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Bremelanotide: New Drug Approved for Treating Hypoactive Sexual Desire Disorder

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Abstract

Objective: To review data regarding bremelanotide, a recently approved therapy for hypoactive sexual desire disorder (HSDD). **Data Sources:** Literature search of Medline, SCOPUS, and EMBASE was performed using the search terms *bremelanotide, bremelanotide injection, Vyleesi*, and *melanocortin 4 receptor agonist* between January 1, 1996, and December 15, 2019. Reference lists from included articles were also reviewed for pertinent citations. **Study Selection/Data Extraction:** We included phase 2 and 3 trials of bremelanotide. There were 2 reports of phase 3 trials and 2 reports of phase 2 trials. Additional information from supplementary analyses was also referenced. **Data Synthesis:** Bremelanotide demonstrates significant improvement in desire and a significant decrease in distress related to lack of desire. The most common adverse effects include nausea (39.9%), facial flushing (20.4%), and headache (11%). **Relevance to Patient Care and Clinical Practice:** Bremelanotide is the second Food and Drug Administration–approved medication for the treatment of HSDD. Bremelanotide's place in therapy is unknown, as the HSDD guidelines were last updated in 2017. Although the trials met statistical significance for change in sexual desire elements and distress related to sexual desire, the clinical benefit may only be modest. **Conclusion:** Bremelanotide is a subcutaneous injection that can be administered as needed approximately 45 minutes prior to sexual activity. Bremelanotide is safe and has limited drug-drug interactions, including no clinically significant interactions with ethanol. Prescribing guidelines recommend no more than 1 dose in 24 hours and no more than 8 doses per month. Individuals should discontinue use after 8 weeks without benefit.

Keywords

bremelanotide, Vyleesi, melanocortin 4 receptor agonist, HSDD

Introduction

Hypoactive sexual desire disorder (HSDD) is a common, yet underdiagnosed condition affecting approximately 10% of pre- and postmenopausal women.[1-3] Historically, female sexual dysfunction has been diagnosed by clinical presentation and patient history.[1]

In the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*), HSDD was defined as a distinct nosologic entity; however, the *DSM-5* combined it with female sexual arousal disorder (FSAD) and termed it female sexual interest/arousal disorder (FSIAD).[1,2] FSIAD includes both desire and arousal elements.[2] This revised classification is controversial among clinical experts.[1] There are few diagnostic validation and treatment evaluation studies for FSIAD, limiting the clinical applicability of the term.[2]

The International Society for the Study of Women's Sexual Health (ISSWSH) Nomenclature Committee and the International Consultation in Sexual Medicine maintain HSDD as an independent diagnostic category, and HSDD is still represented as an independent diagnostic category in the ICD-10 (International Classification of Diseases, 10th Revision) system.[1] Symptoms include lack or loss of motivation to participate in sexual activity due to decreased or absent desire related to spontaneity, erotic cues, sexual stimulation, or maintenance of desire throughout sexual activity for at least 6 months, that is not secondary to any other medical or psychiatric condition, relationship distress, medication, or substance use disorder. Symptoms must cause personal distress.

HSDD significantly affects quality of life, leading to impaired body image, self-confidence, and self-worth and affecting partner intimacy and connectedness.[1] Additionally, a resource utilization study found that women diagnosed

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with HSDD had 16.8% higher total health care expenditures than women without HSDD.[4]

The Female Sexual Function Index–Desire Domain (FSFI-D) is the standard measure for clinical trials of HSDD; however, it lacks items assessing sexually related behaviors and attitudes toward partners, which is addressed in the Female Sexual Distress Scale–Desire/Arousal/Orgasm (FSDS-DAO).[5] Clinical significance is difficult to define using mean treatment differences. Alternatively, the Food and Drug Administration (FDA) has recommended using responder and remitter analyses. Responder analysis refers to the proportion of subjects who respond favorably to treatment. The numerical value often corresponds to a 50% improvement on the scale. A remitter analysis refers to the proportion of subjects who no longer have the disorder being treated. Often this corresponds to an improvement in the score within the normal range.

