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REVIEWS

Ignorance Is Not Bliss: If We Don't Understand Hypoactive Sexual Desire Disorder, How Can Flibanserin Treat It? Commentary

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ABSTRACT

Background: Female sexual dysfunction (FSD) affects as many as 1 in every 3 women, with a significant portion of these with hypoactive sexual desire disorder (HSDD). These figures alone present significant psychological and pharmacologic challenges. Partly in response to this situation, in 2015 the US Food and Drug Administration approved flibanserin for the treatment of HSDD. This approval has drawn criticism on the grounds of efficacy and necessity.

Aim: To better inform potential consumers about FSD, flibanserin and other interventions for the treatment of HSDD, the importance of understanding the mechanism of FSD, and the efficacy of flibanserin and to review existing relevant knowledge.

Methods: A literature review of extant clinic studies and theoretical discussion articles was performed.

Outcomes: Efficacy of flibanserin for addressing symptoms associated with HSDD in premenopausal women.

Results: Extant literature and empirical evidence suggest that the efficacy of flibanserin for the treatment of HSDD in premenopausal women is at least questionable.

Clinical Translation: Clinicians considering the prescription of flibanserin would be well advised to appreciate some of the controversies concerning the efficacy of the drug.

Strengths and Limitations: The prohibitive usage guidelines, tenuous risk-benefit profile, and considerable cost of use of flibanserin are each worthy of consideration. Flibanserin thus far has been trialed in only a narrow patient range: premenopausal women in long-term relationships with acquired or generalized HSDD.

Conclusions: Although we acknowledge that the discovery and use of flibanserin constitute a compelling narrative, we conclude by questioning the specific efficacy and necessity of flibanserin in providing a treatment for HSDD in women. **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; XX:XXX–XXX.**

Key Words: Flibanserin; Female Sexual Dysfunction (FSD); Hypoactive Sexual Desire Disorder (HSDD); Efficacy

THE FEMALE SEXUAL RESPONSE

There is a general consensus that existing therapeutic interventions for the treatment of female sexual dysfunction (FSD) in women are inadequate.[1] Some researchers concentrating on improving the sexual experience for women have devoted their full professional lives to dissecting the female sex response. An understanding of the female sexual response would be the basis for medicalization strategies to enhance the sexual experience. Basson[2] stressed that a stronger recognition that the female sexual response more often stems from intimacy needs (than a "need" for physiologic arousal) is needed.

Puppo and Puppo[3,4] pointed out that FSD has become a multimillion dollar business. Its popularity is possibly driven to some extent by economic motivation but is largely based on the idea of vaginal orgasm (which to date has not been corroborated by anatomic evidence). There have been suggestions that hypoactive sexual desire disorder (HSDD) represents an example of an industry-sponsored condition developed in preparation for a specific treatment.[3,5,6]

Expressions of intimacy are commonly considered an important part of human identity and health. The "classic" female sex response cycle, established by Masters and Johnson,[7] is based on a

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distinct subset of women, namely those who were willing to be observed in a laboratory having intercourse and were orgasmic during the act. Thus, it could hold limited utility for many women.

Comparisons have been drawn between male sexual dysfunction and FSD (notably by the Even the Score group), often citing the highly publicized 1998 approval of and spectacular success of sildenafil (Viagra, Pfizer, New York, NY, USA). However, it has been argued that sildenafil is simply not the standard against which a pro-sexual medication for women should be measured.[8] Male erectile dysfunction is not synonymous with HSDD, and HSDD can occur in women and men. Pharmacotherapy in male sexual disorders appears to serve structural and functional purposes. Comparisons of any kinds of pro-sexual drug between men and women are simply inappropriate because sexual desire (especially for women) is relational and contextual. Women's concerns about sexual desire are qualitatively, quantitatively, and fundamentally different from men's performance and tumescence concerns.

