HSDD - Non-Hormonal Pharmacological Treatments

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Disclosures

- Consultant/Speaker: Sprout, Astellas

Definition of HSDD

Any of the following for a minimum of 6 months:

Lack of motivation for sexual activity manifested by either:

- Reduced or absent **spontaneous** desire (sexual thoughts, fantasies)

  OR

- Reduced or absent **responsive** desire to erotic cues and stimulation or inability to **maintain** desire

Loss of desire to initiate or participate, including behavioral responses such as avoidance, not secondary to a sexual pain disorder

+

Clinically significant personal distress that includes frustration, grief, incompetence, loss, sorrow, or worry

Cannot be better attributed to:

- another primary disorder
- medication
- general medical condition

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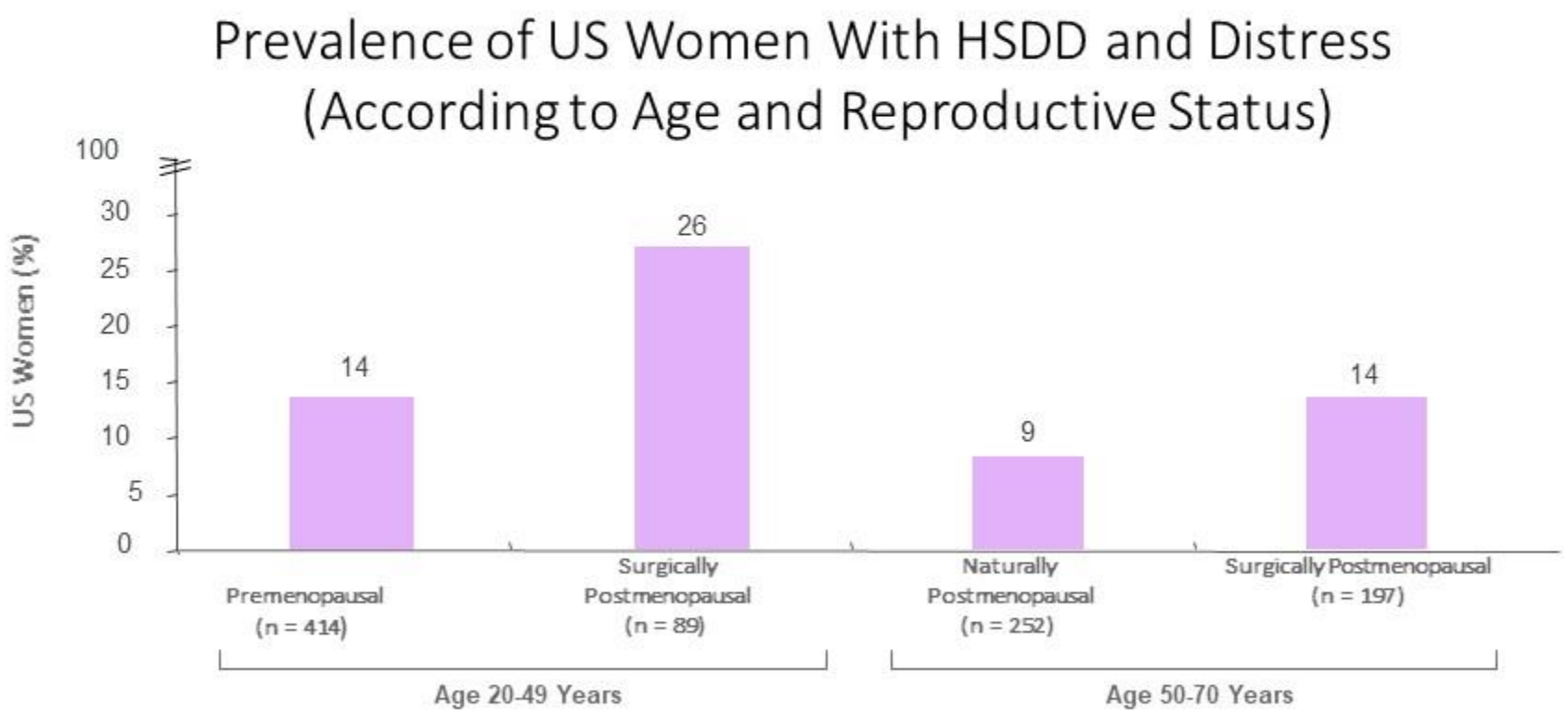
Parish SJ, et al. *J Sex Med.* 2016;13:1888-1906.

Prevalence of HSDD

Women's International Study of Health and Sexuality (WISHeS)



Reprinted with permission: Leiblum SR, Koochaki PE, Rodenberg CA, Barton IP, Rosen RC. Hypoactive sexual desire disorder in postmenopausal women: US results from the Women's International Study of Health and Sexuality (WISHeS). Menopause 2006;1:46-56, http://journals.lww.com/menopausejournal/pages/default.aspx

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Decreased Sexual Desire Screener (DSDS)

1. In the past, was your level of sexual desire/interest good and satisfying to you?	No □	Yes □
2. Has there been a decrease in your level of sexual desire/interest?	No □	Yes □
3. Are you bothered by your decreased level of sexual desire/interest?	No □	Yes □
4. Would you like your level of sexual desire/interest to increase?	No □	Yes □
5. Please check all the factors that you feel may be contributing to your current decrease in sexual desire/interest:		
A. An operation, depression, injuries, or other medical condition	No □	Yes □
B. Medications, drugs or alcohol you are currently taking	No □	Yes □
C. Pregnancy, recent childbirth, menopausal symptoms	No □	Yes □
D. Other sexual issues you may have (pain, decreased arousal, orgasm)	No □	Yes □
E. Your partner's sexual problems	No □	Yes □
F. Dissatisfaction with your relationship or partner	No □	Yes □
G. Stress or fatigue	No □	Yes □

Clinical assessment of patient answers is required.

- On average, the DSDS took < 15 minutes to complete in a clinical study (N = 921)
- DSDS had a sensitivity of 0.836 (84%) and a specificity of 0.878 (88%) (N = 263)

NO to Q1, 2, 3, or 4 = Not generalized acquired HSDD

YES to all Q1–4 and clinician-verified NO to all Q5 factors = Generalized acquired HSDD

YES to all Q1–4 and YES to any Q5 factor = clinician to use best judgment to determine diagnosis

This figure was published in the Journal of Sexual Medicine, Vol 6. Clayton AH, Goldfischer ER, Goldstein I, et al. Validation of the decreased sexual desire screener (DSDS): a brief diagnostic instrument for generalized acquired female hypoactive sexual desire disorder (HSDD). Copyright Elsevier 2009.

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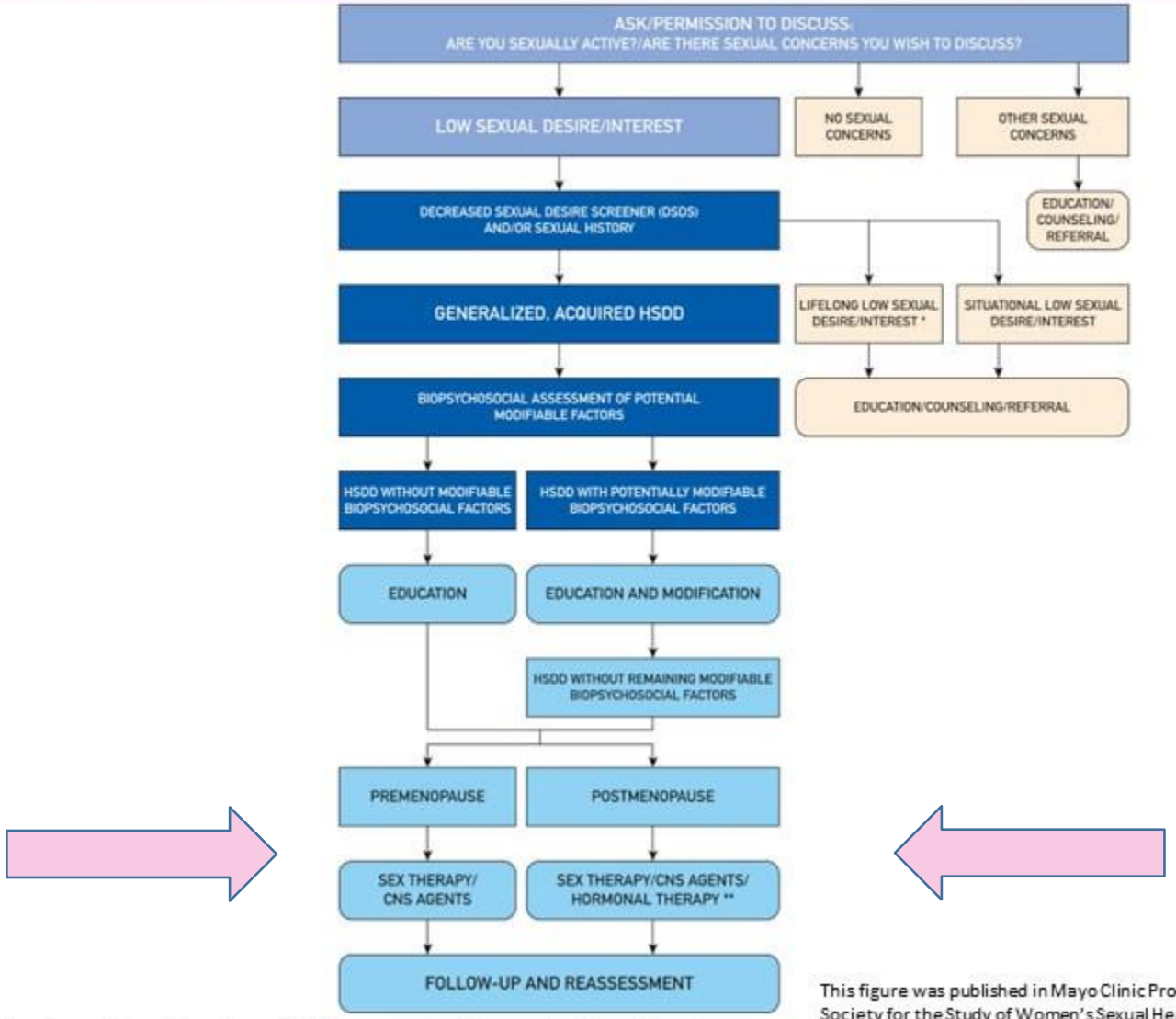
ISSWSH Process of Care for Management of Hypoactive Sexual Desire Disorder (HSDD) in Women



This figure was published in Mayo Clinic Proceedings, Vol 93, Issue 4. Clayton AH et al. The International Society for the Study of Women's Sexual Health Process of Care for Management of Hypoactive Sexual Desire Disorder in Women. Copyright Elsevier 2018.

