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FEMALE SEXUAL FUNCTION

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 $[\Delta] = 1.70$, 95% CI = 0.57–2.84, $P = .004$) and monotherapies (S: $\Delta =$

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1.95, 95% CI = 0.44–3.45, $P = .012$; T: $\Delta = 1.69$, 95% CI = 0.58–2.80, $P = .003$). In women with overactive inhibition, 0.5 mg T + 10 mg B increased the number of SSEs from baseline compared with placebo ($\Delta = 0.99$, 95% CI = 0.17–1.82, $P = .019$) and monotherapies (B: $\Delta = 1.52$, 95% CI = 0.57–2.46, $P = .002$; T: $\Delta = 0.98$, 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 2018;15:201–216.**

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

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

desire.^{10,15,26} Accordingly, the treatment developed for women with low sensitivity to sexual stimuli consists of a novel (dual-route, dual-release, fixed-dose) combination tablet consisting of a T coating for sublingual administration and an inner-core component containing the phosphodiesterase type 5 inhibitor sildenafil (S). The inner-core component is coated with a delayed-release matrix to ensure that the peak plasma concentration of the phosphodiesterase type 5 inhibitor coincides with the window of increased sexual motivation induced by the sublingual T.²⁷ Thus, this combination enables an increase in genital arousal through an increase in responsivity to sexual stimuli. The treatment developed for women with high levels of sexual inhibition also is a combination tablet coated with T and combined with an inner-core component²⁸ containing the 5-hydroxytryptamine (5-HT)_{1A} receptor agonist buspirone (B). The inner core of B also is coated with a delayed release matrix, which ensures that the pharmacologic effects of B coincide with the sexual motivational window induced by T. The requisite serotonergic effect of B is based on studies in which acute treatments with 5-HT_{1A} receptor agonists were found to decrease extracellular concentrations of 5-HT.^{29,30} This in turn dampens 5-HT's phasic inhibitory control in the prefrontal cortex.^{30,31} Thus, during exposure to sexual stimuli, female participants who are prone to sexual inhibition respond to this combined treatment with an increase in physiologic and subjective sexual responses.¹⁷ These 2 combination tablets are designed to be taken "on demand" (ie, only when desired, rather than continuous daily, like flibanserin).

The personalized approach was further enhanced by the invention of a novel demarcation formula based on a combination of genetic, hormonal, and psychological variables that predict decreased sexual excitation or increased sexual inhibition. Accordingly, before the start of treatment, the demarcation formula was used to classify patients with FSIAD into 1 of the 2 subgroups: participants with low levels of sensitivity and participants with high levels of inhibition. In each identified subgroup, we tested the efficacy of placebo, the monotherapies, and 4 different dose combinations of the tablet (see [Methods](#)) associated with the right treatment group in randomized controlled trials. The primary end point was the change in the number of sexually satisfying events (SSEs) from the 4-week baseline to the 4-week mean of the 8-week active treatment period (ATP). This change in the primary end point was recorded for various control conditions (ie, placebo, monotherapies, and active treatments [T + S and T + B]). It was anticipated based on earlier proof-of-concept studies that the 2 combination drugs (especially at the highest doses) would show the highest level of efficacy compared with the control conditions.^{16,17}

METHODS

Ethics Statement

The study protocol was approved by the central institutional review board Chesapeake IRB (Columbia, MD, USA). The

study was carried out in compliance with the Declaration of Helsinki (2008) and with the International Conference on Harmonization Good Clinical Practice guidelines for clinical research (1996).

Study Design and Oversight

Double-blinded, randomized, placebo-controlled, dose-finding phase 2 studies (identical in study design) were conducted at 16 sites in the United States. Data were collected, managed, and analyzed under the supervision of the sponsor, which was monitored by Rasmussen Biotech and Pharma Consulting LLC (Princeton, NJ, USA). The participants, investigators, and site personnel were blinded to study treatment until database lock, as were the sponsor and those members of the vendors' staff who were involved (eg, site monitors). The first study started on September 27, 2011 (first screening visit) and the final study ended on September 26, 2014 (database lock). The PSR-Group (Hoofddorp, The Netherlands) was responsible for data management. The trials are registered under identifiers NCT01432665, NCT01743235, and NCT02101203 ([ClinicalTrials.gov](#)).

Study Population

The requisite sample size was determined by a power analysis, which took account of the effect sizes found in previous studies.^{16,17} The female participants included in this study were 21 to 70 years old and had been diagnosed with HSDD (based on DSM-IV-TR criteria),³² with or without FSAD, but were otherwise healthy. Our inclusion criteria also were consistent with the current DSM-5 diagnosis of FSIAD. All diagnoses were performed by a trained professional. A demarcation formula was used to assign participants to 1 of the 2 FSIAD subgroups (see text and [eTables 1–3](#) and [eFigures 1 and 2](#) of the supporting information for a description of the formula and its development). Participants who had been diagnosed with any psychiatric disorder other than FSIAD were excluded. Those scheduled for any other treatment for female sexual dysfunction during the study period also were excluded. Potential participants were excluded if they were using oral contraceptives containing anti-androgens, estrogen more than 50 µg, potent cytochrome P450 3A4 inhibitors or inducers, nitrates, monoamine oxidase inhibitors, antidepressants, and/or T compounds. The cardiovascular exclusion criteria included a history of myocardial infarction, stroke, or life-threatening arrhythmia in the previous 6 months. Other criteria were uncontrolled hypertension, hypotension, atrial fibrillation or flutter, or any other significant abnormality observed on an electrocardiogram. The gynecologic exclusion criteria included pelvic inflammatory disease, vaginal infection, previous prolapse and incontinence surgery affecting the vaginal wall, abnormal uterine bleeding patterns, pregnancy, and breastfeeding in the past 6 months. Perimenopausal women were excluded, which was defined as cycle shortening or irregular menstrual bleeding in the past 12 consecutive months and/or

