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REVIEW

Pharmacotherapy for female sexual dysfunctions (FSDs): what is on the market and where is this field heading?

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ABSTRACT

Introduction: Female sexual dysfunctions (FSDs) are common in women of any age and have a huge impact on quality of life and relationships. They have a multifaceted etiology limiting the development of pharmacotherapies with a high rate of effectiveness. Safety issues are also a concern.

Areas covered: The authors report the most recent advances in pharmacotherapy for premenopausal and postmenopausal women with a main focus on hypoactive sexual desire disorders (HSDD) and associated sexual symptoms. Good levels of evidence have emerged for psychoactive agents, such as flibanserin and bremelanotide, as well as hormonal compounds (transdermal testosterone). The authors also report briefly on intravaginal DHEA (prasterone), local estrogen therapy (LET), and ospemifene to manage effectively vulvovaginal atrophy/genitourinary syndrome of menopause (VVA/GSM). In addition, they discuss promising therapeutic options highlighting the main reasons that hamper the availability of new labeled products. Finally, they include the importance of the multimodal approach to address FSDs.

Expert opinion: Approved pharmacotherapies for FSD are limited. Validated multidimensional instruments and adequate objective measures of physical and mental responses to sexual external and internal incentives are mandatory to identify women suitable to chronic or on-demand treatments and to assess their pattern of response in research and practice.

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Bremelanotide; dehydroepiandrosterone (DHEA); flibanserin; genitourinary syndrome of menopause (GSM); hypoactive sexual desire disorder (HSDD); local estrogen therapy (LET); ospemifene; psychoactive drugs; testosterone; vulvovaginal atrophy (VVA)

1. Introduction

Several important advances contributed to our understanding of female sexual dysfunctions (FSDs) over the last few decades. It has become definitely clear that the biopsychosocial model is the key to guide research and clinical care of women reporting sexual symptoms and associated distress across their life span. Indeed, biomedical variables interact with intrapersonal and interpersonal factors along with socio-cultural values to shape the individual experience with sex in women of any age. Moreover, it is now evident that each phase of the healthy sexual response (desire, arousal, and orgasm) may overlap in a variable way according to a wide range of internal and external stimuli, which ultimately modulate sexual satisfaction [1–4].

Medical education in sexual history taking is mandatory to train new generations of health-care providers (HCPs) to be able to determine whether FSDs are lifelong or acquired, generalized, or situational, by collecting those bio-psychosocial factors that predispose, precipitate, or maintain sexual symptoms associated with distress [5]. The International Society for the Study of Women Sexual Health (ISSWSH) multidisciplinary, international expert panel proposed a standard process of care (POC) that outlined recommendations for the identification of sexual problems in women and described core and advanced competencies in FSDs in daily consultation. In particular, the POC pinpointed the need for an accurate diagnosis to establish an adequate management, which should include pharmacotherapies for specific conditions, such as hypoactive sexual desire disorder (HSDD) in both premenopausal and postmenopausal women and vulvovaginal atrophy/genitourinary syndrome of menopause (VVA/GSM) in postmenopausal women. On the other hand, the ISSWSH POC delineated a strategy for referral when clinicians become aware that there is an indication for non-pharmacological strategies, including physical and psychosexual therapies, alone or in combination with drugs [6].

Here, we report the most relevant information about current pharmacotherapies for FSDs with a focus on HSDD and we look forward to the future, hoping that new research will offer a wider range of biomedical options for managing the individual woman.

2. Current pharmacological management of FSDs

The management of FSDs is still an evolving topic in both research and practice because there is a certain amount of controversy around the new DSM-V classification that has

