Non-hormonal Pharmacologic Treatments

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Editor Emeritus, *International Journal of Impotence Research*

HSDD – Prevalence and QOL

Prevalence of Female Sexual Dysfunction (PRESIDE)

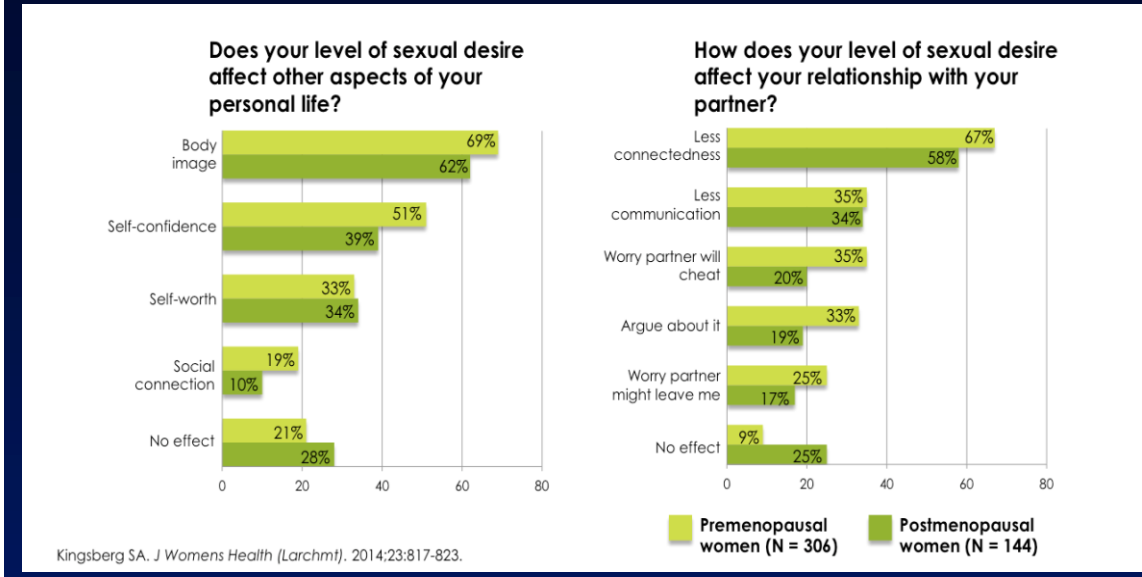
Sexual Complaint	Sexual Problem	Sexual Problem Plus Distress
Desire	38.7%	10.0%
Arousal	26.1%	5.4%
Orgasm	20.5%	4.7%
Any Dysfunction	44.2%	12.0%

N=31,581 women from a survey of 50,002 US households (63% response rate); 18-102 years of age.

Low desire was the most common of the three sexual problems among women of all ages

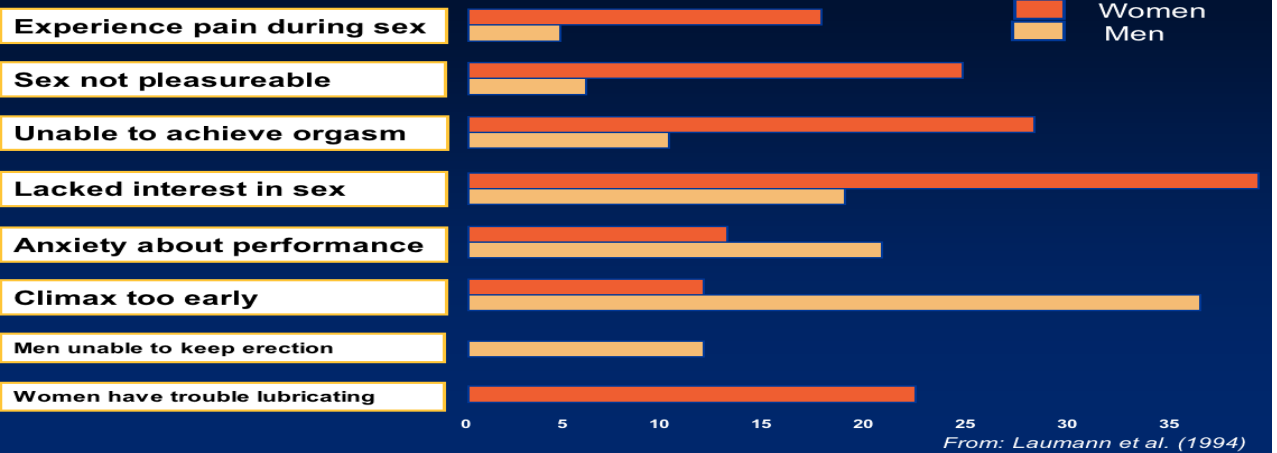
PRESIDE = Prevalence of Female Sexual Problems Associated with Distress and Determinants of Treatment Seeking

Shifren J, et al. *Obstet Gynecol.* 2008;112:970-978.

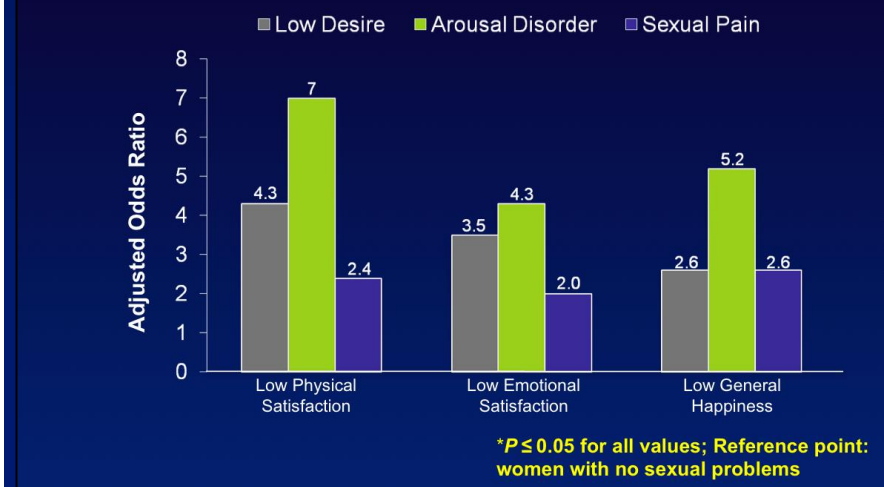


Kingsberg SA. *J Womens Health (Larchmt).* 2014;23:817-823.

Prevalence of Male and Female Sexual Dysfunction - National Health and Social Life Survey (1994)



Impact of Female Sexual Dysfunction (FSD) on General Well-being



Laumann EO, et al. *JAMA.* 1999;281:537-544.

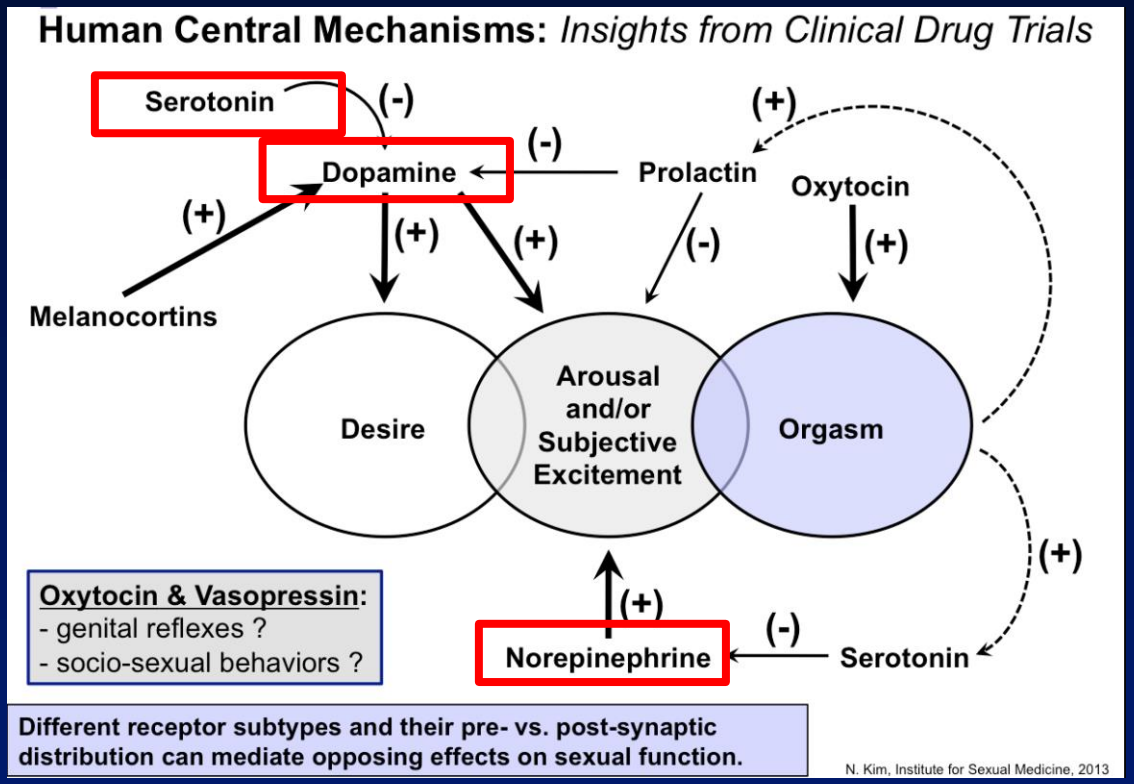
Three Plausible Facts About HSDD

HSDD is caused by excitatory (eg. dopamone and norepinephrine) and inhibitory (eg. serotonin) neurotransmitter imbalances in key regions (eg PFC, NuACC, mPOA) of the brain

ALL TREATMENT OPTIONS FOR HSDD (placebo, sex therapy, non-hormonal, hormonal) imporve sexual desire and lower distress by chaning the balance between excitatory (eg. dopamone and norepinephrine) and inhibitory (eg. serotonin) neurotransmitters in key regions (eg PFC, NuACC, mPOA) of the brain

Prolonged HSDD leads to neuroplasticity

Update on the Central Pathology of Female Sexual Dysfunction
Unifying Basis for Biopsychosocial Intervention



On Switch =

Increased brain blood flow

Off Switch =

Decreased brain blood flow

Women With No History of Sexual Dysfunction (NHSD) versus Women With Hypoactive Sexual Desire Disorder (HSDD): A Functional Magnetic Resonance Imaging Study

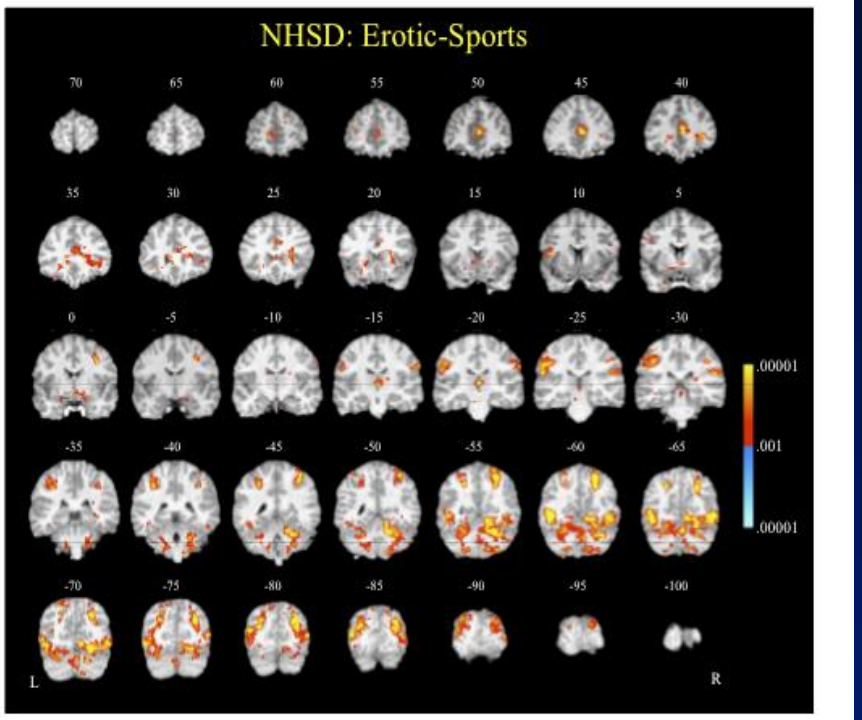


Fig. 3. Brain activations resulting from the contrast of erotic–sports in subjects with NHSD. Activations are based on a random effects analysis of 20 subjects using a *P* threshold of 0.001 (uncorrected). Voxels in which the erotic video segments elicit greater activation than sports is depicted in the red–yellow color scale, whereas sports>erotic is depicted in the blue color scale. The left side of the brain is depicted on the left in this and subsequent figures. Numbers above each section represent the Y MNI coordinates of the coronal sections taken from a normalized brain volume.

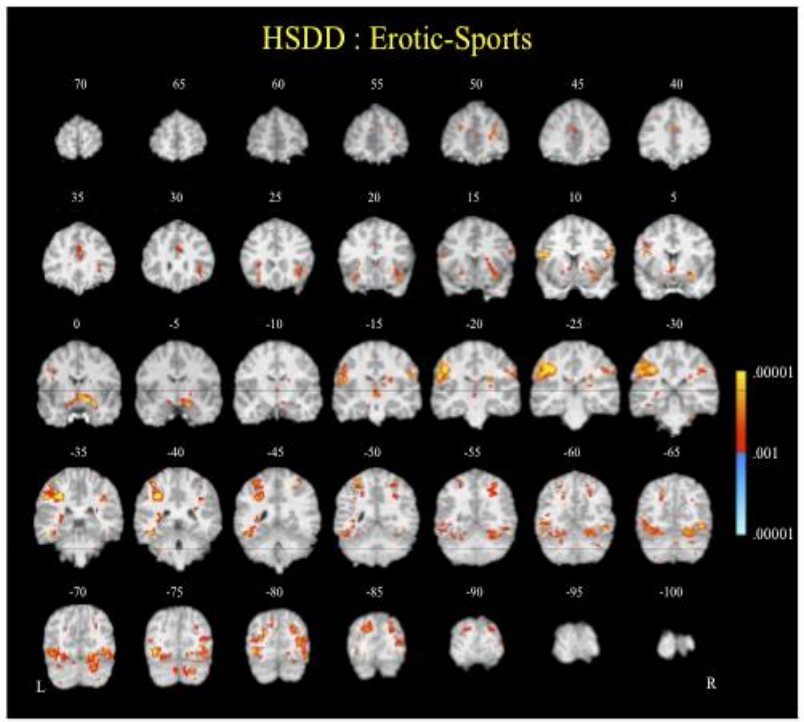


Fig. 4. Average brain activations resulting from the contrast of erotic–sports in subjects with HSDD. Activations are based on a random effects analysis of 16 subjects using a $P<0.001$ threshold (uncorrected). Voxels in which the erotic video segments elicit greater activation than sports is depicted in the red–yellow color scale, whereas sports>erotic is depicted in the blue color scale. Numbers above each section represent the Y MNI coordinates of the coronal sections taken from a normalized brain volume.

On Switch =

Increased brain blood flow

Off Switch =

Decreased brain blood flow

Figures 3 and 4 from Arnow BA, Millheiser L, Garrett A, Lake Polan M, Glover GH, Hill KR, Lightbody A, Watson C, Banner L, Smart T, Buchanan T, Desmond JE. Women with hypoactive sexual desire disorder compared to normal females: a functional magnetic resonance imaging study. *Neuroscience*. 2009;158:484-502.

Activations

Healthy female volunteers watching high erotic movies
Activation

Pathophysiology of Female Sexual Dysfunction

FRONT

BACK

RIGHT

LEFT

UNDERNEATH

TOP

Courtesy Gert Holstege

Georgiadis JR, Kortekaas R, Kuipers R, Nieuwenburg A, Pruim J, Reinders AA, Holstege G. Regional cerebral blood flow changes associated with clitorally induced orgasm in healthy women. Eur J Neurosci. 2006 Dec;24(11):3305-16.

Activations

HSDD female volunteers watching high erotic movies

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Deactivations

Healthy female volunteers watching low erotic movies

De-activation

Pathophysiology of Female Sexual Dysfunction

FRONT

BACK

RIGHT

LEFT

UNDERNEATH

TOP

Courtesy Gert Holstege

Georgiadis JR, Kortekaas R, Kuipers R, Nieuwenburg A, Pruim J, Reinders AA, Holstege G. Regional cerebral blood flow changes associated with clitorally induced orgasm in healthy women. Eur J Neurosci. 2006 Dec;24(11):3305-16.

