Experimental Therapies and Future Research

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Disclosures

Consultant/Advisory Board: Apricus, Emotional Brain, Exploramed, Sprout, Strategic Science & Technologies

Speaker: Ascend, Shionogi

Research: Apricus, Neogyn

Learning objectives:

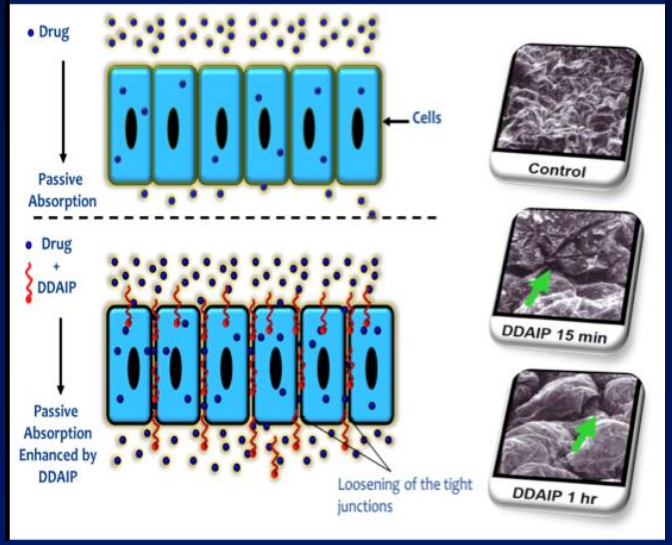
Characterize the pharmacologic agents and devices being developed for FSD

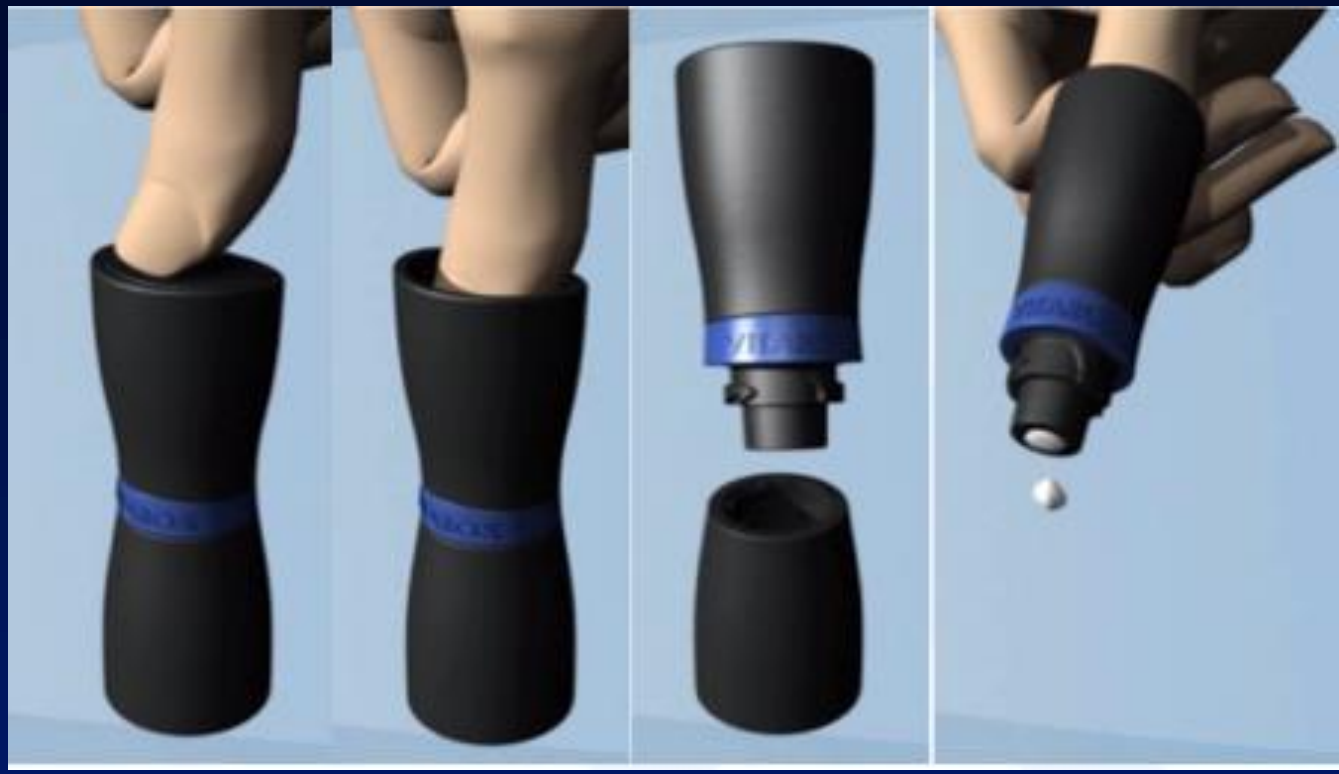
EXPERIMENTAL STRATEGIES

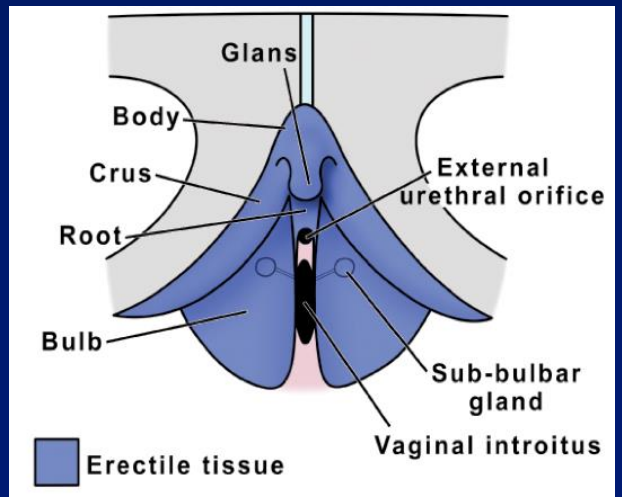
Topical Alprostadil
Flibanserin
Bremelanotide

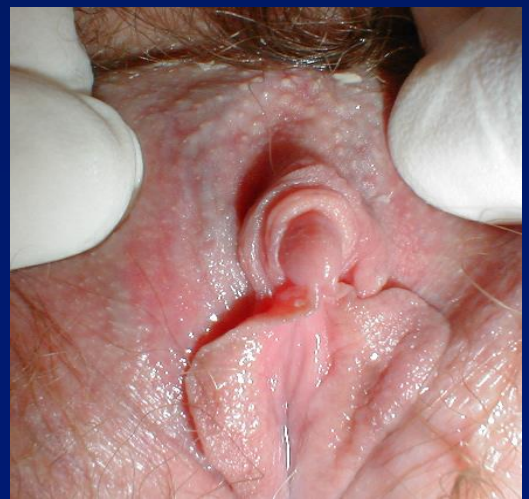
Alprostadil + DDAIP Cream for FSAD

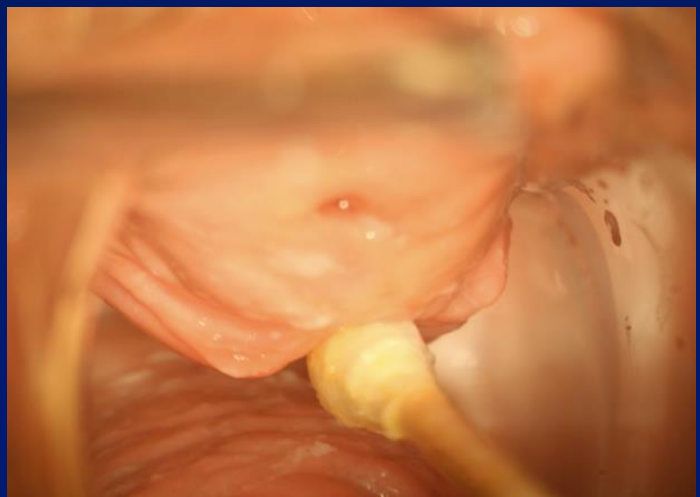
DDAIP is a novel proprietary skin permeation enhancer
It acts by loosening the tight junctions of the skin





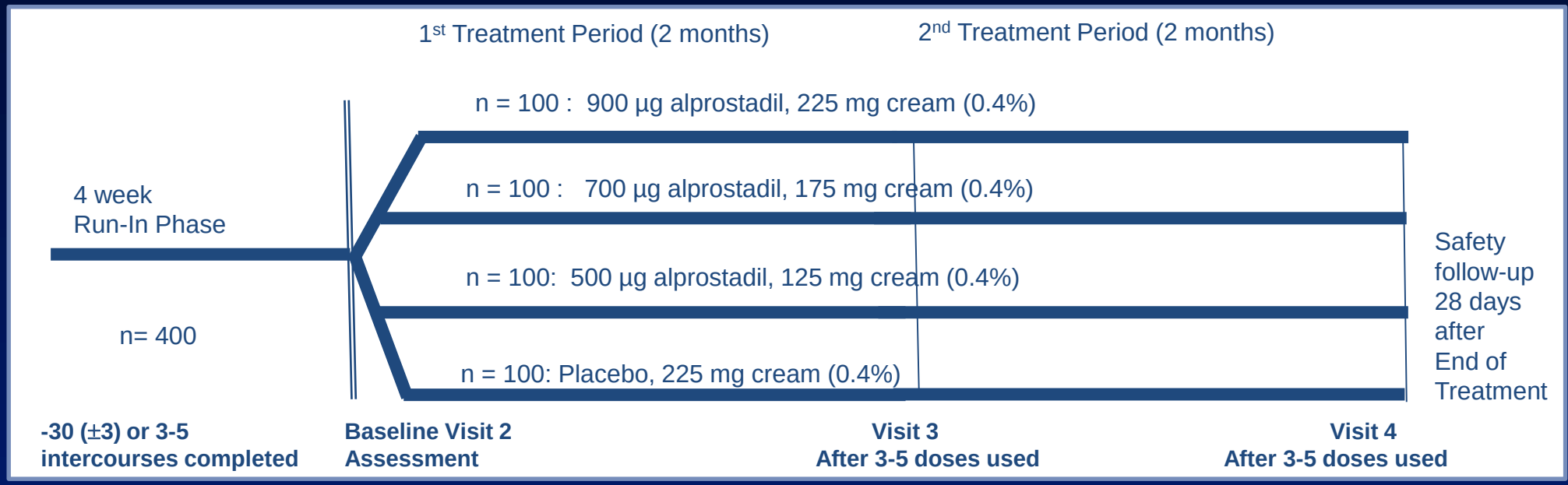






Topical Alprostadil: Clinical Trial in Female Sexual Arousal Disorder (FSAD)

Overall population: n= 400 women with FSAD, 22 to 65 years old, mean age: 60.7 years



Primary Efficacy Endpoints

- Satisfactory Sexual Events (SSE), defined as the number of "Yes" responses to Question 3 of the Female Sexual Encounter Profile (FSEP) divided by number of the sexual encounters.

Secondary Efficacy Endpoint

- Female Sexual Function Index (FSFI), Female Sexual Distress Score (FSDS)
- Global Assessment Question (GAQ)

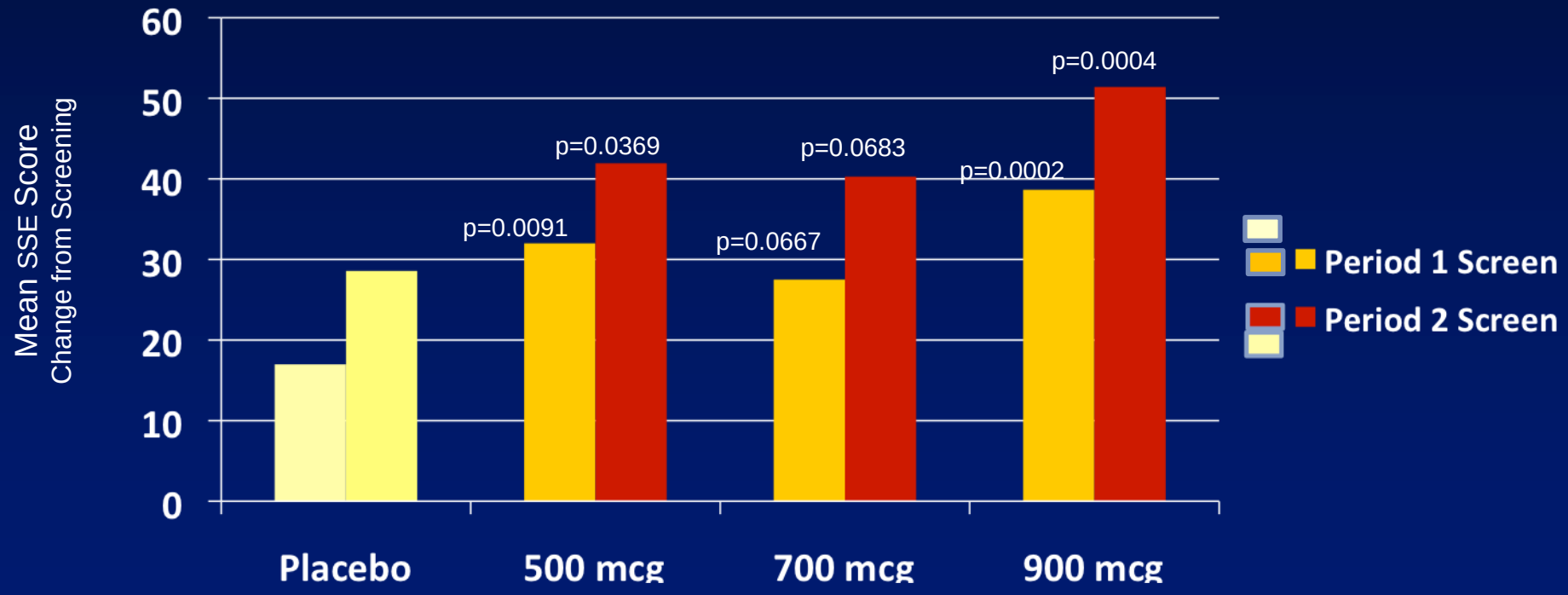
Goldstein, I. J Sex Med 2013;10:S164.

