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Mini review

Drug flibanserin–in hypoactive sexual desire disorder

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ABSTRACT

Hypoactive sexual desire disorder (HSDD) is a widely known type of female sexual dysfunction that could also cause emotional distress and relationship problems. Flibanserin, a benzimidazole, was being studied as a treatment for premenopausal women with hypoactive sexual desire disorder because there was no accurate drug therapy available at the time (HSDD). The US Food and Drug Administration (FDA) approved Flibanserin in 2015 for the treatment of generalised acquired HSDD in premenopausal women. It has a high affinity for postsynaptic 5-HT-1A receptors (agonist) and 5-HT-2A receptors (antagonist), and it tends to work by increasing dopamine and noradrenaline levels in the brain while decreasing serotonin levels. This review was to assess Flibanserin efficacy and safety and it is found the drug Flibanserin benefits did not outweigh the risks in premenopausal and postmenopausal women.

1. Introduction

Hypoactive sexual desire disorder was later coined from the term "inhibited sexual desire disorder" (HSDD). In the Diagnostic and Statistical Manual of Mental Disorders (DSM5), disorders of desire and arousal were integrated into one category called female sexual interest/excitement and arousal disorder (FSIAD). But, HSDD is still addressed in the literature and is an important part of FSAID.[1,2] However, The American College of Obstetricians and Gynaecologists (ACOG) recognizes HSDD as a separate entity.[3] HSDD has been identified as a distinct disorder characterized by reduced sexual fantasies and desire for sexual activity in both men and women. According to research studies, the age range was 18–56 years old, with a mean age of 36 years.[4] This causes significant distress, that can be psychological, emotional, or relationship conflict[5] and it can also occur as a side effect of a variety of medical illnesses known as secondary HSDD.[6] There was no pharmacological treatment for HSDD prior to the drug Flibanserin.[7] Fig. 1 depicts the timeline for Flibanserin approval. Only once in 2011, flibanserin was officially denied. The FDA declined to study it again until Sprout launched a political campaign, backed by the National Organization of Women, to have the FDA recognise HSDD as an unmet medical need and reopen the review of prospective medication therapy.[7,8] After the second review, FDA approved flibanserin for HSDD in August 18, 2015 making it the first medicine to be approved for this indication.[8] Flibanserin has been proven in clinical trials to cause significant improvements in several measures of sexual desire and function in both premenopausal and postmenopausal women when compared to placebo and these gains were sustained over time.[9] Studies support the use of flibanserin in postmenopausal women with HSDD, but it is not FDA approved.[10] It is not recommended for use in children or the elderly groups.[3] It is aserotonin-1A (5-HT_{1A}) agonist and serotonin-2A (5-HT_{2A}) antagonist that act by increasing levels of dopamine and noradrenaline and lowering levels of serotonin in the brain.[11] The FDA also required a risk evaluation and mitigation strategy (REMS), which requires health care providers who prescribe Addyi and pharmacies that dispense Addyi to be certified with the Addyi REMS programme, as well as patient counselling on the risk of hypotension and syncope. In addition, after approval, the FDA requested Sprout to conduct more research into the interaction of Addyi and alcohol. According to the findings, Women who drank up to two alcoholic beverages waited at least 2 h before taking Addyi had a lower risk of severe hypotension and

