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Sexological Clinic

Rigshospitalet

REGION

New Pharma compounds for FSD

Central acting agents

Annamaria Giraldi, Professor, MD, Ph.d

Sexological Clinic, Rigshospitalet, University of Copenhagen, Denmark

Disclosures

- Eli Lilly - lecturer
- Servier - lecturer
- Apricus BioScience – Advisory board
- Emotional Brain – Advisory Board
- Boehringer Ingelheim - grant

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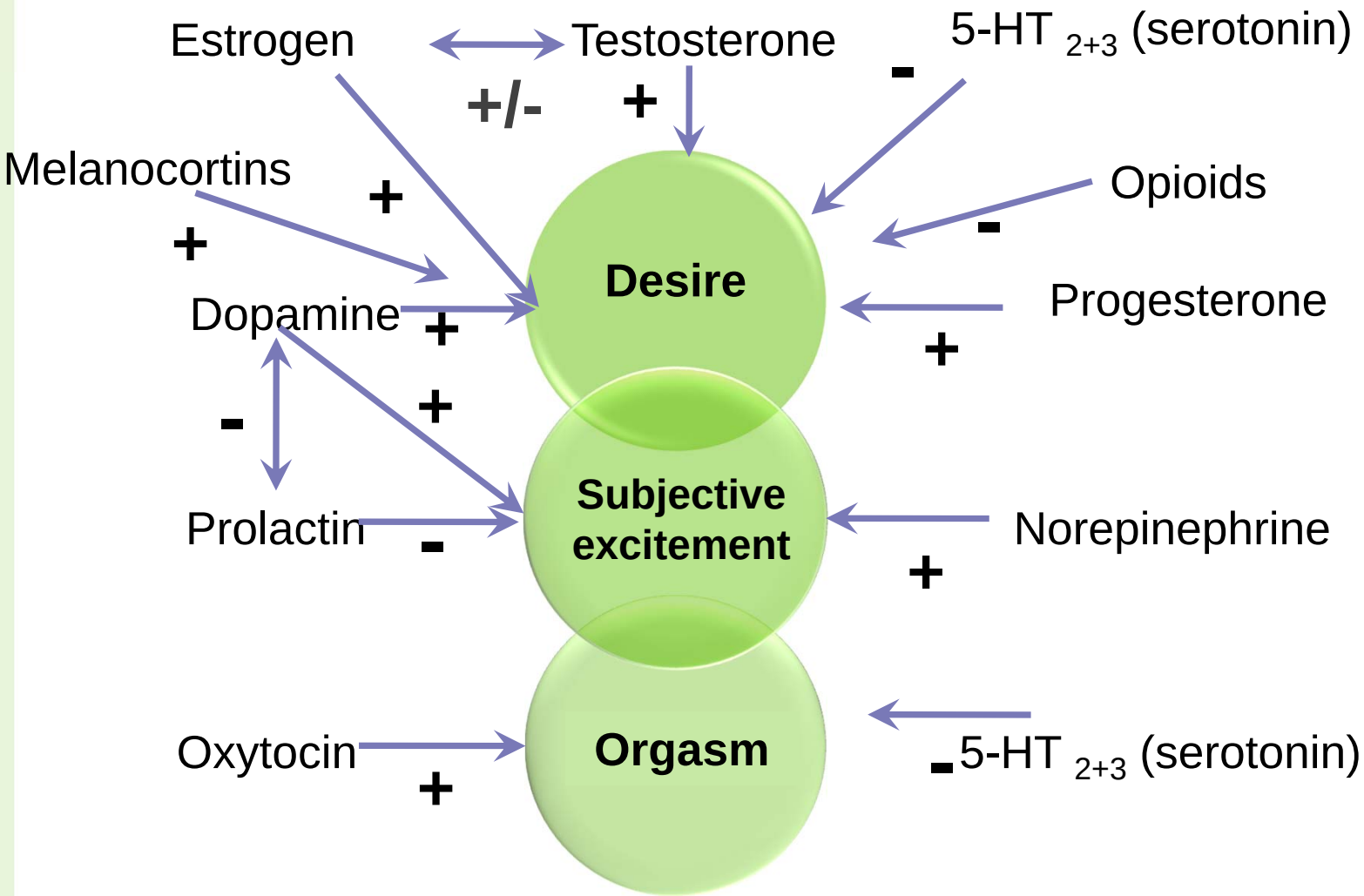
Central effects of neurotransmitters and hormones on sexual functioning

