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To cite this article: Zoe R Belkin BS, Jill M Krapf MD & Andrew T Goldstein MD (2015) Drugs in early clinical development for the treatment of female sexual dysfunction, Expert Opinion on Investigational Drugs, 24:2, 159-167, DOI: [10.1517/13543784.2015.978283](https://doi.org/10.1517/13543784.2015.978283)

To link to this article: <http://dx.doi.org/10.1517/13543784.2015.978283>



Published online: 06 Nov 2014.



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EXPERT OPINION

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Drugs in early clinical development for the treatment of female sexual dysfunction

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Introduction: There is growing recognition of female sexual dysfunction (FSD) as an important women's health concern. Despite an increased awareness of the pathophysiologic components to FSD, currently, there are no drugs approved for the most common sexual complaint in women—decreased sexual desire. In response to an overwhelming demand for therapy for FSD, several drugs are undergoing development and testing.

Areas covered: The aim of this paper is to provide the latest data on pharmacological treatments for FSD currently in Phase I and II clinical trials. These include topical alprostadil, bremelanotide (BMT), intranasal testosterone (TBS-2), intravaginal dehydroepiandrosterone (DHEA), sublingual testosterone with sildenafil, apomorphine (APO), bupropion and trazodone. It should be noted that the definitions of FSD have recently been revised in the diagnostic and statistical manual for mental disorders (DSM) 5, with merging of hypoactive sexual desire disorder (HSDD) and female sexual arousal disorder (FSAD) into female sexual interest/arousal disorder (FSIAD). However, it is noted that the majority of clinical trials discussed in this paper use the DSM IV-R diagnoses of HSDD and FSAD.

Expert opinion: Medications in early phase trials show promise for the treatment of FSD. These therapies focus on treating many possible causes of FSD. Concerns over gender bias within the FDA need to be resolved given the need for new treatment options for FSD.

Keywords: apomorphine, bremelanotide, female sexual dysfunction treatment, intranasal testosterone, intravaginal dehydroepiandrosterone, testosterone with 5-hydroxytryptamine_{1A} receptor agonist, testosterone with phosphodiesterase type 5 inhibitor, topical alprostadil

Expert Opin. Investig. Drugs (2015) 24(2):159-167

1. Introduction

Female sexual dysfunction (FSD) has garnered increasing awareness as a widespread condition. Approximately, 30–50% of American women complain of decrease sexual desire, decreased sexual arousal or both. However, to meet the current criteria for FSD, the woman must be experiencing personal distress caused by lack of sexual desire or arousal. As such, ~10% of American women meet the criteria for hypoactive sexual desire disorder (HSDD) [1,2]. The prevalence of the new diagnosis of FSIAD has yet to be established. FSD encompasses a variety of disorders, many of which are age-related and progressive, which negatively influence emotional and social wellness, as well as overall quality of life [3]. While psychological, sociocultural and interpersonal elements contribute to sexual dissatisfaction, a number of potential pathophysiologic causes of FSD have been identified. However, efforts to establish treatments for other types of FSD are currently underway. In this article, we address the neurological, hormonal, vascular and muscular contributors to FSD in order to discuss emerging treatments for these varied etiologies of FSD. We focus on therapies that have recently undergone Phase I or II clinical trials.

Article highlights.

- Definitions of FSD have recently been revised in the DSM 5, with HSDD and FSAD merged into a single diagnosis called FSIAD. The definition of FOD remains separate.
- Alprostadil is a topical prostaglandin analogue that increases genital vasodilatation and is being studied to treat women with decreased sexual arousal.
- Bremelanotide stimulates melanocortin receptors and is being investigated as a subcutaneous injection for women with decreased desire and decreased arousal.
- Intranasal testosterone is being explored for the treatment of decreased desire and female orgasmic disorder.
- Intravaginal DHEA has shown promise in treating vaginal atrophy in postmenopausal women without raising systemic hormone levels, and may also improve desire.
- Sublingual testosterone is being studied in combination with sildenafil as well as sublingual testosterone combined with bupropion for women with hypoactive sexual desire disorder.
- Apomorphine is a nonselective dopamine agonist which is thought to enhance response to sexual stimuli.

This box summarizes key points contained in the article.

