

Flibanserin: a serendipitous story

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ABSTRACT

Female sexual disorders are increasingly being recognized in the population and hypoactive sexual desire disorder (HSDD) is one of the commonest sexual disorders among females. The prevalence of the disease varies between 10-20% in the Caucasian population. Testosterone is the only treatment that is approved by the European Medical Agency. Flibanserin is a drug that has been approved by the US FDA for HSDD among pre-menopausal women in 2015. Flibanserin is a 5-HT_{1A} receptor agonist and 5-HT_{2A} receptor antagonist that rebalances the neural circuitry involved in processing sexual desire by reducing serotonin activity and enhancing dopamine and epinephrine activity. The efficacy of the drug was confirmed in three pivotal randomized placebo control trials in premenopausal women who consumed the drug for 24 weeks. There was a significant improvement in the number of sexually satisfying events. The most common safety concerns for flibanserin as seen in clinical trials were somnolence, hypotension and syncope. The drug is prescribed at a dose of 100 mg once daily at bed time. The marginal efficacy of the drug coupled with other safety concerns, such as hypo-tensions have given room for much criticism over the drug's approval by the FDA. Nevertheless, on a positive note the serendipitous discovery of flibanserin and its repurposing for HSDD is a compelling narrative in its drug development history. It remains to be seen if the long term safety of the molecule and the efficacy of the molecule in non-trial settings could make it an attractive pharmaco-therapeutic option for HSDD.

Keywords: Flibanserin, HSDD, FSFI, SSE, eDairy score

INTRODUCTION

Female sexual disorders are being increasingly recognized in the clinic and hypoactive sexual desire disorder (HSDD) is one of the common sexual disorders among females. It is described as a condition in which a woman lacks sexual drive or desire or is bereft of sexual fantasies.¹ The disorder puts a heavy toll on a person's interpersonal relationships resulting in remarkable agony.² The prevalence of this disease varies between 5 to 20% from the earlier published literature largely in the Caucasian population.³ The current treatment for HSDD includes hormonal therapies such as testosterone, estrogen and progesterone.⁴ Testosterone is associated with the development of acne and hirsutism unless given by the transdermal route. It is the only drug approved by the European Medical Agency for HSD in post-

menopausal women.⁵ In recent years much work has focussed on the development of molecules that could tilt the dopamine serotonin balance in a favourable way to improve the sexual desire of these patients. Research in this field led to the culmination of new drug getting approved for the treatment of HSDD, namely flibanserin. The development of this molecule was fraught with several hurdles and has certainly opened a Pandora's box in female sexual disorders.⁶ We seek to review the literature on flibanserin bringing to focus the mechanism of action, efficacy, safety and regulatory history of this molecule.

Mechanism of action

Flibanserin is a 5-HT_{1A} receptor agonist and 5-HT_{2A} receptor antagonist. Antagonistic activity at 5-HT_{2A}, is

mostly in the prefrontal cortex. It has been suggested that flibanserin could rebalance neural circuitry involved in processing sexual desire by reducing serotonin activity

and enhancing dopamine and epinephrine activity. Nevertheless, the exact mechanism of flibanserin in improving sexual desire is not known.⁷

Table 1: Summary of findings from phase 3 pivotal studies with flibanserin.

End points Study	Sample size	Study groups	SSE	eDiary	FSDS-R	Item13	FSFI total	FSFI Desire domain	Global access	Adverse events
Daisy Study	1581	Flibanserin 100 mg Flibanserin 50 mg Flibanserin 25 mg Placebo	Improved in 100 mg compared to other flibanserin and placebo groups.	No statistically significant increase compared to placebo	Increased in all three flibanserin groups compared to placebo	Increased in all three flibanserin groups compared to placebo	Increased in all the groups compared to placebo	Increased in all the groups compared to placebo	Increased	Somnolence dizziness fatigue
Violet Study	880	Flibanserin 50 mg Flibanserin 100mg Placebo	Increased in both flibanserin groups compared to placebo	No statistically significant increase compared to placebo	Decreased in 100mg group compared to placebo.	Decreased in 100mg compared to placebo	Increased in both flibanserin groups compared to placebo	Greater increases in both the groups compared to placebo	Increased	Nasopharyngitis somnolence dizziness insomnia head ache
Begonia study	1087	Flibanserin 100mg Placebo	Increased in flibanserin groups compared to placebo	---	Decreased in flibanserin groups compared to placebo	Decreased in flibanserin groups compared to placebo	Increased in flibanserin groups compared to placebo	Increased in flibanserin groups compared to placebo	NM	Somnolence dizziness nausea

FSDS- Female sexual distress scale, FSFI-Female sexual function index, NM- Not measured, SSE- Satisfying sexual events.

