

Take Home Messages and Updates in Women's Sexual Medicine

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Topics

- Update in terminology/classification
- Persistent genital arousal disorder in women: mind and body
- Hormones and women's sexuality
 - Menopause, hormones and oncology
 - Contraception and sexual function
- Pharma compounds for female sexual dysfunction

GSM

Genitourinary Syndrome of Menopause (GSM): New Terminology for Vulvovaginal Atrophy from the International Society for the Study of Women's Sexual Health and The North American Menopause Society

Members of the consensus conference agreed that the term genitourinary syndrome of menopause (GSM) is a medically more accurate, all-encompassing, and publicly acceptable term than vulvovaginal atrophy.

JSM, in print

FEMALE SEXUAL DYSFUNCTIONS: DSM Changes

DSM-IV-TR DIAGNOSIS	CHANGES IN DSM-5 Diagnosis
Female Hypoactive Desire Disorder	Merged into Female Sexual Interest/Arousal Disorder
Female Arousal Disorder	Ditto
Female Orgasmic Disorder	Unchanged
Dyspareunia	Merged into Genito-Pelvic Pain/Penetration Disorder
Vaginismus	Ditto

Ishak & Tobia: DSM-5 Changes in Diagnostic Criteria of Sexual Dysfunctions, Reprod Sys Sexual Disorders, 2013.

ISSWSH Response/Nomenclature Conference

- Describe DSM and how sexual problems fit into this schema and current biopsychosocial model
- DSM represents perspective, not science
- Provide nomenclature for multiple groups of end-users
- Changes in identity need to be addressed: culture/generational transitions/gender assignment
- Research needed on reliability/validity of definitions

ISSWSH CONSENSUS

Draft Orgasm Subgroup

Persistent Genital Arousal Subgroup

Persistent Genital Arousal Disorder is a persistent or recurrent, unwanted or intrusive, bothersome or distressing, genital dysesthesia unassociated with sexual interest, with the following characteristics:

1. Symptoms may lead to despair, frustrations, emotional lability, and/or catastrophizing thoughts
2. Symptoms may be associated with overactive bladder and restless leg syndrome
3. Orgasm may be spontaneous, recurrent, aversive, absent, delayed, muted, and or not associated with pleasure or satisfaction
4. Symptoms have limited, or no resolution, or even aggravation with orgasm
5. Symptoms may be caused by peripheral and central pathophysiologies

Persistent Genital Arousal Disorder (PGAD): Experience with Management in 35 Consecutive Cases

- Results 1: In this review, women (mean age 46 +/- 18 years) had symptoms of PGAD for a mean of 17 +/- 16 years.
- In these women PGAD appeared secondary to the sum of two underlying pathophysiologies:
 - increased peripheral sensory afferent input
 - central sexual arousal reflex center that was under inhibited.
- In these women with PGAD, the central sexual reflex center of the brain appeared to falsely interpret the excess peripheral sensory information as sexual arousal - leading to the spontaneous arousal and orgasm and short refractory period post-orgasm

Persistent Genital Arousal Disorder (PGAD): Experience with Management in 35 Consecutive Cases