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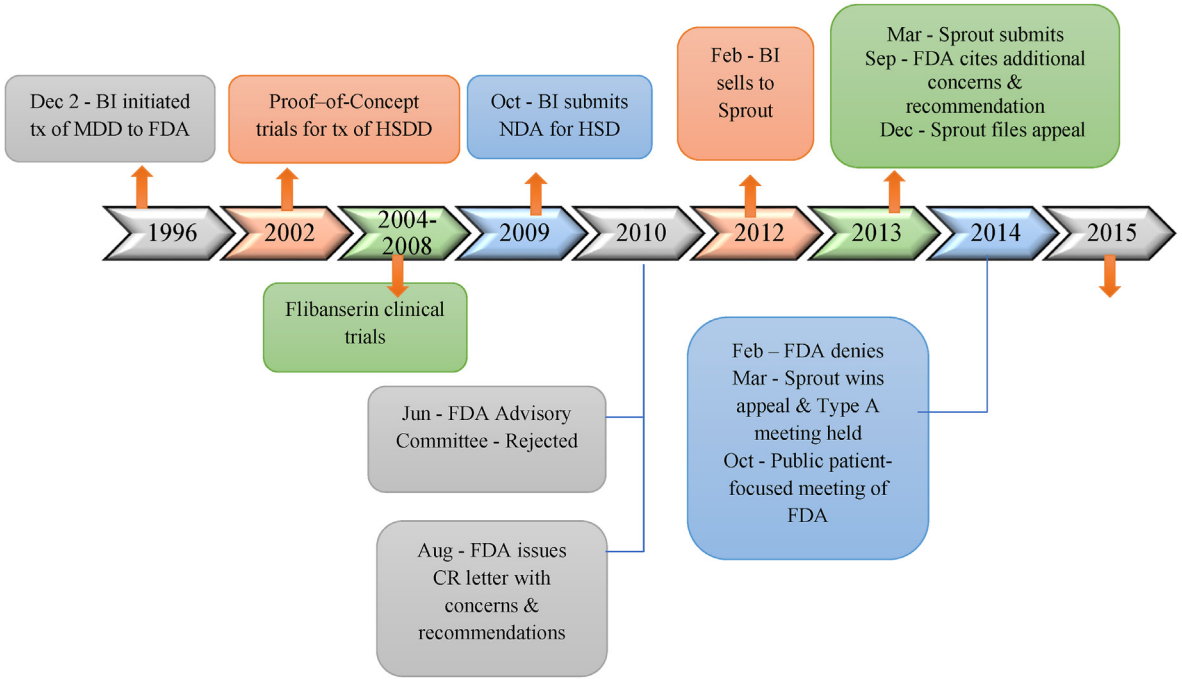

Fig. 1. Timeline to approval of flibanserin. Notes : BI: Boehringer Ingelheim; FDA: US Food and Drug Administration; tx: treatment; HSDD: hypoactive sexual desire disorder; IND: investigational new drug; MDD: major depressive disorder; NDA: new drug application; REMS: risk evaluation and mitigation strategy; CR: complete response.

syncope. The FDA deemed these findings adequate to warrant a change to the boxed warning and contraindication indicating that Addyi and alcohol should not be used together (i.e. not within 2 h).[8] The objective of this review is to assess the drug Flibanserin efficacy and safety in terms of its action, pharmacological properties, adverse effects, contraindications.

2. Flibanserin

2.1. Mechanism of action

Flibanserin is a serotonin agonist that works on 5-HT1A receptors while acting as an antagonist on 5-HT2A receptors[9,12–14] and to a less extent as antagonist of the 5-HT2B, 2C, and D4 dopamine receptors. All these molecular receptive actions induces in neurotransmitter release (increased dopamine and nor epinephrine, and decreased serotonin) that affect reward processing and sexual cue integration. It has been shown to have region-specific effects on monoamine levels in the human brain[15] and it has been proposed that flibanserin may enhance sexual desire by reducing serotonergic activity and increasing dopaminergic and noradrenergic activity within the prefrontal cortex on the basis of these findings.[13] Fig. 2 explains the mechanism of action of Flibanserin. However, the precise mechanism of action or the treatment of HSDD has yet to be determined.

In rats, it acts on cerebral cortex and directly activates postsynaptic serotonin inhibitory responses and acts on medial prefrontal cortex to antagonize postsynaptic 5-HT2A receptors. It also increases the activation of postsynaptic 5-HT1A receptors in the hippocampus. Increased sexual-related behaviours among marmoset male and female pair mates have been observed in some studies, providing support for the treatment of HSDD.[5,16,17] Underwent and Underway Clinical trials of Flibanserin are shown in Table 1.

Notes: HSDD: hypoactive sexual desire disorder.