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Article highlights

- The biopsychosocial model is essential to diagnose and treat FSDs, as well as to guide the development of new pharmacotherapies and multimodal approaches.
- The DSM-V disorder named female sexual interest/arousal disorder (FSIAD) merged hypoactive sexual desire disorder (HSDD) and female sexual arousal disorder (FSAD) into a new entity not well captured by the validated psychometric tools available for diagnosis.
- Premenopausal and postmenopausal women should follow a standard process of care (POC) to establish an adequate therapeutic plan.
- Hypoactive sexual desire disorder (HSDD) and associated sexual symptoms may be treated with two approved psychoactive agents (flibanserin on a daily basis and bremelanotide on-demand) in premenopausal women and with daily transdermal testosterone (approved for use in males) at the physiological dose in postmenopausal women.
- Other psychoactive agents (bupropion, buspirone, and trazodone) are used off-label in the management of FSDs, especially when associated with antidepressant agents.
- Evidence-based treatments [local estrogen therapy (LET), intravaginal dehydroepiandrosterone (DHEA), oral Ospemifene] are available to manage vulvovaginal atrophy/genitourinary syndrome of menopause (VVA/GSM) to avoid the negative vicious circle that may lead to HSDD in postmenopausal women.
- Only few of the most recent candidate drugs to treat FSDs are in late development due to low levels of evidence.
- Two on-demand oral combined drugs [Lybrido: sildenafil (50 mg) plus testosterone (0.5 mg) and Lybridos: testosterone (0.5 mg) with buspirone (10 mg)] aim to treat FSIAD, due to lack of sensitivity to excitation and dysfunctional sexual inhibition, respectively. The novel combination of bupropion and trazodone at different dosages (Lorexys) offers another potential multifunctional solution.

significantly changed well-established definitions, nomenclature, and diagnostic criteria [7]. Indeed, extensive discussion is still ongoing on the diagnostic evaluation of HSDD and female sexual arousal disorder (FSAD), which were merged into a new DSM-V disorder named female sexual interest/arousal disorder (FSIAD), and on subtypes of arousal (cognitive versus genital), pain (genito-pelvic pain and penetration), and orgasmic disorders [8–10]. Therefore, drug development for FSDs is a complex and challenging process from a methodological standpoint. Even though there is evidence that FSDs represent a real burden for many women, difficulties in establishing true epidemiology and identifying adequate validated instruments to formulate discrete diagnoses and to monitor clinical meaningful effects are major limitations to pharmacotherapies [11]. Variable responses to medical interventions are likely to occur because of genetic polymorphisms of drug targets associated with susceptibility to FSDs, as demonstrated for male sexual dysfunction, but research in this area is still scant [12,13]. Moreover, a strong placebo effect is evident in trials for FSDs accounting for two-thirds of improvement in sexual complaints and confirming the multitude of variables involved in the sexual response [14]. On the other hand, safety may also be an issue both in women of childbearing potential, owing to concerns about adverse fetal effects of treatment, and in postmenopausal women due to the risk–benefit balance of pharmacological interventions [15]. Partnership is crucial and a comprehensive couple-approach is advisable, especially in older individuals, because the co-occurrence of male and female sexual symptoms is highly frequent [16]. Finally, sexual attitudes and cultural norms within the society coupled with barriers to discussing sex in daily practice result in poor recognition and care [17].

Significant efforts have been made to achieve an effective management of FSDs, both from the biomedical and the psychosocial standpoint [18]. At present, the first line of treatment is office-based counseling, as well as addressing modifiable factors such as untreated health conditions, chronic use of medications, or relationship issues involved in the manifestation of sexual problems [6]. In addition, HCPs may prescribe some approved and off-label pharmacotherapies of FSDs to relieve specific clinical entities [19,20]. Restoration of the neuroendocrine balance seems crucial to treat acquired, generalized HSDD in premenopausal women, whereas hormonal replacement is the milestone of treating postmenopausal women reporting VVA/GSM, HSDD, or other associated sexual symptoms [21,22].

