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Bremelanotide: A Review of Its Neurobiology and Treatment Efficacy for HSDD

Presented at the
20th World Meeting on Sexual Medicine
September 22–25, 2016 • Beijing, China

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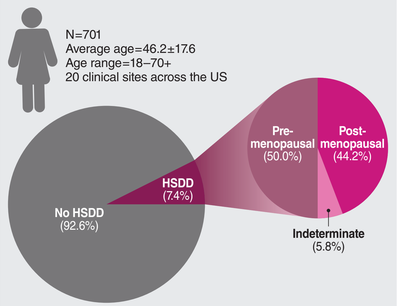
Introduction

- Female sexual dysfunctions (FSD) include a range of distressing, multifactorial conditions for which few treatment options exist.
- In the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV-TR),[1] FSD are classified as dysfunctions of sexual desire (such as hypoactive sexual desire disorder [HSDD]), sexual arousal dysfunctions (such as female sexual arousal disorder [FSAD]), and delay or absence of orgasm, or sexual pain (dyspareunia or vaginismus).
  - —In the DSM-5,[2] HSDD is included within the diagnostic category of sexual interest/arousal disorder.
- In a 2008 study, up to 43% of women aged ≥18 years reported having a sexual problem; 12% also reported distress (score ≥15 on the Female Sexual Distress Scale [FSDS]).[3]
- In a 2012 clinical sample, the overall prevalence of HSDD was reported as 7.4%; HSDD was slightly more common among pre- (50%) versus postmenopausal women (44.2%; **Figure 1**).[4,5]
- Hayes and colleagues noted that although the proportion of women with low desire increased with age, the proportion who were distressed about their low desire decreased with age.[6]

Figure 1. Prevalence of HSDD[5]



HSDD, hypoactive sexual desire disorder.

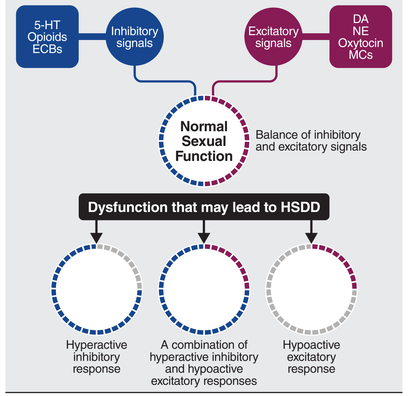
Aim

- To describe how bremelanotide (BMT; PT-141), an analog of the naturally occurring peptide α-melanocyte-stimulating hormone (α-MSH), acts on the physiological and neurobiological components of female sexual function to improve sexual arousal and desire in women with HSDD.

Mechanism of Sexual Response

- Excitatory signals are regulated by dopamine (DA), norepinephrine (NE), oxytocin, and the melanocortins (MCs).[7,8]
  - —DA and the MCs stimulate attention and desire
  - —NE and oxytocin stimulate sexual arousal
- Inhibitory signals are regulated by serotonin (5-HT), opioids, and endocannabinoids (ECBs).[7,8]
  - —5-HT regulates satiety, opioids manage sexual rewards, and ECBs play a role in sedation
- The pathophysiology of HSDD, whether hyperactive-inhibitory, hypoactive-excitatory, or a combination, stems from an imbalance of these excitatory and inhibitory signals (**Figure 2**).[7,8]

Figure 2. Excitatory and Inhibitory Pathways Regulating Sexual Response[5]

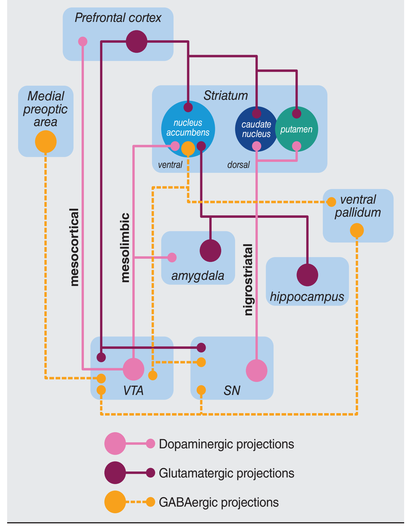


5-HT, serotonin; DA, dopamine; ECBs, endocannabinoids; HSDD, hypoactive sexual desire disorder; MCs, melanocortins; NE, norepinephrine.

