EDITORIAL

Flibanserin: Approval of a controversial drug for a controversial disorder

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Flibanserin (BIMT 17; Addyi; Sprout Pharmaceuticals, North Carolina, USA) is an agonist at postsynaptic (but not presynaptic) serotonin (5HT) 5HT1a receptors and an antagonist at 5HT2 receptors; the binding appears preferential for prefrontal cortex (PFC) pyramidal neurons that regulate monoamine release. Thus, flibanserin dosing results in increased release of dopamine (DA) and norepinephrine (NE) in the PFC. Flibanserin is also associated with decreased release of 5HT in the PFC, nucleus accumbens, and hypothalamus, but not hippocampus. Whereas DA and NE putatively increase sexual desire and arousal and 5HT inhibits sexual desire and arousal, this pharmacodynamic profile may explain the suggested benefits of the drug in women with hypoactive sexual desire disorder (HSDD). Weak and probably nonsignificant actions of flibanserin include antagonism at 5HT2b, 5HT2c, and D4 receptor sites.[1,2]

Flibanserin was originally developed as an antidepressant[3] with a potentially rapid onset of action;[4] it was effective in some but not all animal models of depression.[5] Phase 2 randomized controlled trials (RCTs) failed to find it effective against depression; however, interestingly, the drug outperformed placebo on responses to the question "how strong is your sex drive."[3]

On September 22, 2015, only 76 hits emerged in a PubMed search with the key word flibanserin, and only 9 hits emerged with the clinical trial search filter applied. The failed antidepressant data are unavailable in PubMed and presumably remain unpublished, but the sexual function findings have been released. Kennedy[6] examined data from 4 RCTs of flibanserin (100–200 mg/day) in men (n = 369) and women (n = 523) with major depressive disorder. All RCTs had an active comparison treatment arm, and two RCTs were additionally placebo-controlled. Patients in the RCTs had been assessed using the Arizona Sexual Experiences Scale and the Hamilton Depression Rating Scale (HAM-D) genital symptoms item.

In general, it appeared that flibanserin was associated with low or placebo-level risk of treatment-emergent sexual dysfunction. In one RCT, reported improvement in sexual functioning in women with baseline sexual dysfunction was 70% versus 30% for flibanserin versus placebo groups. In another RCT, flibanserin was associated with significantly greater improvement on the genital symptoms HAM-D item at weeks 4, 6, and 8. In the other RCTs, outcomes related to sexual functioning were inconsistent.[6] Thus, there seemed to be a weak signal suggesting that flibanserin carries benefits for sexual functioning in women with depression.

Four important RCTs and two long-term studies have now been published on the use of flibanserin for HSDD. HSDD is characterized by low sexual desire as a result of which the individual experiences distress or interpersonal difficulty. The condition is not diagnosed if the low desire is due to medications, substances of abuse, a co-existing medical or psychiatric condition, or relationship problems. HSDD is considered to be acquired when it arises in an individual who had normal sexual desire earlier; it is considered generalized when it is not specific to a type of sexual activity, a situation, or a partner.[7]

The four RCTs, with a somewhat sexist slant, were named after flowers: DAISY,[8] VIOLET,[9] BEGONIA,[10] and SNOWDROP.[11] All RCTs were 24 weeks studies, conducted in women with premenopausal HSDD. The mean age of the women was about 36 years, and the mean duration of HSDD was about 5 years. All women in these studies were generally healthy, and so the findings of safety and efficacy cannot be generalized to women with medical and neuropsychiatric conditions, especially those receiving psychotropic drugs. The major outcomes were assessed in the last 4 weeks of treatment relative to baseline.

DAISY compared flibanserin 25 mg twice daily (n = 396), 50 mg twice daily (n = 392), and 100 mg once nightly (n = 395) with placebo (n = 398). Only the 100 mg nightly dose outperformed placebo for satisfying sexual events. Flibanserin did not increase daily diary desire scores (the primary outcome) in any group. All flibanserin groups outperformed placebo in secondary outcome assessments of desire, and distress related to sexual functioning. Among women in the group receiving 100 mg/day, about 46% considered that their HSDD had improved with treatment; this figure was only 30% with placebo.[8]

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VIOLET compared flibanserin 50 mg (n = 295) and 100 mg (n = 290) with placebo (n = 295); treatments were administered at night. Both doses increased satisfying sexual events relative to placebo. Daily diary desire ratings did not differ between groups. Secondary outcomes measuring desire, and distress related to sexual functioning, both improved significantly more in both flibanserin groups than with placebo. Improvement in HSDD was reported by 40%, 50%, and 30% of women, respectively, in the 50 mg/day, 100 mg/day, and placebo groups.[9]

BEGONIA compared flibanserin 100 mg/day (n = 542) with placebo (n = 545). Flibanserin outperformed placebo for satisfying sexual events, sexual desire, and distress related to sexual dysfunction.[10] Similar findings were obtained in the largely similar SNOWDROP RCT.[11] Meaningful benefit was reported by 38% versus 28% of women in flibanserin versus placebo groups, respectively.

Long-term safety and efficacy data on flibanserin are also available. Goldfischer *et al.*,[12] treated 738 HSDD women with open-label, flexibly-dosed flibanserin (50 or 100 mg/day) for 24 weeks. Women were subsequently randomized to flibanserin (n = 163) or placebo (n = 170) if, in the last 4 weeks, relative to baseline, they showed at least 2 additional satisfying sexual events and/or at least 4 days during which they had more than "no" sexual desire. After 24 weeks of treatment, flibanserin outperformed placebo on several outcomes related to desire, satisfying sexual encounters, sexual functioning, and sexual distress.