2.1. Pharmacotherapies of HSDD

Two psychoactive agents are now available on the market, flibanserin in the U.S.A. and Canada and bremelanotide only in the U.S.A., to treat HSDD in premenopausal women officially, whereas the other two drugs, bupropion and buspirone, are off-label [23]. A testosterone (T) cream (brand name Androfeme®) for daily use (1%; 0.5 ml equivalent to 5 mg) licensed for postmenopausal women with HSDD is available only in Australia [24]. However, in agreement with the conclusions of the Global Consensus Position Statement on the Use of Testosterone Therapy for Women, transdermal T approved in men can be used off-label at the dose studied in women treated with the previously available T patch (300 mcg per 24 hours) [25]. These pharmacotherapies of HSDD (Table 1) modulate the neuroendocrine substrates of the female sexual response, which are still under investigation because most of the available evidences were collected in animal models. Some experiments in humans and the use of functional brain imaging have helped to clarify the role of the complex network of excitatory (dopamine, noradrenaline, and melanocortin receptors (MC3R and MC4R)) and inhibitory (serotonin, endocannabinoid, and opioid systems) signals, modulating sexual desire, arousal, orgasm, and satisfaction. Specific nuclei in the brain stem, which maintain projections to various other brain areas and the spinal cord, release this array of molecules. It is likely that HSDD results from the interaction of the serotoninergic system with several neurochemical pathways and involves either a predisposition toward inhibitory pathways in the brain or a neuroadaptation of structures and functions resulting in decreased excitation and/or increased inhibition [26]. Even though circulating levels of sex steroids, namely T and estradiol, do not directly correlate with the diagnosis of HSDD [21], their role in priming excitatory sexual systems in the brain is plausible [27]. Other important neuromodulators linked to the activity of sex steroids and

Table 1. Pharmacotherapies of HSDD.

Drug	Mechanism of action	Clinical Outcomes	Dosage	Common Side-effects	Approved
Flibanserin (Tablet)	Decrease serotonin in the brain, increase norepinephrine and dopamine	Increase satisfying sexual events (SSEs) and sexual desire, decrease sexual distress	100 mg/daily (oral)	Dizziness, somnolence, nausea, fatigue, insomnia, dry mouth	Yes (U.S.A. and Canada) in premenopausal women
Bremelanotide (Injection)	Stimulate dopamine in the hypothalamus	Increase sexual desire, decrease sexual distress	1.75 mg on demand (subcutaneous)	Nausea, flushing, injection site reactions, headache, vomiting, cough, fatigue, hot-flush, paresthesia, dizziness, nasal congestion	Yes (U.S.A.) in premenopausal women
Testosterone (Patch)	Increase circulating testosterone levels	Increase satisfying sexual events (SSEs) sexual desire and other sexual domains, decrease sexual distress	300 mcg/daily (transdermal)	Application site reactions, hirsutism	Yes (Europe) in postmenopausal women, not available anymore
Testosterone (Cream)	Increase circulating testosterone levels	Improve sexual function, mood and well-being	1%/daily (transdermal)	Application site reactions, hirsutism	Yes (Australia) in postmenopausal women

neurotransmitters/neuroactive agents include prolactin, a satiating hormone released following orgasm [28], and oxytocin and vasopressin, the so-called social neuropeptides playing a role in sexual behavior [29,30].