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) diagram shows the number of participants screened, randomized, completed, and analyzed (intention-to-treat group). The number of participants randomized ($n = 497$) differs from the total number allocated ($n = 469$) because 1 placebo arm was disqualified (see below). Imputation was used for missing data of participants who had been discontinued but who had yielded data in at least 2 4-week periods (during the PRI period and the ATP, an observation corresponds to ≥ 1 reported SED with medication intake). ATP = active treatment period; CAG = cytosine, adenine, guanine; PRI = placebo run-in; SED = Sexual Event Diary (primary outcome measure). Figure 1 is available in color online at www.jsm.jssexmed.org.

occurrence of vasomotor symptoms (eg, hot flashes, nocturnal sweats) in combination with increased follicle-stimulating hormone levels (>40 IU/L) for women at least 40 years old; for women with a history of hysterectomy, perimenopausal status was determined by assessing follicle-stimulating hormone levels (>40 IU/L) and/or vasomotor symptoms. Women with clinically relevant endocrine disease, neurologic disease, severe or acute liver disease, or a history of severe hepatic impairment were excluded. Participants were excluded if they had free and/or total T levels that were beyond the upper limit of the central laboratory's reference range. All participants provided written informed consent.

497 women were randomized to 1 of the 12 treatment regimens (Consolidated Standards of Reporting Trials [CONSORT] diagram, Figure 1): placebo, the monotherapies (T 0.5 mg, S 50 mg, and B 10 mg), and 4 types of combination tablets (containing different dose combinations). In participants with low levels of sensitivity, the doses of T + S (milligrams) were T 0.25 + S 25, T 0.25 + S 50, T 0.5 + S 25, and T 0.5 + S 50. The corresponding doses of T + B (milligrams) for participants

with high levels of inhibition were T 0.25 + B 5, T 0.25 + B 10, T 0.50 + B 5, and T 0.50 + B 10 (Figure 2).

Study Objective

The objectives of the clinical research program were to investigate efficacy and safety and to perform dose selection of T + S and of T + B. The goal was to include 210 women in each FSIAD subgroup using the demarcation formula according to the decision tree depicted in Figure 2.

Study Procedures

After a baseline period of 4 weeks, participants underwent an 8-week, single-blinded, placebo run-in (PRI) period, which was intended to stabilize placebo responses before active treatment. The PRI period was followed by an 8-week, double-blinded ATP. Those participants who according to the demarcation formula had low sensitivity (and therefore allocated to T + S treatments) were randomly assigned to 1 of the following treatment arms: (i) placebo, (ii) S 50 mg, (iii) T 0.50 mg,

The participants were interviewed every 4 weeks, at which time they also completed questionnaires designed to assess sexual function and mood. In addition, their vital signs were measured, any signs of hyperandrogenism were evaluated, a pregnancy test

The demarcation formula consisted of 5 biological and 5 psychological variables that are involved in sensitivity to sexual stimuli and sexual inhibition. 4 biological variables are markers of androgenic activity, known to influence sensitivity to sexual stimuli. The 2nd digit to 4th digit ratio (2D:4D) is a marker for prenatal T exposure, which has a critical influence on brain organization during the fetal period.^{33–35} High digit ratios are assumed to have a relatively low sensitivity to sexual cues. The trinucleotide cytosine-adenine-guanine (CAG) repeat expansion of the 1st exon of the androgen receptor polymorph is variable. Longer CAG repeats result in weaker receptor transactivation, resulting in less effective function of the androgen system.^{36,37}

Women with longer CAG repeats might be relatively insensitive to sexual stimuli. The physiologic effects of androgens in women are determined not only by serum testosterone but also by the peripheral conversion of its precursors. The levels of the 2 main metabolites of androgens—androsterone glucuronide and 3- α -androstenediol glucuronide—could be better markers for androgenicity in women.³⁸ Higher levels of these metabolites would be reflective of higher sensitivity to sexual stimuli. The 5th biological variable is the 5-HT_{1A} receptor genotype. There are 3 genotypes: CC, CG and GG. The GG genotype is believed to increase the expression of the presynaptic somato-dendritic 5-HT_{1A} autoreceptor, which indicates enhanced “braking” of the presynaptic serotonergic neuron, decreasing the activity of the serotonin system. The serotonin system with a G allele is characterized by relatively low basal (tonic) activity, a feature that is associated with disinhibition.^{39,40} In these women, stimuli (including threatening stimuli) more easily evoke an emotional response. Women who have had adverse sexual experiences might initially desire sex but, when exposed to actual stimuli, might experience a relatively high phasic serotonin response that leads to sexual inhibition. Conversely, women with the CC genotype might have a serotonin system that is characterized by relatively high basal (tonic) activity, which might be associated with a system that is less sensitive to threatening and rewarding stimuli.