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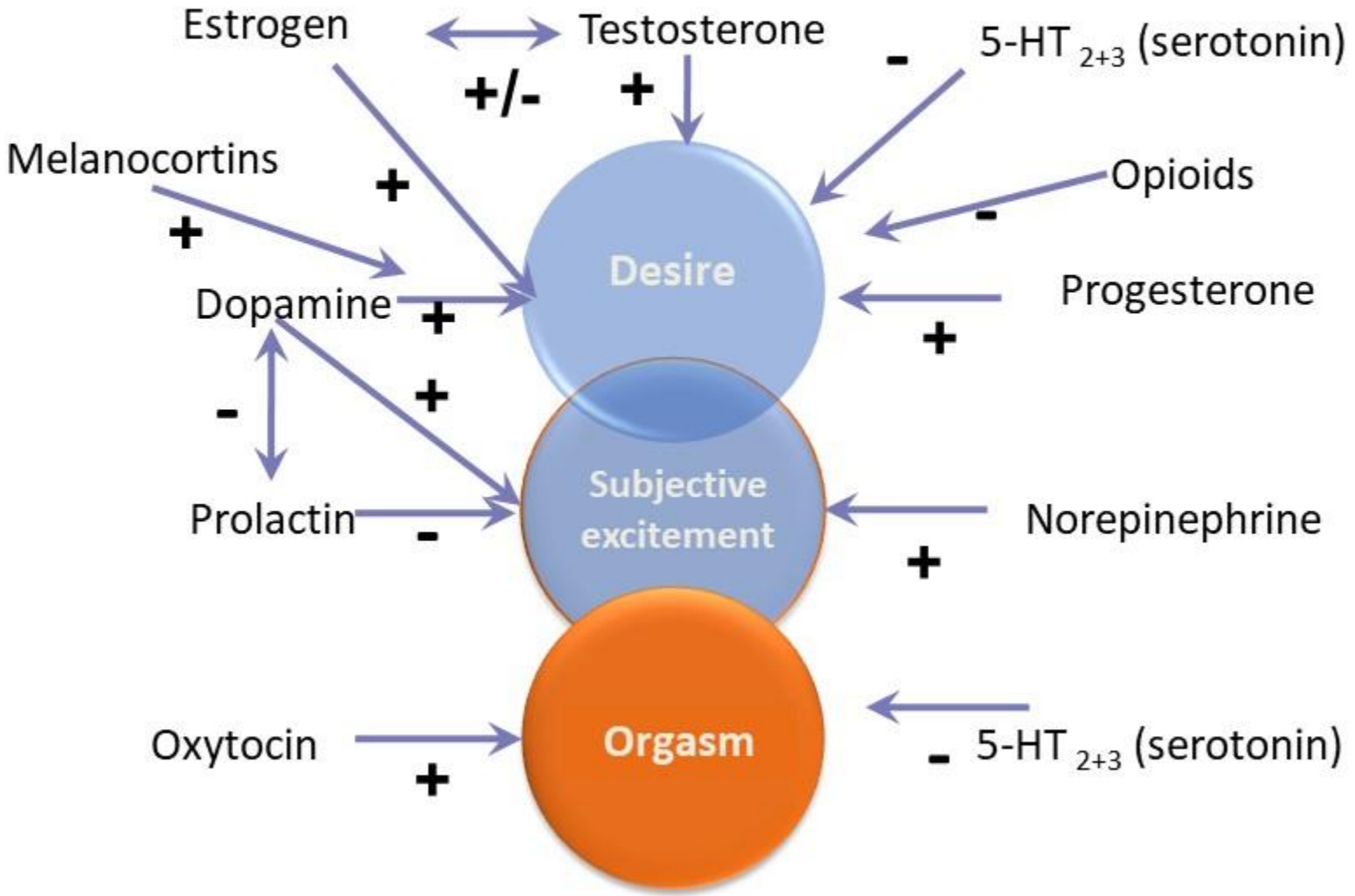
Central Effects of Neurotransmitters and Hormones on Sexual Functioning



This figure was published in the Journal of Sexual Medicine, Vol 4. Clayton AH, Epidemiology and neurobiology of female sexual dysfunction. Copyright Elsevier 2007.

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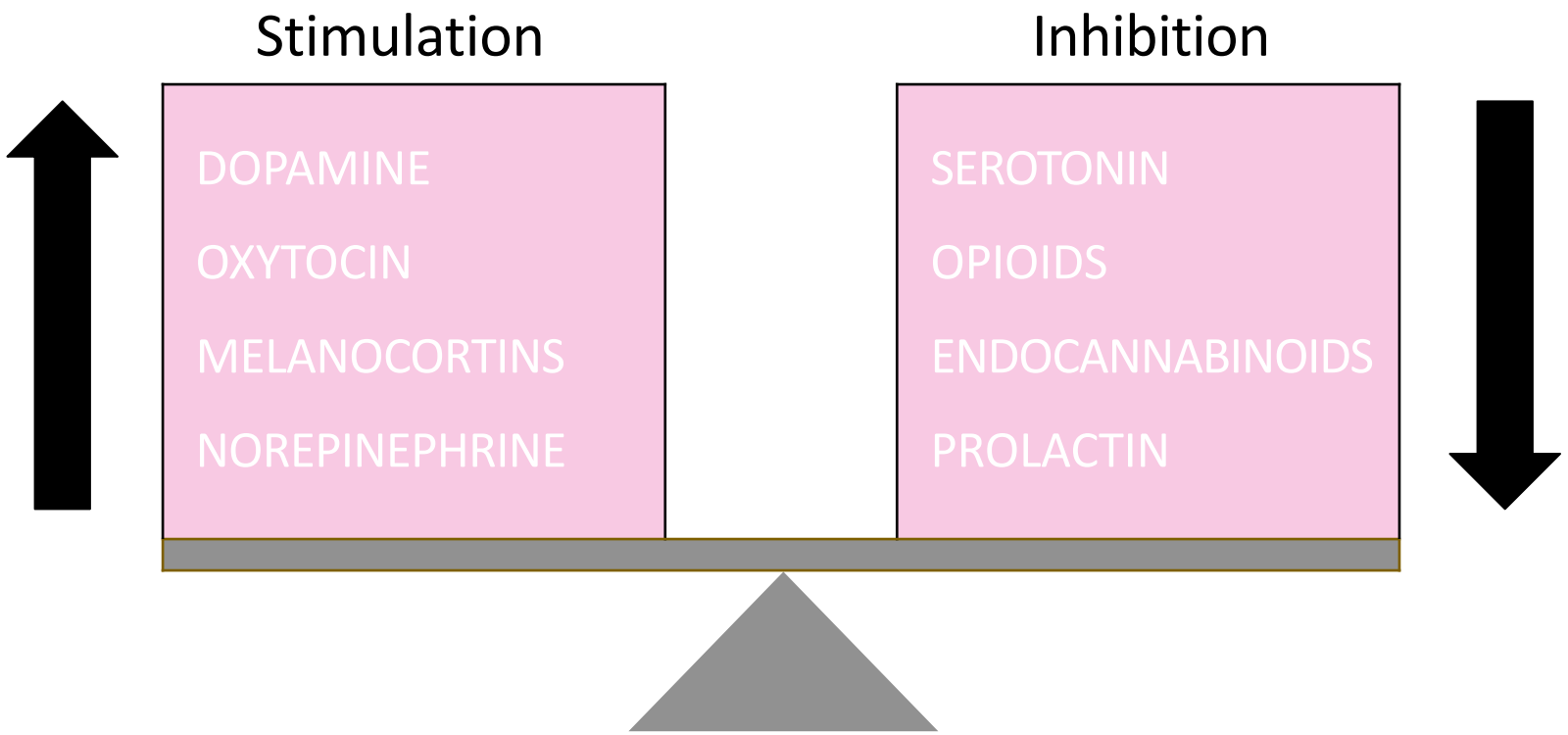
Neurobiology of Sexual Dysfunction



1. Perelman, M. A. (2009). The Sexual Tipping Point®: A mind/body model for sexual medicine. *The journal of sexual medicine*, *6*(3), 629-632.
2. Kingsberg, S. A., Clayton, A. H., & Pfaus, J. G. (2015). The female sexual response: current models, neurobiological underpinnings and agents currently approved or under investigation for the treatment of hypoactive sexual desire disorder. *CNS drugs*, *29*(11), 915-933.

