Commentary on Simon et al

There are relatively few biological/pharmaceutical options for sexual concerns in cis-gender women, particularly in comparison to what is available for men. This disparity has historically been dismissed as an unavoidable consequence of the purported complexity of female sexuality, which defies the (relatively) simple biological approaches to sex issues that have been used with great success in men. While there may be some validity to this perspective, gender bias and a failure of the biomedical establishment to prioritize women's sexual wellness may also play a role in this disparity.

Sexual Medicine prioritizes publication of research that addresses historically marginalized topics, including pharmaceutical management of women's sexual issues. In this issue, Simon et al[1] conduct a post hoc analysis of pooled data from 5 randomized controlled trials of flibanserin, a drug approved by the United States Food and Drug Administration for the treatment of premenopausal women with acquired, generalized hypoactive sexual desire disorder (HSDD). The endpoints of interest are secondary/exploratory endpoints of these previously published studies, specifically Female Sexual Function Index (FSFI) domain scores other than FSFI-desire.

The current study cohort consists of in 4,008 women, 1,640 of whom were post-menopausal, in stable heterosexual relationships. As is common in biomedical research, the study population of Kim et al was majority (>88%) white-identified, with an undisclosed proportion of this population reporting Latinx ethnicity. The authors conclude that there was a statistically significant improvement in sexual desire, sexual arousal, vaginal lubrication, orgasm, and overall sexual satisfaction (as assessed by the FSFI) in flibanserin-treated women, in comparison to baseline scores and to changes observed in the placebo-treated arm. The authors also report odds ratios and number needed to treat ; the endpoints of interest for these calculations and estimates are not clearly stated in the methods section but are relayed in the results section as "self-reported perceived clinical benefit".

These data represent the first peer-reviewed publication of pooled estimates for change in the nondesire domains of FSFI. Two prior meta-analyses have reported statistically significant improvements in sexual desire based on 4 of the same studies cited in the current work by Simon et al.[2,3] These studies differ from other systematic reviews of flibanserin for HSDD which have included the studies cited in Simon et al as well as unpublished studies of this drug. Jasper et al conclude, based on addition of 3 unpublished studies of flibanserin, that minor but troublesome side effects were more common and the benefit in terms of sexual desire less pronounced compared to placebo.[4] Saadat et al came to similar conclusions based on 6 published and 4 unpublished studies.[5] These latter studies are limited in that they address different populations and dosing regimens of flibanserin so may not be an entirely fair comparisons. Nevertheless, heterogeneity in what is reported out in published systematic reviews has left many clinicians, particularly those not deeply immersed in the management of sexual concerns, uncertain of the role of this drug in managing HSDD.

Sexual Medicine also prioritizes debate, critique, and discussion. Spielman's commentary on Simon et al, also published in this issue, expresses concerns about the paper based primarily on numerical concerns regarding effect sizes, means of analysis, and the incident rate of adverse events.[6] In many ways these reflect long standing criticisms of this drug based on modest quantitative assessments of efficacy as well as concerns about a "narrow therapeutic range" based on the make-up of the studies showing benefit (ie premenopausal heterosexual women, the vast majority of whom were white-identified).[7]

In their rebuttal, the authorship team acknowledges the limitations of quantitative data but brings the important perspective of the meaning of even relatively small effect sizes for women struggling with the debilitating and oftentimes dismissed issue of frustratingly low sexual desire. The authors have decades of collective experience caring for sexual issues in women and their clinical work informs their commitment to promoting the benefits of flibanserin for appropriately selected women.[8-10]

Published studies on flibanserin have been a fruitful source of post hoc analyses and systematic reviews. Aggregated data is useful for resolving heterogeneous outcomes in the primary literature. An additional unspoken effect of aggregation of data is that large sample sizes lead to substantial statistical power, which may magnify even small differences into statistical significance. Aggregated data hence has limitations and strengths; what is more fundamentally important to clinicians is how to select a therapy that will help the patient sitting with them in an exam or consultation room. To that end, "self-reported perceived clinical benefit" may be a more clinically meaningful metric than aggregated FSFI domain scores. Alternatively, assessment of what proportion of participants experienced some clinically meaningful increase in FSFI domain score may be more useful to understand how often benefit might be expected.

