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FEATURE

TOO MUCH MEDICINE

Evening the score on sex drugs: feminist movement or marketing masquerade?

Ahead of this month's FDA workshop on patient focused drug development for women's sexual problems, **Ray Moynihan** questions a campaign to get a rejected drug licensed

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A thrice failed antidepressant is at the centre of a new marketing campaign to win approval for what could become the world's first blockbuster sex pill for women. Frustrated by the drug's repeated rejection, proponents have orchestrated a fierce attack, accusing the regulator of unfairness, and enlisting support from several well connected women's organisations in the US. Critics counter that the campaign is exceedingly misleading, that it targets a desire disorder that does not exist, and that approval could see widespread overprescribing of a drug with marginal benefits and real safety concerns.

A few months ago a website called Even the Score emerged, (www.eventhescore.org) attacking the United States Food and Drug Administration with the claim, "Men outscore women 26 to 0 when it comes to FDA approved treatments marketed for Sexual Dysfunction." The argument is that men have sildenafil and a host of other drugs, but women have none. And according to Even the Score's website, 43% of women experience sexual dysfunction.

The campaign uses the broad feminist language of rights, choice, and sex equality, but it has a narrow focus as well: it calls on the FDA to act for women "by approving the first-ever drug to treat the most common form of women's sexual dysfunction." Without using the drug's name, it's a demand for the regulator to approve the thrice failed antidepressant flibanserin, currently being pushed for hypoactive sexual desire disorder— a now obsolescent diagnosis—by new drug company Sprout, a key sponsor of the campaign. Sprout is run by a group of experienced pharmaceutical and investment specialists who reportedly bought flibanserin in 2011 and, according to the business press, have raised tens of millions of dollars from private investors with the hope of delivering a new "global brand."[1]

Feminist campaign?

The Even the Score website is light on detail about who initiated the campaign and who's running it, stating simply that it "was created" as a voice for American women who wanted to level the playing field around sexual dysfunction treatments. But according to the woman chairing the campaign, Susan Scanlan, Sprout Pharmaceuticals was central to its genesis. She was approached by Sprout over a year ago, before the most recent FDA rejection of flibanserin in 2013. "They were trying to educate," she told *The BMJ*.

Scanlan was long time chair of the National Council of Women's Organisations, a network of over 200 US organisations. "I've spent my life looking at inequities, including in women's health," she said, so the approach from Sprout "spurred quite a bit of interest." After looking into it and consulting with trusted colleagues she decided to chair the campaign. "I sincerely believe, based on fairness, women are not getting a fair shake."

Another group approached by Sprout has come to a different conclusion. "Even the Score is a slick pharmaceuticals campaign masquerading as a grassroots feminist movement," says Cynthia Pearson, executive director of the National Women's Health Network, which has written to the FDA supporting its repeated rejection of flibanserin. The network, which does not take money from drug companies, is not opposed to drug treatments but wants them to be safe and effective. "This is a marketing campaign, not a science based effort," says Pearson. "Sprout is trying to find a way to gets its product approved when it didn't pass muster via the scientific process."

Thrice failed drug

Flibanserin originally failed to work out as a potential antidepressant back in the early 2000s**.** The drug, then owned by Boehringer Ingelheim, was later tested for treatment of so called hypoactive sexual desire disorder, which was claimed to affect 1 in 10 women.[2] After closely analysing the evidence about flibanserin and hearing testimony from a range of sources, in 2010, an advisory committee to the FDA voted unanimously to reject it because of a lack of clear benefit and serious safety concerns.[3] Most of the 11 committee members were women. Soon after, the FDA took the committee's advice and rejected the drug. It failed a third time in 2013, when the FDA knocked back Sprout's application for approval,[4] and the company and the FDA are currently in negotiation over the drug's future.

Company funded evidence in 2010 showed that at best, compared with placebo, the drug might offer less than one extra "satisfying sexual event" a month, and an FDA analysis found neither of the two pivotal studies "met the agreed-upon criteria for success in establishing the efficacy of flibanserin." The analysis also found common side effects included nausea, dizziness, fatigue, sleepiness, and sedation, causing almost 15% of women taking flibanserin to drop out of clinical trials.[3]

New View opposition

Leonore Tiefer, the sex therapist who initiated the New View campaign to oppose the medicalisation of women's sexual problems in 2000, is alarmed about this latest company backed campaign. "Even the Score is hijacking feminist language of choice and fairness," Tiefer says. "It's disrespectful of the FDA, it's insulting to feminism, and it misleads the public." Tiefer wrote a long letter to the president of the National Organization for Women, Terry O Neill, one of the women featured on the Even the Score website, offering to meet and discuss the issues, but Tiefer got no reply. She has also launched a petition against the campaign (www.ipetitions.com/petition/end-deceptive-pr-about-womens-sexual-health).

