Diagnosis and Management of HSDD

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HSDD

Hypoactive Sexual Desire Disorder

Definition of HSDD

Any of the following for a minimum of 6 months:

Lack of motivation for sexual activity manifested by either:

- Reduced or absent **spontaneous** desire (sexual thoughts, fantasies)

  OR

- Reduced or absent **responsive** desire to erotic cues and stimulation or inability to **maintain** desire

Loss of desire to initiate or participate, including behavioral responses such as avoidance, not secondary to a sexual pain disorder

+

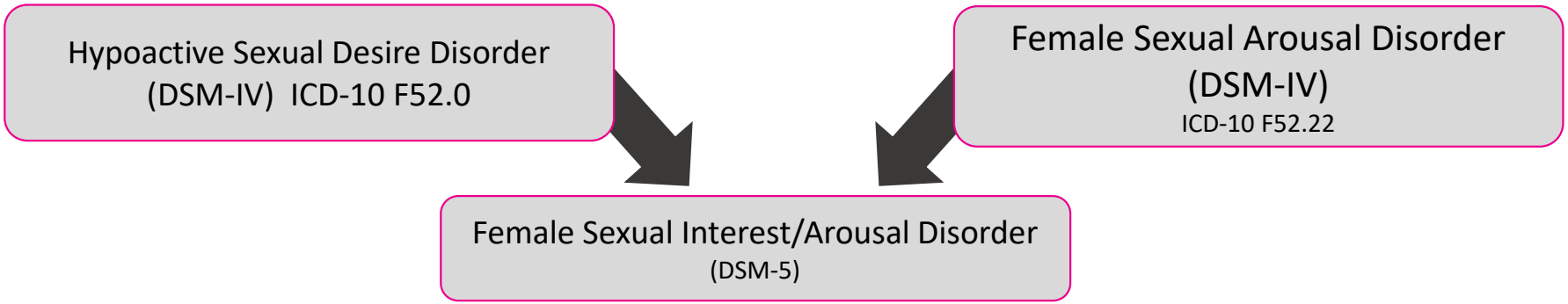
Clinically significant personal distress that includes frustration, grief, incompetence, loss, sorrow, or worry

ISSWSH = International Society for the Study of Women's Sexual Health

Parish SJ, et al. *J Sex Med.* 2016;13:1888-1906.

HSDD is a Well-defined, Long-recognized Condition

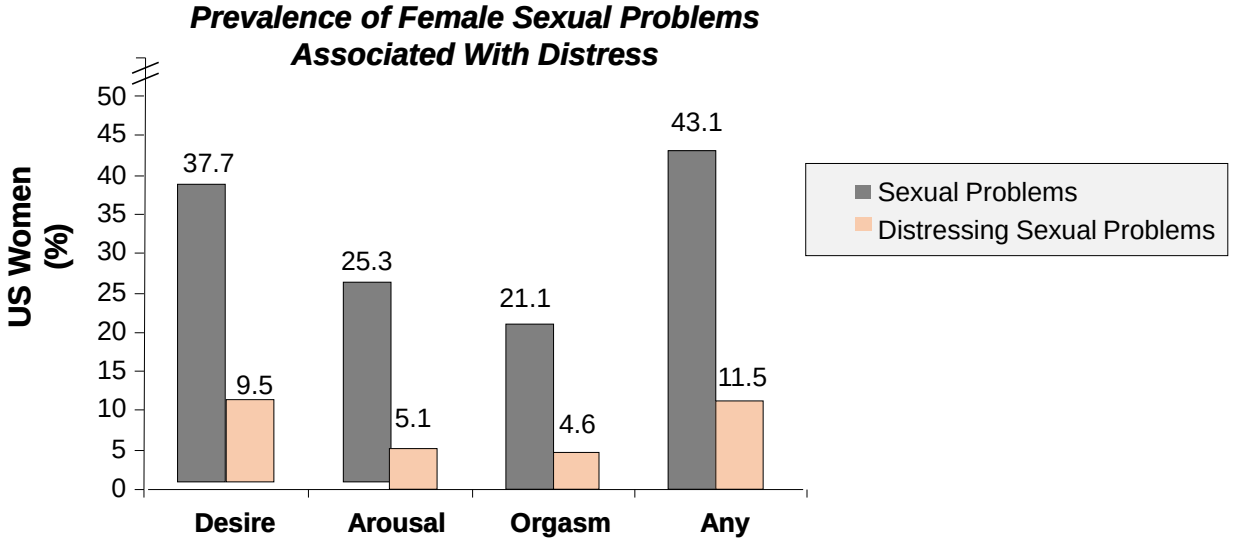
- Lack of sexual interest was first characterized in the medical literature in 1977[1]
- HSDD was first defined in the Diagnostic and Statistical Manual of Mental Disorders in 1987[2]
- Today, HSDD is defined as **persistently** or **recurrently deficient** (or absent) **sexual fantasies** and **desire** for sexual activity accompanied by **clinically significant distress**, and is **not otherwise accounted for** by a general medical or psychiatric condition[3]
  - **HSDD subtypes**: lifelong or acquired, generalized or situational[3]