The 5 psychological variables consisted of 5 5-point Likert scale items that assessed mental arousal and excitement, orgasmic function, masturbation frequency, sensitivity to socio-sexual stimuli (“I enjoy watching sexually attractive people”), and repulsion to sexual arousal (“I am repulsed by sexual feelings”).

See the supporting information for an elaborate description of the demarcation formula and its components.

Medication, Dosing, and Instructions

Sublingual Testosterone + Sildenafil (T + S)

This drug is a dual-route, dual-release, fixed-dose combination of T and S citrate.²⁷ The drug product is a 9-mm, round, biconvex, white, menthol-flavored tablet for sublingual administration. The outer coating (a polymeric film) contains T (0.5 mg) that is released immediately at sublingual administration. The inner core of the tablet, which contains S (50 mg), has a polymeric coating designed to delay the release of that drug for approximately 2.5 hours. When that period elapses, S is released immediately (ie, there is no sustained release).

Sublingual Testosterone + Buspirone (T + B)

This drug is a dual-route, dual-release, fixed-dose combination of T and B hydrochloride.²⁸ The drug product is a 9-mm, round, biconvex, white, menthol-flavored tablet for sublingual and oral administration. The appearance, method of administration, and flavor of T + B are identical to those of T + S. The outer polymeric-film coating contains T (0.5 mg) that is released

immediately at sublingual administration. The inner core of the tablet contains B hydrochloride (10 mg). This inner core has a polymeric coating designed to delay the release of B for approximately 2.5 hours. When that period elapses, B is released immediately (ie, there is no sustained release).

The placebo tablets were identical in appearance and flavor to the fixed-dose combination T + S and T + B tablets containing the active pharmaceutical ingredients. All study medication was manufactured and packaged at Piramal Healthcare UK (Morpeth, UK).

Participants were instructed to keep the tablet under their tongues for 90 seconds and then to swallow it whole, without chewing it or otherwise disrupting the dosage form. They were permitted to take the tablet with a little water. The participants were instructed to engage in sexual activity 3 to 6 hours after ingestion. The dosing instructions were the same for all regimes.

28 doses were provided in the 8-week treatment period. The participants were asked to endeavor to take a minimum of 1 dose per week. They were informed that they could take the remaining doses as required (ie, on demand) throughout the 8-week treatment period. The minimum period between individual doses was 2 days (ie, on alternate days).

Randomization and Masking

Participants who met the inclusion and exclusion criteria were randomized and allocated to a treatment sequence. The randomization list was designed by an independent statistician at Pharma Consulting Group (Uppsala, Sweden). Randomization was performed using an interactive web response system (Viedoc; Pharma Consulting Group), with a unique numeric medication code from the randomization list being assigned to each randomized subject. The corresponding medication kit (bearing the same unique number) was sent to the site by the warehouse where the study medication was stored (Sentry BioPharma Services Inc, Indianapolis, IN, USA). The factors body mass index and menopausal status (pre- or postmenopausal) were balanced across treatment arms. A unique subject identification code was used to ensure that the data were anonymous. Access to the key to this identification code was restricted. An 8-week, single-blinded PRI period was used to dampen the usual placebo effect during active treatments. Investigators were aware that all participants received placebo during the PRI period, but the participants were not. The investigators and site personnel involved were given appropriate instruction and training to minimize potential effects of this knowledge. The blinding could be broken only under exceptional circumstances, for example, if the investigator believed that it was vital for the medical management of the participant in question. In such cases, investigators were required to contact the sponsor’s medical monitor who had access to the sealed code envelopes.

Outcomes and Assessments

Primary and secondary outcome variables were measured using the validated Sexual Event Diary (SED).⁴¹ The SED is a secure web-based diary that participants were required to complete within a period of 24 hours after each sexual event. This information was used to assess each participant's satisfaction and sexual functioning during that event. Participants were asked to indicate whether the event was satisfactory and whether they experienced an orgasm (dichotomous items). They also were asked to indicate the associated levels of sexual desire, pleasure, bodily arousal, and subjective arousal (using 5-point Likert scale items). In addition, they were asked for details of the type and duration of the sexual event in question and whether they used the study medication before that event.

