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Expert Opinion on Pharmacotherapy

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ieop20

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To cite this article: Sarah Cipriani, Chiara Alfaroli, Elisa Maseroli & Linda Vignozzi (2023) An evaluation of bremelanotide injection for the treatment of hypoactive sexual desire disorder, Expert Opinion on Pharmacotherapy, 24:1, 15-21, DOI: 10.1080/14656566.2022.2132144

To link to this article: https://doi.org/10.1080/14656566.2022.2132144

EXPERT OPINION ON PHARMACOTHERAPY
2023, VOL. 24, NO. 1, 15–21
https://doi.org/10.1080/14656566.2022.2132144

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DRUG EVALUATION

An evaluation of bremelanotide injection for the treatment of hypoactive sexual desire disorder

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ABSTRACT

Introduction: Female sexual response implies a deep intertwining between psychosocial and neurobiological mediators. Regulation of central melanocortin signaling may enhance sexual desire. In premenopausal women with hypoactive sexual desire disorder (HSDD), melanocortin receptor agonist bremelanotide (Vyleesi) has been hypothesized to trigger excitatory brain pathways.

Areas covered: Hereby we summarize bremelanotide's proposed mechanism of action, pharmacokinetics, efficacy and safety data derived from clinical trials. A literature search of peer-reviewed publications on the current evidence on the pharmacotherapy with bremelanotide was performed using the PubMed database.

Expert opinion: Bremelanotide appears to be moderately safe and well-tolerated; the most common adverse reaction is nausea (40%). Although data from clinical trials demonstrated a significant change in validated questionnaires, the overall clinical benefit appears to be modest. However, these results should be interpreted in the light of the dramatic challenges in conducting well-designed clinical trials for female sexual dysfunction, due to the significant placebo effect of pharmacotherapy, and the frequent use of outcome measures that are likely to be highly susceptible to expectation biases, such as long periods of recall of sexual and emotional response.

ARTICLE HISTORY
Received 16 February 2022
Accepted 29 September 2022

KEYWORDS
Female sexual dysfunction; bremelanotide; hypoactive sexual desire disorder; female sexual distress

1. Introduction

Sexual health is a crucial aspect of quality of life and sexual symptoms are common in women across all ages. Despite the fact that the interest of the medical community for this field of research has spread over the last few decades, at present there is a lack of universally shared protocols for the work-up of female sexual dysfunction (FSD) [1]. These shortcomings are particularly evident when compared to the male counterpart, for which a fair variety of approved etiological treatments is available on the market for at least two of the most common male sexual dysfunctions (SDs), namely erectile dysfunction and premature ejaculation [2]. Such well-known 'gender gap' reflects a major bias in health-care systems, related to women being underrepresented in clinical trials, since they have different susceptibilities and exposures to risk factors (e.g. during pregnancy or after a diagnosis of hormone-dependent cancer), and often facing embarrassment, poor awareness and inadequate training in health-care providers when referring for sexual counseling [2].

In this context, female sexual desire stands out as a particularly complex topic, since it represents a domain of sexual function in which intrapersonal, interpersonal and social components are deeply intertwined, thus posing a special challenge to our understanding of its biological mechanisms, and consequently to drug discovery in this field. Noteworthy, this last point seems to raise some sensitive issues relating to the emotional and social aspects of sexual desire; namely, a drug treatment for it could be considered inadequate for many reasons, such as unrealistic expectations due to scarce sexual education, pressure from the partner for a more frequent sexual activity and, not least, a history of sexual abuse, that can profoundly influence sexuality, sense of self and interpersonal relationships.

1.1. Hypoactive sexual desire disorder

Hypoactive sexual desire disorder (HSDD) can be considered one of the most common manifestation of FSD, affecting up to 10% of women [3,4]. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV [5] and IV-TR [6], it is substantially determined by the lack of sexual fantasies and desire for sexual activity, associated with distress. Successively, in DSM V [7], it has been collapsed with female sexual arousal disorder (FSAD), generating a new clinical condition labeled as female sexual interest–arousal disorder (FSIAD), although remaining mainly based on sexual desire [3,4]. Such a reclassification has been the topic of considerable scientific debates; however, HSDD is still maintained as an independent diagnostic category in the ICD-11 (International Classification of Diseases, 11th Revision) system [8], as well as

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in the ISSWSH Nomenclature revision proposal [9]. More in detail, according to the ISSWSH Process of Care (POC), HSDD is defined as a lack/loss of interest in engaging in sexual activity due to both decreased/absent desire linked to sexual stimulation, or maintenance of desire throughout sexual activity, for a minimum of 6 months, that is not dependent on any other medical or psychiatric condition, causing significant personal distress [10].