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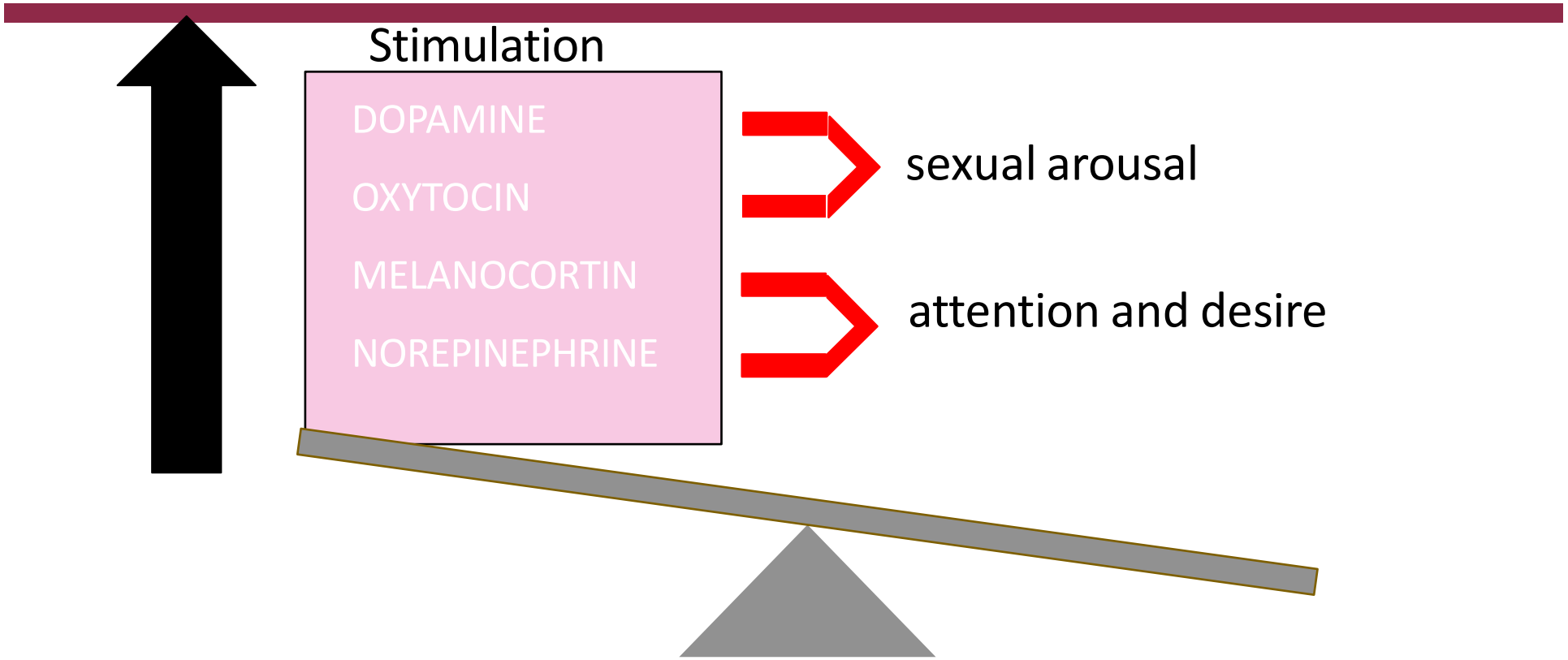
Neurobiology of Sexual Dysfunction



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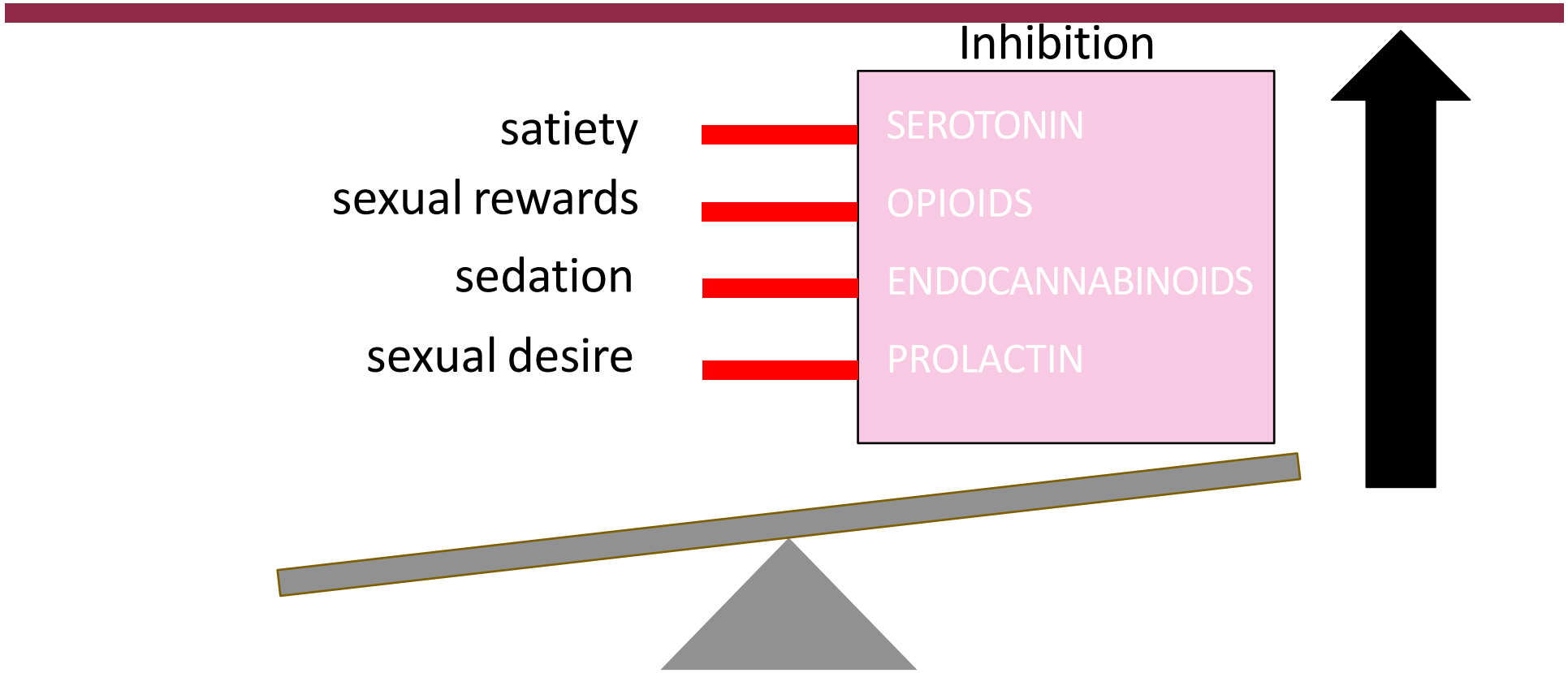
Neurobiology of Sexual Dysfunction



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3. Krysiak, R., Drosdzol-Cop, A., Skrzypulec-Plinta, V., & Okopien, B. (2016). Sexual function and depressive symptoms in young women with elevated macroprolactin content: a pilot study. *Endocrine*, *53*(1), 291-298.

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CNS-acting Agents for HSDD

Flibanserin (2015), Bremelanotide (2019)

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Flibanserin

- Mixed post-synaptic $5HT_{1A}$ agonist and $5HT_{2A}$ antagonist
  - Exact mechanism of action in treating HSDD is unknown
- Activity at dopamine D_4 receptors and moderate affinity for $5HT_{2B}$ and $5HT_{2C}$ receptors
- Region-specific elevations in dopamine/norepinephrine offset inhibitory serotonergic activity resulting in increased desire pathways
- Serotonin = sexual satiety signal

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Flibanserin

- FDA-approved for **acquired, generalized HSDD** in **premenopausal** women not caused by:
  - Medical or psychiatric condition
  - Relationship problem
  - Effects of a medication/drug
- **100 mg PO daily at bedtime**
  - "Administration during waking hours increases risks of hypotension, syncope, accidental injury, and CNS depression" (10/2019 label)
  - Missed doses should be skipped
- May take up to 4 weeks for effects and 8-12 weeks for full response
  - If no response, discontinue at 8 weeks
  - *No data on duration of treatment, "neuroplasticity"

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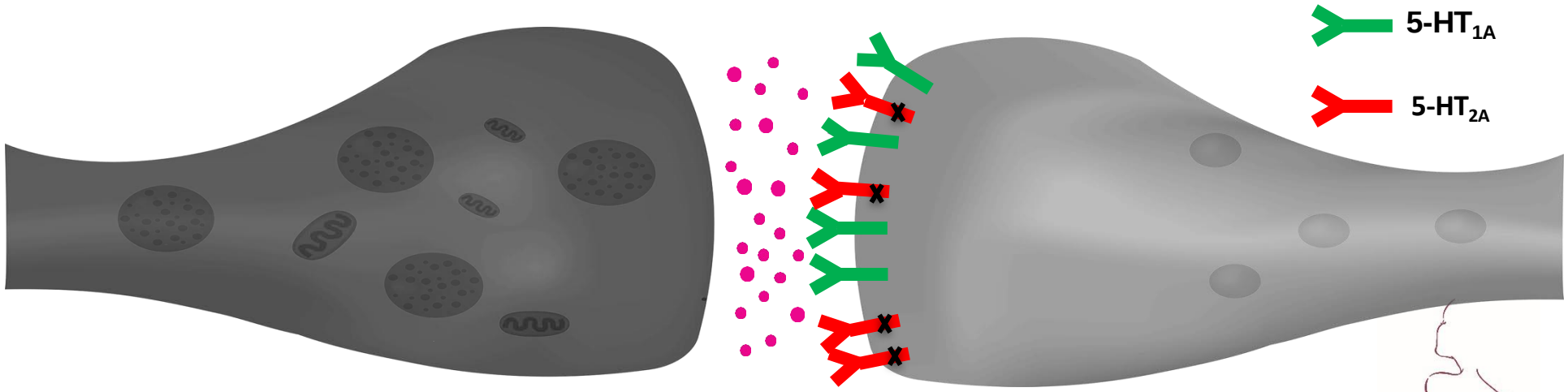
Flibanserin Serotonin Receptor Activity

- Centrally-acting central nervous system agent, thought to act mainly on serotonin receptors in the brain.
  - $5HT_{1A}$ agonists could have pro-sexual effects
  - $5HT_{2A}$ antagonists could have pro-sexual effects



Flibanserin Serotonin Receptor Activity at the Synapse

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Flibanserin

- Improves multiple domains (FSFI)
- Decreases distress associated with FSD (FSDS-DAO)
- FDA-approved for generalized HSDD in <u>premenopausal</u> women not caused by:
  - Medical or psychiatric condition
  - Relationship problems
  - Effects of a medication/drug
- Not Viagra (not performance enhancing)
- Not *YET* indicated for postmenopausal women & men
- Flibanserin is contraindicated:
  - With concomitant use with moderate or strong CYP3A4 inhibitors
  - In patients with hepatic impairment

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Phase 3 Clinical Trials of Safety and Efficacy of Flibanserin

Study population:

- Premenopausal women with acquired, generalized HSDD for >6 months
- 88.6% Caucasian
- Mean age: 36 years (19-55 yrs)
- Mean duration of HSDD: ~5 years
- Mean duration in monogamous, heterosexual relationship: 11 years

Study 1: VIOLET	Study 2: DAISY	Study 3: BEGONIA
Flibanserin (N = 280)	Flibanserin (N = 365)	Flibanserin (N = 532)
Placebo (N = 290)	Placebo (N = 372)	Placebo (N = 536)

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Flibanserin: Three 24-Week Pivotal Trials Involving >2,300 Premenopausal Women[1-3]

Key efficacy measures examined change from baseline in sexual desire, satisfying sexual events, and sexual distress in randomized, double-blind, placebo-controlled trials

	Co-Primary Endpoints	Secondary Endpoints
Studies I & II	Mean change from baseline at Week 24 in: ▪ Monthly sexual desire score (eDiary)[1,2] ▪ Number of monthly satisfying sexual events (SSEs)[5]	Mean change from baseline at Week 24 in: ▪ FSFI-D ▪ Female Sexual Distress Scale-Revised Item 13 (FSDS-R-Q13)[6,7]
Study III	Mean change from baseline at Week 24 in: ▪ Female Sexual Function Index-Desire Domain (FSFI-D)[4] ▪ Number of monthly SSEs[4]	Mean change from baseline at Week 24 in: ▪ FSDS-R-Q13

Safety measures focused on incidence of adverse events

1. Derogatis LR, et al. *J Sex Med*. 2012;9(4):1074-1085. 2. Thorp J, et al. *J Sex Med.* 2012;9(3):793-804. 3. Katz M, et al. *J Sex Med*. 2013;10(7):1807-1815. 4. Gerstenberger EP, et al. *J Sex Med*. 2010;7(9):3096-3103. 5. Kingsberg SA, Althof SE. *J Sex Med*. 2011;8(12):3262-70. 6. Derogatis LR, et al. *J Sex Marital Ther*. 2002;28(4):317-330. 7. Derogatis LR, et al. *J Sex Med*. 2008;5(2):357-364.