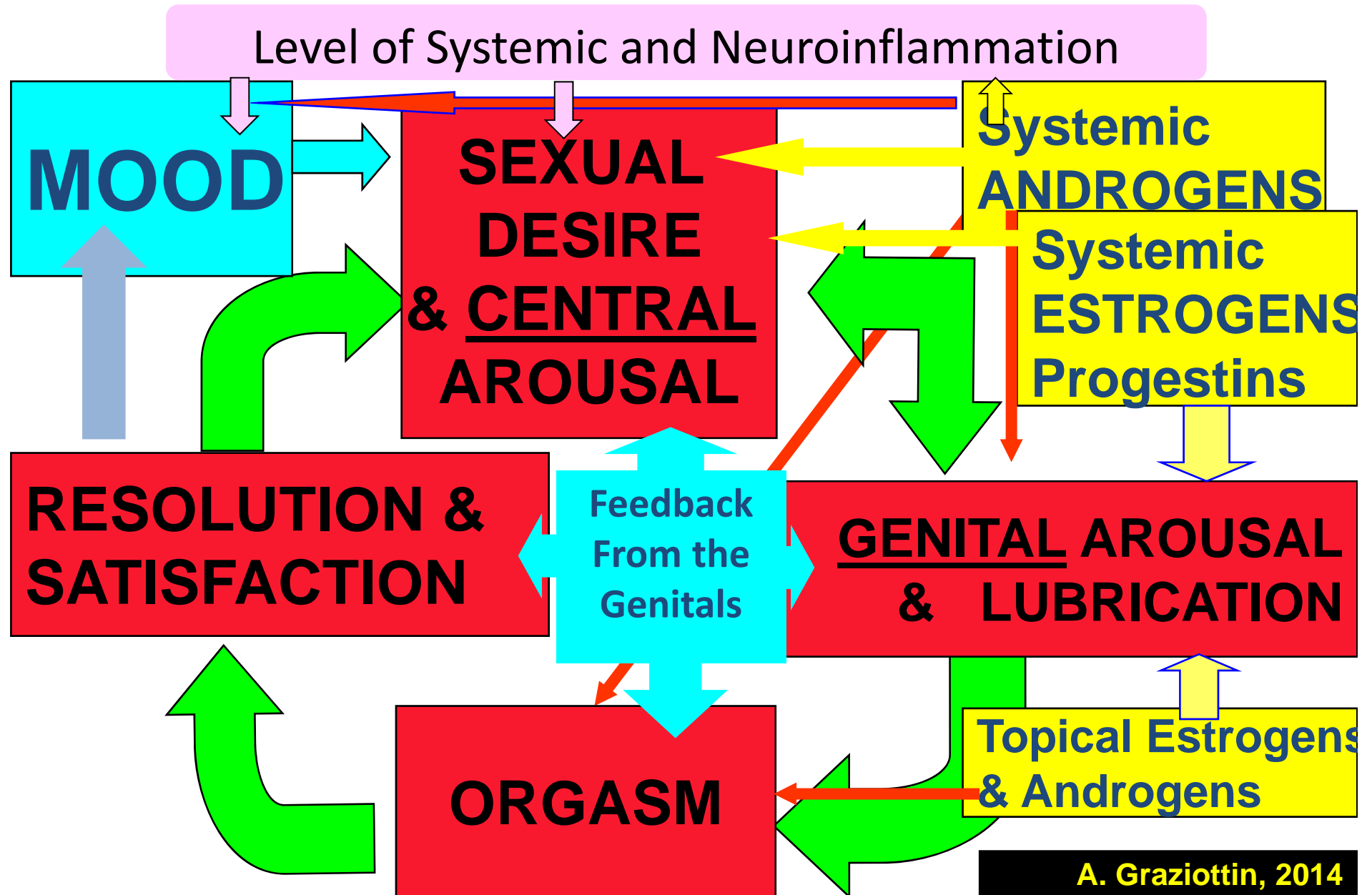
Results:

Treatment of PGAD in this population was **individually based** and included strategies to:

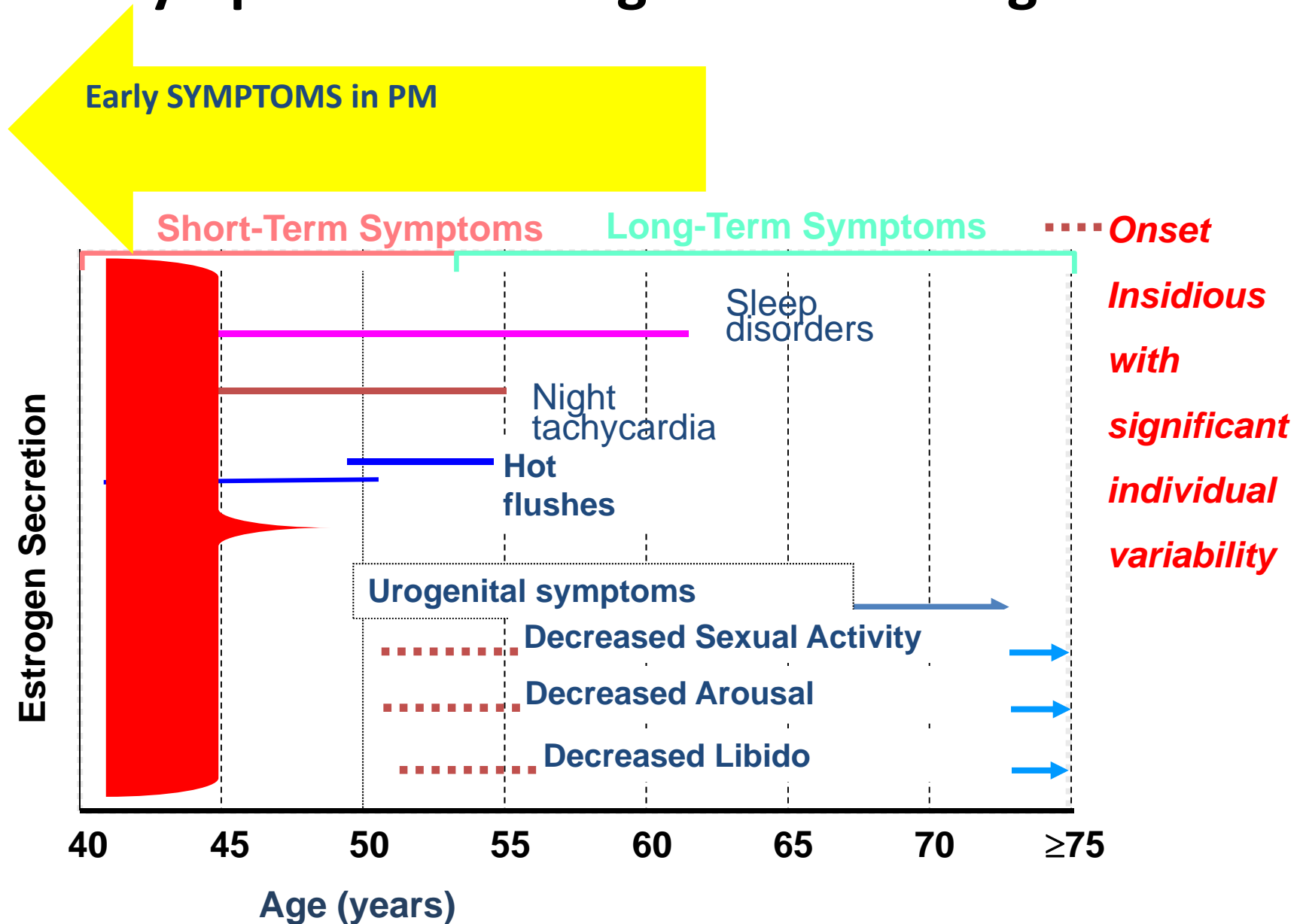
- i) reduce the excess peripheral sensory input – with conservative sex therapy/counseling, pelvic floor, pharmacologic, device and surgical treatments
- ii) increase inhibitory regulation of the uninhibited central sexual reflex center

Successful PGAD management utilized all the strategies, to keep the PGAD condition manageable

Female Sexual Function



Symptoms of Estrogen and Androgen Loss



Contraception and Sexual Function

- Hormonal contraceptives cause:
 - Significant **increase** in sex hormone binding globulin
 - Significant **decrease** in calculated free testosterone
- Variable sensitivity to androgen changes caused by CAG repeat patterns- **which are unique to the individual woman**
 - **Sexual desire** was higher in women with short CAG repeat lengths and **LOWER IN WOMEN WITH LONG CAG REPEAT LENGTHS**
- Evidence exists for a role of androgen receptor sensitivity and sexual desire of hormonal contraceptive users
- CHCs decrease free androgen index, which may be associated with decreased sexual functioning and vestibulodynia
- Other birth control options have some impact on sexual functioning
- IUD = contraceptive option which appears to have few significant sexual side effects and may enhance sexual response.