Although different underpinning factors have been recognized for HSDD, the exact underlying pathophysiological mechanism is not completely understood [3]. As a matter of fact, hormonal, psychological and relational factors, as well as life situation, culture, ethnicity, menopausal status and central nervous system (CNS) activity are deeply intertwined in determining HSDD [11]. On this background, the 2018 ISSWSH POC for the management of HSDD suggests a 'biopsychosocial' approach to patients, including physical examination, laboratory testing as well as elicitation of medical, psychological, sexual and social history, in order to identify potentially reversible factors of the disorder [10]. For example, sex steroids – in particular, estrogens and androgens – act as key biological determinants of sexual interest in women [12,13]; therefore, conditions leading to alterations of their levels (i.e. amenorrhea, natural and surgical menopause, breastfeeding, use of hormonal contraceptives) should be carefully evaluated in order to exclude secondary forms of HSDD. Consequently, therapeutic strategies entail first effective education, and second, modification of contributing factors thought to be playing a role in HSDD. Sex therapy (i.e. cognitive behavior therapy), hormonal therapy or CNS agents can be considered only after this careful assessment, and should always be implemented in a patient- and couple-oriented, multidimensional approach [14].

From a neurobiological perspective, the imbalance between excitatory (dopamine, norepinephrine, melanocortins) and inhibitory (serotonin, endocannabinoids) neurotransmission has also been suggested to play a central role in HSDD etiology [15]. The range of therapies based on the modulation of these central pathways has improved in recent years, and include two agents approved by the U.S. Food and Drug Administration (FDA) for the treatment of HSDD in premenopausal women, respectively in 2015 and 2019: flibanserin (Addyi), a multifunctional serotonin agonist/antagonist, and bremelanotide (Vyleesi), a melanocortin receptor agonist in the central nervous system.

Hereby we summarize bremelanotide's proposed mechanism of action, pharmacokinetics, efficacy and safety data derived from clinical trials. An intensive literature search of peer-reviewed publications to review the current evidence on the pharmacotherapy with bremelanotide was performed using the PubMed database. Articles in English mainly published in the last 10 years have been selected, after screening of the titles of search results and reviewing abstracts for removal of unremarkable literatures and duplicates.

2. Bremelanotide overview

Melanocortins are a group of peptide hormones derived from the pro-hormone proopiomelanocortin (POMC) in the pituitary gland, which include adrenocorticotropic hormone (ACTH), β-endorphins, and the different forms of melanocyte-stimulating hormone (MSH) [16]. They exert their effects by binding to and activating G protein–coupled melanocortin receptors (MCRs). In the brain, the melanocortin system plays a substantial role in the regulation of several pathways, including energy homeostasis and sexual behavior.

In the Eighties, melanotropic peptides, namely melanotan I and II, were developed as tanning agents and lately emerged as potential facilitators of sexual function in animal models [17] and also in male and female humans [18,19]. PT-141, a peptide analogue of binding to central MCR, was demonstrated to selectively stimulate solicitational behaviors in the female rat, and was proposed as a pharmacological agent to treat female sexual desire disorders [20]. Phase II trials of intranasal bremelanotide in both FSD and male erectile dysfunction were interrupted due to adverse effects related to increased blood pressure; the drug was then reformulated to be delivered by injection and trials continued in FSD [21].

Bremelanotide is a MCR agonist developed as an on-demand therapy for FSD with a subcutaneous administration. As a synthetic analogue of endogenous α-MSH, it shows high affinity for MC4R, whose activation has the potential to trigger specific neural pathways involved in sexual desire [22]. This drug was first approved in the U.S. on 21 June 2019 for the treatment of premenopausal women with acquired, generalized HSDD [21], with a subcutaneous injection of 1.75 mg in the abdomen or thigh, at least 45 min before initiation of sexual activity [23].