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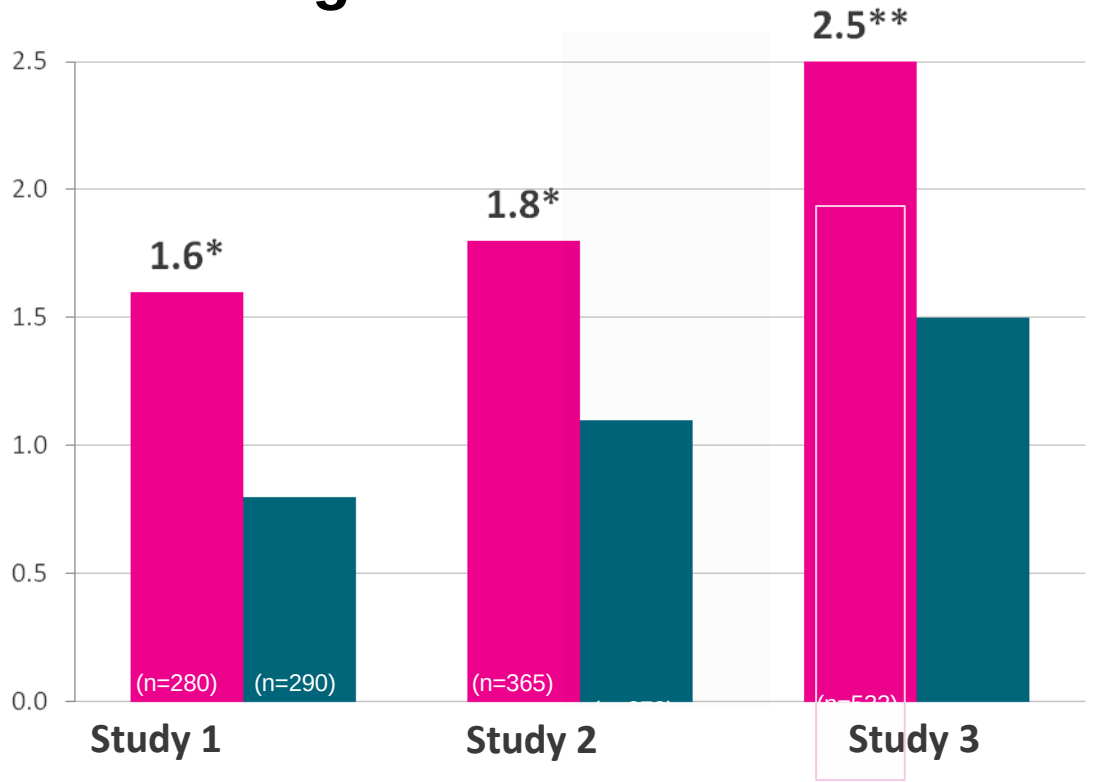
Women Taking Flibanserin Reported Significantly More SSEs vs Placebo

Mean Change from Baseline at Week 24[1-3]



SSEs are of satisfying sexual events: sexual intercourse, oral sex, masturbation, or genital stimulation by the partner that the patient reported as gratifying, fulfilling, satisfactory, and/or successful, irrespective of whether the woman had an orgasm

*P < 0.01 versus placebo
**P < 0.0001 versus placebo

Flibanserin
Placebo

defined as the number

1. Derogatis LR, et al. *J Sex Med*. 2012;9(4):1074-1085. 2 . Thorp J, et al. *J Sex Med*. 2012;9(3):793-804. 3. Katz M, et al. *J Sex Med*. 201 1815.

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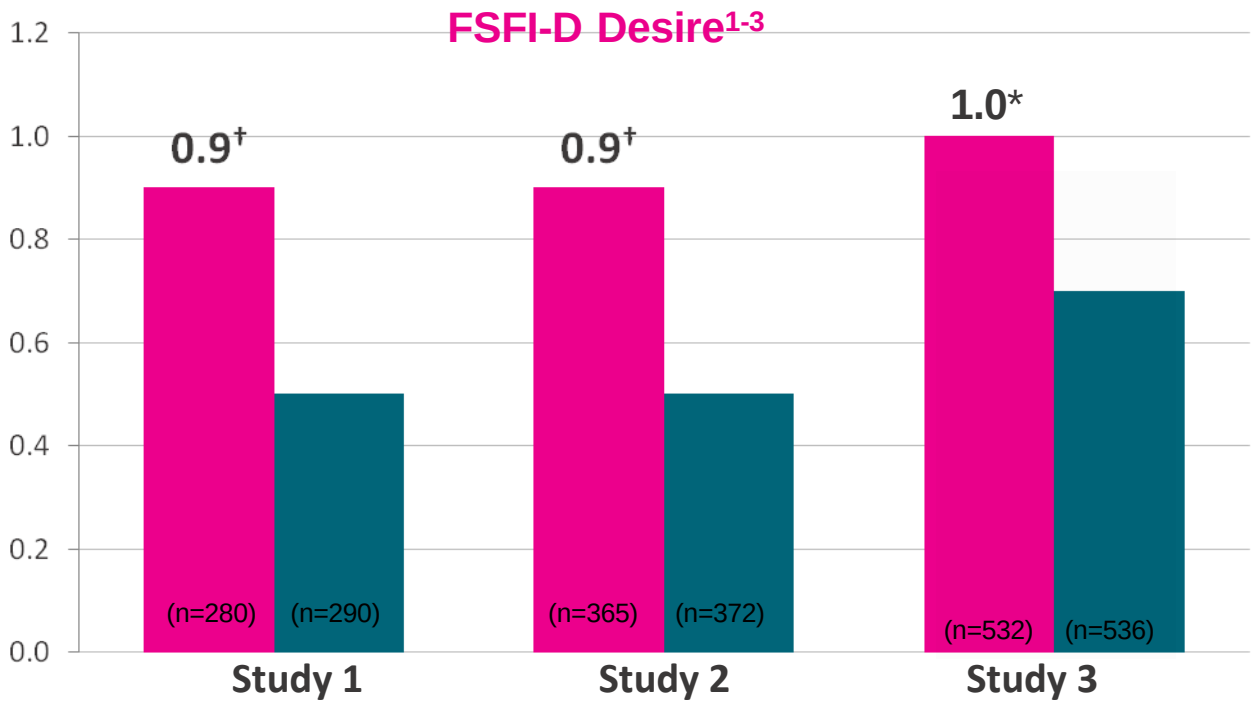
Flibanserin Consistently Improved Sexual Desire vs. Placebo

Mean Change from Baseline at Week 24



† P-value not reported for secondary endpoints because the trials failed on the eDiary co-primary efficacy endpoint

* P < 0.0001

Flibanserin

Placebo

Flibanserin showed consistent improvement in desire using the validated FSFI-D instrument in all three studies

1. Derogatis LR, et al. *J Sex Med.* 2012;9(4):1074-1085. 2. Thorp J, et al. *J Sex Med.* 2012;9(3):793-804. 3. Katz M, et al. *J Sex Med*. 2013;10(7):1807-1815. 4. Flibanserin [package insert]. Raleigh, NC: Sprout Pharmaceuticals; 2015

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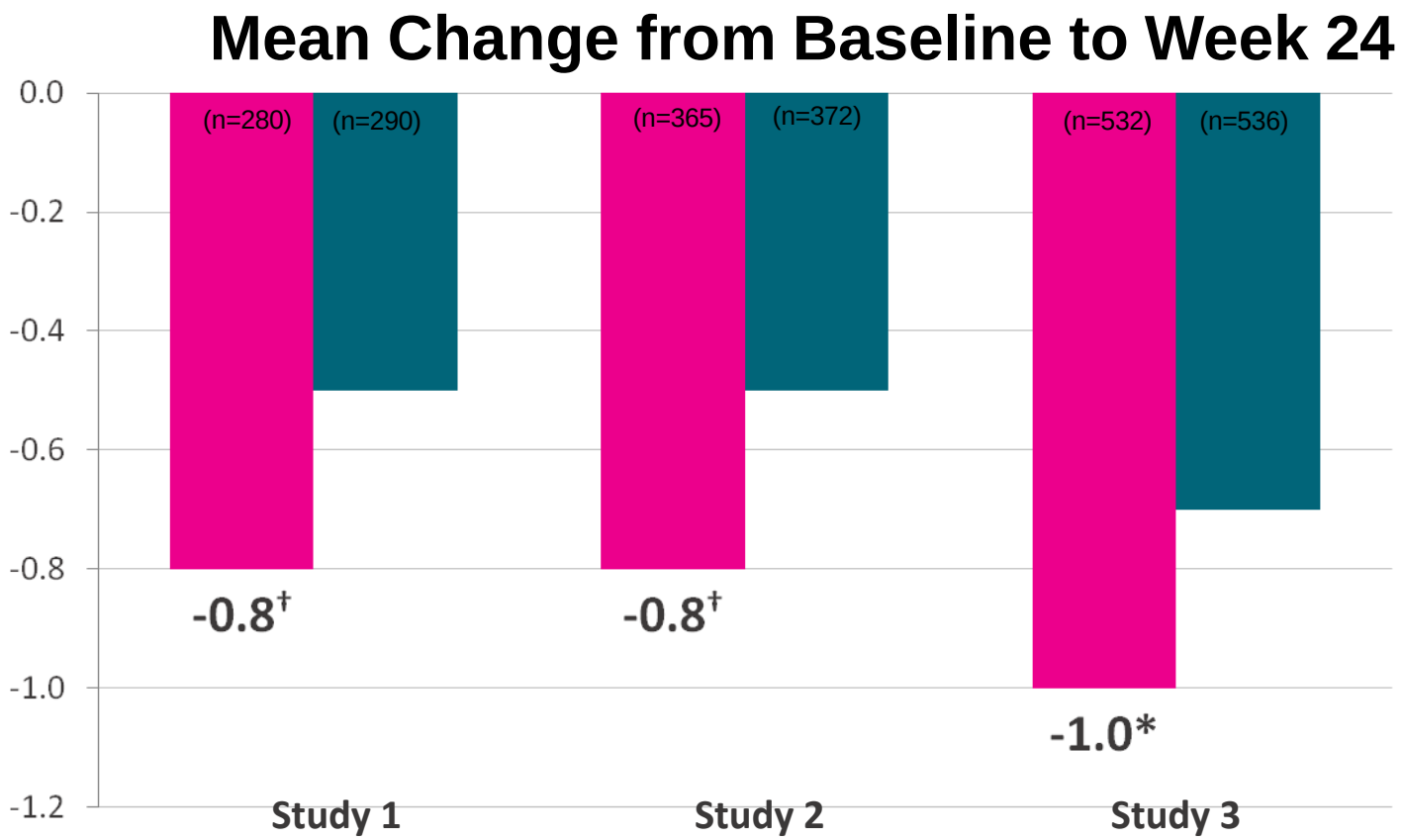
Flibanserin Showed a Decrease in Distress vs. Placebo Across All 3 Studies