Liao Q, Zhang M, Geng L, Wang X, Song X, Xia P, Lu T, Lu M, Liu V. Efficacy and safety of alprostadil cream for the treatment of female sexual arousal disorder: a double-blind, placebo-controlled study in chinese population. J Sex Med. 2008 Aug;5(8):1923-31

The mean change of SSE was significant at the 900 mcg dose

Compared to placebo group, the mean change of SSE for the 900 mcg group was Period 1: 38.65 (p=0.0002) versus Period 2: 51.4 (p=0.0004)

Sexual Arousal Satisfaction Rate (ITT Population)

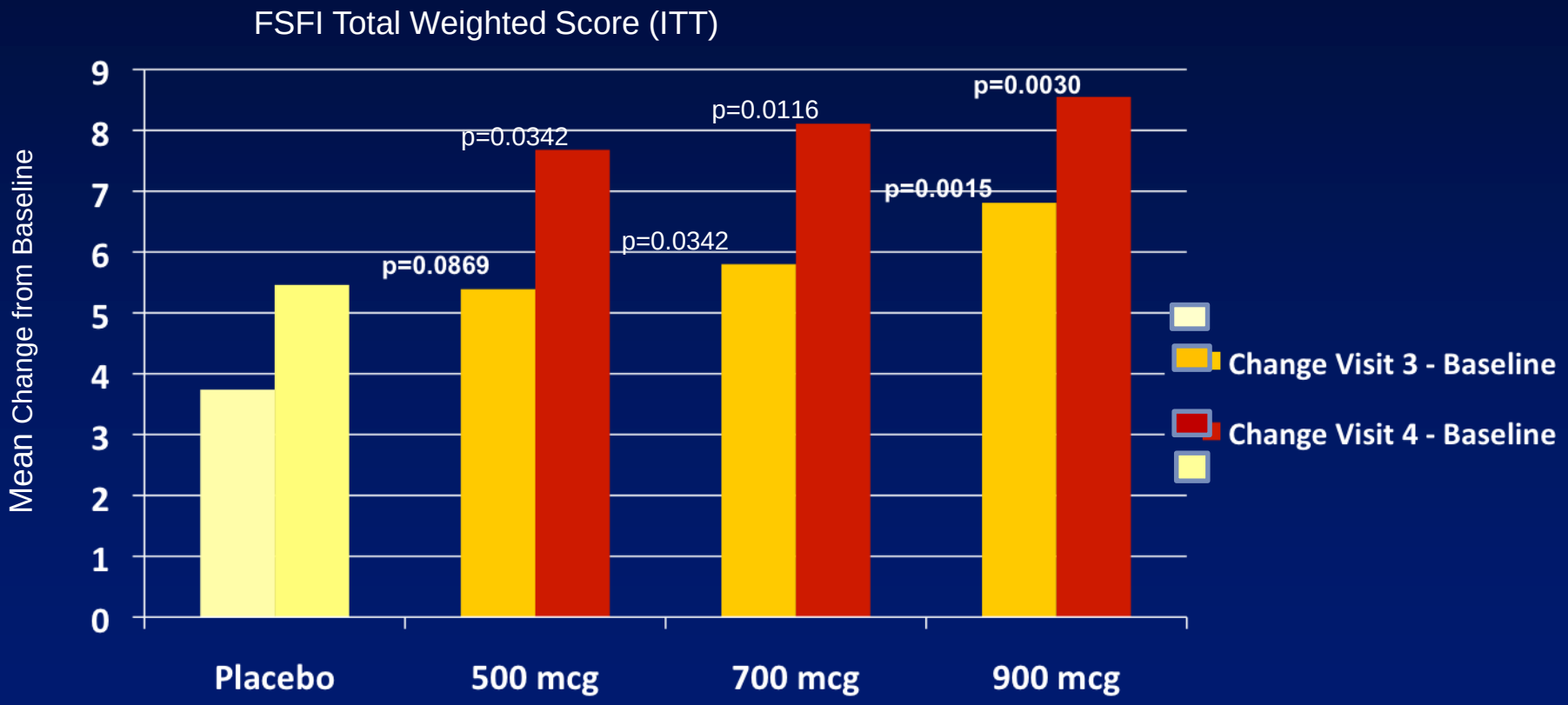


p-values are from ANOVA including all 4 treatment groups

Goldstein, I. J Sex Med 2013;10:S164.

Liao Q, Zhang M, Geng L, Wang X, Song X, Xia P, Lu T, Lu M, Liu V. Efficacy and safety of alprostadil cream for the treatment of female sexual arousal disorder: a double-blind, placebo-controlled study in chinese population. J Sex Med. 2008 Aug;5(8):1923-31

- The mean change of total FSFI score was significant at the 700 and 900 mcg dose during the first period with 5.8 (p=0.0342) and 6.8 (p=0.0015), respectively.
- At end of period 2, change in total FSFI score were 7.7 (p=0.0342), 8.1(p=0.0116) and 8.6 (p=0.0030) for the 500, 700 and the 900 mcg dose, respectively

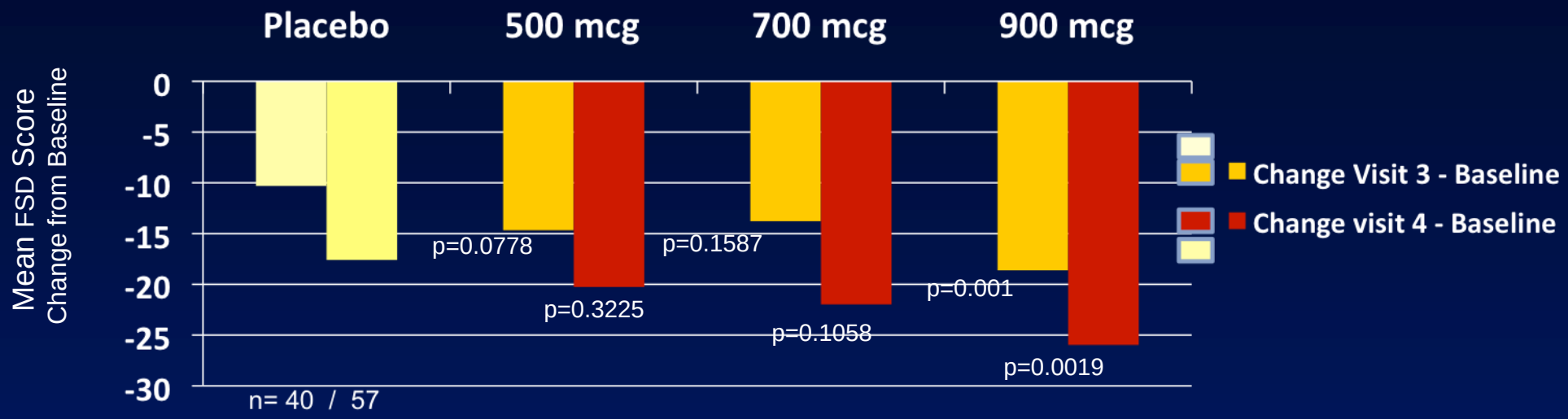


a Zero change was imputed for subject with a missing values at Visit 3 and/or Visit 4.
p-values are from ANOVA including all 4 treatment groups.

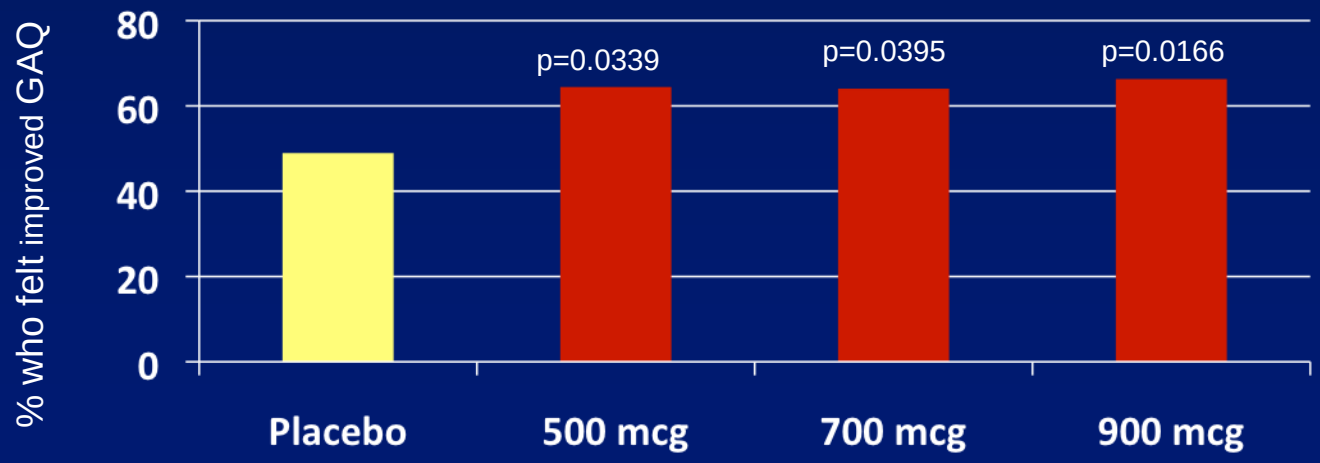
Goldstein, I. J Sex Med 2013;10:S164.

Liao Q, Zhang M, Geng L, Wang X, Song X, Xia P, Lu T, Lu M, Liu V. Efficacy and safety of alprostadil cream for the treatment of female sexual arousal disorder: a double-blind, placebo-controlled study in chinese population. J Sex Med. 2008 Aug;5(8):1923-31

The FSDS score was significant at the 900 mcg dose with a mean change of -18.62 (p=0.0010, period 1) versus -25.97 (p=0.0019, period 2).



The GAQ score showed 66.3% (p=0.0166) of patients at the 900 mcg dose were satisfied with their sexual encounters.

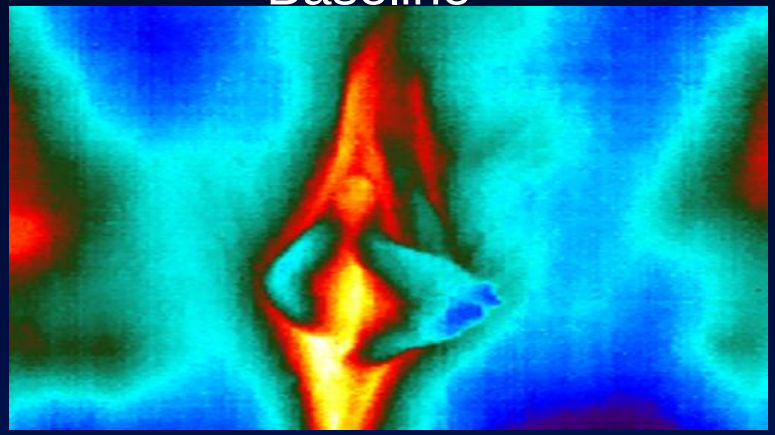


Goldstein, I. J Sex Med 2013;10:S164.

