

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; 15:273–283.**

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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. Basson² 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. Tiefer¹⁰ went as far as to say that all attempts at staging the female sexual response are necessarily artificial.

Previously, Basson² 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 al¹⁴ argued that "women do not seem to attend to genital changes when assessing their subjective feeling state."

Levine et al⁸ 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 al⁸ 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 coprimary 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

diminished interest in sexual activity persisting for several consecutive months within the past year, and this definition has been reported by approximately 33% of premenopausal women.^{20,25} It is unclear whether earlier applications of the HSDD definition might have been too broad and included women with a different cause for citing a sexual issue. Stricter definitions of the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV) criteria on HSDD applied to the general female population have estimated that the number of women affected might be smaller, with prevalence rates of only 3.0% to 9.3%.²⁶ The DSM-IV defines HSDD as “persistent or recurrent deficiency of sexual fantasies and desire for sexual activity” [p 498].²⁷ For a clinical diagnosis, this deficiency must cause distress or interpersonal difficulty. The *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* combined the previously defined HSDD with sexual arousal disorder into female sexual interest/arousal disorder.²⁸ This galvanization has drawn criticisms, but rather than entering into the debate, it seems sufficient to acknowledge its existence.^{29,30}

HSDD is typically associated with marked personal or emotional distress, interpersonal difficulty, or significant relationship problems and is believed to be the most commonly occurring FSD.³¹ Importantly, the presence of symptoms attracting a diagnosis of HSDD might not be better accounted for by another psychiatric or medical condition or substance (eg, a physiologic condition or prescribed medication). Although it involves biological and psychosocial factors, its accurate diagnosis requires a thorough clinical evaluation.^{32,33}

HSDD in particular is especially common in women 40 to 60 years old and in those who have undergone surgical (rather than natural) menopause. Prevalence rates among women of all ages have been estimated at 5.4% to 13.6%.³⁴ Further, Rosen et al²⁴ found that 67.5% of patients on a HSDD registry suggested that they were frequently or always distressed by their own lack of sexual desire.

Estimates of prevalence rates vary dramatically as a function of methodology and specific sample characteristics.³⁵ Truly representative estimates of the prevalence of HSDD might be difficult to obtain because of patient non-disclosure and/or a reluctance to seek help. Further difficulties arise from the fact that ambiguities exist among patients and clinicians about what constitutes low sexual desire.^{36,37} Reasons commonly cited for declining to seek care can stem from the mistaken notion that there are no treatments available for women with sexual disorders or the widely held misconception that diminished sexual desire is an inevitable part of the aging process.¹

In otherwise healthy women who have no other explanation for sexual dysfunction and low libido, pharmacologic therapy has been suggested to be a useful adjunct to psychological and behavioral interventions to improve the female sexual response cycle.³⁸ The recent FDA approval of flibanserin for the treatment of HSDD in premenopausal women has been controversial, because the efficacy of the drug has been called into

question.^{39,40} Some anti-flibanserin campaigners argue that HSDD is an industry-driven idea; pro-flibanserin advocates claim that its approval is progress for women to treat a real medical condition.^{38,41} Flibanserin is the 1st medication approved “on-label” to treat an FSD. However, the medication has not enjoyed universal approval. There have been at least some suggestions that the efficacy of flibanserin is questionable and that further research is needed to detect the long-term effects of the drug.^{40,42}

The male sexual response has had several targeted pathways to manage sexual dysfunction in the form of pharmacologic therapy. Men tend to reach states of sexual arousal more often than women, and for them, sexual arousal is fundamentally linked to physiologic response and readiness. Hence, pharmacologic interventions targeting the physiologic pathways responsible for sexual arousal have proved particularly successful. So successful in fact that the media has been shown to popularize statements that feminists claim that men have access to 26 (approved) drugs for the treatment of various sexual disorders, but for women there are none.⁴³ This attention has led to a shift in focus from men to women to enhance libido and has been largely driven by marketing interest, particularly from a pharmacologic perspective.³⁸

Despite increased efforts and research to design a drug to treat female HSDD, effective pharmacologic therapy has been difficult to achieve. In this article, we broadly explore the barriers of pharmacotherapy research and the utility of flibanserin for female sexual desire disorder in an attempt to understand why it has been challenging to medicalize the female sexual response.