Drugs

- FDA approved for moderate to severe dyspareunia, a symptom of VVA/GSM due to menopause
 - Ospemifene
 - Estring
 - Premarin Cream

In Development:

- Non-hormonal medications in development
 - Flibanserin
 - Bremelanotide
- Hormonal medications in development
 - Lybrido
 - Lybridos
 - Intravaginal DHEA

Ospemifene: Vaginal Atrophy Treatment

First non estrogen oral tablet (SERM)

Phase III study

- Study safety, efficacy, and tolerability of oral Ospemifene 60mg/day vs. placebo (12 weeks)
- N=605 women aged 40-80 years
 - Most bothersome symptom of dyspareunia, dx of vulvar and vaginal atrophy
- Results
 - Efficacy of ospemifene significantly greater than placebo in decreasing dyspareunia, parabasal cells, vaginal pH, increasing superficial cells
- Hot flushes
 - Most frequently reported treatment-related AE (ospemifene 6.6% and placebo 3.6%)

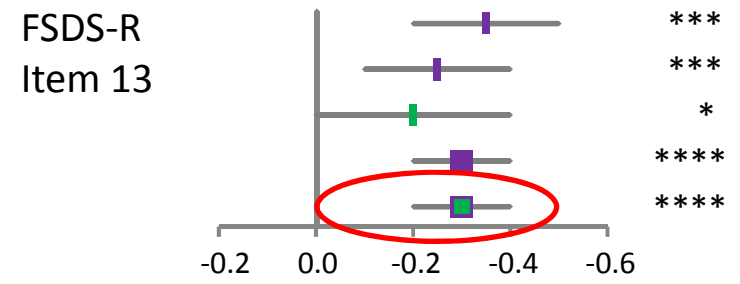
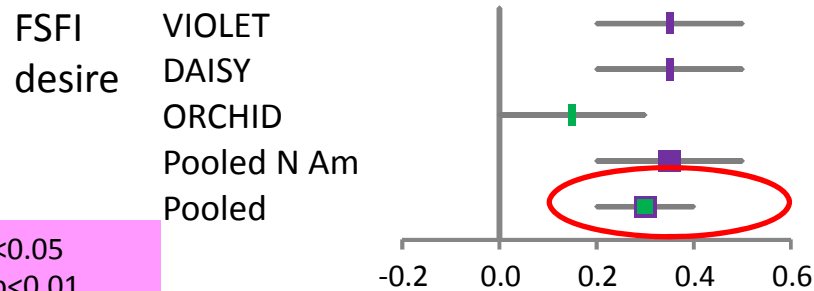
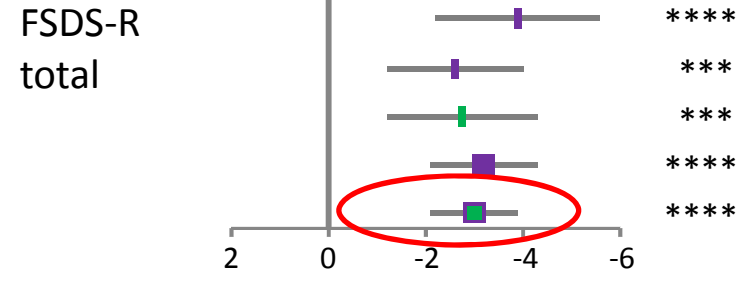
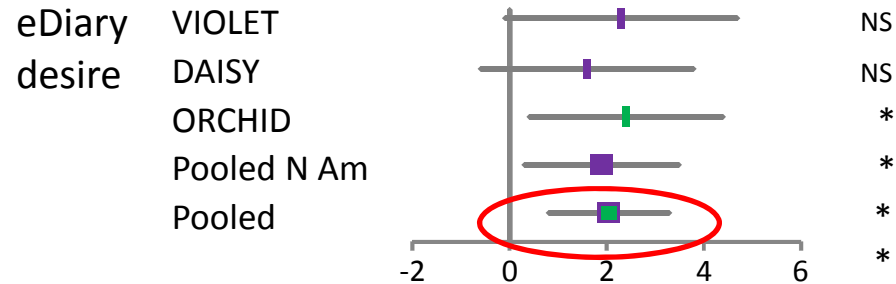
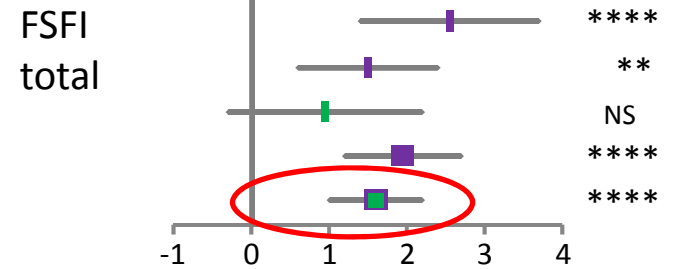
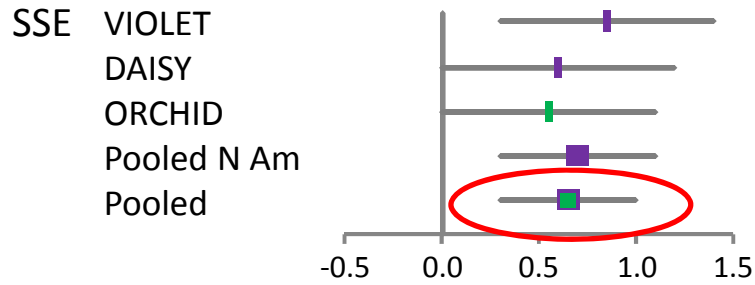
Ospemifene: Endometrial Safety

