We are living in an era in which it is politically correct to accept diversity in sexual orientation and gender identity. It should therefore be logical to accept that such diversity can also exist in the domains of sexual interest and arousal. However, there are sociocultural reasons related to procreation and biological reasons related to sexual needs that drive expectations of mutual sexual activity between adult partners. In this background, although it should be more inclusive to uncritically accept women with low sexual drive, the presence of low sexual interest and arousal elicits distress, is equated with dysfunction, and leads to a DSM 5 diagnosis of female sexual interest/arousal disorder (FSIAD).

A Personalized Approach to Treatment

We are also living in an era in which efforts are being made toward the personalization of medicine. In this context, Bloemers et al.1 hypothesized that different mechanisms explain different components of FSIAD: low sexual interest could emerge from a brain system that is insensitive to sexual cues and low arousal from an increased activity of sexual inhibitory mechanisms. These authors further proposed 3 on-demand interventions:

1. Testosterone, to increase sexual interest and desire. This is because, regardless of plasma levels of testosterone, the administration of sublingual testosterone (0.5 mg) heightens the sensitivity of the brain to sexual cues, whereas plasma levels of testosterone peak 15 min after sublingual administration, and although they return to baseline in 2 to 3 hours (implying that there is a negligible risk of testosterone-related adverse effects when the treatment is used only on demand), the increase in sexual interest and desire happens 3 to 6 hours after the peak in plasma levels. The increase in interest and desire also primes the woman toward an increase in sexual response to stimulation.

2. A phosphodiesterase Type 5 inhibitor, such as sildenafil, to increase genital response to sexual stimulation. This could increase sexual responsiveness in women with low sensitivity to sexual cues. The benefits could be particularly useful after priming with sublingual testosterone.

3. A 5HT1a receptor partial agonist, such as buspirone, to reduce sexual inhibition driven by the prefrontal cortex in response to sexual stimulation. Buspirone, like sildenafil, could also be particularly useful after priming with sublingual testosterone.

Thus, the pharmacotherapy administered could include testosterone and sildenafil, if interest, desire, and arousal are poor, or testosterone and buspirone, if interest and desire are low and inhibition is high.

Testing the Idea

In a 3-arm, 4-week crossover trial conducted in 56 women with hypoactive sexual desire disorder (HSDD), this team of authors2 found that on-demand use of testosterone combined with a PDE5 inhibitor improved physiological and subjective measures of sexual functioning in women with low sensitivity for sexual cues. In a second study of 54 women with HSDD, this team of authors3 found that women with high inhibition experienced improved sexual functioning with a testosterone-buspirone combination relative to placebo and relative to a testosterone-sildenafil combination.

These 2 proof-of-concept trials2,3 set the stage for an impressive 16-center randomized controlled trial (RCT) that was conducted in the USA in women diagnosed with HSDD (DSM-IV-TR); the study selection criteria were consistent with a DSM 5 diagnosis of FSIAD. No woman had a comorbid psychiatric, gynecological, neurological, or...
The Study Findings

The mean age of the sample was 44 years. The sample was 71% Caucasian. Nearly 30% of women were postmenopausal. The average woman was overweight (mean BMI, 28).

In women with low sensitivity, only the higher dose of testosterone (0.5 mg) combined with the higher dose of sildenafil (50 mg) resulted in a statistically significant increase in the number of SSEs relative to baseline; and this combination was also significantly superior to each of the 3 control groups. In the women with high inhibition, the combination treatment groups showed a general improvement over baseline, but the improvement was most marked with the higher dose of testosterone (0.5 mg) combined with the higher dose of buspirone (10 mg); and this combination was also significantly superior to each of the 3 control groups.

In both categories of women, the absolute advantage with treatment was small; the best combination was superior to placebo by just 1.7 SSEs per 4 weeks in the low sensitivity category, and by just 1 SSEs per 4 weeks in the high inhibition category.

The higher dose combinations were superior to placebo for the secondary endpoints as well. The margin of superiority over placebo was again small; for example, it was just 1.1 orgasms per 4 weeks in the low sensitivity category and 0.8 orgasms per 4 weeks in the high inhibition category. Many of the contrasts against active monotherapy were also statistically significant.

Adverse events were uncommon and did not differ across groups. There were no laboratory abnormalities associated with treatment.

Critical Appraisal

Now here is something extraordinary. In this study, the placebo group improved more than expected, and the authors deemed the response to be enormous and anomalous. So, with the permission of the European Medicines Agency and the Food and Drug Administration (USA), they repeated a part of the study, comparing placebo with the high dose combination of testosterone and buspirone. The new placebo group replaced the original placebo group, and the findings presented in the previous section are for active arms against the new placebo arm.

What do we make of these efforts? On the surface, the findings are exciting because they suggest that women with a very difficult to treat condition can be helped with a cleverly conceptualized, cleverly formulated combination treatment that is assigned through a personalized medicine approach. The treatment is on-demand; it does not need to be taken daily, as does flibanserin, and it does not need to be injected, as does bremelanotide, both of which are currently approved treatment for HSDD. The treatment is associated with greater efficacy in terms of number of SSEs, as compared with what was found in the flibanserin and bremelanotide RCTs. The treatment does not require abstinence from alcohol, as does flibanserin. The treatment is well tolerated and does not cause nausea, flushing, and headache, as does bremelanotide.
clinical, biochemical, and genetic assessments. This is a complicated and expensive procedure. More problematic is that it is meant to dichotomize women into low desire or high inhibition categories; so what happens to women who have both low desire and high inhibition, or to women who are midway between two extremes and cannot be easily dichotomized? And can women move between categories, especially with regard to the psychological variables that contribute to the assessment?

An even bigger concern is whether the classification is actually necessary. In the study, the authors did not administer the testosterone-sildenafil combination to women with high inhibition, or the testosterone-buspirone combination to women with low desire. Therefore, they could not rule out the possibility that, for example, a combination of testosterone (0.5 mg) and sildenafil (50 mg) works for all women, regardless of the level of desire and inhibition in the categorization. In other words, there may not be a role for personalized pharmacotherapy, at all.

Concluding Notes

The authors described their investigation as a phase 2 clinical trial. Very clearly, many questions remain to be answered in the phase 3 trials. One question, for example, is whether the findings can be replicated in a study that does not require another replacement of the placebo group! Another question is how the combination treatment fares in a head to head comparison with flibanserin and bremelanotide. The final judgment remains to be passed.

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