Any understanding of the female sexual response is limited by simple virtue of the fact that in her lifetime a woman will likely experience adverse physiologic, psychosocial, and physical events, profound or otherwise, which can markedly interfere with or decrease her ability to engage in or maintain sexual function. This in itself can result in misunderstanding, misdiagnosis, and/or possibly even unnecessary medicalization.

Previous research has suggested that exaggerated focus on genital response and other traditional indicators of desire ignores considerable components of female sexual desire (trust, intimacy, respect, communication).[9,10] Any "1 size fits all" model is bound to draw criticism. There is a broad consensus that no single model of female sexuality adequately captures the significant physiologic variance in sexual patterns.[11] Any diagnosis of an FSD needs to be accompanied by the understanding that there are a number of patterns of female arousal and release. Tiefer[10] went as far as to say that all attempts at staging the female sexual response are necessarily artificial.

Previously, Basson[2] suggested that one of the fundamental aspects of women's sexual health is that female sexual arousal is a subjective mental excitement. Indeed, there have been a number of suggestions that women speaking of sexual arousal are primarily referring to mental excitement.[2,12–14] This might or might not be accompanied by an awareness of physical manifestations of arousal. Consistent with this idea, Laan et al[14] argued that "women do not seem to attend to genital changes when assessing their subjective feeling state."

Levine et al[8] argued that women are used to, and seldom perturbed by, their own nuanced sexuality. Sexual desire can occur in the absence of sexual behavior or vice versa.[15] It has to be kept in mind that loss of sexual desire (variously defined) can result for a multitude of reasons. Most women are entirely comfortable with the vagaries of their own sexual desire and do not consider their lack of sexual interest to be reflective of their own responsibilities, constitutional endowments, self-respect, disappointment with their partner, or symptomatic of any kind of anxiety or depression. Levine et al[8] suggested that women participating in clinical trials believe themselves to have a disorder or are attracted to this illuminating possibility. Furthermore, because financial incentives are typically offered for participation in trials, patients might be overly eager to enroll.

BACKGROUND OF FLIBANSERIN

Flibanserin was originally developed by Boehringer Ingelheim (Ingelheim, Germany) as an antidepressant medication but failed to meet efficacy end points for increasing sex drive in women.[15] Owing to its noted pro-sexual side effects, the drug was re-trialed for this indication in the early 2000s.[16] The reapplication to the US Food and Drug Administration (FDA) by Sprout Pharmaceuticals (Raleigh, NC, USA) in 2013 was accompanied by new data from a trial using the assessment of sexual desire as a co-primary end point. Approval was denied based on safety concerns (risk of hypotension, syncope, somnolence, fatigue, carcinogenicity), the short nature and questionable accuracy of studies on which evidence was based, and marginal efficacy.[16] Although previous advisory committees had unanimously rejected flibanserin and despite the lack of any additional efficacy data, the FDA advisory committee voted to approve flibanserin by an 18-to-6 margin in August 2015. This represented the 1st FDA-approved pharmacologic treatment for premenopausal women with HSDD. However, after approval, 15 of the original 18 endorsees indicated their reluctance to accept approval of the drug.[16] Despite these notable reservations, flibanserin was sold to Valeant Pharmaceuticals (Laval, QC, Canada) for a sum close to $1 billion within 48 hours of the controversial FDA approval and continues to be prescribed as a treatment for HSDD in premenopausal women.[17]

Advisory committee members at the FDA meeting have pointed out that this is one of several controversial regulatory decisions reached at the intersection of science, policy, and advocacy.[18]

Sexual Dysfunction

In the Western world, the point prevalence has been estimated at 43.1% for any sexual problem among women in the United States in 2006.[19] Conservative estimates of sexual dysfunction range from 15% in men and 34% in women.[20,21] Of all potential forms of sexual dysfunction, the prevalence of low sexual desire in adult women has been reported at rates higher than 25% in Australian and US population-based studies.[19,22,23] A large US study (N = 31,581) conducted in 2009 found that 33% of a sample of adult women were classified as having low sexual desire.[24]

The persistent and prolonged experience of these symptoms can lead to HSDD. HSDD has been defined as a lack of or