NEW TOPIC

SEXUAL DYSFUNCTION

A dearth of approved drugs for desire and arousal disorders frustrates women and clinicians alike. The good news? Several products are in the pipeline.

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IN THIS ARTICLE

Since sildenafil (Viagra) was approved by the US Food and Drug Administration to treat erectile dysfunction, women have been calling for research and development of treatments for female sexual dysfunction.

Despite considerable research documenting improvement in sexual responsiveness, genital sensation, and overall well-being among women who were given testosterone after undergoing bilateral oophorectomy, there remains only one testosterone formulation for women. A combination of synthetic estrogen and methyl testosterone (Estratest; Abbott) is indicated for management of moderate to severe vasomotor symptoms associated with menopause in patients who do not respond to estrogens alone.

In the testing stage from BioSante is LibiGel, a transdermal testosterone product. Acrux is developing Luramist, a daily testosterone spray. Proctor & Gamble's efforts to gain approval of a testosterone-containing transdermal patch (Intrinsa) for treatment of low libido were unsuccessful, largely because of concern about potential increases in the risks of coronary artery disease and breast cancer. Pivotal trial data did not demonstrate enhanced risk, but the numbers were too small and the timeframe too short (a maximum follow-up of 2 years) to establish an effect, so the FDA asked for long-term studies. In 2006, European regulators approved Intrinsa to treat low sexual desire in surgically menopausal women.

Then there's flibanserin, which also failed to win approval from an FDA advisory committee after numerous concerns were raised about its safety and efficacy in premenopausal women (see more about this on page 22).

The lack of approved drugs leaves gynecologists and women's health providers with little to offer our patients who are distressed by sexual dysfunction.

In this Update, I discuss:

- the complexity of female sexual function
- what derailed flibanserin
- recent findings that suggest dehydroepiandrosterone (DHEA) may be beneficial
- recommendations for clinical practice.

CONTINUED ON PAGE 21

As understanding of female sexual dysfunction evolves, so do its labels

The fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) divides female sexual dysfunction into four categories:

- **hypoactive sexual desire disorder (HSDD)**—a persistent or recurrent deficiency or absence of sexual fantasies and desire for sexual activity
- **female sexual arousal disorder**—a persistent or recurrent inability to achieve or maintain adequate vaginal lubrication or vulvar swelling (i.e., sexual excitement)
- **female orgasmic disorder**—persistent or recurrent delay in or absence of orgasm following a normal sexual excitement phase
- **dyspareunia**—persistent or recurrent genital pain that is associated with sexual intercourse.

These categories were revised in 2003 by an international consensus committee sponsored by the American Urological Association Foundation; arousal disorder has been subdivided into:

- **combined arousal disorder**—absent feelings of sexual arousal from any type of stimulation, as well as absent or impaired genital sexual arousal (vulvar swelling and vaginal lubrication)
- **subjective arousal disorder**—absent feelings of sexual excitement and pleasure from any type of stimulation in the presence of genital sexual arousal (vulvar swelling and vaginal lubrication)
- **genital arousal disorder**—subjective sexual excitement from nongenital sexual stimuli with reduced sensation from genital touching and an absence of genital sexual arousal from any type of sexual stimulation.

These updated definitions will be incorporated into DSM-V, to be published in 2013.

Also likely to change in DSM-V: HSDD and female sexual arousal disorder may be subsumed into a new category, "sexual interest/arousal disorder in women".[1]

The female response to sexual stimuli is complex

The complexity of sexual arousal disorders in women complicates research into the pathophysiology and potential pharmacologic treatment of these conditions. Conflicting evidence for any benefit of the phosphodiesterase type-5 (PDE5) inhibitors, such as sildenafil, in the treatment of sexual dysfunction in women likely arises from a lack of precision in defining the conditions in which and patients for whom these interventions are appropriate.

Functional magnetic resonance imaging (MRI) studies of men and women reveal differences in areas of brain activity related to sexual arousal. The neurophysiology of sexual desire and response is complex, involving multiple neurotransmitters, peptides, and hormones as well as multiple structural regions within the brain. Dopamine, norepinephrine, melanocortin, oxytocin, and serotonin (at some of its receptors) promote sexual activity, whereas prolactin, gamma amino butyric acid (GABA), and serotonin (at most of its receptors) are inhibitory.

In animal studies, both an increase in dopamine and a change in social environment can trigger increased sexual behavior. In women, a dopaminergic drug such as buproprion may increase arousability and pleasure—but so can a new partner.

All these bits of the "big picture" continue to complicate research in female sexual function.

It is imperative that we begin to understand the nuances of our patients' sexual problems if we are to offer effective suggestions for treatment and management. Objectively determined genital arousal disorder very likely derives from neurovascular causes and is likely to respond to PDE5 inhibitors,

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In the fifth edition of DSM, hypoactive sexual desire disorder and female sexual arousal disorder may be subsumed in a new category: "Sexual interest/arousal disorder in women"

but *subjective* arousal disorder with normal vulvar and vaginal engorgement and lubrication is not likely to respond to these agents.