The exact pathophysiological processes that result in symptoms characterized by HSDD are incompletely understood.[1] In females, sexual desire is thought to be regulated by a complex system of inhibitory and excitatory neuromodulatory processes. Dopamine, oxytocin, norepinephrine, and melanocortins are excitatory components, and serotonin, opioids, and endocannabinoids are inhibitory components.[1,3] There are also psychological and hormonal factors.[1]

The first HSDD treatment guidelines were released in 2017 by ISSWSH.[1] They recommend treatment using both psychosocial and biologic modalities. Psychosocial treatment includes psychotherapy focusing on modifying thoughts and behaviors that interfere with sexual desire. Biological treatment strategies include flibanserin, which is FDA-approved for the treatment of HSDD in premenopausal women,[6] and several off-label options, including transdermal testosterone, bupropion, and buspirone.[1,2] Bremelanotide is the newest addition to this category.

Approved in June 2019, bremelanotide is a melanocortin receptor agonist indicated for the treatment of acquired, generalized, HSDD in premenopausal women. It is a self-administered, subcutaneous injection dosed as needed before anticipated sexual activity.[7]

Data Selection

We performed a systematic review of articles indexed in the MEDLINE/PubMed, SCOPUS, and EMBASE databases as well as the National Institutes of Health Clinical Trials Registry (http://www.clinicaltrials.gov) between January 1, 1996, and December 15, 2019. Search terms included *bremelanotide, bremelanotide injection, Vyleesi*, and *melanocortin 4 receptor agonist*. Only articles published in English and pertaining to premenopausal women were included. Additional data were obtained from prescribing information, references of identified articles, as well as posters and abstracts from scientific meetings, governmental sources, and ongoing clinical trials.

Table 1. Pharmacokinetics of Bremelanotide[7].

Absorption	
Bioavailability	100% after subcutaneous injection
Time to peak	Approximately 1 hour (range 0.5-1 hour) in plasma
Distribution	
Protein binding	21%
Volume of distribution	25.0 ± 5.8 L after a single dose
Metabolism	Primarily amide hydrolysis of the cyclic peptide
Excretion	
Terminal half-life	Approximately 2.7 hours (range 1.9-4.0 hours)
Clearance	6.5 ± 1.0 L/h

Pharmacology

Bremelanotide is a melanocortin receptor agonist.[7] It nonselectively activates MC1R, MC2R, MC3R, MC4R, and MC5R receptor subtypes. Neurons expressing MC4R are present in central nervous system and peripheral tissues. Activation of these receptors modulates brain pathways involved in sexual response.[3,7] Activation of MC1R contributes to a possible side effect of hyperpigmentation.[3]

Bremelanotide was initially developed as an intranasal formulation. This route was associated with wide variability in bioavailability, which increased the incidence of adverse effects.[8] Bremelanotide is currently formulated as a subcutaneous injection with 100% bioavailability.[7]

Bremelanotide has been linked to increased blood pressure related to binding on MC4R.[7,8] An open-label ambulatory blood pressure monitoring study of 127 premenopausal women receiving once daily injectable bremelanotide showed a mean daytime increase in systolic blood pressure of 1.9 mm Hg (95% confidence interval [CI] = 1.0 to 2.7) and in diastolic blood pressure of 1.7 mm Hg (95% CI = 0.9 to 2.4) after 8 days of dosing.[8] The increase was transient and had a mean peak effect in systolic blood pressure of 2.8 mm Hg 4 to 8 hours postdose. The mean peak effect in diastolic blood pressure was 2.7 mm Hg at 0 to 4 hours postdose. This was accompanied by a transient mean decrease in heart rate of 0.5 beats per minute (95% CI = −1.6 to −0.7). The blood pressure values 12 to 24 hours postdose were similar to the predose values.