2.1. Pharmacodynamics

The precise mechanism underlying bremelanotide's efficacy is still a matter of debate. As a MCR agonist, bremelanotide is thought to release dopamine (DA) in key excitatory brain regions involved in sexual desire. This differs from the mechanism of action of flibanserin, which has been reported to blunt inhibitory sexual signals [15].

Similarly to the endogenous α-MSH, bremelanotide binds to several MCR subtypes, but with different affinity and the following order of potency: MC1R, followed by MC4R, MC3R, MC5R and MC2R. At therapeutic doses, bremelanotide efficiently activates MC1R and MC4R, but while MC1R is expressed on melanocytes, MC4R is highly expressed in the hypothalamic and limbic regions of the mammalian brain, two of the most important areas for sexual function [24]. Specifically, melanocortin projections which stems in the arcuate nucleus of the hypothalamus signal not only to other hypothalamic areas, such as the medial preoptic area (mPOA) and the ventral tegmental area (VTA), but also to parts of the limbic system, and to the pituitary [25].

According to preclinical data, activation of presynaptic MC4R on neurons in the mPOA leads to release of dopamine (DA), with postsynaptic activation of D1 receptors [15], thus generating a potent auto-excitatory loop. Indeed, D1 receptors are expressed on γ-aminobutyric acid (GABA) neurons, the main inhibitory system of DA neurons [26]. Therefore, D1 activation finally results in a disinhibition of the main inhibitory GABAergic pathways. Since estradiol increases α-MSH

levels in the hypothalamus in animal studies, it has been suggested that the melanocortin system may be one of the mediators of estrogen action on female reproductive behavior [27].

2.2. Pharmacokinetics and metabolism

After subcutaneous injection, bremelanotide undergoes a rapid absorption, and reaches the peak concentration in the plasma (T_{max}) in a median time of approximately 1 hour. The mean plasma C_{max} (higher concentration) is 72.8 ng/mL. The plateau is achieved for a dose of 7.5 mg, which is more than four times the highest recommended dose [23].

Bremelanotide is 100% bioavailable, independently of the site of subcutaneous administration (thigh or abdomen). Regarding distribution, only 21% has been reported to be protein-bound in serum. The mean volume of distribution following a single administration is 25.0 ± 5.8 L [23].

Being a 7-aminoacid cyclic peptide, the metabolism of bremelanotide consists of multiple hydrolysis reactions of the amide bond. It is eliminated mostly by urine (65%) and secondarily by feces (23%). The mean terminal plasma half-life, namely the time required to divide the plasma concentration by two after reaching pseudo-equilibrium, is approximately 2.7 hours (range: 1.9–4.0 hours). The mean clearance (± standard deviation) of the drug is 6.5 ± 1.0 L/hr. This is a remarkable data, since, as described in the 'Clinical efficacy' section below, the only phase III trials examining bremelanotide provide 28-day recall outcome measures for the primary outcomes, so that drug effects on sexuality were not directly linked to the drug exposure period.

As regards the drug clearance, studies in patients with mild or moderate renal or hepatic impairment did not show a clinically relevant alteration of these pharmacokinetics parameters, therefore these special populations do not require dosage adjustments. On the other hand, bremelanotide should be prescribed cautiously in women with severe renal and hepatic impairment, due to the possibility of increased incidence and severity of adverse events. Indeed, the effect of severe hepatic impairment on the pharmacokinetics was not studied, whereas the exposure increased 2-fold in severe renal impairment.

No clinically significant pharmacokinetic interactions have been demonstrated between bremelanotide and ethanol [28].

As for drug interactions, bremelanotide reduced the absorption of co-administered naltrexone and indomethacin to a relevant degree, probably acting through a slowing of gastric emptying. Pharmacokinetic studies showed that bremelanotide did not significantly affect the oral absorption of norethindrone/ethinyl estradiol, metformin, antidepressants (bupropion, sertraline, venlafaxine), or antihypertensives (lisinopril, losartan, metoprolol, amlodipine). Due to its metabolism by hydrolysis, there is little concern for CYP-related interactions [29].

