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INVITED COMMENTARY

Missed Opportunities in the Patient-Focused Drug Development Public Meeting and Scientific Workshop on Female Sexual Dysfunction Held at the FDA, October 2014

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There were numerous missed opportunities at the October 2014 U.S. Food and Drug Administration (FDA) meeting on female sexual dysfunction (FSD). They included opportunities to hear from a diverse range of patients and to engage in evidence-based discussions of unmet medical needs, diagnostic instruments, trial end points, and inclusion criteria for clinical trials. Contributions of the Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition* (DSM-*5*) *nomenclature, based on extensive research, were dismissed in favor of language favoring a seemingly clear but scientifically unsupportable distinction between women's sexual desire and arousal. Numerous participants, including patients recruited by their physicians, acknowledged travel expenses paid for by interested pharmaceutical companies. Conflicts of interest were manifold. The meeting did not advance the FDA's understanding of women's sexual distress and represents a setback for our field.*

We would like to comment on the one-and-a-half-day conference on female sexual dysfunction (FSD) held at the U.S. Food and Drug Administration (FDA) in October 2014 (Peterson, 2014).[1] This meeting was part of an FDA initiative titled Patient-Focused Drug Development devoted to collecting input from patients and experts on a wide range of conditions reflecting "unmet medical needs." The objectives of the meeting included discussing how the new *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition (*DSM*-5) (American Psychiatric Association, 2013) definitions will affect randomized controlled trials (RCTs) of drugs for FSD, including diagnoses, diagnostic instruments, entry criteria, and end points.

While the first half-day was designated for input from women in the general community suffering from sexual dysfunction and the second for scientific discussion, neither designation proved to be accurate descriptions.

Almost all voices from the "general public" on day one were those of women who had agreed to their clinicians' requests to attend. All of them disclosed that their expenses were paid by Veritas, a pass-through group (medical meetings organizers) connected to the International Society for the Study of Women's Sexual Health (ISSWSH) which collected monies for this purpose from Sprout and other pharmaceutical companies (Peterson, 2014). The patients had met the morning of the first day in their hotel to hear presentations and prepare their talking points.[2] They also each received a

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[1]Transcripts, recordings, agendas, participant lists, and more can be found at the FDA website: http://www.fda.gov/Drugs/NewsEvents/ucm401167.htm.

[2]See https://www.facebook.com/pages/Even-TheScore/1461807247387799?sk=photos_stream.

green shawl, identifying them with the "even the score" campaign that accused the FDA of sexism in handling FSD drug applications.[3] These patients arrived at and departed from the FDA together by chartered bus.

The agenda for the scientific meeting on day two began with three formal presentations (female sexual response by Rosemary Basson; changes in *DSM*-5 by Cindy Meston; patient-reported outcomes measurement by Leonard DeRogatis), followed by the responses of a panel of 13 sexual medicine experts to many questions posed by the FDA related to applying the information in the three presentations to clinical trials for FSD medications.[4] The first two presentations emphasized the current evidence-based understanding of an incentives-based human sexual response, depicting a variable response pattern where arousal and desire can coexist, both being triggered by the mind's appraisal of sexual stimuli (Graham, Brotto, & Zucker, 2014). Evidence was also given to confirm the high prevalence of women reporting sexual satisfaction despite very little sense of desire on a day-to-day basis. This evidence was mostly ignored during the rest of the meeting in favor of quoting from the patients who had reported on day one, often emotionally, a sudden and complete loss of desire ("like a light switch" was a repeated metaphor) that they had found completely devastating.

Despite reference to the lack of evidence supporting *DSM*-IV's hypoactive sexual desire disorder (HSDD) and the evidence presented in support of an incentives-based model of response (e.g., Basson, 2001; Brotto, 2010; Brotto, Heiman, & Tolman, 2009; Carvalheira, Brotto, & Leal, 2010; Goldhammer & McCabe, 2011; Janssen, Everaerd, & Spiering, 2000; Laan & Both, 2008; Stoléru, Fonteille, Cornélis, Joyal, & Moulier, 2012), the focus of many—both members of the panel and the audience—was to assume and strongly recommend the continuance of the *DSM*-IV diagnosis of HSDD. They insisted that distinguishing arousal from desire was *not* difficult and that they "knew" the loss of desire was "the" problem. We have difficulty in reconciling the uniformity of the patients' views with the clear message from published evidence.

