After years of research, drug for 'female sexual dysfunction' remains elusive

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The pharmaceutical industry's push to find a female version of Viagra has been full of letdowns.

Despite a decade of testing pills, patches, gels, nasal sprays and vaginal rings, there is still no approved drug for "female sexual dysfunction." More than a dozen drugs that reached late-stage testing have been abandoned, shelved or recycled for unrelated problems.

Market analysts still see multibillion-dollar opportunity in female sexual complaints. And two drugs -- LibiGel and Flibanserin -- doggedly aspire to become the first to win the FDA's imprimatur.

But female sex disorders have turned out to be far more difficult to define and quantify, let alone fix, than erectile dysfunction.

Kathy Kelley, the Texas founder of HysterSisters, a Web site for women who have had hysterectomies, testified before the U.S. Food and Drug Administration about the clear-cut need for drug therapies.

But she also understands how complex and individual those needs are.

"The brain is a woman's primary sex organ," she said in an interview.

With the 1998 approval of the first male impotence drug, entrepreneurs, researchers and many members of the fairer sex began lusting after a "pink" version.

Indeed, the first drugs to be tested in women were blood-vessel dilating agents that included Viagra and Cialis. The hope was that women would follow the classic male model of sexual response -- interest, arousal, orgasm.

They did not. Pfizer Inc.'s research showed that genital blood flow increased in Viagra-treated women as they watched erotic videos, but the arousal did not make them desire sex.

The complexity of female response has kindled intense debate. How to distinguish normal from abnormal, physiological from psychological, discontent from debilitation?

The answers have financial implications, especially as most drugs for women have been designed to be used regularly and indefinitely, not just as needed to prime the pump.

"In order to get insurance coverage, you have to prove this is a defined medical disorder that is really disrupting your life," said Leslie Sandberg, a market analyst at Trinity Partners in Waltham, Mass. "The vast majority of Viagra sales are cash pay; infrequently is it covered."

In 2000, the FDA issued preliminary guidelines to help companies plan human studies of drugs for female sexual complaints. The guidelines -- still not finalized -- reflected the consensus that had emerged among sex experts at industry-supported conferences around that time.

The FDA said that although "the definition of FSD continues to evolve," it "currently" has four "components:" decreased desire, decreased arousal, sexual pain and orgasm difficulties.

A woman with any one of these is dysfunctional -- but only if she feels "personal distress" about it. Sex experts had added distress to diagnostic

criteria for female sexual dysfunction in 1998, publishing a report in the Journal of Urology and the Journal of Sex and Marital Therapy.

The addition was a recognition that some women are happy with sexual inactivity, but it also foreshadowed the challenge of treating a largely subjective disorder.

Diminished libido, now called hypoactive sexual desire disorder, is what most drugs have focused on. Effectiveness is judged by how many "satisfactory sexual events" the woman reports during the study period, typically three to six months. Unlike an erection, a satisfactory event is whatever the woman thinks it is, from cuddling to coitus.

In study after study, placebos increased satisfying events almost or just as much as the actual drug.

Poor performance was an issue with Intrinsa, the Procter & Gamble testosterone patch for women who experience "surgical menopause" after having their ovaries removed. In 2004, FDA advisers judged the product marginally effective, but rejected it because of a lack of safety data on long-term testosterone use.

P&G, which withdrew Intrinsa's U.S. application, won approval in numerous European countries. The product made just $2.5 million there last year, according to the information firm IMS Health. At that rate, P&G is a long way from recouping its costs; taking a new prescription drug to market costs hundreds of millions of dollars.

"I think the FDA put a pretty big wet blanket" on female sexual-dysfunction drug development, said Andrew Goldstein, a Washington obstetrician-gynecologist and president elect of the International Society for the Study of Women's Sexual Health, founded in 2001.

Another contentious challenge for the industry has been quantifying -- critics would say exaggerating -- how many women suffer from sexual disorders.

