between the partners[20].

Psychogenic factor: Psychogenic distractions affect the sexual arousal in women. Anxiety and life-style have also indubitable impact on women's drive. Psychological factors may include certain stress, guilt, worry, negative thoughts and memories of past[21].

Depression: It is the major cause of declined sexual functioning. Change in sex drive has association with depression. A study in psychosomatic medicine revealed that females who had depression are more prone to hypoactive sexual desire disorder and about one-third of premenopausal females with hypoactive sexual desire disorder are firmly associated with depression[22].

Chronic illness: Serious health issues and chronic illnesses have enormous adverse effects on biological drives. Physical and mental well-being play a significant role in libido expression and execution. Chronic diseases such as diabetes, arthritis and cardiovascular diseases have negative influence on drives and functioning[23]*Hormonal factor*: As women become older the levels of hormones such as estrogen, testosterone and progesterone decrepitude especially after menopause. Low levels of these hormones generally reflect negative impact on sex life. Reduced level indicates female sexual fragility and dysfunctions. Estradiol enhances the sexual desires, but testosterone is also responsible for the alterations in sexual desire of a woman. Low levels of estrogen leans the uterine lining and leads to decrease in sexual desire. Vaginal dryness, painful intercourse, mood swings and unstable sleep patterns are the symptoms of low estrogen. Therefore, hormonal imbalance is considered as a leading cause in reduction of sexual arousal and response[24].

Flibanserin-A Wonder Drug

Flibanserin is a N-alkylpiperazine compound chemically known as 1-(2-(4-(3-trifluoromethylphenyl) piperazin-1-yl)ethyl)benzimidazol(1H)-2-one as a P-Glycoprotein inhibitor[25]. It works as a 5-hydroxytryptamine 1A (5-HT_{1A}) agonist and 5-hydroxytryptamine 2A (5-HT_{2A}) antagonist[26]. Flibanserin behaves as all-inclusive agonist for 5-HT_{1A} receptor in the frontal cortex as well as in the raphe dorsalis, however it acts as partial agonist in the subfield of hippocampus, especially in the CA3 region. Despite much affinity with serotonergic receptors, flibanserin has weak agonistic activity on dopamine receptor (D_4) also. The upshots of flibanserin on intermediate biomolecule adenylyl cyclase are non-identical to that of buspirone which is also a well-known 5-HT_{1A} receptor agonist. Flibanserin has also been found to increase the level of norepinephrine in the prefrontal cortex region[27] (Figure 2).

