Flibanserin for hypoactive sexual desire disorder in premenopausal women

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Flibanserin has shown moderate efficacy in improving low sexual desire, however, it is contraindicated with alcohol use

Flibanserin, FDA-approved in August 2015, is the first medication approved to treat acquired, generalized hypoactive sexual desire disorder (HSDD) in premenopausal women (***Table 1***). In clinical trials,[1-4] the drug has shown modest efficacy in improving symptoms of low sexual desire (number of satisfying sexual events [SSEs], sexual desire, and overall sexual function). Flibanserin is *not* indicated to enhance sexual performance, for HSDD in postmenopausal women, or in men.

Clinical implications

Flibanserin could help premenopausal women who have distressing low sexual desire, which must be acquired and generalized:

- "Acquired low sexual desire" means that a patient had an adequate sexual desire that decreased or ceased for an unknown reason.
- "Generalized low sexual desire" means that lack of sexual desire occurs all the time and in all situations, not only with a certain partner or in some situations.

Women taking flibanserin could experience gradually increased sexual desire, increase in SSEs, and decrease of sexual distress. Flibanserin is indicated for long-term use; however, it should be discontinued after 8 weeks if the patient does not report any improvement in symptoms.

The number needed to treat with flibanserin likely would be rather large, but it is not available because of complex outcome measures in clinical trials. Flibanserin was not approved at 2 previous FDA committee hearings—mainly because of safety issues but also because of concerns about efficacy. For example, during the 2013 FDA hearing, the results presented showed statistically significant, but numerically small, treatment differences at 24 weeks compared with placebo. In an FDA responder analysis of the Phase-III trials, after accounting for the placebo effect, approximately 8% to 13% women were at least "much improved" on at least 1 of the primary outcomes.[5]

Flibanserin is not indicated for women whose low sexual desire is due to (1) coexisting medical or psychiatric condition, (2) effects of medication or substance abuse, or (3) a relationship problem. It is unknown whether supplemental treatment would help these patients; however, it seems reasonable that combining flibanserin with psychosocial

Table 1

Fast facts about flibanserin

Brand name: Addyi
Indication: Hypoactive sexual desire disorder
Approval date: August 2015
Availability date: October 2015
Manufacturer: Sprout Pharmaceuticals
Dosing forms: 100 mg tablets
Recommended dosage: 100 mg at bedtime

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Disclosure

The author reports no financial relationships with any company whose products are mentioned in this article or with manufacturers of competing products.

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treatment, such as sex therapy or individual therapy, could be beneficial because it may be difficult to disentangle sexual dysfunction and relationship issues—2 problems that often are interwoven.

How it works

Flibanserin is a serotonin 1A receptor agonist and serotonin 2A receptor antagonist. In vitro, flibanserin demonstrated high affinity for the following 5-HT receptors:

- agonist activity at 5-HT1A
- antagonist activity at 5-HT2A, mostly in the prefrontal cortex.

Flibanserin also has moderate antagonist activities at the 5-HT2B, 5-HT2C, and dopamine D4 receptors. Flibanserin presumably acts centrally in the CNS; 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. The exact mechanism of how flibanserin improves sexual desire in women is unknown.

Pharmacokinetics

Flibanserin has a mean termination half-life of approximately 11 hours. It is administered once a day (50 to 100 mg) at bedtime. Steady state in healthy women was achieved after 3 days. Based on clinical observations, onset of action seems to be gradual and reaches maximum efficacy in approximately 8 weeks. Patients should discontinue the drug if no improvement is reported after 8 weeks. Flibanserin is readily absorbed from the gastrointestinal tract; however, food slows its absorption. The drug is 98% protein (mostly albumin)-bound.

Flibanserin is primarily metabolized in the liver by cytochrome P450 (CYP) 3A4 and to a lesser extent by CYP2C19. Co-administration of moderate (diltiazem, erythromycin, fluconazole, fosamprenavir, verapamil) or strong (eg, ketoconazole, clarithromycin, nefazodone, ritonavir) CYP3A4 inhibitors increases the concentration of flibanserin. This could lead to severe hypotension and syncope; therefore, co-administering flibanserin with a strong CYP3A4 inhibitor is contraindicated. Grapefruit juice is a moderate inhibitor of CYP3A4, and in a study of 26 healthy females, 240 mL of grapefruit juice increased flibanserin concentration 1.4-fold. Flibanserin is excreted though urine and feces. Flibanserin should be taken once a day at bedtime because of sedation, somnolence, and possible syncope.