Efficacy

The efficacy of flibanserin was tested in three pivotal randomized placebo controlled clinical trials, in premenopausal women, who consumed the drug for twenty four weeks. In the first two trials abbreviated as DAISY and VIOLET, flibanserin was found to have significant improvement in the number of sexually satisfying events, albeit with a marginal magnitude.^{8,9} There was also improvement in other secondary end points such as FSFI, FSDS and item-13 scores. However the sexual desire score as assessed by eDiary score which was one of the co-primary end points did not reach statistical significance. Since this was a major end point that did not show a benefit, a third trial was mandated for demonstrating the drug efficacy. The BEGONIA trial.¹⁰ was designed in a different way as it included the FSFI desire domain as the primary end point instead of eDiary score as experts opined that the FSFI was a better indicator of the sexual desire than daily assessment. The trial did show improvement in all end points measured including the FSFI. The main criticism that has been repeatedly raised by different groups about this drug is the marginal efficacy of the drug. Although the trials were done using appropriate study designs with adequate methodological standards, there was no overwhelming benefit as anticipated. Nevertheless the fact that there are no other better pharmacological alternatives appears to have tilted the scales towards the drug getting approved in the market. Table 1 summarizes the results of the pivotal trials with flibanserin.

Safety

The most common safety concerns for flibanserin as seen in clinical trials were somnolence, hypotension and syncope. These adverse effects are accentuated in patients who take concomitant alcohol with even two drinks. These adverse events can also be expected to occur with increasing frequency in patients who consume other CYP3A4 inhibitors such as protease inhibitors, several antibiotics, and fluconazole; as flibanserin is a substrate for CYP3A4. Animal studies did show an increase in the incidence of mammary tumors in mice, nevertheless the clinical significance of this observation is unknown. Since the drug causes significant drowsiness it should be avoided in those likely to be involved in jobs that require intense concentration at least for six hours after drug intake. In lieu of the adverse effects and drug interactions with flibanserin, the drug is available only through a risk evaluation and mitigation strategy in USA.¹¹ The drug is yet to receive marketing approval from any other regulatory agency.

Pharmacokinetics

The drug is prescribed at a dose of 100 mg once daily at bed time. The median time to reach the C_{max} was between 0.75 to 4 hours. The absolute bioavailability was 33%. The drug is highly protein bound and is extensively metabolized by CYP3A4 and partly by CYP2C9. Drugs such as ketoconazole, itraconazole, grapefruit juice which are strong inhibitors of CYP3A4 can increase the concentration of flibanserin in the plasma significantly. This could result in hypotension. The same effect is also

seen when flibanserin is consumed along with alcohol. The half-life of flibanserin is approximately 11 hours.¹²

Current status and future directions

Some of the issues that need further clarity with flibanserin include its efficacy in the real world setting, the long term safety of the drug especially when more number of patients receive the drug, its utility in persons who do not have monogamous relationship. The fact that there are no other well proven time tested alternatives for the treatment of sexual disorders has given the drug the edge as it is meeting an unmet need though in miniscule fashion. The story of flibanserin is yet another example of a drug serendipitously discovered for an indication that it was not originally created for. Flibanserin was originally an anti-depressant that fared rather poorly in clinical trials with depressive illness. However the drug was found to improve the sexual health of the female participants in the study.¹³ It was this initial observation that spurred on the impetus for developing the molecule in the treatment of hypoactive sexual desire disorder. The drug has also been studied in post-menopausal women and as shown improvement in sexual desire and it increase in the number of sexually satisfying events.¹⁴ It is important that a prescriber ensures that a patient being prescribed flibanserin does not have sexual desire disorder arising out of poor relationship, drug toxicity, other medical or psychiatric illness as the drug is very unlikely to demonstrate benefit in these settings.¹⁵

CONCLUSION

Flibanserin is a novel first-in-class drug approved for the treatment of hypoactive sexual desire disorder. The drug had to overcome several regulatory hurdles before it could be approved in the market on account of its marginal efficacy and questionable safety profile. It remains to be seen if long term safety of the drug could justify its marginal benefit in this disorder. Nevertheless the story of flibanserin is another example of how serendipity and ingenious repurposing of a drug molecule could radically alter its fate during drug development.

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