Moreover, the trials showed an increased frequency of rare but serious adverse events, including depression, unintentional injury, and fainting.

A more recent 2013 study similarly found that premenopausal women taking flibanserin had one more "satisfying sexual event" a month than those in the placebo group and recorded a marginal advantage on questionnaire items about desire of 0.3 on a five point scale.[5] Of seven named investigators, three were drug company employees and two were company consultants; the study and its write up were company sponsored, and a global PR firm helped write up results. We know sponsored trials are far more likely to find favourable results for the sponsors' product,[6] so these marginal benefits could prove even smaller in independent studies. In addition, over a third of women experienced some form of side effects, which included sleepiness, dizziness, nausea, fatigue, and upper respiratory tract infection. One in 25 women experienced adverse events described as "severe."

Promoting a drug for a condition that "doesn't exist any more"

The condition that the drug is supposed to treat, hypoactive sexual desire disorder, is a highly controversial diagnostic construct.[7] Although desire problems are real, and can be debilitating, the idea of a common disorder of desire is now discredited. In fact the construct has been removed from the latest edition of the *Diagnostic and Statistical Manual of Mental Disorders*, DSM-5.[8] DSM-5 includes a new construct called sexual interest/arousal disorder, designed to more accurately reflect the complexity of women's sexual experience. With much stricter diagnostic criteria, prevalence estimates are likely to be a fraction of the 10% claimed for hypoactive sexual desire disorder. The changes are in part designed to "reduce the likelihood of overdiagnosis" says the American Psychiatric Association, "and distinguish transient sexual difficulties from more persistent sexual dysfunction."[8]

A key member of the working group that recommended the change was Canadian researcher and psychologist Lori Brotto, who reviewed the relevant scientific literature. She concluded that a lack of spontaneous desire may in fact be normal for the majority of women, many of whom very much enjoyed their sex lives, and that it "should not be pathologised."[7] Another member of the working group that produced the new DSM-5 definitions puts it more bluntly. "It doesn't exist any more," says Cynthia Graham, "there is no disorder of desire."

A senior lecturer in psychology at the University of Southampton, research fellow at the Kinsey Institute, and editor in chief of the *Journal of Sex Research*, Graham is alarmed by what she has seen on the Even the Score website, including the discredited claim that 43% of women experience sexual dysfunction. "They are putting out information that is exceedingly misleading . . . it's like propaganda," she says. Asked about the claim that the regulator is being unfair, she says that in this case, "the FDA has no case to answer. There is no suggestion on the Even the Score website that there have been medications for women submitted to FDA and not approved, for good reason." She argues the benefits of diagnoses and drugs are being exaggerated and the importance of education and reassurance about sexual difficulties played down. She's most worried about the long term safety of the antidepressant flibanserin—being promoted as a once a day drug—and the potential for overprescribing. "My concern is many women will get a diagnosis and medication they don't need."

Conflicted informants

When I put these criticisms of Even the Score to its chair, Scanlan stressed that she was not a medical expert or statistician, adding, "I am an ignoramus when it comes to chemical issues." She said that when deciding whether to get involved with Even the Score, she had relied heavily on advice from others, chiefly an organisation called the American Sexual Health Association (ASHA), which is named on the website as a supporter. "I sat down with ASHA, and they said yes, this is legit." Also informing Scanlan's decisions to support the campaign were meetings with patients with sexual dysfunction. Asked who had arranged those meetings, she named ASHA and Sprout. Another source of guidance, Scanlan said, was a group of researchers who have been paid advisers to Sprout, including psychiatrist Anita Clayton. Asked who was doing the leg work and organising Even the Score, she identified a consultant called Audrey Sheppard, who she said was well informed and had also "steered" her.

In virtually every case, the advice that has convinced a long time feminist to lend her credibility to this campaign was from sources with financial ties to drug companies, or from people paid by Sprout. A close look at the annual financial accounts of ASHA shows that it receives substantial proportions of its funding from drug and device makers and companies running clinical trials.[9] Clayton did not respond to a request for an interview with *The BMJ*, but in a recent article she disclosed that in the past five years she has consulted to more than 20 companies, including Sprout. [10]

The BMJ was also unable to speak directly with the consultant Audrey Sheppard, though she responded through a third party by referring *The BMJ* back to Scanlan and Sprout's public relations company, Edelman. Scanlan said she did not know who was paying Sheppard to help organise the Even the Score campaign but that it was "absolutely possible" she was being paid by Sprout. Asked why she was chairing a campaign implicitly calling for the approval of a sponsor's drug, Scanlan was clear: "I do not support a particular drug, but if this [flibanserin] goes down," she said, "all the other drugs in the pipeline, that's going to stop, research will stop. I do believe this is a problem."