Pharmacokinetics

The key pharmacokinetic parameters are summarized in Table 1.

Bremelanotide exposure (AUC [area under the curve]) increased 1.2-fold after administration of a single subcutaneous dose to those with mild renal impairment (estimated glomerular filtration rate [eGFR] = 60-89 mL/min/1.73 m^2) and 1.5-fold in those with moderate impairment (eGFR = 30-59 mL/min/1.73 m^2).[7] Moderate hepatic impairment

demonstrated similar results (Child-Pugh A-B, 1.2- to 1.7-fold increase in AUC). No dosage adjustment is required in these conditions. Bremelanotide should be used with caution in severe renal (eGFR = <30 mL/min/1.73 m^2) and hepatic impairment (Child-Pugh C) because of an increase in the incidence and severity of adverse effect such as nausea, vomiting, and flushing.

Bremelanotide slows gastric motility, which may reduce the rate and extent of absorption of concomitantly administered oral medications. However, the subcutaneous injection was only demonstrated to affect the absorption of naltrexone and indomethacin. Several pharmacokinetic studies revealed that bremelanotide did not significantly affect the oral absorption of norethindrone/ethinyl estradiol,[9] metformin,[10] antidepressants (bupropion, sertraline, venlafaxine), or antihypertensives (lisinopril, losartan, metoprolol, amlodipine).[7] The primary metabolic pathway is hydrolyses of the amide bonds of the cyclic peptide; therefore, there is little concern for CYP-related interactions (Table 1).[7]

Concomitant alcohol consumption does not increase the rate of adverse events or significantly alter drug pharmacokinetic parameters.[11] No warnings for food interactions are currently published.[7]

Clinical Trials

An early double-blind study of bremelanotide for the treatment of FSAD in premenopausal women showed moderate improvements in sexual desire measured by change in vaginal pulse amplitude and subject perception of physiological and sexual response using a treatment satisfaction questionnaire.[12] Participants received 20-mg doses of bremelanotide intranasally or matching placebo at one clinic visit and received the alternate medication at a second visit. When women attempted sexual intercourse within 24 hours of the dose, significantly more were satisfied with their level of sexual arousal following bremelanotide compared with placebo. A 12-week phase 2b trial tested bremelanotide at 3 subcutaneous doses (0.75 mg, 1.25 mg, 1.75 mg).[13] The 1.25/1.75 mg pooled population was associated with statistically and clinically significant improvement in sexually satisfying events per month. Most adverse events were not dose dependent, except for nausea.

Phase 3 Trials: RECONNECT Studies

The RECONNECT studies were 2 identical phase 3 trials evaluating the efficacy of bremelanotide in the treatment of HSDD in premenopausal females.[7,14] Each study consisted of a 24-week randomized, double-blind, placebo-controlled treatment period followed by an uncontrolled 52-week open-label extension period. Study inclusion criteria and assessment details are summarized in Table 2.

The majority of enrolled participants reported HSDD with concomitant decreased arousal (74% in Study 1 and 67% in Study 2). Participants were mostly Caucasian (86%) or black (12%). The mean age was 39 years (range of 19-56 years).[7] The mean duration of HSDD was 4 years.

The core study phase of the trials included a 1-month no drug qualification period, a 1-month single blind placebo period, and a 24-week double-blind treatment period.[14] Participants were randomized to subcutaneous injections of bremelanotide 1.75 mg (n = 635) or placebo (n = 632). They were instructed to self-administer via autoinjector as needed, approximately 45 minutes prior to anticipated sexual activity. Participants were instructed to administer a maximum of 1 dose per 24-hour period and a maximum of 10 doses per month. The median number of injections was 10 in the 24-week double-blind period and 12 during the open-label extension period. Most participants used bremelanotide 2 to 3 times per month and no more than once per week.