2. Classifications and definitions of female sexual disorders

The definitions of FSD have recently been revised in the diagnostic and statistical manual for mental disorders (DSM) 5. The DSM IV-R diagnoses of HSDD and female sexual arousal disorder (FSAD) have been merged in the DSM 5 into a single syndrome called female sexual Interest/arousal disorder (FSIAD). The definition of female orgasmic disorder (FOD) remains in the DSM 5. It should be noted, however, that the majority of clinical trials discussed in this paper used the DSM IV-R diagnoses of HSDD and FSAD, not the DSM 5 diagnosis of FSIAD. It is also important to note that subjective sexual arousal, a crucial component of women's sexual response, is omitted in the DSM-IV. Lastly, both the DSM-IV and the DSM-5 diagnoses require that the disorders cause significant distress or interpersonal difficulties, are not better explained by another mental disorder, drug or medical condition, and persist consistently or intermittently for a duration of at least 6 months [4,5]. The definition of FSIAD, HSDD, FSAD and FSOD are:

2.1 Female sexual interest/arousal disorder

A. The of lack of, or significantly reduced sexual interest/arousal, as manifest by at three of the following:

- i) Absent/reduced interest in sexual activity
- ii) Absent/reduced sexual/erotic thoughts or fantasies

- iii) No/reduced initiation of sexual activity, and typically unreceptive to a partner's attempt to initiate
- iv) Absent/reduced sexual excitement during sexual activity in almost all sexual encounters
- v) Absent/reduced sexual interest/arousal in response to any internal or external sexual/erotic cues
- vi) Absent/reduced genital or non-genital sensations during sexual activity in almost all sexual encounters.

B. The symptoms have persisted for a minimum of 6 months.

C. The symptoms cause significant personal distress.

2.2 Hypoactive sexual desire disorder

HSDD is characterized by a significant decline or absence of sexual fantasies and desire for sexual activity and can present in a variety of forms including acquired or lifelong [5]. HSDD has been estimated to be the most common subtype of FSD. In 2006, the US results from the Women's International Study of Health and Sexuality (WISHes) found 9 – 14% of women between the ages of 20 and 70 meet the criteria of diagnosis of HSDD [6]. This number increased to up to 26% in women who were surgically postmenopausal. Additionally, among women experiencing sexual dissatisfaction, complaints of decreased sexual desire are exceedingly common [7].

2.3 Female sexual arousal disorder

FSAD is characterized by recurrent or persistent inability to reach or maintain a state of sexual arousal. FSAD can manifest as inadequate genital lubrication and swelling in response to sexual stimuli. It is distinguished from HSDD in that desire for sexual activity is not absent [4].

2.4 Female orgasmic disorder

FOD manifests as difficulty achieving orgasm or decreased intensity of orgasm in 75 – 100% of sexual experiences [4]. Variances in FOD age are based on degree of sexual stimulation, age and sexual experience. Additionally, FOD can be diagnosed as lifelong or episodic. The prevalence of FOD is estimated to be between 4 and 7% [8].

2.5 Genito-pelvic pain/penetration disorder

Genito-pelvic pain/penetration disorders, formerly identified in the DSM IV as dyspareunia and vaginismus, encompass a broad spectrum of disorders marked by chronic or provoked vulvovaginal or pelvic pain.

3. Physiology of sexual response

Sexual desire (libido) has been shown to be modulated by the interactions of both sex steroids and neurotransmitters [8]. Although the exact central neuroendocrine mechanisms remain undiscovered, several areas of the brain including the hypothalamus and the amygdala appear important in sexual

desire [9]. There are both excitatory and inhibitory factors that can influence sexual desire. Excitatory factors (neurotransmitters and hormones) include testosterone, melanocortin, oxytocin, dopamine and norepinephrine [10]. Inhibitory factors include 5-hydroxytryptamine (5-HT), prolactin and endogenous opioids. It has been hypothesized that if the excitatory hormones and neurotransmitters are high then sexual behavior is 'tipped' in the direction of sexual desire and vice versa [8,10]. This balance between excitation and inhibition is best described by Perelman's sexual tipping point model. [10].

