Flibanserin

Stephen B. Levine¹

Published online: 16 September 2015
© Springer Science+Business Media New York 2015

Until August 2015, there was no Federal Drug Administration (FDA)-approved drug for women who are distressed by the seemingly common loss of their sexual desire in committed relationships. There have always been concerns about the medicalization of sexuality, but these became passionately polarized soon after the FDA's judgment in October 2010 that the clinical trial data did not warrant approval. Professional passion reached a crescendo at the October 2014 FDA hearing on the evaluation of women's sexual responses in clinical trials and is continuing in the media as various factions weigh in.

Boehringer-Ingelheim, the company that conducted three flibanserin trials, sold the rights to the product to a privately held company, Sprout Pharmaceuticals, after the first unanimous FDA rejection. Sprout reapplied and was rejected. Subsequently, in 2013, the company sought guidance from the FDA about what additional studies were necessary. In June 2015, an advisory panel voted 18–6 in favor of approval accepting flibanserin's efficacy in increasing subjective desire and satisfying sexual events. Immediately upon approval, Valeant Pharmaceuticals purchased Sprout for a reported one billion dollars. For some, this is a success story.

Those who develop medications, conduct clinical trials, or teach about the use of the product after approval are correctly regarded as economic stakeholders in the product. The professional and the general public reasonably wonder to what extent their judgments are unduly influenced by their involvement with the arduous processes of bringing a medication to the marketplace. Economic stakeholders emphasize the objective facts and political sensibilities.

For those skeptics who have been critics of the promotion and acceptance of flibanserin, this is a crass story of the subversion of judgment about risk/benefit considerations through an organized public relations campaign. They fear that, at best, flibanserin will engender patient disappointment and, at worst, will threaten the well-being of those who expectantly take the medication. Many of these critics believe that the loss of sexual desire is a reflection of the unexamined ordinary complexity of life processes rather than disease.

Both sides talk about women as though they are one entity either suffering from an undefined brain problem or a defined psychosocial existential one. Their positions are similar to, but far more intense than, the pre-Viagra controversy about whether most cases of erectile dysfunction in physically healthy men were psychogenic or biogenic. Viagra and its educational marketing, however, were based on the conspicuous efficacy of sildenafil (~82 %) compared to placebo (~24 %). Many thought leaders posit that erectile dysfunction begins with a small penile blood vessel disorder, is treatable with a PDE-5 inhibitor, and is not a sufficient, practical or cost-efficient reason to explore a man's emotional life. The marketing of these drugs has created the impression that no mental health professional ordinarily needs to be involved. This pleases many patients. I concluded from diverse controversies involving treatments for sexual difficulties that stakeholders interpret science for us in ways that support their political ideological views, economic interests, or skill sets. The worry about flibanserin is that physicians do not have the time, interest, or skills to elucidate the pathogenesis of women's loss of sexual desire.

Compared to the placebo group, in each of the trials there was one more satisfying sexual event (sexual intercourse, oral sex, masturbation, or genital stimulation by the partner) during the last month of the trial compared to baseline. In two of the three clinical trials, there was no significant difference between the groups on the average daily sexual desire as recorded in an

✉ Stephen B. Levine
sbl2@case.edu

¹ Center for Marital and Sexual Health, 23425 Commerce Park, Suite 104, Beachwood, OH 44122-5402, USA

electronic diary over the last month in the trial. The electronic diary method was not used in the third trial. In all three trials, a statistically significant improvement was noted in desire scores over the previous month as measured by two items on the Female Sexual Function Index and a significant lessening of bother as measured during Week 24. Sprout conducted a fourth trial that demonstrated an increase of 0.5 satisfying sexual events and an increase in the two question rating of 0.3. In the original three trials, when those who ranked themselves very much improved or much improved were compared in the flibanserin vs. placebo groups using the Satisfying Sexual Events measure, the findings were 29–39 vs. 21–31 % (difference of 8–9 %). When using the sexual desire questions, the findings were 43–48 vs. 31–38 % (difference of 10–12 %), and when using the distress scale the findings were 21–34 vs. 14–25 % (difference of 7–9 %).

So now physicians have a daily new SSRI medication with at least a 30-day latency until improvement begins. Women will be urged to stay on the medication for 8 weeks before declaring no benefit. The expected improvements may include transient genital pleasurable sensations either spontaneously or in response to foreplay, urges to masturbate, erotic fantasies, sexual initiation, or receptivity followed by more intense arousal to orgasm (if previously orgasmic). About 10 % of patients can expect one of these side effects: somnolence, fatigue, dizziness, or nausea along the way. Alcohol is to be strictly avoided to prevent hypotensive syncope. Physicians and pharmacists will have to carefully scrutinize that approximately 25 drugs that severely inhibit CYP3A4 or CYP2C19 are not concomitantly administered (oral contraceptives are weak CYP3A4 inhibitors). Patients must have normal liver function. Prescribers can expect that approximately 45 % of properly diagnosed woman may feel that they have benefited from the medication if taken properly. Some of these will be placebo responders.