The primary end point was the change in the number of SSEs (as recorded by the SED) in the interval from the 4-week baseline to the 4-week mean of the 8-week ATP. This end point is one of the FDA's accepted primary end points for clinical trials in HSDD and FSIAD. The following formula was used to calculate change in the number of SSEs from baseline (ΔSSE) for each participant:

$$\Delta SSE = \frac{(\sum SSE_{ATP1-4} + \sum SSE_{ATP5-8})}{2} - \left(\sum SSE_{BLE1-4} \right)$$

where ATP1–4 represents ATP weeks 1 through 4, ATP5–8 represents ATP weeks 5 through 8, and BLE1–4 represents baseline establishment at weeks 1 through 4. The key secondary end point was the change (during the same interval) in the cumulative level of subjective sexual satisfaction (4-item mean of desire, pleasure, bodily arousal, and subjective arousal) during the SSEs produced by the treatments. Another secondary end point was the change in the number of orgasms (as recorded by the SED) from the 4-week baseline to the 4-week mean of the 8-week ATP. The PRI period was not used in the analyses because it was intended only to stabilize placebo responses.

Additional secondary outcome variables were assessed using the Weekly Diary (WD). Each week, participants filled out the WD at home using the same secure web-based platform as the SED. The WD assessed how often participants experienced sexual desire and arousal during the preceding week, ranging from “not at all” to “more than a couple of times a day” on a 6-point scale. Also, subjects were asked whether the perceived change was caused by the study medication.

For a description of the hormone and biomarker assays, see the supporting information.

Statistical Analyses

To assess the primary end point, interaction effects were calculated among the highest-dose combinations, the placebo condition, and the monotherapies (S or B and T alone). This allowed the comparison of the change in the number of SSEs from the 4-week baseline establishment period to the 4-week mean of the 8-week ATP. The primary end point and the

method of analysis were agreed upon with the regulatory agencies (FDA and European Medicines Agency [EMA]). A similar approach was used to assess the key secondary end point and the other secondary end points. The interaction effects were derived by using regression analyses on each imputed dataset (see supporting information for a description of the imputation methods). The difference between baseline and active treatment was used as the dependent variable and the treatment group indicator was used as the independent variable. The regression coefficient of the treatment group indicator represents the difference in change from baseline between the 2 treatment groups. Regression coefficient estimates and standard errors were combined according to Rubin's Rules.^{42,43}

The α value was set at 0.05 (2-sided). Statistical analyses were performed in line with the statistical analysis plan as described in the clinical study protocols (see supporting information; note that the SED was formerly named SSEQ) using IBM SPSS Statistics 21.0 for Windows (IBM Corp, Armonk, NY, USA) and R 3.2 (The R Project for Statistical Computing, The R Foundation, Vienna, Austria).

The safety analysis population consisted of all those participants who received at least 1 dose of study medication. Descriptive statistics were calculated for all safety data. All adverse events were listed, as were the number of participants in each treatment group involved and details of the incidence of these events. For the incidence assessment, cases in which a single participant experienced adverse events on more than 1 occasion were counted as single incidents.

RESULTS

Of 1,126 women who were screened, 497 were randomized to 1 of the 12 treatment regimens. Data from 397 participants were analyzed (CONSORT diagram, Figure 1). Baseline characteristics and demographics are presented in Table 1. Baseline hormonal values were in the normal female reproductive and/or postmenopausal range. None of the dependent variables were influenced by menopausal status or hormonal contraception.

Safety

Treatments with T + S and T + B were well tolerated. No serious adverse events related to treatment were reported, and no safety concerns with respect to vital signs, signs of hyperandrogenism, or laboratory values were detected. Sublingual T administration did not show a treatment-related increase on endogenous T levels when comparing the start of the ATP with follow-up (Table S4). The most common drug-related side effects were flushing (1 participant reported this during T + S treatment [3%] and 1 during T + B treatment [2%]), headache (1 participant reported this during placebo treatment [2%] and 3 during T + S treatment [9%]), dizziness (2 participants reported this during T + B treatment [3%]), and nausea (1 participant reported this during T + S treatment [3%] and 1 during T + B treatment [2%]).

Table 1. Baseline characteristics and demographics

Characteristics	Sample (N = 397)
Age (y), mean $\pm$ SD	44.1 $\pm$ 11.2
Race, n (%)	
Caucasian	281 (70.8)
Black	81 (20.4)
Asian	5 (1.3)
Other	30 (7.6)
BMI (kg/m ²), mean $\pm$ SD	27.6 $\pm$ 6.4
Menopausal status, n (%)	
Premenopausal	280 (70.5)
Postmenopausal	117 (29.5)
Contraceptive, n (%)	
Hormonal	96 (24.2)
Contraceptive pill	58 (14.6)
IUD (levonorgestrel)	26 (6.5)
Vaginal ring (progestin and estrogen)	4 (1)
Other (implant, patch)	8 (2.0)
Non-hormonal (condoms, sterilization)	212 (53.4)
None	89 (22.4)

BMI = body mass index; IUD = intrauterine device.

Efficacy

Primary End Point

Figure 3 (upper panel) shows the results in changes in SSEs between baseline measurement and the T + S treatment arms (ie, ATP minus baseline) and between the control conditions (placebo and T and S monotherapies) and the active treatments (T + S). Because the T + S and T + B studies were identical, and because the samples were relatively small, with a substantial amount of patient attrition, we chose an integrative data analysis approach and pooled the results of placebo and T of the 2 studies for the comparison with the responses of the different dosages of T + S and T + B. Omission of an anomalous placebo arm (see below) inflated the attrition rates. Attrition was equally distributed over the PRI period and ATP and over treatment arms. Table 3 presents the results over the 3 trials separately (un-pooled data).