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HSDD female volunteers watching low erotic movies

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Unifying Central Strategies: Female Sexual Dysfunction

Components of Desire: Causal Factors of HSDD

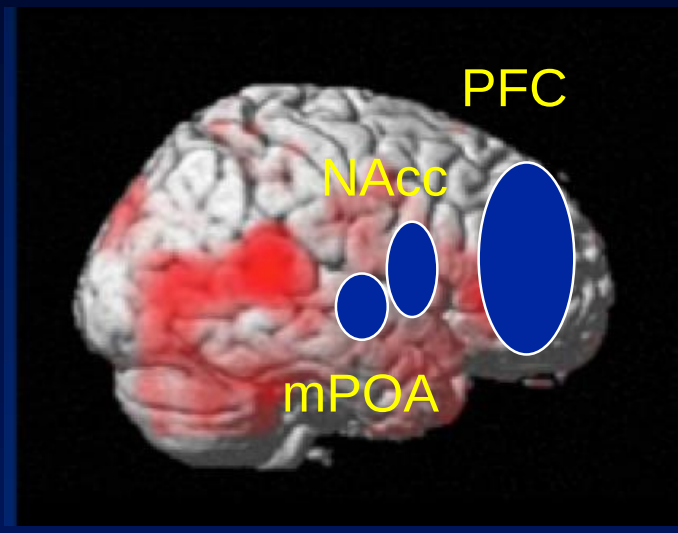
DRIVE:
Biological component based on neuroendocrine mechanisms

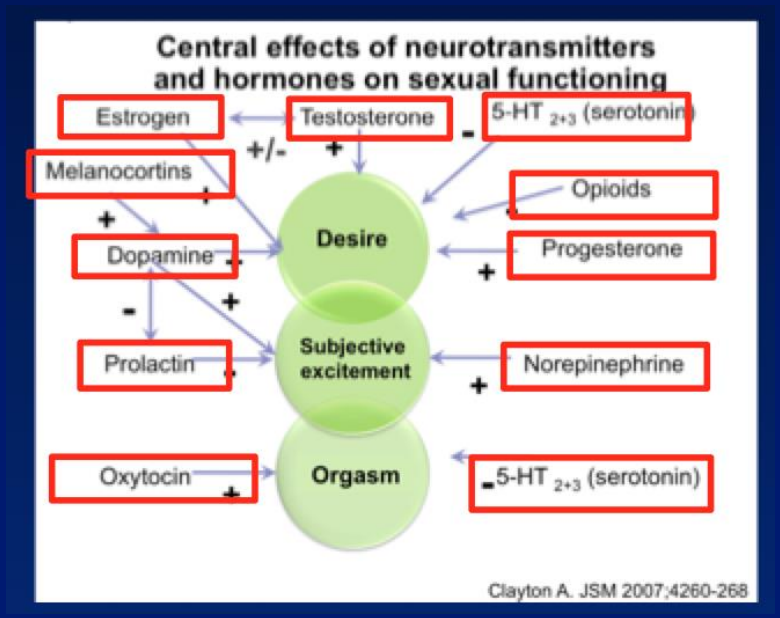
COGNITIVE:
Reflects expectations, beliefs and values

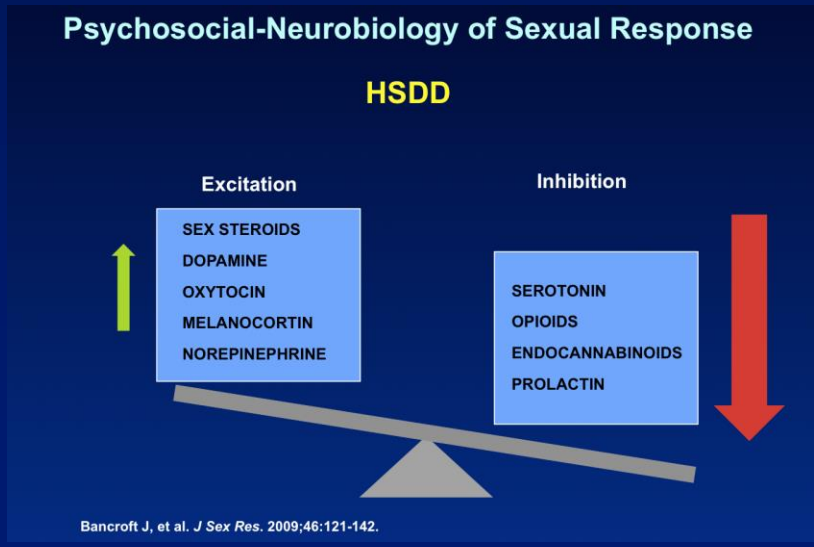
MOTIVATION:
Willingness to engage in sexual activity

Hull EM, Lorrain DS, Du J, et al. *Behav Brain Res*. 1999;105(1):105-16.
Levine S. Sexual Life, 1994

HSDD Rx's:
Placebo
Sex therapy
Testosterone
Flibanserin
Bupropion
Buspirone







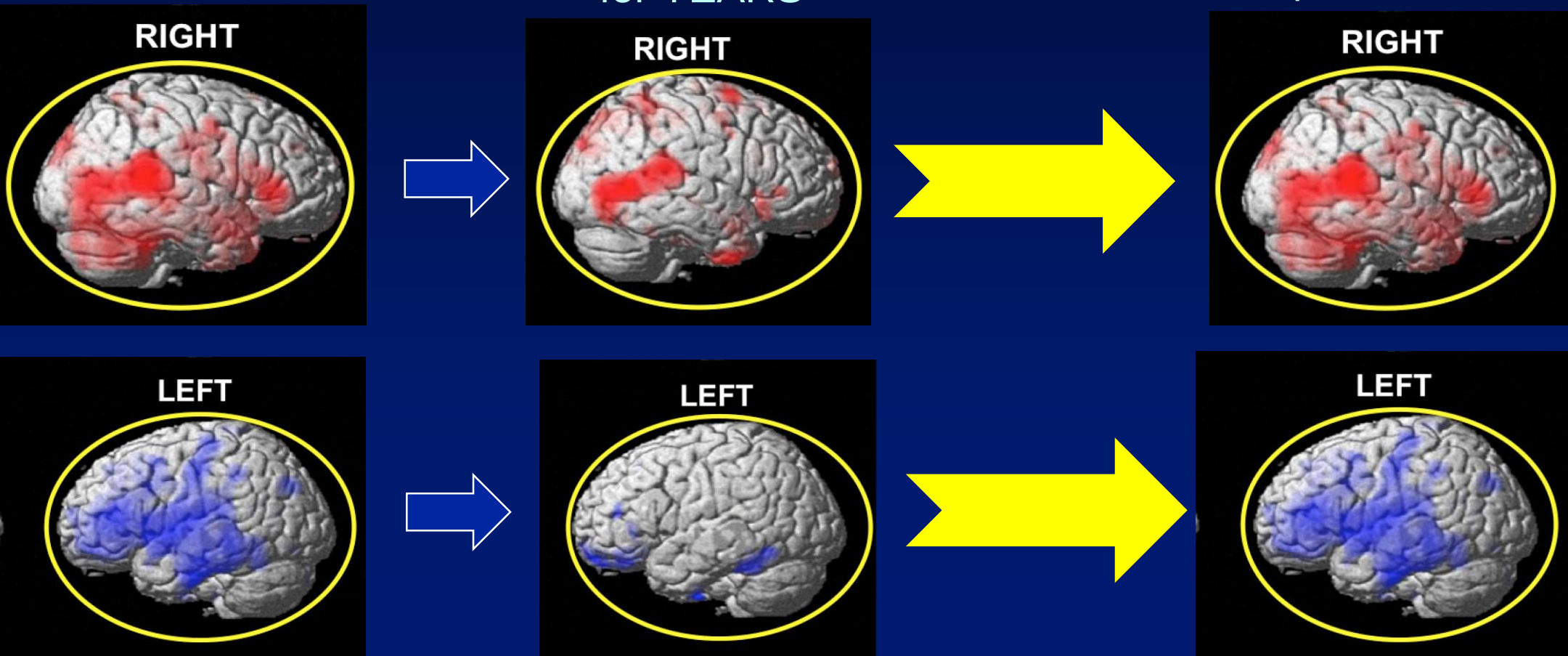
Neuroplasticity in HSDD

Neuroplasticity - brain plasticity, - umbrella term describing lasting change to the brain - research showed many aspects of the brain remain changeable (or "plastic") even into adulthood

NHSD

Generalized Acquired HSDD for YEARS

Prolonged Treatment of Generalized Acquired HSDD



Placebo Outcomes in Female Sexual Dysfunction Studies

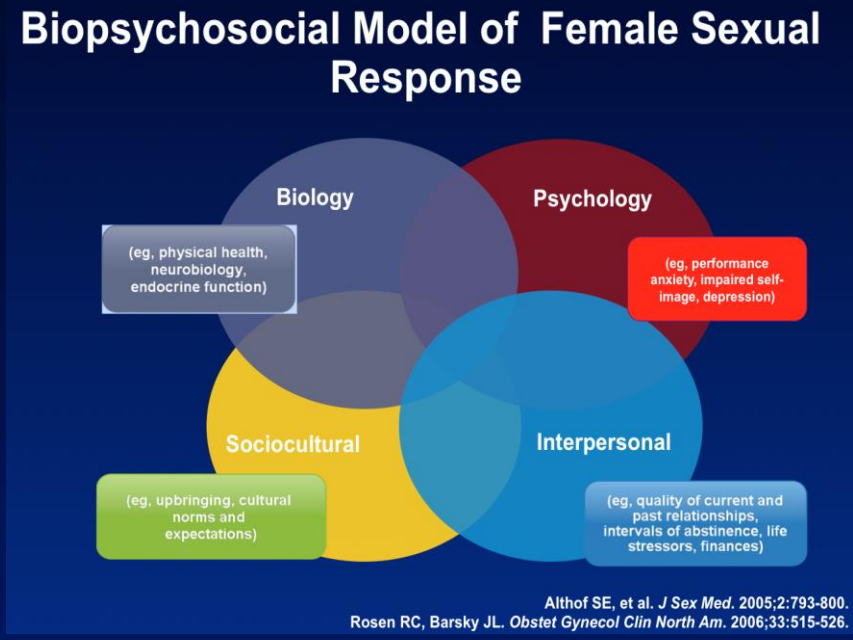
~ 30-40% or more of women reported significant improvement while on placebo in FSD studies

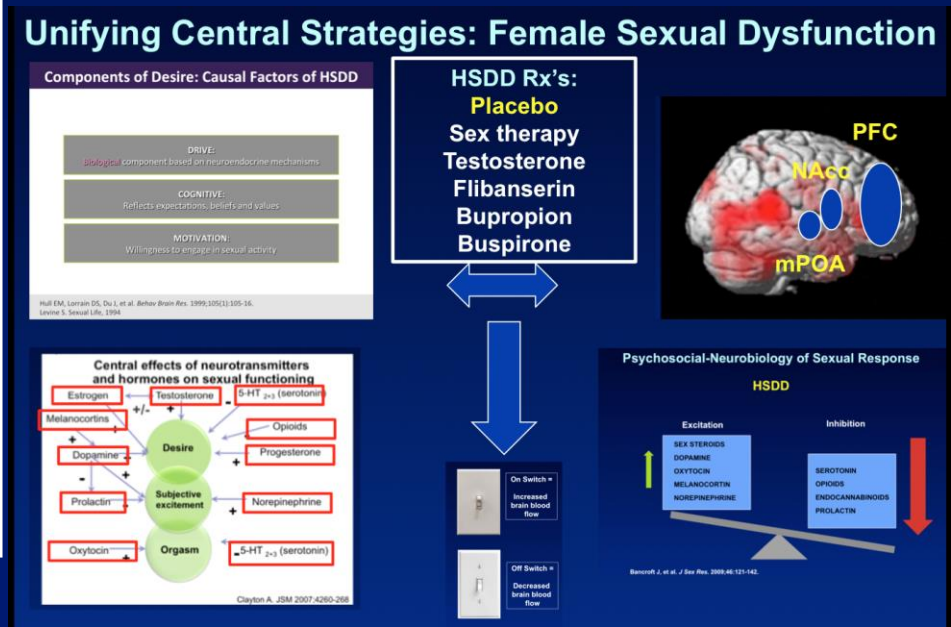
Potential reasons for placebo response rate in FSD clinical trails include:

1. Reliance on patient-reported outcomes
2. Enrollment in a clinical trial may cause behavioral changes that are therapeutic

   Self-monitoring may heighten subjects' attention and awareness to own responses and behaviors

   Increased focus may facilitate positive behavioral changes
3. Consistent interaction with a caregiver
4. Anticipation of treatment effects





Bradford A. *J Sex Med*. 2013;10:451-459.

Sex Therapy for HSDD

A variety of psychotherapeutic techniques have been suggested for the treatment of HSDD: i) basic counseling, ii) body-centered therapy, iii) couples therapy, and iv) cognitive behavioral therapy

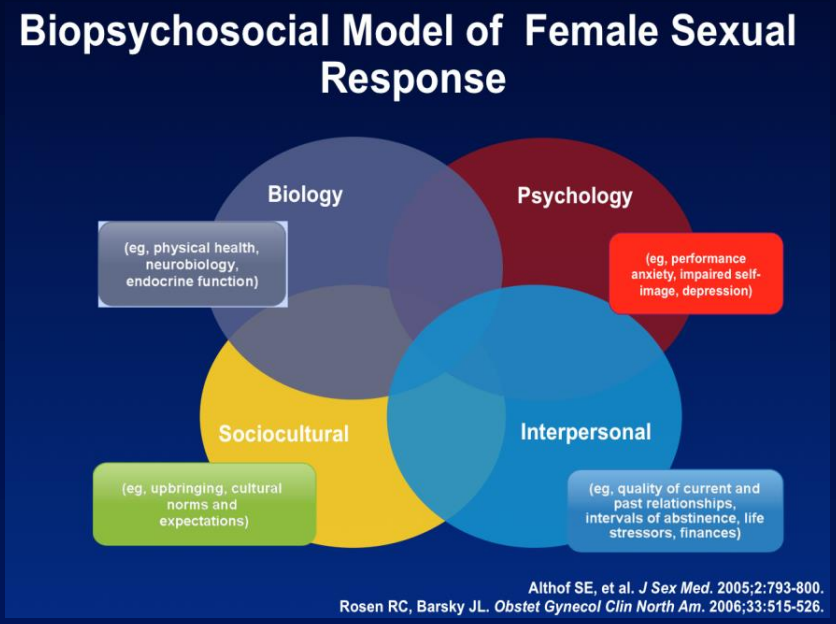
Cognitive behavioral therapy (CBT) - targeted program focusing on communication skills, sexual skills, as well as intimacy issues and performance anxiety (typically consists of 10-12 sessions)

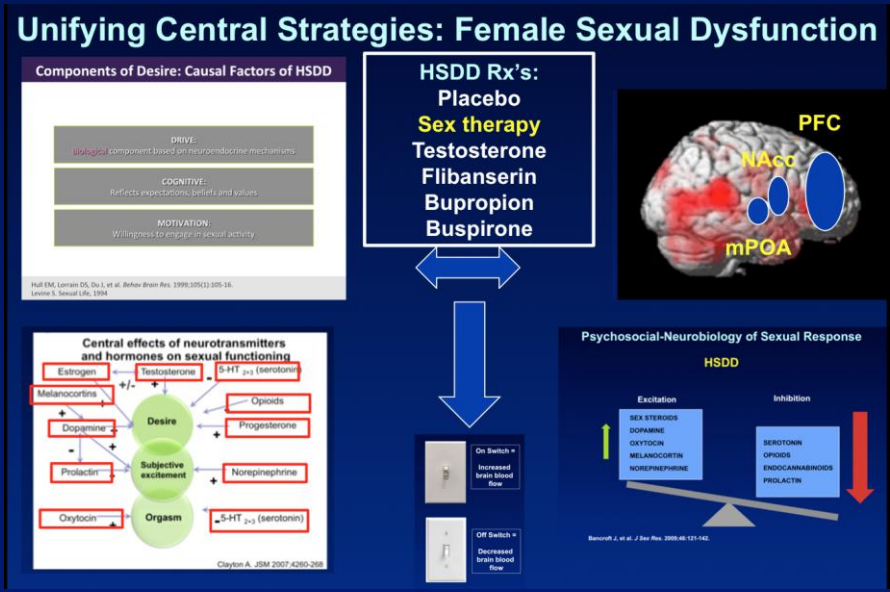
McCabe et al found CBT to be effective in 44.4% of women:

–Most likely to be effective in women with anorgasmia and sexual arousal disorder

–Least effective in women who experienced a lack of sexual interest

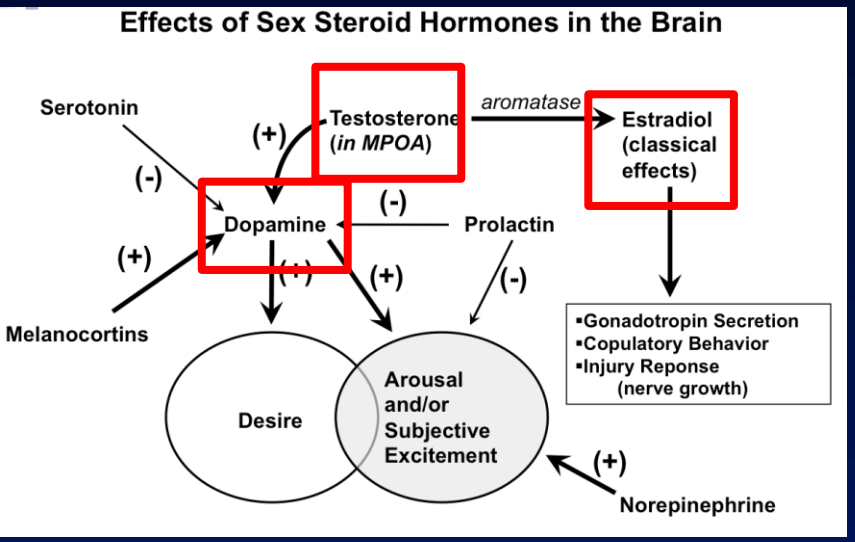
▪54% still reported a lack of sexual interest posttherapy



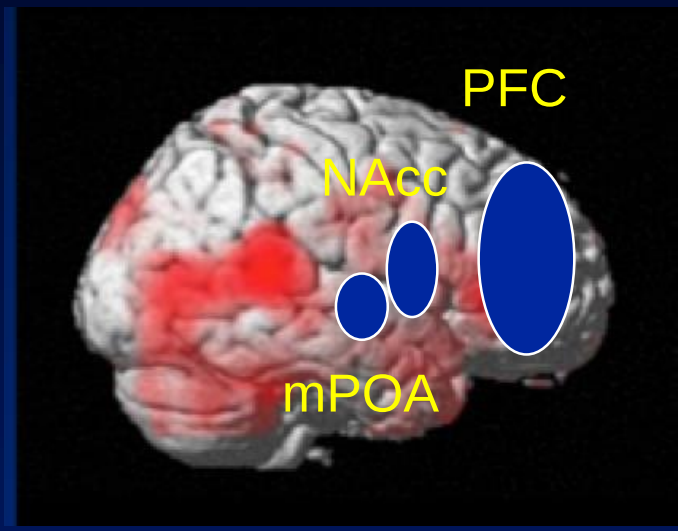


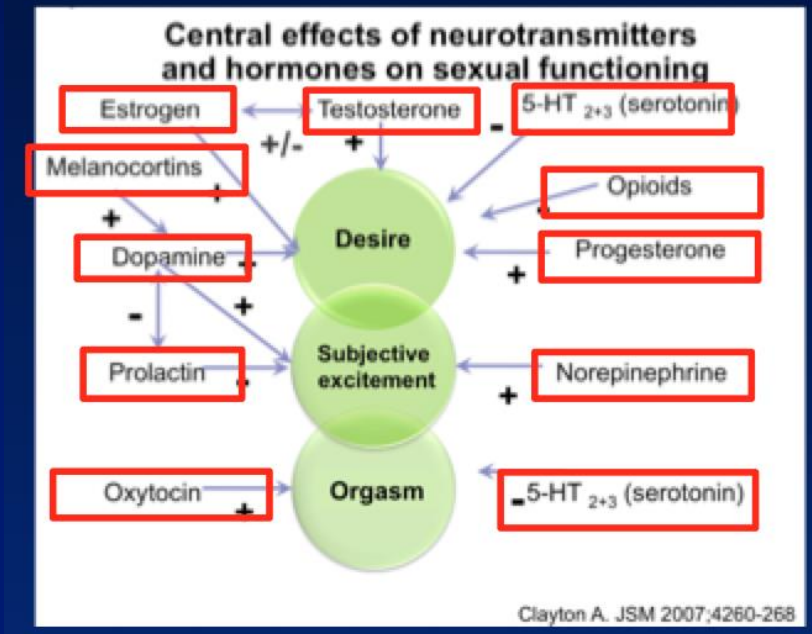
Bitzer J, Brandenburg U. *Maturitas*. 2009;63:160-163.
McCabe MP, et al. *J Sex Med*. 2010;7:327-336.
McCabe MP. *J Sex Marital Ther*. 2001;27:259-271.

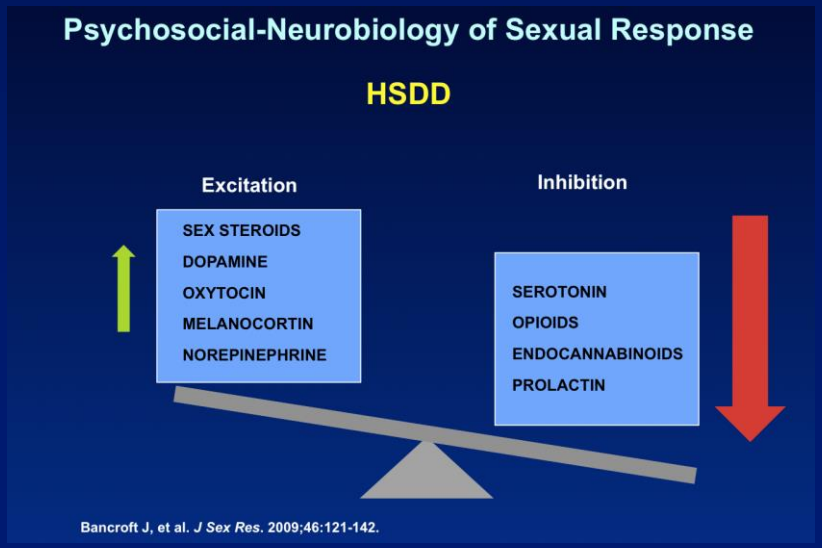
Unifying Central Strategies: Female Sexual Dysfunction



Sex Steroid Hormone Rx for HSDD:
Testosterone
Estradiol





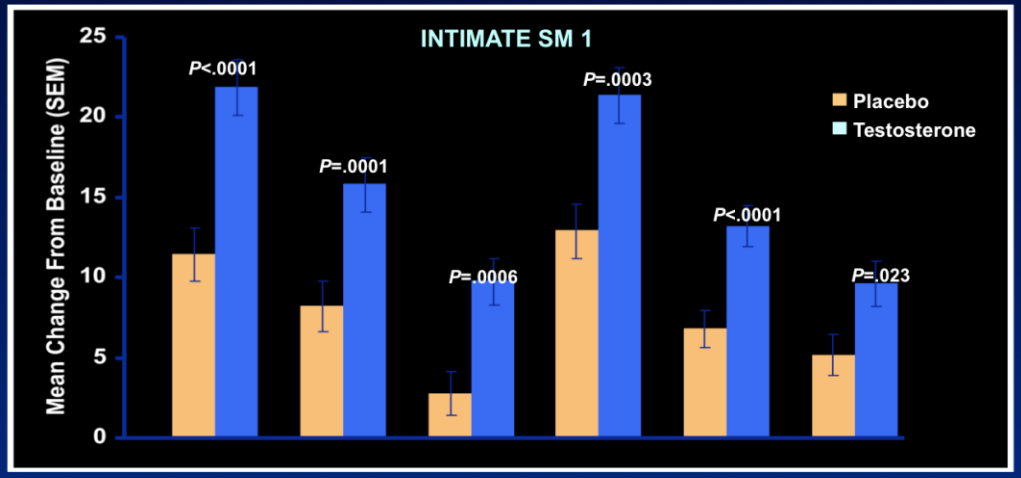


Published Randomized Studies Demonstrating Efficacy of Testosterone (Patch) in Postmenopausal Women with HSDD

	Doses (mcg/d)	Subjects (n)	Estrogen
Shifren et al, 2000	150/300	SM (75)	+
Braunstein, et al 2005	150/300/450	SM (447)	+
Buster et al, 2005	300	SM (533)	+
Simon et al, 2005	300	SM (562)	+
Davis et al 2006	300	SM (61)	+ (patch)
Davis et al, 2006	300	SM (76)	+ (aromatase inhibitors)
Shifren et al, 2006	300	NM (486)	+
Liu et al, 2008	300	NM (431)	+
Davis et al, 2008	150/300	NM/SM (814)	-
Panay et al, 2010	300	NM (272)	+/- groups

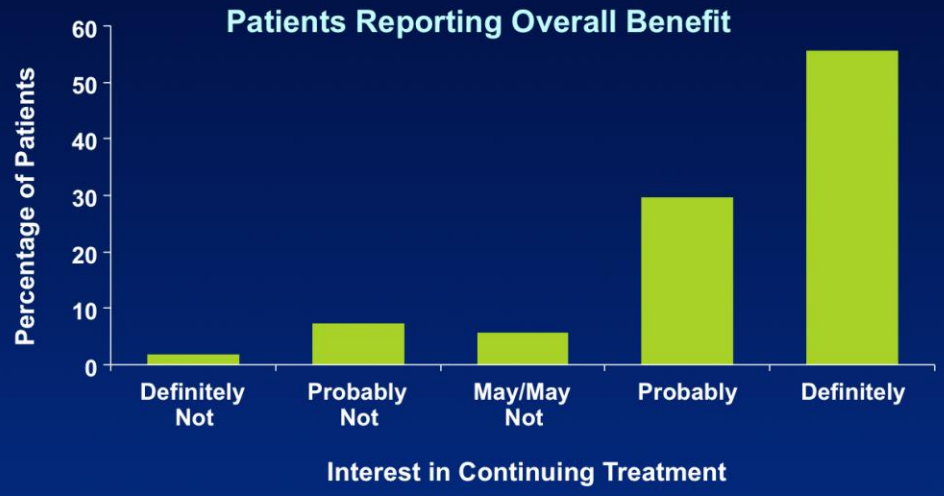
NM= naturally menopausal
SM= surgically menopausal

Profile of Female Sexual Functioning (PFSF) Domains at 24 Weeks – Other Than Desire



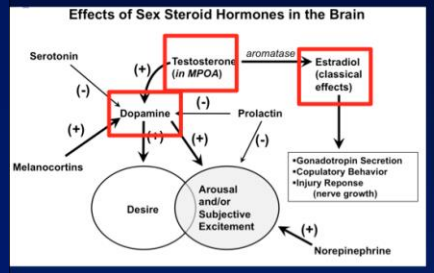
Kingsberg S. *J Sex Med*. 2007;4(Suppl 3):227-234.
Simon J, et al. *J Clin Endocrinol Metab*. 2005;90(9):5226-5233.

Interest in Continuing Treatment



Kingsberg S, et al. *J Sex Med*. 2007;4(4 Pt 1):1001-1008.

Unifying Central Strategies: Female Sexual Dysfunction



Sex Steroid Hormone Rx for HSDD:
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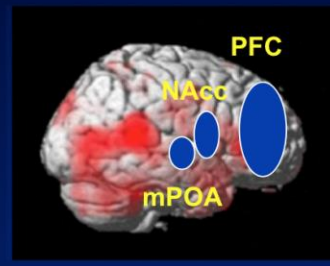
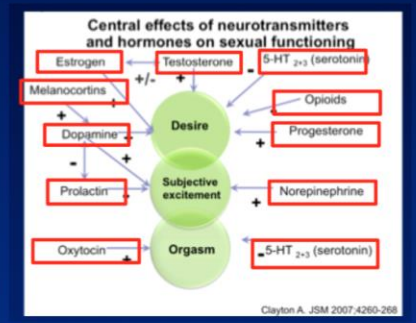
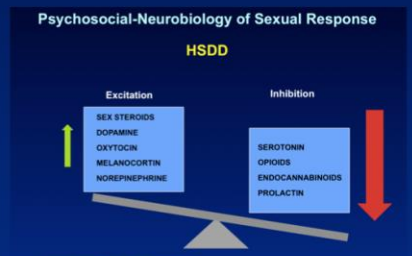
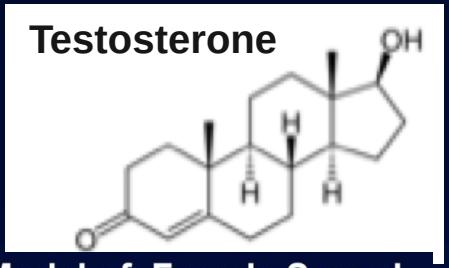


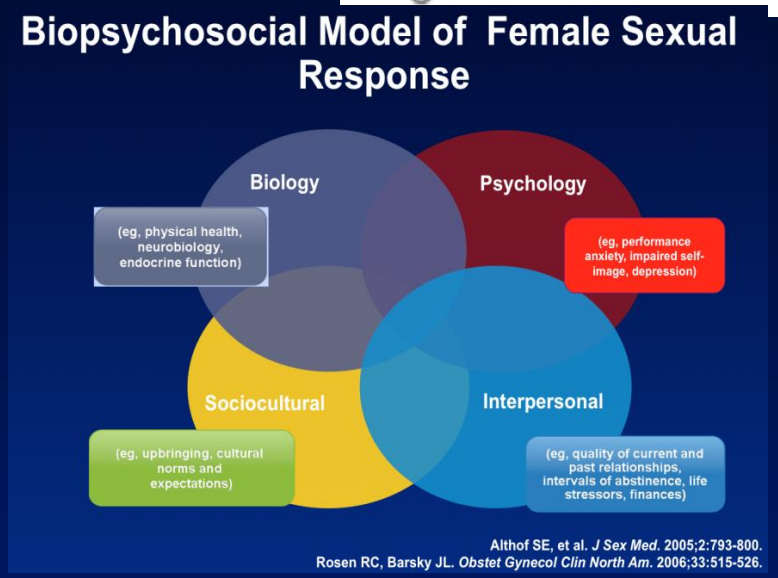


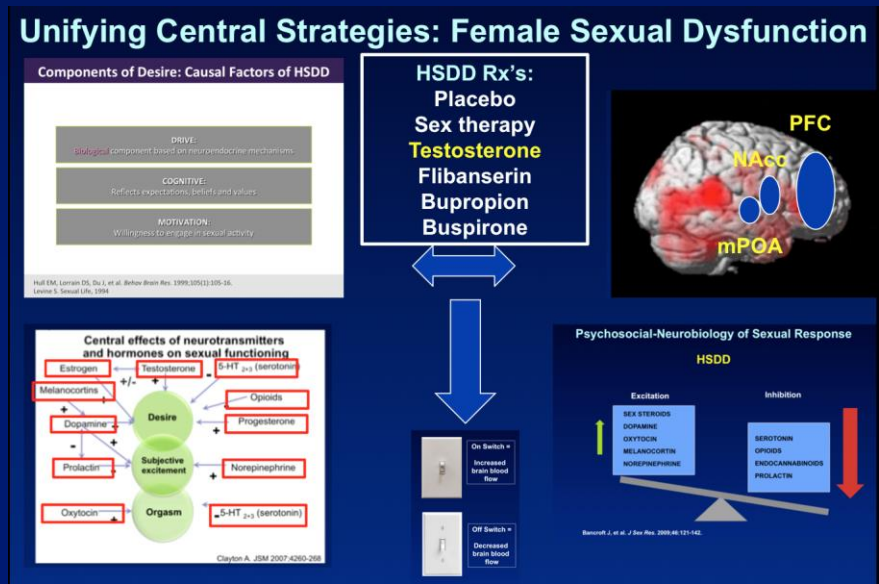


Testosterone: Hormonal pharmacologic option for HSDD



- **Double blind placebo controlled studies investigating testosterone therapy for treatment of HSDD were conducted in postmenopausal women (both naturally occurring and surgically induced)[1-5]**
  - **Efficacy established but lack of long-term safety data (median study duration ~6 months)**
- **Few studies in premenopausal women with HSDD and in those reporting low or diminished sexual function[5-8]**
  - **Efficacy in some only for arousal while other showed increases in sexual interest, activity, and the number of satisfying sexual events (SSEs)**