This is the state of our basic science knowledge in 2010. What's out there and on the horizon for us to offer our patients?

Flibanserin gets an unequivocal thumbs down

***Phase-3 Trial 511.71**. A twenty-four week, randomized, double-blind, placebo-controlled, safety and efficacy trial of flibanserin 50 milligrams every evening and flibanserin 100 mg every evening in women with hypoactive sexual desire disorder in North America. NCT00360529.*

***Phase-3 Trial 511.75.** Best tolerability: 50 mg twice daily versus 100 mg in the evening versus 25 mg twice daily versus placebo in younger women in North America. NCT00360555.*

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In phase 2 trials, flibanserin proved to be superior to placebo in improving sex drive in women

Flibanserin is a 5HT 1A agonist, 2A antagonist, and weak dopamine agonist. It was originally studied as a treatment for major depressive disorder. In phase-2 trials, it was ineffective for management of depression but superior to placebo and an active comparator in improving sex drive (based on validated questionnaires). These results formed the basis for studying flibanserin as a treatment for HSDD. More than 5,000 women have been involved in phase-2 and phase-3 trials in the United States, Canada, and Europe.

Following FDA guidance for sponsors developing treatments for HSDD, drug maker Boehringer Ingelheim defined the primary endpoints for the pivotal trials as an increase in the number of sexually satisfying events (SSEs) and sexual desire, as measured by a daily diary. Sexual events included:

- genital touching by the partner
- masturbation
- oral sex
- intercourse
- orgasm.

Sexual desire was rated daily by the participants using an eDiary.

In North American phase-3 trials, 2,462 premenopausal women with acquired HSDD in stable, monogamous, functionally heterosexual, communicative relationships for at least 1 year were enrolled. Comorbid arousal and orgasmic disorders were allowed if they were secondary to decreased desire. Mean age of the participants was 35 to 36 years, and they were predominantly white, highly educated women in long-term relationships.

Two important exclusions worth noting:

- women who had depression, breast or other cancers (except skin cancer), or any major medical condition
- women who were taking any of the medications on a five-page list of excluded drugs (due to metabolism with the enzyme cytochrome P3A4).

Once they were screened, women completed a 4-week baseline assessment of sexual activity and desire, followed by a 24-week study period. They were randomized to receive 50 mg or 100 mg of flibanserin or placebo daily. Improvements in sexual function, compared with the 4-week baseline, had to be both statistically and clinically significant for the studies to be successful.

Flibanserin's effects were clinically unimpressive

At a daily dosage of 100 mg, flibanserin was associated with a significant increase in the number of SSEs, compared with placebo. However, the co-primary endpoint of an increase in desire, as assessed by the eDiary, was not achieved in the active treatment

When the public got to talk about flibanserin, it had a lot to say

Attendees who spoke during the open public hearing on flibanserin, held June 8 in Gaithersburg, Md, had mixed opinions of the drug's utility in premenopausal women with hypoactive sexual desire disorder (HSDD). Some believe approval of a "female Viagra" is long overdue. Others, not so much.

"In 1920, women were given the right to vote," said Sue Goldstein, clinical trial coordinator at San Diego Sexual Medicine in San Diego, Calif. "What we're asking now is that women be empowered again, that they be given the right to choose to be treated with an FDA-approved product for HSDD." She added: "Once again, we are the forgotten gender."

Leonore Tiefer, PhD, sees things differently.

"The simple but appealing notion that a new brain drug can help you with [hypoactive sexual desire disorder] because, well, desire is in the brain, has been peddled for the past year as if it were a fancy pair of shoes," said Tiefer, clinical associate professor of psychiatry at New York University School of Medicine. "Flibanserin is not a choice when it's promoted by bad science and half-truths and when self-diagnosis checklists are passed off as medical care." Her last comment was a reference to sexbrainbody.com, a Web site sponsored by Boehringer Ingelheim that offers, among other resources, a "sexual satisfaction checklist."

Many other attendees had a personal interest in the issue or represented advocacy groups, and their responses were just as mixed.

Michelle King Robson, founder and CEO of EmpowHer, a women's health media company, favored approval of flibanserin.

"Women are struggling to find solutions to their sexual dysfunction," she said.

Liz Canner, director of the feature documentary film Orgasm, Inc., which takes as its subject "the strange science of female pleasure," accused Boehringer Ingelheim of "disease mongering" (and held a viewing of her film in a room down the hall).

One of the last to speak was Amy Allina, program director of the National Women's Health Network, who asserted that flibanserin offers "little benefit for real women in the real world."

There may one day be an effective agent for HSDD, she said.

"This drug is not it," she added.

—Janelle Yates, Senior Editor

group. Women who took flibanserin had a response rate of 30% to 40%, compared with 15% to 30% for women who took placebo. Although this difference was significant, it was clinically unimpressive, with fewer than 50% of participants experiencing significant improvement (**TABLE 1**).