Results are presented for the placebo, S 50 mg, T 0.5 mg, and the 4 dose combinations of T (0.25 and 0.5 mg) + S (25 and 50 mg) compared with the baseline measurement for each of these conditions. The change in the number of SSEs from baseline was significantly higher in the T 0.5 + S 50 condition than for the (i) placebo (difference in change Δ = 1.70 SSEs, 95% CI = 0.57–2.84, P = .004), (ii) S (Δ = 1.95, 95% CI = 0.44–3.45, P = .012), and (iii) T (Δ = 1.69, 95% CI = 0.58–2.80, P = .003; Figure 3) conditions. The effect sizes (Cohen d) showed large effects (approximately 0.7) for the comparison between the 0.5 T + 50 S group and the placebo, S, and T groups (Table 2).

Figure 3 (lower panel) presents the results for the placebo, B 10 mg, T 0.5 mg, and the 4 dose combinations of T (0.25 and

0.5 mg) + B (0.50 and 10 mg). There was an anomalous placebo effect in the study investigating T + B. Although the increase in SSEs between baseline and ATP was statistically significant for the highest dosage of T + B and in the expected direction, this effect was diluted by an enormous increase in SSEs in the placebo condition. All analyses indicated that this observation was an anomaly and a statistical outlier condition. See supporting information eFigure 3 and text for a description of the anomalous result and all investigations and analyses performed. In consultation with the regulatory authorities (EMA and FDA), we conducted an additional 2-arm study comparing placebo with the highest dose of T + B. The results of this additional study, which were used to replace those of the anomalous condition, were included in the present analysis. The results for T + B showed that the change in the number of SSEs from baseline was significantly higher than the values associated with the placebo (Δ = 0.99, 95% CI = 0.17–1.82, P = 0.019), B (Δ = 1.52, 95% CI = 0.57–2.46, P = .002) and T (Δ = 0.98, 95% CI = 0.17–1.78, P = .018; Figure 3) conditions. For the effect sizes, the comparison between the 0.5 T + 10 B condition and the placebo (0.47) and T (0.46) indicated medium effects. A large effect size was found for the comparison with B (0.78; Table 2).

Secondary End Points

Because the highest-dose combinations outperformed the lower-dose combinations for the primary end point in the 2 subgroups, secondary end points were assessed for the highest-dose combinations compared with the placebo and monotherapies.

The change in subjective sexual satisfaction from baseline was significantly larger in the 0.5 T + 50 S condition compared with the placebo (Δ = 6.01, 95% CI = 1.64–10.39, P = .008), S (Δ = 6.35, 95% CI = 0.71–12.00, P = .028), and T (Δ = 5.75, 95% CI = 1.72–9.79, P = .006; Figure 4A) conditions. The effect sizes (Cohen d) showed medium to large effects for the comparison between the 0.5 T + 50 S group and the placebo (0.66), S (0.62), and T (0.67; Table 2) groups. The change in the number of orgasms from baseline was significantly larger in the 0.5 T + 50 S condition compared with placebo (Δ = 1.10, CI = 0.09–2.11, P = .033; Figure 4C), with a medium effect size of 0.53 (Table 2). Although the increase in the number of orgasms did not show a significant difference between 0.5 T + 50 S and T, Cohen d showed a medium effect in the difference in the increase in orgasms (0.41; Table 2 and Figure 4C).

The change in subjective sexual satisfaction from baseline was significantly larger in the 0.5 T + 10 B condition compared with the placebo (Δ = 3.54, 95% CI = 0.43–6.66, P = .026), B (Δ = 5.12, 95% CI = 1.62–8.63, P = .005), and T (Δ = 3.29, 95% CI = 0.41–6.16, P = .026; Figure 4B) conditions. The effect sizes (Cohen d) showed medium effects for the 0.5 T + 10 B group compared with placebo (0.44) and T (0.44) and a large effect for the 0.5 T + 10 B condition compared with B (0.70;

Figure 3. Results for primary end point in all T + S and T + B treatment arms. The top and bottom panels show mean change in the number of SSEs between baseline and each of the treatment arms (error bars = standard error of the mean) for the T + S and T + B studies, respectively. The levels of significance of these changes are indicated above the associated bars. *P* values above the lines between 2 bars represent statistically significant interaction effects in the changes in the number of SSEs at the highest-dose combination compared with the placebo and monotherapies. Variances between the groups being compared were equal. Bars and error bars represent raw (non-imputed) data. *P* values and numbers shown are based on the multiply imputed data. B = buspirone; S = sildenafil; SSEs = satisfactory sexual events; T = testosterone.