2.3. Clinical efficacy

Bremelanotide has been examined in one early randomized clinical trial (RCT), one phase I study (NCT03973047), two phase II studies (NCT00425256 and NCT01382719) and two identical phase III RECONNECT studies [301 (NCT02333071) and 302 (NCT02338960)] (Table 1).

In 2006, the earliest clinical study of bremelanotide was conducted in 18 premenopausal women primarily diagnosed with FSAD [30]. Enrolled patients randomly received a single intranasal dose of 20 mg bremelanotide or matching placebo on the first in-clinic visit and the alternate medication during the second one [30]. During each treatment session, patients watched a short sexually explicit video after a neutral video of

Table 1. Summary of bremelanotide clinical trials.

Study number	Phase	Study design	# Subjects enrolled	Dose (mg)	Duration (weeks)	(Co)primary endpoints used
NA	NA, Pilot study	PC, DB, R, crossover	18	Bremelanotide 20, intranasal	1	-Subjective measurements of sexual arousal and desire evaluated using questionnaires -Vaginal vasocongestion measured by vaginal photoplethysmography
NCT03973047	I	PC (for ondansetron), QB, R	Bremelanotide + placebo or bremelanotide + ondansetron: total 288	Bremelanotide 1.75, subcutaneous Ondansetron 8, oral	1-day double-blind period, single dose	Incidence of treatment-emergent nausea following bremelanotide with or without concomitant use of ondansetron
NCT00425256	II	PC, DB, R	NA	Intranasal, dosage NA	8	NA
NCT01382719	IIb	PC, DB, R	Placebo: 97 Bremelanotide 0.75 mg: 100 Bremelanotide 1.25 mg: 99 Bremelanotide 1.75 mg: 98	0.75, 1.25, 1.75 subcutaneous	12	Change in satisfying sexual events/month
NCT02333071 (301)	III	PC, DB, R	Bremelanotide: 313 Placebo: 315	1.75, subcutaneous	24	Change in FSFI-D and FSDS-DAO
NCT02338960 (302)	III	PC, DB, R	Bremelanotide: 282 Placebo: 288	1.75, subcutaneous	24	Change in FSFI-D and FSDS-DAO

DB: Double-blind; PC: Placebo-controlled; R: Randomized; QB: Quadruple-blind (participant, care provider, investigator, outcomes assessor); NA: Not available; FSFI-D: Female Sexual Function Index-Desire domain score; FSDS-DAO: Female Sexual Distress Scale-Desire/Arousal/Orgasm.

the same duration. As assessed by a treatment satisfaction questionnaire, after the bremelanotide dose, women reported a moderate to high sexual desire (p = 0.0114), as well as better sensations of genital arousal (p = 0.0833) and a more satisfying sexual arousal in sexual intercourses attempted in the following 24 h (p = 0.0256), compared to placebo [30]. Conversely, bremelanotide or placebo did not induce any significant variation in vaginal vasocongestion, as evaluated through vaginal photoplethysmography [30].