Frequency of side effects is troubling

Among women who took the active drug, 34.6% discontinued the medication because of side effects, compared with 6.8% of women who took placebo. Most common side effects (and their incidence) were:

- nausea (12%)
- dizziness (11%)
- fatigue (11%)
- daytime somnolence (9.5%)
- anxiety (2%).

In the healthy study population, no major safety issues were associated with flibanserin. However, concomitant use of alcohol, a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI), or a triptan was associated with a marked increase in side effects.

In addition, women who were predisposed to depression or suicidal ideation were more likely to develop suicidal tendencies while taking flibanserin, compared with placebo.

Given the long list of prohibited medications (CYP3A4 promoters or inhibitors), many of which are in widespread use, and given the lack of pharmacodynamic assessment by the sponsor of circulating levels of active drug if used with any of these medications, FDA reviewers and advisory panel members grew concerned about the potential for major side effects if flibanserin were to be released for commercial use.

Ultimately, the FDA advisory panel

TABLE 1 **Flibanserin increased the mean number of sexually satisfying events—but improvement was modest**

Phase-3 trial	Measure	Placebo	Flibanserin	*P* value
511.71	Baseline	2.7	3.0	
	24 weeks	3.5	4.6	.005
511.75	Baseline	2.7	2.6	
	24 weeks	2.6	4.4	.024

voted unanimously to withhold approval of flibanserin for treatment of HSDD in premenopausal women but encouraged the company to continue studies in postmenopausal women. Recruitment is under way for NCT00996372.

Intravaginal DHEA improves postmenopausal sexual function

Labrie F, Archer D, Bouchard C, et al. Effect of intravaginal dehydroepiandrosterone (Prasterone) on libido and sexual dysfunction in postmenopausal women. Menopause. 2009;16(5):923–931.

DHEA has been studied as a treatment for female sexual dysfunction in postmenopausal women, in whom it acts as a precursor for both estrogen and androgen synthesis. In this study by Labrie and colleagues, all aspects of female sexual function—desire, arousal, orgasm, and pain—improved significantly with intravaginal DHEA (**TABLE 2**).

This phase-3, multicenter, placebo-controlled, randomized clinical trial of 216 participants—50 in each arm—randomized women to placebo or 3.25 mg, 6.5 mg, or 13 mg of DHEA daily. Median age of participants was 58.

The study began with a 4-week baseline screening phase, followed by 12 weeks of placebo or active treatment. Women were enrolled if they were postmenopausal and experienced vaginal dryness or vulvar or vaginal irritation or pain. Most women had moderate to severe symptoms.

Topical or systemic hormone therapy was prohibited, and women who had preexisting cancer (except skin cancer) or endometrial hyperplasia were excluded. The primary endpoint was improvement in the four domains of sexual dysfunction.

Although women were not initially

TABLE 2 **Women using intravaginal DHEA experienced improvement in all four domains of female sexual function**

Domain	Improvement after 12 weeks of 1% DHEA	*P* value
Desire	49%	<.0001
Arousal	68%	.0004
Orgasm	75%	<.0001
Dryness (pain)	57%	.0001

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All aspects of female sexual function—desire, arousal, orgasm, and pain—improved significantly among postmenopausal women using intravaginal DHEA

selected for this trial based on measures of personal distress related to their sexual dysfunction (marked distress or interpersonal difficulty is required by DSM-IV for a diagnosis), approximately 50% indicated a desire for improvement on the intake questionnaire. Women were not excluded from this study if they were taking other medications known to affect sexual function, with the exception of systemic or topical hormonal treatment.

The robust results in this study were achieved without increasing circulating levels of estrogen, testosterone, or DHEA beyond the normal postmenopausal range.

What can we offer to our patients?

Female sexual dysfunction is more difficult to categorize and certainly more difficult to measure scientifically than male sexual dysfunction. The distinction between desire, arousal, and pain disorders in women is easily blurred. Certainly, the ability to declare success in clinical trials is straightforward and unequivocal for men. Not so for women.

Female sexual dysfunction that causes distress for our patients is not uncommon. It is a source of frustration for our patients and for us as providers. For now, in the absence of a "little pink pill," we can offer:

- **techniques to eliminate pain** such as topical estrogen for atrophy and physical therapy and biofeedback for secondary vaginismus
- **adjustment of medications** that may thwart sexual desire, arousal, or orgasm, such as SSRIs and antihypertensive regimens
- **counseling and psychotherapy** to help focus the relationship back to intimacy and sexuality. Remember that just enrolling in the clinical trials I described and paying attention to sexuality increased measures of female sexual function by as much as 30%
- **encouragement about a healthy lifestyle,** such as regular exercise, which increases blood flow to the genitalia—as does discontinuation of smoking. Sildenafil may have a role in managing SSRI-induced or vascular disease–related genital arousal disorder.[2]

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In the trials described in this article, simple enrollment and increased focus on sexuality improved sexual function by as much as 30%

Stay tuned

Despite recent disappointments in pharmacotherapy, our awareness about and knowledge of female sexual dysfunction continues to grow. Safe and effective treatments for HSDD and the other conditions affecting women's sexual function are in the pipeline.

References

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