2.2. Pharmacokinetics

Flibanserin has a 33% absolute bioavailability after oral dosage.[18] It reaches steady state concentration after 3 days. When given a single dose of 5–150 mg orally, the kinetics are linear, but when given multiple doses of 60–300 mg (total daily oral dose), the kinetics are dose proportional.[3] Flibanserin reached peak plasma concentrations within 45 min (range: 0.75–4 h). It has an approximate half-life of 11 h and 98% protein (albumin) bound. Food increases its absorption. It undergoes extensive metabolism primarily via CYP3A4 and to lesser extent by CYP2C19. Only 2 metabolites, (6, 21-dihydroxy-flibanserin-6; 21-disulfate and 6-hydroxyflibanserin-6-sulfate) achieve a plasma concentration out of 35, but

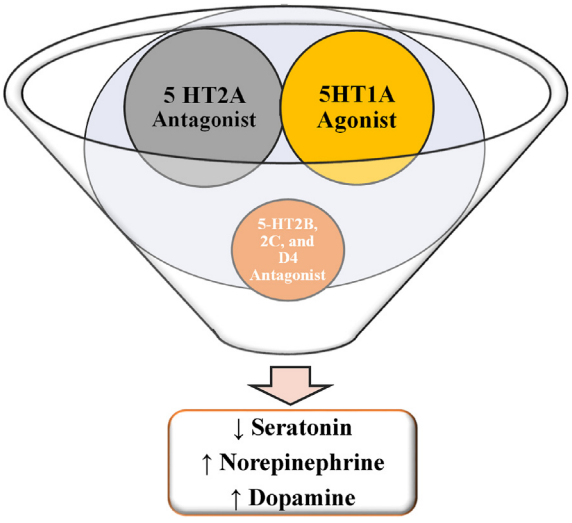

Fig. 2. Mechanism of action of Flibanserin.

Table 1
Underwent and underway clinical trials of flibanserin.

No	Study	Trial No	Location	Year	Phase	Status	Indication	Population Involved
1	DAHLIA[5,7,11]	NCT00360243	USA	2016	III	Completed	HSDD	Premenopausal
2	DAISY[5,7,11] (Thorp et al.)	NCT00360555	USA & Canada	2012	III	Completed	HSDD	Premenopausal
3	VIOLET[5,7,11] (DeRogatis et al.)	NCT00360529	USA & Canada	2012	III	Completed	HSDD	Premenopausal
4	BEGONIA[5,7,11] (Katz et al.)	NCT00996164	USA	2013	III	Completed	HSDD	Premenopausal
5	ORCHID (EU study)	NCT00491829	Europe	2014	III	Completed	HSDD	Premenopausal
6	ROSE[5,7,11] (Goldfischer et al.)	NCT00277914	USA & Canada	2011	III	Completed	HSDD	Premenopausal
7	MAGNOLIA[5,7,11]	NCT00601367	Europe	2014	III	Completed	HSDD	Premenopausal
8	SNOWDROP[5,7,11] (Simon et al.)	NCT00996372	USA	2014	III	Completed	HSDD	Postmenopausal
9	PHARMACOKINETICS OF FLIBANSERIN IN POSTMENOPAUSAL WOMEN WITH HYPOACTIVE SEXUAL DESIRE DISORDER (HSDD)	NCT01188603	USA	2010	I	Completed	Sexual Dysfunctions, Psychological	Postmenopausal
10	A STUDY OF FLIBANSERIN IN BREAST CANCER SURVIVORS ON TAMOXIFEN OR AROMATASE INHIBITORS	NCT03707340	USA	2018	–	Recruiting	Breast Cancer HSDD	Premenopausal women on Tamoxifen with early stage breast cancer and hypoactive sexual desire disorder (HSDD)
11	EFFECTS OF FLIBANSERIN ON THE PRE- AND POST-MENOPAUSAL FEMALE BRAIN	NCT02770768	USA	2016	–	Active, not recruiting	HSDD	Pre and Postmenopausal
12	PLUMERIA[5,7,11]	NCT01057901	USA & Canada	2014	III	Terminated	HSDD	Postmenopausal
13	12 Week safety trial[5,7,11]	NCT01040208	USA	2016	III	Terminated	HSDD	Premenopausal
14	SUNFLOWER[5,7,11]	NCT00441558	USA & Canada	2014	III	Terminated	HSDD	Premenopausal
15	OLEANDER[5,7,11]	NCT01103362	USA & Canada	2014	III	Terminated	HSDD	Pre and Postmenopausal
16	FLIBANSERIN (ADDYI®) VS. FLIBANSERIN AND SEX THERAPY	NCT02714049	USA	2016	IV	Terminated	HSDD	Premenopausal Women

neither is pharmacologically active. Excretion is mostly through bile and the kidney as inactive metabolites. Flibanserin is associated with an increased risk of severe hypotension, syncope and central nervous system (CNS) depression in patients with hepatic impairment. Renal impairment also increases its concentration in blood.[3,5]

