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GUEST EDITORIAL

Flibanserin

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On June 4, 2015, an advisory committee to the U.S. Food and Drug Administration (FDA) voted 18-6 in favor of approving the desire drug for women known as flibanserin. Two months later, on August 18, 2015, the FDA announced its approval of flibanserin (to be sold as Addyi). And 2 months after that, on October 17, 2015, Addyi was available for prescription in the United States.

There has been no shortage of controversy surrounding the study, vote, and finally the approval of flibanserin, with scientists, clinicians, sex therapists, patients, the public, and the media expressing their opinions about the process and the nature of women's sexual desire. In the pro-flibanserin camp, advocates have claimed that sexism at the FDA contributed to its rejecting the approval of flibanserin twice (2010 and 2013) before the eventual 2015 approval, especially since a reported "26 drugs" are available for men's sexual dysfunction. Critics in the anti-flibanserin camp take issue with the Even the Score campaign (www.eventhescore.org), which purportedly used slick marketing tactics to increase fear mongering around the "disease" of hypoactive sexual desire disorder, a condition in the 4th edition of the DSM (American Psychiatric Association, 2000). There has been widespread coverage of both sides of this polarized debate in nearly every major televised, radio, in-print, and on-line media outlet. Entire books have been written about the underlying issues and the medicalization of women's sexuality (Cacchioni, 2015; Moynihan & Cassels, 2006; Moynihan & Mintzes, 2010). I will not attempt to detail nor summarize the range of issues in this brief Editorial. Readers interested in my perspective can read http://brottolab.com/project/larry-fedoruk-show-5-things-we-learned-this-week/ or http://www.theglobeandmail.com/life/health-and-fitness/health-advisor/female-viagara-wont-help-many-but-thats-not-stopping-the-drug-company/article24820653/.

Instead, I would like to focus my comments on the opportunity that flibanserin offers. Specifically, with the approval of flibanserin, there is an opportunity to evaluate the long-held hypothesis by numerous sexual health experts that combination therapy may be more beneficial than either pharmaceutical or psychological treatment alone. Combination therapy may involve the administration of a pharmaceutical drug while simultaneously delivering psychological or sex therapy. The advantage of the combined approach may be particularly pertinent in cases where there is a clear psychosocial precipitant or in lifelong cases where the individual's psychological responses to the sexual concern may interfere with the compliance or efficacy of a prescribed medication. Perelman (2003) has used the term "coaching" to refer to strategies used by a clinician, in the context of pharmacological treatment, to target obstacles to sexual activity such as restrictive sexual patterns, avoidance of sex, and difficulties discussing sex with a partner. Perelman outlined the goals of coaching as follows: (1) to identify and resolve the patient's resistance to medical therapy, (2) to reduce or eliminate a patient's performance anxiety, (3) to help him or her gain or regain sexual confidence, and (4) to modify his or her maladaptive sexual "scripts."

In the case of combination therapy for men's premature ejaculation (PE), a recent meta-analysis of four studies examining the efficacy of psychological treatment combined with medication found significantly greater effects than either treatment alone, with effect sizes ranging from $d = 0.53$–1.94 (Frühauf, Gerger, Schmidt, Munder, & Barth, 2013). With erectile dysfunction (ED), combination approaches have been found to be especially useful given that the phosphodiesterase type 5 (PDE5) inhibitors are typically efficacious in 70 % of men with ED, but 60–70 % of these men fail to continue treatment. It has been suggested that the addition of psychological/sex therapy to medication

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management can address issues such as resuming a sex life after a prolonged period of abstinence, partner resistance issues, partner sexual difficulties, lack of confidence or sexual self-esteem, mood and anxiety issues, unconventional sexual scripts or beliefs, and unrealistic expectations. A meta-analysis reviewing eight controlled trials of combination therapy for men with ED using group or individual psychotherapy, couples therapy, psychoeducation, cognitive behavioral sex therapy, telephone therapy, or internet-based cognitive behavioral therapy, with one of the PDE5 inhibitors concluded that, in nearly all studies, there was a superior effect of combination treatment for the primary symptom of erectile concerns compared to either treatment alone (Schmidt, Munder, Gerger, Frühauf, & Barth, 2014). Combination therapy was also superior for sexual satisfaction in this population, and female partners reported higher levels of satisfaction in the combination therapy arm.