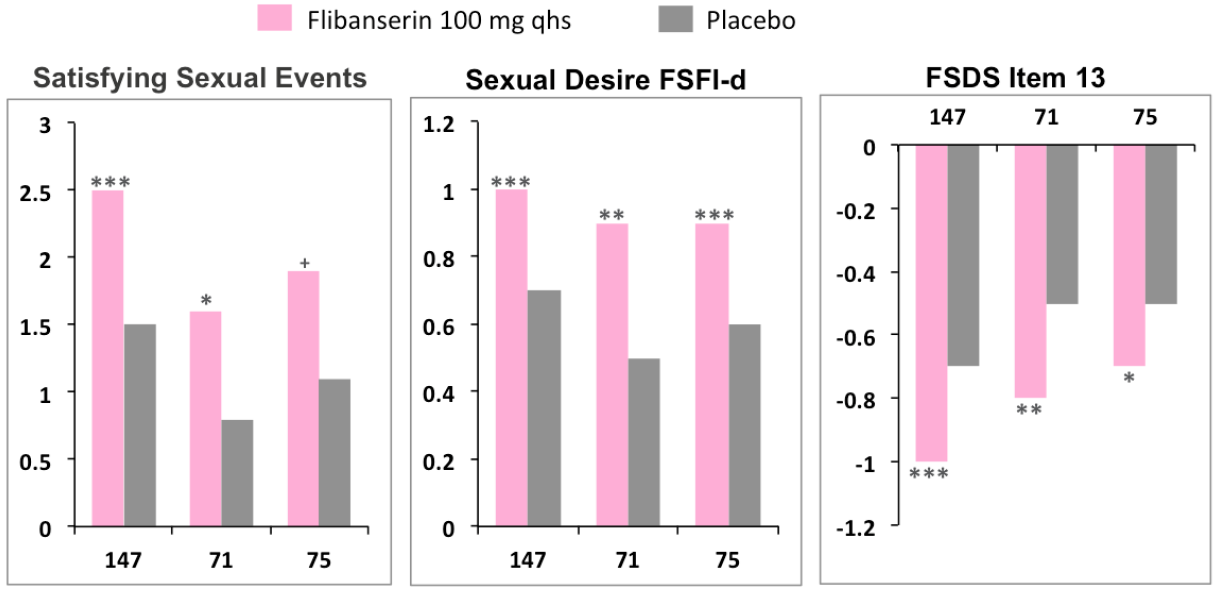




1. Somboonporn W, et al. *Cochrane Database Syst Rev*. 2005;4:CD004509.
2. Heard-Davison A, et al. *J Sex Med*. 2007;4:209-217.
3. Tuiten A, et al. *Arch Gen Psychiatry*. 2000;57:149-153.
4. Shufelt C, et al. *J Clin Endocrinol Metab*. 2010;95:4985-4992.
5. Woodis CB, et al. *Pharmacotherapy*. 2012;32:38-53.
6. Chudakov B, et al. *J Sex Med*. 2007;4:204-208.
7. Goldstat R, et al. *Menopause*. 2003;10:390-398.
8. Davis S, et al. *Ann Intern Med*. 2008;148:569-577

Update on the Central Pathology of Female Sexual Dysfunction
Unifying Basis for Biopsychosocial Intervention

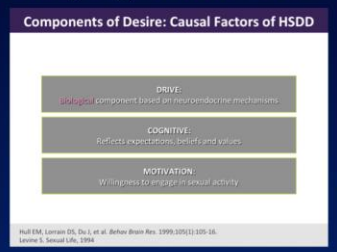
Efficacy (Change from Baseline)– Three US Phase III Clinical Trials*



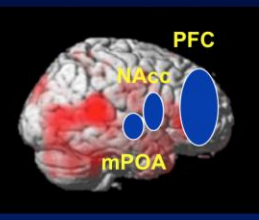
*last observations carried forward at end of study; ***p<0.0001; **p<0.001; *p<0.01; +p<0.05

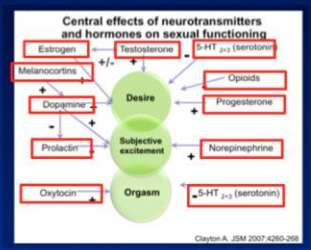
147 – M. Katz, L. DeRogatis, R. Ackerman, P. *Sex Med* 2013 (ePub 14 May 2013)
71 – DeRogatis LR, Komer L, Katz M, et. al. *J Sex Med* 2012 9(4): 1074-1085.
75 – Thorp J, Simon J, Dattani D, et. al. *J Sex Med* 2012, 9(3): 793-804.

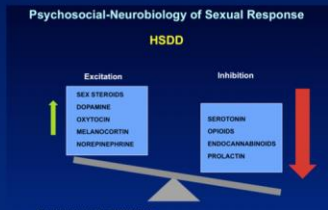
Unifying Central Strategies: Female Sexual Dysfunction



HSDD Rx's:
Placebo
Sex therapy
Testosterone
Flibanserin
Bupropion
Buspirone

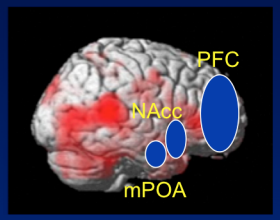






Flibanserin Regional Selectivity: Effects on Dopamine, Norepinephrine, and Serotonin

After acute administration, there are regional selectivities of Flibanserin in the PFC, Nacc, mPOA - for DO, NE, 5 HT



PFC – Flibanserin ↑ Dopamine Norepinephrine

PFC – Flibanserin ↓ Serotonin

NAcc –Flibanserin ↓ Serotonin

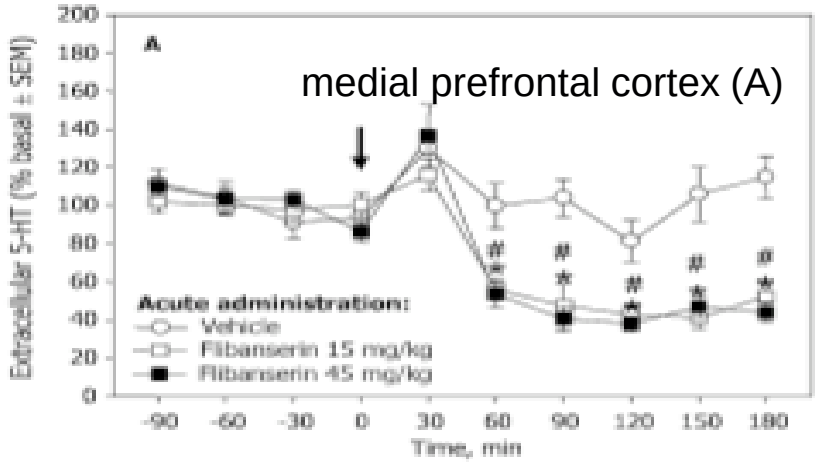
mPOA - Flibanserin ↑ Dopamine Norepinephrine

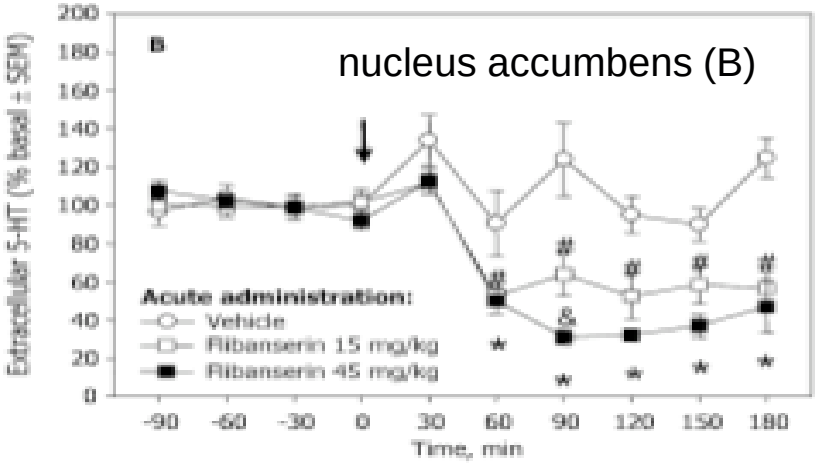
mPOA - Flibanserin ↓ Serotonin

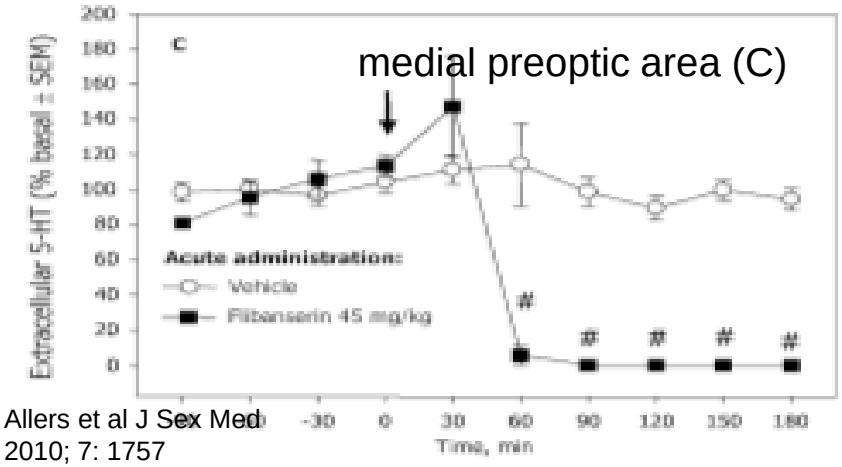
mPOA, medial preoptic area of the hypothalamus; NAcc, nucleus accumbens; PFC, prefrontal cortex.

Stahl SM, et al. *J Sex Med*. 2011;8:15-27.

Flibanserin - Mechanism of Action







Allers et al J Sex Med 2010; 7: 1757

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

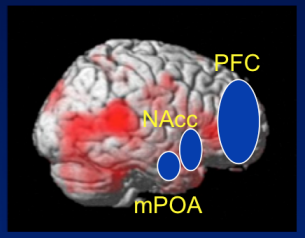
*P < 0.05 in comparison with vehicle, 15 mg/kg flibanserin-administered group

#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

Flibanserin Regional Selectivity: Effects on Dopamine, Norepinephrine, and Serotonin

After acute administration, there are regional selectivities of Flibanserin in the PFC, Nacc, mPOA - for DO, NE, 5 HT



PFC – Flibanserin ↑ Dopamine Norepinephrine

PFC – Flibanserin ↓ Serotonin

NAcc –Flibanserin ↓ Serotonin

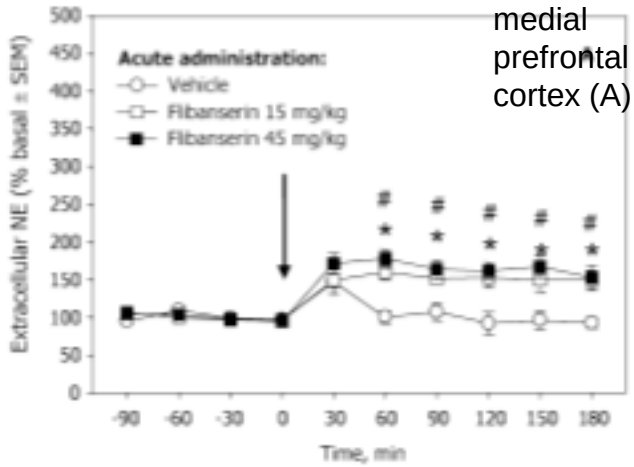
mPOA - Flibanserin ↑ Dopamine Norepinephrine

mPOA - Flibanserin ↓ Serotonin

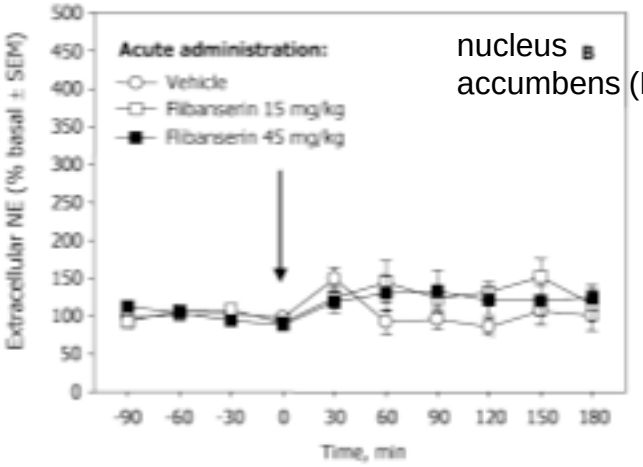
mPOA, medial preoptic area of the hypothalamus; NAcc, nucleus accumbens; PFC, prefrontal cortex.

Stahl SM, et al. *J Sex Med.* 2011;8:15-27.

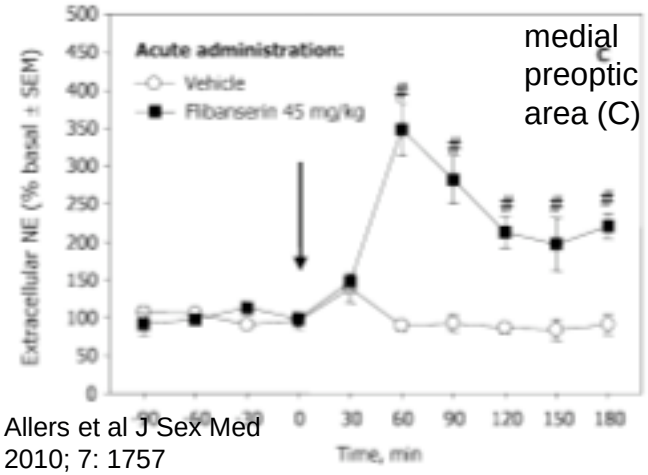
Flibanserin - Mechanism of Action



medial prefrontal cortex (A)



nucleus accumbens (B)



medial preoptic area (C)

Allers et al J Sex Med 2010; 7: 1757

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

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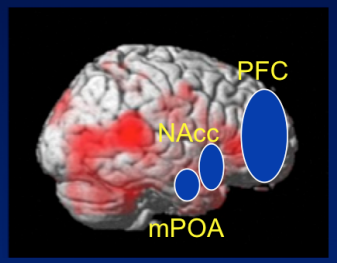
Flibanserin Regional Selectivity: Effects on Dopamine, Norepinephrine, and Serotonin

After acute administration, there are regional selectivities of Flibanserin in the PFC, Nacc, mPOA - for DO, NE, 5 HT



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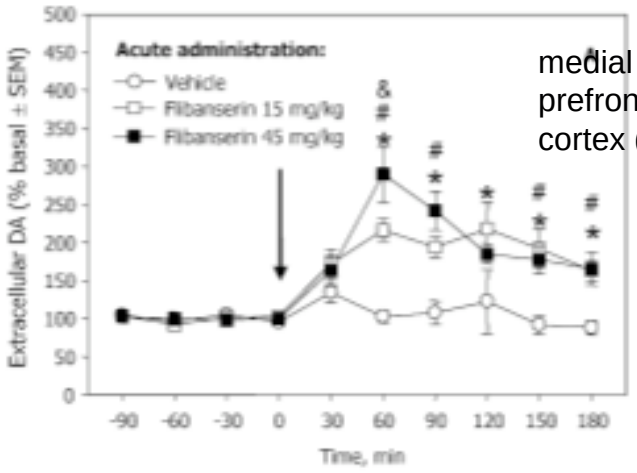

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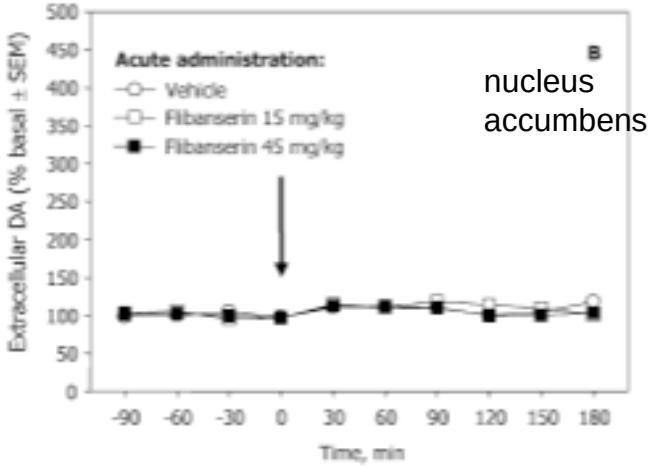
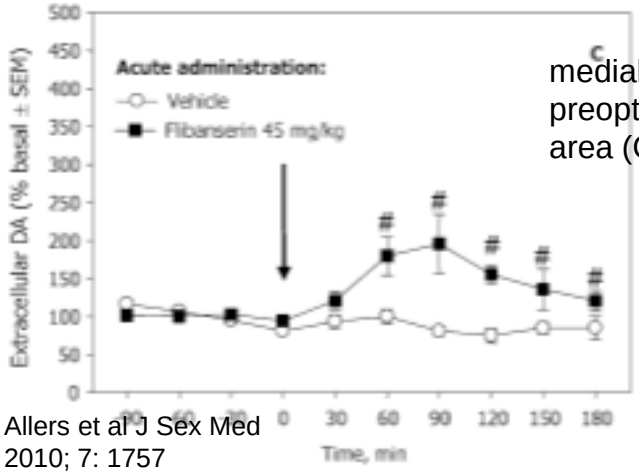


nucleus accumbens (B)



medial preoptic area (C)