Potential Role of Flibanserin in Treating HSDD Among Women

Flibanserin is classed as a postsynaptic serotonin-1A receptor agonist and serotonin-2A antagonist. There are other properties of flibanserin that elicit moderate agonist activities at the serotonin-2B, serotonin-2C, and dopamine D4 receptors. These properties translate to important functions that act on the serotonin and dopamine pathways within the brain (Figure 1).^{44,45}

Flibanserin has been shown to activate the serotonin-1A receptor but inhibit the serotonin-2A receptor. Serotonin is an important monoamine neurotransmitter in the human body and is implicated in several vital functions.⁴⁶ As a neurotransmitter, serotonin enables the communication between several important intracerebral structures involved in sensory processing, cognition, motor activity, and, most importantly, emotion regulation. Dysregulation of serotonin can lead to disturbance in mood, an increase in depressive symptoms, and an increase in anxiety-like symptoms. Serotonin interacts with 14 serotonin receptors, including the serotonin-1A and serotonin-2A receptors, and these receptors act as the “eyes” and “ears” of the cell, constantly receiving and conveying chemical signals. Serotonin receptors are expressed in varying degrees throughout the brain; therefore, common antidepressant or anxiolytic medications require a particular balance of excitatory and inhibitory effects on

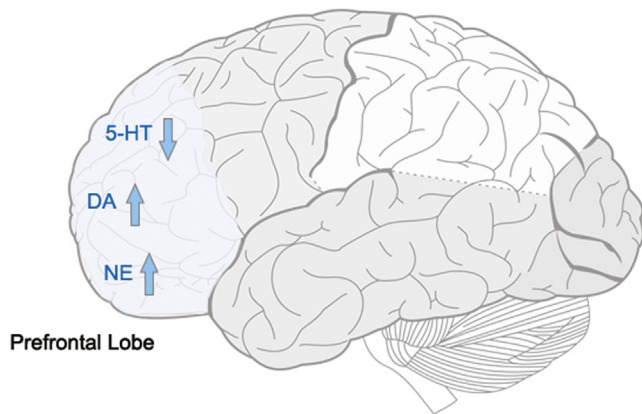


Figure 1. Illustration representing the proposed action mechanism of flibanserin. Flibanserin is proposed to decrease 5-HT and simultaneously increase DA and NE in the prefrontal lobe. 5-HT = serotonin; DA = dopamine; NE = norepinephrine. Figure 1 is available in color at www.jsm.jsexmed.org.

serotonin receptors at multiple junctures. Flibanserin purports such a function. With excitatory and inhibitory effects on relevant serotonin receptors, flibanserin can work to resolve mood disturbance in individuals, lending to the original suggestion of flibanserin as an antidepressant medication.

Flibanserin also has been shown to have a moderate agonist effect on the dopamine D₄ receptor. Dopamine is involved in the regulation of locomotion, cognition, neuroendocrine secretion, and mood and affect.⁴⁷ Flibanserin has been shown to have moderate agonist effects on the dopamine D₄ receptor, meaning the medication could contribute to an upregulation of dopamine within the brain, subsequently aiding the regulation of these functions. There is additional evidence to support the potential multifunctional actions of flibanserin, with a residual excitatory effect observed for norepinephrine levels in the prefrontal lobes.

Although the properties of flibanserin are not novel and can be seen among several current antidepressant medications, the exact mechanism of this medication in relation to HSDD is not known. According to the drug manufacturing information, flibanserin could work by restoring function in the prefrontal cortex, ultimately regulating the brain's motivation and reward structures, which in turn could allow sexual desire to manifest. It also is assumed that because of the interactions with serotonin and dopamine receptors, flibanserin could help alleviate mood disturbance, thereby indirectly promoting sexual interest. What is less understood is the mechanism behind flibanserin that supports its use as a specific medication for the treatment of HSDD in women.