Nitric oxide, vasoactive peptide and acetylcholine probably all play significant roles in genital sexual arousal [11]. Sexual stimulation releases nitric oxide from the autonomic nerve supply of the smooth muscle of the genital vasculature which stimulates the release of guanylate cyclase, which then converts GTP into cGMP. This stimulates smooth muscle relaxation thereby increasing blood flow in the vulva, vagina and clitoris. In addition, vasoactive peptide and acetylcholine increase smooth muscle relaxation and increase blood flow.

While the exact central and peripheral mechanisms of orgasm are still being studied, activation in the bilateral primary somatosensory cortex, the left secondary somatosensory cortex, the left supplemental motor area and the amygdala [11] has been observed and is understood to be primarily modulated by dopamine and norepinephrine. Peripheral nervous system component of orgasm rely on the pudendal, pelvic and hypogastric nerves.

4. Therapies

As the understanding of the diversity and complexities of FSD disorders has grown, so too have the efforts to develop innovative treatment options. The following potential therapies are currently in early phase trials.

4.1 Topical alprostadil

Alprostadil ([1 α , 13E, 15s] 1,15-dihydroxy-9-oxoprosta-13-2n-1-oic-acid) is a potent vasodilator involved in regulating blood flow to the female reproductive tract, as well as potentiating sensory afferent nerves. Alprostadil is a synthetic form of eicosanoid prostaglandin E1 (PGE1) that acts on membrane-bound receptors in order to increase adenylate cyclase and intracellular cAMP levels. As cAMP levels rise, protein kinase is activated, leading to smooth muscle relaxation and vasodilation. While efficacy of topical alprostadil for penile erection has been established, investigations for clitoral application are underway.

There have been six studies investigating alprostadil in the treatment of FSAD: two trials examining use in the clinical setting and four studying at-home use. The first study found that application of 0.1% alprostadil caused a significant increase in self-reported lubrication and transudate volume, with 0.2% alprostadil also significantly increasing vaginal erythema in response to visual stimulation. There was no change in vaginal photoplethysmography (VPA) [12]. A multi-centre

Phase II clinical trial found that the 400 mcg dose of alprostadil produced genital vasocongestion and enhanced arousal in response to visual stimulation in the clinical setting [13]. In examining at-home application of alprostadil, two studies found an increase in successful and satisfactory sexual encounters with the 400 mcg dose, one study reported an increase in mean arousal success rates with a 900 mcg dose and another study failed to show a statistically significant difference in arousal success rates between doses up to 1500 mcg and placebo [14].

In a multi-centre, randomized, double-blind placebo controlled Phase III clinical trial examining topical alprostadil cream 0.4% with a skin penetration enhancer, an ester of *N,N*-dimethylalanine and dodecanol (DDAIP), a dose of 900 mcg showed statistically significant improvement in both arousal, including lubrication and orgasm, and pain as assessed by the Female Sexual Function Index (FSFI). In addition, the cream was found to be well tolerated with no serious adverse events reported. Of note, lubrication and orgasm correlated with arousal, whereas desire did not, providing support that disorders of arousal and desire may be two separate entities [15].

Alternatively, many sex researchers have shown a lack of correlation with the amount of genital blood flow in women and subjective sexual arousal. This is especially evident in women with decreased sexual desire. This suggests that the role of the central processing of sexual stimuli is very important and was one of the main rationales for combining HSDD and FSAD into the new diagnosis of FSIAD. As such, the role of vasoactive medications that act only on the genitalia might be limited for FSD [16].

4.2 Bremelanotide

Bremelanotide (BMT) is a cyclic melanocortin peptide that acts as a melanocortin (MC) 4 receptor agonist. Although it was originally designed for sunless tanning, the synthetic analog of melanocyte-stimulating hormone, which activates the melanocortin receptors MC3 and MC4 receptors in the CNS, was found to increase sexual arousal and desire. During Phase II trials, BMT administered intranasally showed promising results for the treatment of HSDD and FSAD; however, reports of increased blood pressure halted the trial.