Table 2. Mean differences in change from baseline between treatments—pooled data*

Comparison with T + S maximum dose																
Placebo				S				T								
	MD	SE	95% CI	Cohen d	MD	SE	95% CI	Cohen d	MD	SE	95% CI	Cohen d				
Primary end point																
	SSE (SED)	1.704	0.569	0.57	2.837	0.721	1.945	0.749	0.439	3.451	0.715	1.688	0.558	0.577	2.799	0.716
Key secondary end point	SSS (SED)	6.011	2.196	1.635	10.388	0.658	6.353	2.808	0.71	11.996	0.623	5.754	2.026	1.722	9.786	0.673
Secondary end point	orgasm (SED)	1.101	0.506	0.093	2.108	0.525	0.762	0.702	-0.649	2.173	0.3	0.851	0.495	-0.134	1.836	0.408
Comparison with T + B maximum dose																
Placebo				B				T								
	MD	SE	95% CI	Cohen d	MD	SE	95% CI	Cohen d	MD	SE	95% CI	Cohen d				
Primary end point																
	SSE (SED)	0.992	0.414	0.17	1.815	0.472	1.517	0.474	0.573	2.462	0.775	0.977	0.406	0.171	1.782	0.463
Key secondary end point	SSS (SED)	3.544	1.571	0.426	6.661	0.444	5.121	1.759	1.615	8.627	0.702	3.287	1.451	0.409	6.164	0.436
Secondary end point	orgasm (SED)	0.778	0.358	0.068	1.487	0.432	1.094	0.434	0.229	1.96	0.612	0.528	0.35	-0.166	1.222	0.292

B = buspirone; MD = mean difference; SE = standard error; SED = Sexual Event Diary; SSS = subjective sexual satisfaction; T = testosterone.
*Comparisons of T + S treatment subgroup: T 0.5 mg + S 50 mg vs placebo, T 0.5 mg + S 50 mg vs T, and T 0.5 mg + B 10 mg vs T.
placebo, T 0.5 mg + B 10 mg vs B, and T 0.5 mg + B 10 mg vs T.

Table 2). The change in the number of orgasms from baseline was significantly larger in the 0.5 T + 10 B condition compared with placebo ($\Delta = 0.78$, 95% CI = 0.07–1.49, $P = .032$) and B ($\Delta = 1.09$, 95% CI = 0.23–1.96, $P = .014$; Figure 4D). The effect sizes showed a medium effect for the 0.5 T + 10 B group compared with placebo (0.43) and a medium to large effect for the comparison with B (0.61; Table 2). Table 3 presents secondary end-point results over the 3 trials separately (un-pooled data).

Figure S4 shows the analyses of the secondary end points desire, arousal, and perceived drug-related improvement as assessed by the WD. The 2 highest-dose combinations outperformed the placebo condition and the monotherapies. Our analysis also showed significant interaction effects, with medium to large effect sizes (eTable 5).

DISCUSSION

This report describes a personalized medicine approach to differentiate and treat 2 possible etiologies in FSIAD: women with low sensitivity to the central processing of sexual cues vs high levels of inhibition to such processing. This approach differs from the traditional 1-size-fits-all approach, which assumes that a drug works for everyone with the same complaint. However, in general, a significant percentage of patients do not respond at all and some respond even counterproductively. We started a research program with the assumption that apparently different underlying mechanisms are responsible for the same symptoms and complaints (in our case, low sexual desire) in patients. The present results demonstrate the clinical utility of this approach. The highest-dose combinations of T + S and T + B produced statistically significant increases in the number of SSEs and outperformed the placebo and monotherapies over an 8-week period for subjective sexual satisfaction. Thus, the combination of T + S appears to be very promising as a potential personalized, on-demand treatment option for individuals with FSIAD who have low sensitivity to sexual cues. The same is true of the combination of T + B for individuals with FSIAD resulting from the over-activation of sexual inhibitory mechanisms. An increase of 1 to 2 SSEs was reported to be clinically relevant in a sample of 450 pre- and postmenopausal women with self-described low sexual desire and related distress.⁴⁴ The increases reported in the present studies range from 1 to 2 SSEs per 4 weeks. Moreover, this number is substantially larger than the pooled mean differences for SSE change from baseline of flibanserin vs placebo, which was 0.49.⁷ Therefore, it is anticipated that the increases induced by T + S and T + B are clinically relevant. Treatments with T + S and T + B were well tolerated, there were few adverse events, no serious treatment-related adverse events were reported, and there were no safety concerns with respect to vital signs, signs of hyperandrogenism, or laboratory values.

Despite approving flibanserin for the treatment of HSDD, the FDA has the opinion that there is still “a medical need for development of drugs with a favorable benefit-risk profile to treat

Figure 4. Results for subjective sexual satisfaction and orgasm at the highest-dose combinations for placebo and monotherapies. Panels A and B show the comparisons between the high-dose combinations (T 0.5 + S 50 and T 0.5 + B 10, respectively) and the placebo and monotherapies (T 0.5, S 50, B 10) for change from baseline in subjective sexual satisfaction. Panels C and D show the comparisons between the high-dose combinations and the placebo and monotherapies, respectively, for change in arousal from baseline. Panels C and D also show the comparisons of high-dose combinations with placebo and monotherapies, respectively, for change in the number of orgasms from baseline. *P* values above each bar represent the level of significance of the change from baseline in the treatment arm in question. *P* values above the lines between 2 bars represent the interaction effects in changes of subjective sexual satisfaction and the changed number of orgasms at the highest-dose combination compared with placebo and monotherapies. Variances between the groups being compared were equal. The bars and error bars represent the raw (non-imputed) data. *P* values and numbers are based on multiply imputed data. Imputed data analysis did not differ substantially from the complete case analysis. B = buspirone; NS = not significant; S = sildenafil; SED = Sexual Event Diary; T = testosterone.