Liao Q, Zhang M, Geng L, Wang X, Song X, Xia P, Lu T, Lu M, Liu V. Efficacy and safety of alprostadil cream for the treatment of female sexual arousal disorder: a double-blind, placebo-controlled study in chinese population. J Sex Med. 2008 Aug;5(8):1923-31

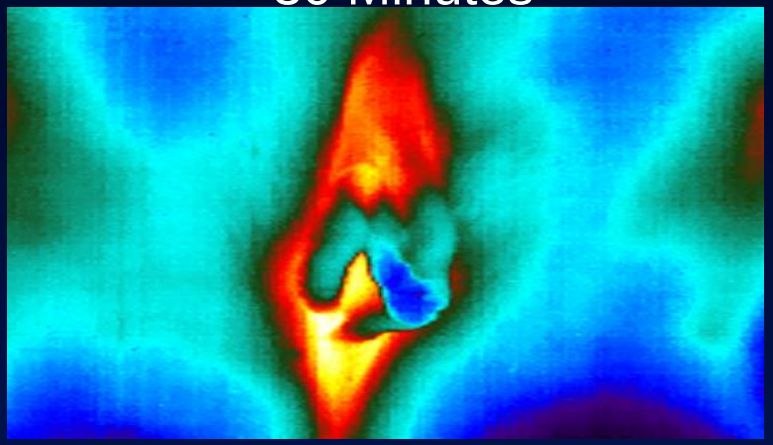
Patient 011 Study Drug A

Baseline



Vestibular Temp – 34.8˚ celsius
Clitoral Temp – 34.9˚ celsius
Vulvar Temp – 34.1˚ celsius

30 Minutes

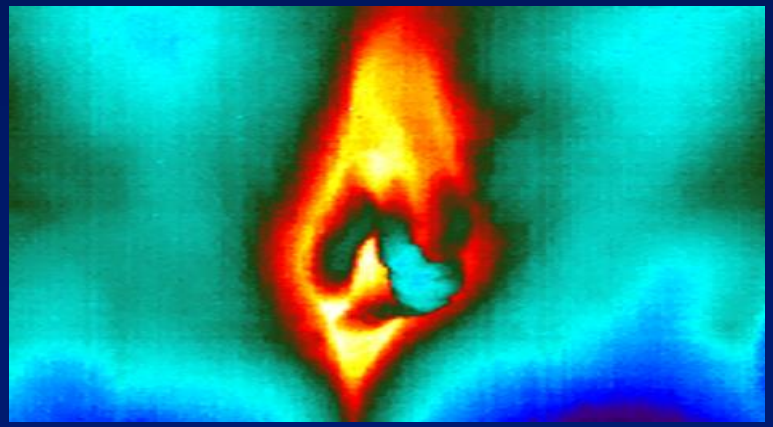


Vestibular Temp – 35.1˚ celsius
Clitoral Temp – 35.4˚ celsius
Vulvar Temp – 34.2˚ celsius

Max Change
in Temperature

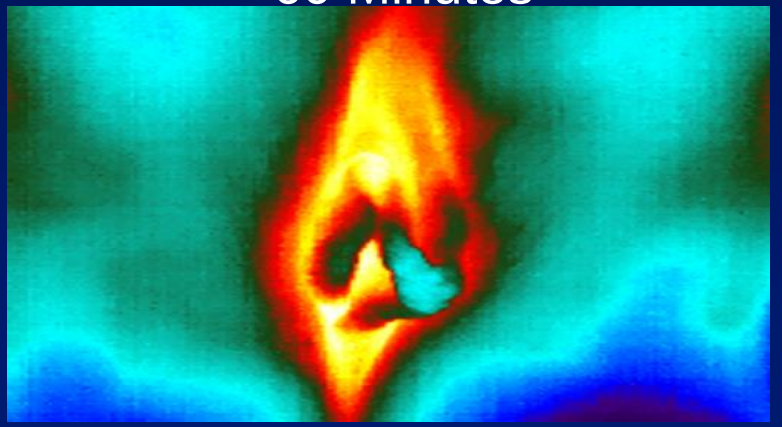
Vestibule – 1.1 ˚ C
Clitoral – 1.5 ˚ C
Vulvar – 0.7 ˚ C

45 Minutes



Vestibular Temp – 35.5˚ celsius
Clitoral Temp – 36.1˚ celsius
Vulvar Temp – 34.5˚ celsius

60 Minutes

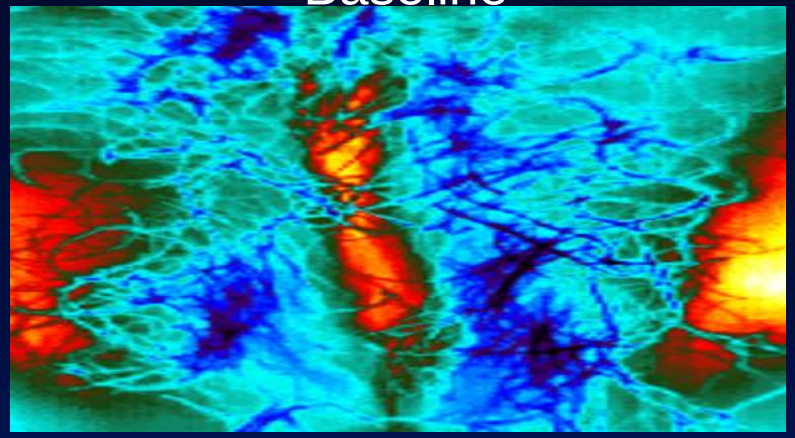


Vestibular Temp – 35.9˚ celsius
Clitoral Temp – 36.4˚ celsius
Vulvar Temp – 34.6˚ celsius

Courtesy Dr. Goldstein

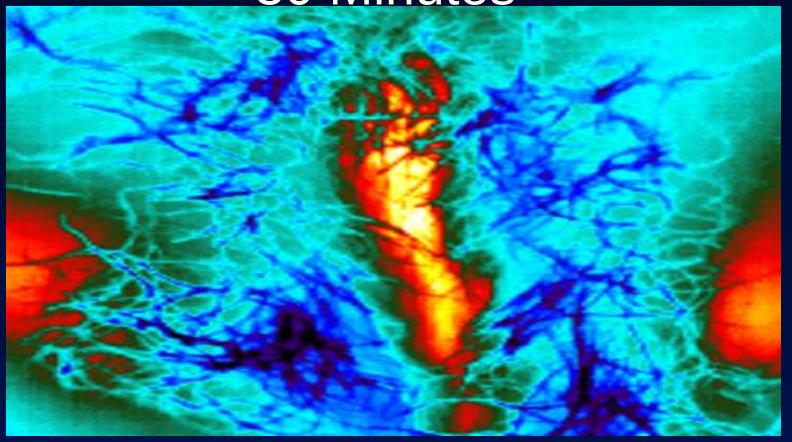
Patient 012 Study Drug A

Baseline



Vestibular Temp – 32.9˚ celsius
Clitoral Temp – 32.9˚ celsius
Vulvar Temp – 32.7˚ celsius

30 Minutes

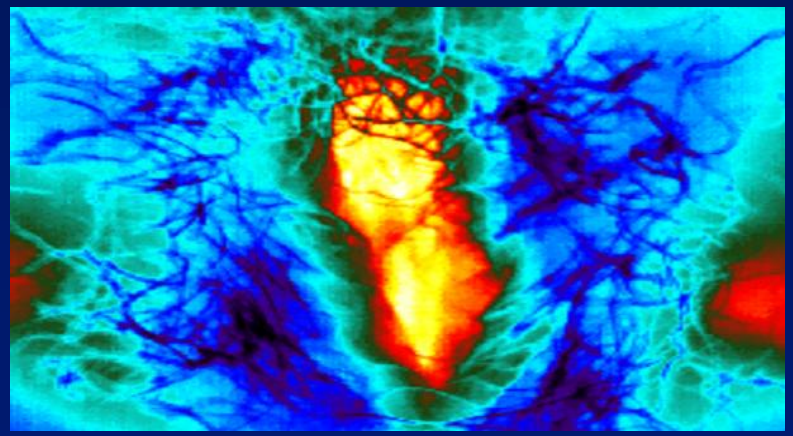


Vestibular Temp – 33.8˚ celsius
Clitoral Temp – 33.5˚ celsius
Vulvar Temp – 32.6˚ celsius

Max Change
in Temperature

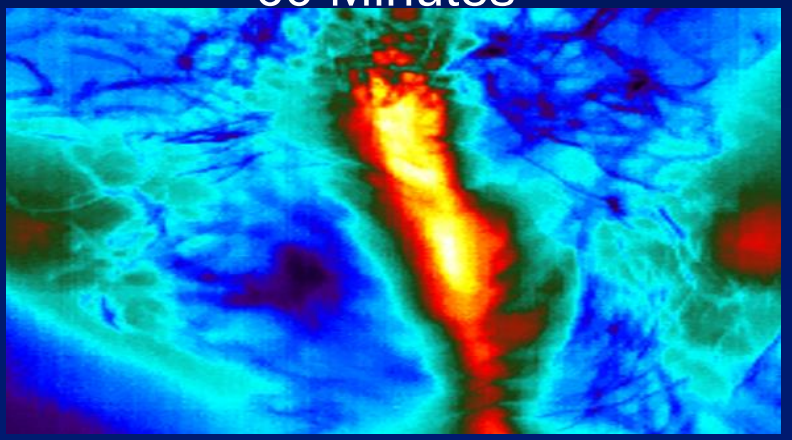
Vestibule – 2.9 ˚ C
Clitoral – 2.5 ˚ C
Vulvar – 1.1 ˚ C

45 Minutes



Vestibular Temp – 35.7˚ celsius
Clitoral Temp – 35.2˚ celsius
Vulvar Temp – 33.6˚ celsius

60 Minutes

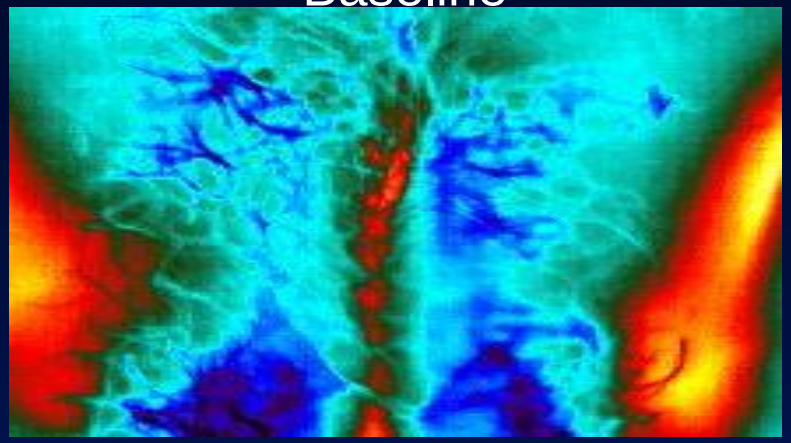


Vestibular Temp – 35.1˚ celsius
Clitoral Temp – 35.1˚ celsius
Vulvar Temp – 33.5˚ celsius

Courtesy Dr. Goldstein

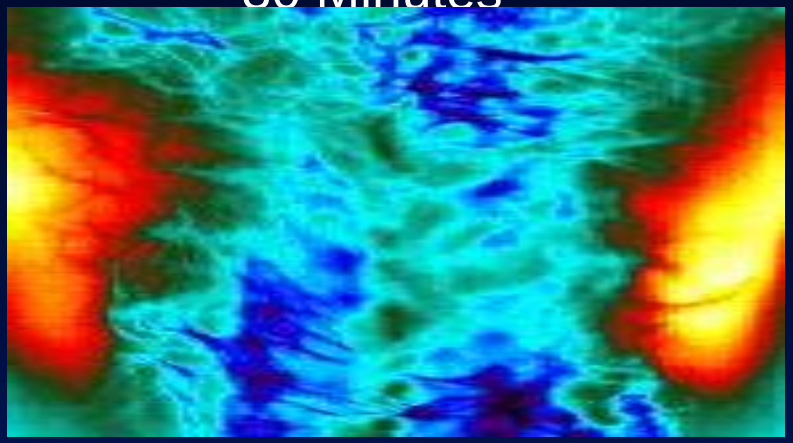
Patient 012 Study Drug B

Baseline



Vestibular Temp – 32.4˚ celsius
Clitoral Temp – 32.4˚ celsius
Vulvar Temp – 32.8˚ celsius

30 Minutes

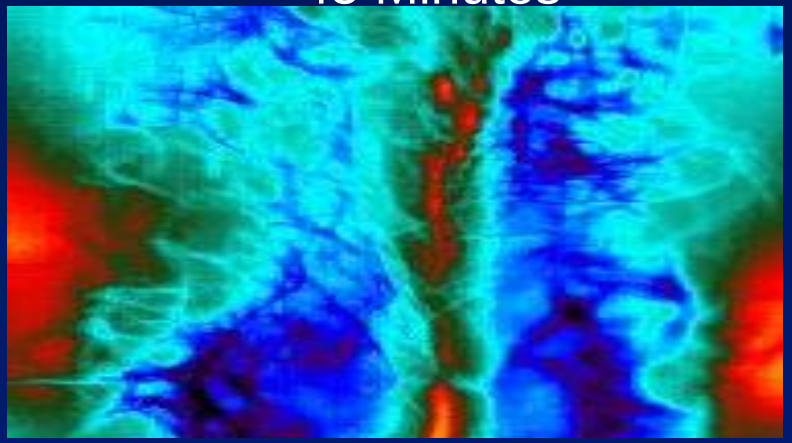


Vestibular Temp – 32.2˚ celsius
Clitoral Temp – 32.4˚ celsius
Vulvar Temp – 31.8˚ celsius

Max Change
in Temperature

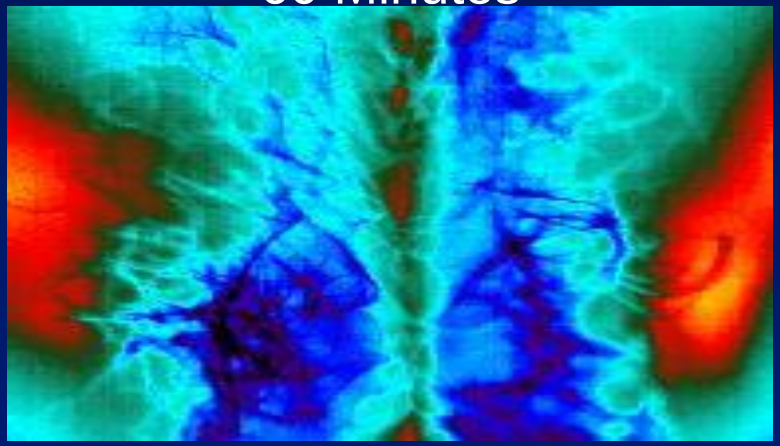
Vestibule – 0.5 ˚ C
Clitoral – 0.6 ˚ C
Vulvar – 0 ˚ C

