JMM
pISSN: 2288-6478, eISSN: 2288-6761
http://dx.doi.org/10.6118/jmm.2016.22.1.9
Journal of Menopausal Medicine 2016;22:9-13

Review Article

Flibanserin for Treating Hypoactive Sexual Desire Disorder

Jae Hong Sang[1], Tae-Hee Kim[2], Soo Ah Kim[3]

[1]Department of Obstetrics and Gynecology, Soonchunhyang University Gumi Hospital, Soonchunhyang University College of Medicine, Gumi, [2]Department of Obstetrics and Gynecology, Soonchunhyang University College of Medicine, Bucheon, [3]Department of Obstetrics and Gynecology, School of Medicine, Chosun University, Gwangju, Korea

There have been several products developed for male sexual dysfunction. However, developing agents for female sexual dysfunction is lagging behind for various reasons. Sildenafil citrate (Viagra) and Tadalafil (Cialis), which have been prescribed for male sexual function disorders, are known to act on vessels.[1] On the other hand, flibanserin is thought to act on brain. Flibanserin has been approved by U. S. Food and Drug Administration (FDA) for treatment of hypoactive sexual desire disorder (HSDD) of premenopausal women in 2015, and is expected to be released in South Korea soon. Authors wrote this article to acknowledge flibanserin to sexologists for females or physicians for menopausal medicine, so that this agent can be safely used for females who have HSDD. **(J Menopausal Med 2016;22:9-13)**

Key Words: Flibanserin · Sexual behavior · Sexual dysfunctions, psychological · Sildenafil citrate

Introduction of Flibanserin

From now on, molecular study regarding female sexuality has focused on female sexual hormone, like estrogen receptor (ER) and ER derivatives.[1,2] But flibanserin is an agent of 5-hydroxytryptamin (5-HT) type 1A receptor and an antagonist of 5-HT type 2A and thus a new molecular entity.[3] Flibanserin was originally developed as antidepressant drug. In clinical stage 2a as antidepressant, flibanserin could not prove its effectiveness, but almost no sexual function disorder was reported in subjects. For this reason, the Arizona Sexual Experiences Scale (ASEX) was used for making a comparison of the sexual function effectiveness of flibanserin on antidepressant vs. placebo proven in stage 2b studies among four depression programs.[4] Stage 2b studies have failed to prove its general effectiveness on depression, but in answering this question "How intense is your sexual desire?" in the ASEX, flibanserin turned out to be more excellent in both placebo and active-comparator. Since then, drug development has changed its directivity toward being a potential medicine for treating hypoactive sexual desire disorder (HSDD).

Diagnostic Criteria of HSDD

HSDD is characterized by constant and repeated lack or absence of sexual fantasy and sexual desire associated with personal pain in the 4th edition of the Diagnostic and Statistical Manual-Text Revision (DSM-IV-TR).[5] Determining lack or absence is done by clinicians by considering the factors influencing sexual activitie such as age and contexts of personal life. Disturbance caused difficulties associated with clear pain and interpersonal relations. Sexual function disorder is not explained well by other Axis 1 disorders (except other sexual function

Received: February 28, 2016 **Revised:** March 16, 2016 **Accepted:** March 28, 2016
Address for Correspondence: Soo Ah Kim, Department of Obstetrics and Gynecology, School of Medicine, Chosun University, 365 Pilmun-daero, Dong-gu, Gwangju 61453, Korea
Tel: +82-62-220-3783, Fax: +82-62-232-2310, E-mail: ksa@chosun.ac.kr

disorders) and also it is not that it is caused only by direct physiological effects of materials (i.e., drug overuse, drug) or overall medical status. The DSM-5 completed in 2013 addresses new illness called as female sexual interest/arousal disorder (FSIAD), which has both properties of HSDD and another illness of DSM-IV known as female sexual arousal disorder. So HSDD does not exist as single clinical picture any longer in DSM-5.