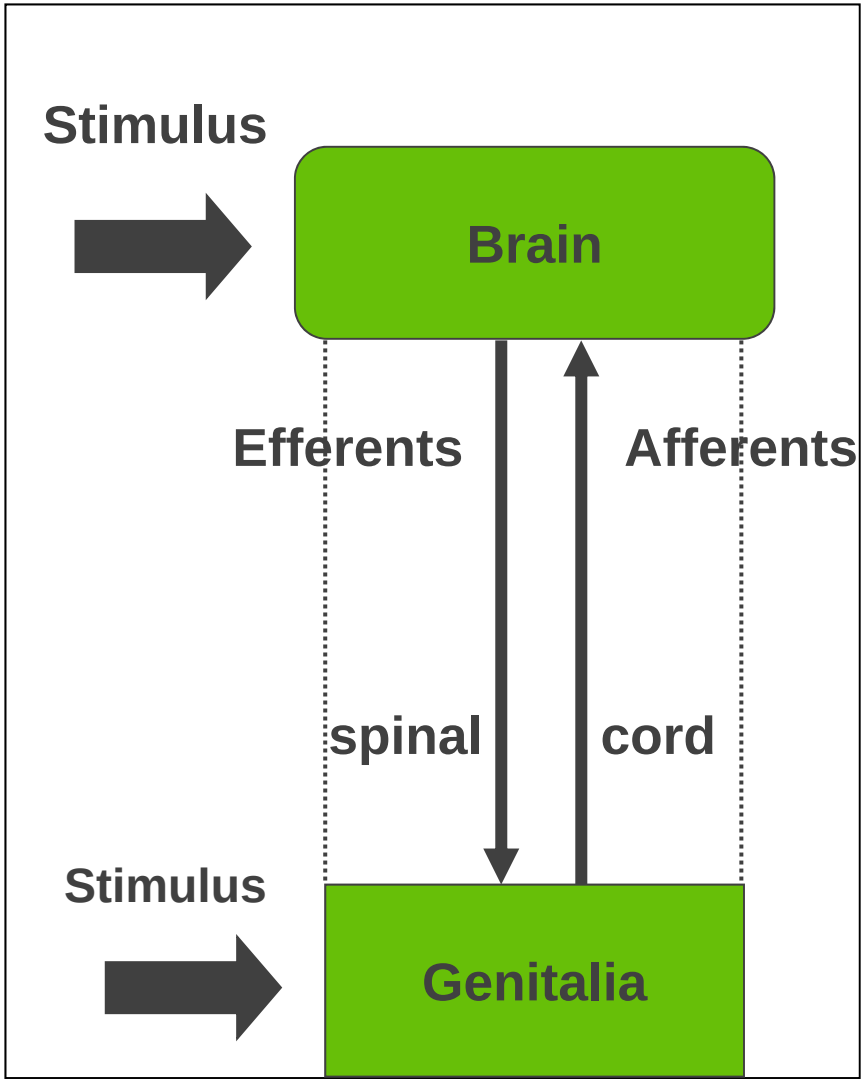


Clayton A. JSM 2007;4260-268

Sexual response – an interaction between brain and genitals

Efferent signals from brain activate arousal changes in genitalia

Afferent signals from genitalia feed information to brain to activate further efferent output



Serotonergic system - effect on sexuality

- Activation of the 5HT2 and 5HT3 serotonergic receptor inhibits sexual desire, ejaculation and orgasm
- Activation of the 5HT1A serotonergic receptor decrease the 5HT inhibition with an beneficial effect on desire

Kennedy & Rizvi J.Clin:Psychopharmacol. 2009:29
Bijlsma et al. Biochem.Behav. 2004:121;88

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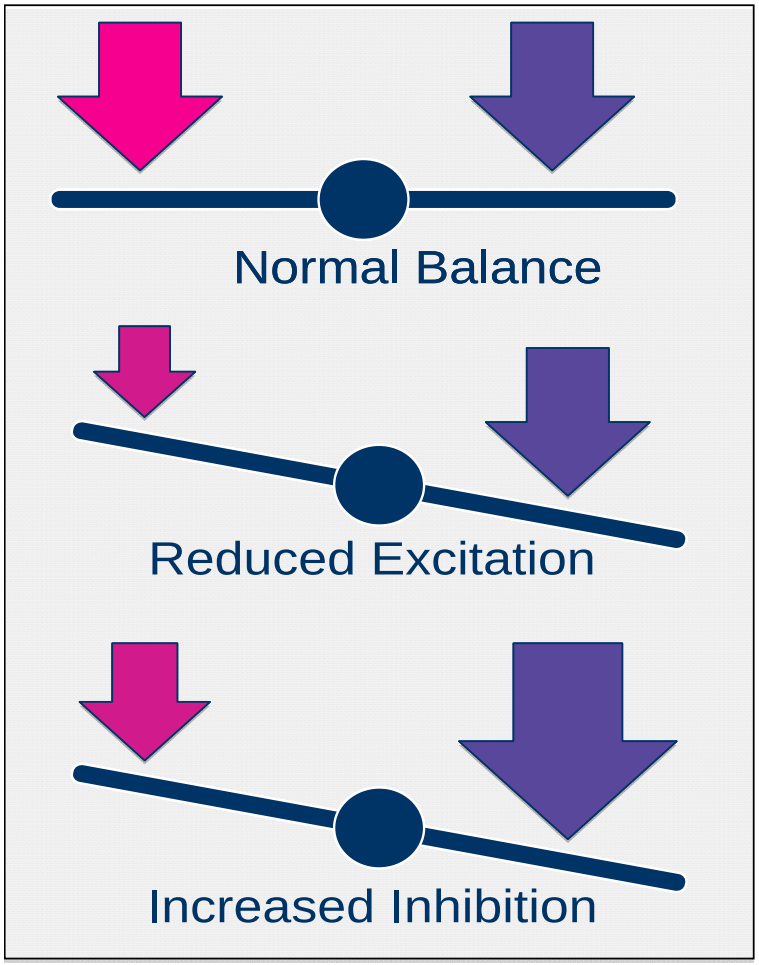
Pathophysiology of low sexual desire seen in HSDD: Hypothesis

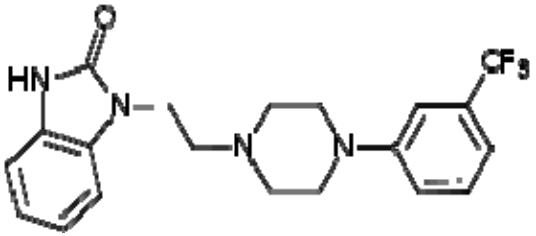


Pfaus JG. J Sex Med. 2009;6:1506-33

FLIBANSERIN

Flibanserin®

- A 5-HT1A serotonin receptor agonist and a 5-HT2A serotonin receptor antagonist



- In animals shown to reduce the 5-HT and increase noradrenaline and dopamine in the prefrontal cortex

Invernizzi et al. Br.J.Pharmacol. 2003:139;1281-88
Thorp et al. BJOG 2014:121;1328-32