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* P < 0.0001

Flibanserin
Placebo

Derogatis LR, et al. *J Sex Med*. 2012;9(4):1074-1085. Thorp J, et al. *J Sex Med*. 2012;9(3):793-804. Katz M, et al. *J Sex Med*. 2013;10(7):180

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Flibanserin Adverse Reactions

Adverse reactions reported in clinical trials in ≥2% of patients receiving 100 mg of flibanserin at bedtime and at a higher incidence than placebo-treated patients

	Flibanserin (n=1543)	Placebo (n=1556)
Dizziness	11.4%	2.2%
Somnolence	11.2%	2.9%
Nausea	10.4%	3.9%
Fatigue	9.2%	5.5%
Insomnia	4.9%	2.8%
Dry mouth	2.4%	1.0%

The majority of these adverse reactions began within the first 14 days of treatment

- Adverse reactions leading to discontinuation of ≥1% of patients receiving flibanserin 100 mg at bedtime and at a higher incidence than placebo-treated patients were: dizziness, nausea, insomnia, somnolence, and anxiety
- Discontinuation rate due to adverse reactions was 13% for flibanserin 100 mg and 6% for placebo

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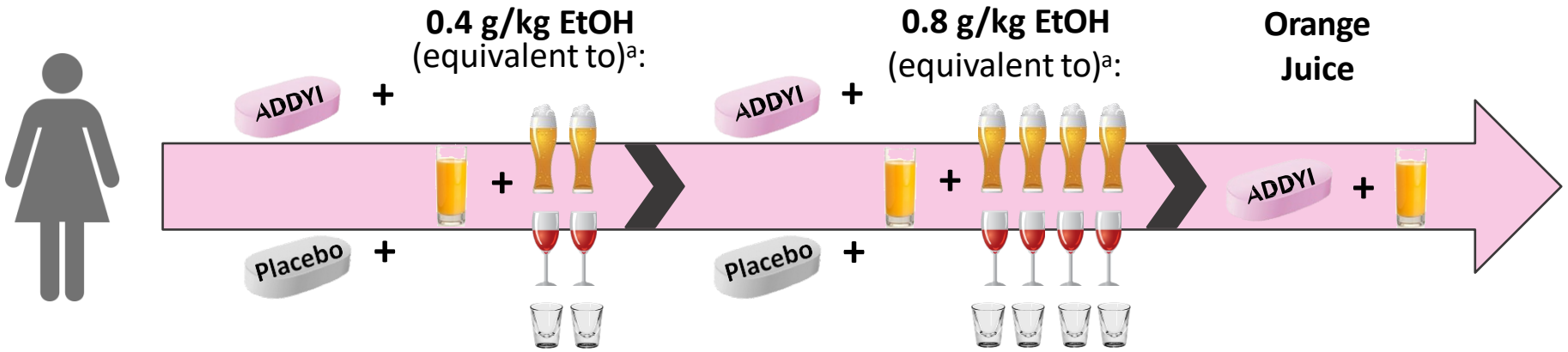
Effects of Alcohol Administered with Flibanserin in Healthy Premenopausal Women

- In this large, 7-treatment, 12-sequence, crossover study, administration of alcohol with flibanserin was not associated with an increased risk of hypotension and syncope
- 1 Subject in the ADDYI + 0.4 g/kg EtOH group experienced hypotension
- The adverse event profile for concomitant administration of mild (0.2 g/kg) or moderate (0.4 g/kg) quantities of ethanol with flibanserin was similar to that of flibanserin alone
- Increased drowsiness following administration of flibanserin (with or without ethanol) in this study supports the recommended (bedtime) dosing



96 Premenopausal Women
Mean age: 31 years (18-45)
BMI of 18 to 35 kg/m2
Fasted for 10 hours
Ate a light breakfast

Administered Study Drug: 100mg ADDYI or Placebo[b]

Given up to 10 minutes to ingest liquid solution (ethanol [EtOH] + orange juice or just orange juice)

[a]equivalents in a 70 kg (~154 lb) person: 12 oz of beer containing 5% alcohol content; 5 oz of wine containing 12% alcohol content; 1.5 oz of 80-proof spirit. [b]Study consisted of 5 single dose study periods; subjects received each of the 5 treatments

1. Sicard, E; Effects of Alcohol Administered with Flibanserin on Dizziness, Syncope, and Hypotension in Healthy Premenopausal Women

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Bremelanotide

- Cyclic, 7-amino acid melanocortin-receptor agonist
  - high affinity for the type-4 melanocortin receptor
  - analog of α-melanocyte-stimulating hormone (MSH)
  - Synthetic analog of naturally occurring hormone alpha-MSH (melanocyte-stimulating hormone)
  - Developed as intranasal formulation; now subcutaneous administration improves tolerability
  - On-demand use with rapid onset; well-tolerated
- BMT is delivered via an auto-injector on an “as desired” basis
  - FDA approved 2019
  - First in class

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Melanocortins

- Melanocortins: peptide hormones
- Melanocortin receptors: 7-transmembrane G-protein coupled receptors
  - stimulate the cAMP signal transduction pathway
  - naturally occurring agonists and antagonists
- Extensive potential for targeted therapeutic activity
  - HSDD, heart failure, obesity, diabetes, inflammatory diseases (IBS, nephritis, uveitis)
  - pharmacologic challenges of drug delivery related to metabolic instability and subsequent rapid degradation of peptides

1. Cai, M., & J Hruby, V. (2016). The melanocortin receptor system: a target for multiple degenerative diseases. *Current Protein and Peptide Science*, *17*(5), 488-496.
2. Singh, M., & Mukhopadhyay, K. (2014). Alpha-melanocyte stimulating hormone: an emerging anti-inflammatory antimicrobial peptide. *BioMed research international*, *2014*.
3. Yang, Y. (2011). Structure, function and regulation of the melanocortin receptors. *European journal of pharmacology*, *660*(1), 125-130.

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Melanocortin Receptors: 5 Subtypes

MC1R:

- location: skin, keratinocytes, endothelial cells, mucosal cells, chondrocytes, melanocytes, osteoblasts, macrophages, monocytes, dendritic cells, mast cells, neutrophils, CD8+ T cells, B lymphocytes
- pigmentation, skin cancer, anti-inflammation, pain

MC2R:

- location: adrenal cortex, adipocytes, skin, melanoma cells, osteoblasts, dendritic cells, chondrocytes
- adrenal steroid secretion

MC3R:

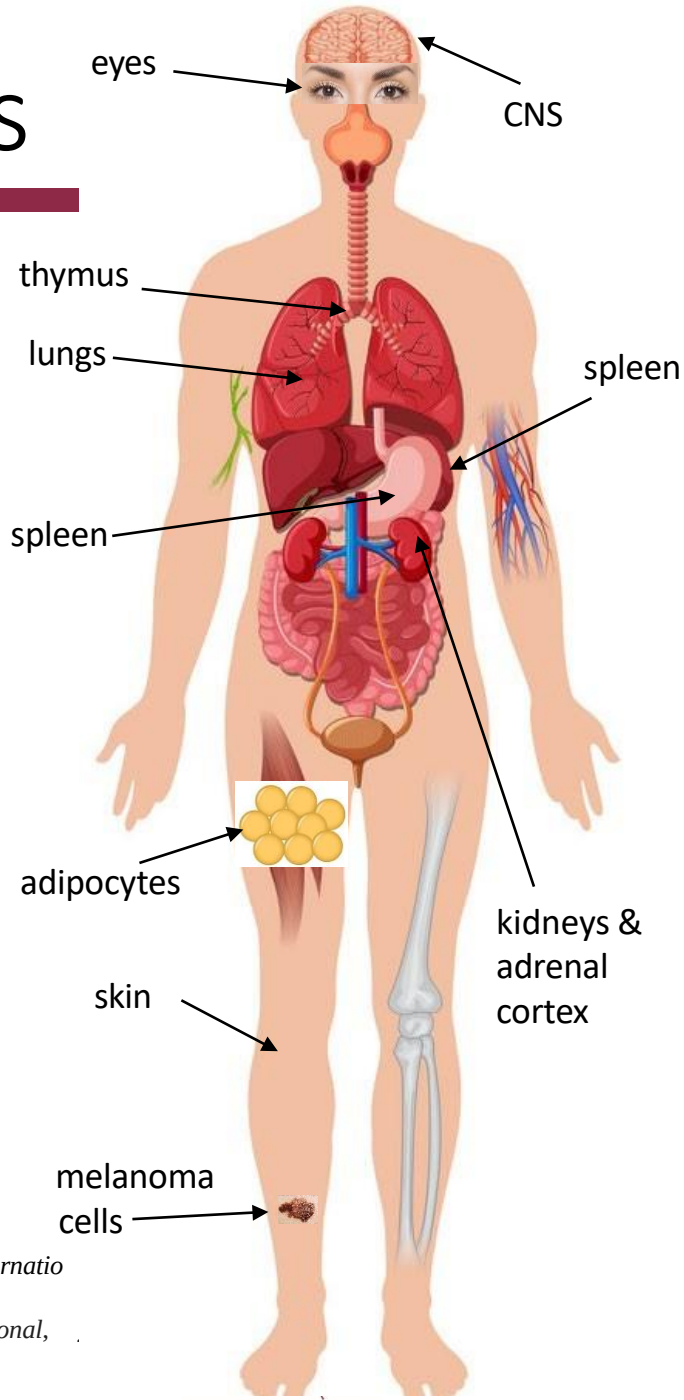
- location: CNS (hypothalamus), stomach, kidneys, heart, gut, thymus, placenta, macrophages, monocytes, dendritic cells, CD4+ T cells, B lymphocytes
- function: feeding, energy, homeostasis & anti-inflammation