A 12-week phase IIb trial tested self-administered, as-desired bremelanotide at three different subcutaneous doses (0.75 mg, 1.25 mg, 1.75 mg) vs. placebo [31]. Subjects were premenopausal women (aged ≥ 21 years) diagnosed with HSDD, FSAD or a combination of them for ≥ 6 months (n = 327, modified intent-to-treat population, mITT). Those administered with the two highest doses of bremelanotide (1.25 or 1.75 mg) showed statistically significant and clinically considerable improvements in the number of satisfying sexual events (SSEs) from baseline to end of the study as a primary outcome (mean change +0.7 vs. +0.2 SSEs/month; p = 0.018) [31]. For 1.25/1.75-mg pooled vs. placebo, a significant improvement (+3.6 vs. +1.9, p = 0.0017) in the Female Sexual Function Index (FSFI) total score and in the Female Sexual Distress Scale-Desire/Arousal/Orgasm (FSDS-DAO) total score (−11.1 vs. −6.8, p = 0.0014) was observed [31]. As a result of a responder analysis carried out from this study, 1.75 mg bremelanotide was the dosage chosen to additionally assess its efficacy and safety in two phase III, double-blind, placebo-controlled, multicenter RCTs (RECONNECT studies 301 and 302) [22]. Women aged ≥ 18 years with a diagnosis of HSDD for ≥ 6 months were assigned to bremelanotide 1.75 mg or placebo group (study 301 n = 313 and 315; study 302 n = 282 and 288, respectively) for 24 weeks [32]. Concerning the two co-primary efficacy endpoints, in both studies from baseline to the end of them, subjects receiving bremelanotide showed a significant increase in sexual desire (RECONNECT 301 0.30, RECONNECT 302 0.42, integrated studies 0.35, all p < 0.001) and a significant reduction in low desire-related distress (RECONNECT 301 − 0.37, p < 0.001, RECONNECT 302 − 0.29, p = 0.005, integrated studies −0.33, p < 0.001), compared with placebo [32]. In addition, the difference from baseline to end of the study in the number of SSEs occurring within 16 h of bremelanotide/placebo administration and notified within 72 h was considered as a secondary endpoint. Although this number did not show any significant difference between the two groups [32], in a *post hoc* analysis, the percentage of SSEs was from two- to threefold higher with bremelanotide respect for placebo (23.6% vs. 8.4%, p < 0.0001 for study 301 and 26.6% vs. 11.3%; p < 0.0001 for study 302) [14]. The efficacy of bremelanotide was confirmed in patients who continued the use of the drug (n = 254, roughly 80%) in 52-week extensions of the two studies, with maintained improvement in FSFI-Desire (FSFI-D) and FSDS-DAO scores as well as in the number of SSEs [33].

2.4. Safety and tolerability

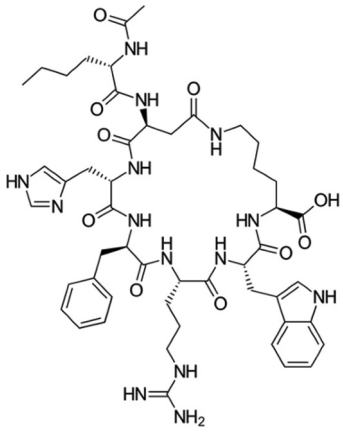
In the 2006 early study presented above, intranasal formulation of bremelanotide was not associated with any adverse effect [30]. Successively, the aforementioned phase I study was conducted in a randomized double blind manner, with the aim to evaluate safety and pharmacokinetics of the drug if administered with ethanol [28]. The study concluded that bremelanotide was not associated with a significant increase in the incidence of adverse events, nor with clinically significant changes in blood pressure or pharmacokinetic interactions with ethanol [28]. Conversely, in the phase IIb study NCT01382719, the most common treatment-emergent adverse events (TEAEs) were experienced in the bremelanotide 1.25 and 1.75 mg groups, being nausea (22–24%), flushing (14–17%) and headache (9–14%) the most frequent ones [31]. A minority of patients experienced injection-site reactions and only three bremelanotide subjects reported severe TEAEs, that were related to underlying diseases [31]. Similarly, resulting from the RECONNECT studies, mild or moderate nausea (39.9%), facial flushing (20.4%) and headache (11%) were the most common bremelanotide-related adverse events; only two serious adverse events (one each of vomiting/nausea and headache) were reported [34]. Furthermore, no clinically significant changes in vital signs, biochemical or electrocardiogram data were observed [29]. Safety data in the open-label extension phases of the RECONNECT studies were similar to the core study results; nevertheless, the following three TEAEs were documented: acute hepatitis with restoration of liver tests 4 months after treatment discontinuation [34], mild, transient increases in systolic and diastolic blood pressure and isolated, mild, transient decreases in pulse rate [33]. Interestingly, 1% of subjects taking up to 8 monthly doses (the recommended maximum) of bremelanotide reported potentially permanent focal hyperpigmentation, principally affecting breasts, face and gingiva [34]. Although it can not be considered as a severe TEAE, it can lead to considerable emotional distress, being an impactful adverse event to take into account.

Noteworthy, the not negligible rate of symptomatic adverse events, especially that of nausea presenting after injection, could lead to an expectation bias, whose extent in a trial can be measured by asking every participant which treatment they thought they were taking. Although the study population of the RECONNECT studies completed a General Assessment Questionnaire, measures of unblinding have not been reported to date, not in the FDA review either [35].