45 Minutes



Vestibular Temp – 32.0˚ celsius
Clitoral Temp – 31.9˚ celsius
Vulvar Temp – 31.1˚ celsius

60 Minutes

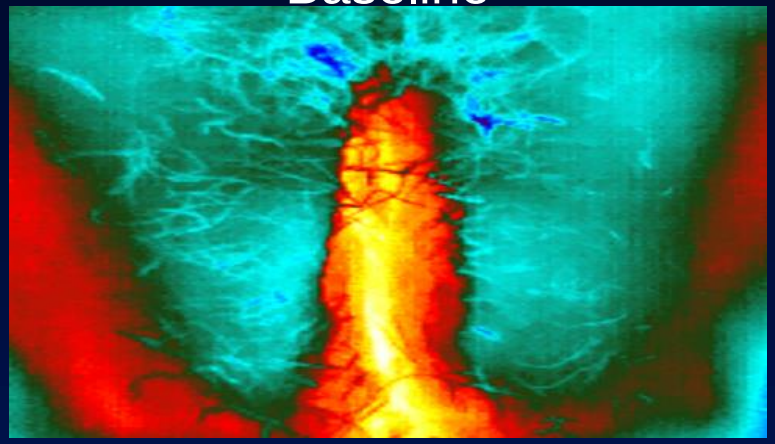


Vestibular Temp – 32.1˚ celsius
Clitoral Temp – 31.4˚ celsius
Vulvar Temp – 30.9˚ celsius

Courtesy Dr. Goldstein

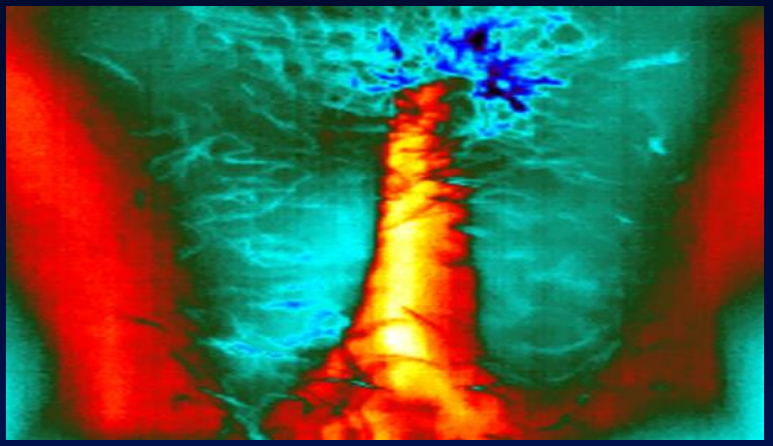
Patient 015 Study Drug B

Baseline



Vestibular Temp – 35.4˚ celsius
Clitoral Temp – 35˚ celsius
Vulvar Temp – 34.7˚ celsius

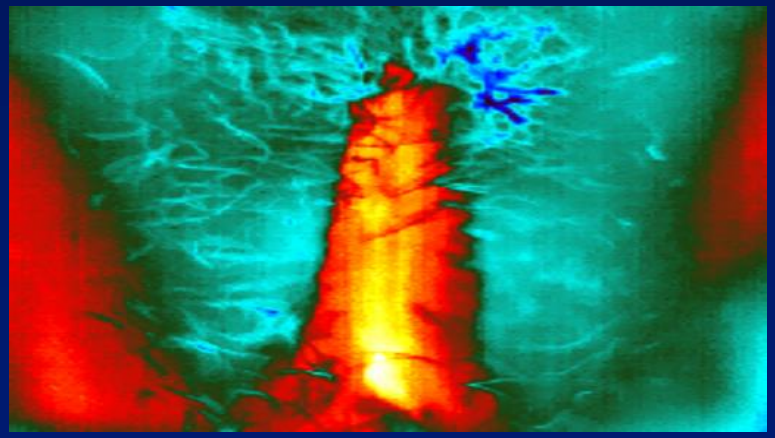
30 Minutes



Vestibular Temp – 34.6˚ celsius
Clitoral Temp – 34.4˚ celsius
Vulvar Temp – 34.1˚ celsius

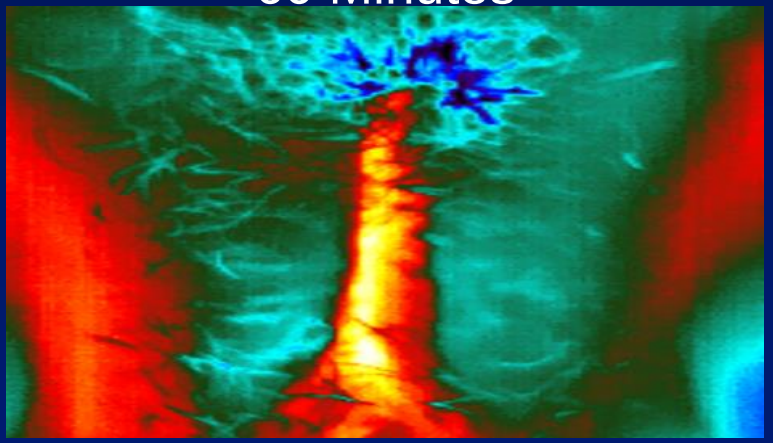
No Increase in Temperatures

45 Minutes



Vestibular Temp – 35.2˚ celsius
Clitoral Temp – 34.8˚ celsius
Vulvar Temp – 34.2˚ celsius

60 Minutes

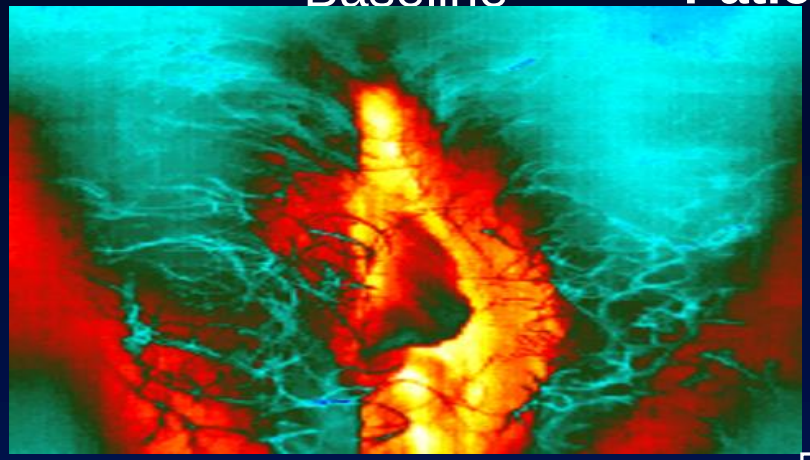


Vestibular Temp – 34.7˚ celsius
Clitoral Temp – 34.5˚ celsius
Vulvar Temp – 34.2˚ celsius

Courtesy Dr. Goldstein

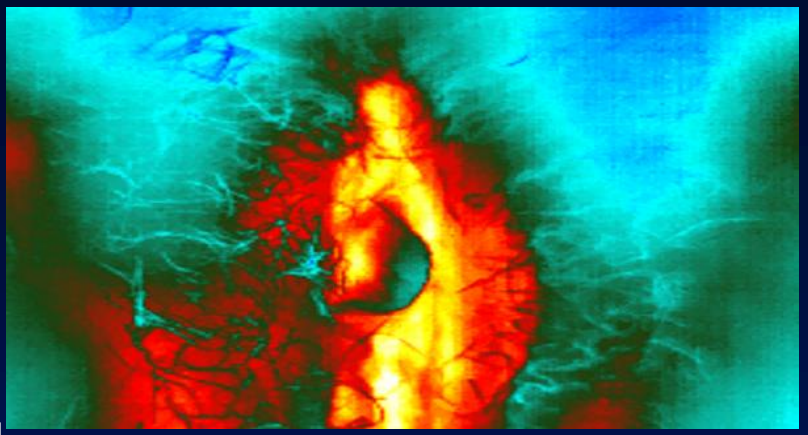
Patient 014 Study Drug A

Baseline



Vestibular Temp – 34.7˚ celsius
Clitoral Temp – 34.6˚ celsius
Vulvar Temp – 33.8˚ celsius

30 Minutes

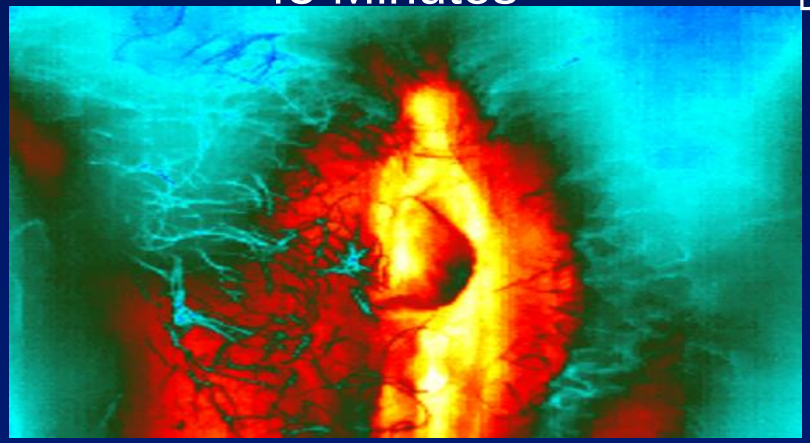


Vestibular Temp – 35.0˚ celsius
Clitoral Temp – 34.7˚ celsius
Vulvar Temp – 33.7˚ celsius

Max Change
in Temperature

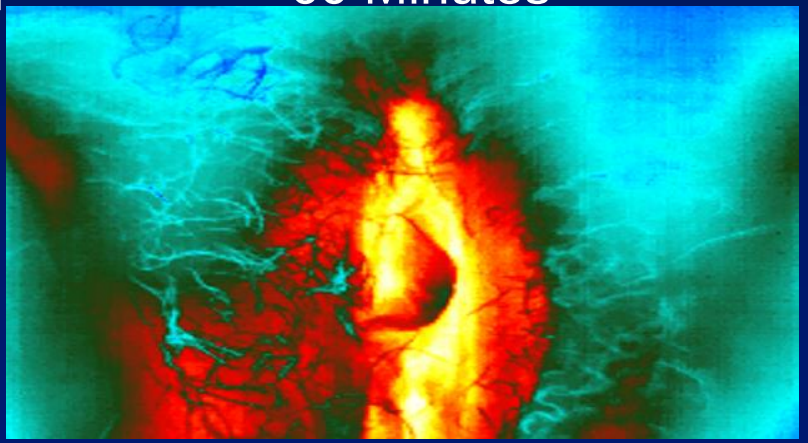
Vestibule – 0.9 ˚ C
Clitoral – 0.8 ˚ C
Vulvar – 0.5 ˚ C

45 Minutes



Vestibular Temp – 35.6˚ celsius
Clitoral Temp – 35.3˚ celsius
Vulvar Temp – 34.2˚ celsius

60 Minutes

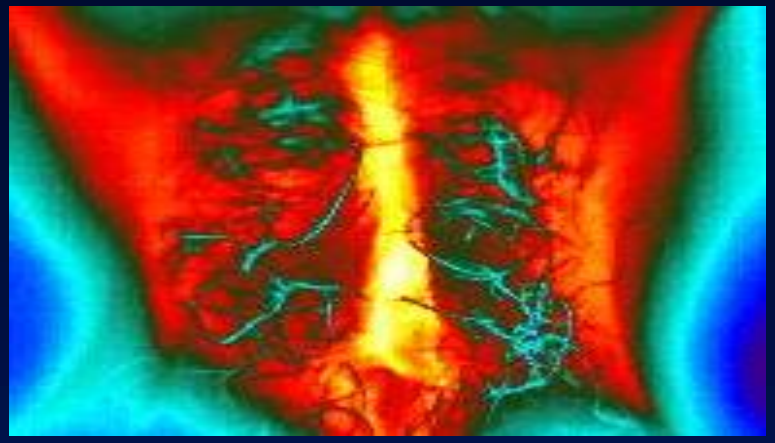


Vestibular Temp – 35.6˚ celsius
Clitoral Temp – 35.4˚ celsius
Vulvar Temp – 34.1˚ celsius

Courtesy Dr. Goldstein

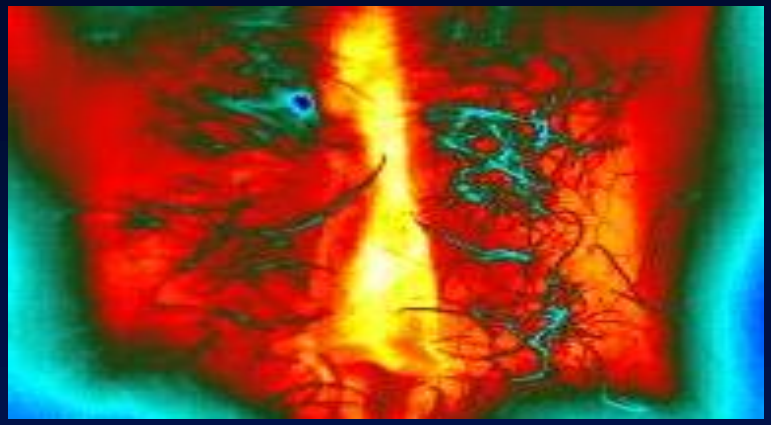
Patient 013 Study Drug A

Baseline



Vestibular Temp – 35.3˚ celsius
Clitoral Temp – 35.1˚ celsius
Vulvar Temp – 34.5˚ celsius