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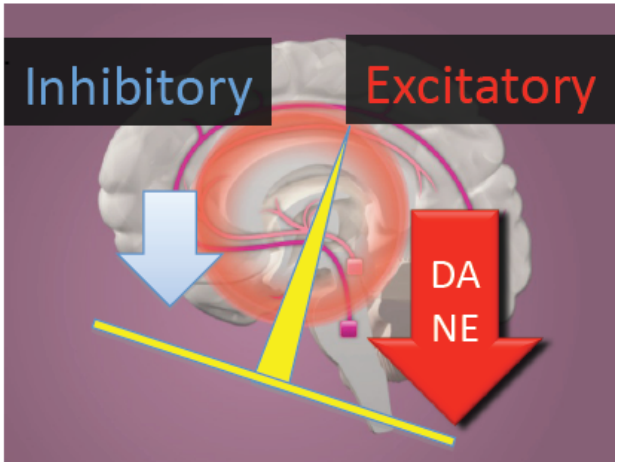
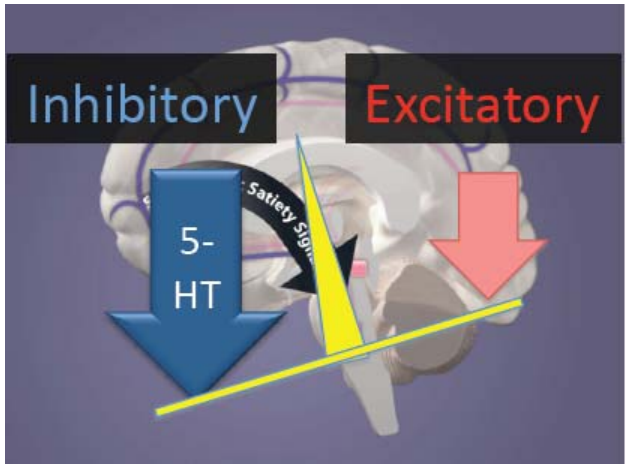
What is Desire in the brain?

- Balance between excitatory activity driven by DA (desire) and NE (arousal) and inhibitory activity driven by 5-HT (satiety) is necessary for a healthy sexual response.
- This balance may be disrupted in sexual dysfunction
- By selectively modulating these neurotransmitters in a regionally specific way, flibanserin may act to re-balance these systems in HSDD women

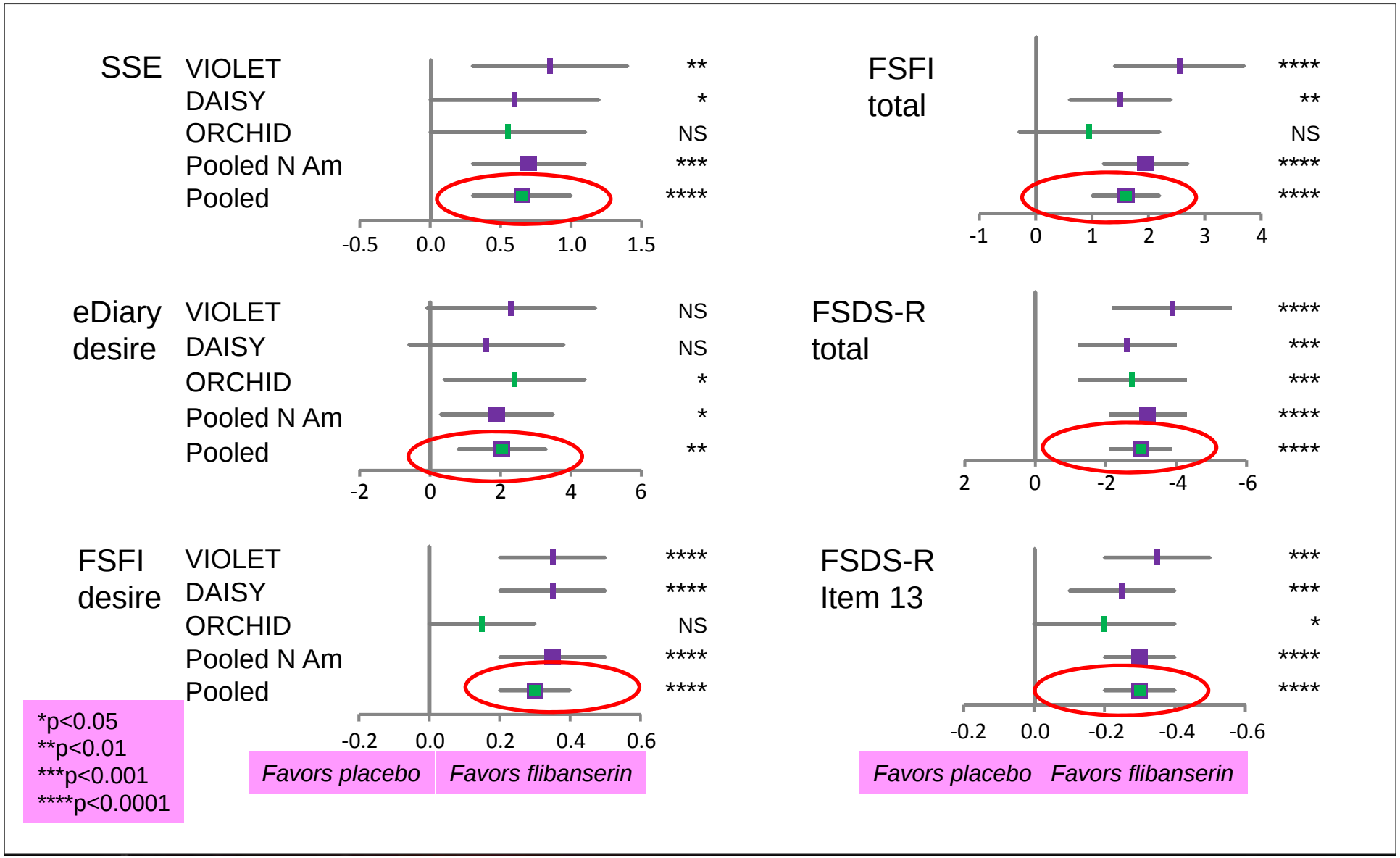




Pfaus JG. J Sex Med. 2009;6:1506-33

Flibanserin 100 mg qhs vs placebo. Premenopausal women with HSDD

Mean (95% CI) treatment difference



Postmenopausal women (n=949)