2.3. Dosing

The drug is to be taken orally, with a minimum effective dose of 100 mg taken once daily at night (as it produces adverse effects in morning such as hypotension, syncope, accidental injury, and depression). If a dose is missed, it should be taken at bedtime the following day. Rather, do not double the dose. If there is no improvement after 8 weeks of treatment, the drug should be stopped.[8]

2.4. Drug interactions

Toxicity increases in poor CYP2D6 and CYP2C19 (antifungal, selective serotonin reuptake inhibitors, proton-pump inhibitors and benzodiazepines) metabolizers and decreases in CYP2C9 metabolizers.[3] The drug concentration rises when combined with moderate or strong CYP3A4 inhibitors such as fluconazole, itraconazole, ketoconazole, or grapefruit juice.[5] When combined with weak CYP3A4 inhibitors such as oral contraceptives, there is an increased risk of syncope and hypotension. Thus, Flibanserin should be discontinued more than 2 days prior to initiating such CYP3A4 inhibitors and be reinitiated 2 weeks after CYP inhibitor discontinuation. CYP3A4 inducers (eg. rifampicin, phenobarbital) decreases Flibanserin concentration and this combination is not recommended. Inhibition of P-glycoprotein by Flibanserin increases concentration of drugs transported through P-glycoprotein (eg. digoxin).[3] Its concentration rises when combined with digoxin, ethinyl estradiol, and simvastatin. However, its concentration decreases with levonorgestrel and the active metabolite of bupropion. Flibanserin pharmacokinetics is not altered by alcohol, but it does increase the risk of CNS depression, hypotension and syncope.[3,5]

2.5. Adverse drug reactions

Flibanserin is a CNS depressant which can cause somnolence and sedation. So, concomitant use with CNS depressants may increase the risk of hypotension and syncope. It is also known to cause with nausea, fatigability, insomnia and dry mouth. Doctors should advise patients taking Flibanserin not to engage in other activities or drive for 6 h after taking the medication.[3,5]

2.6. Contraindications

Flibanserin is contraindicated in patients with hepatic impairment, who use alcohol, or who are taking moderate or strong CYP3A4 inhibitors. Also not recommended during pregnancy or lactation (excreted in rat milk, but not reported in human studies).[3,5] It is not advised for postmenopausal women or men.[3,19]

2.7. Clinical trials

2.7.1. Efficacy in premenopausal women with HSDD

In three randomized, double-blinded, placebo-controlled studies of flibanserin conducted in premenopausal women with HSDD (the VIOLET, DAISY, and BEGONIA studies), treatment with flibanserin 100 mg once daily for 24 weeks was associated with an increase in satisfying sexual events (SSEs), an improvement in sexual desire as measured by the Female Sexual Function Index desire domain (FSFI-d), and a decrease in sexual distress as measured by the Female Sexual Distress Scale–Revised (FSDS-R) item 13 score. These studies characterized the safety and tolerability of flibanserin in premenopausal women with HSDD. Mean Change in Efficacy Parameters at 24 Weeks are shown in Table 2.

Two coprimary outcomes were compared in the DAISY study between placebo (n = 398) and three flibanserin arms: 25 mg twice daily (n = 396), 50 mg twice daily (n = 392), and 100 mg once daily at bedtime (n = 395). Changes in the number of SSEs and sexual desire score from baseline at 24 weeks were defined as coprimary outcomes. A daily electronic diary was used to record reports from both destinations.

Table 2
Flibanserin 100 mg in Phase 3 Clinical Trials: mean change in efficacy parameters at 24 Weeks.