2.1.1. Flibanserin

Flibanserin is a centrally acting, non-hormonal oral medication. It acts as a 5HT1A agonist and a 5HT2A antagonist and may increase levels of dopamine and norepinephrine [31]. Initially developed as an antidepressant, flibanserin demonstrated positive signals on sexual function, especially desire, when post hoc analyses were conducted upon comparative data with placebo and antidepressants (fluoxetine and paroxetine) [32], which are well-known drugs to eventually induce sexual-side effects [33]. These early findings provided a rational basis for developing flibanserin for the treatment of HSDD [34]. Boehringer Ingelheim (BI) started a full research program in North America and in Europe to prove efficacy and safety in premenopausal women but discontinued development efforts following FDA concerns in 2009. Thereafter, Sprout Pharmaceuticals, Inc. (SPI) acquired flibanserin from BI and conducted new clinical studies elaborating also additional data from BI-initiated studies [35]. The Bouquet study program [36–39] supported that treatment with flibanserin 100 mg once daily at bedtime (qhs) induced statistically and clinically significant improvement in the number of satisfying sexual events (SSEs), level of sexual desire, and reduction of distress relative to placebo after 24 weeks and up to 52 weeks in open arms. The mean age of the women was about 36 years in the three pivotal trials involving approximately 2400 premenopausal women with HSDD [36,37,39]. Flibanserin increased the number of SSEs per month by around one and sexual desire score by around 0.3, whereas decreased sexual distress by 0.3 in respect with placebo [31]. A recent analysis based on the patient global impression of improvement (PGI-I) showed that responder rates were significantly higher for premenopausal women on flibanserin (46.1%–55.2%) than placebo (34.1%–44.2%) for all three key efficacy end points (SSEs, desire, and distress) [40]. One additional trial was conducted in naturally postmenopausal women, proving that flibanserin induced significant improvements in the number of SSEs and sexual desire, as well as reduced sexual distress, compared to placebo [41]. Based on efficacy, safety, and tolerability, in 2015, the FDA finally approved flibanserin (brand name ADDYI®) only in premenopausal women requesting a boxed warning that states that alcohol must be avoided during treatment. In addition, the FDA required a risk evaluation and mitigation strategy (REMS), with the aim to counsel patients about the risk of hypotension and syncope, and three post-approval trials to further elucidate the alcohol interaction in women, plus enhanced pharmacovigilance for hypotension, syncope, accidental injury, and death [42]. Of note, in 2019, the FDA issued a safety labeling change order to Sprout Pharmaceuticals for their drug [43]. Following a careful review of post-marketing studies [44–46], the FDA required that women should discontinue drinking alcohol at least 2 hours before taking ADDYI® at bedtime, without consuming alcohol at least until the morning after, or should not take ADDYI® the night they have consumed alcohol till late. It is also worth to mention that flibanserin is metabolized by the liver via the cytochrome P450 system (predominantly CYP 3A4 and 2C19), and some interactions with agents that induce or inhibit these enzymes may occur [43]. Independent studies are ongoing to increase the bioavailability of flibanserin, and nanocrystal-based sublingual tablets seem a suitable option with a two-fold increase in bioavailability and a faster onset of action as compared to the commercially available oral formulation [47].

Flibanserin is the first drug in its class with a controversial history of approval [48], mainly due to the perception of a small clinical efficacy in light of significant side effects [49]. However, the availability of flibanserin has paved the way to a better understanding of the complexity in the treatment of sexual difficulties in women and has stimulated further research [50].

2.1.2. Bremelanotide

Bremelanotide (brand name VYLEESI®) is another centrally acting, non-hormonal medication, self-administered, subcutaneously on-demand, approved in 2019 to treat acquired, generalized HSDD in premenopausal women [51]. Initially developed by Palatin Technologies as an intranasal on-demand drug in women with FSAD, a subcutaneous formulation of bremelanotide was tested in subsequent studies to minimize side effects on blood pressure in women with HSDD, FSAD, or a combination of both [52]. In the final stage, following the results of the Phase 3 trials in women

with HSDD, AMAG Pharmaceuticals Inc completed the development and marketed the drug in the U.S.A. [51].

Bremelanotide is a synthetic peptide analog of the neuropeptide hormone alpha melanocyte-stimulating hormone (α-MSH) with high affinity for the MC4R in presynaptic neurons of the hypothalamus, activating the release of dopamine. Preclinical studies suggested its clinical role in modulating several brain excitatory pathways involved in sexual arousal and desire [53]. In a phase 2b, randomized, double-blind, placebo controlled, dose-finding trial, self-administered subcutaneous bremelanotide (0.75, 1.25, or 1.75 mg), taken as needed for up to 12 weeks, showed dose-responsive improvements in desire, arousal, and associated distress, as well as increases in the number of SSEs, compared to placebo [54]. Then, in phase 3 the FDA recommended two separate, identically designed clinical trials, the so-called RECONNECT pivotal studies, in which the 1.75 mg dose of bremelanotide was selected [55]. The pooled sample included 1267 women (mean age: 39 years). Studies included a core study phase consisting of a 4-week screening period, a 4-week baseline period (single blind, placebo-only treatment period), and a 24-week randomized, double-blind, placebo-controlled treatment period. Outpatients could self-administer a maximum of 12 doses as needed (approximately 45 minutes before anticipated sexual activity) in each 4-week period, with no more than one dose per 24-hour period [55]. A 52-week open-label extension study phase was optional for patients who completed the core study phase [56]. Primary analyses from the RECONNECT clinical trials demonstrated statistically significant and clinically meaningful improvements in sexual desire and related distress with bremelanotide, as compared to placebo in premenopausal women with HSDD [55]. In more detail, bremelanotide was significantly superior to placebo by 0.3 points in a pooled analysis; the effect size was 0.39 (desire score measured by Female Sexual Function Index). A similar result was evident for the distress item score measured by the Female Sexual Distress Scale (0.33 points in a pooled analysis; effect size 0.27) [55]. Even though the effect size appeared to be relatively small, the multiple-responder analyses performed on phase 2b data offered a valuable approach for determining clinically important effects of bremelanotide for HSDD with or without FSAD [57]. The most common treatment-emergent adverse events occurring in more than 10% of patients taking the active drug compared to placebo were nausea, flushing, and headache. However, side-effect profile was manageable and patients reported less tolerability issues when they perceived improvements in sexual desire and reductions in associated distress [55]. During the 52-week open-label extension of the RECONNECT, premenopausal women treated with bremelanotide exhibited sustained improvements in HSDD symptoms without reporting new safety signals, but about 21% of these women dropped out due to adverse events [56].

