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Efficacy and Safety of On-Demand Use of 2 Treatments Designed for Different Etiologies of Female Sexual Interest/Arousal Disorder: 3 Randomized Clinical Trials

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ABSTRACT

Background: In women, low sexual desire and/or sexual arousal can lead to sexual dissatisfaction and emotional distress, collectively defined as female sexual interest/arousal disorder (FSIAD). Few pharmaceutical treatment options are currently available.

Aim: To investigate the efficacy and safety of 2 novel on-demand pharmacologic treatments that have been designed to treat 2 FSIAD subgroups (women with low sensitivity for sexual cues and women with dysfunctional over-activation of sexual inhibition) using a personalized medicine approach using an allocation formula based on genetic, hormonal, and psychological variables developed to predict drug efficacy in the subgroups.

Methods: 497 women (21−70 years old) with FSIAD were randomized to 1 of 12 8-week treatment regimens in 3 double-blinded, randomized, placebo-controlled, dose-finding studies conducted at 16 research sites in the United States. Efficacy and safety of the following on-demand treatments was tested: placebo, testosterone (T; 0.5 mg), sildenafil (S; 50 mg), buspirone (B; 10 mg) and combination therapies (T 0.25 mg + S 25 mg, T 0.25 mg + S 50 mg, T 0.5 mg + S 25 mg, T 0.5 mg + S 50 mg, and T 0.25 mg + B 5 mg, T 0.25 mg + B 10 mg, T 0.5 mg + B 5 mg, T 0.5 mg + B 10 mg).

Outcomes: The primary efficacy measure was the change in satisfying sexual events (SSEs) from the 4-week baseline to the 4-week average of the 8-week active treatment period after medication intake. For the primary end points, the combination treatments were compared with placebo and the respective monotherapies on this measure.

Results: In women with low sensitivity for sexual cues, 0.5 mg T + 50 mg S increased the number of SSEs from baseline compared with placebo (difference in change [Δ] = 1.70, 95% CI = 0.57−2.84, P = .004) and monotherapies (S: Δ = 1.95, 95% CI = 0.44−3.45, P = .012; T: Δ = 1.69, 95% CI = 0.58−2.80, P = .003).

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In women with overactive inhibition, 0.5 mg T + 10 mg B increased the number of SSEs from baseline compared with placebo (Δ = 0.99, 95% CI = 0.17−1.82, P = .019) and monotherapies (B: Δ = 1.52, 95% CI = 0.57−2.46, P = .002; T: Δ = 0.98, 95% CI = 0.17−1.78, P = .018). Secondary end points followed this pattern of results. The most common drug-related side effects were flushing (T + S treatment, 3%; T + B treatment, 2%), headache (placebo treatment, 2%; T + S treatment, 9%), dizziness (T + B treatment, 3%), and nausea (T + S treatment, 3%; T + B treatment, 2%).

Clinical Implications: T + S and T + B are promising treatments for women with FSIAD.

Strengths and Limitations: The data were collected in 3 well-designed randomized clinical trials that tested multiple doses in a substantial number of women. The influence of T + S and T + B on distress and the potentially sustained improvements after medication cessation were not investigated.

Conclusions: T + S and T + B are well tolerated and safe and significantly increase the number of SSEs in different FSIAD subgroups. **Tuiten A, van Rooij K, Bloemers J, et al. Efficacy and Safety of On-Demand Use of 2 Treatments Designed for Different Etiologies of Female Sexual Interest/Arousal Disorder: 3 Randomized Clinical Trials. J Sex Med 2017;XX:XXX−XXX.**

Key Words: Female Sexual Interest/Arousal Disorder; Personalized Medicine; On-Demand Treatment; Testosterone; Sildenafil; Buspirone

INTRODUCTION

Low sexual desire and/or arousal are the most common sex-related complaints reported by women.[1,2] This often results in sexual dissatisfaction, which in turn affects psychological well-being and can result in severe personal distress.[3] These complaints are classified in the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (DSM-5) as female sexual interest/arousal disorder (FSIAD).[4] Although effective pharmacologic treatments for erectile dysfunction have been available for 2 decades,[5] there are limited treatment options for women with FSIAD. There is a clear need for pharmacologic treatment options, which is evident from the large number of off-label testosterone prescriptions for women with sexual dysfunction in the United States (∼4.1 million annually).[6] Attempts to develop a drug treatment for FSIAD have been guided by the principle of "1 size fits all" but have failed to acknowledge the complexity of female sexuality. The US Food and Drug Administration (FDA) recently approved flibanserin (Addyi; Sprout Pharmaceuticals, Raleigh, NC, USA) for the treatment of hypoactive sexual desire disorder (HSDD; the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision* [DSM-IV-TR] classification of low sexual desire problems) in premenopausal women, making it the first drug for this indication. However, this was not without controversy.[7] The average treatment effects were small, with only approximately 10% more patients on flibanserin reporting clinically meaningful improvement compared with placebo. Moreover, there were major safety concerns.[8] Another drug candidate for HSDD is the injectable bremelanotide, which has recently successfully completed 2 phase 3 trials,[9] albeit with a high incidence of adverse events. Such 1-size-fits-all approaches inherently leave many women untreated, which is the reason we have taken a different approach.

We describe the development of 2 on-demand products for the treatment of FSIAD that use a novel personalized approach to sexual medicine.[10] This approach to treatment is guided by known neurobiological mechanisms that are critically important in sexual excitation and inhibition.[11−14] In 1 subgroup of patients, low sexual desire or arousal results from a central nervous system that is relatively insensitive to sexual cues. In these individuals, exposure to sexual stimuli (internal or external) fails to trigger activation of the brain's sexual excitatory mechanisms. In another subgroup of patients, FSIAD symptoms result from dysfunctional high levels of sexual inhibition elicited by sexual stimulation.[10,15−17]

The 2 drug treatments described in this article are based on a delay in the effect of sublingual testosterone (T) on sexual motivation or desire. The administration of a single dose of 0.5 mg sublingual T produces a short-duration peak in the plasma level of T within 15 minutes, with a return to baseline within 2 to 3 hours.[18,19] However, during a period of 3 to 6 hours after peak plasma levels, sublingual T produces an increase in vaginal arousal and in subjective sexual responses in sexually functional women.[18,20] This delay in the effect of T has been observed in other emotional and cognitive functions[21,22] and likely involves protein synthetic events caused by T in the hypothalamus and elsewhere. Interestingly, the exogenously induced peak in T mimics the endogenous peak that occurs naturally during ovulation, and it is during this phase of the menstrual cycle that women typically experience increased sexual motivation and desire.[23−25]

For men and women, an increase in sexual motivation is required for phosphodiesterase type 5 inhibitors to increase genital vasocongestion. Conversely, sublingual T increases the brain's responses to sexual cues, which in turn increases sexual motivation and primes a conscious awareness of sexual