FLIBANSERIN'S PATH TO MARKET

The regulatory path leading to the FDA approval of flibanserin was peculiar and noteworthy.¹⁸ Shortly after the 2nd FDA rejection of flibanserin in 2013, an advocacy group and campaign (initially created by a consultant to the manufacturer of flibanserin), called Even the Score, was formed. Its principal

concern was championing “gender equality” in accessing treatments for sexual dysfunction.⁴⁸ The consumer advocacy group, supported by pharmaceutical manufacturers, claimed that although there were 26 unique approved medications for sexual dysfunction in men, 0 existed for women. This suggestion has since been refuted by the FDA. The campaign lobbied strongly for a positive evaluation of flibanserin, citing sexism and not science as being responsible for previous approval failure. The extent of the advocacy efforts exercised by the group seemed particularly vigorous and included extensive social media campaigns and letters from members of the US Congress.⁴⁹

The pathway to reapplication with the FDA in 2013 raises questions. Flibanserin failed to meet the efficacy threshold as an antidepressant but was noted to exhibit “pro-sexual” side effects and was re-trialed for this purpose in the early 2000s.¹⁶ The FDA denied the application for the approval of flibanserin as a pharmacologic treatment for HSDD in 2010 based on the lack of significant data from 2 phase 3 trials. Sprout Pharmaceuticals reapplied in 2013 with data from a 3rd trial, which used a subjective, retrospective design to assess sexual desire during the 4 weeks before administration. The journey from the failure as an antidepressant to potential success as a treatment of HSDD in women is an interesting course.

Flibanserin has been reviewed 3 times by the FDA. The properties of the drug did not alter between each phase of application to the FDA. The same drug that was seen to lack efficacy in treating depression is the same drug proposed to treat HSDD in women. The properties of the medication are still those commonly observed in current antidepressant and anxiolytic medications. Therefore, flibanserin might simply contribute to the regulation of mood state in women, ultimately decreasing emotional obstacles to sexual desire and arousal. Currently, there is no objective evidence that supports the efficacy of flibanserin as a specific treatment for HSDD over and above common antidepressant medications. This lack of pharmacologic differentiation is at least noteworthy and suggests that the approval and acceptance of the medication could, to a lesser or greater extent, stem from effective marketing.

EFFICACY DATA

The eventual approval by the FDA of flibanserin as a treatment for HSDD was based primarily on 3 randomized, double-blinded, placebo-controlled studies.^{39,50} In each case women involved in the study were premenopausal (19–55 years old) with generalized, acquired HSDD and were in a long-term monogamous, heterosexual relationship (mean duration = 11 years). Treatment periods were 24 weeks in each of the trials (4-week baseline) and in all cases participants received flibanserin 100 mg once daily or a placebo. Co-primary end points for these studies included the number of self-reported sexually satisfying events (SSEs) in a given month (studies 1, 2, and 3); the change in monthly self-reported sexual desire score (studies 1 and 2); and

Table 1. Positive and negative outcome measures in published clinical flibanserin trials*