Sexology journals should expect to see manuscript submissions addressing some of the following issues over the ensuing years:

1. Do the improvement rates for those who persist in taking the medication match the clinical trial data? General experience with approved drugs is that the community responses are less than the clinical trials.
2. Do the majority of those who begin flibanserin comply for eight weeks (69 % of patients completed the 24-week trials; 13 % said that they discontinued because of side effects)?
3. How long will the positive results be maintained? When 738 positive responders at the end of the pivotal trials were randomized to placebo or flibanserin and continued for an additional 24 weeks, the flibanserin group was superior on all measures (Goldfischer et al., 2011). In a separate open label 52-week study of 962 women, 42 % of the nonremitters

remitted and 90 % of remitters maintained their improved status (Jayne, Simon, Taylor, Kimura, & Lesko, 2012).

4. Will improvements be maintained after the drug is discontinued? This is not known.
5. Will simply agreeing to take this medication change the dynamics of the couples' lives and create an immediate or subsequent sexual improvement or deterioration? There can be both placebo and nocebo effects of participation and medication.
6. Will sexual dysfunction specialists, most of whom do not have prescription privileges, find a way to recommend and employ flibanserin? Although this would be beyond the scope of their licenses, they may use a physician or a nurse practitioner as a prescriber and do the clinical monitoring themselves.
7. Will gynecologists and primary care physicians provide flibanserin as indiscriminately as physicians prescribe the PDE-5 inhibitors? Pfizer invested a great deal of money in physician education; some would say with little effect.
8. Will prescribers flock to meet the FDA's requirement to take the Risk Evaluation and Mitigation Strategy on-line course in order to write for this medication? Having this requirement in place for flibanserin when physicians prescribe far more dangerous drugs without the need for additional credentialing makes some think this is discriminatory against women and physicians. The PDE-5 inhibitors can cause serious hypotension with certain concomitant medications.
9. Will the flibanserin and alcohol contraindication diminish the utility of the product? The drug will be prescribed to women other than those who resembled those in the pivotal trials, some of whom will use alcohol.

Sexual desire is a central organizing concept of human sexuality. No sexual topic can be discussed without invoking it. Desire is integrally related to psychological and biological development, adolescent and adult relationship formation and evolution, illness experience, and aging. Biological sex and culture are major influences. I am hard pressed to identify any major aspect of private and public life that is irrelevant to sexual desire. Individuals in the arts, literature, psychology, business, education, law, religion, philosophy, medicine, the mental health professions, and the pharmaceutical industry have their unique interests in desire's well-known vagaries. The role of sexual desire in the culture, however, is different than sexual desire in the result-oriented medical and mental health worlds.

After more than 80 years of mental health professionals abstrusely referring to desire as libido, a diagnosis for its relative absence was created in 1980. Hypoactive Sexual Desire Disorder came to be applied predominantly to women because

men with the same phenomenology were misperceived as having erectile dysfunction. Even though a diagnosis was defined, sexual desire itself was not. DSM-5 named the problem differently noting that desire and arousal are inextricably linked and the separate diagnoses for desire and arousal could not be accurately distinguished. Drug development processes sliced and diced the diverse manifestations of desire in order to qualify for scientific study. For pharmacological research, a subject is qualified not simply by history but by cutoff scores on rating scales.

When the insufficiencies of sexual desire failed to be easily improved by psychological therapies, the idea of medication and its invariable companion, biological etiology, arose. Flibanserin is the product of a pharmacological quest that began with sildenafil for women, moved to various forms of testosterone, DHEA, and other lesser-known compounds. In 35 years, we have gone from attempting to define the fuzzy nature of sexual desire, to refining the diagnosis of one of its problematic manifestations, to developing a medication to treat the brain presumed to be deficient in some chemical process.

Clinicians already know that simple ideas do not work in this arena. This is because Sexual Interest/Arousal Disorder is one small aspect of a more complicated life situation. Professional careers are spent studying sexuality, refining nosology, defining a treatment approach, and improving the scientific method of studying it or providing direct care. We each have something to contribute but whatever we do, we should admit we are humbled

by our failures to attain the ideal of the healing arts—to make a diagnosis that leads to a specific intervention that quickly improves the problem.

Let us hope flibanserin can measurably help some women and their partners to live a more satisfying intimate life. Whether it proves to be a useful tool or not, this marks a new beginning in therapeutics for women. The search for effective pharmacologic agents will continue. Some may prove to be “me too” drugs and others may be incremental improvements. I consider the passion about flibanserin to be far more about this particular medication than about having an effective safe drug for women. Stay tuned. This is only the beginning.

Acknowledgment Dr. Levine was a site investigator in one of the flibanserin trials and currently is a site investigator for a bremelanotide trial.

References

- Goldfischer, E. R., Breau, J., Katz, M., Kaufman, J., Smith, W. B., Kimura, T., et al. (2011). Continued efficacy and safety of flibanserin in premenopausal women with hypoactive sexual desire disorder (HSDD): Results from a randomized withdrawal trial. *Journal of Sexual Medicine*, 8, 3160–3172.
- Jayne, C., Simon, J. A., Taylor, L. V., Kimura, T., & Lesko, L. M. (2012). Open-label extension study of flibanserin in women with hypoactive sexual desire disorder. *Journal of Sexual Medicine*, 9, 3180–3188.