30 Minutes

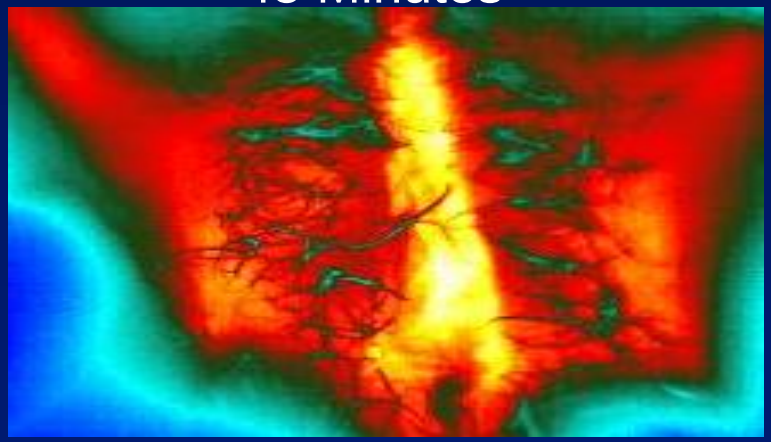


Vestibular Temp – 36.2˚ celsius
Clitoral Temp – 35.8˚ celsius
Vulvar Temp – 35.1˚ celsius

Max Change
in Temperature

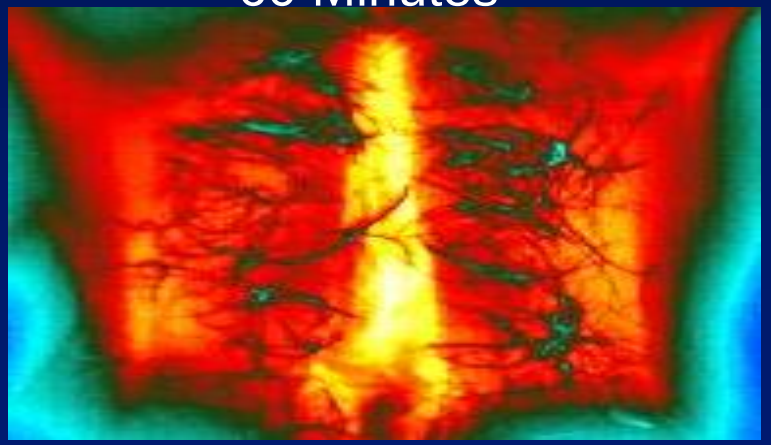
Vestibule – 1.2 ˚ C
Clitoral – 1.1 ˚ C
Vulvar – 0.9 ˚ C

45 Minutes



Vestibular Temp – 36.3˚ celsius
Clitoral Temp – 35.9˚ celsius
Vulvar Temp – 35.2˚ celsius

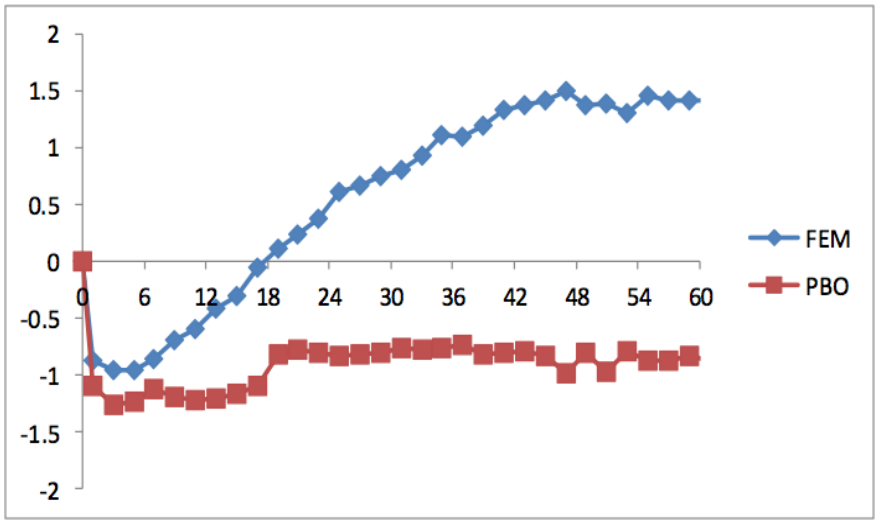
60 Minutes



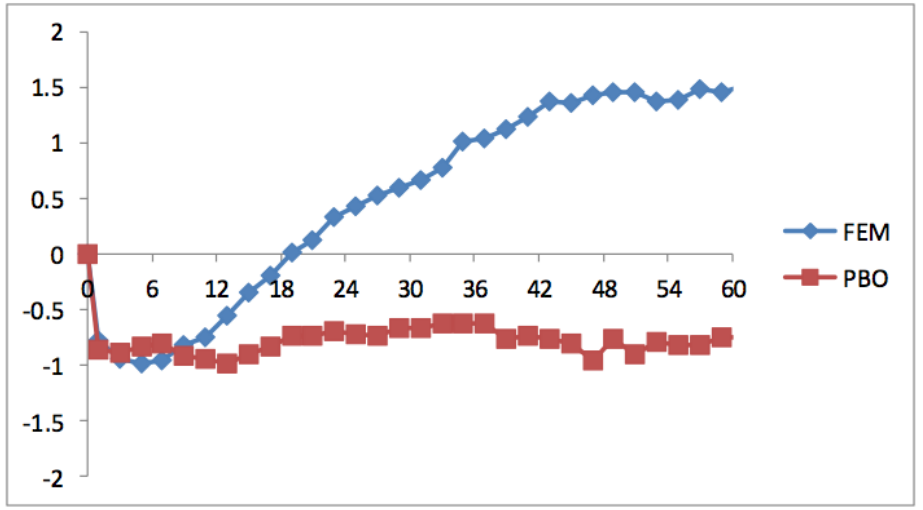
Vestibular Temp – 36.4˚ celsius
Clitoral Temp – 35.9˚ celsius
Vulvar Temp – 35.6˚ celsius

Courtesy Dr. Goldstein

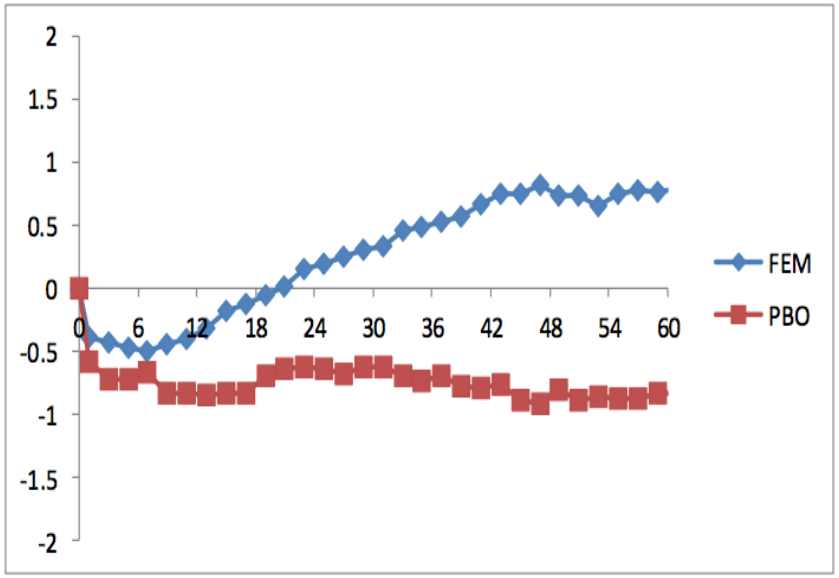
Mean Change from Baseline for Vestibule Temperature



Mean Change from Baseline for Clitoral Temperature



Mean Change from Baseline for Vulvar Temperature



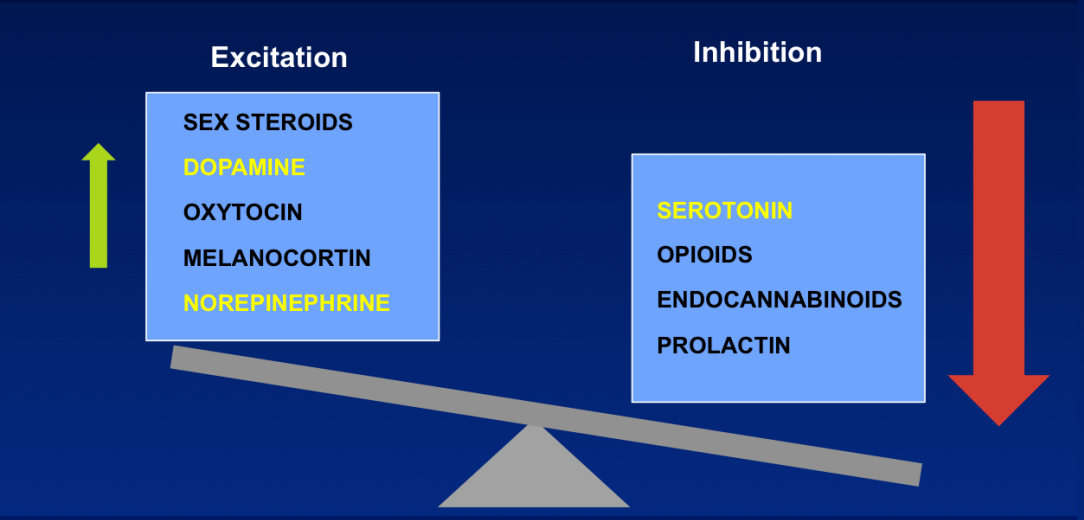
Courtesy Dr. Goldstein

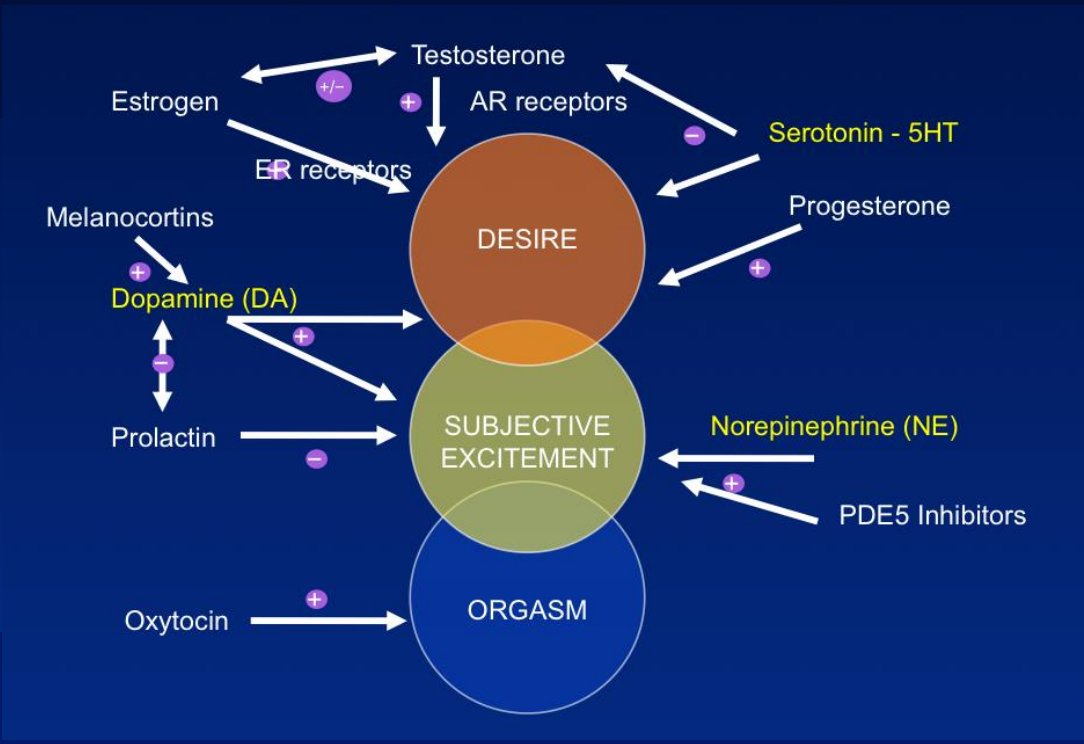
NEW NON-HORMONAL STRATEGIES

Topical Alprostadil
Flibanserin
Bremelanotide
Lybrido and Lybridos

Psychosocial-Neurobiology of Sexual Response

HSDD





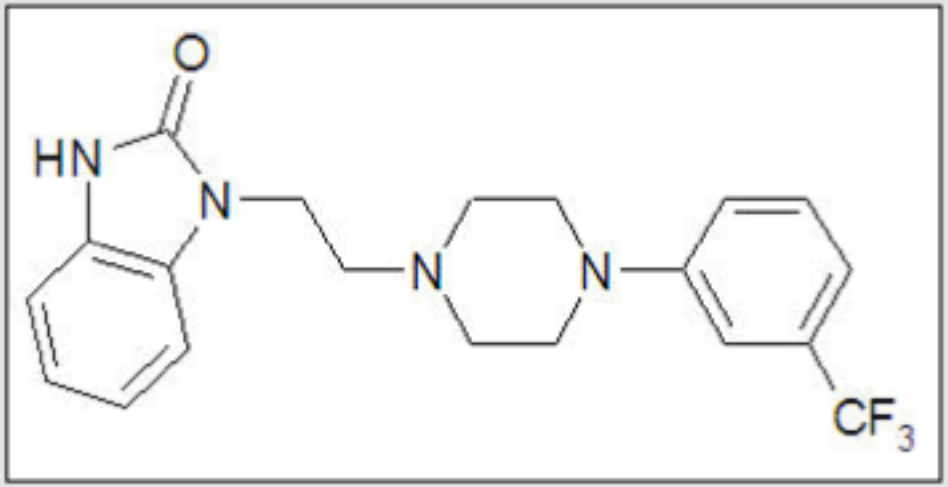
FLIBANSERIN

- Novel, non-hormonal therapy that works on key sexual pathways in the brain
- Over 10,000 women studied in trials to date
- Once daily pill taken at bedtime
- Demonstrated efficacy on measurements of desire, distress and satisfying sexual events (SSEs)
- Well tolerated safety profile. Most common side effects – dizziness, somnolence, nausea
- Flibanserin acquired by Sprout Pharmaceuticals from Boehringer Ingelheim
- Re-submission to FDA with 12 new trials scheduled for 2013