HSDD remains a core component of FSIAD[3,4]

Prevalence of FSD: PRESIDE

- OBJECTIVES: Estimate the prevalence of self-reported sexual problems (any, desire, arousal, and orgasm),
  the prevalence of problems accompanied by personal distress, and describe related correlates
- POPULATION: 31,581 US female respondents ≥18 years of age from 50,002 households
- RESULTS*: Response rate was 63% (n=31,581 / 50,002)



Age-Stratified Prevalence of Distressing Desire Disorders in Women

Age-stratified prevalence	18-44	45-64	65+
Desire **2868/28,447**	8.9	12.3	7.4

***Prevalence of sexual problems increased with age, but they were less distressed

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

Interpersonal Issues

- Chronic discord
  - Emotional estrangement
  - Disappointment
- Ghosts of past relationships
  - Fear of making oneself vulnerable
  - Negative expectations
- Partner sexual problems
  - Erectile dysfunction, rapid ejaculation, low or discrepant desire
  - Sexually maladroit partner
- Partner psychiatric illness
  - Addiction, depression

The Impact of Sexual Dysfunction on a Relationship

When sex is good

It adds 15-20% additional value to a relationship

When sex is bad/non-existent

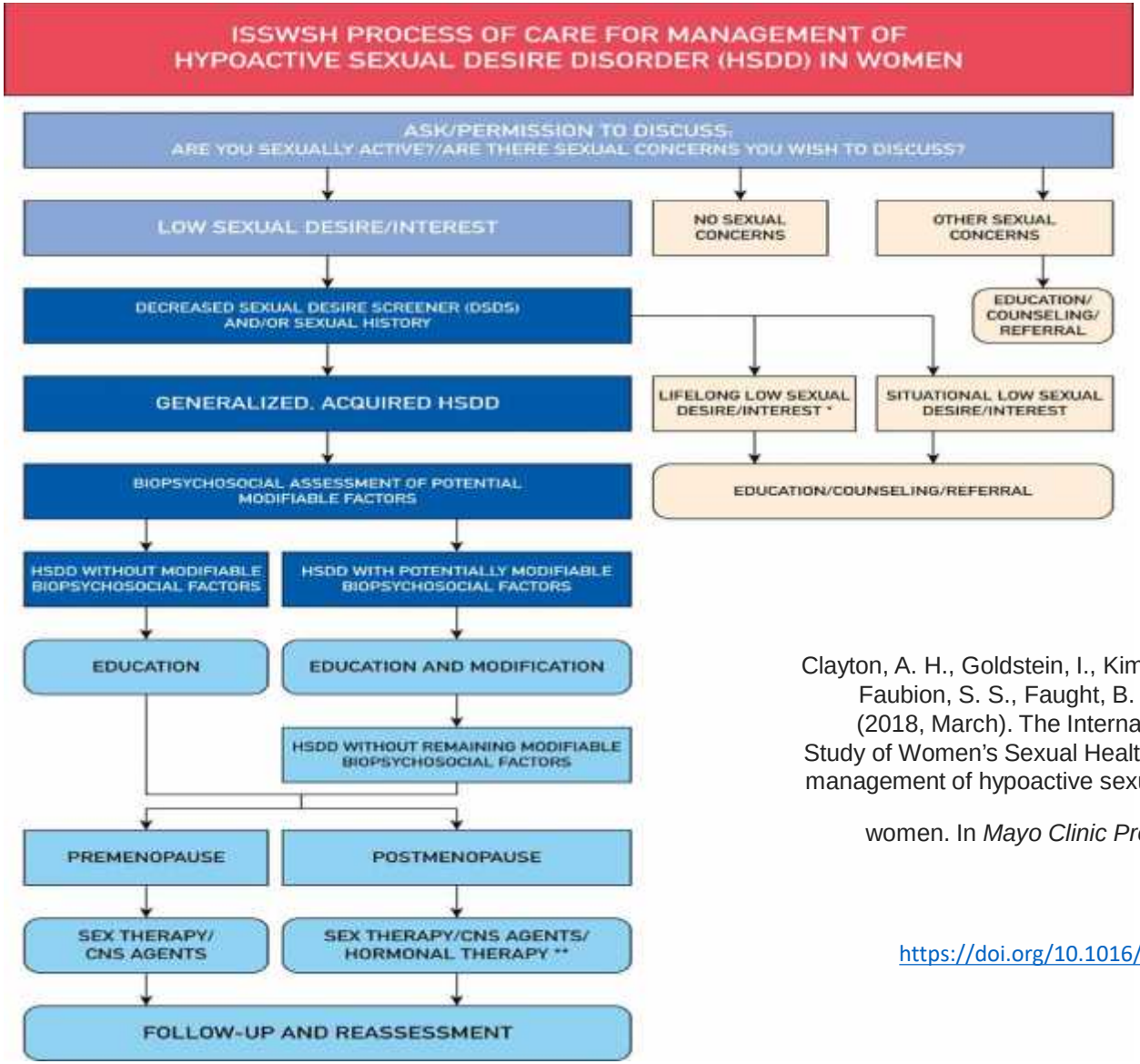
It plays an inordinately powerful role draining the relationship of all positive value, about 50-70%!