women with sexual dysfunction.”⁴⁵ However, there has been much discussion about the pros and cons of pharmacologic and psychological treatments of HSDD and FSIAD. A recent review article describing pharmacologic and psychological approaches for the treatment of HSDD and FSIAD showed that progress has been made on both sides.⁴⁶ Psychological treatments and pharmacologic treatments have shown promising effects, but comparisons between the 2 remain difficult. In psychological studies, the end points are multidimensional (eg, quality of relationship, self-esteem) and differ from the pharmacologic end points (eg, SSE, sexual desire). Moreover, trials investigating psychological treatments face methodologic challenges that pharmacologic trials do not have (eg, the inability to blind subjects for

treatment), making them prone to bias.⁴⁶ However, the 2 treatment approaches and innovative studies thereof remain vital to our field.

A leading idea in our research is that disorders such as FSIAD result from an interplay among biological (genetic) influences, experiences, and current circumstances. For example, high sexual inhibition might result from, on the one hand, the combination of genes, hormones, and neurotransmitters that increase the brain's sensitivity to sexual cues (biological level) and, on the other hand, a negative attitude toward sex, which could be caused by different influences, such as upbringing, (first) sexual and romantic experiences, peer relationships, and so on. A system sensitive to sexual stimuli combined with positive sexual

Table 3. Mean differences in change from baseline between treatments—un-pooled data over 3 trials*

		Comparison with T + S maximum dose																	
		Placebo						S					T						
		MD	SE	95% CI		<i>P</i> value	Cohen d	MD	SE	95% CI		<i>P</i> value	Cohen d	MD	SE	95% CI		<i>P</i> value	Cohen d
Primary end point	SSE (SED)	1.438	0.682	0.066	2.809	.040	0.58	1.945	0.749	0.439	3.451	.012	0.715	1.383	0.617	0.144	2.621	.029	0.606
Key secondary end point	SSS (SED)	4.709	2.667	−0.651	10.069	.084	0.486	6.353	2.808	0.710	11.996	.028	0.623	4.879	2.263	0.336	9.423	.036	0.583
Secondary end point	orgasm (SED)	0.923	0.614	−0.310	2.156	.139	0.415	0.762	0.702	−0.649	2.173	.283	0.3	0.547	0.586	−0.629	1.723	.354	0.253
		Comparison with T + B maximum dose—study 1																	
		Placebo						B					T						
		MD	SE	95% CI		<i>P</i> value	Cohen d	MD	SE	95% CI		<i>P</i> value	Cohen d	MD	SE	95% CI		<i>P</i> value	Cohen d
Primary end point	SSE (SED)	1.402	0.548	0.298	2.506	.014	0.728	1.639	0.568	0.496	2.783	.006	0.815	1.415	0.599	0.211	2.620	.022	0.654
Key secondary end point	SSS (SED)	6.002	2.122	1.73	10.273	.007	0.802	6.173	2.109	1.928	10.417	.005	0.824	5.245	2.255	0.713	9.776	.024	0.642
Secondary end point	orgasm (SED)	1.308	0.488	0.324	2.292	.010	0.765	1.432	0.549	0.328	2.536	.012	0.737	1.181	0.493	0.190	2.172	.021	0.666
		Comparison with T + B maximum dose—study 2																	
		Placebo						B					T						
		MD	SE	95% CI		<i>P</i> value	Cohen d	MD	SE	95% CI		<i>P</i> value	Cohen d	MD	SE	95% CI		<i>P</i> value	Cohen d
Primary end point	SSE (SED)	1.167	0.559	0.041	2.292	.042	0.585												
Key secondary end point	SSS (SED)	3.977	2.052	−0.151	8.104	.059	0.543												
Secondary end point	orgasm (SED)	0.657	0.460	−0.270	1.584	.160	0.404												

B = buspirone; MD = mean difference; S = sildenafil; SE = standard error; SED = Sexual Event Diary; SSS = subjective sexual satisfaction; T = testosterone.

*The comparison between T + B maximum dose and placebo of study 1 uses the placebo arm of study 2. Comparisons for T + S treatment subgroup: T 0.5 mg + S 50 mg vs placebo, T 0.5 mg + S 50 mg vs S, and T 0.5 mg + S 50 mg vs T; T + B treatment subgroups: T 0.5 mg + B 10 mg vs placebo, T 0.5 mg + B 10 mg vs B, and T 0.5 mg + B 10 mg vs T; T + B treatment subgroups from additional study: T 0.5 mg + B 10 mg vs placebo.

experiences can lead to a pleasant and enjoyable sexual life. However, adverse sexual experiences can have a greater impact on those whose brains are more sensitive to sexual cues. A combination of a highly sensitive brain and adverse experiences can lead to a learned and automatic sexual inhibitory response in which sexual events and adverse associations are automatically linked. Our view reflects the possibility that biological mechanisms elicit a sexual inhibitory response that opens the window for a pharmacologic intervention. In this example, underlying biological mechanisms determine the rationale for one kind of treatment in favor of the other. However, our solution does not exclude psychological interventions as a possible treatment option, for example, those aimed at unlearning of negative sexual associations and to replace them with positive associations.