Sexual and Reward Circuitry

- These neurochemicals act on similar regions of the brain, such as the medial preoptic area (mPOA) in the hypothalamus, attention- and reward-related regions of the limbic system, and the prefrontal cortex (PFC).
  - —Help to modulate DA signaling in the brainstem and the striatum. Gamma aminobutyric acid projections help regulate DA signaling in the brainstem via the nucleus accumbens (NAcc) and ventral pallidum (**Figure 3**).[5]

Figure 3. Sexual and Reward Center Circuitry[5]



At the center is the striatum, which contains the NAcc and caudate nucleus. Mesolimbic DA projections arise from the VTA and signal the NAcc; nigrostriatal DA projections arise from the SN and signal the dorsal striatum; mesocortical DA projections arise from the VTA and signal the PFC; glutamatergic projections arise from the PFC, the amygdala, and the hippocampus.

DA, dopamine; GABAergic, gamma aminobutyric acid; NAcc nucleus accumbens; PFC, prefrontal cortex; SN, substantia nigra; VTA, ventral tegmental area.

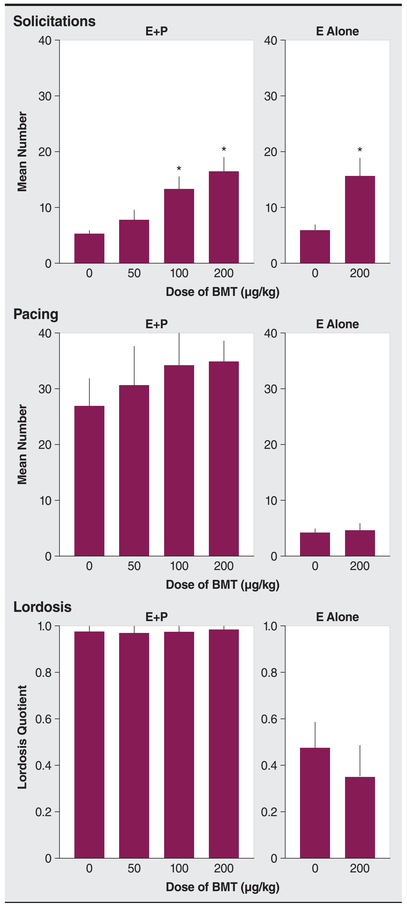
Bremelanotide

- MCs are a diverse set of neuropeptides derived from proopiomelanocortin.
  - —Includes β-endorphin, adrenocorticotrophic hormone, and α-MSH.
- Neurons may stimulate DA release in the mPOA, a locus implicated in the sexual behavior of both sexes of several species.[9]
- BMT is a novel cyclic 7-amino acid MC-receptor agonist, with high affinity for the type-4 receptor,[10] giving it a potential to modulate brain pathways involved in sexual response.[11]

Rat Study

- BMT's downstream CNS effects of increasing arousal and desire are thought to result from its action as a MC-receptor agonist.
- Among female rats primed with estrogen and progesterone or estrogen alone, BMT significantly increased measures of solicitation without altering pacing or lordosis when administered peripherally or via infusion directly into the lateral ventricles or mPOA, but not the ventromedial hypothalamus (**Figure 4**).[12]

Figure 4. Dose–Response Effects of BMT on Sexual Behavior in Rats[12]

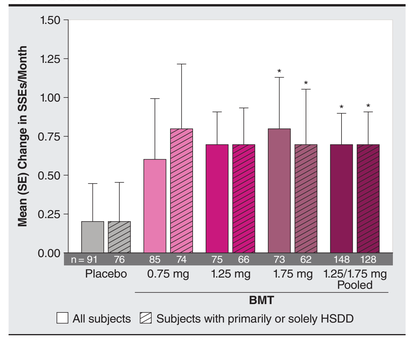


Data are means±SEM. *P<0.05 versus control.
BMT, bremelanotide; E, estrogen; P, progesterone; SEM, standard error of mean.

Human Study

- Among premenopausal women with HSDD with or without FSAD, subcutaneous (SC) administration of BMT 1.25 mg or 1.75 mg significantly increased the number of sexually satisfying events (SSEs) versus placebo when taken 45 minutes before sexual activity.
  - —Mean change (standard error) in number of SSEs from baseline to study end was +0.7 (2.4) events/month for BMT 1.25/1.75 mg pooled, compared with +0.2 (2.3) for placebo (P=0.018; **Figure 5**).[13]

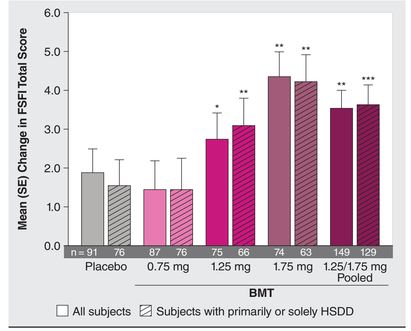
Figure 5. Mean Change in SSEs/Month After BMT Treatment[13]



Van Elteren test stratified by diagnosis. *P<0.05 versus placebo.
BMT, bremelanotide; HSDD, hypoactive sexual desire disorder; SE, standard error; SSEs, sexual satisfying events.