Allers et al J Sex Med 2010; 7: 1757

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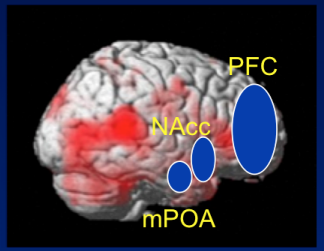

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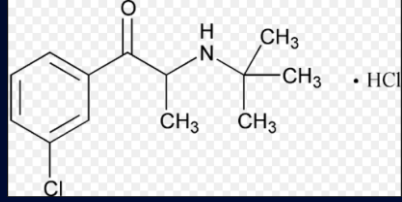
BUPROPION



Antidepressant also approved to aid in smoking cessation

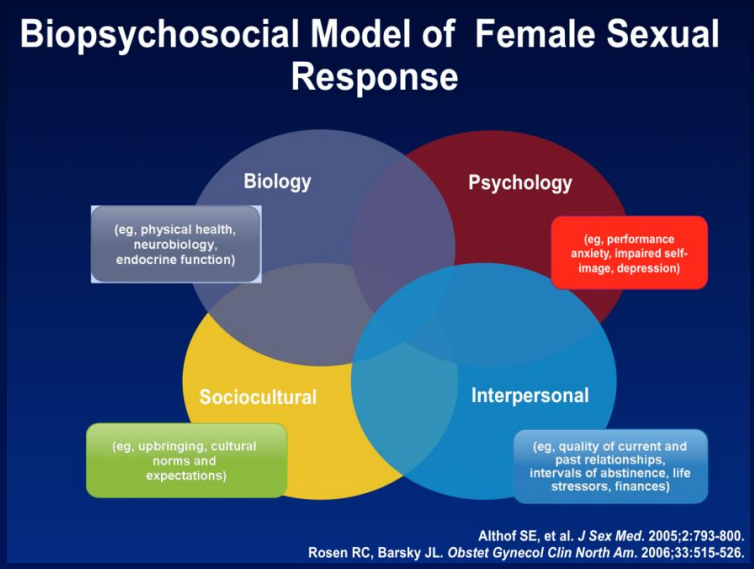
Classified as a norepinephrine-dopamine reuptake inhibitor (NDRI)

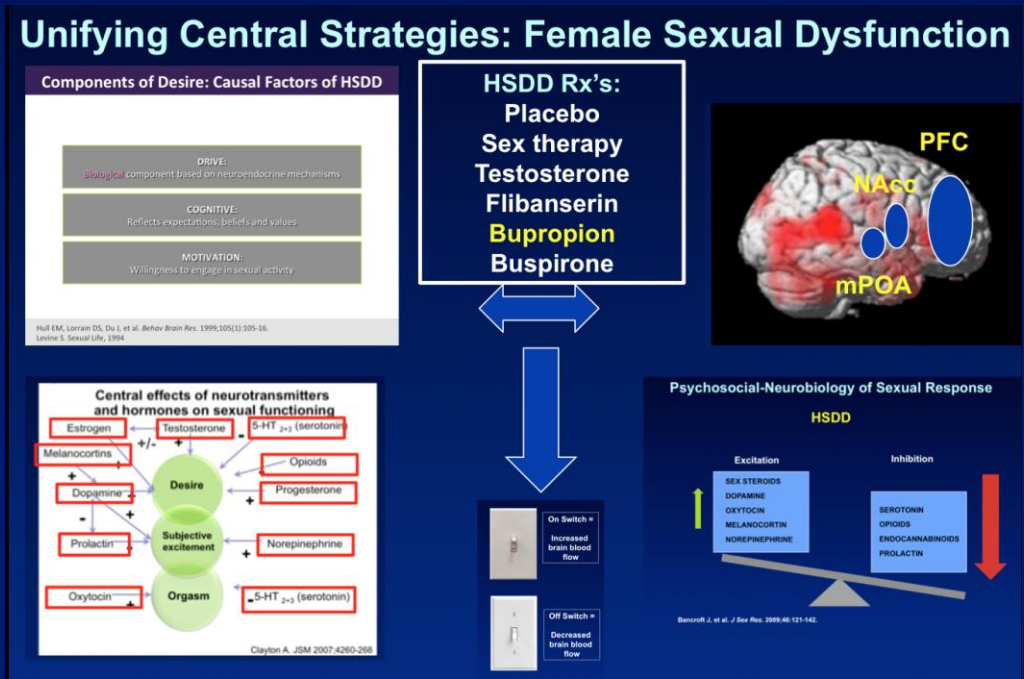
Inhibits dopamine transporter (DAT) and norepinephrine transporter (NET)

Low occupancy rate for dopamine transporter (~20%) at therapeutic concentrations

Investigated in several clinical trials for the treatment of HSDD

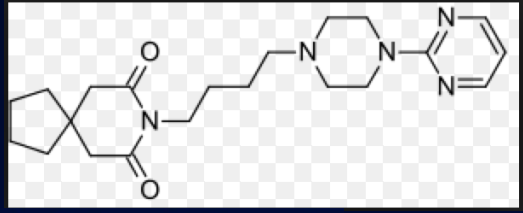
Bupropion improved sexual function (as measured by CSFQ and BISF-W)





Wellbutrin (bupropion hydrochloride) [prescribing information]. Research Triangle Park, NC; GlaxoSmithKline; revised 7/2014.
Stahl SM, et al. Prim Care Companion J Clin Psychiatry. 2004;6:159-166.
Meyer JH, et al. Psychopharmacology (Berl). 2002;163:102-105.
Carroll FI, et al. Adv Pharmacol. 2014;69:177-216.
Segraves RT, et al. J Sex Marital Ther. 2001;27:303-316.
Segraves RT, et al. J Clin Psychopharmacol. 2004;24:339-342.
Safarinejad MR, et al. BJU Int. 2010;106:832-839.

BUSPIRONE



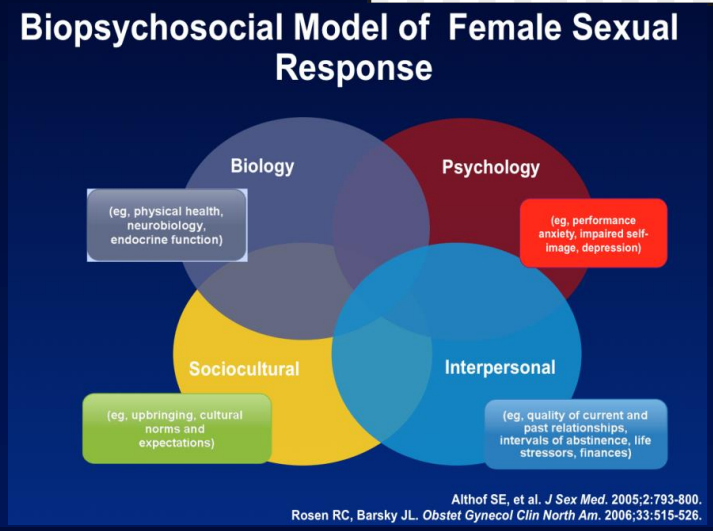
Anxiolytic approved for the management of generalized anxiety disorder or the short-term relief of the symptoms of anxiety

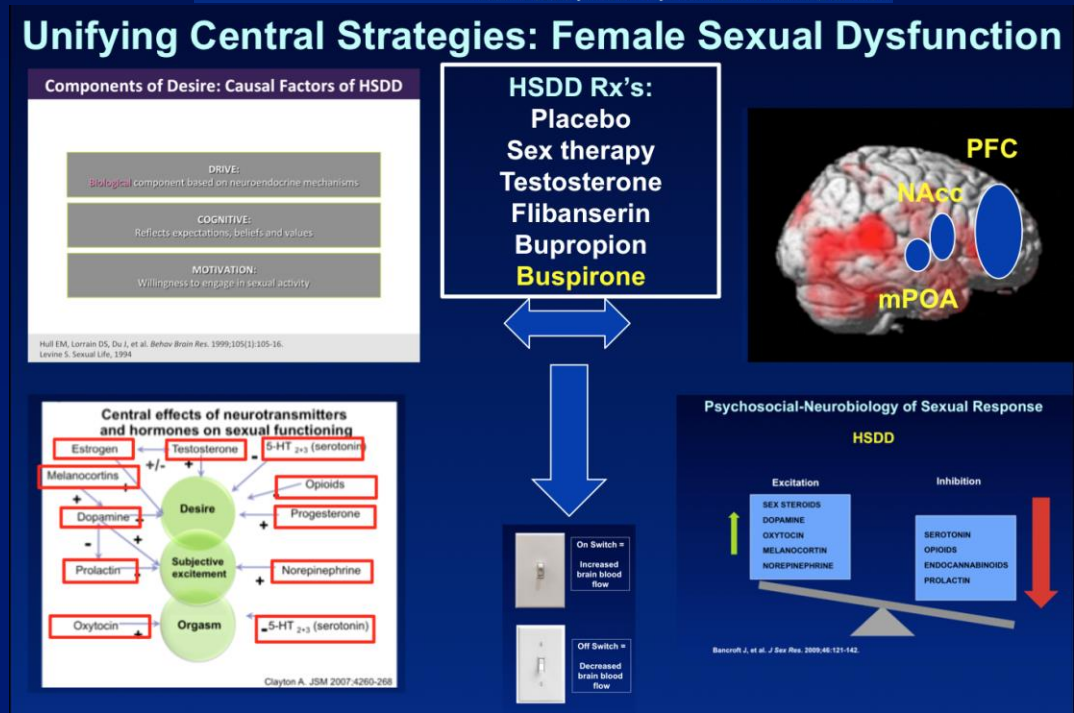
Classified as a serotonin 5-HT1A partial agonist

Greater presynaptic than postsynaptic effects, resulting in a reduction in serotonergic tone

Post hoc analysis of add-on buspirone to a selective serotonin reuptake inhibitors (SSRI) for the treatment of depression showed improvement in SSRI-induced sexual dysfunction

- **58% of subjects treated with buspirone reported an improvement in sexual function, compared with 30% treated with placebo**





Buspirone hydrochloride [prescribing information]. Teva Pharmaceuticals USA Inc. Revised 8/2013.
Loane C, Politis M. Brain Res. 2012;1461:111-118.
Landén M, et al. J Clin Psychopharmacol. 1999;19:268-271.

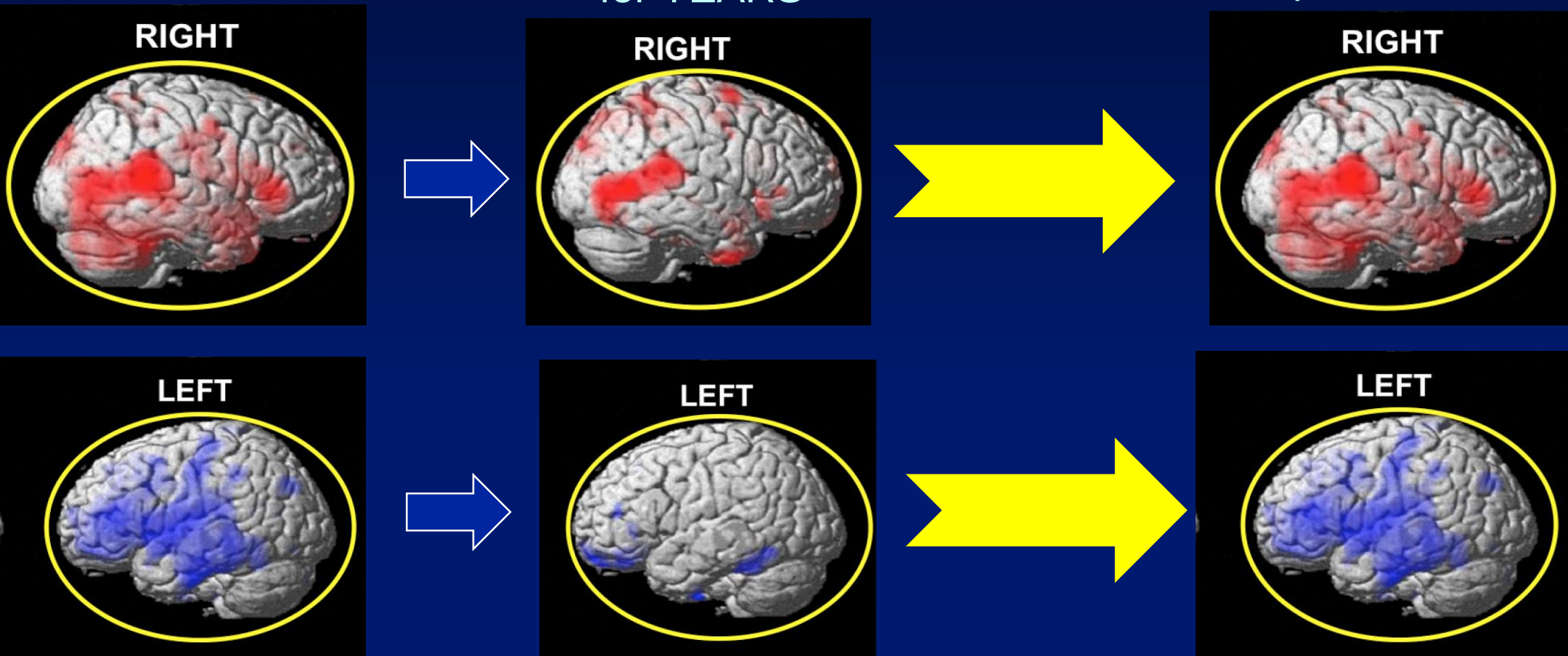
Neuroplasticity in HSDD

Neuroplasticity - brain plasticity, - umbrella term describing lasting change to the brain - research showed many aspects of the brain remain changeable (or "plastic") even into adulthood

NHSD

Generalized Acquired HSDD for YEARS

Prolonged Treatment of Generalized Acquired HSDD



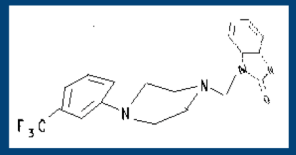
Neuroplasticity in HSDD

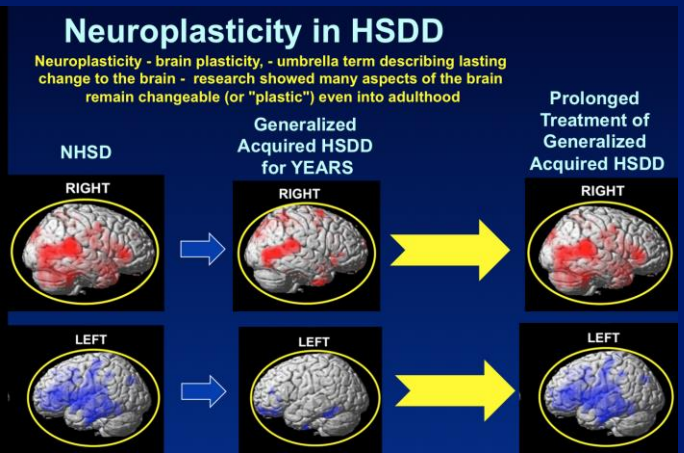
Flibanserin History - February 2006

Neuroplasticity - brain plasticity, - umbrella term describing lasting change to the brain - research showed many aspects of the brain remain changeable (or "plastic") even into adulthood

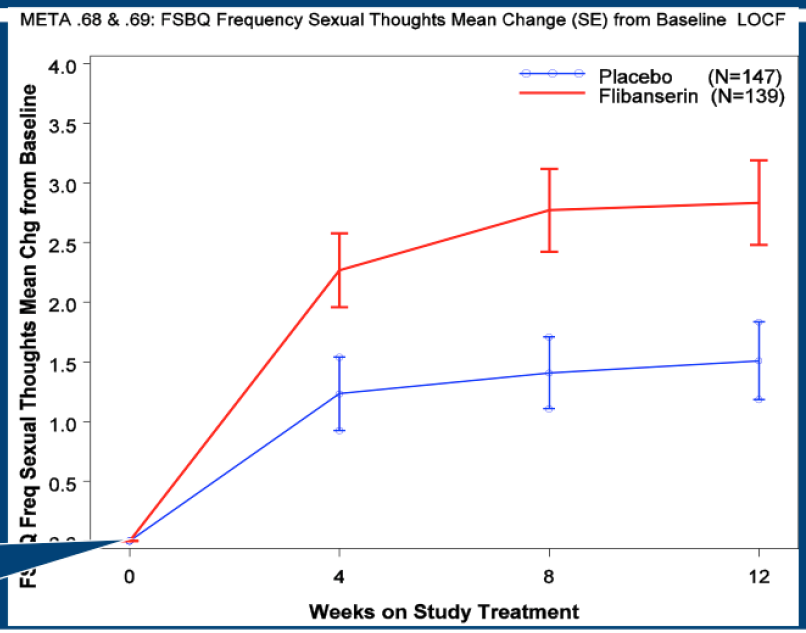
Flibanserin: a brief history...