Clinical Studies of Flibanserin

Flibanserin underwent New Drug Application (NDA) as original drug in 2009. The two central Phase 3 studies (VIOLET[6], DAISY[7]) all used e-Diary and did not show big statistical improvement compared to placebo in the pre-specified co-primary efficacy endpoint that assessed daily sexual desire. In both VIOLET[6] and DAISY[7] studies, flibanserin showed an increase in satisfying sexual events (SSE) and Female Sexual Function Index (FSFI) and reduction in Female Sexual Distress Scale-Revised (FSDS-R), but did not show a meaningful increase in e-Diary scores compared to placebo. In both studies, the most commonly reported adverse effects in women prescribed with flibanserin include drowsiness (11.8%), vertigo (10.5%), and fatigue (10.3%).[6,7] These studies show a statistically significant improvement in secondary end points that measured sexual desire with other tools known as FSFI compared to placebo. Applicants told that the effectiveness of flibanserin against sexual desire is better explained with FSFI, but most advisory committees did not agree to alteration in the e-Diary evaluation method set as the one designed to evaluate sexual desire. The safety consciousness expressed by the advisory committees includes adverse effects such as fatigue and drowsiness as well as drug-drug interactions (DDIs) and flibanserin-alcohol interactions. U. S, Food and Drug Administration (FDA) refused to approve. This medicine was resubmitted to FDA for reexamination in 2013. This resubmission included three Phase 3 study findings. Another central stage 3 study is BEGONIA,[8] which set SSE, FSFI, FSDS-R as major evaluation methods rather than using e-Diary in the existing VIOLE and DAISY studies and reported that flibanserin shows a statistically significant increase in SSE and FSFI and reduction in FSDS-R compared to placebo. However, many problems with safety were brought up in the second submission, too. Vertigo, drowsiness, and vomiting are the most commonly reported adverse effects, and these occurred 2% to 3%, respectively if using placebo during stage 3 placebo-control premenopausal HSDD, whereas occurred close to 11% in subjects who used flibanserin as 100 mg every night at bedtime. Events matching central nervous system depression (fatigue, drowsiness, and vertigo) occurred close to 21% in subjects who used flibanserin as 100 mg every night at bedtime and this proportion is three times higher than in placebo group. Flibanserin is very difficult to endure if taking in combination with fluconazole and strong cytochrome P450 3A4 (CYP3A4) suppressant and this combination may increase the risk of swoon and symptomatic low blood pressure. And ethanol administered in combination with flibanserin greatly increases the risk of drowsiness, fatigue, orthostatic hypotension, and swoon. Additionally, these studies were limited to general healthy women who did not take benzodiazepines, sleep aid, narcotics and many other drugs. The effectiveness was not so big in general, and considering these concerns, FDA refused to approve it again and recommended that additional safety studies are required.

According to the latest FDA review, there is no data indicating new efficacy. Instead, flibanserin sponsors submitted additional safety data next day including research data proving that there is no obstacle to driving, data comparing the commercialized products and the side effects profile of these products, and analysis clarifying the potential effects of alcohol on side effects.[9] Despite the trustfulness of highly influential studies, FDA product review is not a fundamental comparison, in fact, and so comparison of safety between individual products may be misunderstood. In particular, alcohol interaction study was conducted in 25 healthy volunteers as a sample, among which only two were female.

Since the refusal from FDA in 2013, a civic group called as Even the Score was formed to support what was called as "gender equality" in the manner approaching sexual function disorder treatment.[10] This group insisted that there is no treatment for women although even 26 items