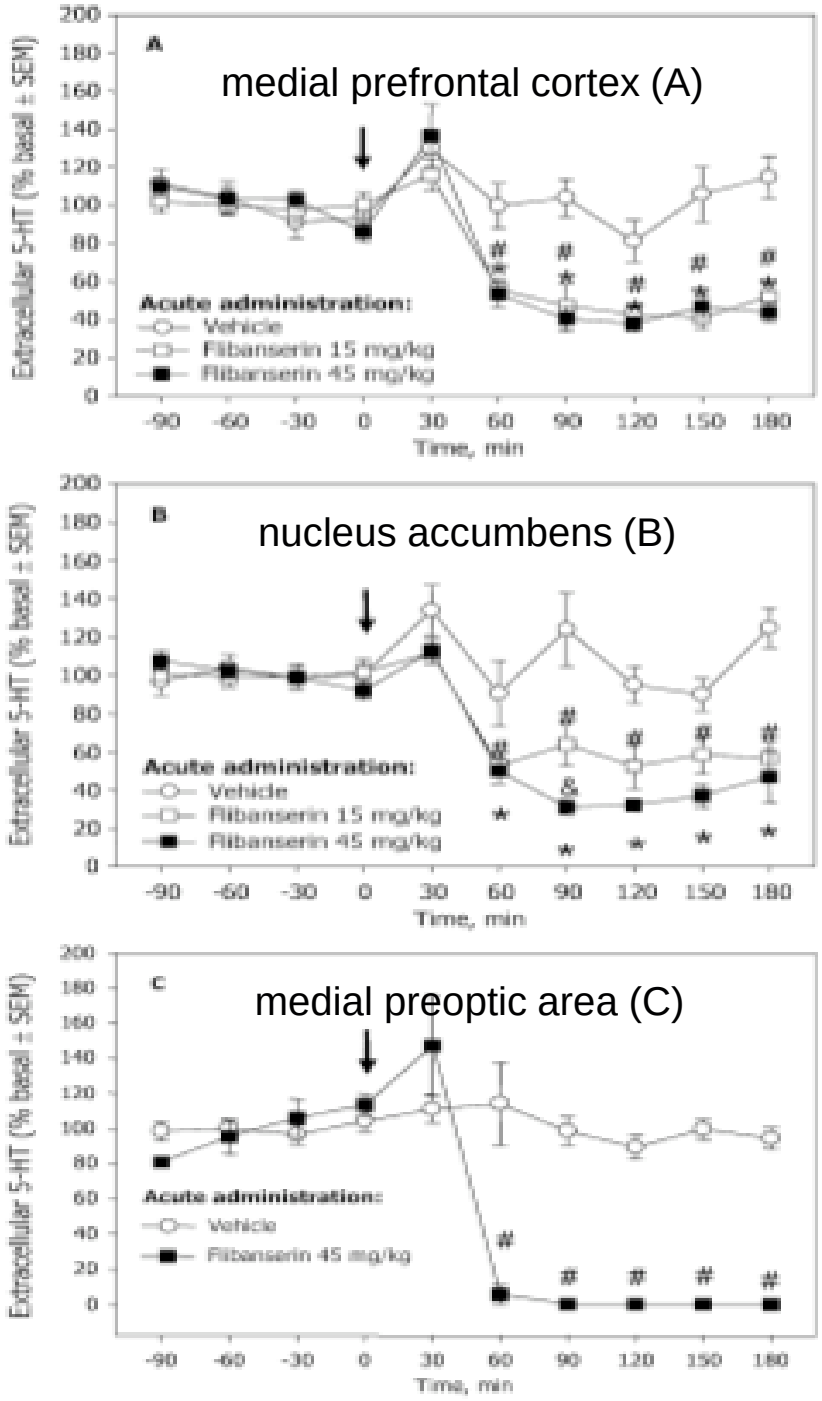
Thorp J, Simon J, Dattani D, Taylor L, Kimura T, Garcia M Jr, Lesko L, Pyke R; DAISY trial investigators. Treatment of hypoactive sexual desire disorder in premenopausal women: efficacy of flibanserin in the DAISY study. J Sex Med. 2012 Mar;9(3):793-804.

FLIBANSERIN: STRUCTURE MECHANISM OF ACTION

- Serotonin may have a role in HSDD by acting as a sexual satiety signal.
- Serotonergic agents such as the SSRIs inhibit desire, arousal, and orgasm.
- Flibanserin is a 5-HT1A receptor agonist
- Stimulating the serotonin 5-HT2A receptor has been associated with decreased sexual behavior (male rodents)
- Flibanserin is a 5-HT2A antagonist which might have pro-sexual effects.



Thorp J, Simon J, Dattani D, Taylor L, Kimura T, Garcia M Jr, Lesko L, Pyke R; DAISY trial investigators. Treatment of hypoactive sexual desire disorder in premenopausal women: efficacy of flibanserin in the DAISY study. J Sex Med. 2012 Mar;9(3):793-804.



Effect of acute administration of vehicle or flibanserin (15 or 45 mg/kg, arrow) on 5-HT levels in:

*P < 0.05 in comparison with vehicle, 15 mg/kg flibanserin-administered group

#P < 0.05 in comparison with vehicle, 45 mg/kg flibanserin-administered group

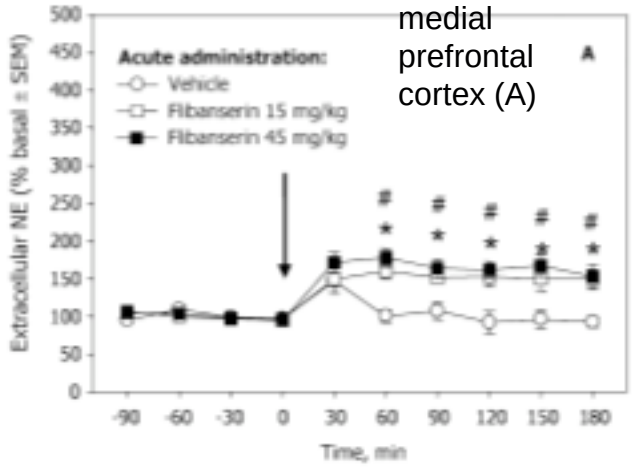
&P < 0.05, 45 mg/kg flibanserin in comparison with 15 mg/kg flibanserin-administered group

Acute and Repeated Flibanserin Administration in Female Rats Modulates Monoamines Differentially Across Brain Areas: A Microdialysis Study

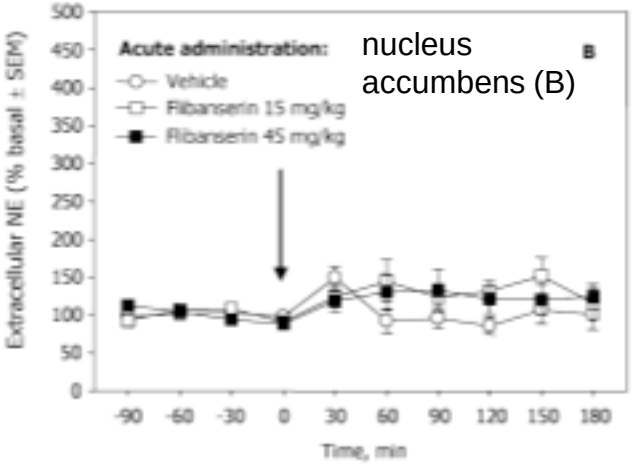
J Sex Med 2010;7:1757–1767

Kelly A. Allers, PhD,* Eliyahu Dremencov, PhD,† Angelo Ceci, PhD,* Gunnar Flik, PharmD,* Boris Ferger, PhD,* Thomas I.F.H. Cremers, PhD,† Carina Ittrich, PhD,* and Bernd Sommer, PhD*

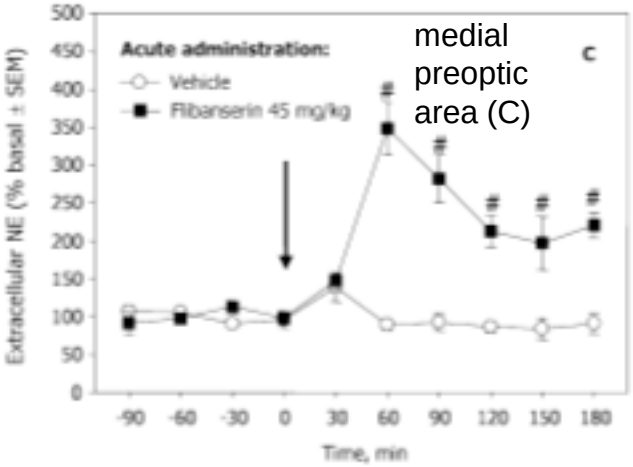
*Boehringer Ingelheim Pharma GmbH, Biberach an der Riss, Germany; †Brains On-Line B.V., Groningen, the Netherlands



medial prefrontal cortex (A)



nucleus accumbens (B)



medial preoptic area (C)

Effect of acute administration of vehicle or flibanserin (15 or 45mg/kg, arrow) on norepinephrine (NE) levels in:

*P < 0.05 in comparison with vehicle, 15 mg/kg flibanserin-administered group
#P < 0.05 in comparisonwith vehicle, 45 mg/kg flibanserin-administered group

Acute and Repeated Flibanserin Administration in Female Rats Modulates Monoamines Differentially Across Brain Areas: A Microdialysis Study

J Sex Med

Kelly A. Allers, PhD,* Eliyahu Dremencov, PhD,† Angelo Ceci, PhD,* Gunnar Flik, PharmD,* Boris Ferger, PhD,* Thomas I.F.H. Cremers, PhD,† Carina Ittrich, PhD,* and Bernd Sommer, PhD*

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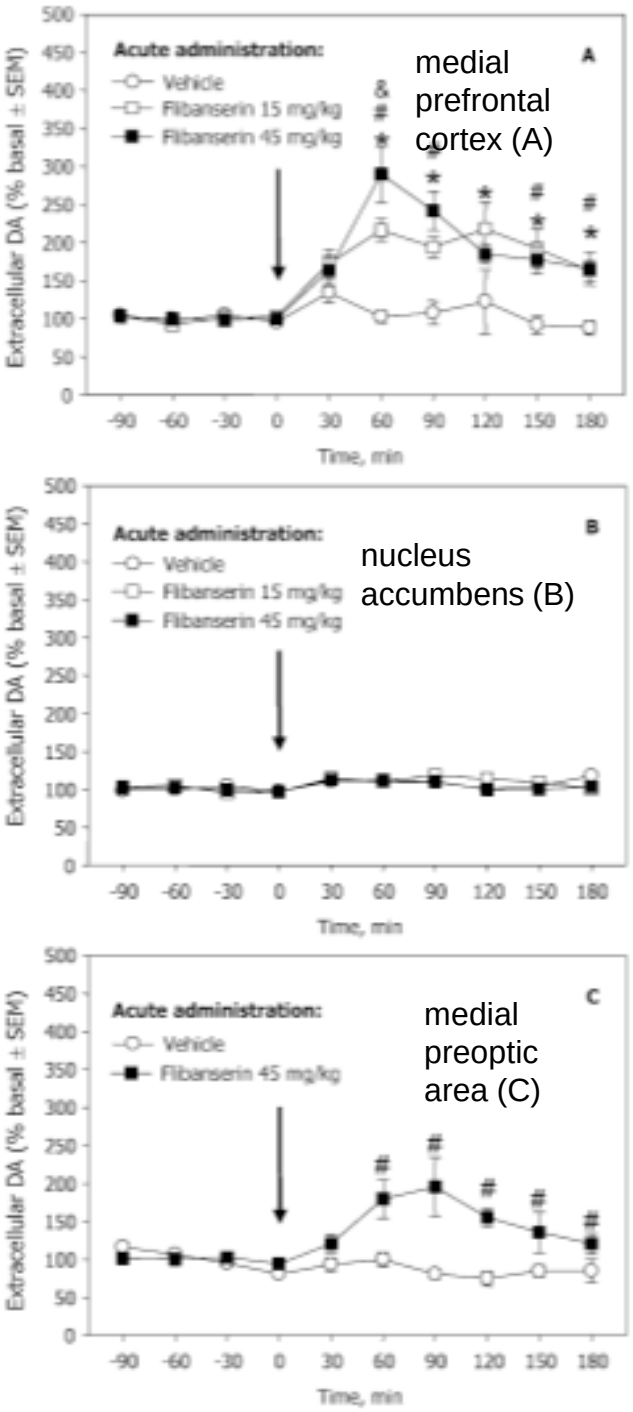