- 1992:
  - Evidence that primary effects of SSRIs can be reproduced by 1 of 15 known 5-HT receptors: 5-HT1a
  - Blier and deMontigny (McGill) suggest that blockade of the 5-HT2a receptor would result in enhanced effectiveness of a 5HT1a agonist
  - BI initiates drug discovery for a combined 5-HT1a agonist/5-HT2a antagonist, produces BIMT-17 (flibanserin)





PoC Trials Pooled - Sexual Thoughts Days per Month, Mean Change From Baseline



Baseline Means about 3.5 days/ month

FSBQ Frequency Thoughts Mean Change from Baseline			
P-Value	0.03	0.01	0.01

ANCOVA comparing treatment against placebo, controlling for Center & Baseline
LS Means are adjusted for Center and Baseline

Three Plausible Facts About HSDD

HSDD is caused by excitatory (eg. dopamone and norepinephrine) and inhibitory (eg. serotonin) neurotransmitter imbalances in key regions (eg PFC, NuACC, mPOA) of the brain

ALL TREATMENT OPTIONS FOR HSDD (placebo, sex therapy, non-hormonal, hormonal) imporve sexual desire and lower distress by chaning the balance between excitatory (eg. dopamone and norepinephrine) and inhibitory (eg. serotonin) neurotransmitters in key regions (eg PFC, NuACC, mPOA) of the brain

Prolonged HSDD leads to neuroplasticity

HSDD Screening: The Clinical Interview

Techniques for Discussing Patient's Sexual History

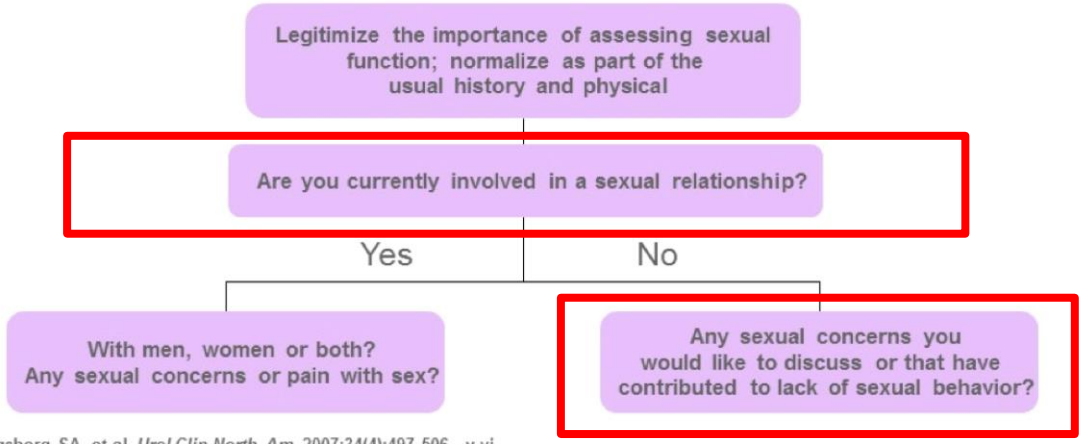
Inquiry techniques include

- Starting with general questions about sexual activity then becoming more specific
- Using a written scale or questionnaire (eg, asking patients to rate their sexual activity on a 1-10 scale)
- Using 2 types of questions:
  - Direct: "Do you have any problems related to sex?"
  - Ubiquity style: "Many women over age __ note some problems with sexual activity"

Sadovsky R, et al. *J Sex Med.* 2006;3(5):795-803.

Questions That Elicit Detailed Responses From Patients

Basic screening for sexual function: the 2-3 minute assessment



Kingsberg SA, et al. *Urol Clin North Am.* 2007;34(4):497-506, v-vi.

Decreased Sexual Desire Screener

Decreased Sexual Desire Screener (DSDS)

Dear Patient,

Please answer each of the following questions:

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

When complete, please give this form back to your clinician.

- **Specifically designed to screen for acquired, generalized HSDD**
- **Intended for use in practicing clinicians with little to no experience in recognizing HSDD**
- **Patient must answer Yes to questions 1-4 and No to all rule-outs assessed by question 5 to screen positive for HSDD**

Validated in 263 women in 27 centers across the US and Canada; compared with standard diagnostic interview, DSDS had a: i) Sensitivity of 83.6% (138/165 screened as having HSDD by both measures), ii) Specificity of 87.8% (86/98 screened as not having HSDD by both measures)

Clayton AH, et al. *J Sex Med.* 2009;6:730-738.

Non-hormonal Pharmacologic Treatments
FLIBANSERIN

History of BIMT 17

Mechanism of Action

Efficacy Clinical Trial Data

Safety Clinical Trial Data

Prescribing Information

Special Populations

Patient Testimonials

Dr. G- I have been on Flibanserin for just couple weeks now and am feeling good. I am splitting the pill in half, like we discussed, since I am also on Nexium daily. I am taking it at night and this is working out well with no side effects. I am just starting to feel like I'm getting back to my old self and am actually not dreading bedtime with my husband! I'm really hoping that some more time on this and I will be a new woman! Keep you posted…and I am also still enjoying a glass of wine almost every night with no problems at all. Talk soon, S

Patient Testimonials

Hi Dr. G, as you know I'm still in the first month of taking Flibanserin so I haven't felt the full effects. However, what I have felt is nothing short of exciting! Not only am I initiating sex with my husband but I think about it even when I'm not home with him. I probably haven't felt like this since I was a young bride many, many years ago. It's exciting to feel that as we look toward our 60s, we are going to have a healthy active sex life. Thank you so much for recommending Flibanserin! A

Patient Testimonials

Hi Dr. G, Thanks for checking in and I apologize for my delay in getting back to you. The medicine works! It kicked in in about 2 weeks and my husband and I are extremely happy. It was a bit of trouble getting Walmart to fill the prescription at first (three people working in the pharmacy looked like they were deer with headlights in their eyes), but I gave the manager the rep's phone no. and my prescription was ready to pick up the next day (they did not have any in stock). Flibanserin is a lifesaver for me and my marriage. I don't have any questions for now. Thanks for all your help. A

Patient Testimonials

Hi Dr. Goldstein- My experience with Flibanserin has been really positive. It was a slow start. After taking it for a month, the pharmacy that supplied it went out of business and finding a new place was very difficult. I mention this because it is really appalling a drug that really truly helps women is not made available to us! When I was able to start again, I was nervous because I did not see results immediately. I had basically given up hope that something would help me. But thanks to you and stories of other women who had had success, I kept taking Flibanserin and now in the second month I have started to experience results. And.... things are still improving! I still can't believe there is finally something to help. It is funny but now that I have started to see results, it is amazing how much this affects my life. Obviously my marriage is even stronger, but as you can imagine it has helped with anxiety and overall happiness :) The only side effect that I have noticed so far is that it has helped me sleep - frankly this is also pretty great. I am thankful that there is something to help. I will check back in at the end of month two and month three and let you know about any more improvements. D

Patient Testimonials

I can't sleep until I send this!! Well, after a week(ish) break for my period, Flibanserin still works!! I was actually excited to pick up where we left off and things were just as before. I used to dread the nights I knew we'd be doing something sexual. But not this time. AND, I was ready and interested again the next night. Even entertained the thought to myself of having multiple orgasms that night. But we both fell asleep before that could happen. Good thing I didn't have Matt's hopes up :) The benefits of this little pink pill far exceed the side effects - oh wait, there are none for me! Big thanks to those who pushed so hard to get this great tool added to the toolbox of those who work in sexual medicine, and with women everywhere. I am so glad I gave Flibanserin a chance! J

Patient Testimonials

I cannot believe the difference now that I am near the end of my second month! I am actually INITIATING sex! It is so amazing as I have not initiated in at least 20 years, maybe longer. I orgasm faster and more intensely And I lubricate as soon as I am aroused, which is amazing. It used to take a while for that to happen and we used KY jelly when we had intercourse, which was maybe once a month. Last week, we were on vacation and had intercourse four times. In a normal week, I supplied my husband with an orgasm,about twice, but normally did not have intercourse That is not happening at all anymore. Flibanserin is making me so happy! J

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  - Evidence that primary effects of SSRIs can be reproduced by 1 of 15 known 5-HT receptors: 5-HT1a
  - Blier and deMontigny (McGill) suggest that blockade of the 5-HT2a receptor would result in enhanced effectiveness of a 5HT1a agonist
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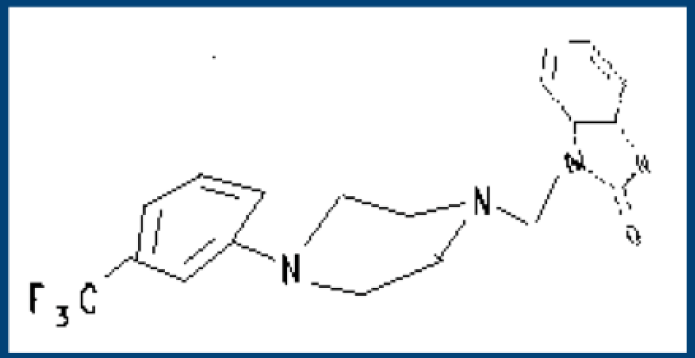
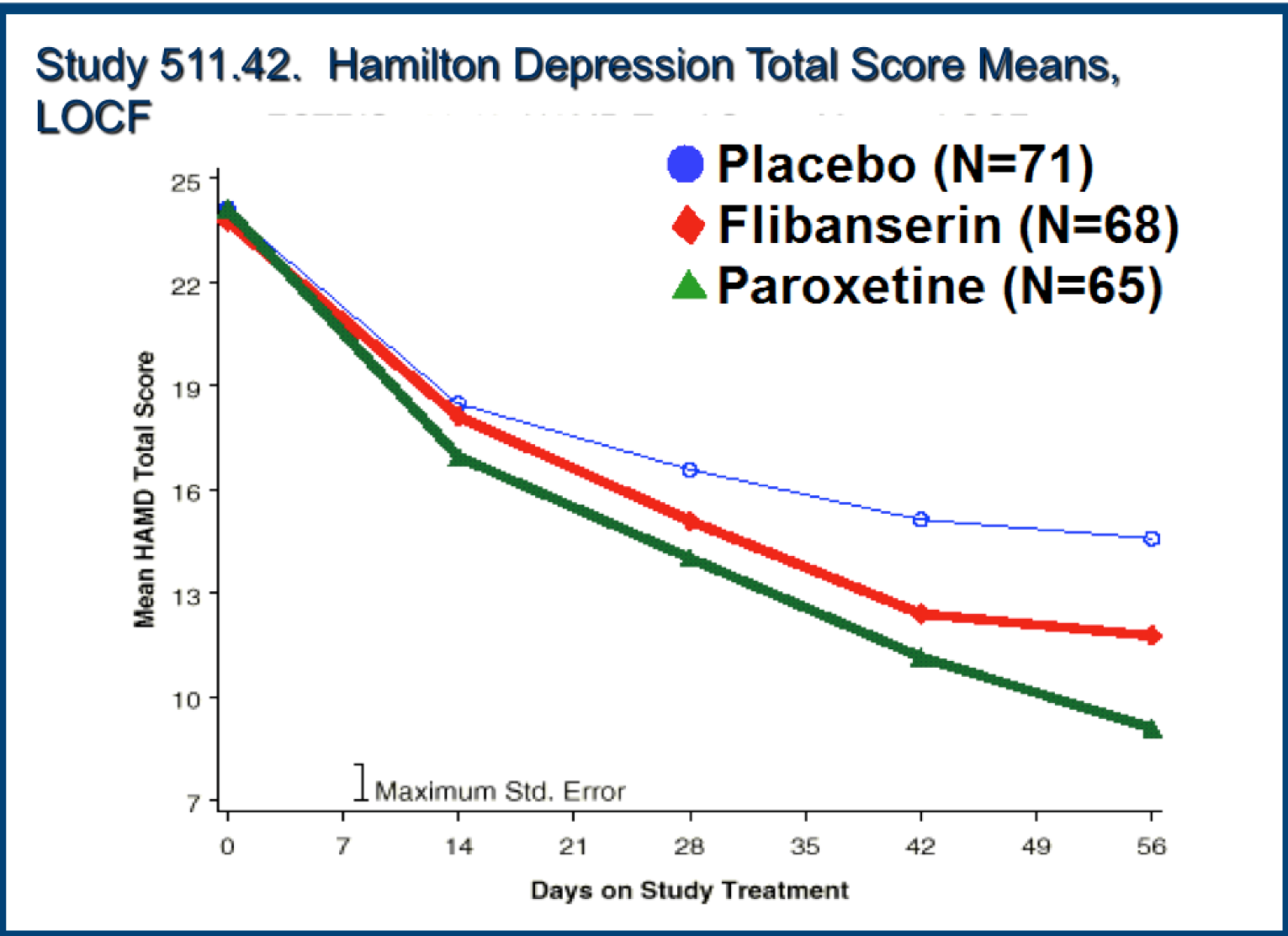


Flibanserin – Clinical Pharmacology, Safety

- PK ETC: CNS-active, pl. Cmax ~ 1 hr, $t_{1/2}$ ~7 hr, CYP 3A4 metabolism
- SIDE EFFECTS - dose-related, somewhat transient (median, 1-4 wks)
  - Sedation/somnolence/tiredness for ~1-4 hrs
  - Dizziness, nausea
- SAFETY: no effect on gonadal steroids, ECG (QT), BP, etc.
  - Corneal opacities in dogs fed 75-100 mg/kg/day chronically
    - No eye abnormalities > with placebo in humans
  - No excess suicidal ideation or attempts in depressed pts
  - No evidence abuse potential (overuse, highs, withdrawal events)
  - Minor anticoagulant effects - like other serotonergic agents?
    - Non-serious bleeding - mainly menstrual in women
      - more risk when taking ASA/NSAIDs, 5.4% vs 1.5% w/ placebo.