- BMT was also associated with significant increases (improvement) in total scores on the Female Sexual Function Index (FSFI).
  - —Mean change in FSFI total score was +3.6 (5.7) with BMT versus +1.9 (5.9) for placebo; P=0.0017 (**Figure 6**).[13]

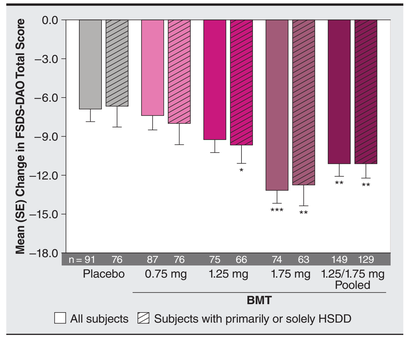
Figure 6. Mean Change in FSFI Total Score After BMT Treatment[13]



Van Elteren test stratified by diagnosis. *P<0.05 versus placebo. **P<0.01 versus placebo. ***P<0.001 versus placebo.
BMT, bremelanotide; FSFI, female sexual function index; HSDD, hypoactive sexual desire disorder; SE, standard error. From baseline to end of study.

- BMT was associated with decreases in both total score and the desire, arousal, and orgasm items of the Female Sexual Distress Scale–Desire-Arousal-Orgasm (FSDS-DAO) measure.
  - —Mean change in FSDS-DAO was –11.1 (12.0) with BMT versus –6.8 (13.6) with placebo; P=0.0014. Decreasing value represents less distress (**Figure 7**).[13]

Figure 7. Mean Change in FSDS-DAO Total Score After BMT Treatment[13]



Van Elteren test stratified by diagnosis. *P<0.05 versus placebo. **P<0.01 versus placebo. ***P<0.001 versus placebo.
BMT, bremelanotide; FSDS-DAO, Female Sexual Distress Scale–Desire-Arousal-Orgasm; HSDD, hypoactive sexual desire disorder; SE, standard error. From baseline to end of study. Decreasing values represent less distress.

- At all BMT doses, the most common treatment-emergent adverse events were nausea, flushing, and headache. Of these, only nausea had a slight dose-dependence.
- Physical examination, electrocardiograph, and clinical laboratory findings showed no clinically significant trends. Small, transient increases in ambulatory blood pressure (BP; ~3 mm Hg in systolic and diastolic BP confined to the first 4 hours postdose) were accompanied by small (~5%) decreases in heart rate.
- In premenopausal women with HSDD, with or without FSAD, double-blind BMT self-administered SC on an at-home, as-desired basis over 12 weeks showed significant efficacy with robust consistency versus placebo, as demonstrated by an increase in the monthly number of SSEs and by multiple episodic and longer-term (longitudinal) measures. BMT was safe and well tolerated.

Conclusions

- BMT is a novel MC-receptor agonist with a potential to modulate brain pathways involved in sexual response.
- BMT 1.25 mg and 1.75 mg SC, self-administered as desired, improve female sexual function and SSEs in women with HSDD.

Support This study was funded by Palatin Technologies, Inc. Editorial assistance was provided by The Curry Rockefeller Group, LLC, which was funded by Palatin Technologies, Inc.

Disclosures Dr Clayton has received royalties from the Changes in Sexual Functioning Questionnaire, Guilford Publications; has received research support or consulting fees from Auspex, Forest Research Institute, Inc, now Allergan, Genomind, Lundbeck, Palatin Technologies, Inc, Pfizer Inc, S1 Biopharma, and Sprout Pharmaceuticals, a division of Valeant; and has stocks, stock options, or ownership interest, excluding diversified mutual funds, from Euthymics and S1 Biopharma. Dr Lucas, Mr Jordan, and Dr Spana are employees and stockholders of Palatin Technologies, Inc. Dr Pfaus has received consulting fees from Emotional Brain and Palatin Technologies, Inc.

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