Study	Sample characteristics	Main positive outcomes	Main negative outcomes
Goldfischer et al ⁵¹	738 premenopausal women with HSDD	Improvements in sses and FSFI domain score	Somnolence, fatigue, nausea, dizziness, headache each reported by 8–14% of women
Jayne et al ⁵²	1,723 premenopausal women with HSDD who previously completed another flibanserin trial	Improvement in sexual function; most women believed their treatment had meaningful benefits	Somnolence, sedation, fatigue, dizziness, nausea, and vomiting each experienced by 2.6–15.8% of women
DeRogatis et al ⁵³	880 premenopausal women with HSDD	Improvements in SSEs and FSFI domain score	Mild to moderate AEs (somnolence, nausea, dizziness, fatigue) reported by 2/3 of women
Thorp et al ⁵⁴	1,583 premenopausal women with HSDD	Some improvements in SSEs and FSFI domain score	Mild to moderate AEs (somnolence, dizziness, fatigue) reported by 58.8–72.2% of women (depending on dosage)
Simon et al ³⁵	481 postmenopausal women with HSDD	Improvements in SSEs and FSFI domain score	Mild to moderate AEs (dizziness, somnolence, nausea) reported by 2/3 of women
Katz et al ⁵⁵	1,087 premenopausal women with HSDD	Improvements in SSEs and FSFI domain score	Mild to moderate AEs (dizziness, somnolence, nausea) reported by nearly 2/3 of women
Portman et al ^{56,†}	745 postmenopausal women with HSDD	Improvements in FSFI domain score	Mild to moderate AEs (insomnia, dizziness, somnolence, nausea) reported by 56.1% of women

AEs = adverse events; FSFI = Female Sexual Function Index; HSDD = hypoactive sexual desire disorder; SSEs = sexually satisfying events.

*SSEs and FSFI scores were measured subjectively.

†Study discontinued prematurely by the sponsor.

self-reported sexual desire as measured by scores on the Female Sexual Function Index (FSFI).⁵⁰ In each of the 3 trials there were statistically significant improvements (from baseline levels) in the number of SSEs reported. In addition, study 3 demonstrated a statistically significant improvement in FSFI score.

Gao et al¹⁵ conducted a systematic review of the published literature to assess the safety and efficacy of flibanserin for women with HSDD. Overall analysis was based on 4 double-blinded placebo-controlled trials (total N = 3,414). Efficacy was established through a number of end points. Monthly SSEs were shown to increase by 0.59 (above placebo rates); sexual desire score increased by 1.91; and FSFI desire domain scores increased by 0.32. In addition, subjective Patient Global Impression of Improvement (PGII) scores and Patient Benefit Evaluation scores indicated further effectiveness of flibanserin. Although a significantly larger proportion of women in the flibanserin groups (vs placebo) experienced an adverse event (AE;

odds ratio = 1.54), a nervous system disorder (odds ratio = 2.58), or fatigue (odds ratio = 1.71), the investigators suggested most of these were mild or moderate and that in general flibanserin was well tolerated. They concluded that flibanserin is a safe and effective treatment for HSDD.

Jaspers et al⁴² conducted a systematic review examining data from 5 published and 3 unpublished clinical trials including a total of 5,914 women participants. Pooled self-reported SSEs (0.49), sexual desire (1.63), and FSFI scores (0.27) were noted to increase among treated women. Notably, study discontinuation owing to AEs was more than twice as high in the flibanserin groups than in the placebo groups (odds ratio = 2.19). Odds ratios were high for dizziness (4.00), somnolence (3.97), nausea (2.35), and fatigue (1.64). PGII scores indicated overall negligible to minimal improvement. The investigators concluded that the overall quality of evidence in favor of flibanserin was low, and that additional efficacy data (including studies looking at women

from a range of demographic backgrounds) are needed before flibanserin could be recommended in guidelines and clinical practice. Table 1 presents a summary of published clinical trials. It should be noted that each positive outcome measure reported in a given trial was from a subjective self-report evaluation.

Efficacy data can be artificially distorted for a number of reasons. Trials failing to demonstrate favorable outcomes are rarely published. In addition, pharmaceutical companies are typically (financially) motivated to “expedite” the trialing process to whatever extent they can.^{8,57} Lengthy trials can increase costs and delay the time until the product arrives at market and begins to be profitable.