Jayne *et al*.[13] described a 52 weeks open-label extension study of flibanserin (50 or 100 mg/day) in 1723 HSDD women who had completed a flibanserin RCT. At the end of the study, 42% of women who were baseline Female Sexual Function Index (FSFI) nonremitters entered remission; and the proportion of baseline FSFI remitters in remission increased from 83% at week 4 to a plateau of around 90%. However, only 962 (56%) women completed the extension study; adverse events led to drop out in 185 (10.7%) women. Of those who completed, 883 received a dose of 100 mg nightly for at least 180 days. Adverse events reported included somnolence (15.8%), sedation (1.6%), fatigue (7.6%), dizziness (6.9%), nausea (6.3%), and vomiting (1.4%).

The new data on flibanserin were summarized at the USA Food and Drug Administration (FDA) website. The flibanserin data for HSDD had twice been presented to the FDA, and the application for approval was rejected both times on the grounds that the risk-benefit ratio was unfavorable.[3] On August 18, 2015, however, after reviewing additional data, the FDA approved flibanserin for acquired, generalized HSDD in premenopausal women with the caveat that the drug be dispensed through a special risk management program. No other treatment has been approved for this indication.[7]

The risk management program was recommended because flibanserin can cause hypotension and syncope, the risk of which is increased by alcohol and by concurrent liver disease or CYP3A4 inhibitor drugs that increase flibanserin levels. Women who take flibanserin are required to abstain from alcohol, and their ability to abstain must be evaluated by the physician who prescribes the drug.[7]

The FDA summary noted that flibanserin 100 mg nightly was examined in three 24-week, placebo-controlled RCTs. Altogether, about 2400 premenopausal women with acquired, generalized HSDD participated in the trials. The findings were statistically significant in favor of flibanserin but were clinically unimpressive. For example, relative to placebo, flibanserin increased the number of satisfying sexual events by 0.5–1.0 per month. The drug increased sexual desire during the preceding 4 weeks by 0.3–0.4 points (on a 1.2–6.0 point scale). It decreased distress related to low sexual desire by 0.3–0.4 points (on a 0–4 point scale).[7] Across the three RCTs, the benefits associated with treatment were considered meaningful in only 10% more women who received flibanserin than those who received placebo. Flibanserin had no effect on sexual performance.

The FDA has also received data from an additional study on flibanserin and its interaction with alcohol; and from a study on the lack of impairment on next-day driving.[3]

The controversy regarding the flibanserin approval has arisen for several reasons, and these are briefly considered below:

- Does HSDD exist? An argument can be made that diminished sexual desire may be a normal variation, even if it is acquired. The counter-argument is that something is not normal merely because it is common; so, if HSDD produces distress or dysfunction, then attempts to treat it are justified at least to reduce the associated distress and dysfunction. As an analogy, being short is not abnormal; yet, women seek to appear taller by wearing high heels, something that can also be associated with adverse health effects (as might drugs).
- If HSDD exists, is drug treatment the right way forward? The argument here is that greater emotional and physical intimacy, more foreplay, and perhaps psychosexual interventions may bring about improvement in sexual desire and functioning. The counter-argument is that emotional support and psychotherapy helps depression, but this does not mean that antidepressant drugs are unnecessary. In addition, the argument for greater intimacy and foreplay implies that the partner is failing in some regards, yet nobody suggests that drug treatments are inappropriate for erectile dysfunction with the implication that the partner is somehow responsible.

- Does flibanserin have a sufficiently favorable risk-benefit profile to justify its approval? The FDA considered the risk of hypotension and syncope sufficiently great to prohibit concurrent alcohol use, something that may not be easy for women in developed countries; requiring the marketing of flibanserin through a risk management system is an added difficulty. In the face of these disadvantages, the very small advantages (over placebo) associated with the drug hardly seem to justify its approval. A counter-argument is that as with depression and anxiety, two conditions in which there is a large placebo effect, patients experience combined drug plus placebo effects when they are treated in real life situations; so, the net effect may be greater than merely marginal.
- Was the switch in primary endpoint an approvable step? In the initial studies, the primary endpoint was desire as rated daily in an eDiary; flibanserin proved to be no better than placebo on this outcome. The primary endpoint was then switched to desire as rated on the FSFI desire subscale, examining the 4-week recall of frequency and intensity of desire.[3]
- Women's group advocacy seemed to have contributed to the FDA decision; with over 20 treatments and formulations available for male sexual dysfunction, it could have been seen to be discriminatory to deny the approval of a treatment for female sexual dysfunction.[3]

We, the authors of this article, do not take a stand either for or against either the disorder or the drug. Our reasons are simple: The arguments for and against are cogent, depend on perspective, and prevent dichotomous decision-making. There is perhaps some good and some bad; gray exists between black and white, and this fact of life must be appreciated here and elsewhere. One hopes that the step taken by the FDA will truly improve the lives of premenopausal women with acquired, generalized HSDD; time will tell. Whether the findings can be generalized to other women with HSDD remains to be established.

A concluding note: Flibanserin is dosed once nightly; thus, if blood pressure falls, the peak effect will occur during sleep, when it will not result in a clinical adverse event. A therapeutic trial with flibanserin should not exceed 8 weeks; it is pointless to continue the drug if benefits are not observed within this time frame.

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Access this article online	
Website: www.indianjpsychiatry.org	Quick Response Code
DOI: 10.4103/0019-5545.166630	

How to cite this article: Sathyanarayana Rao TS, Andrade C. Flibanserin: Approval of a controversial drug for a controversial disorder. Indian J Psychiatry 2015;57:221-3.