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Review Article

Real World Evidence about the Efficacy of Flibanserin in Treating Premenopausal Women with Hypoactive Sexual Desire Disorder (HSDD): The Indian Scenario

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ABSTRACT

The most common form of Female Sexual Dysfunction (FSD), known as Hypoactive Sexual Desire Disorder (HSDD), is exhibited in a variety of ways. According to certain ideas, HSDD is related to neurotransmitter abnormalities of a neurological component. One of the innovations in established psychological techniques was the "off-label" use of dopaminergic substances like bupropion and testosterone. Before the FDA approved the drug flibanserin to treat the disorder, no treatments were available. Based on its antagonistic tendency to serotonin specifically created for HSDD treatment, flibanserin has gained acceptability as a nonhormonal alternative. Its use has shown some observable effects, including elevated sexual drive scores and fulfilling sexual experiences. Additionally, flibanserin has lessened FSD-related distress in premenopausal women with HSDD diagnoses as well as in a small postmenopausal group. Similar to other CNS medications, flibanserin can cause nausea, dizziness, drowsiness and in rare instances, syncope. Despite disagreements regarding its approval as an HSDD treatment, flibanserin unmistakably offers relief to FSD-afflicted women and is a crucial addition to promoting women's health.

Keywords: Flibanserin; HSDD; 5HT-1A; Female sexuality; Female sexual dysfunction

INTRODUCTION

According to the World Health Organization (WHO), women are more prone to hormonal imbalance whereas men typically resist change. Menstruation, which is cyclical and heavily influenced by external factors including environmental pollution, a poor diet and harmful lifestyle choices, has a profound impact on female physiology [1]. Women's overall health and specific health issues are usually linked to the hormonal makeup of their bodies. Among these challenges include pregnancy, menopause and the environment around female organs. Gender discrimination is a key element that adversely affects the health and well-being of women for sociocultural reasons. Depression, anxiety and hormonally unbalanced conditions are more likely to influence women's health and libido. Libido is commonly understood to be a person's desire for sexual activity. Force is what initiates intimate contact between a man and a woman. This illness, also known as Hypoactive Sexual Desire Disorder (HSDD), may result in hyposexuality if the person lacks the motivation, though. Hypoactive Sexual Desire Disorder (HSDD) is characterized by a continuous or recurrent lack of sexual thoughts and desire for sexual action that greatly impairs one's capacity to engage with others and produces significant misery. HSDD is not brought on by the use of drugs, alcohol or other substances.

Although HSDD is common in females, it is frequently neglected or not adequately treated. Numerous population-based studies have shown that between 8% and 10% of women meet the main diagnostic requirements for HSDD. Women, on the other hand, report experiencing poor sexual desire (low desire and accompanying distress) in the range of 36% to 39%. The prevalence of HSDD was 7.4% in a group of women who underwent normal medical care at 20 obstetrics and gynecology

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or primary care clinics. Because low sexual desire tends to increase with age while associated suffering tends to decrease, the frequency of HSDD is largely stable throughout adult life in women. The new drug flibanserin has been given FDA approval in the US to treat hypoactive sexual drive condition. Based on various literature reviews, an interpretation of the drug's significance has been achieved [2].

Pathophysiology of HSDD

The foundation of female desire is composed of a variety of neurotransmitters, sex hormones and a variety of psychosocial elements. Human sexual desire is associated with the limbic system and higher cortical brain areas. A key neurotransmitter in the regulation of sexual desire is dopamine. The primary dopamine source for the mesocortical and mesolimbic pathways is the Ventral Tegmental Area (VTA). The mesolimbic pathway connects the VTA to the nucleus accumbens, while the mesocortical pathway connects it to the frontal cortex.

In rats, dopamine appears to promote sexual desire, the thrill felt during sexual stimulation and the desire to carry on with sexual activity. In rats, estradiol encourages dopamine release and testosterone boosts nitric oxide production. So it would seem that steroid hormones increase the amount of dopamine that is present, creating a neurochemical environment where sexual cues are more likely to elicit a sexual response. Serotonin levels can be raised by inhibiting reuptake, such as with SSRIs and other selective serotonin reuptake inhibitors, to minimize the negative effects of dopamine on sexual function. Even though serotonergic neurotransmission may be crucial during resolution, it decreases sexual desire when it is excessive and/or prolonged [3].

Raphe nuclei in the brain send messages directly to the regions of the brain that control the sexual response *via* serotonergic pathways. Serotonin also affects the midbrain and brainstem through specific indirect pathways that originate in the prefrontal cortex. Endogenous opioids, which support the subjective experience of pleasure and reward, also regulate the impression of sexual arousal. It takes a build-up of sexual tension for natural rewards like an orgasm to achieve their maximum potential for pleasure. After an orgasmic experience, desire declines and takes some time to regain its prior level and intensity. Contrary to the motivating effects of dopamine in the expectation of reward, opiates may reduce the desire for pleasure and as a result, the orgasmic experience. Because of this, they might suppress sexual desire.