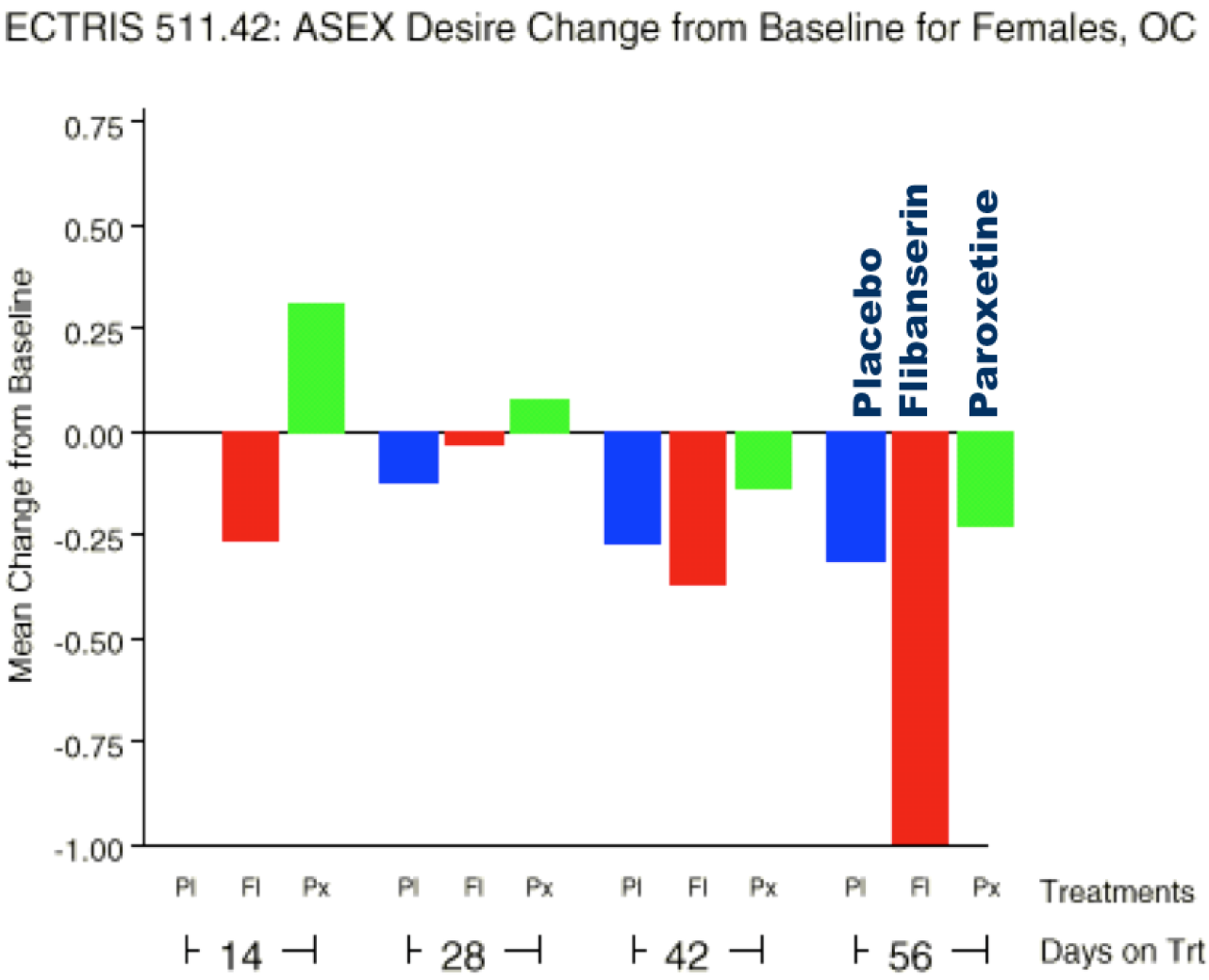
Flibanserin History - February 2006

In pts w/ Major Depression: not as good as SSRIs



Flibanserin History - February 2006

Flibanserin did help restore sexual desire in depressed women in some studies.



Flibanserin History - February 2006

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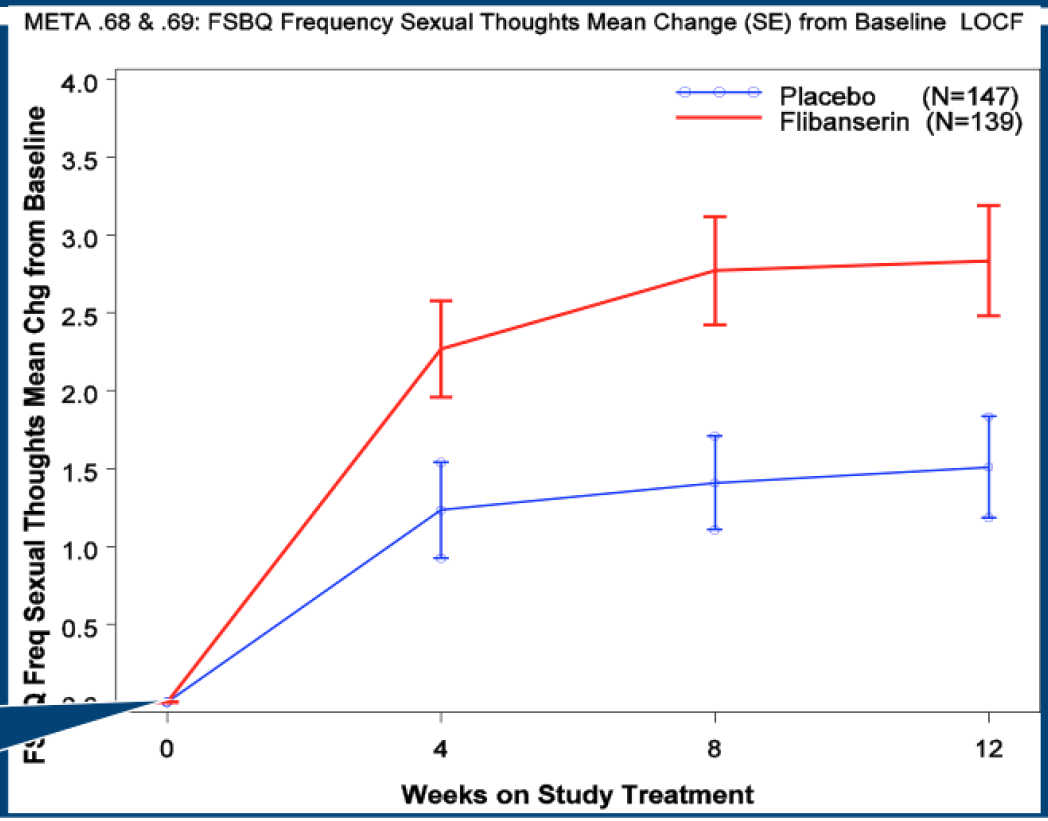

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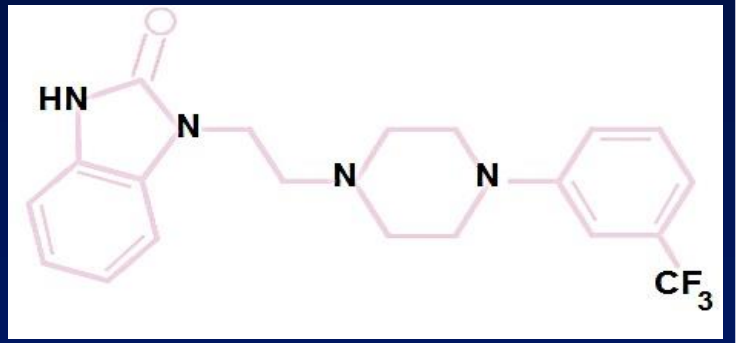
Flibanserin: Structure/Mechanism of Action

- In vitro binding studies: Addyi has high affinity for serotonin 5-HT_{1A} and 5-HT_{2A} receptors[1]
- In vitro binding studies: Addyi functions as a 5-HT_{1A} agonist and 5-HT_{2A} antagonist[1]
- In vitro binding studies: Addyi moderately blocks 5-HT_{2B}, 5-HT_{2C}, and dopamine D_4 receptors[1]



1. Borsini F, Evans K, Jason K, et. al. Pharmacology of flibanserin. *CNS Drug Rev.* 2002;8(2):117-42.

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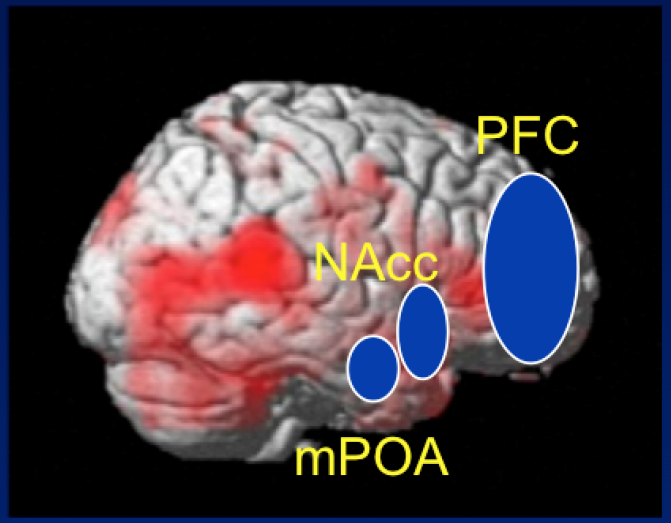

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Mechanism of Action

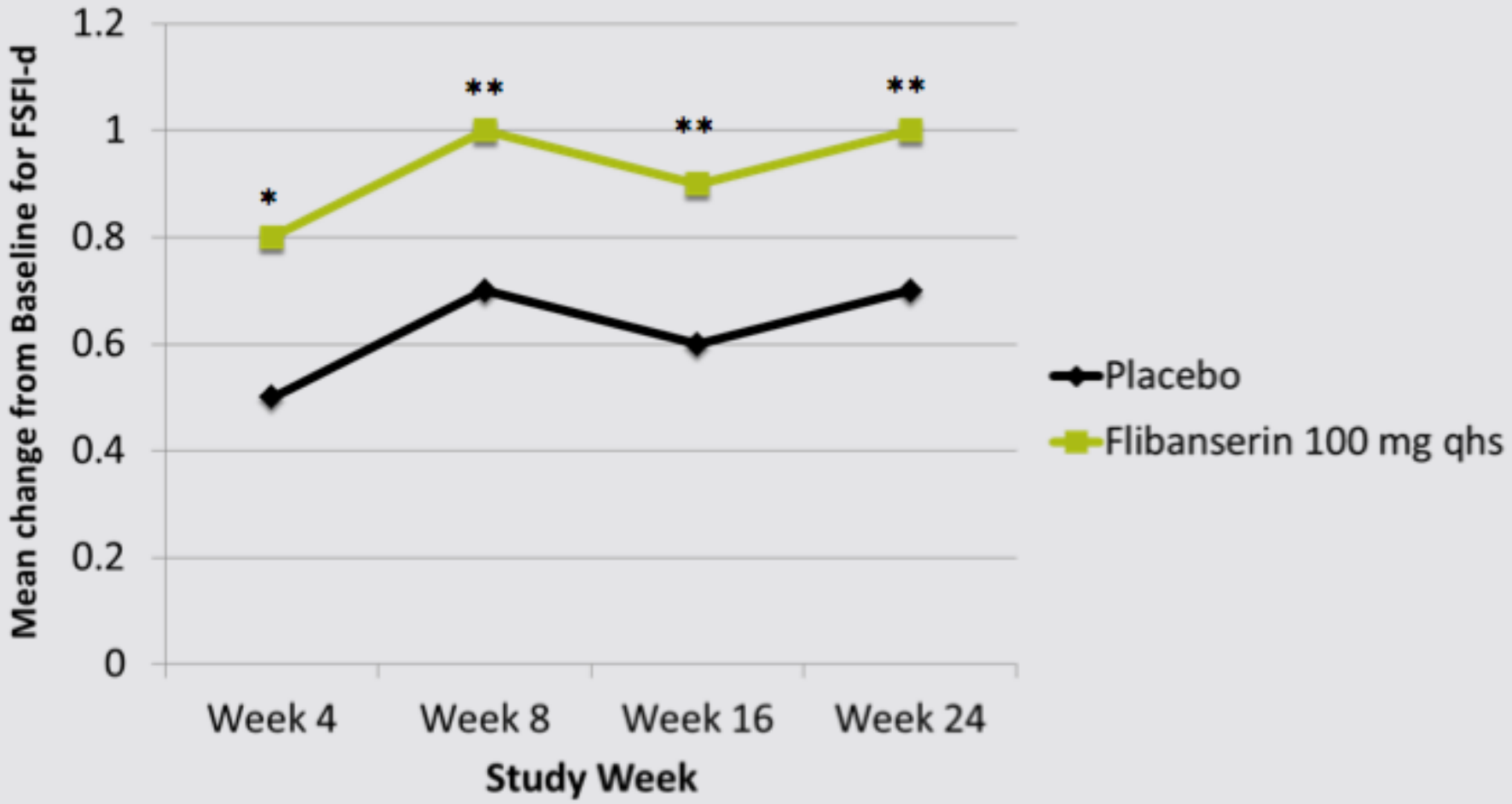
Efficacy Clinical Trial Data

Safety Clinical Trial Data

Prescribing Information

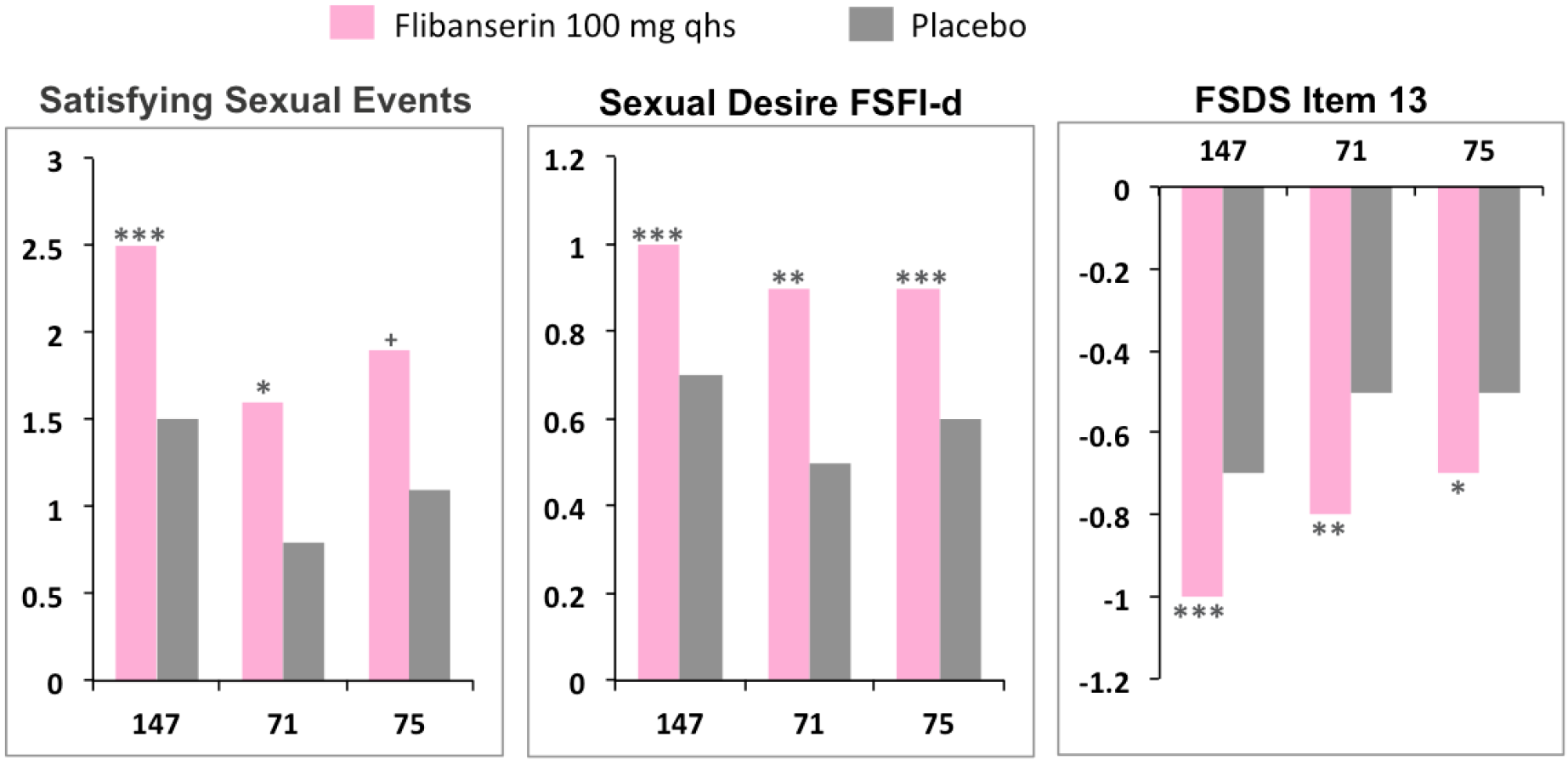
Special Populations

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



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

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.

Efficacy

Flibanserin was evaluated in three pivotal 24-week randomized Phase 3, six-month, double- blind, placebo-controlled, parallel-group, North American studies of premenopausal women with a median age of 36.

The women in the flibanserin clinical trials were in long term relationships for 10 years, they had HSDD for half of that time on average (4-5 years) and within 6 months flibanserin improved 43%-60% of them.

Flibanserin consistently demonstrated statistically significant difference over placebo on three key efficacy endpoints: increase in sexual desire, decrease in distress from the loss of sexual desire and increase in the number of satisfying sexual events.