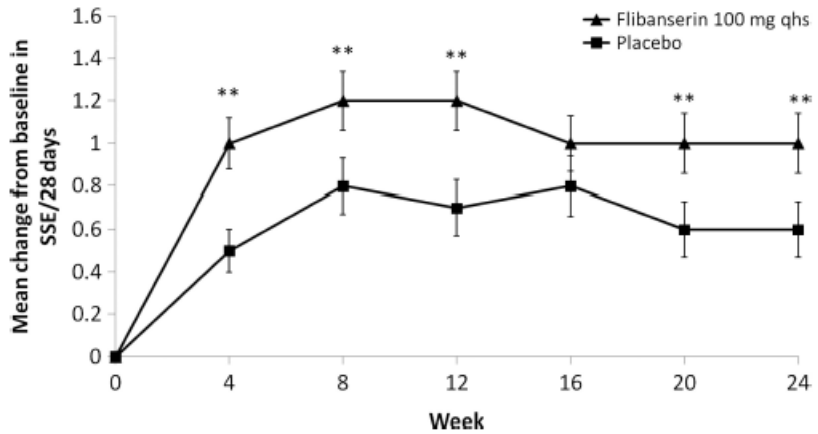


FIG. 2. Change in the number of satisfying sexual events (SSEs) from baseline to week 24. Last-observation-carried-forward analysis on the full analysis set. Data are presented as means; error bars denote SE. $^{**}P < 0.01$ for flibanserin 100 mg at bedtime (qhs) versus placebo.

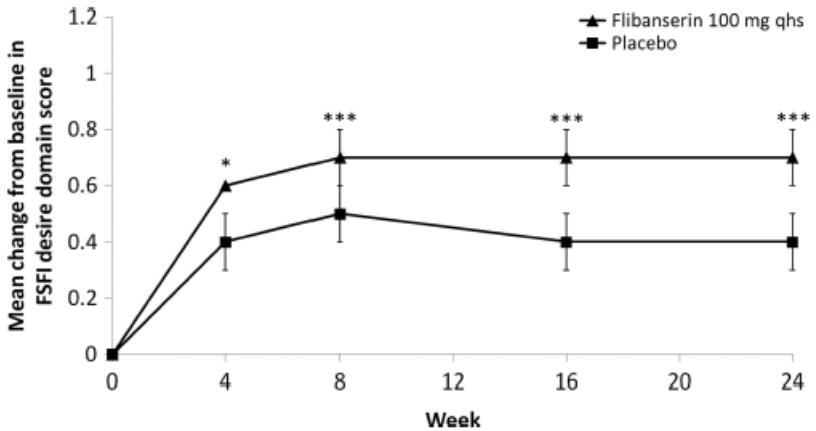


FIG. 3. Change in Female Sexual Function Index desire domain (FSFI-d) score from baseline to week 24. Last-observation-carried-forward analyses on the full analysis set. Data are presented as adjusted (least squares) means; error bars denote SE. $^{*}P < 0.05$, $^{***}P < 0.001$ for flibanserin 100 mg at bedtime (qhs) versus placebo.

Satisfying sexual event **Female Sexual Function Desire Index**

Simon et al. J.N. Am.Menopause Soc.2013:21;633-40

Postmenopausal women (n=949)

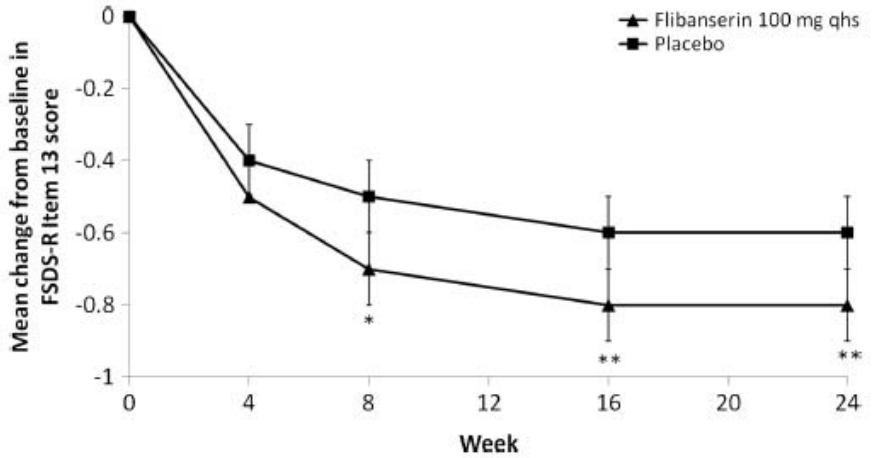


FIG. 4. Change in Female Sexual Distress Scale—Revised (FSDS-R) item 13 score from baseline to week 24. Data are presented as adjusted (least squares) means; error bars denote SE. Last-observation-carried-forward analysis on the full analysis set. $*P < 0.05$, $**P < 0.01$ for flibanserin 100 mg at bedtime (qhs) versus placebo.