Between reactivity to partner approach and testosterone, which seems to be the main sex steroid influencing desire and may be involved in initiating sexual activity, progesterone may act as a mediator. There have been mixed findings in attempts to connect circulating testosterone levels to female sex desire. Serotonin and dopamine neurotransmitters primarily act through the hypothalamus and associated limbic areas to affect testosterone activity. In addition, low levels of bioavailable testosterone can alter sexual function, including desire, sexual receptivity and pleasure, as well as androgen insufficiency symptoms including persistent fatigue and dysphoria. Pituitary hormone prolactin has a detrimental effect on sexual function both directly and indirectly through an inverse relationship to dopamine activity. Desire is also impacted by testosterone down-regulation. Serotonin, opioids and prolactin operate as inhibitors of sexual desire, whereas dopamine, estrogen, progesterone and testosterone act as stimulants [4].

Overview about flibanserin

The medicine affects serotonergic and dopaminergic neurotransmitter systems differently. It has recently been proposed for FDA approval to treat premenopausal women's low sexual desire, however with some restrictions. According to the sexual side effects of antidepressants whose mechanisms of action are at least generally understood, flibanserin should increase sexual responsiveness. The reality is less remarkable and neither is flibanserin's efficacy, so it does not serve as an example of how knowledge is transferred from the bench to the bedside. As a nonhormonal alternative for its specified HSDD treatment, flibanserin was approved. There has been an upsurge in the use of several medications "off-label" as alternative treatments based on psychological techniques. The risk of side effects has grown due to this prescription, which is regularly given in doses that are prohibited.

The antidepressant and smoking cessation uses of bupropion hydrochloride (found in Wellbutrin, Zyban and other generic versions) have both received FDA approval. A few negative effects include hypertension, agitation, insomnia, neuropsychiatric issues, decreased appetite, weight loss and an increased risk of seizures. It is also known that testosterone increases women's desire and sexual satisfaction, perhaps because of a dopaminergic mechanism.

Increased desire and sexual satisfaction are observed in women who currently have two to three SSEs per month. However, epidemiological studies have not consistently linked serum testosterone levels or androgen metabolites to female sexual desire. While the FDA has approved a number of testosterone therapies for men, no testosterone therapies have been approved for women. They are typically administered in smaller amounts that are more suitable for female consumers [5].

Mechanism of action of flibanserin

An agonist of the 5-HT1A serotonin receptor, flibanserin also inhibits the 5-HT2A and to a lesser amount, the 5-HT2B, 2C and D4 dopamine receptors. Increased dopamine, decreased serotonin and no epinephrine are the results of these molecular receptive actions, which have an effect on reward processing and sexual integration. Based on research demonstrating that flibanserin has region-specific effects on monoamine levels in the human brain, it has been hypothesized that flibanserin increases sexual desire by decreasing serotonergic activity and increasing dopaminergic and noradrenergic activity within the prefrontal cortex.

However, it is still unknown what causes HSDD or how to treat it. It influences the cerebral cortex to directly trigger postsynaptic serotonin inhibitory responses and influences the medial prefrontal cortex of rats to antagonize postsynaptic 5-HT2A receptors. Additionally, it increases the activity of

postsynaptic 5-HT1A receptors in the hippocampus. According to certain research, male and female marmoset pair mates exhibit more sexually linked behaviors, which supports the HSDD treatment.

Pharmacokinetics

90% of the dose of flibanserin immediately enters the systemic circulation following administration, whether as a drug or a metabolite. Maximum Plasma Concentration (C_{max}) is typically reached 45 to 60 minutes after oral administration. Absolute bioavailability after oral dosing is 33%. Food has a minor impact on how quickly and how much is absorbed. Its metabolism involves CYP3A4 and to a lesser extent, CYP2D6. As a conjugated metabolite, it is excreted by the kidney and bile. To get through the terminal, it takes between 9 to 12 hours [6].

Pharmacodynamics

Flibanserin is a 5-HT2A antagonist and postsynaptic 5-HT1A agonist, according to research. Flibanserin differs from buspirone and bupropion in that they cannot bind to these receptors selectively. Flibanserin does not cause an increase in DA in the nucleus accumbens, according to acute and long-term therapy trials in rats (NAcc). Only the medial preoptic region of the hypothalamus and the medial Prefrontal Cortex (mPFC) experience an increase in its abundance. These parts of the brain work together to process rewards in ways that result in sexual reward. These connections most likely link the limbic system and the mPFC. Allers et al., observed escalations in the basal levels of DA in the mPFC and of the baseline of NE in the mPFC and NAcc in response to chronic flibanserin treatment. Treatment with long-term flibanserin had no effect on 5-HT levels in the start.

