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James A. Simon
George Washington University

Irwin Goldstein

Noel Kim

Murray Freedman

Sharon Parish

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Flibanserin Approval: Facts or Feelings?

James A. Simon, MD, CCD, NCMP, IF, FACOG,[1] Irwin Goldstein, MD,[2] Noel N. Kim, PhD,[3] Murray A. Freedman, MS, MD, FACOG,[4] and Sharon J. Parish, MD, NCMP, IF[5]

On August 18, 2015, the U.S. Food and Drug Administration (FDA) approved a first in class multifunctional serotonin agonist and antagonist medication, flibanserin, for the treatment of generalized acquired hypoactive sexual desire disorder (HSDD) in premenopausal women. This approval was surrounded by political posturing that has resulted in naysayers attacking the science based on their feelings rather than the facts. Although the FDA was criticized for gender bias—after all, they had fast-tracked sildenafil for men with erectile dysfunction within 6 months with fewer than 2,000 subjects, whereas flibanserin for women with HSDD was repeatedly required to perform additional clinical trials and filed with approximately 11,000 subjects—whether there was actual gender bias in the FDA is no longer relevant. What is relevant is that science requires that the facts speak for themselves.

In what might be an unprecedented action, Hylton Joffe, in his role as director of the Division of Bone Reproductive and Urologic Products at the FDA, and his colleagues in this division, defended their decision of flibanserin as having a positive risk-benefit ratio.[1] However, their commentary reinforced and perpetuated some of the agency's concerns (their feelings) surrounding the flibanserin approval.

The International Society for the Study of Women's Sexual Health (ISSWSH)[2] is the pre-eminent international organization dedicated to the science of sexual medicine in women and education in women's sexual health. The Executive Committee of ISSWSH applauds the publication of the article by Joffe et al[1] in the *New England Journal of Medicine* that summarizes the historic development program of flibanserin and their first-ever women's sexual health approval of a safe and effective drug for the treatment of HSDD.

Unfortunately, Joffe et al mischaracterized the benefits of flibanserin as "small" (Table 1 in Joffe et al[1]) and overemphasized the risks of flibanserin. We believe that emphasizing the facts would be helpful for those health care practitioners who are uncertain as to benefit of flibanserin for their premenopausal patients with bothersome low sexual interest.[1]

The FDA's analyses underestimate the clinical meaningfulness for biopsychosocial conditions such as HSDD. With HSDD, the clinical benefits get "watered down" by non-responders, placebo response, and high levels of baseline "duty" sex.[3] Responder analyses (conspicuously absent[1]) clarify the actual benefits of this medical therapy. Responders, defined by self-report on the Patient Global Impression of Improvement, show a return to near normal premenopausal frequencies of sexual activity[4] in 8 weeks, despite HSDD of 4.5 years' duration (mean) in these trials. Responders also show significant improvement in desire scores on the Female Sexual Function Index and decreases in sexually related distress on the Female Sexual Distress Scale, and these are validated instruments.

The FDA's overemphasis on the "major safety concerns" of flibanserin, citing "hypotension, and syncope," which are rare to infrequent events[5] when flibanserin is taken properly at bedtime, also is excessive. Labeling prohibiting concomitant alcohol use is unwarranted, because this recommendation was based on an extreme alcohol challenge study in which subjects rapidly (within 10 minutes) consumed the equivalent of two to four "alcoholic drinks" in the morning with flibanserin or placebo. It had been known since early in the phase 2 dosing regimen trials (circa 2006–2007) that flibanserin should be dosed at bedtime (not in the morning) because of its sedating side effects. The three pivotal North American phase 3 trials in which flibanserin was dosed at bedtime and alcohol was not restricted demonstrated that, among the 58% of participants who admitted to "social drinking," the overall rate of syncope and pre-syncope was 0.5% in the flibanserin group and 0.3% in the placebo group.[6,7] These rates of syncope and pre-syncope are similar to existing FDA-approved active central nervous system agents. For example, the package insert data for bupropion show that the placebo-corrected rate for hypotension is 0.3% and that for syncope is 0.7%.[8] The package insert data for paroxetine show that the placebo-corrected rate for postural hypotension is 0.7%.[9] It should be emphasized that flibanserin requires a Risk Evaluation and Mitigation Strategy program, unlike bupropion

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[1]President-Elect of the ISSWSH Executive Committee Obstetrics and Gynecology, George Washington University, Washington, DC, USA;

[2]IF President of the ISSWSH Executive Committee, Sexual Medicine, Alvarado Hospital, San Diego, CA, USA;

[3]Secretary of the ISSWSH Executive Committee, Institute for Sexual Medicine, San Diego, CA, USA;