In a Phase IIB trial, BMT was reformulated as a lower dose, subcutaneous injection to measure efficacy for HSDD and/or FSAD treatment in premenopausal women. In a 4-week at-home trial, 1.75 mg BMT showed statistically significant improvements as compared with placebo in five measures of FSD: number of satisfying sexual events per month, total and sexual domain scores on the FSFI and total and desire domain scores on the FSDS. BMT was observed to be associated with minimal and transient increases in blood pressure (~ 3 mm Hg) that were limited to the first 4 h of administration. Protocol-defined blood pressure withdrawal criteria were not met at increased frequency in BMT-treated subjects than those taking placebos [17]. Further studies on BMT dosing have suggested optimal increase in arousal, desire and satisfaction with sexual events with 1.25 mg and 1.75 subcutaneous injections. At these

doses, adverse events included nausea (22 and 24%, respectively) placebo 3%, flushing (14 and 17% respectively), placebo 0% and headache (9 and 14%, respectively) placebo 3%. [18,19]. MC3 and MC4 receptors are involved in many physiological systems, and there may be theoretical risks of activating these receptors. The long-term effects of BMT are unknown.

It has been suggested that the motivation for sexual intercourse in long-term relationships is not necessarily sexual desire (libido) and that desire starts *after* initiation of sexual activity. While some women may experience spontaneous desire, others do so more rarely (potentially fulfilling a diagnosis of HSDD), and are therefore more likely to ascribe to a sexual response cycle that is more circular as described by Basson [20]. As such, although the data for BMT appears promising, the willingness of women to use an injectable medication for FSD may limit the acceptance of this medication.

4.3 Intranasal testosterone (TBS-2: Tefina™)

TBS-2 is a low-dose nasal testosterone gel being investigated as an as needed treatment option for women with FOD and follows on the heels of a recent 2014 FDA approval of a high-dose formulation for treatment of hygonadism for males. This innovative formulation of testosterone is readily absorbed through nasal mucosa into the systemic circulation, providing ease of administration with no expected risk of inadvertent skin-to-skin transfer of testosterone [21]. Tefina, a testosterone gel administered with a multidose nasal applicator, is being developed by Trimel Pharmaceuticals and is currently in Phase II clinical trials. Trimel has explored TBS-2 for both HSDD and FOD in the early trials discussed below and selected FOD as a primary indication based on physiological response to TBS-2 administration as measured by VPA.

Initial studies investigated the pharmacokinetic profile of TBS-2 in healthy premenopausal women to define dosing levels. Testosterone from TBS-2 was found to be rapidly absorbed. A total of 24 healthy premenopausal women were included in this randomized, open-label parallel group study. Subjects were randomly assigned to receive a single dose of TBS-2 at doses of 0.6, 1.2 or 1.8 mg. A total of eight subjects sampled from these three cohorts continued with the multiple-dose portion and received 1.2 mg TBS-2 t.i.d. for 2 days and once on the morning of the third day (7 doses). Although peak levels (mean C_{max} 139.7 ng/dl) of serum total testosterone for the highest dose exceeded the upper level of normal for a short period of time, the 24 h mean testosterone concentration was within the normal reference range for all dose levels, limiting safety concerns. No dose-related differences in any of the safety parameters were observed. It should be noted that testosterone concentrations exceeding the upper limit of the physiological range for a limited amount of time following dosing can be expected due to the peak and trough PK profile of TBS-2 [22]. It is unknown if such temporary supraphysiological levels could be harmful.

A randomized, parallel group, placebo and active comparator study was performed to determine the pharmacokinetic profile and pharmacodynamic efficacy of TBS-2 in women

with HSDD and FOD. Sixteen women with HSDD and 16 women with FOD received five doses of either TBS-2, placebo TBS-2 in the FOD cohort, or a testosterone patch (Intrinsa™) in the HSDD cohort for 3 consecutive days. Intranasal TBS-2 was found to be well absorbed with increasing doses producing a near-proportional increase in plasma testosterone levels. In the FOD cohort, the high-dose TBS-2 group had **significantly** higher VPA response as soon as 30 min following administration, when compared to placebo. The low-dose TBS-2 group showed a significant increase in VPA response, 4.5 h following administration compared to placebo. In the HSDD cohort, women who received high-dose 300 TBS-2 had a **significant** increase in sexual arousal and sensuality, as demonstrated by the subjective arousal questionnaires (SAQ, AFSDQ) compared to women who received the testosterone patch. A statistically significant increase in positive affect was also seen in women with HSDD receiving high-dose TBS-2 compared to women receiving the testosterone patch at both 30 min and 4.5 h after administration. There were no safety concerns identified [23].