Efficacy

The efficacy of flibanserin for treating HSDD was established in three 24-week, randomized, double-blind, placebo-controlled studies (***Table 2, page 62***). The target population in these studies was premenopausal women (mean age 36; range, 19 to 55) with acquired HSDD lasting at least 6 months (mean duration, approximately 5 years). The 3 studies included 1,187 women who received flibanserin, 100 mg at bedtime, and 1,188 women who received placebo. Participants were mostly white (88.6%), and included black (9.6%) and Asian (1.5%) women. The completion rates were 69% for flibanserin and 78% for placebo. Some of the trials included arms with a lower dosage of flibanserin (25 mg and 50 mg), which are not included in this analysis.

As noted in the package insert, these trials each had 2 co-primary efficacy endpoints, SSEs and sexual desire:

- change from baseline to Week 24 in the number of monthly SSEs (ie, sexual intercourse, oral sex, masturbation, or genital stimulation by the partner)
- change in sexual desire from baseline to 24-week endpoint.

In Study 1 and 2, change in sexual desire from baseline to Week 24 was measured daily by using an electronic diary. Every day, patients rated their sexual desire level by answering the question, "Indicate your most intense level of sexual desire" from 0 (no desire) to 3 (strong desire). These responses

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Table 2

Results of clinical trials evaluating efficacy of flibanserin

	Study 1		Study 2		Study 3	
	Flibanserin (n = 280)	Placebo (n = 290)	Flibanserin (n = 365)	Placebo (n = 372)	Flibanserin (n = 532)	Placebo (n = 536)
Number of satisfying sexual events (per 28 days)						
Baseline (mean)	3.0	2.7	2.6	2.7	2.5	2.7
Change from baseline (mean)	1.6	0.8	1.8	1.1	2.5	1.5
Treatment difference (95% CI)	0.9 (0.3-1.4)		0.6 (–0.03-1.2)		1.0 (0.4-1.5)	
Electronic diary sexual desire						
Baseline (mean)	12.9	11.8	12.1	10.2	Not used	Not used
Change from baseline at week 24 (mean)	9.1	6.9	8.3	6.7		
Treatment difference (95% CI)	2.3 (–0.1-4.7)		1.7 (–0.5-4.0)			
FSFI Desire domain						
Baseline (Mean)	1.9	1.9	1.8	1.8	1.9	1.9
Change from baseline at Week 24 (mean)	0.9	0.5	0.9	0.5	1.0	0.7
Treatment difference (95% CI)	0.4 (0.2-0.5)		0.3 (0.2-0.5)		0.3 (0.2-0.4)	

FSFI: Female Sexual Function Index

Source: Addyi [package insert]. Raleigh, NC: Sprout Pharmaceuticals; 2015

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Flibanserin is contraindicated in patients using alcohol because of an increased risk of hypotension and syncope

were totaled over a 28-day period to yield the monthly sexual desire score, which ranged from 0 to 84. These 2 studies also used the Female Sexual Function Index (FSFI) Desire domain as a secondary endpoint.

Study 3 used the FSFI Desire domain, comprising 2 questions, as the sexual desire co-primary endpoint:

- "Over the past 4 weeks, how often did you feel sexual desire or interest?" Responses ranged from 1 (almost never or never) to 5 (almost always or always).
- "Over the past 4 weeks, how would you rate your level (degree) of sexual desire or interest?" Responses ranged from 1 (very low or none at all) to 5 (very high).

In all 3 trials, flibanserin was associated with a small, yet statistically significant, improvement in change in monthly SSEs from baseline to Week 24 compared with placebo. In Study 1 and 2, there were no statistically significant differences between flibanserin and placebo for the electronic diary sexual desire endpoint. In the third study, there was statistically significant improvement in the change in sexual desire using the FSFI Desire domain with flibanserin compared with placebo. The FSFI Desire domain findings were consistent across all 3 trials. Flibanserin was associated with a decrease in sexual distress compared with placebo in all 3 studies.

Tolerability

Flibanserin was well tolerated in the 3 clinical trials. As the FDA noted, clinical trials are conducted under widely varying condi-

tions and therefore adverse reaction rates observed in trials of flibanserin cannot be directly compared with those reported in clinical trials of another drug and might not reflect rates observed in clinical practice.

The discontinuation rate due to adverse reactions was 13% among patients treated with flibanserin, 100 mg at bedtime, and 6% among those taking placebo. The most common side effects were somnolence, dizziness, fatigue, nausea, insomnia, and dry mouth, which appear dose-dependent. Onset of most of these adverse events was within 14 days after the start of treatment.