Data at the level of the individual patient might help us better answer the truly fundamental question facing clinicians caring for women with HSDD. . ."Should THIS woman in my clinic/office be offered a trial of flibanserin?" With more clarity on which women are likely to benefit from this drug we can better determine which patients should trial it and which will be better served considering alternatives. Data such as this would allow us to improve upon the number needed to treat of 5 for premenopausal women reported in this study. Additional important questions include: Is this drug efficacious in women from racial/ethnic minority groups?; In women in nonheterosexual relationships?; In men or persons who are transgender or gender

nonbinary? These questions can only be addressed with original research designed to resolve these unanswered questions.

Science is a complex undertaking. Researchers and clinicians are held to very high standards regarding design and implementation of clinical trials. Human biology is complex and psychology moreso, which further complicates the conduct and execution of clinical studies that study complex biopsychosocial concepts such as sexual desire. Existing in the real world as we do, it is impossible to conduct "the perfect study" so limitations and shortcomings are inevitable despite our collective best efforts. Authors of original research, even when derived from secondary endpoint data of existing datasets, deserve credit for the work they do. Credit must also be given to critics and reviewers, who articulate concerns and point out areas for future consideration and development.

In the end, science cannot progress inside an echo chamber free of criticism or controversy. Challenge and confrontation, in person or in written form, engenders strong emotions. What is essential is that all parties in a debate maintain appropriate respect for contrarian points of view, careful and honest consideration of critiques, and respect for the venue of discussion. We must also all be aware of our own preconceptions and biases and keep them in mind when relating to our colleagues and, more importantly, our critics.

The value of (finally) having a medical option for women with HSDD is substantial. Particularly in the context of a very low rate of major or irreversible adverse events from use of flibanserin, there appears to be a role for this drug in the armamentarium of those who care for women with HSDD. It behooves us to recognize the unknowns and limitations of this and any other drug, to continually strive to better understand the options we have, and to find novel therapies for our patients.

Alan W. Shindel, MD, MAS
Department of Urology, University of California,
San Francisco, CA, USA

Corresponding Author: Alan W. Shindel, MD, MAS, Department of Urology, University of California, 400 Parnassus Ave, Suite A-610, San Francisco, CA 94143-0738, USA. Tel: 415-353-9386; E-mail: alan.shindel@ucsf.edu

Conflict of Interest: The author has received financial renumeration for participation in advisory boards for Sprout Pharmaceuticals (one in 2021 and one in 2022).

Funding: None.

https://doi.org/10.1016/j.esxm.2022.100586

REFERENCES

1. Simon JA, Clayton AH, Goldstein I, Kingsberg SA, Shapiro M, Patel S, Kim NN. Effects of flibanserin on subdomain scores of the Female Sexual Function Index in women with hypoactive sexual desire disorder. **Sex Med 2022;10:100570.**
2. Simon JA, Thorp J, Millheiser L. Flibanserin for premenopausal hypoactive sexual desire disorder: Pooled analysis of clinical trials. **J Womens Health (Larchmt) 2019;28:769–777.**
3. Gao Z, Yang D, Yu L, et al. Efficacy and safety of flibanserin in women with hypoactive sexual desire disorder: A systematic review and meta-analysis. **J Sex Med 2015;12:2095–2104.**
4. Jaspers L, Fey F, Bramer WM, et al. Efficacy and safety of flibanserin for the treatment of hypoactive sexual desire disorder in women: A systematic review and meta-analysis. **JAMA Intern Med 2016;176:453–462.**
5. Saadat SH, Kabir A, Rahmani K, et al. Systematic review and meta-analysis of flibanserin's effects and adverse events in women with hypoactive sexual desire disorder. **Curr Drug Metab 2017;18:78–85.**
6. Spielmans GI. Pooled analysis confirms flibanserin's unimpressive efficacy, raises measurement questions: A commentary on Simon et al. **Sex Med 2022;10:100579.**
7. Anderson R, Moffatt CE. Ignorance is not bliss: If we don't understand hypoactive sexual desire disorder, how can flibanserin treat it? Commentary. **J Sex Med 2018;15:273–283.**
8. Kornstein SG, Simon JA, Apfel SC, et al. Effect of flibanserin treatment on body weight in premenopausal and postmenopausal women with hypoactive sexual desire disorder: A post hoc analysis. **J Womens Health (Larchmt) 2017;26:1161–1168.**
9. Kingsberg SA, McElroy SL, Clayton AH. Evaluation of flibanserin safety: Comparison with other serotonergic medications. **Sex Med Rev 2019;7:380–392.**
10. Clayton AH, Brown L, Kim NN. Evaluation of safety for flibanserin. **Expert Opin Drug Saf 2020;19:1–8.**