Laan *et al.* conducted a randomized, single-blind, placebo-controlled study to evaluate the effect of a single dose of TBS-2 on the occurrence of orgasm during sexual stimulation in women with FOD, as demonstrated by an inability to achieve orgasm within 20 min with the aid of visual sexual cues and vibrotactile stimulation to the glands clitoris. Fifty-nine women with lifelong and secondary acquired FOD were randomized to receive either TBS-2 or placebo. The stimulation was timed for 0.5, 2.0, 4.0 or 8.0 h following dosing. Four subjects in the TBS-2 group and two subjects in the placebo group self-reported an orgasm. An additional eight subjects in the TBS-2 group reported 'sensations indicative of an orgasm following treatment.' These eight subjects were patients with primary FOD who had never experienced an orgasm prior to study and therefore may not have recognized what was occurring. It should be noted that they did not self-report orgasm at the time of the treatment session; however, during a post-treatment structured interview, they described sensations that would be consistent with orgasm. Women treated with TBS-2 reported more intense feelings of sexual arousal after stimulation and showed an increase genital response by VPA, which were statistically significant compared to placebo. TBS-2 was well tolerated in the study [24].

4.4 Intravaginal dehydroepiandrosterone (Prasterone)

Dehydroepiandrosterone (DHEA), produced primarily by the adrenal cortex as well as by the ovaries, is one of the major precursors for extragonadal estrogen and androgen production in postmenopausal women. DHEA and its sulfate DHEAS are converted to estrone or testosterone, and testosterone is subsequently modified to either estradiol or dihydrotestosterone in extragonadal tissues such as the brain, bone and adipose. Although systemic DHEA has not shown consistent benefit for postmenopausal women with FSD,

intravaginal administration of DHEA has shown promise in alleviating vaginal atrophy in postmenopausal women [25,26], as well as positively affecting HSDD [27].

Labrie *et al.* conducted a multi-centre randomized double-blind placebo-controlled trial to determine the effects of vaginally administered DHEA (prasterone) on FSD in postmenopausal women. Two hundred and eighteen postmenopausal women with vulvovaginal atrophy (VVA) with either dyspareunia, vaginal dryness or vaginal irritation were randomized to placebo, 0.25% (3.25 mg), 0.5% (6.5 mg) or 1% (13 mg) DHEA vaginal cream applied nightly using an applicator for 12 weeks. The investigators found a time- and dose-dependent improvements in sexual desire, sexual arousal, orgasm and dyspareunia, as assessed by the Menopause Specific Quality of Life (MENQOL) and Abbreviated Sex Function questionnaires [27]. In addition, there was an increase in genital sensitivity and ease of achieving orgasm after 12 weeks on the DHEA 1% vaginal cream.

Daily administration of intravaginal DHEA significantly improved vaginal atrophy at 2 weeks, decreasing percentage of parabasal cells, increasing superficial cells and decreasing vaginal pH in all treatment groups with no effects noted in the placebo group. Comparable effects were observed at the 0.25 and 1.0% DHEA doses [27]. Serum levels of DHEA and measured metabolites measured with highly sensitive mass spectrometry remained in the normal postmenopausal range with minimal or no changes during the 12-week observation period [28]. The authors concluded that intravaginal prasterone results in local formation of sex steroids in peripheral tissues without significant release of estradiol or testosterone in the circulation [29]. Further analysis of 114 postmenopausal women with dyspareunia as the most bothersome symptom of VVA showed a decrease in the severity of sexual pain score by 1.4–1.6 on a 0–3 (none-severe) pain scale at all three treatment doses of DHEA. These results differed significantly from placebo [30]. In addition, postmenopausal women with VVA reported similar benefits of prasterone on desire and arousal, regardless of having moderate/severe dyspareunia at baseline. The authors suggest that VVA and sexual dysfunction may be two separate medical entities, both related to sex steroid deficiency but differing in their responses to estrogens versus androgens [31].