Effect of acute administration of vehicle or flibanserin(15 or 45mg/kg, arrow) on dopamine (DA) levels in:

#P < 0.05 in comparison with vehicle, 45 mg/kg flibanserin-administered group
&P < 0.05, 45 mg/kg flibanserin in comparison with 15 mg/kg flibanserin-administered group

Acute and Repeated Flibanserin Administration in Female Rats Modulates Monoamines Differentially Across Brain Areas: A Microdialysis Study

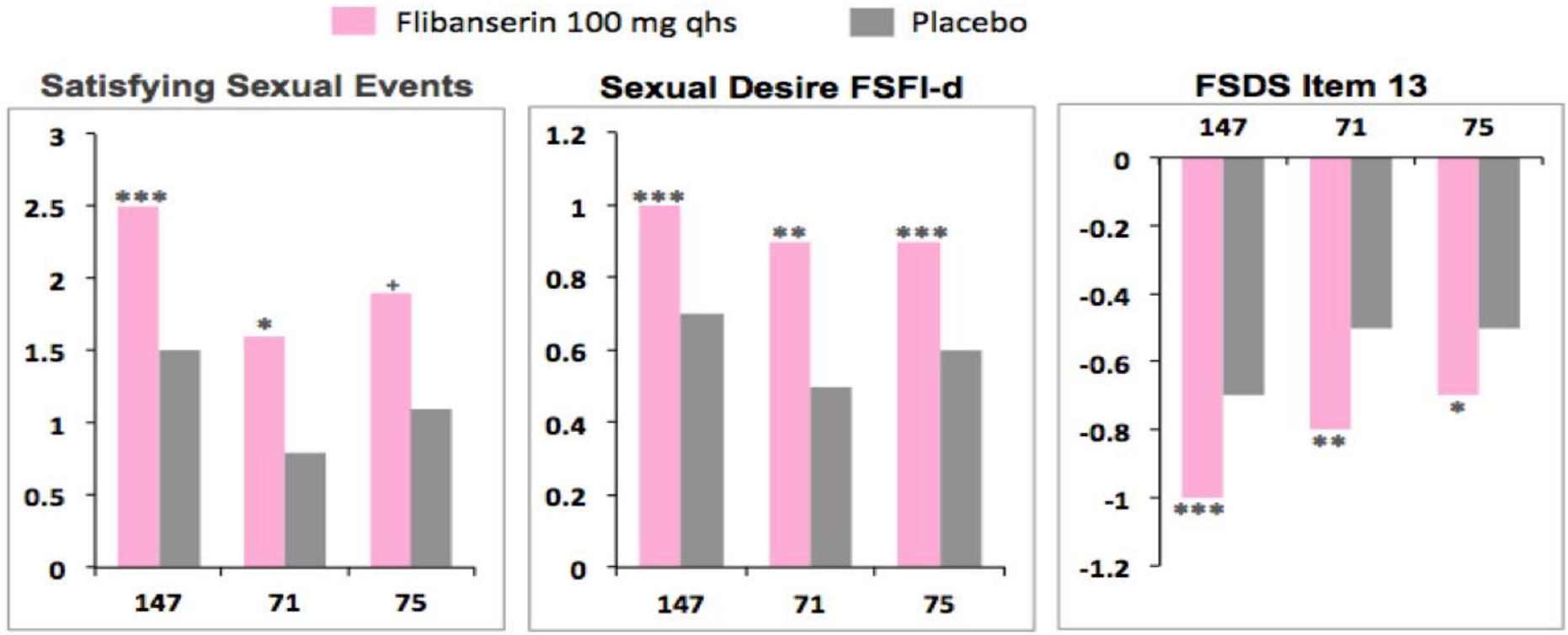
J Sex Med

Kelly A. Allers, PhD,* Eliyahu Dremencov, PhD,† Angelo Ceci, PhD,* Gunnar Flik, PharmD,* Boris Ferger, PhD,* Thomas I.F.H. Cremers, PhD,† Carina Ittrich, PhD,* and Bernd Sommer, PhD*

*Boehringer Ingelheim Pharma GmbH, Biberach an der Riss, Germany; †Brains On-Line B.V., Groningen, the Netherlands

Pharmaceutical Agents for Desire/Arousal

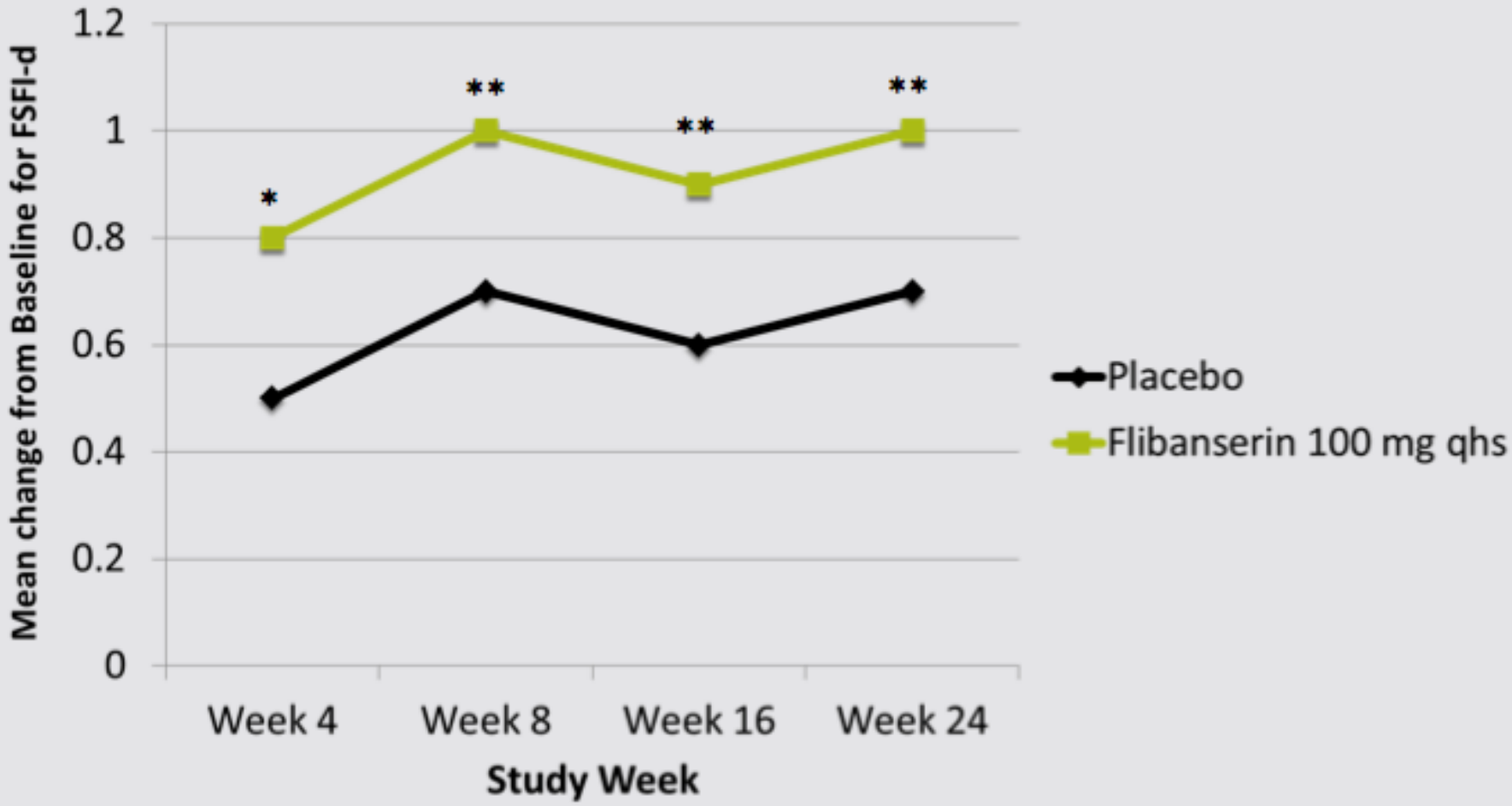
Consistent Efficacy (Change from Baseline)– Three US Phase III Clinical Trials*



*last observations carried forward at end of study; ***p<0.0001; **p<0.001; *p<0.01; +p<0.05

147 – M. Katz, L. DeRogatis, R. Ackerman, P. *Sex Med* 2013 (ePub 14 May 2013)
71 – DeRogatis LR, Komer L, Katz M, et. al. *J Sex Med* 2012 9(4): 1074-1085.
75 – Thorp J, Simon J, Dattani D, et. al. *J Sex Med* 2012, 9(3): 793-804.

CHANGE FROM BASELINE FOR FSFI-DESIRE DOMAIN (FSFI-d) – STUDY 511.147



* p = 0.0002; ** p < 0.0001 difference between placebo and flibanserin

Thorp J, Simon J, Dattani D, Taylor L, Kimura T, Garcia M Jr, Lesko L, Pyke R; DAISY trial investigators. Treatment of hypoactive sexual desire disorder in premenopausal women: efficacy of flibanserin in the DAISY study. J Sex Med. 2012 Mar;9(3):793-804.

ADVERSE EVENTS THAT OCCURRED IN > 5% OF SUBJECTS IN THE PHASE 3 NDA TRIALS AND IN STUDY 511.147

Studies 511.70, 71, 75, and 77

Preferred Term	Placebo N (%)	Flibanserin 100 mg N (%)
Number of Subjects	1360	1001
Dizziness	34 (2.5%)	120 (11.9%)
Nausea	58 (4.3%)	119 (11.9%)
Fatigue	77 (5.7%)	110 (11.0%)
Somnolence	40 (2.9%)	95 (9.5%)
Insomnia	32 (2.4%)	51 (5.1%)

Study 511.147

Preferred Term	Placebo N (%)	Flibanserin 100 mg N (%)
Number of Subjects	545	542
Dizziness	6 (1.1%)	56 (10.3%)
Nausea	12 (2.2%)	41 (7.6%)
Fatigue	18 (3.3%)	31 (5.7%)
Somnolence	19 (3.5%)	78 (14.4%)
Upper Respiratory Tract Infection	13 (2.4%)	28 (5.2%)

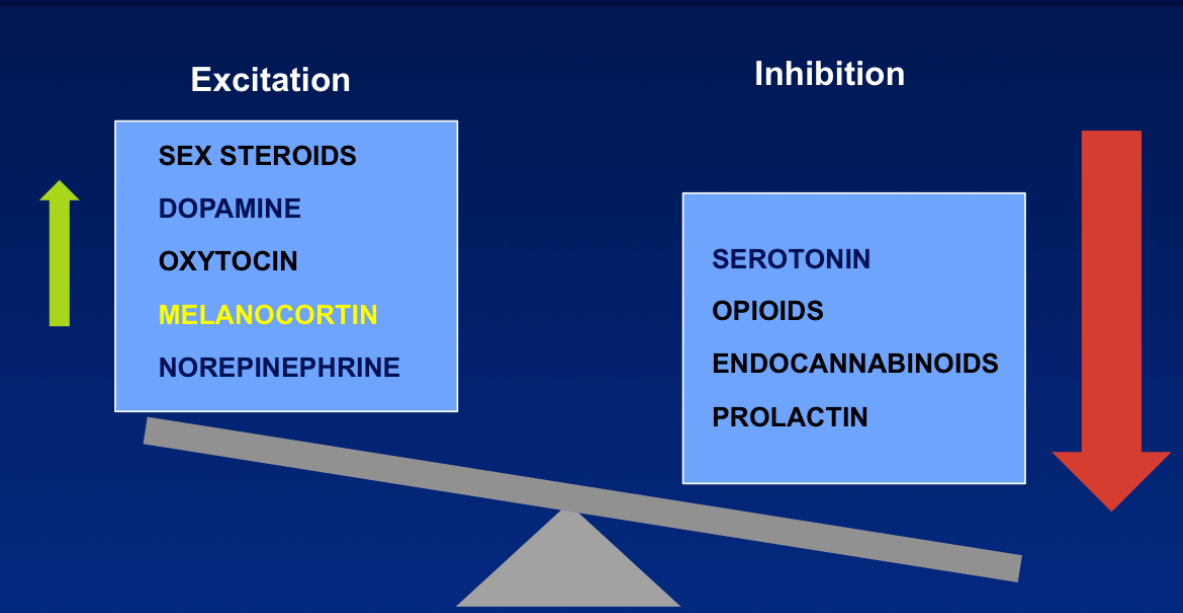
Thorp J, Simon J, Dattani D, Taylor L, Kimura T, Garcia M Jr, Lesko L, Pyke R; DAISY trial investigators. Treatment of hypoactive sexual desire disorder in premenopausal women: efficacy of flibanserin in the DAISY study. J Sex Med. 2012 Mar;9(3)

