Review of Potential Role for Bremelanotide (PT-141) in Treating Female Sexual Dysfunction

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ABSTRACT

This presentation reviews research to date regarding the potential use of bremelanotide for the treatment of female sexual dysfunction (FSD). Bremelanotide is a synthetic peptide analog of α-melanocyte stimulating hormone and is an agonist at melanocortin receptors MC3R and MC4R. Six research paths suggest a potential role for bremelanotide in FSD treatment: 1) Clinical trials have demonstrated induction of significant erectile activity in healthy male volunteers and ED patients, supporting the hypothesis that bremelanotide is a central initiator of sexual activity in men. Anatomical similarities between the genders suggest many of the same types of benefits may accrue to women. 2) A preclinical study demonstrated effects of bremelanotide on proceptive sexual behaviors in ovariectomized female rats. Appetitive behavior in female rats may have a human analog in sexual interest, desire, or arousal. 3) In 2003, 32 healthy women were treated with either placebo or subcutaneously administered bremelanotide. Bremelanotide was safe and well tolerated. 4) An in-clinic, double-blind, placebo-controlled, crossover study evaluating the effects of two concurrent doses of 10 mg intranasal bremelanotide on objective and subjective measures of sexual arousal and desire in 18 premenopausal patients with female sexual arousal disorder found that more women reported moderate or high sexual desire after bremelanotide than placebo and there was a trend toward more positive responses after bremelanotide regarding feelings of genital arousal. In-depth interviews were conducted post-study with some of the women reporting increased desire following bremelanotide treatment. 5) A similar study enrolling postmenopausal women with FSD was recently completed and results comparable to the premenopausal data were suggested. 6) An at-home, multi-site clinical trial with approximately 100 premenopausal women with FSD is under way. These clinical and preclinical data, taken collectively, evoke both a cautious optimism and strong recommendation for continued assessment of bremelanotide for the treatment of FSD. Additionally, contextual sensitivity of female sexual response may require the use of combination treatment, where sexual pharmaceuticals and sex coaching is integrated more frequently for women than it has been for men. A number of signals suggest that bremelanotide might be an excellent agent for such a purpose.

INTRODUCTION

- While the understanding of the pathophysiology of male erectile dysfunction (ED) has progressed rapidly in the past decade and led to several new therapeutic modalities, much less has been done to address female sexual dysfunction (FSD), despite evidence that the incidence and prevalence of sexual dysfunction is greater in women than in men[1-5]
- Bremelanotide (PT-141) is a synthetic peptide analog of α-melanocyte stimulating hormone (α-MSH; **Figure 1**) that acts as an agonist at melanocortin receptors MC3R and MC4R

Figure 1. Peptide Sequences of Bremelanotide and α-MSH

Bremelanotide:
Ac-Nle-Asp-His-DPhe-Arg-Trp-Lys-OH

α-MSH:
Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val

- It has been shown in animal models that melanocortins affect multiple physiological responses via a central mechanism, including sexual behaviors[6]
- Bremelanotide is currently in development for the treatment of both FSD and ED
- This review examines research to date regarding the potential use of bremelanotide for the treatment of FSD

METHODS

- Findings from six distinct research paths are summarized

RESULTS

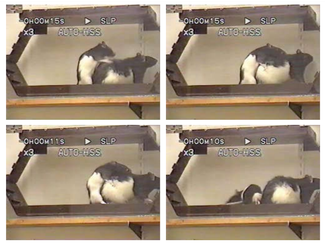
1. Clinical Trials in Men

- Significant erectile response demonstrated in
  - Men with organic ED[7]
  - Men with psychogenic ED[8]
  - Healthy men and men with inadequate response to sildenafil[9]
  - Healthy men and men with mild-to-moderate ED[10]
  - Men with ED; co-administration with sildenafil[11]
  - Healthy men[12]
  - Men with ED[13]
- Certainly gender differences exist in the patterning of psychophysiological reactions to sexual stimulation, but there are also anatomical and embryological parallels in genital response
  - Reasonable to hypothesize that an agent with efficacy in men may also have efficacy in women with similar disorders

2. Animal Model of Female Sexual Behaviors

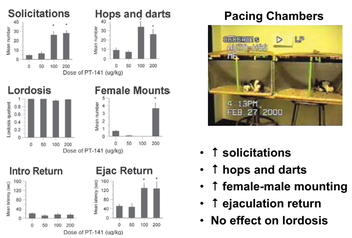
- Pfaus and colleagues conducted a preclinical study of the dose-response effects of bremelanotide on proceptive sexual behaviors, such as solicitation, hops and darts, and pacing, and receptive sexual behaviors, such as lordosis, in ovariectomized female rats[14] (**Figure 2**)