In summary, the results of these early phase trials of intravaginal DHEA provide evidence that it might be a useful treatment for postmenopausal women with VVA, without the risk of increased systemic levels of estrogens or androgens. In addition, these early data suggest that intravaginal DHEA may also have the potential to treat FSIAD.

4.5 Testosterone with phosphodiesterase type 5 inhibitor and testosterone with 5-hydroxytryptamine_{1A} receptor agonist

Single doses of 0.5 sublingual testosterone have been shown to increase the sensitivity of the brain to sexual cues [32]. However, in many women, particularly those with HSDD, the

effects of testosterone alone may not be sufficient for reaching necessary levels of arousal and desire for sexual activity. While proposed etiologies of HSDD are widely varied, two prominent understandings of HSDD have emerged. The first describes HSDD as the result of an insensitive brain system for sexual cues, and the second assigns responsibility to over-active sexual inhibitory mechanisms. Thus, due to the divergent nature of these etiologies, two therapies are under development.

In a 2012 study conducted by Emotional Brain limited liability company in The Netherlands, women diagnosed with HSDD were divided into categories of high or low sensitivity to sexual stimuli by testing their preconscious attentional bias for sexual cues using a masked version of an emotional Stroop test. In this test, words were presented for 26 ms in four different colors to participants viewing a laptop computer.

Words were backwardly masked to prevent conscious processing of the words. Participants were instructed to name the color of the masks as quickly as possible and the length of time to vocal response was recorded. Thirty-two unambiguous neutral words from one category (furniture; examples are ‘chair’ and ‘table’) and 32 unambiguous erotic words (examples are ‘penis,’ ‘coitus’ and ‘vagina’) were presented to the participants. The differences between the mean reaction times of the erotic and the neutral words were used to categorize participants as ‘high sensitivity to sexual cues’ (reaction time to neutral words < erotic words) and ‘low sensitivity to sexual cues’ (reaction time to neutral words > erotic words).

For women with low sensitivity, efforts were aimed at increasing sensitivity to sexual cues. Sexual stimulation causes the release of nitric oxide from nerves and endothelium, resulting in an increase in cGMP. The rise in cGMP is key in the relaxation of smooth muscle for the enlargement of erectile tissue. PDE5 hydrolyze, cGMP and consequently PDE5 inhibitors (PDE5i) prolong the action of vasodilation. In order for PDE5i to act on vasodilation, central stimulation must be present. Thus, testosterone, which increases the brain’s response to sexual cues, combined with PDE5i, aimed to enhance genital sexual response, was coupled in a coinciding time-delay manner and tested in a double-blind, placebo-controlled crossover study with 56 women with HSDD. Women were treated with testosterone 0.5 mg and PDE5i (sildenafil 50 mg) (T+PDE5i) 4 h prior to sexual activity. Participants were permitted to use the medication up to 14 times in a 4-week period with a minimum of 48 h between doses. Women taking the T+PDE5i for 4 weeks had an improved physiological and subjective sexual response as measured by institutional psychophysiological lab standards and by at-home evaluations as compared with women taking placebo. More specifically, participants on T+PDE5i showed increased preconscious attention for sexual cues as well as statistically significant increases in subjective sexual function, such as genital arousal and desire. Additionally, participants who were evaluated to have low sensitivity to sexual cues demonstrated much greater benefit from T+PDE5i therapy than woman

assessed as high sensitivity to sexual clues who did not have an increase intensity or satisfaction of sexual events [33,34].