Co–primary endpoints included FSFI-D and FSDS-DAO, Desire (Item 13) scores.[15] Secondary endpoints were change from baseline in FSFI total, arousal, lubrication, orgasm, and satisfaction scores; FSDS-DAO total and arousal item scores; Women's Inventory of Treatment Satisfaction (WITS-9) scores; self-assessment of benefit defined by General Assessment Question 3 (GAQ3); and items from the Female Sexual Encounter Profile–Revised (FSEP-R), including satisfying sexual events.[14,15]

Both studies show statistically significant benefit related to the co–primary endpoints (Table 3).[7,14] Compared with participants in the placebo arm, those randomized to bremelanotide had a greater increase in FSFI-D score, indicating an increase in desire, and a decrease in FSDS-DAO scores, indicating a reduction in distress related to low sexual desire.

The secondary endpoints included the results of patient-reported outcomes instruments that measure longitudinal and episodic treatment effects.[16] Both trials met the majority of secondary endpoints. Bremelanotide was associated with statistically significant improvement for scores on total, satisfaction, orgasm, lubrication, and arousal domains from the FSFI; significantly improved distress from arousal and total scores on the FSDS-DAO; improved scores for satisfaction with desire and arousal according to the FSEP-R (nonsignificant in one study and significant in the other); and significantly higher WITS-9 scores compared with placebo. Although the number of satisfying sexual events was higher in the bremelanotide group, statistical significance was not met in either of the 2 trials (Table 3).

Most adverse events were considered mild or moderate.[14] The most common were nausea (39.9%), facial flushing (20.4%), and headache (11%).[17] Treatment emergent adverse events were responsible for 18% of study participants discontinuing or interrupting treatment, with the highest cause of discontinuation being nausea (9.9% and 6.6%) and vomiting (1.5% and 0.7%). Only 2 serious adverse events were documented (nausea/vomiting and headache) and there were

Table 2. Summary of Inclusion Criteria and Assessments for RECONNECT Studies.

Inclusion Criteria[14]	
Premenopausal, nonpregnant, and ≥18 years old Current stable relationship ≥6 months Diagnosed with HSDD (with or without decreased arousal) ≥6 months Experienced "normal" sexual function at some point in the past ≥2 years Willing to engage in sexual activities ≥1×/month during the study Had *all* of the following at screening: • PHQ-9 total score <10, score of 0 on question 9 • FSFI total score ≤26 *or* FSFI desire domain score ≤5 regardless of total FSFI score • FSDS-DAO total score >18	
Assessments[5,14,21]	
Patient Health Questionnaire–9 (PHQ-9)	Self-administered 9-item Likert-type scale measure used to assess depression severity • Total score ranges from 1 to 27 • A score of <10 correlates to minimal or mild depression • Question 9 on the scale relates to thoughts of self-harm
Female Sexual Function Index (FSFI)	19-Item measure used to assess the severity of sexual dysfunction Consists of 6 key domains: desire, arousal, lubrication, orgasm, satisfaction, and pain Score range from • 0 to 6 for domains of arousal, lubrication, orgasm and pain • 1.2 to 6 for desire • 0.8 to 6 for satisfaction Total score ranges from 2 to 36 (sum of all domain scores) A higher score indicates greater level of sexual function
Female Sexual Distress Scale-Desire/Arousal/Orgasm (FSDS-DAO)	15-Item Likert-type scale measure of sexual-related distress in the last 30 days • Total score ranges from 0 to 60 • Item 13 relates to feeling bothered by low sexual desire A higher score indicates greater sexual-related distress
General Assessment Questionnaire (GAQ)	Self-administered questionnaire to assess perceived benefit Question 3 utilized for responder analysis: "To what degree do you think you benefited from taking the study drug?" • 7-point Likert-type scale • Score ≥5 considered "responder"

no clinically significant changes in vital signs, clinical laboratory, or electrocardiogram data in either study.