	DAISY[21]		VIOLET[20]		BEGONIA[22]	
	Placebo (n = 398)	Flibanserin (n = 395)	Placebo (n = 295)	Flibanserin (n = 290)	Placebo (n = 545)	Flibanserin (n = 542)
Number of SSEs, mean (SD)	1.1 (0.2)	1.9 (0.3) (P < 0.001)	0.8 (0.2)	1.6 (0.23) P < 0.01	1.5 (4.5)	2.5 (4.6) (P < 0.001)
SFI desire domain score, mean (SE)	0.6 (0.1)	0.9 (0.1) (P < 0.001)	0.5 (0.1)	0.9 (0.1) (P < 0.001)	0.7 (0.1)	1.0 (0.1) (P < 0.001)
FSFI total score, mean (SE)	2.6 (0.3)	4.1 (0.3) (P < 0.001)	2.4 (0.4)	5.0 (0.4) (P < 0.001)	3.5 (0.3)	5.3 (0.3) (P < 0.001)
FSDS–R item 13 score[a], mean (SE)	−0.5 (0.1)	−0.7 (0.1) (P < 0.001)	−0.5 (0.1)	−0.8 (0.1) (P < 0.001)	−0.7 (0.1)	−1.0 (0.1) (P < 0.001)
FSDS–R total score, mean (SE)	−5.2 (0.5)	−7.8 (0.5) (P < 0.001)	−4.9 (0.7)	−8.9 (0.7) (P < 0.001)	−6.1 (0.6)	−9.4 (0.6) (P < 0.001)

Notes: SD: standard deviation; SE: standard error; SSEs: satisfying sexual encounters; FSFI: female sexual function index; FSDS–R: female sexual distress scale–revised.
[a] Bothered by low sexual desire.

Change in FSDS–R overall score and FSDS–R item 13 score at week 24 were secondary outcomes. Only the 100-mg flibanserin therapy increased SSEs statistically significantly (1.9 versus 1.1; P < 0.01). Sexual desire increased statistically with all dosage levels of flibanserin compared to placebo, with the highest rise reported in the 100-mg group versus placebo (0.9 versus 0.6, respectively; P < 0.0001).[21]

Patients were assigned to one of three groups: placebo (n = 295), flibanserin 50 mg (n = 295), or flibanserin 100 mg once daily at bedtime (n = 290) in the VIOLET study. Changes from baseline to week 24 were examined using the same coprimary and secondary outcomes as the DAISY experiment. An electronic diary was used to capture both coprimary endpoints. In comparison to the placebo group (mean standard error: 0.8), both the 50-mg and 100-mg flibanserin treatment groups demonstrated a statistically significant increase in SSEs (1.4, P < 0.05; 1.6, P < 0.01 respectively). When compared to placebo mean (mean standard error: 0.5), sexual desire for flibanserin 50 mg once a day (0.8; P < 0.05) and flibanserin 100 mg once a day (0.9; P < 0.0001) was considerably higher at the end of the experiment.[20]

The BEGONIA experiment investigated coprimary endpoints of change in the number of SSEs over 28 days and the Female Sexual Function Index (FSFI) score were in the. The SSEs were tracked using an electronic diary on a daily basis, while the FSFI was determined every four weeks using a two-question questionnaire in which participants rated their sexual desire on a range of 1–5. Secondary outcomes included changes in the FSFI total score, FSDS–R total score, and FSDS–R item 13 score from baseline (bothered by low sexual desire). For 24 weeks, premenopausal women were given either a placebo (n = 545) or flibanserin 100 mg (n = 542) daily at bedtime. Flibanserin increased the frequency of SSEs (2.5 versus 1.5; P 0.0001) and the FSFI score of sexual desire (5.3 versus3.5; P ≤ 0.0001) compared with placebo.[22]

2.7.2. Safetyin premenopausal women with HSDD

Dizziness was the most commonly reported adverse event in premenopausal women in phase 3 clinical studies (the VIOLET, DAISY, and BEGONIA trials). Headache, dizziness, fatigue, somnolence, and nausea were among the most common side effects recorded. Due to its antagonism of 5-HT2A, flibanserin appears to have a dose-dependent sedative effect. This impact can be mitigated, but not totally, by taking the medicine at bedtime. The DAISY trial found that the frequency of administration of flibanserin 50 mg twice daily resulted in 16.3% somnolence and 11.9% with 100 mg once daily at bedtime resulted in 11.9% somnolence. In clinical trials, 0.2% of flibanserin-treated individuals experienced hypotension or syncope, compared to less than 0.1% of placebo-treated patients.[20–22] Common adverse effects associated with flibanserin from the trials are reported in Table 3.