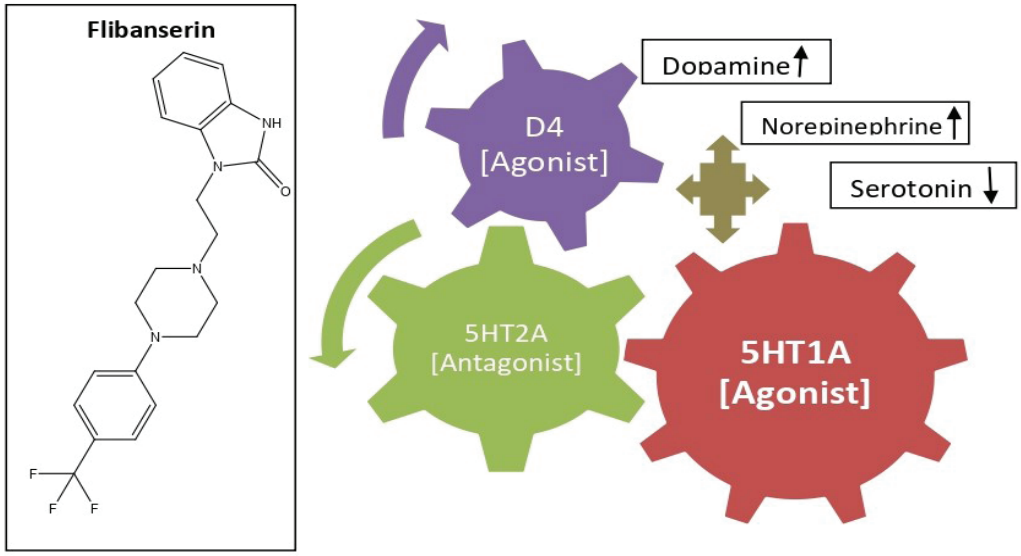

Figure 2: Flibanserin - mechanism of action

Both dopamine and norepinephrine manifest significant role in sexual excitement. The norepinephrine shows exciting role in sexual arousal while dopamine has important contribution in boosting desires. Flibanserin has very weak blocking activity on 5-HT_{2C} as well as 5-HT_{2B} receptors. It has also been reported to decrease the level of serotonin in the prefrontal cortex with long time administrations. The receptor 5-HT_{1A} acts primarily as an autoreceptor in brain and inhibits firing of 5-HT neurons from the nerve endings[28].

Flibanserin shows an absolute bioavailability of 33% from oral route. It exhibits linear pharmacokinetics from dose 100mg to 250 mg in adult healthy women and achieves maximum concentration after 45 minutes of administration. Flibanserin shows high protein binding property and extensively undergoes first-pass metabolism through hepatic isoenzymes. The endorsed dose of flibanserin is 100 mg at bed time and maximum course of medication is up to eight weeks[29]. The drug is now defined as a key drug in the treatment of female sexual interest / arousal disorder (FSAID) in premenopausal women.

Conclusion

Flibanserin is a new drug used to treat hypoactive sexual desire disorder in female and has wide link with 5-HT_{1A} autoreceptor. It has also antagonistic relations with $5HT_{2A}$, but preferentially stimulates $5HT_{1A}$ receptor and has also been found to increase the levels of dopamine and norepinephrine in the prefrontal cortex. It is generally used in the treatment of premenopausal women. Flibanserin is the first US-FDA approved drug for stimulating the female sexual desire. The drug is benzimidazole compound and generally enhances the sexual performance as well as number of satisfactory events of a month in premenopausal women. Flibanserin is available as 100mg tablet which should be taken orally once at bedtime. Bioavailability of Flibanserin is 33% and 98% of the drug shows high bound to protein mostly albumin while the half-life is of 11 hours and this drug is generally metabolized by liver enzymes. The woman who receives flibanserin experiences significant increase as compared to placebo in the frequency of sexual events. Female sexual disorder is also known by a term 'female sexual interest/arousal disorders (FSIAD)'. It includes the changes in orgasm, reduced genital and non-genital sensations. Low libido is mostly recorded sexual problem with pervasiveness of 38.7% as compared to 10% prevalence when patient feels low desire along with distress. Many agents have been discovered to treat the patient suffering from female sexual desire generally low libido. But Flibanserin is the first FDA approved drug for the treatment of low libido

or impaired sexual fantasies.

Ethical Clearance: This article has been routed through the anti-plagiarism cell of Institutional Review Board.

Conflict of Interest: The authors declare that they have no conflict of interests.