- 52 week long-term safety extension study
- Placebo vs. Ospemifene 30mg/day vs. Ospemifene 60mg/day
- Results
 - Daily doses of Ospemifene 30mg and 60mg demonstrated *no endometrial changes* in postmenopausal women with a uterus
- Ospemifene effectively prevents and treats breast cancer in Mtag.TG Transgenic Mouse.

**DRUGS IN DEVELOPMENT
FOR FEMALE SEXUAL
DYSFUNCTION**

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 Favours flibanserin

Favors placebo Favours flibanserin

Postmenopausal women (n=949)

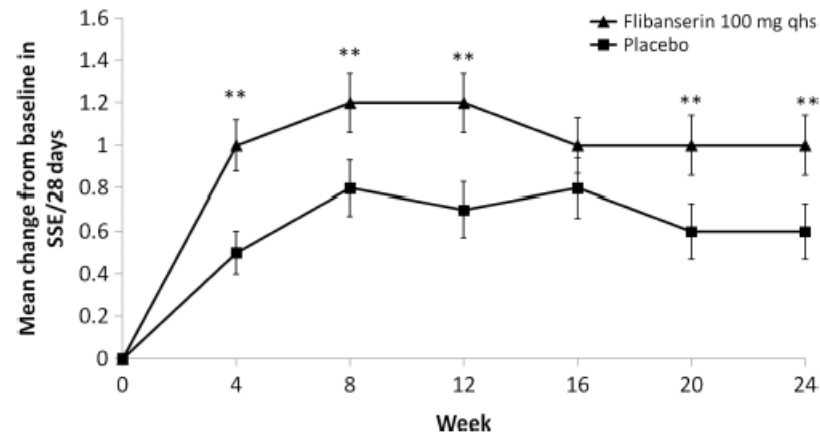


FIG. 2. Change in the number of satisfying sexual events (SSEs) from baseline to week 24. Last-observation-carried-forward analysis on the full analysis set. Data are presented as means; error bars denote SE. **** $P < 0.01$** for flibanserin 100 mg at bedtime (qhs) versus placebo.