Women receiving flibanserin reported a 53% increase in sexual desire, as measured by the Female Sexual Function Index (FSFI) desire domain score compared to baseline.

Efficacy

Flibanserin doubled the number of satisfying sexual events.

Women receiving flibanserin experienced a nearly 30% decrease in sexual distress, as measured by the Female Sexual Distress Scale-Revised (FSDS-R) total score compared to baseline.

Women treated with flibanserin showed significant improvements at every point of measurement in all pivotal clinical trials, with benefits seen as early as four weeks and sustained over the 24-week treatment period.

Women in the clinical trials themselves judged their improvements to be clinically meaningful to them.

Flibanserin – Efficacy Summary

Flibanserin is a novel, non-hormonal drug that has been clinically studied in more than 11,000 women

Flibanserin helps restore control over the brain's motivation and reward structures enabling sexual desire - accomplished by the rebalancing of neurotransmitters that influence sexual desire

Flibanserin increases dopamine and norepinephrine (both responsible for sexual excitement) while transiently decreasing serotonin (responsible for sexual satiety/inhibition)

Flibanserin will not work to restore desire for all women

Clinical studies have shown that it will work for some women who have biologically-rooted HSDD sexual dysfunction

Non-hormonal Pharmacologic Treatments
FLIBANSERIN

History of BIMT 17

Mechanism of Action

Efficacy Clinical Trial Data

Safety Clinical Trial Data

Prescribing Information

Special Populations

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. 2013 Mar;9(3)

Does abruptly stopping Flibanserin lead to an increase in adverse events?

Withdrawal effects were assessed after women were switched from the open-label period (all receiving Flibanserin) to the double-blind period - half receiving placebo, half continuing to receive Flibanserin

Parameter	Women Switched From Flibanserin to Placebo (N = 170)	Women Who Continued on Flibanserin (N = 163)
Women with any AE	**32.4% (55)**	**32.5% (53)**
Headache	2.9% (5)	2.5% (4)
Dizziness	2.9% (5)	0.6% (1)
Paresthesia	1.2% (2)	0
Nausea	3.5% (6)	1.2% (2)
Dyspepsia	0	1.8% (3)
Insomnia	1.8% (3)	1.8% (3)
Diarrhea	0	1.2% (2)
Depression	0.6% (1)	2.5% (4)
Altered mood	0	1.2% (2)
Anxiety	1.2% (2)	0
Irritability	2.4% (4)	0.6% (1)
Fatigue	1.8% (3)	0.6% (1)

Goldfischer ER, et al. *J Sex Med*. 2011;8:3160-3172.

Table 1 Adverse Reactions* Leading to Discontinuation in Randomized, Double-blind, Placebo-controlled Trials in Premenopausal Women with HSDD

	Placebo (N=1556)	ADDYI (N=1543)
Dizziness	0.1%	1.7%
Nausea	0.1%	1.2%
Insomnia	0.2%	1.1%
Somnolence	0.3%	1.1%
Anxiety	0.3%	1%

*Adverse reactions leading to discontinuation of ≥1% of patients receiving 100 mg ADDYI at bedtime and at a higher incidence than placebo-treated patients.

Hypotension and syncope were not noted in Table 1 because these complaints were less than 1%

Flibanserin Packge Insert

Table 2 Common Adverse Reactions* in Randomized, Double-blind, Placebo-controlled Trials in Premenopausal Women with HSDD

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

* Adverse reactions reported in ≥2% of patients receiving 100 mg ADDYI at bedtime and at a higher incidence than placebo-treated patients.

Prevalence of Flibanserin-Associated Hypotension and Syncope

Table 2. Subjects with Hypotension/Syncope-Related AEs in Phase 3 Studies of Flibanserin

Adverse Event, % (N)	Placebo (n=1,905)	Flibanserin 100 mg qhs (n=1,543)	Flibanserin Any Dose (n=3,973)
Syncope	0.1% (2)	0.3% (4)	0.2% (7)
Vasovagal syncope	<0.1% (1)	0	<0.1% (1)
Postural dizziness	<0.1% (1)	0	<0.1% (2)
Loss of consciousness	0	<0.1% (1)	<0.1% (2)
Decreased blood pressure	0	0	<0.1% (1)
Hypotension	0	0.2% (3)	0.1% (4)
Circulatory collapse	<0.1% (1)	<0.1% (1)	<0.1% (1)
Total patients	**0.3% (5)**	**0.5% (8)**	**0.4% (16)**

No signals for syncope or hypotension-related adverse events (AEs) were noted during Phase 3 trials

Prevalence of Flibanserin-Associated Hypotension and Syncope

Table 1. Overall incidence of hypotension/syncope-related AEs in clinical trials of flibanserin

Study	Hypotensive/Syncope-Related Events	Population Size	Incidence Rate
Phase 3 trials*	16	3973	0.4%
Phase 1 studies†	6	1235	0.5%
Phase 1 **CYP3A4 inhibitor combination studies**	4	62	6%
Phase 1 **Alcohol Study**	10	25	40%

Data on file.* Patients who experienced hypotensive/syncope-related events on any dose of flibanserin in 5 Phase 3 trials

† Patients who experienced hypotensive/syncope-related events on flibanserin alone in 38 Phase 1 studies

No signals for syncope or hypotension-related adverse events (AEs) were noted during Phase 3 trials or Phase 1 studies in premenopausal women

Prevalence of Flibanserin-Associated Hypotension and Syncope

Table 1. Overall incidence of hypotension/syncope-related AEs in clinical trials of flibanserin

Study	Hypotensive/Syncope-Related Events	Population Size	Incidence Rate
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Data on file.* Patients who experienced hypotensive/syncope-related events on any dose of flibanserin in 5 Phase 3 trials

† Patients who experienced hypotensive/syncope-related events on flibanserin alone in 38 Phase 1 studies

Clinically significant AEs of hypotension and syncope were observed in three Phase 1 studies of flibanserin: daytime dosing and either i) high exposure due to co-administration of a CYP3A4 inhibitor, ii) direct administration of a supra-therapeutic dose of flibanserin, or iii) concomitant alcohol use

Flibanserin Alcohol Interaction

A single-center, randomized, double-blind, single-dose, 5-treatment crossover study was conducted in twenty-five healthy subjects (23 males and 2 premenopausal women)

The study was conducted to assess the impact of co-administering two concentrations of ethanol, 0.4g/kg (equivalent of 2 glasses of wine) and 0.8 g/kg (equivalent to 4 glasses of wine) with Flibanserin 100 mg

1. 100 mg of Flibanserin alone
2. 0.4 g/kg 95% ethanol (equivalent to two 12-ounce cans of beer containing 5% alcohol content, two 5-ounce glasses of wine containing 12% alcohol, or two 1.5-ounce shots of 80 proof spirit in a 70 kg person)
3. 0.8 g/kg 95% ethanol (equivalent to four 12-ounce cans of beer containing 5% alcohol content, four 5-ounce glasses of wine containing 12% alcohol, or four 1.5-ounce shots of 80 proof spirit in a 70 kg person)
4. 100 mg of Flibanserin in combination with 0.4 g/kg 95% ethanol
5. 100 mg of Flibanserin in combination with 0.8 g/kg 95% ethanol

All doses of 95% ethanol were administered in the morning, diluted with orange juice to a total volume of 240 ml and administered orally over 10 minutes

Flibanserin Alcohol Interaction

Four of 23 subjects (17%) coadministered Flibanserin 100 mg and
0.4 g/kg EtOH (the equivalent of 2 glasses of wine) had events of hypotension or syncope

- **Systolic blood pressure reductions from 28 to 54 mm Hg**
- **Diastolic blood pressure reductions from 24 to 46 mm Hg**

Six of the 24 subjects (25%) coadministered Flibanserin 100 mg and 0.8 g/kg EtOH (the equivalent of 4 glasses of wine) experienced orthostatic hypotension when standing from a sitting position

- **Systolic blood pressure reductions from 22 to 48 mm Hg**
- **Diastolic blood pressure reductions from 0 to 27 mm Hg**

Flibanserin and Moderate or Strong CYP3A4 Inhibitors

STRONG: Ketoconazole, itraconazole, posaconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, boceprevir, telaprevir, telithromycin, and conivaptan

MODERATE: Amprenavir, atazanavir, ciprofloxacin, diltiazem, erythromycin, fluconazole, fosamprenavir, verapamil, and grapefruit juice

The concomitant use of Flibanserin with moderate or strong CYP3A4 inhibitors increases Flibanserin exposure compared with the use of Flibanserin alone

The risk of hypotension and syncope is increased with concomitant use of Flibanserin and moderate or strong CYP3A4 inhibitors.

The concomitant use of Flibanserin with moderate or strong CYP3A4 inhibitors is contraindicated

Fl;ibanserin and Patients With Hepatic Impairment

Contraindicated in Patients With Hepatic Impairment

The use of Flibanserin in patients with hepatic impairment increases Flibanerine concentrations, which can cause severe hypotension and syncope

Therefore, Flibanserin is contraindicated in patients with hepatic impairment

Non-hormonal Pharmacologic Treatments
FLIBANSERIN

History of BIMT 17

Mechanism of Action

Efficacy Clinical Trial Data

Safety Clinical Trial Data

Prescribing Information

Special Populations

Flibanserin Prescribing Information

Indication

Flibanserin is indicated for the treatment of premenopausal women with acquired, generalized hypoactive sexual desire disorder (HSDD) as characterized by low sexual desire that causes marked distress or interpersonal difficulty and is NOT due to:

i) A co-existing medical or psychiatric condition,
ii) Problems within the relationship
iii) Effects of a medication or other drug substance

Decreased Sexual Desire Screener (DSDS)

Dear Patient,

Please answer each of the following questions:

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

When complete, please give this form back to your clinician.

Flibanserin Packge Insert

Clayton AH, et al. *J Sex Med.* 2009;6:730-738.

Flibanserin Prescribing Information

DOSAGE AND ADMINISTRATION

Recommended dosage Flibanserin 100 mg taken once daily at bedtime

Flibanserin is dosed at bedtime because administration during waking hours increases risks of hypotension, syncope, accidental injury, and central nervous system (CNS) depression

Discontinue treatment after 8 weeks if no improvement

DOSAGE FORMS AND STRENGTHS

Administration during waking hours increases the risks of hypotension, syncope, accidental injury, and central nervous system depression (such as somnolence and sedation).

If a dose of Flibanserin is missed at bedtime, instruct the patient to take the next dose at bedtime on the next day.

Instruct the patient to not double the next dose.

Flibanserin Safety Information

WARNING: HYPOTENSION AND SYNCOPE IN CERTAIN SETTINGS

See full prescribing information for complete boxed warning

Use of Flibanserin and **alcohol increases the risk of severe hypotension and syncope**; therefore alcohol use is contraindicated.

Before prescribing Flibanserin, assess the likelihood of the patient abstaining from alcohol.

Counsel patients prescribed Flibanserin about the importance of abstaining from alcohol

Flibanserin is available through a restricted program called the **Flibanserin REMS program**

Severe hypotension and syncope can occur when Flibanserin is used with **moderate or strong CYP3A4 inhibitors**

Severe hypotension and syncope can occur when Flibanserin is used with in **patients with hepatic impairment**

Therefore, Flibanserin use in these settings is contraindicated

Non-hormonal Pharmacologic Treatments
FLIBANSERIN

History of BIMT 17

Mechanism of Action

Efficacy Clinical Trial Data

Safety Clinical Trial Data

Prescribing Information

Special Populations

Flibanserin and Oral Contraceptives

Oral contraceptives (OC) are classified as weak CYP3A4 inhibitors

Concomitant use of Flibanserin and OC may increase risk of AEs

- **Co-administration with OC resulted in a slight increase in the incidence of dizziness, somnolence, and fatigue when compared with Flibanserin treatment alone**

Meta-analysis results from phase 1 studies showed exposure to Flibanserin was slightly increased when coadministered with OC

- **1.4-fold increase in AUC and 1.3-fold increase in C_{max}**

AUC, area under the plasma concentration–time curve; C_{max}, maximum plasma concentration.

Flibanserin and Oral Contraceptives

Open-label, randomized, 2-way crossover, phase 1 study, 24 healthy premenopausal women were randomized to receive:

- **A single morning dose (fasting) of 30 µg EE/150 µg LNG alone**
- **VERSUS after 14 days of Flibanserin 100 mg once-daily (evening dose) treatment**

Steady-state levels of Flibanserin increased the EE C_{max} by 1.06-fold and the EE $AUC_{0-\infty}$ by 1.09-fold

Steady-state levels of Flibanserin decreased the LNG C_{max} by 1.02-fold but did not change the LNG $AUC_{0-\infty}$

All adverse events were mild to moderate in intensity (incidence of 12.5% and 100% for EE/LNG treatment alone and with coadministration of Flibanserin, respectively)

EE, ethinyl estradiol; LNG, levonorgestrel.
AUC, area under the plasma concentration–time curve; C_{max}, maximum plasma concentration.

Flibanserin and SSRI's

Preferred Term, % (n)	Placebo (n = 38)	Flibanserin Total[a] (n = 73)
Total with any AE	**71.1% (27)**	**65.8% (45)**
Headache	18.4% (7)	5.5% (4)
Insomnia	2.6% (1)	5.5% (4)
Dry mouth	2.6% (1)	5.5% (4)
Sedation	5.3% (2)	4.1% (3)
Fatigue	5.3% (2)	4.1% (3)
Anxiety	5.3% (2)	2.7% (2)
Diarrhea	5.3% (2)	2.7% (2)
Nasopharyngitis	10.5% (4)	2.7% (2)
Sinusitis	5.3% (2)	2.7% (2)
Increased appetite	5.3% (2)	2.7% (2)
Somnolence	7.9% (3)	1.4% (1)
Nausea	5.3% (2)	0
Weight increased	5.3% (2)	1.4% (1)

[a]Includes 28 patients on fixed 100 mg qhs dose and 45 patients on up-titrated dose (50 mg qhs first 2 weeks, followed by 100 mg qhs for remainder of the study).

EE, ethinyl estradiol; LNG, levonorgestrel.
AUC, area under the plasma concentration–time curve; C_{max}, maximum plasma concentration.

Flibanserin and SSRI's

QIDS-SR$_{16}$© (depressive symptoms)

- **15% fewer subjects on Flibanserin had worsened depression symptoms at week 12 compared with those on placebo**

Beck Anxiety Inventory

- **At week 12, there was no increased risk of anxiety when adding Flibanserin to an SSRI or an SNRI regimen**

C-SSRS (suicidal behavior/ideation)

- **No indication for increased risk of suicidal behavior or suicidal ideation**

No evidence of withdrawal AEs after abrupt discontinuation of Flibanserin

C-SSRS ©, Columbia Suicide Severity Rating Scale; QIDS-SR16 ©, Quick Inventory of Depressive Symptomatology-Self Report.

C-SSRS ©, Columbia Suicide Severity Rating Scale; QIDS-SR16 ©, Quick Inventory of Depressive Symptomatology-Self Report.

Flibanserin and Depression and Suicidality

Treatment with Flibanserin did not increase the incidence of depression when compared with placebo

- Depression (as an AE) was reported in 0.8% (20/2459) of the subjects taking Flibanserin 100 mg qhs and in 0.9% (24/2792) of the subjects taking placebo

Treatment with Flibanserin did not increase suicidality when compared with placebo

- Suicidal ideation was reported in <0.1% (2/2459) of the subjects taking Flibanserin 100 mg qhs and in 0.1% (4/2792) of the subjects taking placebo
- There was 1 suicide attempt in a subject taking Flibanserin; however, the subject failed to disclose a history of depression

Flibanserin and Co-Morbid Conditions

Diabetes: **women with well controlled diabetes (as determined by the investigator) with a hemoglobin A1c (HbA1c) level <7% were permitted to participate in the trials**

Hypertension: women with hypertension defined as a resting diastolic blood pressure ≥95 mm Hg were excluded from the studies

Obesity: body mass index was not used as an inclusion or exclusion criteria in the phase 3 studies

Pain*: pain due to fibromyalgia was not assessed during the Flibanserin clinical trials

Anxiety*: anxiety was included as an AE reported by 1.8% of Flibanserin-treated premenopausal women and 1.0% of placebo-treated premenopausal women

Flibanserin and Post-Menopausal Women

The efficacy and safety of Flibanserin 100 mg qhs in *postmenopausal women* was demonstrated in a 24-week randomized, double-blind, placebo-controlled study

Safety and efficacy results were similar to those seen in premenopausal women

Flibanserin is not approved for use in postmenopausal women with HSDD