 http://dx.doi.org/10.6118/jmm.2016.22.1.9

for male sexual function disorder were already approved. This argument was rejected by FDA on the ground that there are no approved products for low sexual desire in men and the 26 items for treatment contain various mixtures of testosterone. Despite the fact that flibanserin is supported by consumer advocacy groups and consequently not the first product supported by pharmaceutical companies, FDA's argument on gender bias while regulating is worthy of notice in that the range of making efforts against this argument is from campaigns via social media even to letters from the members of the National Assembly.[11] Another noteworthy feature in application for flibanserin to FDA is use of the findings on sexual desire reported by patients as primary efficacy variable for approval. Sexual desire can be seen by those who experience it and the results reported by patients can be measured without confounding this concept from others. The results reported by patients have become more important in studies and other drugs that have such results as primary end point have been approved (although none were based on sexual desire). Among all new molecular entities and biological permit applications approved by FDA from 2006 to 2010, Gnanasakthy et al.[12] found that among which, 17% (20 in 116) used the results reported by acknowledged patients as primary outcome in approval labels. The complex element in evaluating flibanserin lies in recalling the frequency of desire and extent of intensity and then measuring with FSFI index four weeks after the daily records of the most intense desires when applying for the primary desire end point first time. FDA raised some concerns about optimizing FSFI as desire assessment tool, including the validity of contents and the period of recall, but the recent advisory committees did not focus on changing the primary end points or consulting the validity of FSFI. The final concern with flibanserin is associated with its use in clinical settings and this was an important issue for the committees. Despite little reliable estimate of HSDD prevalence, this product will be used obviously in women in a broader sense than had been studied so far like others, many will not satisfy the official diagnostic criteria of HSDD, and many will increase the risk of adverse effects or be administering other drugs. The concerns with its use without labeling were reemphasized again by speakers who argued that they need flibanserin, but at the same time, it was reported that those who were diagnosed with cancer or in menopause should be excluded from treatment with flibanserin by labeling when sold. On June 4, 2015, FDA called a committee meeting to review the efficacy and safety of flibanserin, and after the meeting, the committee approved flibanserin under the condition that risk management tools should be enforced mandatorily. Despite the presence of many problems with flibanserin, FDA finally approved it under the condition that Risk Evaluation and Mitigation Strategies (REMS) should be enforced for flibanserin. In the future, flibanserin is expected to gradually increase in amount with changes from off-label to on-label. If prescription with flibanserin is determined as necessary, before using it, it is important to check prescription criterion, possible adverse effects after prescription, and precautions during administration. To get a prescription with flibanserin, the first criteria is premenopausal women aged 18 year or more who met the Stages of Reproductive Aging Workshop (STRAW) criteria. The STRAW criteria are that she has a regular menstrual cycle for 21 to 35 days in the previous twelve months and a normal level of follicle stimulating hormone (FSH). In addition, it should be prescribed if primary diagnosis is HSDD according to DSM-IV-TR criteria or if there is any secondary sexual arousal disorder or female disposition disorder accompanied by HSDD. Besides, its prescription is likely to be considered if the FSDS-R (range, 0-52) score[13] used in clinical studies is 15 points or higher. In addition, in case that sexual desire disorder comes from disease, psychiatric problems, and interpersonal problems or in case that it does so from medications or other substances taken in conjunction, these cases are not the diseases for which medicine is efficacious. Besides, postmenopausal women and sexual desire decline disorder male patients are not adapted during use and it is not intended for reinforcing sexuality.[14,15]

Precautions in Prescription of Flibanserin

The adverse effects most common in prescribing flibanserin are reported as vertigo, fatigue, vomiting, insomnia, and mouth dryness. Precautions in prescription

include avoiding the use of other substances associated with CYP3A4 and cytochrome P450 2C19 (CYP2C19) which are associated with drug metabolism, for example, administration with ketoconazole as CYP3A4 inhibitor and grapefruit juice and fluconazole as CYP3A4 or CYP2C19 inhibitor, which are likely to increase the risk of orthostatic hypotension side effects. Furthermore, selective serotonin reuptake inhibitors and selective norepinephrine reuptake inhibitors (SSRI/SNRI) may cause anxiety, drowsiness, fatigue, insomnia, and vertigo, if used. So carefulness is required. Alcohol is contraindication because if administered with alcohol, it is highly likely to cause central nervous system depression (fatigue, drowsiness, and vertigo), low blood pressure, and swoon. Hormonal contraceptives are known as weak CYP3A4 inhibitors, and likely to cause side effects such as vertigo, drowsiness, and fatigue if coadministered with flibanserin. Triptans is used for treating migraine as agonist of 5-HT type 1B and 1D receptor and may cause side effects of drowsiness if administered with flibanserin. In addition, if flibanserin is administered to patients with decline in liver failure, increase in concentration of drug in blood is observed and thus it's considered that adverse effects are likely to occur. Besides, taking it with herb extracts and digesters and gastroprotective drugs requiring no doctor prescription is likely to cause the risk of adverse effects and the use of flibanserin to women who are breast-feeding is contraindication.