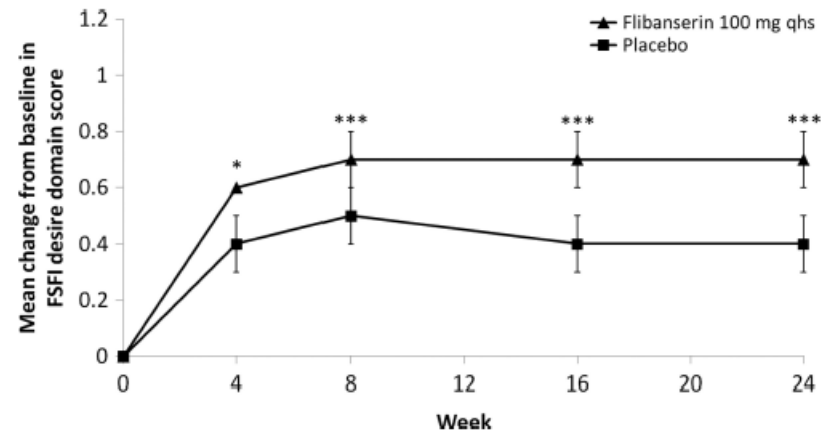
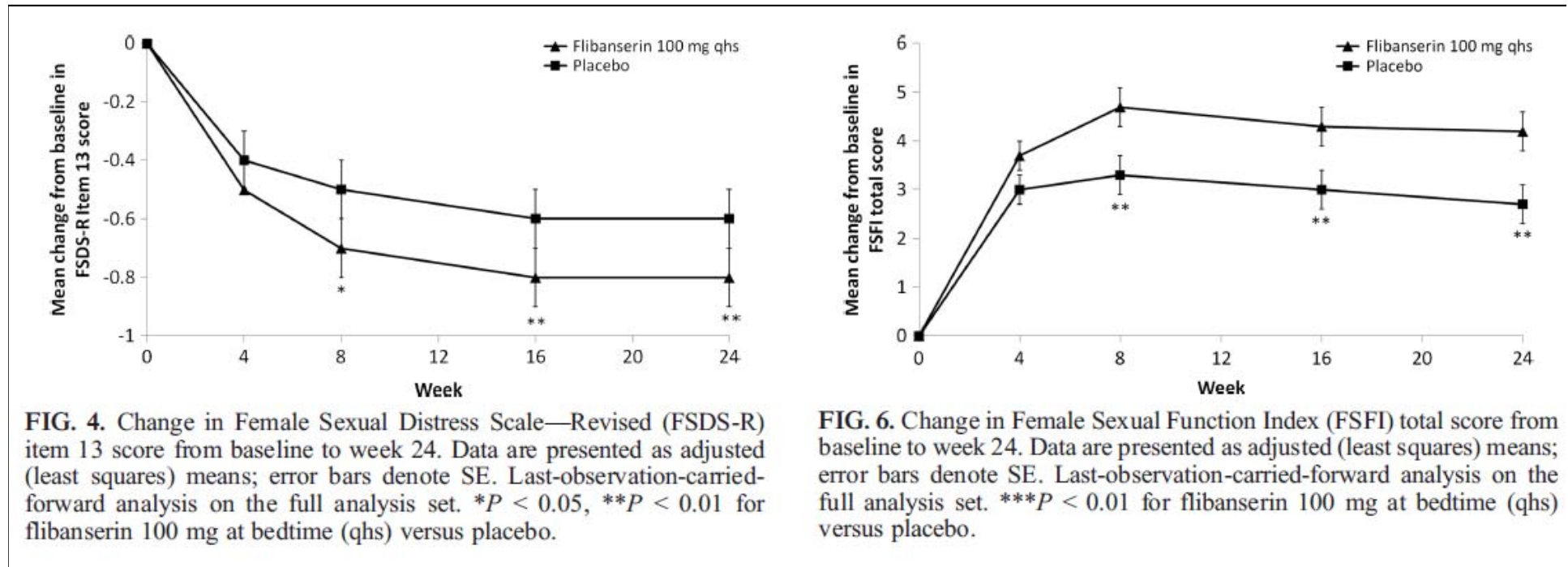