It has been proposed that the acting mechanism of flibanserin involves the normalization of CNS neurotransmitter levels (increased DA and NE, decreased 5-HT). The effects of flibanserin on these three monoamine neurotransmitters involved in sexual stimulation and inhibition have been observed as the basis for this idea. Information on dopaminergic circuits was gathered from animal research as well as from human medications that have been known to have sexual negative effects.

LITERATURE REVIEW

The literature review revealed that various research to ascertain the efficacy of flibanserin had been conducted. In numerous clinical trials, we found that flibanserin functioned better on HSD. The scientific article "flibanserin for hypoactive sexual desire disorder: Place in therapy" by Faina Gelman and Jessica Atrio examined the effect of flibanserin on HSDD. They found that flibanserin treatment for Major Depressive Disorder (MDD) led to improvements in the subjects' sexual drive and desire. This led to investigation into flibanserin's effects on HSDD.

Based on three randomized, double-blinded and placebo-controlled clinical trials including premenopausal women between the ages of 19 and 55, flibanserin was approved as a treatment for HSDD and a report was filed to the US Food and Drug Administration (US FDA). Participants in all trials received either flibanserin 100 mg once daily at bedtime or a placebo with a 78% completion rate.

The endpoint for studies 1 and 2 (strong want) was the response to "identify your most intense level of sexual desire," scoring 0 (no desire) to 3 (major sexual desire). Changes from baseline to week 24 based on this response were examined. Participants' daily responses were compiled into a 28-day total to provide a monthly score for sexual desire. The primary indicator of sexual desire used in research 3 was the Female Sexual Function Index (FSFI desire). SSEs increased statistically significantly from baseline in all three clinical studies.

George M, et al., reported on more clinical studies in "flibanserin: A serendipitous story," one of their publications. In order to evaluate the efficacy of the medication, premenopausal women who took flibanserin for twenty-four weeks took part in three significant randomized placebo-controlled clinical trials. In the first two studies, DAISY and VIOLET, it was discovered that flibanserin considerably increased the number of sexually gratifying encounters, albeit by a modest margin [7].

The FSFI, FSDS and item-13 scores are examples of secondary endpoints that also shown improvement. According to their research, the sexual desire score, which was one of the co-primary end objectives and was based on the diary score, did not reach statistical significance. This was a critical endpoint that failed to show a benefit, necessitating a third trial to demonstrate the drug's efficacy.

Another investigation by Portman JD et al., included conducting clinical trials. They concluded this project with a 24-week experiment that was randomized, double-blinded, placebo-controlled, multi-center and conducted from January 2010 to January 2011 at 95 locations in North America (the United States and Canada). NCT01057901 on clinical trials gov. After a 28-day screening period, patients were randomly assigned in a 1:1 ratio to receive once-daily 100 mg flibanserin tablets for 24 weeks or a matched placebo. According on the type of center, blocks of patients were randomly assigned (through interactive voice or web response system). Flibanserin was first administered at a dose of 50 mg once daily for 14 days and then for the remaining 14 days of the research, the dose was increased to 100 mg once a day.

DSM-IV-TR criteria said that eligible individuals had a current episode lasting longer than six months and a diagnosis of HSDD. All patients had been in stable, monogamous, heterosexual relationships for at least a year and were willing to participate in sexual activity at least once per month (oral sex, sexual intercourse, genital stimulation or masturbation). Other inclusion criteria included a minimum score of 15 on the FSDS-R and a score of 0 or 1 on item 2 (receptivity) of the sexual interest and desire inventory female at screening or baseline, indicating that sexual activity was always or almost always performed out of duty and with little to no enthusiasm. We only included naturally postmenopausal women who had at least one ovary and who reported experiencing spontaneous amenorrhea for more than 12 months straight.

Patients with a history of any psychiatric condition that might affect sexual function, those who had just started taking medication that might worsen or impair sex or those who had previously used drugs excessively within the previous 12 months were all excluded from the study.

The adverse effect of flibanserin

Flibanserin is not recommended for those with hepatic abnormalities. Alcohol and potent CYP3A4 inhibitors such birth control pills shouldn't be used together when with flibanserin. It was anticipated that the FDA's mandatory Risk Evaluation and Mitigation Strategy (REMS) program would be implemented at the time of publication. The only method to receive flibanserin is through prescription, therefore this teaches prescribers and pharmacists how to select the correct individuals for flibanserin treatment and manage the dangers, like hypotension and syncope associated to alcohol intake.