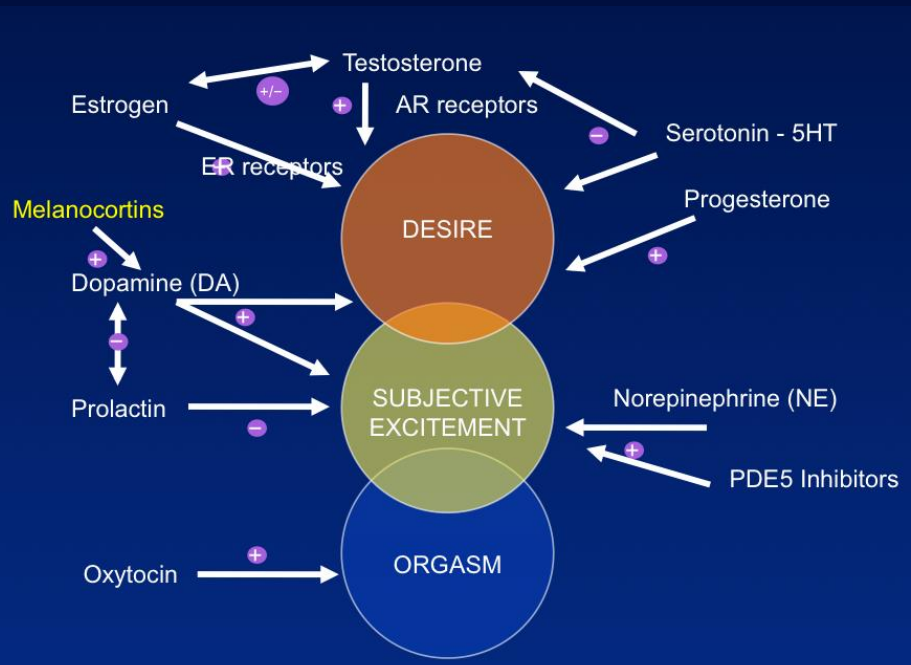
NEW NON-HORMONAL STRATEGIES

Topical Alprostadil
Flibanserin
Bremelanotide
Lybrido and Lybridos

Psychosocial-Neurobiology of Sexual Response

HSDD



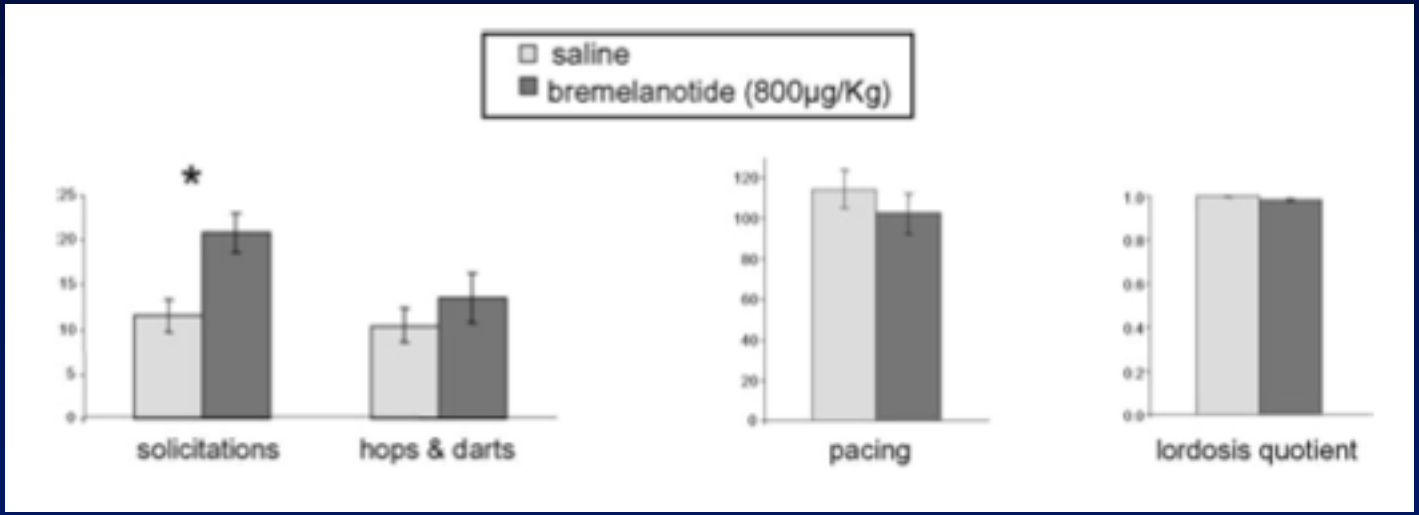


Bremelanotide: An Overview of Preclinical CNS Effects on Female Sexual Function

J Sex Med 2007;4(suppl 4):269–279

James Pfaus, PhD,* François Giuliano, MD, PhD,† and Hélène Gelez, PhD‡

*Concordia University—Psychology, Montreal, Canada; †Raymond Poincaré Hospital—Department of Physical Medicine and Rehabilitation, Garches, France; ‡Pelvipharm—Domaine CNRS, Gif-sur-Yvette, France



Bremelanotide increased measures of solicitation in female rats, without altering pacing or lordosis, following both peripheral (subcutaneous) administration or infusions directly into the lateral ventricles or medial preoptic area (mPOA)

An Effect on the Subjective Sexual Response in Premenopausal Women with Sexual Arousal Disorder by Bremelanotide (PT-141), a Melanocortin Receptor Agonist

J Sex Med 2006;3:628–638

Lisa E. Diamond, PhD,* Dennis C. Earle, BS,* Julia R. Heiman, PhD,† Raymond C. Rosen, PhD,‡ Michael A. Perelman, PhD,§ and Ronald Harning, PhD*

*Palatin Technologies, Inc., Cranbury, NJ, USA; †Kinsey Institute, Indiana University, Bloomington, IN, USA; ‡Department of Psychiatry, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, Piscataway, NJ, USA; §Weill Medical College of Cornell University, Psychiatry, Reproductive Medicine, and Urology, NY, USA

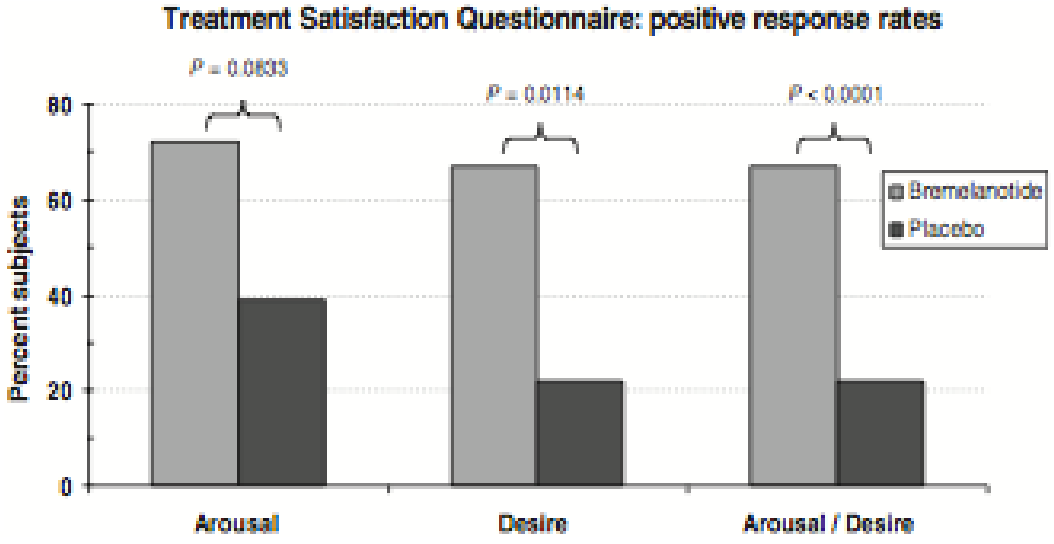


Figure 1 Positive response rates of subjects after treatment with bremelanotide and after treatment with placebo to Treatment Satisfaction Questionnaire questions: "Did you have any feelings of genital arousal?" and "Did you experience any sexual desire?," and response rate of subjects who reported a positive response to both questions.

Clinical Application of CNS-Acting Agents in FSD

J Sex Med 2007;4(suppl 4):280–290

Michael A. Perelman, PhD

NY Weill Medical College of Cornell University, New York, NY, USA

Trials completed to date, primary adverse effects reported to be associated with bremelanotide were nausea, vomiting, flushing, headache, nasal congestion, and transient (1–3 hours post single dose) increases in systolic blood pressure

There may be potential, for dose reduction, to improve the adverse event profile while maintaining good efficacy outcome

Blunt Trauma to the Perineum - Female

Women's Bike Seats: A Pressing Matter for Competitive Female Cyclists

J Sex Med 2011;8:3144–3153

Marsha K. Guess, MD,* Sarah N. Partin, BA,† Steven Schrader, PhD,‡ Brian Lowe, PhD,‡ Julie LaCombe, MD,§ Susan Reutman, PhD,‖ Andrea Wang, MD,¶ Christine Toennis, BS,‖ Arnold Melman, MD,** Madgy Mikhail, MD,†† and Kathleen A. Connell, MD*

Ergonomics of 2 Bicycle Saddles

Prof. Dr. Ingo Froböse, Prof. Dr. Luc Baeyens, Kim Tofaute et.al.

Pressure at the Pudendal Area in Women of a Normal Saddle with Gel and of a Saddle with a Hole

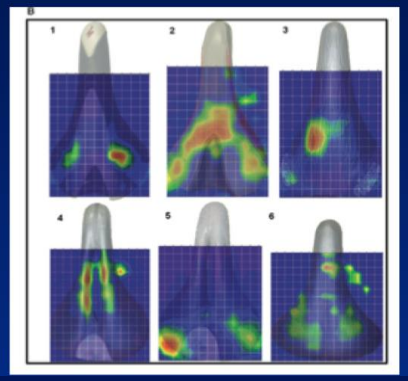


Table 4 Multivariable regression model of mean total saddle pressure

Final model for mean total saddle pressure ($F_{(3,\ 37)} = 24.53$, $R^2 = 0.6654$, N = 41)

Predictor variable	Coefficient (95% CI)	*P* value
BMI	0.56 (0.27, 0.86)	<0.000
Saddle width	−2.41 (−3.62, −1.19)	<0.000

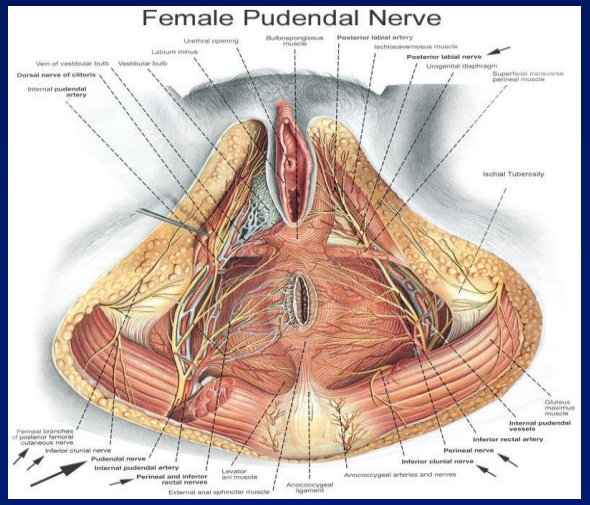
CI = confidence interval; BMI = body mass index.

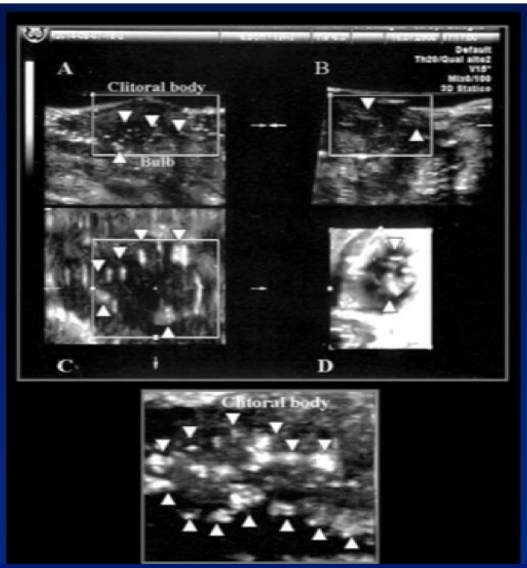
Ultrasonographic and Doppler Findings of Subclinical Clitoral Microtraumatisms in Mountain Bikers and Horseback Riders

J Sex Med 2009;6:464–468

Cesare Battaglia, MD, PhD,* Rossella Elena Nappi, MD,† Fulvia Mancini, MD, PhD,* Arianna Cianciosi, MD,* Nicola Persico, MD,* and Paolo Busacchi, MD*

*Department of Obstetrics and Gynaecology, University of Bologna, Bologna, Italy; †Department of Obstetrics and Gynaecology, University of Pavia Research Centre for Reproductive Medicine, Pavia, Italy

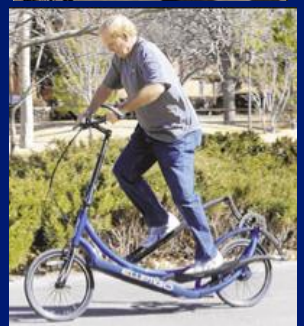




Goldstein I, Alexander JL. Practical Aspects in the Management of Vaginal Atrophy and Sexual Dysfunction in Perimenopausal and Postmenopausal Women. J Sex Med 2005 Sep(s3):154-165.

How to Prevent Blunt Trauma to the Perineum – Female/Male While Bicycle Riding

Sex-Friendly Alternative to Bicycling



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Derogatis LR, Komer L, Katz M, Moreau M, Kimura T, Garcia M Jr, Wunderlich G, Pyke R; VIOLET Trial Investigators. Treatment of hypoactive sexual desire disorder in premenopausal women: efficacy of flibanserin in the VIOLET Study. J Sex Med. 2012 Apr;9(4):1074-85.

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