Figure 2. Animal Model of Female Rat Sexual Behaviors



- Results indicated a pharmacological initiation of appetitive sexual behaviors in female rats primed with estrogen and progesterone or with estrogen alone (**Figure 3**)

Figure 3. Effects of Bremelanotide on Female Sexual Behaviors



- ↑ solicitations
- ↑ hops and darts
- ↑ female-male mounting
- ↑ ejaculation return
- No effect on lordosis

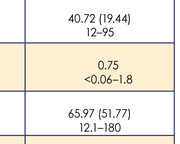
- It is unclear what might be the human analog to appetitive behavior in female rats; may be speculated that sexual interest, desire, and perhaps arousal are associated with these behaviors

3. Clinical Trial in Healthy Female Volunteers

- Thirty-two healthy female volunteers were treated with either placebo, 0.3, 1.0, 3.0, or 5.0 mg subcutaneously administered bremelanotide[15]
- Vaginal photoplethysmography was used at baseline and post-dosing to measure vaginal pulse amplitude (VPA) during visual sexual stimulation (VSS)

Figure 4. Psychophysiological Studies and Sexual Response

- Women watch a neutral video followed by an erotic one
- Increased blood congestion around vagina measured with a vaginal photoplethysmograph



- All subcutaneous dose levels of bremelanotide were safe and well-tolerated
- A statistically significant increase in VPA during VSS, compared to baseline, was detected after administration of the 3.0 and 5.0 mg doses

4, 5. In-Clinic Study in Premenopausal and Postmenopausal Women with FSD

- Eighteen premenopausal women (**Table 1**) and 27 postmenopausal women with a primary diagnosis of female sexual arousal disorder (FSAD) were enrolled in a randomized, double-blind, placebo-controlled, crossover study

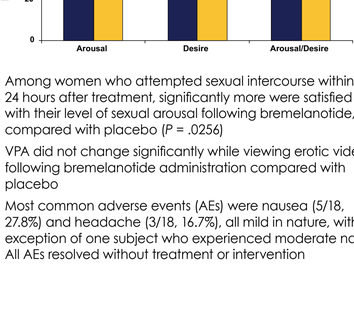
Table 1. Baseline Demographics[16]

Characteristic	Premenopausal (N=18)
Age (years)	
Mean (SD)	34.2 (8.0)
Range	22–44
Weight (kg)	
Mean (SD)	71.8 (10.1)
Range	58.6 – 91.3
Height (cm)	
Mean (SD)	163.4 (6.7)
Range	149.9–177.8
Body Mass Index (kg/m²)	
Mean (SD)	27.0 (4.2)
Range	19.8–35.2
Race (%)	
African American	44.4
White	33.3
Latino/Hispanic	22.2
FSFI Scores: Mean (SD); Range	
Desire	2.13 (1.05); 1.2–4.8
Arousal	1.93 (0.51); 1.2–2.7
Lubrication	2.62 (1.14); 0.6–5.1
Orgasm	1.95 (0.94); 1.2–4.0
Satisfaction	2.21 (0.69); 1.2–3.6
Pain	5.11 (1.25); 2.4–6.0
FSDS Score	
Mean (SD)	50.5 (1.36)
Range	40–60
Total Testosterone (ng/dL)*	
Mean (SD)	40.72 (19.44)
Range	12–95
Free Testosterone (pg/mL)†	
Median	0.75
Range	<0.06–1.8
Sex Hormone Binding Globulin (nm/L)‡	
Mean (SD)	65.97 (51.77)
Range	12.1–180
Method of Birth Control: n (%)	
Hormonal contraceptives	15 (83.3)
Bilateral tubal ligation	3 (16.7)

*Normal range: 6-82 ng/dL (Bio-Reference Laboratories, Elmwood Park, NJ). Mean (SD) total testosterone for subjects <34 years: 50.63 (20.02) ng/dL; for subjects ≥34 years: 32.8 (15.66) ng/dL.
†Normal range: 0.06–2.57 pg/mL (Bio-Reference Laboratories, Elmwood Park, NJ).
‡Normal range: 18-114 nm/L (Bio-Reference Laboratories, Elmwood Park, NJ). Mean (SD) SHBG for subjects <34 years: 75.13 (65.24) nm/L; for subjects ≥34 years: 58.65 (40.23) nm/L.
FSFI = female sexual function index; FSDS = female sexual distress scale.