Moreover, without reference to any supportive evidence, it was repeatedly stated by panel members that an ongoing sense of desire (e.g., throughout a four-week period that might be recalled in a diagnostic instrument, such as the Female Sexual Function Index; Wiegel, Meston, & Rosen, 2005) is the norm. The distressing lack of this ongoing desire was said to constitute a "medical brain disorder" that was "in urgent need of pharmacological treatment," but again no supportive evidence was given. This brain basis was asserted despite the first scientific presentation explaining that the reality of medication-associated dysfunction is not evidence that sexual dysfunction stems from intrinsic brain pathology.

A major focus of the first presentation on sexual response, namely the *DSM*-IV's ignoring of sexual arousal as a mental state—involving an increasing focus on sexual sensations, loss of distractions, nonsexual thoughts, and awareness of sense of time—was not addressed (e.g., de Jong, 2009; Nelson & Purdon, 2011; Nobre & Pinto-Gouveia, 2008). Instead, a more limited understanding of arousal as constituted by genital events (that had prevailed in sexology earlier; see Graham, 2010, for a review) was promoted, and a continuance of the simplistic notion of *DSM*-IV female sexual arousal disorder advocated. Rejection of the new *DSM*-5 category of female sexual interest/arousal disorder as "maybe clinically useful but not useful for clinical trials" prevailed.

Discussion on both days frequently constituted expression of beliefs and opinions rather than an evidence-based approach. This may have been promoted by the almost casual question-and-answer approach of the FDA to the expert panel. It also was predisposed by the preceding several months of online campaigning and "Even the Score" briefings and the rally atmosphere of the green shawls and "#womendeserve" buttons that many wore. The intrusion of political issues into the discussion by "Even the Score" included letters from congresswomen and feminist organizations to the FDA solicited by Sprout Pharmaceuticals and ISSWSH, along with online videos by sexology professionals making gender equity arguments (Moynihan, 2014). "Even the Score" had argued online and in numerous handouts that there were "0" drugs for women but "26 drugs" for male sexual dysfunction. This biased, inaccurate, and simplistic calculation mobilized support but did not stand up to examination. It was repeated at the FDA, but the fact that the majority of medications listed for men are various formulations of testosterone for an endocrine deficiency state was never clarified.

We deeply regret the missed opportunity to begin an evidence-based discussion of what is true pathology in need of treatment (potentially including pharmacological treatment), and then moving onto appropriate diagnostic instruments, trial end points, and inclusion criteria for clinical trials. The repeated insistence that "men have drugs so women deserve drugs" created tension and made nuanced discussion impossible. We regret the missed opportunity to hear from a wide variety of women with sexual complaints who investigated different avenues of intervention and experienced different benefits or harms (e.g., Frühauf, Gerger, Schmidt, Munder, & Barth, 2013). That type of information would have enlightened the FDA officials about the contexts of women's experiences.

The involvement of depression with women's sexual desire, despite being linked by multiple epidemiological

[3]See http://eventhescore.org.

[4]All slides from the three presentations as well as all FDA questions and the answers from the panel are available on the FDA website: http://www.fda.gov/Drugs/NewsEvents/ucm401167.htm.

studies (Bancroft, Loftus, & Long, 2003; Cyranowski et al., 2004; Dennerstein, Lehert, & Guthrie, 2002; Hartmann, Philippsohn, Heiser, & Rüffer-Hesse, 2004; Mitchell et al., 2013), was challenged by a panel member's statement that in recent RCTs for FSD few women had to be excluded due to depression. This was despite the speaker acknowledging that women with depression were excluded during the phone screening process for those very RCTs.

At one point the panel seemed to express a consensus that women in FSD trials to date have not been relevant to the clinical population and a suggestion that women with treated depression would be included in future trials. However, soon this was replaced with a general sense that in the first instance "to substantiate that a drug is effective" women with treated mood disorders would still be excluded.

There were also missed opportunities to focus on medical areas that are of major clinical importance, namely the need for effective sexually neutral antidepressants, vaginal selective estrogen receptor modulators that are safe for women with a past history of estrogen sensitive cancers, as well as vaginal medication to address perimenopausal loss of genital sexual sensitivity. Instead, the FDA meeting was characterized by an adversarial atmosphere that did not advance our understanding of women's sexual distress. It was a missed opportunity and a low point in the long struggle for women's sexual emancipation.

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