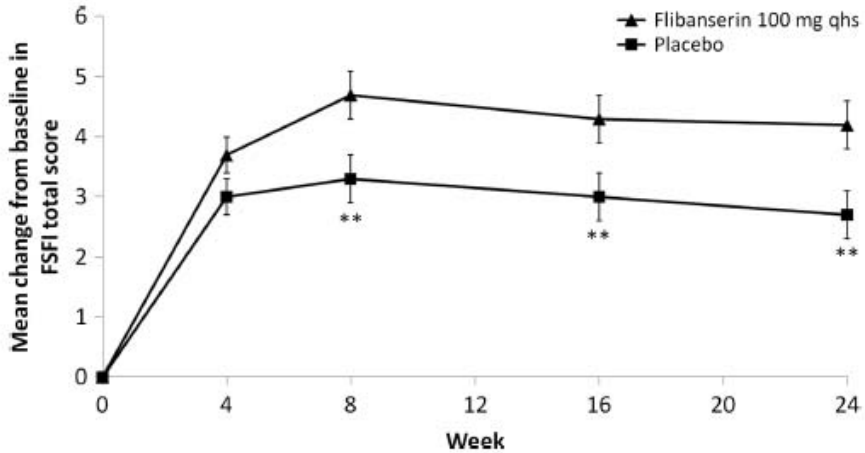


FIG. 6. Change in Female Sexual Function Index (FSFI) total score from baseline to week 24. Data are presented as adjusted (least squares) means; error bars denote SE. Last-observation-carried-forward analysis on the full analysis set. $***P < 0.01$ for flibanserin 100 mg at bedtime (qhs) versus placebo.

Female Sexual Distress Scale

Female Sexual Function Index

Simon et al. J.N. Am.Menopause Soc.2013:21;633-40

BREMELANOTIDE

Melanocortin system

- Melanocortins are believed to act via acticvation of the melanocortin recoptor on dopaminergic neurons located in hypothalamic center and thereby stimulate sexual desire and arousal

Uckert et al. Expert Opinio Investg. Drugs 2014:23.

- Bremelanotide is a melanocortin 1 & 4 receptor agonist

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

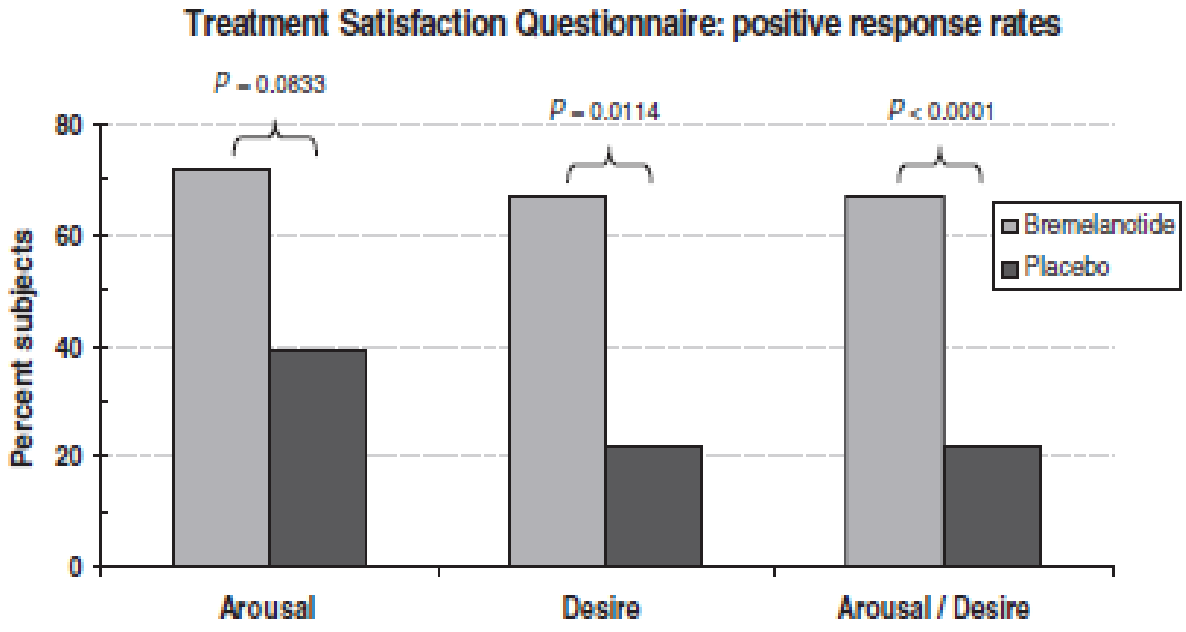


Figure 1 Positive response rates of subjects after treatment with bremelanotide and after treatment with placebo to Treatment Satisfaction Questionnaire questions: "Did you have any feelings of genital arousal?" and "Did you experience any sexual desire?," and response rate of subjects who reported a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