In summary, especially based on the results of the phase III studies, it can be concluded that bremelanotide is safe and moderately well-tolerated, being associated with mild to moderate adverse events at most [29]. However, it is noticeable that patients taking the drug showed a higher percentage of withdrawals as compared with those taking placebo (18% vs 2% in the core phases of the RECONNECT studies). Additionally, bremelanotide can induce transient increases in blood pressure and decreases in heart rate [34,36]; consequently, patients' cardiovascular risk should be assessed before initiating bremelanotide treatment.

A drug summary is presented in Box 1.

Box1. Durg Summary

Drug name (Generic)	Bremelanotide
Phase	Registered (Phase III complete)
Indication	Premenopausal women with acquired, generalized HSDD
Pharmacology	MCR agonist in the central nervous system
Route of administration	1.75 mg administered on demand, subcutaneously in the abdomen or thigh, at least 45 minutes before anticipated sexual activity
Chemical structure	
Pivotal trial(s)	Phase III, double-blind placebo-controlled efficacy and safety trials [31–34]

HSDD: Hypoactive Sexual Desire Disorder; MCR: Melanocortin receptor.

2.5. Company agreements and regulatory affairs

Bremelanotide was patented by Palatin Technologies and subsequently out-licensed in North America to AMAG Pharmaceuticals Inc in January 2017 [21]. Later in 2017, Palatin granted rights to Shanghai Fosun Pharmaceutical and to Kwang Dong Pharmaceutical, to develop and commercialize bremelanotide for FSD in Republic of Korea and in mainland China, Taiwan, Hong Kong S.A.R. and Macau S.A.R, respectively [21]. Bremelanotide received its first approval in the U.S. on 21 June 2019 [37]. At a later time, in 2020, Palatin Technologies mutually terminated the 2017 license agreement which granted AMAG Pharmaceuticals exclusive North American rights to market bremelanotide [38].

Previously in 2015, the process of FDA approval for flibanserin, the first drug for the treatment of women with low sexual desire, had been troubled, due to allegations of gender bias in the FDA by advocacy groups [35]. More in detail, a public relations campaign called 'Even the Score' was conducted, which also included lobbying of the FDA by female politicians and women's movements [35]. In this context, in October 2014 the FDA held a panel with the aim of hearing both patients' and experts' testimonies on female sexual dysfunction, but it had been claimed that nearly all of them had their expenses covered by the same founder of 'Even the Score' and their presentations and talking points had been planned before [35].

Furthermore, mainly because the concomitant use of alcohol markedly increases the risk of hypotension/syncope, flibanserin had been licensed with a risk evaluation and mitigation strategy, requiring the physician to complete a Patient-Provider Agreement form before prescription [39]. The approval of bremelanotide in 2019 followed the regulatory precedent set by flibanserin and stimulated an intense debate in the scientific community and in the general public. Indeed, some called upon an excessive, industry-led medicalization of women's sexuality, and criticized several features of key premarket trials for both drugs, including the shifts in primary outcome measures required by the applicant companies [35]. In more detail, the FDA initially agreed with the 4-week FSFI-D scale as a coprimary outcome measure, together with the number of SSEs within 16 hours after injection. Consequently to flibanserin's approval, the 4-week FSDS-DAO score became a coprimary outcome, shifting the number of SSEs to a secondary one [35]. Firstly, this shift in primary outcomes has been criticized since it mostly relies on 4-week recall outcome measures, a period during which women have negligible to no drug exposure, due to its pharmacokinetics. Additionally, there are concerns regarding the unclarity of the instructions preceding the questions about desire and the simplistic 'more is better' framing into which female sexual desire appears to be inserted based on such questionnaires [35].