In addition to being assigned to treatments of T+PDE5i and placebo for 4 weeks each, women in the trial were administered 4 weeks of testosterone with 5-hydroxytryptamine_{1A} receptor agonist (T+5-HT_{1A}ra). The T+5-HT_{1A}ra treatment was aimed at addressing overactive sexual inhibition processes. Serotonin or 5-hydroxytryptamine (5HT_{1A}) is a neurotransmitter important for mediating inhibitory mechanisms localized in the prefrontal cortex (PFC). As the PFC is an important regulator of inhibition, and as 5HT_{1A} is a critical neurotransmitter in the PFC, it was hypothesized that acute treatment with a 5HT_{1A}ra could limit the effects of 5HT_{1A} thereby decreasing inhibition of sexual response. After acute administration, a 5HT_{1A}ra binds to somatodendritic autoreceptors of the raphe nuclei in the midbrain. The hyperpolarizing effect of activated 5-HT_{1A} autoreceptors decreases both serotonergic firing activity and inhibition of 5-HT release from the presynaptic terminal thereby reducing 5-HT levels in the PFC. In a similar fashion to the T+PDE5i treatment, T+5-HT_{1A}ra were designed to act maximally 3 – 6 h after administration. In participants considered to have high inhibition, taking T+5-HT_{1A}ra showed statistically significant increases in sexual satisfaction, desire, genital arousal and sexual function and VPA as compared with placebo. In contrast, the low inhibition group did not show statistically significant changes in these areas. Furthermore, the low inhibition group showed much greater improved on these measures with treatment of T+PDE5i [35]. Therefore, as hypothesized, the low sensitivity group responded best to T+ PDE5i, while the high sensitivity group showed greatest improvements with the T+5-HT_{1A}ra. Pharmacokinetic studies of the combined T (0.5 mg) +PDE5i showed [36] the peak levels of serum total testosterone (mean C_{max} 7.84 ± 3.69 ng/ml) the T_{max} measured in hours was 0.201 ± 0.04, and the half-life T_{1/2} was 0.598 ± 0.08 h. Given the relatively low T_{max} and short T_{1/2}, it is unlikely that these levels will produce any androgen-related side effects.

4.6 Apomorphine

Apomorphine (APO) is a nonselective dopamine agonist which acts on both D₁-like and D₂-like receptors. Originally indicated for hypomobility in Parkinson's disease, APO has been suggested for the use of sexual dysfunction in women. Currently, some evidence points to neural substrates in the medial preoptic hypothalamus area (MPOA) as an important regulator of female sexual behavior. As a dopamine stimulator primarily targeted to the MPOA, APO is believed to enhance response to sexual stimuli [37]. However, it is important to note that dopamine stimulation is not specific to sexual response, but rather to a more general system of cognition, integrative and reward processes [38]. Nevertheless, in female rats, APO has been shown to increase hormone-dependent genital vasocongestion and patterned behavioral sexual arousal response [39]. Similarly, in rabbits, APO administration was

shown to increase vaginal and engorgement when coupled with pelvic nerve stimulation [40].

To assess the effects of APO on human FSD, 24 women diagnosed with FOD were randomized in a double-blind crossover prospective study to two groups. During a first time visit, group one was assessed after vibrator stimuli plus placebo and then subsequently evaluated after receiving 3 mg sublingual APO in a second visit. Group 2 was judged on the same criteria after receiving APO on the first visit and the vibrator stimuli with placebo on the second visit. Objective measures included pre- and post-vibrator effects on clitoral artery peak systolic velocity (PSV), end diastolic velocity (EDV) and resistive index (RI) using a color duplex Doppler ultrasound using a 7.5 MHz 'small parts' linear transducer. Subjective evaluations graded arousal and lubrication on a 0 – 2 scale (0: absent; 1: mild to moderate; 2: intense) and presence or absence of orgasm achievement. Results showed statistically significant improvement in subjective arousal and lubrication but not in orgasm. Objective measures of PSV and EDV were greater with APO than with placebo [41].

In another study assessing the effects of APO on HSDD, 62 premenopausal women underwent a two-part study, the first of which was a 4-week, open-label, dose-escalation, as-needed administration of sublingual APO. After having started on a 2 – 3 mg beginning dose 4 weeks prior, non-responders proceeded to part two of the study where they were randomly allocated to one of six sequences of three 2-week double-blind crossover study periods with 2 or 3 mg APO, washout and placebo. Subjective assessment of arousal, desire, orgasm, enjoyment and frequency of sexual relationships were assessed by Personal Experiences Questionnaire using the 5-point Likert scale. Reported effects were much greater with daily intake than as-needed dosing, and increased dose-response was observed between 2 mg and 3 mg APO. Nevertheless, both doses showed significant effects when compared with placebo for arousal, desire, orgasm, enjoyment and satisfied by frequency scores. Adverse effects during daily use included nausea 14%, vomiting 7%, headaches 7% and dizziness 7% [42].