N=18, visual sexual stimulation

Diamond et al. JSM 2006:3;628-38

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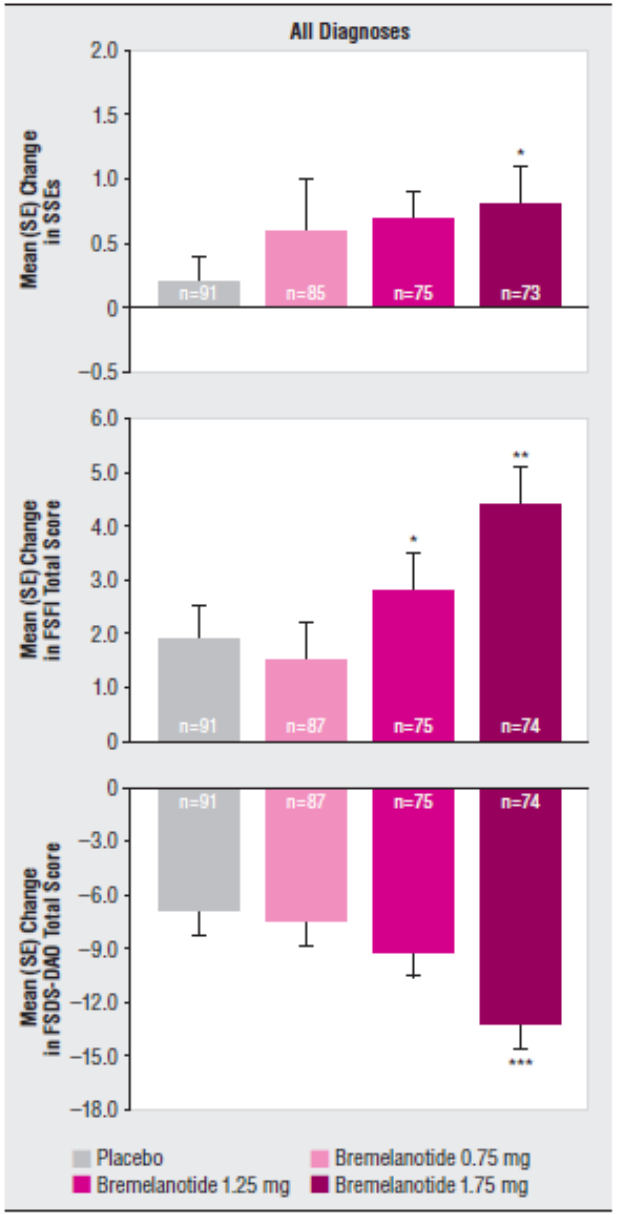
Bremelanotide (melanocortine peptide) for HSDD/FSAD

P.N S.C dosing
45 minutes before sexual activity

Jordan et al. ISSWSH, New Orleans, 2013

Figure 2. Mean (SE) Change in SSEs, FSFI Total Score, and FSDS-DAO Total Score From DB Baseline to EOS Among At-Home Users of DB Study Drug



*$p<0.05$; **$p<0.01$; ***$p<0.001$; Van Elteren test.
EOS, end of study; SE, standard error.

LYBRIDO/ LYBRIDOS

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Dual Control Model

Excitation

Inhibition

Psychological
Neurophysiological
Cultural
Social

Lybrido

- Women with low desire (HSDD), low sexual motivation and insensitivity to sexual cues
- Sublingual testosterone (0.5 mg) and sildenafil (50 mg)
- Increase sensitivity to external and internal sexual cues and the physiological sexual response

Lybridos

- Women with HSDD induced by dysfunctional sexual inhibition mechanism
- Sublingual testosterone (0.5 mg) and 5-HT1A receptor agonist (buspirone 10 mg)
- Increase sexual motivaiton and inhibit overactive sexual inhibition