[4]Treasurer of the ISSWSH Executive Committee, Department of Obstetrics and Gynecology, Medical College of Georgia, Augusta, GA, USA;

[5]Immediate Past President of the ISSWSH Executive Committee, Clinical Medicine/Clinical Psychiatry, Weill Cornell Medical College, White Plains, NY, USA

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and paroxetine. In addition, the reassuring results of the next-day driving study demonstrated the statistically significant benefits of flibanserin on cognitive function and driving performance[10] that are conspicuously absent from the commentary by Joffe et al.[1]

Joffe et al's Table 2 supposedly illustrates the absence of sexual bias in the FDA's drug approval processes. However, including vulvovaginal atrophy therapies in Table 2 and excluding more than 12 branded male testosterone products and countless male testosterone generic products is misleading. Vulvovaginal atrophy or dyspareunia, now referred to as genitourinary syndrome of menopause,[11] results from hypogonadism but is erroneously classified as a sexual dysfunction, as if it, too, were a biopsychosocial phenomenon like HSDD. Genitourinary syndrome of menopause is an estrogen deficiency syndrome very effectively treated with estrogenic therapies locally and systemically and often adequately ameliorated with over-the-counter lubricants and moisturizers.

What is clearly relevant and simultaneously misleading is Joffe et al's misrepresentation of sexual equality in drug approvals. For example, men's testosterone therapies are FDA "approved only for replacement (hypogonadism) … not for … sexual dysfunction," implying menopausal women don't suffer symptomatic hypogonadism or androgen insufficiency syndrome.[12] Male testosterone product approval requires efficacy studies judged solely by restoration of normal testosterone concentrations and short-term safety trials (typically 6 months). In contrast, female testosterone trials necessitate HSDD treatment efficacy, the requisite restoration of normal testosterone concentrations, *and* long-term safety studies of 5 years' duration.[13] *This difference is the true double-standard sexual bias.*

The feelings of the Executive Committee of ISSWSH are based on science and the facts deserve to speak for themselves; therefore, this report is being published in an official publication of the ISSWSH to give the reader the opportunity to make a decision about this first in class drug based on the facts.

Corresponding Author: Irwin Goldstein, MD, Sexual Medicine, Alvarado Hospital, 5555 Reservoir Drive, Suite 300, San Diego, CA 92120, USA; E-mail: dr.irwingoldstein@gmail.com

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REFERENCES

1. Joffe HV, Chang C, Sewell C, et al. FDA approval of flibanserin—treating hypoactive sexual desire disorder. **N Engl J Med 2016;374:101-104.**
2. International Society for the Study of Women's Sexual Health (ISSWSH). Available at: http://www.isswsh.org. Accessed March 11, 2016.
3. Meston CM, Buss DM. Why women have sex: understanding sexual motivations from adventure to revenge (and everything in between). New York: St. Martin's Press; 2009.
4. Kinsey Institute. Percentage of women reporting frequency of vaginal sex, N = 2,393. Available at: http://www.kinseyinstitute.org/resources/FAQ.html. Accessed June 17, 2015.
5. Guidelines for preparing core clinical safety information on drugs. 2nd Ed. Report of CIOMS Working Groups III and IV. CIOMS Geneva 1999. http://www.cioms.ch/publications/reporting_adverse_drug.pdf. Accessed March 11, 2016.
6. Flibanserin Advisory Committee. Sprout briefing document, Table 20. Available at: http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/drugsafetyandriskmanagementadvisorycommittee/ucm449090.pdf. Published June 2015.
7. Flibanserin Advisory Committee. FDA briefing document, Table 28. Available at: www.fda.gov/downloads/AdvisoryCommitteesmeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM449088.pdf. Published June 2015.
8. Bupropion package insert. London: GlaxoSmithKline.
9. Paroxetine package insert. London: GlaxoSmithKline.
10. Natarajan K, Sicard E, Kay GG, et al. Efficacy and sedation-related safety of flibanserin in premenopausal woman; Abstract 117. Presented at: 20th Annual Fall Scientific Meeting of the Sexual Medicine Society of North America (SMSNA). **J Sex Med 2015;12(Suppl. 2):143.**
11. Portman DJ, Gass ML. Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and the North American Menopause Society. Vulvovaginal Atrophy Terminology Consensus Conference Panel. **J Sex Med 2014;11:2865-2872.**
12. Bachmann G, Bancroft J, Braunstein G, et al. Female androgen insufficiency: the Princeton consensus statement on definition, classification and assessment. **Fertil Steril 2002;77:660-665.**
13. Davis SR, Parish SJ. Testosterone in women: can the challenges be met? **Lancet Diabetes Endocrinol 2015;3:588-590.**