MC4R:

- location: CNS (hypothalamus), dendritic cells, osteoblasts
- function: anti-inflammation, *sexual behaviors*, feeding control, energy homeostasis

MC5R:

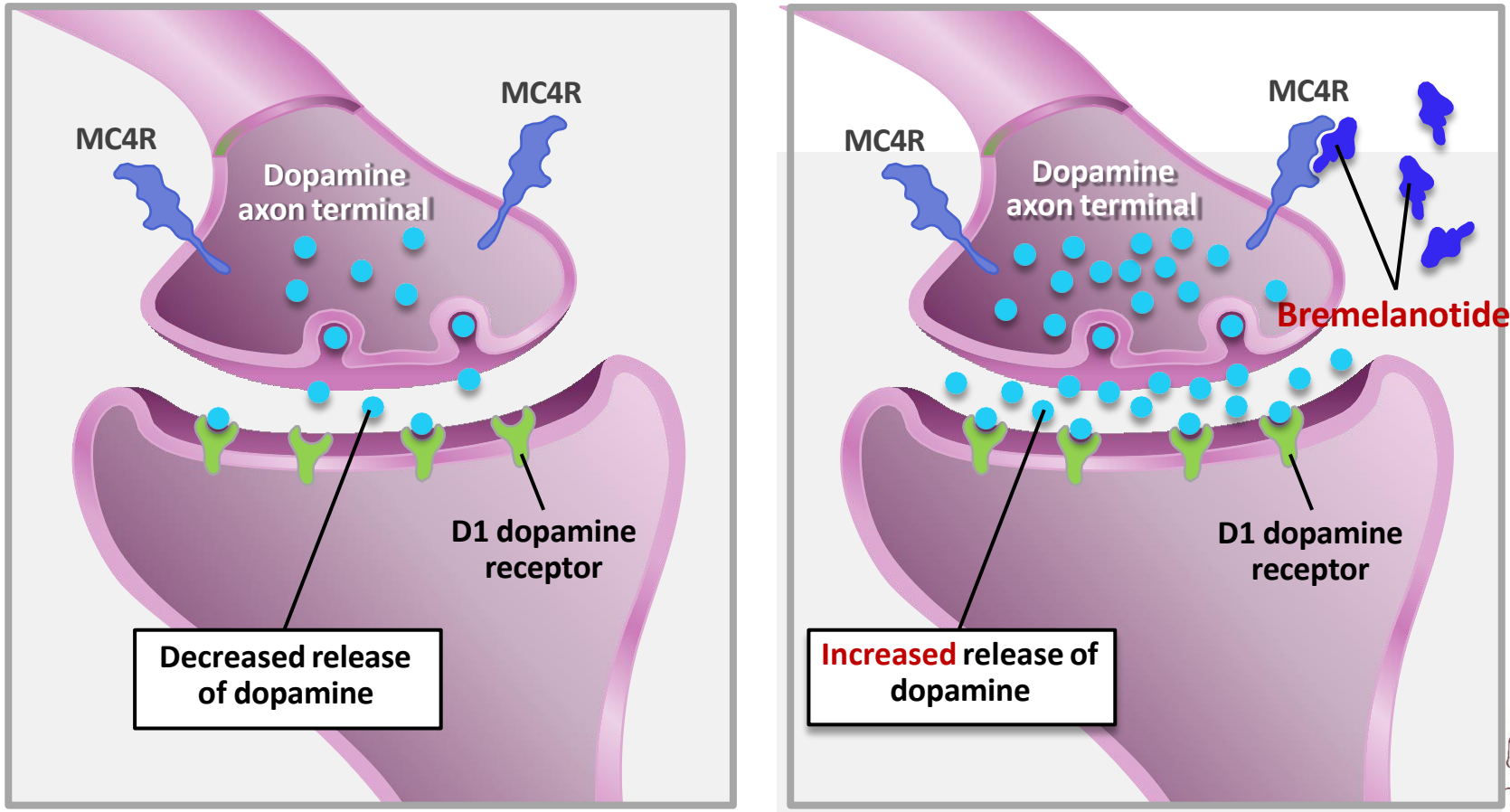
- location: CNS, peripheral tissues, exocrine glands, spleen, skin, lung, sexual organs, adiopose tissues, exocrine cells, sebocytes, macrophages, dendritic cells, mast cells, chondrocytes, CD4 T cells, B lymphocytes, NK cells
- function: exocrine secretion, lipolysis, regulation of body temp



1. Ahmed, T. J., Montero-Melendez, T., Perretti, M., & Pitzalis, C. (2013). Curbing inflammation through endogenous pathways: focus on melanocortin peptides. *Internatio inflammation*, *2013*.
2. Singh, M., & Mukhopadhyay, K. (2014). Alpha-melanocyte stimulating hormone: an emerging anti-inflammatory antimicrobial peptide. *BioMed research international*,
3. Yang, Y. (2011). Structure, function and regulation of the melanocortin receptors. *European journal of pharmacology*, *660*(1), 125-130.

Bremelanotide: Mechanism of Action

HSDD-related dopamine release | **Treatment of HSDD with bremelanotide**



In pre-clinical animal studies, efficacy was blocked by dopamine antagonist[1]

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[1] Pfaus, J., Giuliano, F., & Gelez, H. (2007). Bremelanotide: an overview of preclinical CNS effects on female sexual function. The journal of sexual medicine, 4, 269-279..

Bremelanotide

- Evaluated in 31 clinical studies, over 2,500 people, showing efficacy in both HSDD and reduced distress
- The RECONNECT study comprises 2 randomized, double-blind, placebo-controlled, phase 3 studies of BMT administered as-desired for the treatment of HSDD in premenopausal women
- In 327 premenopausal women clinically meaningful, statistically significant effects for BMT vs placebo
- 1.75mg dose
  - Improves multiple domains (FSFI)
  - Decreased distress associated with FSD (FSDS-DAO)
  - Influences downstream behavior
  - SSE improvement form baseline
  - FSFI-total score mean change vs placebo
  - FSDS-DAO-total score mean change vs placebo

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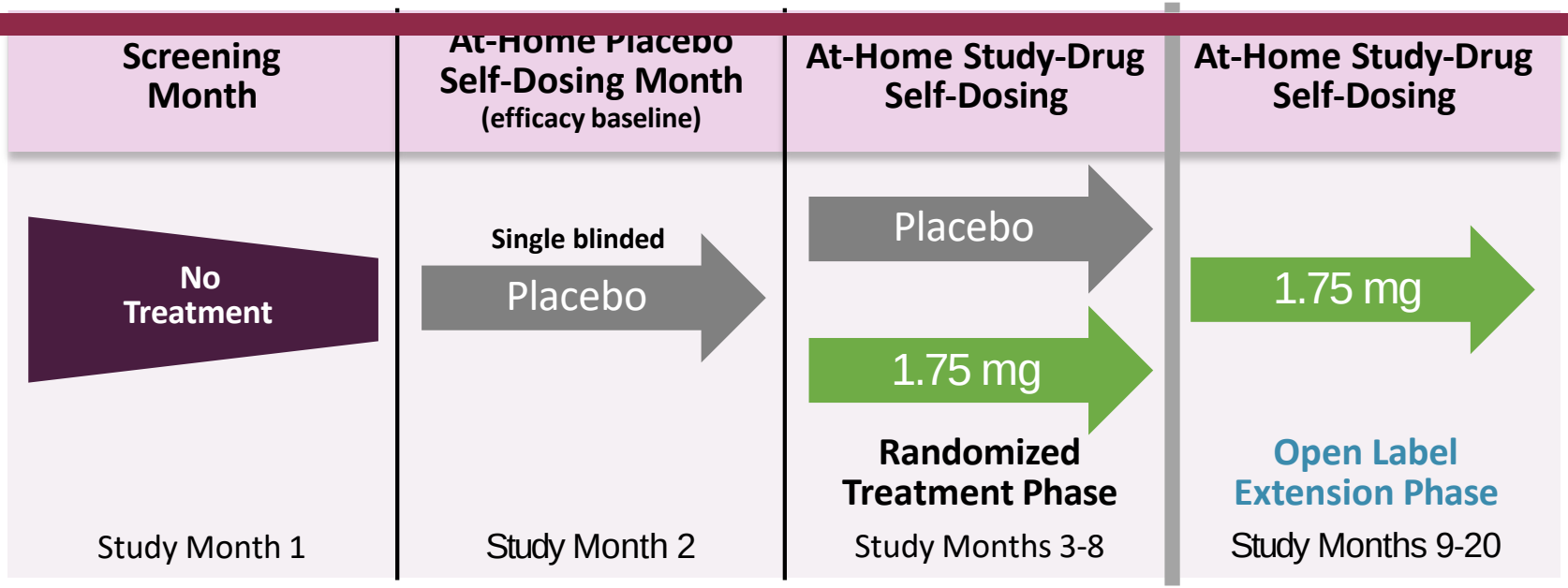
Phase 3 Program



- Randomized ~1,200 women with HSDD
  - 1:1 ratio bremelanotide or placebo
- Patients self-administered bremelanotide 1.75 mg or placebo using the auto-injector as needed in anticipation of sexual activity
  - Dose selection based on positive Phase 2 data
- The double blind efficacy portion consisted of a 24-week treatment evaluation period