3. Flibanserin in postmenopausal women

The efficacy of flibanserin for postmenopausal women with HSDD was demonstrated in SNOWDROP trial.[23] This study evaluated the safety and efficacy of once-daily flibanserin 100 mg to treat naturally postmenopausal women with HSDD. In this study, flibanserin was generally safe and well tolerated, although the incidence of adverse events was generally somewhat lower in postmenopausal compared with premenopausal women.[20–22] Findings from SNOWDROP trial is shown in Table 4. But, Flibanserin is only licenced for the treatment of premenopausal women with HSDD.[8]

4. Other related drugs

Bremelanotide, a drug approved by the FDA in 2019, is another treatment for acquired, generalised HSDD (Vyleesi). Bremelanotide is an investigational cyclic heptapeptide agonist of the melanocortin-4-receptor. As an analog of the neuropeptide, a-melanocyte-stimulating hormone, bremelanotide indirectly activates dopaminergic neurons believed to be involved in regulating sexual responses such as desire and arousal.[24–26] Due to its poor oral bioavailability, it is administered through parental route which is subcutaneous injection into the abdomen

Table 4
Findings from SNOWDROP trial in postmenopausal women.

SNOWDROP TRIAL[23]	Findings
Naturally postmenopausal women with HSDD (n = 481 Placebo, n = 468 flibanserin 100 mg HS) for 24 weeks.	Mean (SE) change from baseline in FSFI score Placebo: 0.4 (0.1) flibanserin100 mg HS: 0.7 (0.1), P < 0.001 Mean (SE) change from baseline in SSEs Placebo: 0.6 (0.1) flibanserin100 mg HS: 1.0 (0.1), P = 0.004 Most common AEs: dizziness (9.9%), somnolence (8.8%), nausea (7.5%); discontinuation due to AEs: 8.1% of flibanserin treated patients

Table 3
Flibanserin 100 mg safety in Phase 3 clinical trials: frequency of adverse effects n(%).

	DAISY[21]		VIOLET[20]		BEGONIA[22]	
	Placebo (n = 398)	Flibanserin (n = 395)	Placebo (n = 295)	Flibanserin (n = 290)	Placebo (n = 545)	Flibanserin (n = 542)
Any AE	234 (58.8)	274 (69.4)	175 (59.3)	193 (66.6)	275 (50.5)	337 (62.2)
Somnolence	14 (3.5)	47 (11.9)	9 (3.1)	32 (11.0)	19 (3.5)	78 (14.4)
Dizziness	8 (2.0)	48 (12.2)	5 (1.7)	26 (9.0)	6 (1.1)	56 (10.3)
Nausea	16 (4.0)	47 (11.9)	12 (4.1)	33 (11.4)	12 (2.2)	41 (7.6)
Fatigue	27 (6.8)	38 (9.6)	8 (2.7)	18 (6.2)	18 (3.3)	31 (5.7)
URTI	20 (5.0)	25 (6.3)	15 (5.1)	13 (4.5)	13 (2.4)	28 (5.2)

AE: adverse effect ; URTI : upper respiratory tract infection.

or thigh. It has no drug-drug interactions and has no adverse effects when combined with alcohol, unlike flibansern. We cannot say it is superior to flibanserin, as there have not been any studies comparing these two drugs.[27]

5. Conclusion

HSDD is a common but underdiagnosed illness that can be effectively controlled by physicians with proper examination and personalised treatment. Flibanserin is the first medicine of its kind to be approved for the treatment of FSIAD in premenopausal women. Flibanserin has shown modest efficacy in improving SSEs and FSFI sexual desire ratings in clinical trials. Dueto lack of therapy options for HSDD available to women, it is preferable if it is used by well educated women who are aware of the potential side effects and drug interactions. To sum it all up, flibanserin provides some progress, however limited, as a treatment option that may enhance sexual function and outcomes for some women.

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Declaration of competing interest

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