Bloemers J et al. JSM. 2013:10:791

Lybrido: T + PDE-5 inhibitor. Effect on sexual satisfaction

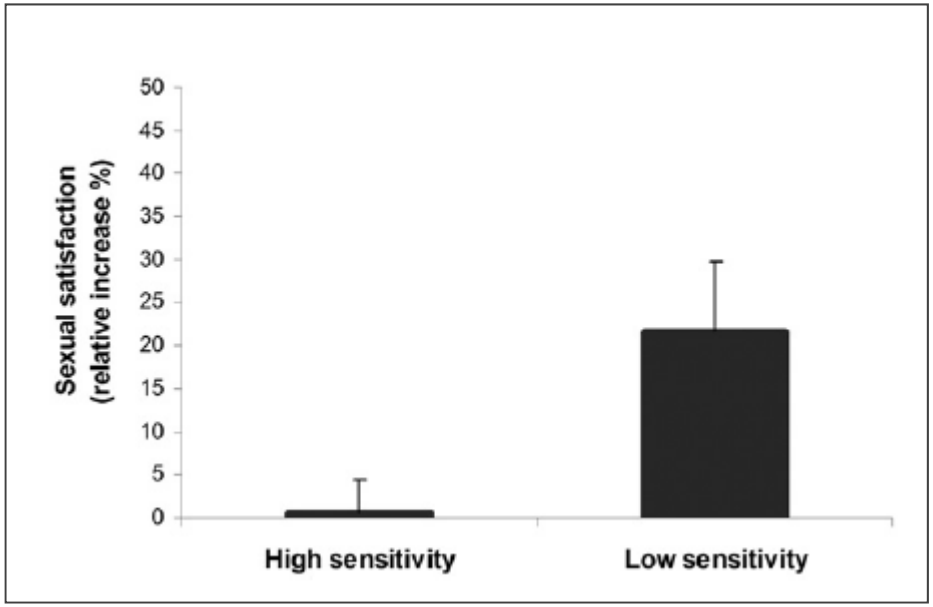
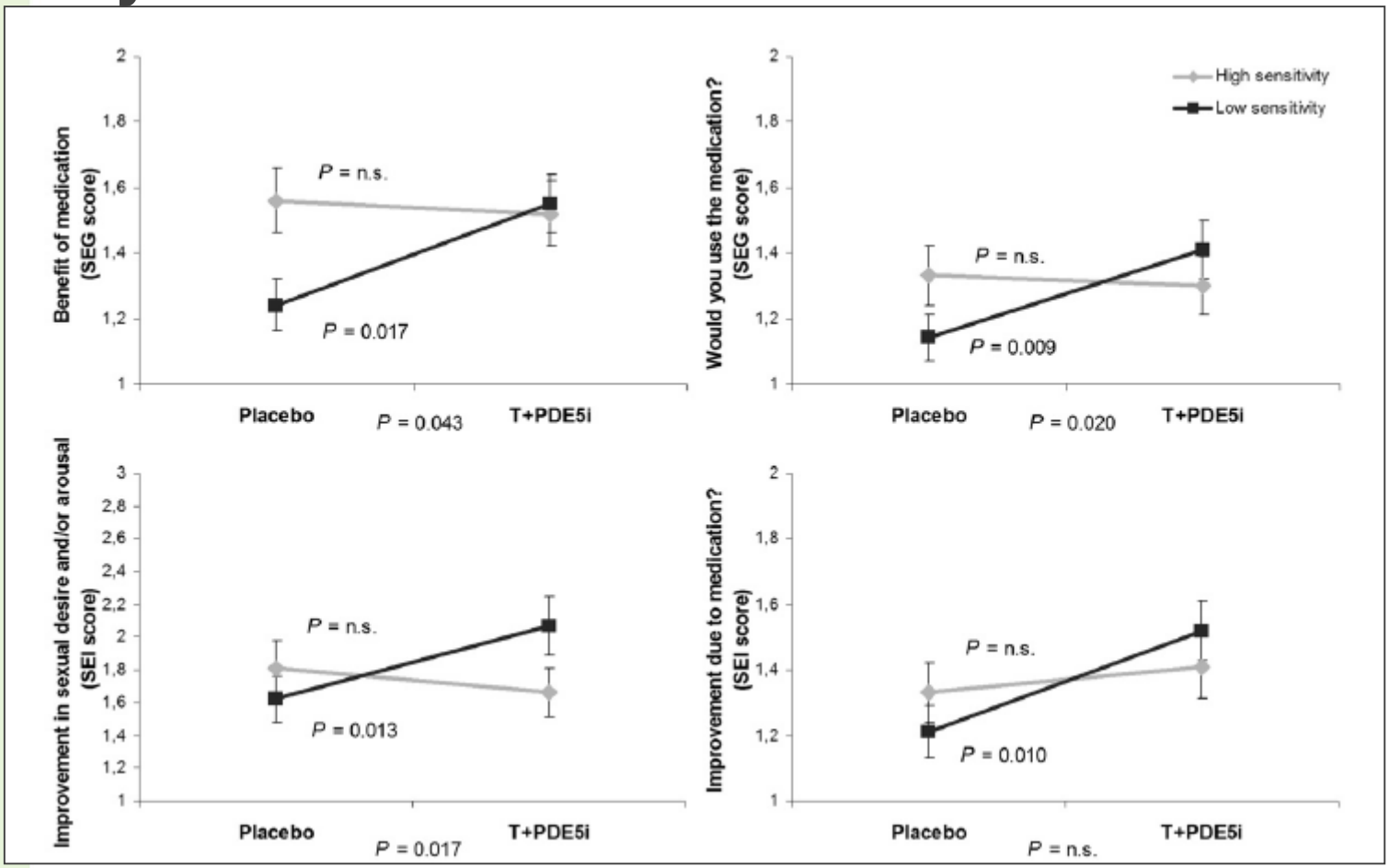


Figure 6 Bedroom experiment: The relative increase in sexual satisfaction following T+PDE5i treatment. In women with a relative insensitivity for sexual cues treatment with T+PDE5i increased sexual satisfaction with 22%, relative to placebo, while in the high sensitive group there was no such relative increase

Poels S JSM 2013:10;810

Lybrido



Effect of T+PDE-5 inhibitor relative to placebo on the subjective indices of subjective evaluation. Significant effect of drug vs. Placebo and between groups

Poels S JSM 2013:10;810

Lybrido

- Women with low desire (HSDD), low sexual motivation and insensitivity to sexual cues
- Sublingual testosterone (0.5 mg) and sildenafil (50 mg)
- Increase sensitivity to external and internal sexual cues and the physiological sexual response

Lybridos

- Women with HSDD induced by dysfunctional sexual inhibition mechanism
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Bloemers J et al. JSM. 2013:10:791