A recent review [58] stated that bremelanotide is safe and has limited drug–drug interactions, including no clinically significant interactions with ethanol. Based on available data, it is recommended to use no more than 1 dose in 24 hours and no more than 8 doses per month. Moreover, discontinuation of the drug is indicated after 8 weeks of use without benefit [55]. Even though the modest clinical benefit is raising controversy [59,60], the perspective of patients who received bremelanotide supported improvement in the partner relationship [61].

2.1.3. Transdermal testosterone

The Global Consensus Position Statement on the Use of Testosterone Therapy for Women has recently recommended transdermal T to treat postmenopausal women with HSDD [25] based on the results of a systematic review and meta-analysis to assess potential benefits and risks of testosterone for women [62]. In addition, ISSWSH has recently revised limited data to support its use also in late reproductive age premenopausal women offering clinical practice guideline to provide standards for safely prescribing T to women with HSDD, including identification of appropriate patients, dosing, and monitoring [63]. Especially, women with premature ovarian insufficiency should be considered optimal candidates for T treatment in the context of the biopsychosocial model [64]. The transdermal route of T administration at the dose of 300 μg per 24 hours (brand name Intrinsa®, Procter & Gamble Co) tested in several randomized controlled trials has shown short-term efficacy in terms of improvement of sexual function in naturally and surgically menopausal women affected by HSDD, either on or not on hormone therapy with estrogen and progestin [65]. As compared to placebo or a comparator (estrogen, with or without progestin), transdermal T significantly increased SSEs frequency, sexual desire, pleasure, arousal, orgasm, responsiveness and self-image, and reduced sexual concerns in postmenopausal women [62]. Even in patients on a stable dose of a serotonin-specific reuptake inhibitor (SSRI) or serotonin noradrenaline reuptake inhibitor (SNRI), T patch has been proven to be effective in increasing the 4-week frequency of SSEs at 12 weeks in a double-blind, randomized, placebo-controlled study [66]. The daily dose of 300 μg of T is safe, apart from some androgenic adverse events such as acne [62,65], but long-term data on women's health conditions are lacking and other routes of T administration may negatively influence the cardio-metabolic profile [67]. A 1% testosterone transdermal gel (300 μg per 24 hours) was also tested planning a long-term phase 3 safety trial, and interim data demonstrated a continued low rate of cardiovascular events and breast cancer in postmenopausal women at increased cardiovascular risk [68]. At present, T is an off-label therapy because following European approval T patch has been withdrawn from the market in 2012. Therefore, informed consent should be obtained, circulating levels should be monitored, and if women do not experience clinically meaningful improvement treatment should be discontinued following 6 months of use [62].