CRITICISMS OF FLIBANSERIN

That the primary measure of efficacy (on which approval was based) was a subjective patient-reported outcome also is of concern.¹⁸ The patient-reported outcome of sexual desire is inherently personal and known only to the person reporting it. This end point measures a concept without any interpretation from an objective source. Accurately characterizing transient sexual desire is extraordinarily challenging because improvements are subjective and subtle.⁸

Opponents of flibanserin also point to the fact that patients enrolled in trials in which FDA approval was based were subject to a number of adverse reactions. Many of these were similar to those typically caused by selective serotonin reuptake inhibitors: dizziness (11.4%), somnolence (11.2%), nausea (10.4%), fatigue (9.2%), and insomnia (4.9%).^{1,50} The more alarming side effects included severe hypotension (requiring treatment), central nervous system depression, somnolence, and syncope (with the concomitant use of alcohol). In addition, the safety of flibanserin for long-term use and for women who hope to or become pregnant while taking the drug is unclear.³⁶

Flibanserin is restricted to women who have normal liver function, are not taking drugs that affect liver enzymes, and who will abstain from alcohol. A study conducted by Stevens et al⁵⁸ using 23 of 25 male participants indicated that the combination of alcohol and flibanserin can cause syncopal hypotension. Women desiring treatment with flibanserin are expressly instructed to abstain from alcohol and other drugs containing CYP3A4 inhibitors, such as oral contraceptives and fluconazole, while taking it.

Baksh et al³⁶ suggested the controversial FDA approval of flibanserin has been met with criticism and disagreement for a number of reasons. These include the fact that the FDA recognize HSDD as an area of unmet medical need; the product's history of 2 prior failed FDA reviews; the advocacy and politicization of the product's relevance to female sexual health; the fact that studies have indicated the medication performs only slightly better than placebo and that the long-term side effects of

flibanserin are currently unknown; and perhaps, most importantly, its tenuous risk-benefit profile.^{18,42}

Clinicians are instructed to advise the patient that they need to maintain daily usage of the drug for 8 weeks to determine responsiveness (it has been reported that it takes many weeks to start seeing effects and only works in a portion of women); avoid concomitant use of alcohol; and administer the drug daily (regardless of if or when sexual activity is expected).⁸ In this light, the financial expense of the medication is worth considering. Because a single pill can cost upward of US\$10 (daily dosage can cost up to US\$400 per month) and efficacy has thus far been demonstrated over a 24-week period, ongoing treatment might be inaccessible for many women.¹

In their meta-analysis of clinical trials, Jaspers et al⁴² noted that the risk of study discontinuation because of AEs, such as dizziness, syncope, hypotension, somnolence, or an inability to perform tasks, was 2.19 times higher in treatment (vs placebo) groups. Given these significant concerns, they questioned the cost-benefit ratio of flibanserin, citing the clinically insignificant margin of improvement (an additional 0.5 SSE per 4 weeks) offered by the treatment. In addition, they questioned the overall generalizability and applicability of the data given that participants were exclusively or predominately premenopausal, Caucasian, married or in a committed long-term relationship, overweight, and heterosexual. They suggested that across the 8 studies the overall quality of evidence was low and recommended that biopsychosocial models of intervention addressing medical, psychiatric, psychological, couple-relationship, and sociocultural domains be explored as a primary therapy.

Of concern is that flibanserin is likely to be used “off-label” by a more broad population of women than has been studied.³⁶ This concern seems particularly reasonable given the lack of efficacy data for women who are non-white, unmarried, postmenopausal, identify as non-heterosexual, or have concomitant diseases.¹ Owing in part to a potentially serious interaction with alcohol, flibanserin treatment will be restricted to the general public, available through sexual medicine experts, urologists, and certified health care professionals only.³ This is similar to when sildenafil was 1st approved to urologists. Patients and physicians are required to review and complete a Patient-Provider Agreement Form, explicitly emphasizing that the patient abstain from alcohol use while on the drug because of the significant risks of low blood pressure and syncope.