The collective findings for combination therapies in men with PE and ED led the 4th International Consultation on Sexual Medicine (Brotto et al., 2015) to recommend that combination therapies be considered as a front-line treatment for men with PE and ED with the highest level of recommendation.

By comparison, the literature on combination therapies for women's sexual dysfunction is nearly non-existent. In the only published study of combination therapy for women that I was able to locate, Meston, Rellini, and Telch (2008) randomized 68 women with sexual arousal complaints (with or without comorbid sexual desire complaints) to receive either a placebo, ginkgo biloba extract (300 mg/daily for 8 weeks), sex therapy focused on teaching women to attend to genital sensations, or a combination of sex therapy plus ginkgo biloba. Ginkgo biloba is known to increase blood flow and relax smooth muscles. The combination approach led to significantly greater improvements in self-reports of sexual desire and sexual satisfaction compared to placebo, the latter of which also improved sexual desire. It is unfortunate that neither this research team nor others have attempted to replicate this novel finding.

Three pivotal Phase 3 clinical trials evaluating the efficacy of 100 mg flibanserin against a placebo control group revealed a statistically significant increase in the number of sexually satisfying events and a decrease in sex-related distress compared to placebo (FDA Briefing Document, 2015). A total of 3548 women were randomized in these three trials, with $n = 2310$ in the flibanserin group and $n = 1238$ in the placebo group. Compared to the placebo group, the increase in sexually satisfying events was between 0.5 and 1.0 events per month. When sexual desire was measured with a daily diary, there was no significant improvement with flibanserin over placebo; however, when desire was measured with the Female Sexual Function Index (Rosen et al., 2000), flibanserin was found to improve desire significantly more than placebo. The FDA Briefing Document noted that there was limited efficacy after 4 weeks of flibanserin use (across all endpoints), and that it may take up to 8–16 weeks for the treatment effect to plateau.

One might argue that these efficacy data can really only be generalized to populations of women who resemble those who participated in the pivotal Phase 3 clinical trials. However, in reality, flibanserin will be prescribed by non-expert physicians seeing a much broader range of sexual desire difficulties in a more heterogeneous population. Not only might complementing a flibanserin script with sex education and therapy be useful, I would predict that a combination approach will be necessary.

That flibanserin's efficacy was not evident until at least 8 weeks of daily use suggests that this may be a critical period for addressing personal and relational barriers that contribute to the low sexual desire, and which may interfere with flibanserin compliance. It seems reasonable that a distressed woman experiencing long-standing loss of sexual desire may become impatient as she waits for flibanserin's efficacy to manifest. She and her partner might benefit from identifying and correcting maladaptive sex-related myths, fostering healthy sexual communication, and identifying arousal strategies during this time as a means of making sex more pleasurable (and thus desirable). It is also likely that women prescribed flibanserin will not meet the very strict inclusion criteria of the women participating in the pivotal Phase 3 clinical trials, namely in their absence of psychological pathology, medical comorbidities, and relationship conflict. The addition of psychological therapy may be necessary to address these comorbidities lest they mask any potential positive effect of flibanserin. Women participating in the pivotal trials needed to agree to engage in sexual activity at least monthly, and this has been criticized as a lofty goal for women with chronic sexual desire difficulties. It seems senseless that women who will now be prescribed flibanserin will agree to this sexual frequency at the outset, and psychological and/or sex therapy may be necessary to invite women to explore the benefits and costs of engaging in sexual activity, with a discussion of approach- and avoidance-related goals (Muise, Impett, & Desmarais, 2013).

The availability of flibanserin allows these hypotheses about the additive benefits of medication plus psychological/sex therapy to be empirically evaluated. My hope is that both the sponsor, Valeant Pharmaceuticals International Inc., and governmental funding agencies will fund this much needed research.

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