2.1.4. Other available options

Off-label use of psychoactive agents (bupropion and buspirone) approved for conditions such as depression and anxiety, respectively, has shown some benefits on sexual function and HSDD in patients with mood disorders, as well as in women with SSRI-induced HSDD [69]. Interestingly, bupropion has a non-serotonergic mechanism of action, being a norepinephrine and dopamine reuptake inhibitor (NDRI), whereas buspirone is an azapirone with a strong affinity for serotonin 5HT1A receptors,

where it acts as a partial agonist, and a weak affinity for serotonin 5HT2 receptors. It also acts as a weak antagonist on dopamine D2 auto-receptors, with no effect on benzodiazepine GABA receptors. Given their pharmacological characteristics, these drugs have been studied as augmentation agents/antidotes or substitution agents in the management of FSDs associated to antidepressant agents [70]. Even trazodone, an antidepressant with a sedative effect acting as a serotonin antagonist (5-HT2A/2C) and reuptake inhibitor (SARI) may serve the same scope [71]. These data reinforce the idea that an imbalance of excitatory and inhibitory neurochemical processes caused by hypo-functional excitation, hyper-functional inhibition, or their combination forms the basis of HSDD and the positive modulation of the dopamine/serotonin ratio is a key element for its treatment [26,72]. In keeping with this view, as soon as it was approved for men with erectile dysfunction, the dopamine agonist apomorphine was tested sublingually (3 mg) also in premenopausal women with desire and arousal disorders and showed positive results. However, side effects and lack of impact on the frequency of sexual behavior discouraged further research [13].

Sildenafil, a phosphodiesterase type 5 (PDE5) inhibitor, promoting vasodilation via sustained effects of nitric oxide (NO) in the vascular system, could help engorgement of clitoral and vaginal tissues [73], but results were conflicting and did not apply to HSDD [73]. Indeed, a role of sildenafil at variable dosages seem to be limited to FSAD secondary to multiple sclerosis, diabetes, or antidepressant use [74]. The discordance between genital and subjective measures of sexual response, particularly in women with HSDD, led to discontinuation of research programs with vasoactive agents, such as topical NO donors, alprostadil (prostaglandin E1), or oral phentolamine mesylate, a combined α-1 and α-2 adrenergic agonist [13,17,75,76].

Many herbal and natural products claim to enhance the sexual response in women, but there is a lack of high-quality evidence [77]. A recent systematic review and meta-analysis showed that *Tribulus terrestris* was associated with an improvement in overall sexual performance, whereas *Panax ginseng* might be effective in ameliorating sexual desire and arousal in women with FSDs when compared to placebo [78].

2.1.5. Addressing the VVA/GSM comorbidity in postmenopausal women with HSDD

The ISSWSH POC for the management of HSDD [79] endorsed also by the International Menopause Society (IMS) [22] fully supports the need to treat VVA/GSM effectively in order to improve other dimensions of postmenopausal sexuality. Indeed, the strong association between VVA/GSM and FSDs has been extensively explored in population-based and clinical studies [80,81]. On the other hand, HSDD may be even a consequence of vaginal dryness and sexual pain due to VVA/GSM [82].

Systemic hormone therapy is effective in the improvement of VVA/GSM and eventually of HSDD [83], but its main indication is the management of vasomotor symptoms and the prevention of osteoporosis [84]. Low-dose local estrogen therapy (LET) represents the first-line hormonal treatment of VVA/GSM, and long-term data are available to prove efficacy and safety [85]. Intravaginal dehydroepiandrosterone (DHEA, brand name INTRAROSA®), a pro-hormone exerting a dual estro-androgenic action on VVA/GSM symptoms, is another effective treatment [85,86]. The only orally available treatment to treat vaginal dryness and dyspareunia is Ospemifene (brand name OSPHENA®), a selective estrogen receptor modulator (SERM) that can be possibly used even in women with contraindications to conventional hormone therapy [85,86]. Non-pharmacological approaches, including vaginal laser therapy, may be an effective and safe treatment for VVA/GSM [86]. However, international societies do not endorse its use due to the poor results in comparison to sham-laser control groups [87,88].