However, completely preventing women who might not strictly fulfill formal diagnostic criteria for HSDD, are postmenopausal, or have concomitant medication or alcohol use will likely prove problematic. In addition, Puppo and Puppo³ cautioned that flibanserin has not been shown to enhance sexual performance and that women need to fully understand the associated risks and costs before considering it as a treatment option. Adriane Fugh-Berman, a professor at Georgetown

Table 2. Alternative intervention therapies for the treatment of HSDD

Study	Intervention	Sample characteristics	Main positive outcomes	Main negative outcomes
Waynberg and Brewer ⁷¹	2,000-mg formulation of <i>Muira puama</i> and Herbal vX daily for 1 mo—pharmacologic intervention	202 women currently in relationship reporting low sex drive	Improvements in frequency of sexual desires, sexual intercourse, fantasies, and satisfaction	Mild AEs (sweats, headache, irritability) in 4% of women
Simon et al ⁶⁰	Testosterone patch 300 $\mu\text{g}/\text{d}$ —pharmacologic intervention	562 surgically menopausal women	Improvements in SSEs and sexual desire, decrease in stress	Mild AEs (headache, acne) reported; 30% of women exhibited application site reactions
Ito et al ⁷³	Dietary supplementation with arginmax—non-pharmacologic	108 women (22–73 y) reporting lack of sexual desire	Improvements in sexual desire and satisfaction, frequency of intercourse	No significant side effects (visual disturbance, blood pressure alterations, dizziness, hypersensitivity) noted
Shifren et al ⁶¹	Testosterone patch 300 $\mu\text{g}/\text{d}$ —pharmacologic intervention	483 naturally menopausal women with HSDD	Improvements in SSEs and sexual desire, decrease in stress	Some mild to moderate AEs (application site reactions, upper respiratory infections, facial hair changes)
van Rooij et al ⁶³	Single dose of sublingual testosterone—pharmacologic intervention	54 women (21–70 y) with HSDD or FSAD	Improvements in sexual function	Well tolerated by pre- and postmenopausal women
Poels et al ⁶⁴	Sublingual testosterone 0.5 mg—pharmacologic intervention	56 women (21–70 y) with HSDD or FSAD	Improvements in SSEs, physiologic and subjective sexual responding	Mild to moderate transient AEs
Akhtari et al ⁷²	<i>Tribulus terrestris</i> extract 7.5 mg/d—pharmacologic	67 married women of childbearing age with HSDD	Improvements in total FSFI, lubrication, sexual desire, arousal, and satisfaction	Recorded side effects included abdominal pain, cramping, nausea, vomiting, diarrhea, and constipation

AEs = adverse events; FSAD = female sexual arousal disorder; FSFI = Female Sexual Function Index; HSDD = hypoactive sexual desire disorder; SSEs = sexually satisfying events.

University's medical school who had testified in opposition to the drug, said that flibanserin was "a mediocre aphrodisiac with some side effects. And marketing won out over science."⁵⁹

PHARMACOLOGIC (AND OTHER) TREATMENTS FOR HSDD

Although there is currently no FDA-approved alternative pharmacologic treatment for premenopausal women with HSDD, a number of promising avenues exist.¹

In a placebo-controlled trial, Simon et al⁶⁰ had surgically menopausal women with HSDD (concurrently undergoing estrogen therapy) wear patches releasing testosterone at the rate of 300 $\mu\text{g}/\text{day}$ for a continuous 24-week period or nothing (placebo condition). In the treatment group, SSEs increased by 1.12 per month; sexual desire scores increased ($P = .0006$); and personal distress scores decreased ($P = .05$). Shifren et al⁶¹ conducted a similar study with physiologically menopausal women. Administering testosterone transdermally led to an

increase of 2.1 SSEs vs 0.5 in the placebo group. Davis and Braunstein⁶² reviewed the current body of knowledge concerning transdermal testosterone administration for the treatment of HSDD. They concluded that safety data for testosterone were reassuring and that transdermal application appears to be an effective and safe therapy for women with HSDD.

Van Rooij et al⁶³ reported that a combination treatment of sublingual testosterone and oral bupirone led to significantly higher vaginal pulse amplitude measures and subjective sexual desire compared with placebo ($P = .006$ and $.014$, respectively). In addition, testosterone combined with sildenafil resulted in significant improvements in sexual desire ($P = .017$).⁶⁴ Although bupirone and sildenafil were associated with AEs (flushing, headache, lightheadedness, and dizziness), none caused patients to withdraw from either study.