Conclusion

As we discussed above, flibanserin was refused to approve by FDA in 2009 for its adverse effects and discordance of its efficacy from different evaluation methods. Most common side effects were central nervous system depression, like fatigue, drowsiness, and vertigo. Safety problems were also obstacles in resubmission to FDA in 2013. DDIs with fluconazole, ethanol, and many other drugs were mainly discussed and FDA refused to approve it again recommending additional safety data. With the additional profile and analysis which can prove their safety compared with other products, flibanserin was also advocated by patients who experienced it effective. On June 4, 2015, FDA finally approved it on the grounds that REMS should be enforced, and soon we can get flibanserin on-label under the strict prescription. Flibanserin can be prescribed to premenopausal women aged 18 years or higher who has a regular menstrual cycle, but if liver function fails, if breast-feeding, and if drinking alcohol, the use of flibanserin is contraindication. Also, its administration with fluconazole, ketoconazole, SSRI/SNRI, triptans, hormonal contraceptives, herb extracts, and several other drugs requiring no doctor prescription is prohibited because it is likely to increase the risk of adverse effects. We are waiting for patients' reaction, considering the cost and effectiveness, in countries where flibanserin will be on sale, and more agents like Unicenta (UNCNT) and Melsmon, which proved as having a efficacy of menopausal symptoms, have to be studied as treating for female sexual dysfunction.[16]

Acknowledgement

This research was supported by the Dalim Biotec.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

References

1. Kim MJ, Kim TH, Lee HH. G-protein coupled estrogen receptor (GPER/GPR30) and women's health. J Menopausal Med 2015; 21: 79-81.
2. Kang BM. Menopausal symptoms and comwplementary and alternative therapy. J Korean Soc Menopause 2007; 13: 164-72.
3. Borsini F, Evans K, Jason K, Rohde F, Alexander B, Pollentier S. Pharmacology of flibanserin. CNS Drug Rev 2002; 8: 117-42.
4. Kennedy S. Flibanserin: initial evidence of efficacy on sexual dysfunction, in patients with major depressive disorder. J Sex Med 2010; 7: 3449-59.
5. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC:

American Psychiatric Association; 2000.
6. Derogatis LR, Komer L, Katz M, Moreau M, Kimura T, Garcia M, Jr., et al. Treatment of hypoactive sexual desire disorder in premenopausal women: efficacy of flibanserin in the VIOLET study. J Sex Med 2012; 9: 1074-85.
7. Thorp J, Simon J, Dattani D, Taylor L, Kimura T, Garcia M, Jr., et al. Treatment of hypoactive sexual desire disorder in premenopausal women: efficacy of flibanserin in the DAISY study. J Sex Med 2012; 9: 793-804.
8. Katz M, DeRogatis LR, Ackerman R, Hedges P, Lesko L, Garcia M, Jr., et al. Efficacy of flibanserin in women with hypoactive sexual desire disorder: results from the BEGONIA trial. J Sex Med 2013; 10: 1807-15.
9. U. S. Food and Drug Administration. FDA briefing document: Joint meeting of the bone, reproductive and urologic drugs advisory committee (BRUDAC) and the drug safety and risk management (DSaRM) advisory committee. Silver Spring, MD: U. S. Food and Drug Administration, 2015. [cited by 2015 June 29]. Available from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM449088.pdf.
10. Pollack A. 'Viagra for Women' gets push for F.D.A. approval. New York, NY: The New York Times Company, 2015. [cited by 2015 June 24]. Available from: http://www.nytimes.com/2015/06/01/business/groups-press-fda-to-approve-womens-viagra.html?_r=2#.
11. Taverinise S, Pollack A. Aid to women, or bottom line? Advocates split on libido pill. New York, NY: The New York Times Company, 2015. [cited by 2015 June 24]. Available from: http://www.nytimes.com/2015/06/14/us/aid-to-women-or-bottom-line-advocates-split-on-libido-pill.html#.
12. Gnanasakthy A, Mordin M, Clark M, DeMuro C, Fehnel S, Copley-Merriman C. A review of patient-reported outcome labels in the United States: 2006 to 2010. Value Health 2012; 15: 437-42.
13. Derogatis L, Clayton A, Lewis-D'Agostino D, Wunderlich G, Fu Y. Validation of the female sexual distress scale-revised for assessing distress in women with hypoactive sexual desire disorder. J Sex Med 2008; 5: 357-64.
14. Kwak EK, Park HS, Kang NM. Menopause knowledge, attitude, symptom and management among midlife employed women. J Menopausal Med 2014; 20: 118-25.
15. Kim HK, Kang SY, Chung YJ, Kim JH, Kim MR. The recent review of the genitourinary syndrome of menopause. J Menopausal Med 2015; 21: 65-71.
16. Kim S, Park HT, Lee BI, Shin JH, Park HM, Kim T. Comparison of the efficacy and safety of the unicenta and melsmon injection for the menopausal symptoms. J Korean Soc Menopause 2013; 19: 36-44.