3. Pharmacotherapies of FSDs in development

Several compounds have been studied as candidate drugs to treat FSDs, but only few of them are in late development due to low levels of evidence [13,17,75,76,89]. Recently, a personalized approach based on the Phenotype Prediction Score (PPS), which included genetic, biological, and psychological markers, identified two subtypes of women with FSIAD: 1) those with a relatively insensitive excitatory system in the brain for sexual cues and 2) those with a dysfunctional activation of brain mechanisms for sexual inhibition [90]. Such methodological approach was tested in a randomized double-blind controlled study versus placebo suggesting a positive effect of on-demand sublingual sildenafil (50 mg) plus testosterone (0.5 mg) in women with FSIAD due to low sensitivity to sexual cues [91]. A similar positive effect was observed when testosterone (0.5 mg) was combined with buspirone (10 mg) in women with FSIAD due to high sensitivity to sexual cues [91]. However, whether a peculiar dysfunctional response in the delicate balance between excitatory and inhibitory signals driving desire and arousal may offer guidance to an individualized treatment of FSDs awaits for further studies. Indeed, these two on-demand oral combined drugs [Lybrido: sildenafil (50 mg) plus testosterone (0.5 mg) and Lybridos: testosterone (0.5 mg) with buspirone (10 mg), Emotional Brain BV, The Netherlands] still lack an ongoing phase 3 clinical study program [18,75]. The novel combination of bupropion and trazodone at different dosages (Lorexys, S1 Biopharma New York, NY, USA) offered another multifunctional solution [19]. Such product is still in phase 2b trial following a phase IB/IIA study in a population of premenopausal women with HSDD that has shown superiority over bupropion alone in the proportion of responders on standard measures of sexual desire [92]. A formulation of testosterone nasal gel (TBS-2) approved for treating male hypogonadism (Natesto®, Acerus Pharma, Ontario, Canada) has been tested at different dosages (Tefina™) on demand in healthy premenopausal women with HSDD or anorgasmia [13], but no further published data are available [75,76].

Ovoca Bio (Dublin, Ireland) is currently developing Orenetide (BP-101), a novel synthetic peptide, as a potential nasal spray for first-in-class treatment to stimulate sexual motivation [88]. Experimental placebo-controlled data showed that acute intranasal BP101 administration moderately increased the frequency of solicitations, an indicator of sexual motivation in female rats, by acting within the hypothalamus under different hormonal conditions [93]. A Phase 2,

multicenter, double-blind, randomized, placebo-controlled trial is ongoing in New Zealand and Australia to demonstrate the efficacy and safety of different doses of BP101 in premenopausal women with HSDD [89].

Finally, it is worth to mention a fascinating area of investigation linking sexual function and relationship by the use of intranasal oxytocin administration [18]. In a small sample of healthy heterosexual couples, oxytocin appeared to increase the intensity of orgasm and satisfaction after sexual intercourse [94]. However, on-demand intranasal oxytocin (32 IU) administered in premenopausal and postmenopausal women with FSDs did not show superiority compared to placebo [95]. In a randomized controlled trial, 400 IU oxytocin gel per night has also been tested intravaginally as a non-estrogenic modality to reverse VVA/GSM signs and symptoms [96], but its potential role in postmenopausal women with FSDs remains unclear.

Collectively, these preliminary data on the most promising candidate treatments for FSDs underline the importance of a stereoscopic view of human sexual behavior, which is multifactorial, multidimensional, and, therefore, extremely challenging both in research and practice.

4. Multimodal therapy to manage FSDs

The identification of specific therapeutic targets and promising drugs is still a work in progress in the field of FSDs because of the overlapping symptomatology and coexistence of multiple etiologies. For instance, orgasmic disorders are frequently linked to poor arousal, and sexual pain may facilitate HSDD [8]. In addition, psychosocial determinants, lack of sexual skills, and relational aspects play a fundamental role [2,3,6] in explaining controversies in the real effectiveness of pharmacotherapies [15]. Ideally, FSDs should always receive an integrated biopsychosocial care, which becomes even more important when drugs are contraindicated as it occurs in oncological settings [97] or in long-lasting vulvar painful conditions [98]. In this context, multimodal pelvic floor physical therapy, combining education, manual therapy, pelvic floor muscle exercises using biofeedback, and home exercises, improved psychosexual outcomes in gynecological cancer survivors with dyspareunia [99]. On the other hand, cognitive-behavioral therapy or mindfulness alone or in conjunction with physiotherapy approaches was effective in women with overactive pelvic floor and provoked vestibulodynia [100,101]. These data indicate that a multidisciplinary model of care that can target pain pathways simultaneously should be the optimal approach instead of any single modality (i.e. antinociceptive and anti-inflammatory agents, neuro-modulating medications, hormonal agents, muscle relaxants, vestibulectomy) [102]. Indeed, twice-repeated injections of 50 units of botulinum toxin A, a neurotoxin causing a localized and temporary muscular paralysis and analgesic effects, in women with provoked vestibulodynia did not reduce dyspareunia or pain at tampon use against placebo [103]. Instead, multimodal physical therapy was effective for pain, sexual function, and sexual distress as compared with overnight topical lidocaine (5% ointment) [104]. Then, more attention should be given to pelvic floor muscle training as a nonpharmacological strategy for FSDs alone or, eventually, in combination with other strategies across the life span of women, including menopause 105.