80% of women completing the Phase 3 studies choose to participate in the rollover safety study

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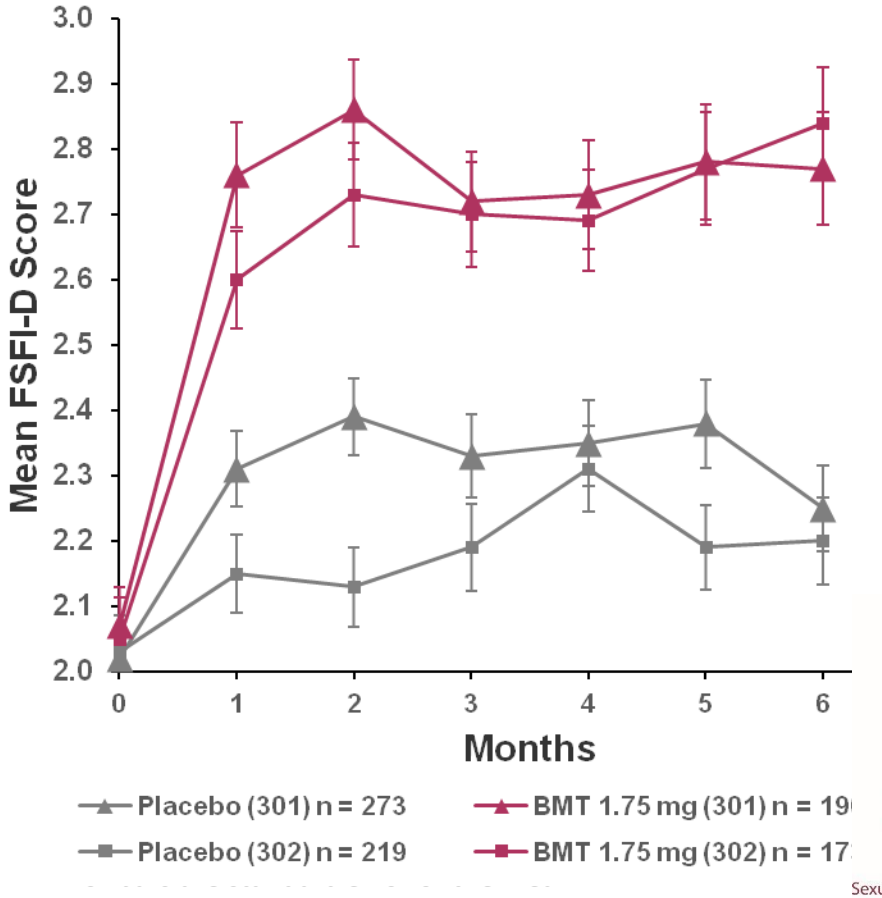
Efficacy Results: FSFI-D (Completers)

- Relative to placebo, the FSFI-D score increased in women using BMT 1.75 mg from the first month of double-blind treatment
- Following a sensitivity analysis that assumed all dropouts were treatment failures, the effect size decreased but results still showed statistically significant improvement in comparison to placebo

Mean FSFI Desire Domain Scores for Placebo and BMT Over the Core (Double-Blind) Phase



BMT, bremelanotide; FSFI-D, Female Sexual Function Index desi

1. Simon, J., Portman, D., Kingsberg, S., Clayton, A., Jordan, R., Lucas, J., & Spana, C. (2017). 017 Bremelanotide (BMT) for Hypoactive Sexual Desire Disorder (HSDD) in the RECONNECT Study: Efficacy Analyses in Study Completers and Responders. The Journal of Sexual Medicine, 14(6), e35 e357.2. Koochaki, P., Revicki, D., Wilson, H., Pokrzywinski, R., Jordan, R., Lucas, J., ... & Krop, J. (2021). The Patient Experience of Premenopausal Women Treated with Bremelanotide for Hypoactive Sexual Desire Disorder: RECONNECT Exit Study Results. Journal of Women's Health, 30(4), 587-595.

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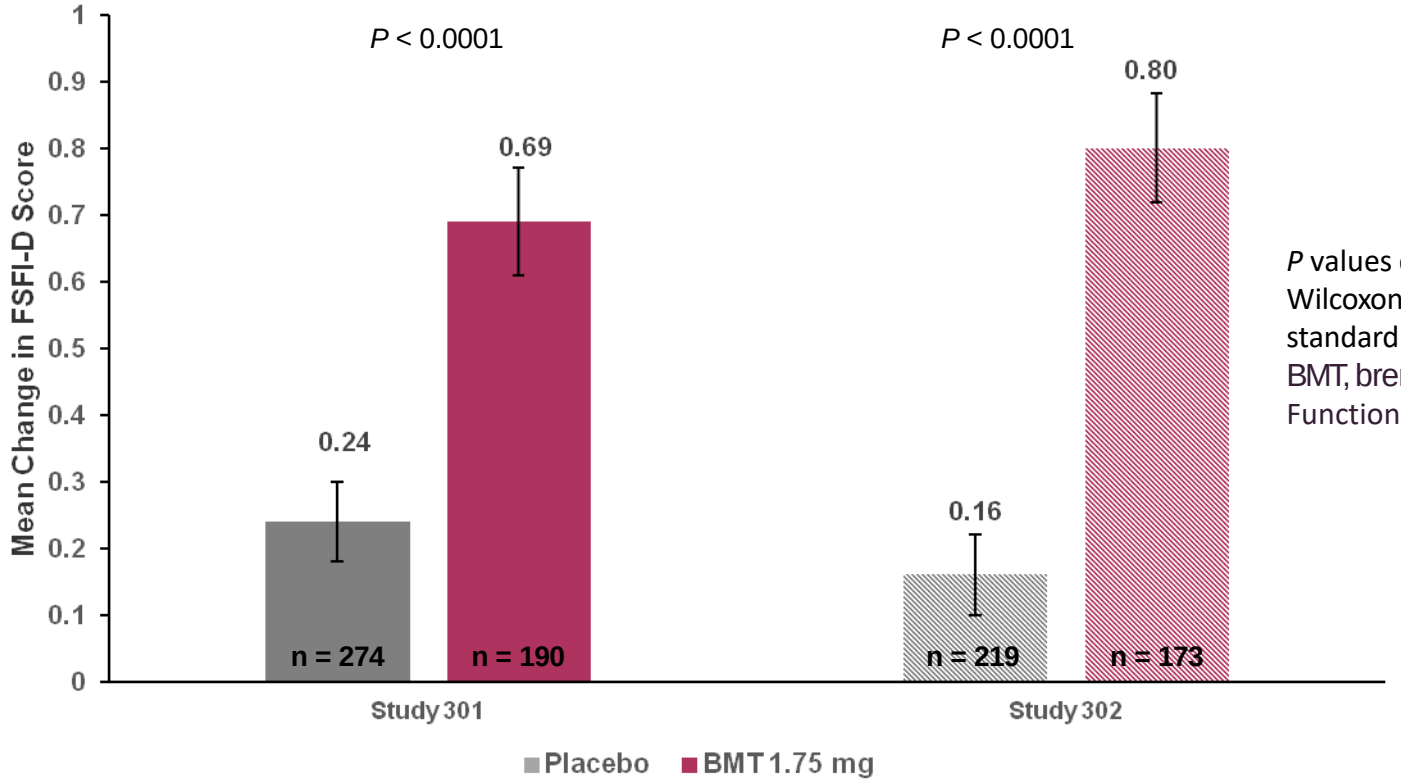
Efficacy Results: FSFI-D (Completers)

Compared with those taking placebo, women taking BMT had significantly increased scores on the desire domain of the FSFI at 6 months, indicating an increase in desire

Change in FSFI Desire Domain Score from Baseline to End of Core (Double-Blind) Phase



P values determined by unadjusted Wilcoxon rank-sum test. Error bars are standard error of the mean.
BMT, bremelanotide; FSFI-D, Female Sexual Function Index desire domain.

1. Simon, J., Portman, D., Kingsberg, S., Clayton, A., Jordan, R., Lucas, J., & Spana, C. (2017). 017 Bremelanotide (BMT) for Hypoactive Sexual Desire Disorder (HSDD) in the RECONNECT Study: Efficacy Analyses in Study Completers and Responders. The Journal of Sexual Medicine, 14(6), e356-e357.2. Koochaki, P., Revicki, D., Wilson, H., Pokrzywinski, R., Jordan, R., Lucas, J., ... & Krop, J. (2021). The Patient Experience of Premenopausal Women Treated with Bremelanotide for Hypoactive Sexual Desire Disorder: RECONNECT Exit Study Results. Journal of Women's Health, 30(4), 587-595.