On the other side of the sexual sensitivity coin, if a patient has a brain that is relatively insensitive to sexual stimuli (eg, because of genetically or biologically determined constraints), it will be difficult or even impossible to increase sexual desire by psychological interventions alone. That said, HSDD or FSIAD is not the only result of a brain that is relatively insensitive to sexual stimuli. Experiences and circumstances are just as important or might even be decisive. A person with a relatively insensitive brain for sexual stimuli could have fewer sexual problems than someone in the same circumstances who, because of a genetic fate, has a more sensitive system. For HSDD or FSIAD, psychological interventions can help to accept these nature-given boundaries or to learn to be sexually satisfied within the context of lower level of sexual excitability.

We encourage investigating pharmacologic and psychological approaches, or combinations thereof, from a personalized perspective of this disorder, which has been described in the literature in one form or other for at least 100 years.⁴⁷ For the moment, we argue that the on-demand treatments discussed in this study clearly benefit 2 differentiated subgroups of 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. However, there are a number of limitations that deserve discussion.

Safety issues associated with the use of T in the treatment of sexual dysfunctions, particularly in women, have generated a great deal of debate. Most studies on the influence of T on female sexual behavior involve the regular administration of T (as does hormone replacement therapy in menopausal women).^{48–50} The regular administration of T and associated steady-state plasma levels have been associated with significant safety concerns. In contrast, on-demand sublingual T causes a steep increase in total and free T levels, which then return to baseline within approximately 2 hours.^{18,19} Thus, the safe, convenient, and well-tolerated sublingual dosing of T does not result in a sustained increase in T levels, which decreases untoward adverse

events. Furthermore, it is unlikely that increasing the dose of T in T + S or T + B would increase their efficacy. The increase in the free fraction of T has been hypothesized to underlie the influence of sublingual T on sexual stimulus sensitivity. Investigating 3 doses of sublingual T showed that the free fraction does not differ between doses of 0.5 and 0.75 mg but does differ between 0.25 and 0.5 mg.¹⁹

Increasing the doses of S in T + S or B in T + B could have a beneficial influence on sexual functioning in the respective subgroups. However, it is also likely that higher doses would increase the frequency and severity of adverse events related to these doses, so there would be a tradeoff with efficacy on the one hand and safety on the other, with the latter potentially inhibiting the former. We currently believe this is the optimal dose combination for this population.

Another important aspect of FSIAD that needs to be assessed is the distress experienced by patients. The finding that the 2 combination products have more robust effects on measurements of individual sexual events than they do on regular weekly measurements reflects the intrinsic on-demand nature of these products. Producing increased satisfaction in response to individual sexual events during a relatively short period of treatment has no direct effect on a patient's level of distress. Such distress can be expected to wane after a more protracted series of SSEs. The primary focus of our phase 3 program involves changes in distress coupled with changes in SSEs. It also should be noted that the beneficial sexual effects of on-demand medications are expected to produce a sustained improvement in psychological and social well-being, and it was a limitation of the present trial that we could not test this. Also, the number of subjects per arm was relatively small. This led to some analyses not being statistically significant, although the effect sizes were substantial.

The trials were designed in accordance with regulatory guidance. The single-blinded PRI periods were incorporated solely to decrease the placebo effect over time by habituation and thus increase the power of the study. Decreasing the participants' placebo responses over time makes their subsequent responses to an active treatment more valid and produces lower placebo comparator responses during the ATP. Phase 3 trials will not make use of the PRI period to mimic actual clinical practice, and by applying longer treatment periods and larger samples potential power issues will be circumvented.

The demarcation formula that was used to differentiate the 2 FSIAD subgroups appears to be valid because of the positive effects T + S and T + B had on women with low sensitivity and those with and high inhibition, respectively. However, these studies were not designed to test the efficacy of the drugs in the expected non-responder groups, so these data cannot definitively answer that question. However, previous studies have shown that women with low sensitivity do not or only minimally respond to T + B and that women with high inhibition do not or only minimally respond to T + S,^{16,17} so it is to be expected that the formula is valid.

CONCLUSIONS

The focus of the present program was to improve sexual functioning and satisfaction during sexual events. This involved the use of a personalized medicine approach to develop separate treatments for the identified patient subtypes. We have developed study medication that specifically targets underlying central and peripheral mechanisms. For these separate combination therapies to be most effective, we have applied a demarcation formula to a combination of biological and psychological variables to allocate individuals to distinct FSIAD subtypes. This personalized treatment method has proved to be successful and is very promising not only for the treatment of FSIAD but also for further investigation of novel approaches to personalized medicine in general.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.jsxm.2017.11.226>.