Quantitative and qualitative exit interviews were administered at the end of the core study to consenting individuals (n = 242).[18] Women randomized to the treatment arm (n = 102) consistently reported meaningful benefit compared with placebo (n = 140). When asked if they would continue treatment if available, 57.8% of those in the treatment arm agreed while 47.9% in the placebo arm agreed ($P = 0.2981$). The injection device was rated as excellent or very good by 62.4% of the participants. Participants also found the study treatment easy to use (86.8%) and appreciated as needed dosing (79.3%).

RECONNECT Open-Label Extension Study

Participants who successfully completed the 24-week core study phase, continued to meet enrollment criteria, and reported no serious adverse events were eligible for the 52-week open-label extension study (N = 684).[19] Efficacy was assessed using the FSFI, FSDS-DAO, FSEP-R, and GAQ. Safety was assessed by recording and monitoring adverse events, concomitant medication use, and clinically significant changes in physical exam, electrocardiogram, vital signs, and laboratory assessments. Safety data were similar to the core study results. FSFI, FSDS-DAO, and GAQ score improvement was maintained for those in the treatment arm and significantly improved within 4 weeks for those in the placebo arm of the core study phase. This supports the use of bremelanotide in this population.

Discussion

Based on the results of the phase 3 studies, the authors concluded that bremelanotide is effective and safe. Adverse events are common, but mild to moderate.

Bremelanotide affects blood pressure and heart rate, causing a transient increase and decrease, respectively.[7,8] Both

Table 3. Results From the Core Study Phase.[7,14]

	Study 1		Study 2	
	Bremelanotide 1.75 mg Subcutaneous (N = 313)	Placebo (N = 315)	Bremelanotide 1.75 mg Subcutaneous (N = 282)	Placebo (N = 288)
Efficacy results for the FSFI–Desire Domain Score (MITT population)				
Mean baseline (SD)	2.1 (0.9)	2.0 (0.8)	2.0 (0.8)	2.1 (0.8)
Mean change from baseline	0.5 (1.1)	0.2 (1.0)	0.6 (1.0)	0.2 (0.9)
Median change from baseline	0.6	0	0.6	0
P value	.0002		<.0001	
Efficacy results for the FSDS-DAO Q13 score in premenopausal HSDD patients (MITT population)				
Mean baseline (SD)	2.9 (1.0)	2.8 (0.9)	2.9 (0.9)	2.9 (0.9)
Mean change from baseline	−0.7 (1.2)	−0.4 (1.1)	−0.7 (1.1)	−0.4 (1.1)
Median change from baseline	−1	0	−1	0
P value	<.0001		.0053	
Efficacy results for the number of satisfying sexual events in premenopausal HSDD patients (MITT population)				
Mean baseline (SD)	0.7 (1.0)	0.8 (1.1)	0.8 (1.1)	0.7 (1.0)
Mean change from baseline	0.0 (1.4)	−0.1 (1.4)	0.0 (1.3)	0.0 (1.2)
Median change from baseline	0	0	0	0
P value	.76		.70	

Abbreviations: FSFI, Female Sexual Function Index; MITT, modified intention-to-treat; FSDS-DAO Q13, Female Sexual Distress Scale–Desire/Arousal/Orgasm Question 13; HSDD, hypoactive sexual desire disorder.

returned to baseline after 12 hours in most cases, and no additive effects were seen over 16 days of repeat doses. Clinicians should consider cardiovascular risk. Bremelanotide is contraindicated in those with uncontrolled hypertension or unknown cardiovascular disease and should be avoided in those with a high risk of heart disease. Individuals should be advised to separate doses by at least 24 hours to avoid more pronounced blood pressure effects.

Focal hyperpigmentation was reported in 1% of individuals receiving up to 8 monthly doses of bremelanotide.[7] This mainly affected the face, gingiva, and breasts and was more likely to occur in those with dark skin. Hyperpigmentation was not confirmed to resolve after bremelanotide was discontinued. Based on this risk, bremelanotide should be used 8 times per month maximum and should be discontinued if hyperpigmentation develops, as it can be permanent.