Source of Funding : Self

References

1. WHO. Women and Health Today's evidence Tomorrow's agenda. World Health Organization; 2009.
2. Regitz-Zagrosek V. Sex and gender differences in health. EMBO reports. 2012;13(7):596–603.
3. Fernandez S V, Russo J. Estrogen and xenoestrogens in breast cancer. Toxicologic pathology. 2010;38(1):110–22.
4. Jung BH, Jeon MJ, Bai SW. Hormone-dependent aging problems in women. Yonsei medical journal. 2008;49(3):345–51.
5. Davis SR, Guay AT, Shifren JL, Mazer NA. Endocrine Aspects of Female Sexual Dysfunction. The Journal of Sexual Medicine. 2004;1(1):82–86.
6. Rao TSS, Nagaraj AKM. Female sexuality. Indian journal of psychiatry. 2015;57(Suppl 2):S296-302.
7. Merghati-Khoei E, Pirak A, Yazdkhasti M, Rezasoltani P. Sexuality and elderly with chronic diseases: A review of the existing literature. Journal of research in medical sciences . 2016;21:136.
8. Montgomery KA. Sexual desire disorders. Psychiatry (Edgmont). 2008;5(6):50–5.
9. Bancroft J. Hormones and human sexual behavior. Journal of Sex & Marital Therapy. 1984;10(1):3–21.
10. Swerdloff RS, Odell WD. Hormonal mechanisms in the onset of puberty. Postgraduate medical journal. 1975;51(594):200–8.
11. Qureshi SS, Gupta JK, Shah K, Upmanyu N. Prevalence and risk factor of polycystic ovarian syndrome. Asian Journal of Pharmaceutical and Clinical Research. 2016;9(2):23–25.
12. Jaafarpour M, Khani A, Khajavikhan J, Suhrabi Z. Female sexual dysfunction: prevalence and risk factors. Journal of clinical and diagnostic research. 2013;7(12):2877–80.
13. Mitchell KR, Jones KG, Wellings K, Johnson AM, Graham CA, Datta J, Copas AJ, Bancroft J, Sonnenberg P, Macdowall W, Field N, Mercer CH. Estimating the Prevalence of Sexual Function Problems: The Impact of Morbidity Criteria. Journal of sex research. 2016;53(8):955–967.
14. Lodise NM. Female sexual dysfunction: a focus on flibanserin. International journal of women's health. 2017;9:757–767.
15. Basson R. Women's sexual dysfunction: revised and expanded definitions. CMAJ. 2005;172(10):1327–33.
16. Krysiak R, Drosdzol-Cop A, Skrzypulec-Plinta V, Okopien B. Sexual function and depressive symptoms in young women with elevated macroprolactin content: a pilot study. Endocrine. 2016;53(1):291–8.
17. Wallen K, Lloyd EA. Female sexual arousal: genital anatomy and orgasm in intercourse. Hormones and behavior. 2011;59(5):780–92.
18. Nappi RE, Gardella B. What are the challenges in prescribing pharmacotherapy for female sexual dysfunctions? Expert Opinion on Pharmacotherapy. 2019;20(7):777–779.
19. Celano CM, Freudenreich O, Fernandez-Robles C, Stern TA, Caro MA, Huffman JC. Depressogenic effects of medications: a review. Dialogues in clinical neuroscience. 2011;13(1):109–25.
20. Althof SE, Needle RB. Psychological and interpersonal dimensions of sexual function and dysfunction in women: An update. Arab journal of urology. 2013;11(3):299–304.
21. Sipski ML, Alexander CJ, Rosen RC. Physiologic parameters associated with sexual arousal in women with incomplete spinal cord injuries. Archives of physical medicine and rehabilitation. 1997;78(3):305–13.
22. Fabre LF, Smith LC. The Effect of Major Depression on Sexual Function in Women. The Journal of Sexual Medicine. 2012;9(1):231–239.
23. Basson R, Rees P, Wang R, Montejo AL, Incrocci L. Sexual Function in Chronic Illness. The Journal of Sexual Medicine. 2010;7(1):374–388.
24. Anastasiadis AG, Davis AR, Salomon L, Burchardt M, Shabsigh R. Hormonal factors in female sexual dysfunction. Current opinion in urology. 2002;12(6):503–7.

25. Vallejos X, Wu C. Flibanserin. Journal of Pharmacy Practice. 2017;30(2):256–260.
26. Dooley EM, Miller MK, Clayton AH. Flibanserin: From Bench to Bedside. Sexual Medicine Reviews. 2017;5(4):461–469.
27. Invernizzi RW, Sacchetti G, Parini S, Acconcia S, Samanin R. Flibanserin, a potential antidepressant drug, lowers 5-HT and raises dopamine and noradrenaline in the rat prefrontal cortex dialysate: role of 5-HT(1A) receptors. British journal of pharmacology. 2003;139(7):1281–8.
28. Stahl SM, Sommer B, Allers KA. Multifunctional Pharmacology of Flibanserin: Possible Mechanism of Therapeutic Action in Hypoactive Sexual Desire Disorder. The Journal of Sexual Medicine. 2011;8(1):15–27.
29. Sathyanarayana Rao TS, Andrade C. Flibanserin: Approval of a controversial drug for a controversial disorder. Indian journal of psychiatry. 2015;57(3):221–3.