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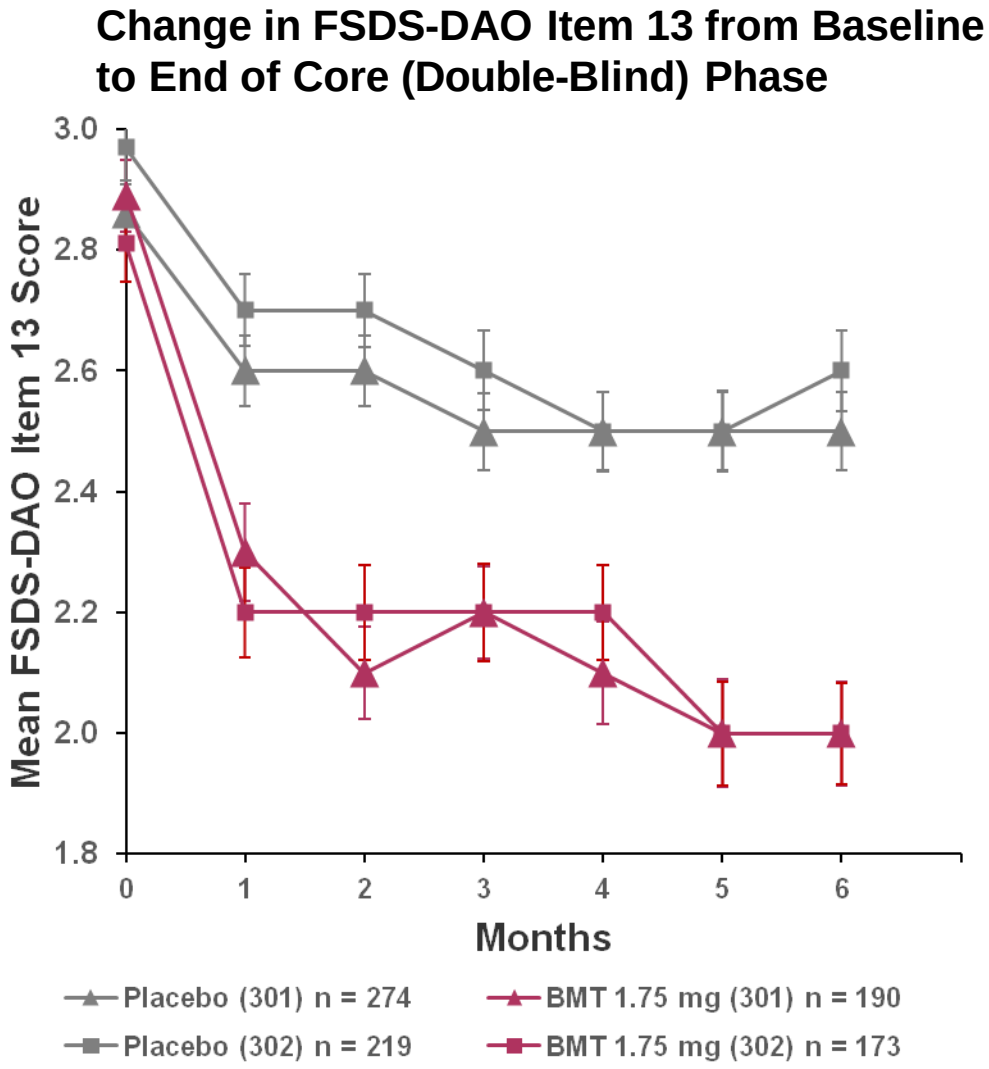
Efficacy Results: FSDS-DAO Item 13 (Completers)

Relative to placebo, FSDS-DAO Item 13 score decreased in women taking BMT 1.75 mg from the first month of double-blind treatment



Error bars are standard error of the mean.
BMT, bremelanotide; FSDS-DAO, Female Sexual Distress Scale-Desire/Arousal/Orgasm.

1. Simon, J., Portman, D., Kingsberg, S., Clayton, A., Jordan, R., Lucas, J., & Spana, C. (2017). 017 Bremelanotide (BMT) for Hypoactive Sexual Desire Disorder (HSDD) in the RECONNECT Study: Efficacy Analyses in Study Completers and Responders. The Journal of Sexual Medicine, 14(6), e356-e357.2. Koochaki, P., Revicki, D., Wilson, H., Pokrzywinski, R., Jordan, R., Lucas, J., ... & Krop, J. (2021). The Patient Experience of Premenopausal Women Treated with Bremelanotide for Hypoactive Sexual Desire Disorder: RECONNECT Exit Study Results. Journal of Women's Health, 30(4), 587-595.

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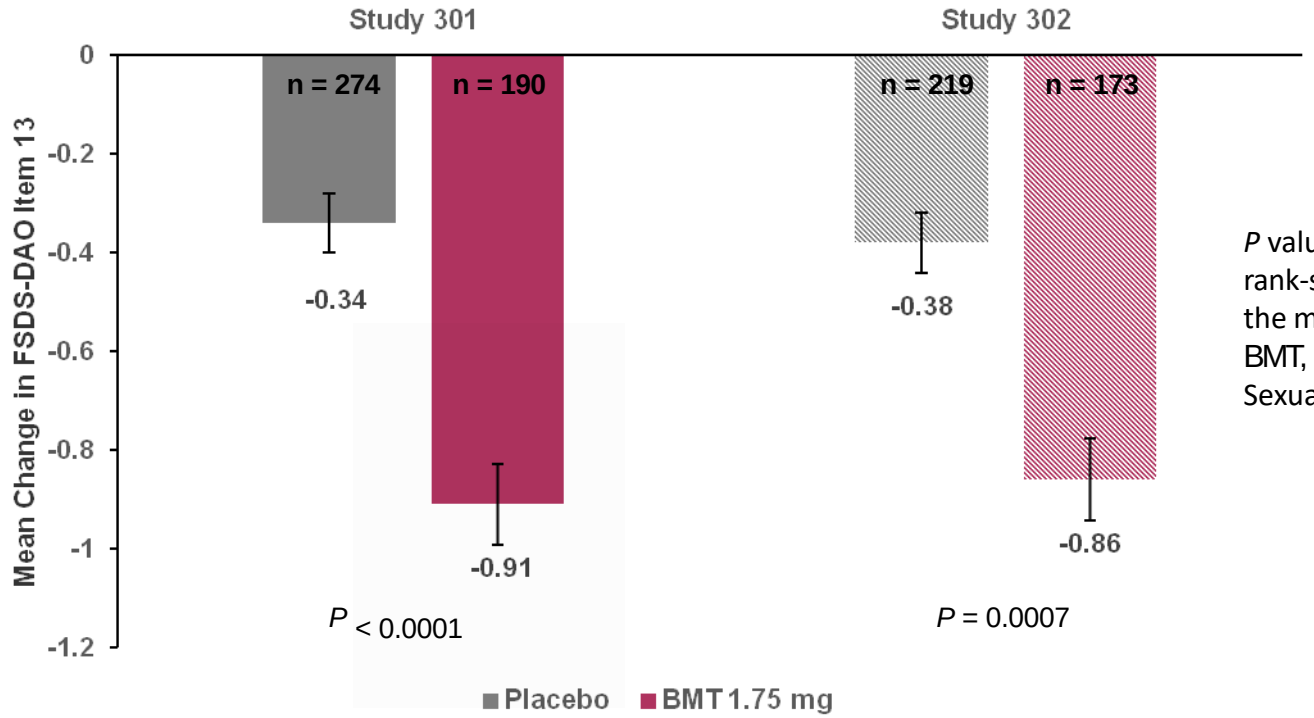
Efficacy Results: FSDS-DAO Item 13 (Completers)

Compared with those taking placebo, women using BMT had a significant reduction in their FSDS-DAO Item 13 score at 6 months, indicating a reduction in distress related to low sexual desire

Figure 4. Change in FSDS-DAO Item 13 from Baseline to End of Core (Double-Blind) Phase



P values determined by unadjusted Wilcoxon rank-sum test. Error bars are standard error of the mean.
BMT, bremelanotide; FSDS-DAO, Female Sexual Distress Scale-Desire/Arousal/Orgasm.

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Safety Profile in Phase 3 Controlled Studies

Most Common Adverse Events (AEs) in >2% of Subjects

Event	Bremelanotide 301 n (%)		Bremelanotide 302 n (%)	
	Placebo n=319	BMT n=324	Placebo n=301	BMT=303
Nausea	8 (2.5)	138 (42.6)	0	112 (37)
Flushing	2 (0.6)	85 (26.2)	1 (0.3)	42 (14.2)
Headache	8 (2.5)	32 (9.9)	5 (1.7)	37 (12.2)

- Most common AEs were nausea, flushing and headache
- Vast majority of AEs were mild-to-moderate in severity
- Only two treatment related SAEs
  - Both occurred in one subject (nausea/vomiting)
- TEAEs led to treatment discontinuation/interruption in approximately 18% of women taking bremelanotide (vs. 2% in placebo)

Simon, J., Portman, D., Kingsberg, S., Clayton, A., Jordan, R., Lucas, J., & Spana, C. (2017). 017 Bremelanotide (BMT) for Hypoactive Sexual Desire Disorder (HSDD) in the RECONNECT Study: Efficacy Analyses in Study Completers and Responders. The Journal of Sexual Medicine, 14(6), e356-e357.

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OTC Agents for HSDD

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Ristela – newest L arginine Supplement

1

Peri-menopause

PACR improves emotional, physical health and sexual function in peri-menopausal women.[1] 8-week, randomized, double-blind, placebo-controlled study conducted in 80 peri-menopausal women ages 40-50.

2

Post-menopause

Lady Prelox improves sexual function in post-menopausal women.[2] 8-week, randomized, single-blind, placebo-controlled study in 83 post-menopausal women ages 45-55.

3

Pre-menopause

Lady Prelox® improves sexual function in generally healthy women of reproductive age.[3] 8-week, active-controlled lifestyle study in 100 pre-menopausal women ages 37- 45.

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1. R Stanislavov and P Rohdewald. JWomen's Health Care 2014; 3:1-6. 2. A Bottari, G Belcaro, A Ledda, et al. *Panminerva Medica* 2012;54:3-9. 3. A Bottari, G Belcaro, A Ledda, et al. Minerva Ginecologica 2013;65:435-444

MOA: Increased Overall and Regional Blood Flow

Blood flow is vital to sexual comfort and pleasure.

- Lower levels of estrogen cause a decrease in blood flow to the vagina.
- Lack of blood flow to the genital areas can lead to:
  - Reduced sensitivity to touch
  - Reduced receptivity to physical arousal
  - Reduced vaginal lubrication
- Can ultimately lead to painful or uncomfortable intercourse and reduced sexual desire.
- Sexual dysfunction is common in peri and post-menopausal women and may be caused by the decline in nitric oxide and estrogen levels, both strong vasodilators.

[Berman 2005]

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L arginine and L Citruline

- During female sexual response, Endothelial Nitric Oxide Synthase (eNOS) is produced, an enzyme that converts arginine and citrulline into nitric oxide (NO).
- This increase in eNOS-NO leads to vasodilation, transudation (lubrication), and relaxation of the smooth muscle cells in the vagina.3
- eNOS activity is important for healthy sexual function, but it can decrease with age and hormonal changes.
- Pycnogenol and Rosvita: strong herbal antioxidants, prevent the degradation of nitric oxide by inhibiting free radicals, leading to improvement of endothelial function.

Fitzpatrick D, et al. *J Cardiol Pharmacol*. 1998;32:509-515.

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Investigational Agents for HSDD

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Lybrido, Lybridos-RCT Study Results

- Lybrido: low sensitive women with HSDD report significantly more sexual satisfaction during sexual events when using Lybrido compared to placebo.
- Lybridos: high inhibitory women with HSDD report significantly more sexual satisfaction during sexual events when using Lybridos compared to placebo
  - US Phase 2B to be published soon
  - Phase 3 trials expected to start early 2016

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