Although hypotension and syncope rarely were seen with flibanserin alone in clinical trials, these adverse events occurred more frequently in the morning and when taken with alcohol and with some drugs (moderate or strong CYP3A4 inhibitors), and in patients with hepatic impairment. Therefore, women who drink alcohol or take a moderate or strong inhibitor of CYP3A4—both of which are contraindicated—and those with hepatic impairment should not take flibanserin.

Flibanserin should be taken at bedtime, because the risk of hypotension and syncope is higher when flibanserin is taken in the morning and because of associated sedation and somnolence.

Unique clinical issues

Flibanserin is the first FDA-approved medication for treating HSDD. It is important to note that the drug originally was developed as an antidepressant, but failed to show efficacy. Researchers noted that the drug was more effective than placebo when patients were asked, "How strong is your sexual desire?" The focus of development then shifted to a potential treatment of HSDD.

Flibanserin was not approved at 2 previous FDA hearings, mainly because of safety concerns. For the second hearing, the manufacturer, Boehringer Ingelheim, which sold the rights to the drug to Sprout Pharmaceuticals in 2011,[6] did not present any new efficacy data, but provided additional safety data, such as research suggesting the absence of next-day driving impairment and data related to alcohol use (the study confirming hypotension associated with alcohol abuse used a small sample, and only 2 of 25 participants were women).

Contraindications

Flibanserin is contraindicated in patients using alcohol because of an increased risk of hypotension and syncope. A patient's alcohol use should be evaluated before administering flibanserin, and patients should be counseled about the importance of abstaining from alcohol.

Similarly, concomitant use of flibanserin with a moderate or strong inhibitor of CYP3A4 increases the concentration of flibanserin and raises the risk of hypotension and syncope. Therefore, the use of a moderate or strong inhibitor of CYP3A4 in patients taking flibanserin is contraindicated. Similarly, patients with liver impairment should not take this drug.

Strong CYP2C19 inhibitors (proton-pump inhibitors, selective serotonin reuptake inhibitors, benzodiazepines, antifungals) could increase flibanserin exposure, which may increase risk of hypotension, syncope, and CNS depression. Discuss these risks with your patients; doing so is particularly important when treating women of Chinese heritage and some other Asian women, because 20% of these populations are genotypic CYP2C19 poor metabolizers.

Because of the increased risk of hypotension and syncope with alcohol use, flibanserin is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Addyi REMS Program. Flibanserin can be prescribed or dispensed only by physicians and pharmacists who watch this program's online slide presentation and pass a comprehension test.[a]

[a]Information about Addyi REMS and a list of qualified pharmacies are available at www.AddyiREMS.com or by calling 844-746-5745.

continued

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Flibanserin was associated with a small, yet statistically significant, improvement in monthly satisfying sexual events

Pregnant women should not take flibanserin because the effect on the fetus is unknown. Also, because the interaction with some oral contraceptives is unknown, patients should be cautioned about unwanted pregnancy. Women who are breastfeeding also should avoid using flibanserin because it is not known whether the drug is excreted in breast milk.

Women taking flibanserin also should avoid grapefruit juice, which increases flibanserin levels, and avoid using herbal products, resveratrol, and some over-the-counter drugs such as cimetidine. Women who have a depressive disorder also should avoid using flibanserin because their low sexual desire is more likely due to depression, which is not a therapeutic target for the drug.

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Length of treatment has not been determined, but patients should stop flibanserin if they do not experience any benefit after 8 weeks

Dosing

Flibanserin is provided in 100-mg film-coated tablets. It should be taken once a day at bedtime; titration is unnecessary. Length of treatment has not been determined, but it is recommended that patients stop flibanserin if they do not experience any benefit after 8 weeks. Although there is no guidance in the prescribing information, the medication probably could be stopped without tapering because withdrawal effects have not been observed.

Related Resources

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Drug Brand Names

Cimetidine • Tagamet
Clarithromycin • Biaxin
Diltiazem • Cardizem
Erythromycin • E-Mycin
Flibanserin • Addyi
Fluconazole • Diflucan
Fosamprenavir • Lexiva
Ketoconazole • Nizoral
Nefazodone • Serzone
Ritonavir • Norvir
Verapamil • Isoptin

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Bottom Line

Flibanserin is FDA-approved for treating generalized, acquired hypoactive sexual desire disorder in premenopausal women. In clinical trials, the drug increased the number of satisfying sexual events and sexual desire, as measured by a diary and rating scales. Alcohol use and use of any moderate or strong inhibitor of cytochrome P450 3A4 are contraindicated in patients taking flibanserin because of an increased risk of hypotension and syncope.