FIG. 3. Change in Female Sexual Function Index desire domain (FSFI-d) score from baseline to week 24. Last-observation-carried-forward analyses on the full analysis set. Data are presented as adjusted (least squares) means; error bars denote SE. *** $P < 0.05$** , ***** $P < 0.001$** for flibanserin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

Satisfying sexual event

Female Sexual Function Desire Index

Postmenopausal women (n=949)



Female Sexual Distress Scale

Female Sexual Function Index

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

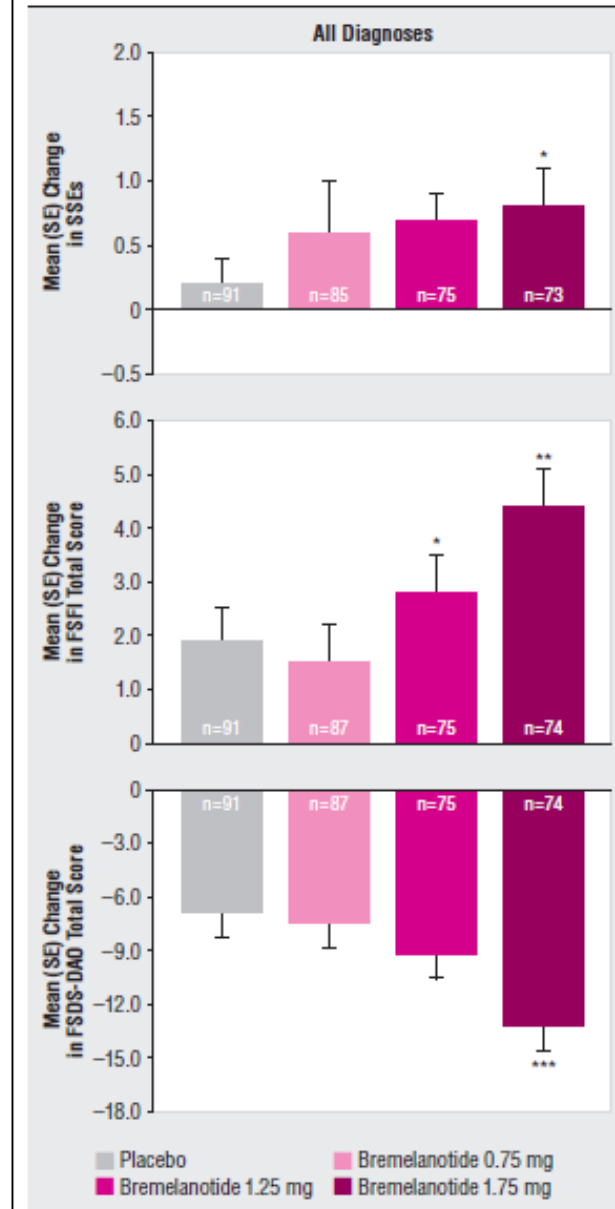
- Women with HSDD induced by dysfunctional sexual inhibition mechanism
- Sublingual testosterone (0.5 mg) and 5-HT1A receptor agonist (buspirone 10 mg)
- Increase sexual motivation and inhibit overactive sexual inhibition

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.