3. Conclusion

It is universally recognized that SD can adversely affect quality of life and the FDA declared that 'there is a medical need for the development of drugs with a favorable benefit-risk profile to treat women with sexual dysfunction' [40]. Particularly, the prevalence of HSDD among women is considerable, as well as the percentage of distress related to it [1]. Within this framework, the availability of bremelanotide, especially in countries outside the U.S. where no drugs indicated for HSDD are on the market, could be of clinical relevance to offer many women access to treatment to improve sexual function. Although its clinical efficacy seems to be modest, its dosages and side effects, including interactions with alcohol and other drugs, have been tested in specific female populations, differently from other drugs currently used 'off-label' for the treatment of HSDD. Specifically designed trials are needed to boost bremelanotide's tolerability (particularly regarding nausea) and to better assess its efficacy, using adequate outcome measures and minimizing biases (see section below).

4. Expert opinion

Clinical evidence shows that, in premenopausal HSDD women, bremelanotide improves sexual desire with a good safety profile and a moderate tolerability (the most common adverse reaction being nausea, up to 40%). The main contraindications are uncontrolled hypertension or known cardiovascular disease, which are not common in young women, and contraception should be advised in case of child-bearing potential. On a positive note, bremelanotide has no key cytochromes or alcohol interactions.

Regarding efficacy, it must be noted that, although data from clinical trials apparently indicate that bremelanotide significantly improved FSFI and FSDS scores, the real clinical benefit appears to be modest. As discussed above, there are some key methodical aspects to consider in the evaluation of the efficacy of the drug. Firstly, the notable rate of symptomatic adverse events, especially of nausea, could lead to an expectation bias, whose extent has not been reported to date, although the study populations of the Phase III trials completed a questionnaire measure of unblinding. Secondly, the aforementioned shift in primary outcomes mainly relies on 4-week recall outcome measures, a period during which women have ineffective drug exposure, due to its pharmacokinetics. Moreover, such questionnaires have been criticized for the unclarity of the instructions and the simplistic idea of 'more is better' related to female sexual desire they convey. Such weaknesses in the field could be solved with the employ of measures of unblinding and more reliable and objectiveable outcome measures in clinical trials, this last point representing a long-lasting challenge of the investigation of female sexuality, however. As a matter of fact, these results should be interpreted in the light of the dramatic challenges in conducting well-designed clinical trials for FSD, due to the significant placebo effect of pharmacotherapy, and the inability to minimize the myriad of potential biases involved in the female sexual response [41].

Concerning tolerability of bremelanotide, nausea represents a considerable distressing factor, which can lead to drug discontinuation. Specifically designed and larger studies are needed to improve tolerability of the drug (e.g. with a different route of administration?).

Another relevant aspect to consider are the high costs of bremelanotide, which could preclude access to therapy. Its AWP (average wholesale price) is currently (year 2022) around $1000 per box, containing 4 disposable prefilled single-dose autoinjectors [42]. In the U.S., these costs may be covered by insurance.

Finally, a major shortcoming is the lack of indication of bremelanotide for postmenopausal women. Only a phase 2 trial, with an intranasal bremelanotide formulation, has been conducted in this population, although postmenopausal women present HSDD more often than women in the fertile age [1]. However, a lower efficacy may be expected in menopausal women due to the decrease in sex steroids, which have been reported to act as positive modulators of the melanocortin systems. Indeed, preclinical studies indicate that not only estrogens, but also androgens, activate MC4R signaling in the brain [15,17,20].

In conclusion, when prescribing pharmacotherapy for HSDD, physicians should always be aware that, as FSD is multifactorial, so should be its treatment. In the context of a biopsychosocial approach to sexual medicine, education of both patients and health care providers is crucial in order to acquire new skills and overcome barriers to an effective work-up of sexual difficulties in women and couples. Without forgetting the importance of a general clinical assessment, hormonal evaluation and psychosexual counseling, only the availability of safe and effective drugs will ultimately allow clinicians to provide a tailored treatment to women with HSDD. In this view, the use and study of bremelanotide can make an important contribution to the knowledge and the preservation of women's sexual health; nevertheless, future studies are needed to better assess its mechanism of action and improve its efficacy and tolerability for a broader use.

Funding

This research was supported by a PRIN grant ('Progetti di Rilevante Interesse Nazionale': 2017S9KTNE).

Declaration of interest

L Vignozzi has received funding for scientific research, advisory board attendance and speaker honoraria from Therascience, Theramex, Bayer Schering Pharma, Intercept, Lipocine, Ibsa. 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.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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