5. Conclusions

There are only a few treatments approved to manage FSDs effectively. Psychoactive agents are suitable mainly for premenopausal women, whereas hormonal compounds are the first-line choice for postmenopausal women. Psychosocial interventions alone, or combined with drugs, may be beneficial in both cases. Intensive investigation is mandatory to allow women informed choices by reducing the boundaries between physical and mental determinants of FSDs and involving the partner, whenever indicated. HCPs may benefit from the development of further psychometric instruments able to capture motivations and expectations of women consulting for sexual problems. Indeed, the magnitude of the effects of a given prescription seems to be rather subjective and even little changes over placebo may be relevant to some women as long as the treatment is safe. On the other hand, objective measures do not adequately reflect the clinical significance of treating women with FSDs.

6. Expert opinion

FSDs are non-life-threatening conditions with significant consequences on quality of life and relationships. Pharmacological treatment should be an integral part of a more comprehensive treatment program, including physical, psychosocial, and educational intervention. However, effective and safe choices are limited, and HCPs are insecure about their ability to select the best option for the individual woman. Even researchers are struggling to identify suitable instruments to formulate accurate diagnoses taking into account the multitude of contributors, ranging from straight medical variables, such as age, weight, and use of drugs, to personal and contextual factors. Reproductive life stage is a very important additional variable, as well as the fulfillment of reproductive goals and the use of exogenous sexual hormones. The constant debate in the arena of sexual medicine fosters a deeper knowledge into the multispecialty approach to FSDs. In addition, it helps to increase awareness about gender equality and women's needs in respect to the availability of many treatments for male sexual dysfunctions. On the other hand, the multi-faceted etiology of FSDs contributes to raise or lower the bar for diagnosis and, therefore, for evidence-based treatment of symptoms clinically relevant. The swinging pendulum in treatment for FSDs is moving from chronic to on-demand administration and from a single approach to a multimodal strategy addressing several pathways stimulating or inhibiting sexual response. Of note, only few innovative pharmacotherapies for FSDs are in real development, and experimental data cannot completely guide research into human sexuality. That being so, there is a lack of investment in such a field, which is both promising and slippery. Indeed, the target market is potentially broad, but the amount of criticism surrounding recently approved

psychoactive drugs for HSDD, along with the withdrawal of T patch, have slowed down further funding for drug development.

That notwithstanding, sexual health remains important and an increasing number of women would like to gain a better knowledge into their sexual functioning and be willing to find solutions for distressing sexual symptoms. Routine questions during general consultations may help to uncover sensitive topics and lead to investigations into specialized services. The challenge is to identify those women who may be at higher risk due to genetic and epigenetic factors impinging on biomedical and psychosocial substrates of the sexual response. A deep knowledge of the full history, along with the availability of validated multidimensional instruments and possible objective measures of physical and mental responses to sexual external and internal incentives will help to identify those women more vulnerable to FSDs. Moreover, the same elements will enable us to recognize those women who will respond to specific treatments, as well as those who will be more sensitive to the placebo effect. The presence of caring HCPs coupled with a constant self-assessment might amplify the positive effects of any interventions, whereas early negative sexual experiences and discrepancies within the couple might reduce effectiveness even of treatments targeting well-established conditions. An intense exchange of information between regulatory authorities and sexual medicine experts is desirable to establish the most suitable endpoints in clinical trials to assess efficacy and safety. Finally, the assessment of women's perspectives seem to be equally important to find innovative pharmacotherapies for FSD with a fair balance between potential risks and meaningful benefits.

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