4.7 Bupropion and trazodone (Lorexys™)

Antidepressants bupropion and trazodone both work to restore the balance of dopamine, 5-HT and norepinephrine. As these neurotransmitters play an important role in regulating sexual inhibition and exhibition, S1 Biopharma is currently investigating a combination of bupropion and trazodone, Lorexys, for the treatment of HSDD in Phase IIa clinical trials. No data are currently available on these treatments.

4.8 Conclusions

Conclusion There are several active and exciting research programs that continue the search for medications to treat FSIAD, HSDD, FSAD and FSOD. Over the past two decades, our understanding of the sexual response cycle has

evolved and scientists have made great progress in unraveling the hormonal, biochemical and neurologic mechanisms underlying sexual desire, arousal and orgasm. Pharma companies have been using this new basic science knowledge to develop new drugs to treat FSD.

5. Expert opinion

Despite the high prevalence of FSD, and HSDD in particular, there is a paucity of medications approved to treat FSD. Over the last decade, there has been great progress in basic science research examining the physiology of female sexual desire, arousal and orgasm. This knowledge has been used to develop drugs currently in Phase I and II clinical trials to treat women with FSIAD, HSDD, FSOD and FSAD. Medications currently in clinical trials for FSD include medications that raise sex steroids, increase vasodilatation and genital blood flow, stimulate excitatory pathways in the CNS that are responsible for sexual desire and inhibit inhibitory pathways in the brain crucial to sexual desire.

Of the previously discussed medication, the authors are especially excited about the combined potential of the testosterone with phosphodiesterase type 5 inhibitor (T+PDE5i) and testosterone with 5-hydroxytryptamine_{1A} receptor agonist (T+5-HT_{1A}ra) for HSDD. Emotional Brain, Inc. the medical science company responsible for this research has developed a proprietary diagnostic algorithm based on hormonal factors, genetic factors and psychological testing to determine if women with HSDD have low libido either because they have low sensitivity to sexual cues or if they have an anxiety response in the frontal cortex that inhibits sexual desire. As of yet, this algorithm has not been published in a peer-reviewed medical journal. However, it was presented in a podium presentation at the 2014 Annual Meeting of the International Society for the Study of Women's Sexual Health held in February 2014 in San Diego, California. In addition, this algorithm and the ongoing Phase III clinical trials have been widely discussed in the lay press, including a featured article in the *New York Times Magazine* [43]. While this diagnostic algorithm is essentially based on Bancroft's dual control model of desire, it goes much further [44]. This diagnostic algorithm acknowledges that HSDD is multi-factorial. More importantly, it is an attempt to develop treatments

(medications) based on a persons' unique combination of hormones, genetics and psychosocial make-up. As such, this put sexual medicine in the forefront, along with fields such as oncology, in the development of 'individualized' treatments.

Lastly, the authors want to discuss an additional roadblock for drugs for FSD that most drugs in development do not face. There have been accusations in the lay media that there is a gender bias at the American Federal Drug Administration (FDA) against medications for FSD [45]. As of the writing of this paper, there have been 26 medications approved by the FDA for the treatment of male sexual dysfunction (although the majority have been approved for the treatment of erectile dysfunction) but none for FSD other than for symptoms of vulvovaginal atrophy. Citing this apparent bias, a coalition of consumer advocacy groups and drug makers recently launched an online campaign to pressure the FDA to approve drugs to treat FSD. The initiative has garnered congressional support and headlines.

In January 2014, four Congresswomen wrote the FDA to express concern about the lack of drugs for FSD and representatives from eight different women's groups, including the National Organization of Women, met with Janet Woodcock, who heads the FDA division that oversees drug reviews, to protest the rejection of flibanserin, a drug that has undergone extensive Phase IIIA and IIIB testing for FSD. Even though the FDA states "we are committed to supporting the development of therapies for medical conditions related to FSD," the path towards development of drugs for FSD is somewhat ambiguous as the FDA issued draft guideline for FSD drug development in 2000, but later withdrew the document and a new version has yet to be released. A 2-day public forum on women's sexual dysfunction is planned in late October 2014 in Washington DC.

Declaration of interest

AT Goldstein is on the advisory board for Emotional Brain LLC, and Strategic Science and Technologies, LLC. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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