- Subjects were randomly assigned to receive a 20-mg dose of intranasal bremelanotide (2 x 10 mg) or matching placebo during the first treatment session, and the alternate medication during the second treatment session (**Figure 5**)

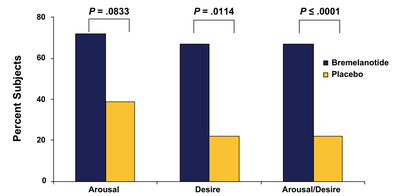
Figure 5. Bremelanotide Nasal Spray



Premenopausal Women

- During each treatment session, scheduled 2-7 days apart, subjects viewed a 20-minute neutral video, which began 5 minutes after administration of study drug, followed 10 minutes later by a 20-minute sexually explicit video
- Vaginal photoplethysmography was used to measure VPA during the neutral and sexually explicit videos. Treatment Satisfaction Index—a 14-item self-administered questionnaire that assesses levels of sexual desire, genital arousal and, if applicable, satisfaction with sexual activity—was used to assess experience 24 hours post-dose.
- More women reported moderate or high sexual desire following bremelanotide treatment vs. placebo, and a trend toward more positive responses regarding feelings of genital arousal occurred after bremelanotide compared with placebo (**Figure 6**)

Figure 6. Rate of Positive Responses to Questions About Arousal and Desire on Treatment Satisfaction Questionnaire



- Among women who attempted sexual intercourse within 24 hours after treatment, significantly more were satisfied with their level of sexual arousal following bremelanotide, compared with placebo ($P = .0256$)
- VPA did not change significantly while viewing erotic videos following bremelanotide administration compared with placebo
- Most common adverse events (AEs) were nausea (5/18, 27.8%) and headache (3/18, 16.7%), all mild in nature, with the exception of one subject who experienced moderate nausea. All AEs resolved without treatment or intervention

Postmenopausal Women—Preliminary Results

- Primary Endpoint
  - Treatment Satisfaction Index—14-item questionnaire
- Efficacy
  - Arousal: 76% bremelanotide vs. 23% placebo
  - Desire: 46% bremelanotide vs. 19% placebo
- Safety
  - Nausea, headache, and nasal congestion

6. At-Home Trial in Premenopausal Women with FSD

- An at-home, multi-site clinical trial with approximately 100 premenopausal women with FSD is under way

FUTURE?

Figure 7. The Sexual Tipping Point™: A model to conceptualize etiology, diagnosis & combination treatment of female and male sexual dysfunction[17]

- Contextual sensitivity of female sexual response may require the use of a combination treatment, where sexual pharmaceuticals and sex coaching is integrated more frequently for women than it has been for men[18,19]
- A number of the above signals suggest that bremelanotide might be an excellent agent for such a purpose[20]

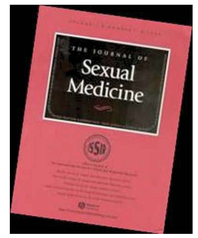
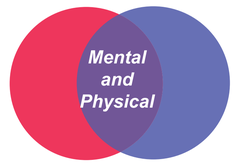


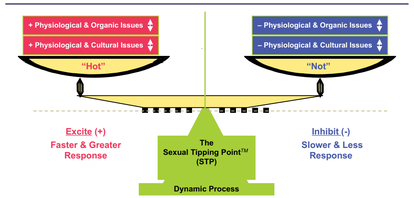
Figure 8. Combination of Factors Involved in Most Cases of Sexual Dysfunction



Adapted from CIEF

- Most health care professionals are aware that the etiology of sexual dysfunction is typically caused by both mental and physical factors. Yet these mental and physical factors have the potential to both excite and inhibit sexual response, thus determining the Sexual Tipping Point™.[17,19,21]

Figure 9. Balancing the Sexual Tipping Point™: The Multifactorial Etiology of Male and Female Sexual Function



The Sexual Tipping Point™: An individual's unique threshold for a sexual response that may vary within and between sexual experiences.

Figure 10. The Multifactorial Etiology of Female Sexual Dysfunction

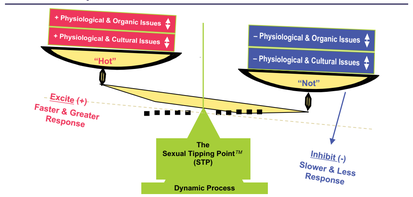


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Figure 11. What Treatment Should Be Used to Optimize Response?

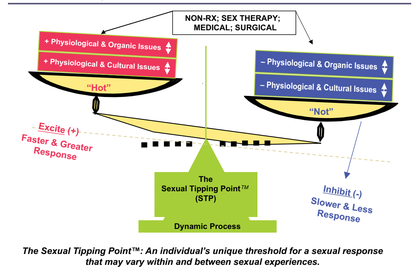

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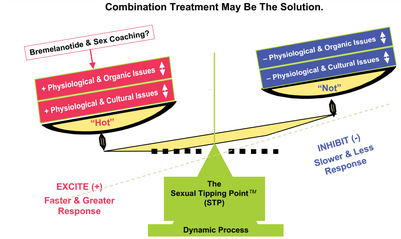
Figure 12. How to Optimize Treatment Risk/Benefit for FSD?



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