New Pharma compounds for FSD
Central acting agents

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Disclosures

• Eli Lilly - lecturer
• Servier - lecturer
• Apricus BioScience – Advisory board
• Emotional Brain – Advisory Board
• Boehringer Ingelheim - grant
Central effects of neurotransmitters and hormones on sexual functioning

- Estrogen → Desire
- Testosterone → Desire
- Melanocortins → Desire
- Dopamine → Desire
- Prolactin → Desire
- Oxytocin → Desire
- 5-HT_{2+3} (serotonin) → Desire
- Opioids → Desire
- Progesterone → Desire
- Norepinephrine → Desire
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- 5-HT_{2+3} (serotonin)

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
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

Thorp et al. BJOG 2014:121;1328-32
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

**p<0.05
***p<0.01
****p<0.001
*****p<0.0001

Favors placebo  Favors flibanserin
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

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

Melanocortin system

• Melanocortins are believed to act via activation of the melanocortin receptor on dopaminergic neurons located in hypothalamic center and thereby stimulate sexual desire and arousal


• 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
Bremelanotide (melanocortine peptide) for HSDD/FSAD

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

Jordan et al. ISSWSH, New Orleans, 2013
LYBRIDO/ LYBRIDOS
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 motivation 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
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

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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\textsubscript{1A}ra treatment. In women with high inhibition, treatment with T+5-HT\textsubscript{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
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 agonist and 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?
Conclusion

• Several central acting agents are under development for FSD
• The results are promising
• Are we ready for these new treatment modalities?