The most widely cited prevalence estimate is taken from a national survey published in 1999 in the influential *Journal of the American Medical Association*. The study found that 43 percent of American women ages 18 to 59 were sexually dysfunctional, compared with only 31 percent of men.

The really surprising thing, though, was that the rate wasn't higher. Here's what the survey, which did not inquire about personal distress, asked:

Over the past year, has there ever been a period of several months or more when you "lacked interest" in sex, or "didn't find pleasure" in it, or climaxed too quickly, or not at all, or found intercourse painful?

The results of the study -- funded by the federal government and the Ford Foundation -- became a staple of drug companies' efforts to raise awareness of the apparent epidemic of female sex disorders and the lack of drug remedies.

More recent surveys that included questions about distress found that 3 percent to 12 percent of women were sexually dysfunctional.

Yet the startling 43 percent statistic lives on.

Female Sexual Dysfunction Online, an educational Web site for doctors and researchers, offers several recent instructional presentations that cite that statistic. The Web site is supported by Intrinsa-maker Procter & Gamble and by Boehringer Ingelheim, which is developing Flibanserin.

The other company in the race for FDA approval is BioSante Pharmaceuticals. Last month, a news release about its testosterone gel, LibiGel, declared that "approximately 40 million American women suffer from some type of sexual disorder." Doing the math, that's 43 percent.

Lenore Tiefer, a psychologist and sex therapist at New York University, denounces this as "inflated epidemiology" calculated to make sexually healthy women worry that they're not.

For the past decade, she has led a widely reported campaign against what she calls "disease-mongering" by the drug industry and "agents of medicalization," such as publicists and gullible journalists. She promotes an alternative view of women's sexuality that stresses psychological, cultural and relationship factors.

"I'm frustrated by how little of our positive understanding of sexuality has gotten out," she said.

Goldstein's rebuttal: "I think these people aren't talking to women who have the problem. Baby boomers came of age during the 'sexual revolution' and took ownership of their sexuality. ... When they lose that, for some it's like losing a body part."

Goldstein is a consultant to Boehringer, the German company developing Flibanserin, a drug that acts on brain chemicals involved in mood. It was originally tested as an antidepressant until female subjects reported feeling no cheerier, just unexpectedly frisky.

Boehringer won't say how Flibanserin has performed, but it hopes to complete studies of premenopausal women with low libido this year, spokeswoman Lara Crissey said.

BioSante, meanwhile, readily shares a study in which its daily testosterone gel increased surgically menopausal women's satisfying sexual events an average of five per month -- three more than a placebo.

Women make testosterone, the quintessential male hormone, in small amounts. It has always been a leading candidate for sexual therapy because for some women, it works. Prescription data show that several million of them order customized testosterone compounds from pharmacies or use men's testosterone therapies in lower doses.

However, prescriptions for all female hormones have plummeted in recent years because of a landmark federal study showing that the risks of estrogen-progestin therapy outweighed the benefits. Last month, Solvay Pharmaceuticals stopped making Estratest, a menopausal estrogen-testosterone product that had been prescribed for decades to boost female sex drive, even though it was not approved for that purpose.

The science and safety of female testosterone supplementation also remains unclear. In general, female libido declines with age, as does testosterone, yet blood levels of the hormone don't correlate with desire, arousal or function, studies show.

"Despite some 70 years of clinical use, we do not have a fully satisfactory rationale for testosterone therapy," Canadian gynecologist and sex researcher Rosemary Basson wrote last year in the Annals of Internal Medicine.

BioSante is undaunted. After lengthy negotiations with the FDA, the Lincolnshire, Ill., firm is conducting an unprecedented safety study of 3,000 women to track the incidence of breast cancer and cardiovascular events such as heart attacks. The company plans to seek approval after 12 months _ in late 2010 -- but will follow the women for an additional

four years, chief executive Stephen Simes said.

"Competition has fallen away, and we're pushing ahead," Simes said. "Why? Our company is dedicated to women's health. I think women deserve options."

He also thinks LibiGel, at $4 a day, will feel the love: "I'm confident it will be between a $500 million- and a $1 billion-a-year product."

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