Lybridos. T + 5-HT1A agonist. Effect on sexual satisfaction

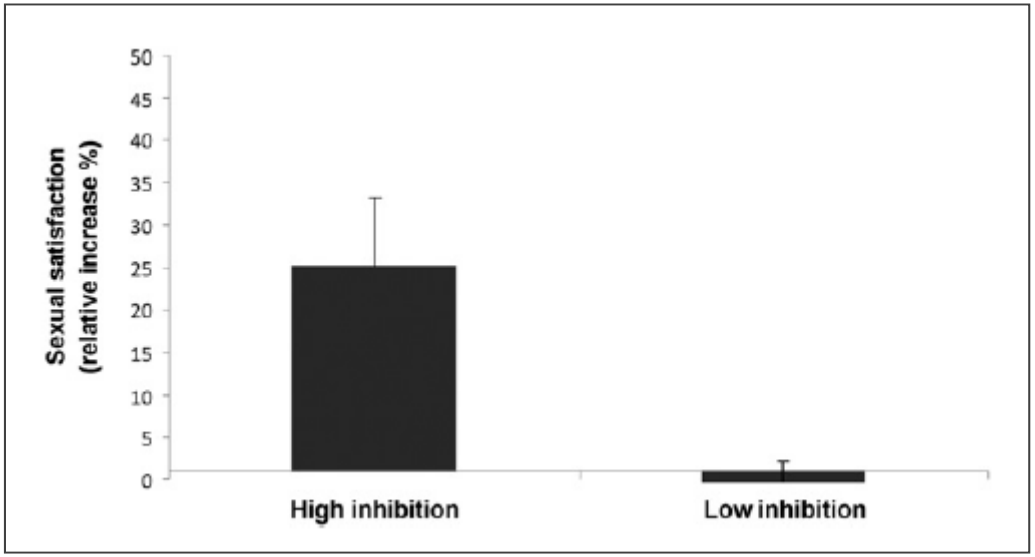
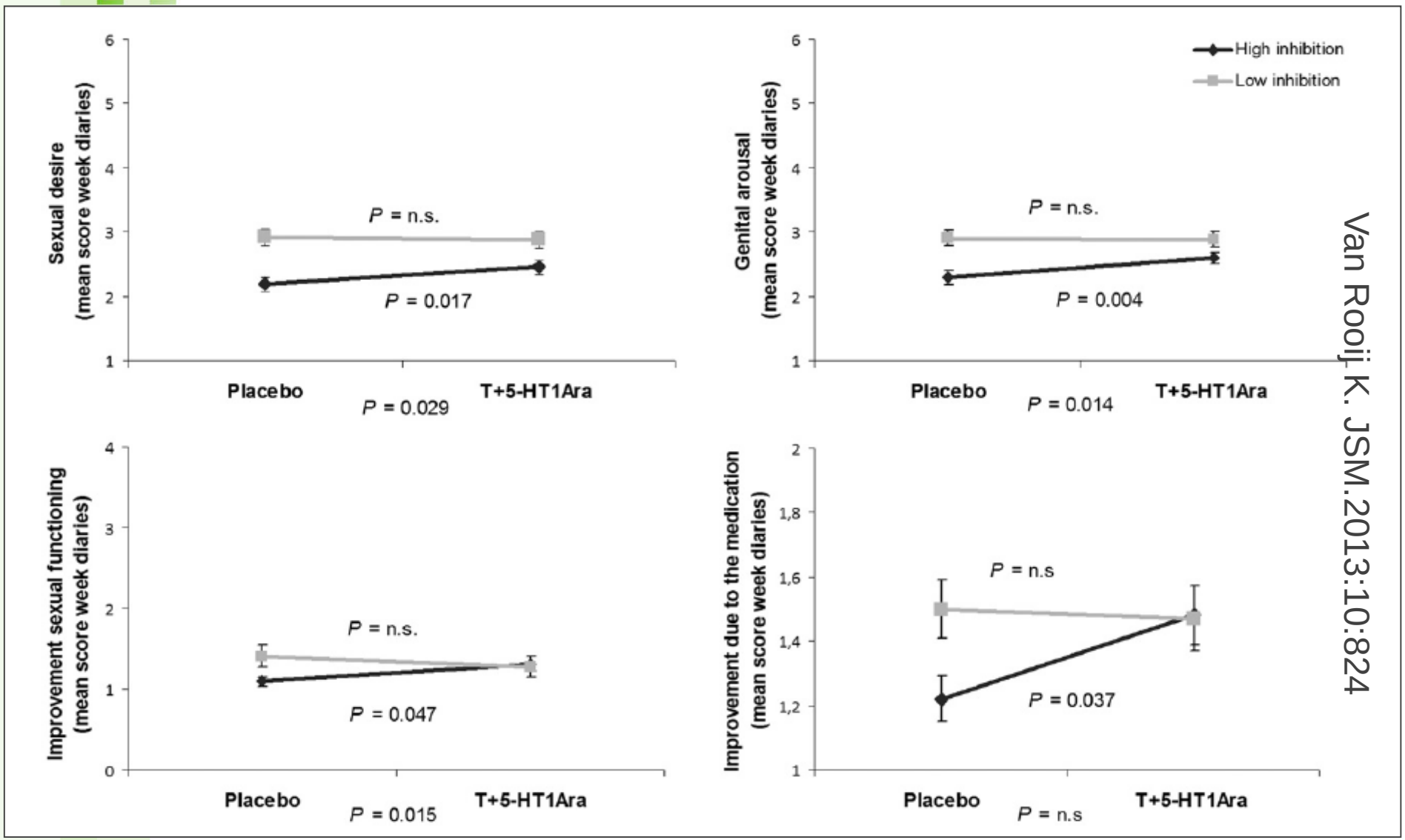


Figure 3 Bedroom experiment: The relative increase in sexual satisfaction following T+5-HT_{1A}ra treatment. In women with high inhibition, treatment with T+5-HT_{1A}ra increased sexual satisfaction with 25%, relative to placebo, while in the low inhibition group there was no such relative increase.

Van Rooij K. JSM.2013:10:824



Van Rooij K. JSM.2013:10:824

Effect of T+5-HT1A relative to placebo on subjective indices of the week diaries. Significant interaction between drug and placebo and the two groups

Personalized treatment?

- Based on the dual control model (inhibition/excitement) and sexual cues:
- Testosterone combined with PDE-5 inhibitor
  - increasing sensitivity to sexual cues and enhance genital response
- HT1a receptor agonistand testosterone
  - Reduce sexual inhibition and increase sensitivity to sexual cues

Conclusion

- Several central acting agents for treatment of FSD are under development
- The results are promising
- Are we ready for this treatment modality of FSD?

http://www.newviewcampaign.org/

AnnaMaria Giraldi - Outlook W... | Nyheder - seneste nyt - Politik... | Annamaria Giraldi

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Sex for *our* pleasure or *their* profit?

new view campa

Challenging the Medicalization of Sex

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WELCOME

The New View Campaign was formed in 2000 as a grassroots network to challenge the distorted and oversimplified messages about sexuality that the pharmaceutical industry relies on to sell its new drugs.

The pharmaceutical industry wants people to think that sexual problems are simple medical matters, and it offers drugs as expensive magic fixes. But sexual problems are complicated, sexuality is diverse, and no drug is without side effects.

The goal of the New View Campaign is to expose biased research and promotional methods that serve corporate profit rather than people's pleasure and satisfaction. The Campaign challenges all views that reduce sexual experience to genital biology and thereby ignore the many dimensions of real life.