It should be noted that testosterone has been associated with a number of adverse effects, including hirsutism, acne, and occasionally virilization, but has been shown to have an overall favorable safety and toxicity profile.¹ In 2006 the Endocrine

Society Clinical Practice Guidelines recommended against the use of androgen therapy for women and that the use of testosterone for the treatment of HSDD should be discouraged.⁶⁵ The investigators suggested that these recommendations are based in part on a lack of data relating to the long-term safety of androgen administration. However, these suggestions were refuted by Traish et al⁶⁶ who cited a number of studies indicating an overwhelming favorable risk-benefit profile for the administration of testosterone.^{67–70} In addition, a transdermally applied testosterone gel (LibiGel, BioSante, Lincolnshire, IL, USA) specifically formulated for the treatment of HSDD was submitted for FDA approval but denied because efficacy data failed to show superiority over placebo.⁶⁷

Herbal supplementation has been indicated as a non-pharmacologic alternative for the treatment of HSDD. Many of these treatments have come under scrutiny as a result of their questionable (and non-FDA-regulated) production qualities, active ingredients, dosage concentrations, and safety concerns. Although these results should be interpreted with caution, there have been demonstrations of efficacy.

Waynberg and Brewer⁷¹ surveyed 202 women before starting a 4-week course of Herbal vX (*Muira puama* and *Gingko biloba*) and then after completion of their treatment. Improvements in sexual desire, intercourse, fantasy, and satisfaction were recorded in 65% of participants. Akhtari et al⁷² found that *Tribulus terrestris* (vs a placebo group) resulted in increased FSFI scores, desire scores, sexual satisfaction scores, and lubrication ($P < .001$ for all comparisons). Significant improvements in arousal ($P = .0037$) and pain ($P = .041$) also resulted. Ito et al⁷³ noted improvements in desire ($P = .03$) and satisfaction ($P = .01$) scores over a placebo group after using ArginMax (L-arginine, ginseng, ginkgo, damiana) for a 4-week period. A summary of these intervention therapies is presented in Table 2.

Other non-pharmacologic intervention therapies (sex therapy, vaginal dilation, use of the EROS clitoral therapy device [NuGyn, St Paul, MN, USA], etc) could be effective in the treatment of HSDD. Pyke and Clayton⁷⁴ reviewed published data on the efficacy of cognitive behavioral therapy and mindfulness meditation training for HSDD and other disorders of sexual desire. Trial results suggested that there was evidence that these 2 modalities resulted in significant improvements for various sexual desire measures. 3 controlled trials supported the use of cognitive behavioral therapy and 2 supported the use of mindfulness meditation training.

CONCLUSION

The medicalization of the female sexual response to treat sexual disorders in women has had an inadequate response compared with sexual function treatment options and research for men. The difficulty appears to lie in our limited understanding of the female sexual response cycle, and unless a proper target is found, pharmacotherapy will continue to have restricted

potential. Other therapies including psychotherapy and behavioral interventions can be a primary intervention with pharmacologic treatment used as an adjunct, because HSDD could have underlying psychosocial elements. Further research is required to establish how medicalization can be useful to provide for a population that currently seems to be underserved.

Although flibanserin holds potential as a treatment for HSDD in premenopausal women, its efficacy is currently questionable and the risk-benefit profile is tenuous and salient. It seems prudent to acknowledge that the female sexual response is fundamentally different than the male sexual response. That female sexual desire is considerably nuanced and subject to the vagaries of internal psychology, environmental circumstance, temporal disposition, and myriad other difficult-to-quantify factors absolutely needs to be considered before any effective treatment or intervention for HSDD, FSD, or similar condition is advocated.

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STATEMENT OF AUTHORSHIP

Category 1

- (a) **Conception and Design**
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- (b) **Acquisition of Data**
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Category 2

- (a) **Drafting the Article**
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Category 3

- (a) **Final Approval of the Completed Article**
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