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The Neurobiology and Efficacy of Bremelanotide in HSDD

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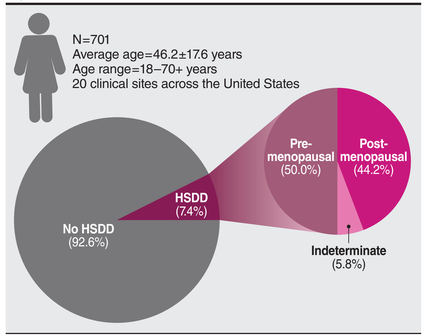
Introduction

- Female sexual dysfunctions are classified as dysfunctions of desire (eg, hypoactive sexual desire disorder [HSDD]), arousal (eg, female sexual arousal disorder [FSAD]), delay or absence of orgasm, or sexual pain (dyspareunia or vaginismus)[1]
- These are distressing conditions, particularly for younger women,[2] for which few treatment options exist
- 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 7.4%; HSDD was slightly more common among pre- (50%) vs postmenopausal (44.2%) women (**Figure 1**)[4]

Figure 1. Prevalence of HSDD[4]



HSDD, hypoactive sexual desire disorder.

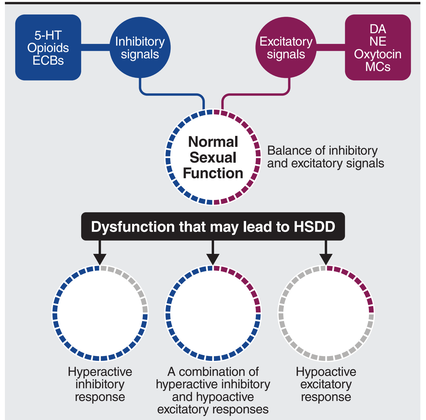
Aim

- 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)[5,6]
  - 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)[5,6]
  - 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 signals (**Figure 2**)[5,6]

Figure 2. Excitatory and Inhibitory Pathways Regulating Sexual Response[4]

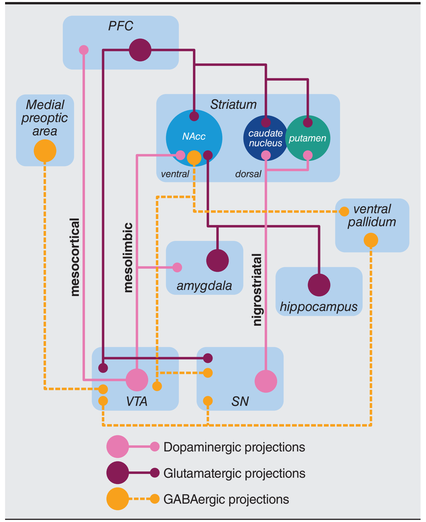


5-HT, serotonin; DA, dopamine; ECBs, endocannabinoids; HSDD, hypoactive sexual desire disorder; MCs, melanocortins; NE, norepinephrine.

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
  - Gamma aminobutyric acid projections help regulate DA signaling in the brainstem via the nucleus accumbens (NAcc) and ventral pallidum (**Figure 3**)[4]

Figure 3. Sexual and Reward Center Circuitry[4]



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.

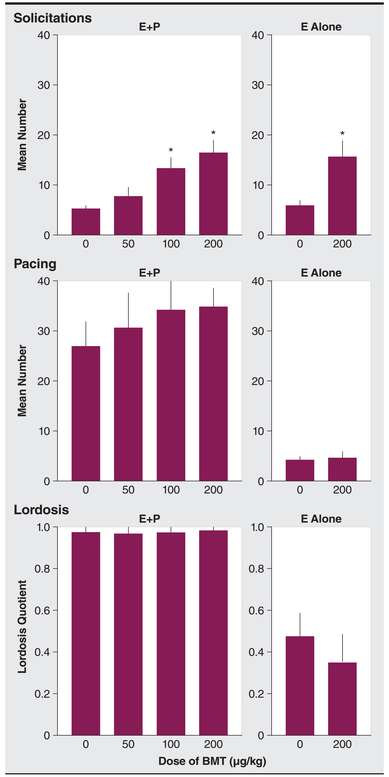
Bremelanotide

- MCs (eg, β-endorphin, adrenocorticotrophic hormone, and α-MSH) are a diverse set of neuropeptides derived from proopiomelanocortin (POMC)
- Neurons may stimulate DA release in the mPOA, a locus implicated in the sexual behavior of both sexes of several species[7]
- BMT is a novel cyclic 7-amino acid MC-receptor agonist, with high affinity for the type-4 receptor,[8] giving it a potential to modulate brain pathways involved in sexual response[9]

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**)[10]

Figure 4. Dose–Response Effects of BMT on Sexual Behavior in Rats[10]

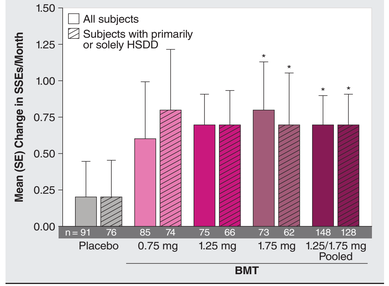


Data are means±SEM. *P<0.05 versus control.
BMT, bremelanotide; E, estrogen; P, progesterone; SEM, standard error of mean.

Human Study

- Among premenopausal women with HSDD with or without FSAD, subcutaneous (SC) administration of BMT 1.25 or 1.75 mg:
  - Significantly increased the number of sexually satisfying events (SSEs) vs placebo when taken 45 minutes before sexual activity. Mean (standard error [SE]) change from baseline to study end was +0.7 (2.4) events/month vs +0.2 (2.3); BMT 1.25/1.75 mg pooled vs placebo, respectively (P=0.018; **Figure 5**)[11]

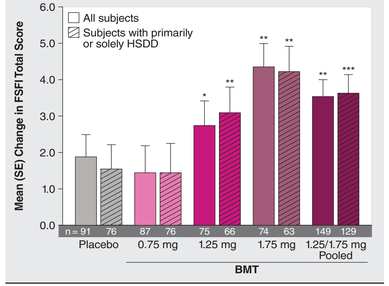
Figure 5. Mean Change in SSEs/Month After BMT Treatment[11]



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

  - Significantly increased (improvement) total scores on the Female Sexual Function Index. Mean (SE) change, +3.6 (5.7) vs +1.9 (5.9); BMT vs placebo, respectively (P=0.0017; **Figure 6**)[11]

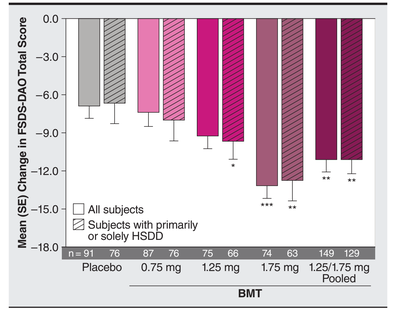
Figure 6. Mean Change in FSFI Total Score After BMT Treatment[11]



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

  - Decreased (less distress) both the total score and scores on the desire, arousal, and orgasm items of the FSDS–Desire-Arousal-Orgasm measure. Mean (SE) change, –11.1 (12.0) vs –6.8 (13.6); BMT vs placebo, respectively (P=0.0014; **Figure 7**)[11]

Figure 7. Mean Change in FSDS-DAO Total Score After BMT Treatment[11]



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

- The most common treatment-emergent adverse events with BMT were nausea, flushing, and headache; only nausea had a slight dose-dependence
- 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

Conclusions

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

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