Sprout representatives also met several times with the National Women's Health Network but failed to persuade its members to support flibanserin. On the contrary, the network joined several other health organisations, writing a strongly worded letter to FDA supporting their evidence based evaluation and rejection of flibanserin. "The problem with flibanserin" said the letter "is not gender bias at the FDA but the drug itself." Pearson explained to *The BMJ* "the concept of Even the Score resonates

in the heart of every woman who has ever felt things aren't quite fair. That sense of injustice is real, but it is misused so badly by this campaign."

For almost 20 years drug companies and a small cohort of their paid researchers have used the absurd claim that almost half of women have female sexual dysfunction to create the appearance of massive "unmet need" for drug treatment (see box on 43%). Paradoxically such hyperbole undermines attempts to describe and prevent the genuine problems of the much smaller group of women for whom a medical diagnosis may be necessary and for whom a safe and effective treatment might prove helpful. It's still unclear whether Even the Score will succeed in bullying the FDA to approve flibanserin. If it does, and marketing goes into overdrive, not only may millions of women be overdiagnosed and overtreated at great cost and untold harm, a new low in corporate regulator bashing will be set, and the future of evidence based drug regulation will be under threat.

Competing interests: I have read and understood BMJ policy on declaration of interests and declare I have written widely about medicalisation, including a book called *Sex, Lies and Pharmaceuticals*.

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Prevalence of 43% is a discredited fantasy

The claim by Even the Score that 43% of women have sexual dysfunction has long been discredited. It comes from an old survey that asked women whether, over the past year, there was a period of several months or more when they lacked interest in sex, felt anxious about sexual performance, were unable to orgasm, came to orgasm too quickly, had trouble getting aroused, experienced pain on intercourse, or just didn't find sex pleasurable. If women answered yes to just one of these seven, they were classified as having a sexual dysfunction.

Former director of the Kinsey Institute John Bancroft says the 43% have dysfunction claim is outrageous and that "it doesn't stand up scientifically."[11] Reductions in sexual interest or other problems are often healthy adaptive responses and "an understandable reaction to adverse conditions in the relationship . . . or in the individual's general life situation," he says. Even the lead author on the paper which first featured the 43%, Ed Laumann, professor of sociology at the University of Chicago, is concerned the figure has been misused. "I don't think that these things are medical dysfunctions in the sense that they should require active interventions." [7]

CEO previously accused of misleading promotion

In 2010 the FDA sent a warning letter about misleading promotion of a testosterone product to Robert Whitehead, then of Slate Pharmaceuticals, currently chief executive of Sprout. [12] The letter outlined how Slate promoted unapproved uses for the drug, omitted or minimised important risk information, broadened indications, overstated efficacy, and presented unsubstantiated superiority claims. The letter noted that the FDA was "extremely concerned by the breadth and scope of violations," and that the company had committed to immediately cease using the promotional materials.

Asked about this matter, and a range of other questions about their investments, their role in Even the Score, and who they were paying as consultants, Sprout's president Cindy Whitehead declined an interview, instead releasing a statement to *The BMJ*: "Sprout, along with the 21 other organizations in the Even the Score Coalition, including the nine inaugural organizations, signed their support on the basis of the following statement pasted here from the website: As supporters of the Even the Score campaign, we believe that women have the right to make their own informed choices concerning their sexual health; that gender equality should be the standard when it comes to access to treatments for sexual dysfunction; and that the approval of safe and effective treatments for women's sexual dysfunction should be a priority for action by the FDA."

What are the appropriate outcome measures?

Later this month the FDA will host a two day workshop on "patient-focused drug development" for women's sexual difficulties, exploring how best to diagnose and treat them. In particular, the meeting will revisit the ongoing scientific controversy over what should be the most appropriate outcome measures in clinical trials. Drugs keep failing to meaningfully beat placebo on the key measure of "satisfying sexual events"—testosterone and sildenafil both failed before flibanserin. But if researchers use a range of questionnaires to measure women's experience it's much easier to show some kind of benefit—for example, a slight movement up or down on a certain scale. This is unsurprising given that drug companies often fund the development of these measurement tools and company linked researchers often design them, as was the case with the widely used female sexual function index.

At an industry funded meeting in Paris in 2009, Anita Clayton and other colleagues with financial ties to drug makers unveiled a plan to persuade drug regulators to start relying more heavily on these kinds of questionnaires, giving them at least equal weight to "satisfying sexual events." This strategy, she told the 2009 conference, should lead to "improved ability to demonstrate efficacy when such an effect exists." The demand appears to be that industry and their financially linked researchers provide both the products, and the main tools to measure the success of those products.