The most frequent side effects of flibanserin are nausea, dizziness, fatigue and weariness; they occur between 5% and 17% more frequently in the pharmaceutical groups than in the placebo groups (1% to 10%). The majority of these side events were mild to moderate and less than 0.8% of women experienced a serious adverse event. The researchers did not think that flibanserin was responsible for any SAEs from any trials. Flibanserin's most severe adverse effects were headaches, nausea, dizziness and sleepiness. According to the SNOWDROP trial (511.130) in postmenopausal women, the frequency range for the placebo group was 1 to 5% as opposed to 6 to 10% for each of the flibanserin groups. The study articles written by Dhanuka I and Simon A. J describe the findings of flibanserin clinical studies. Three cases of drug-related syncope were reported during phase I research, according to their publication. In all three instances, there was some sort of drug or alcohol contact.

There was one occurrence of syncope when flibanserin was combined with alcohol, a potent CYP3A4 inhibitor and either a moderate or potent CYP3A4 inhibitor. According to additional study, the interaction between CYP3A4 inhibitors, such as flibanserin and alcohol increases the risk of syncope and hypotension. In the 7096 patient phase III clinical research, 60% of women reported engaging in light to moderate drinking. In these phase III trials, the incidence of hypotension and/or syncope was quite low [8].

Users of flibanserin suffered eight occurrences of hypotension and/or syncope, compared to none in the placebo group. In a separate study termed the "alcohol challenge study," which looked at the interaction with alcohol, only two of the 25 participants were women. It demonstrated that heavy drinking increased the risk of hypotension and syncope. It's critical to keep in mind that during these "challenge" trials, participants had to consume the alcoholic equivalent of a full to a half bottle of wine on an empty stomach in 10 minutes. It's possible that differences in how men and women absorb alcohol and differences in body size are to blame for the extremely small percentage of female people who could consume that much alcohol plus the test material without vomiting. The consequences of drinking on women will be made clearer by future study. Studies show that flibanserin (up to 200 mg) taken before bed without alcohol has no effect on a person's ability to drive the next day. The negative effects of flibanserin were only slightly exacerbated by SSRIs and SNRIs. Flibanserin has been shown to be well tolerated over a long length of time (114 women were exposed for at least 18 months). Additionally, there is no evidence that flibanserin is genotoxic to humans and it is unknown whether it affects a woman's capacity to conceive [9].

DISCUSSION

Flibanserin, a cutting-edge first-in-class drug, has been authorized for the treatment of hypoactive sexual desire condition. The medication had to overcome a number of regulatory challenges before it could be approved for sale because of its subpar efficacy and questionable safety profile. We don't yet know whether the medication's long-term safety will offset its minuscule benefit in curing this sickness. The story of flibanserin, however, is yet another example of how chance events and intelligent drug development may drastically alter the course of a medical molecule [10].

CONCLUSION

The effects of flibanserin on HSDD have been demonstrated to be statistically significant even when the placebo effect is taken into consideration, which is particularly potent for many CNS medications. The primary causes of the efficacy disagreement are the use of the e-diary results in contrast to the FSFI wish domain questions and criticism of the negligible numerical increases in the number of SSEs noticed in the average subject (without accounting for "nonresponders"). The FSFI want domain inquiries, along with a significant reduction in psychological suffering, were finally persuasive enough to win FDA approval. These inquiries have been approved as a way to identify and gauge the severity of sexual dysfunction. It is important to note that the increase in SSEs per month does not take into consideration the difference between an event where the woman initially does not desire sex and perceives the interaction to be pleasant and one where she actively desires the sexual encounter to occur. The baseline SSEs should not be regarded as a measurement of a woman's desire (for emotional connection, obligation and intimacy, for example), as a woman may initiate or consent to sexual activity for a variety of reasons without desire. The association between an increase in reported desire and an increase in the frequency of SSEs is intriguing since it implies that the person is not only seeking sex more intensely but also more frequently. The positive effects on women's lives that the restoration of sexual arousal and desire may have are highlighted by patient testimonies. Despite criticism that the increase is "small," it is important to keep in mind that the goal of flibanserin is to restore a woman's sex drive to a "previous norm" that is comfortable for her rather than to intensify it to the point of hyper sexuality. This only applies to people with acquired HSDD because it is not recommended for women with lifelong HSDD to utilize flibanserin as a treatment. With the aid of an appropriate treatment strategy that suggests taking this medication before bed and makes patients aware of the potential interactions

between flibanserin and alcohol and CYP3A4 inhibitors, the risks of flibanserin, which are comparable to those of other CNS medications (such as SSRIs and SNRIs), are manageable in comparison to these significant advantages.

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