Subgroup analyses were performed for certain medications with high use in the target population. Approximately 12% of women with HSDD also have diabetes mellitus, and no clinically significant interactions were found with metformin and bremelanotide.[10] Similarly, 18.4% of the core study population used some form of hormonal contraceptive. An analysis of this group found no effect on outcomes due to the type of contraceptive used.[9,20]

Relevance to Patient Care and Clinical Practice

Bremelanotide's place in therapy is unknown, as the HSDD guidelines were most recently updated in 2017.[1] Although the trials met statistical significance for change in FSFI and FSDS scores, the clinical benefit may only be modest. There was no statistically significant change in sexually satisfying events, which may affect the perceived benefit of bremelanotide.

The only other FDA-approved treatment indicated for HSDD is flibanserin, which was approved in 2015.[3] Prior HSDD treatments were used off-label. The availability of drugs with a specific HSDD indication has the potential to give many women access to improved sexual functioning.

Bremelanotide's current AWP is $269 per autoinjector, available in a box of 4 autoinjectors for a total of $1078 per box.[21] The cost may be outweighed by the benefits over flibanserin, including dosing on demand and as needed.

Flibanserin is an oral medication dosed as 100 mg daily at bedtime.[6] Unlike bremelanotide, flibanserin did not increase blood pressure but did cause hypotension and syncope. Flibanserin has several key interactions, including CYP3A4, CYP2C19, and alcohol. Concomitant use of flibanserin and alcohol markedly increases the risk of hypotension/syncope; therefore, a boxed warning exists to abstain from alcohol during use. Bremelanotide and alcohol do not interact based on a placebo-controlled double-blind crossover study.[7,11]

Flibanserin is approximately $960 for 30 tablets,[22] which may represent a cost-savings compared with the maximum monthly bremelanotide regimen. Alcohol consumption, concomitant medications, cardiovascular risk, and cost should all be considered when determining if a patient is a candidate for flibanserin or bremelanotide.[6,7] Additional

Table 4. Prescribing Considerations.[7]

Dosing/administration	1.75 mg injected subcutaneously into the abdomen or thigh; use as needed at least 45 minutes prior to anticipated sexual activity; do not use more than 1 dose in 24 hours or 8 doses per month.
Storage	Store at or below 25°C (77°F). Do not freeze. Protect from light.
How supplied	1.75 mg bremelanotide in 0.3 mL solution in a single-dose, prefilled autoinjector; 4 autoinjectors per carton
Common adverse reactions	Nausea (8%), flushing (1%), injection site reaction (1%), headache (2%)
Warnings and precautions	• Transient increase in blood pressure and reductions in heart rate • Focal hyperpigmentation • Nausea
Contraindications	Uncontrolled hypertension or known cardiovascular disease
Drug interactions	Naltrexone, Indomethacin • Slows gastric emptying so may affect time-dependent drugs
Use in specific populations	Pregnancy • Avoid in pregnancy; use contraception if child-bearing potential; discontinue use if pregnancy suspected Lactation • Use with caution; no data available Pediatric/geriatric • Safety/efficacy not studied Renal impairment • Caution in severe renal impairment (eGFR <30 mL/min/1.73 m^2) Hepatic impairment • Caution in severe hepatic impairment

Abbreviation: eGFR, estimated glomerular filtration rate.

prescribing considerations for bremelanotide are outlined in Table 4.

Conclusion

Bremelanotide is a novel treatment option for premenopausal women with HSDD. It may offer advantages over flibanserin, the only other FDA-approved HSDD treatment, for certain individuals. Those using bremelanotide should be advised to follow dosing recommendations to avoid adverse events. Further studies are needed to review the use of this drug in menopausal and postmenopausal populations and to determine its place in therapy.

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