Barry McCarthy 1997 JSMT

Sexual Health Value and Cost

- Women ranked having a healthy sex life higher than career satisfaction, home ownership, traveling and social life
- 57% of women believed they were having too little sex
- Women with HSDD are 8 to 10 times more likely than women with normal desire to report feeling unhappy, disappointed, frustrated, ashamed and bitter
- Loss of Sexual Desire has similar QoL burdens on general health impact as other chronic conditions such as diabetes and back pain[2]
- Sex is critical to the survival of relationship:
  - When sex is good: It adds 15-20% additional value to a relationship
  - When sex is bad/non-existent: It plays an inordinately powerful role draining the relationship of all positive value, about 50-70%![4]

Diagnosing HSDD



Clayton, A. H., Goldstein, I., Kim, N. N., Althof, S. E., Faubion, S. S., Faught, B. M., ... & Davis, S. R. (2018, March). The International Society for the Study of Women's Sexual Health process of care for management of hypoactive sexual desire disorder in women. In *Mayo Clinic Proceedings*. Elsevier.

Open access:
https://doi.org/10.1016/j.mayocp.2016.09.018

Office Based Counseling for Sexual Problems: Follow PLISSIT Model

- Permission to talk about sexual issues, reassurance and empathy
- Limited Information
  - e.g., education about genital anatomy or educational resources
- Specific Suggestions
  - e.g., use of lubricants, altering position
- Intensive Therapy
  - e.g., referral for psychotherapy/sex therapy

Clinical Presentation

Sexual dysfunction may present in several ways:

- Having no interest in any type of sexual activity
- Never or only seldom having sexual fantasies or thoughts
- Being concerned by lack of sexual activity or fantasies

Having a basic knowledge about how to approach female sexual pain or dysfunction of any kind can help the clinician discuss this source of distress with women and their partners

[Low sex drive in women Mayo Clinic 2018; Hague Conns Current Therapy 2019]

Diagnosis

- **Complete physical exam:** identify possible contributing factors
- **Pelvic exam:** identify physical changes in labia or vagina
- **Blood tests:** hormone levels, thyroid function, diabetes, elevated cholesterol, and liver disorders

  ***when appropriate
- **Specialist referral:** specialized counselor may be helpful

[Low sex drive in women Mayo Clinic 2018]

Psychological Contributions

Mood

- Depression, irritability, rage
- Fear, shame, embarrassment

Anxiety, Sexual Self Confidence

Sleep Disturbance

- Decreases psychological resilience

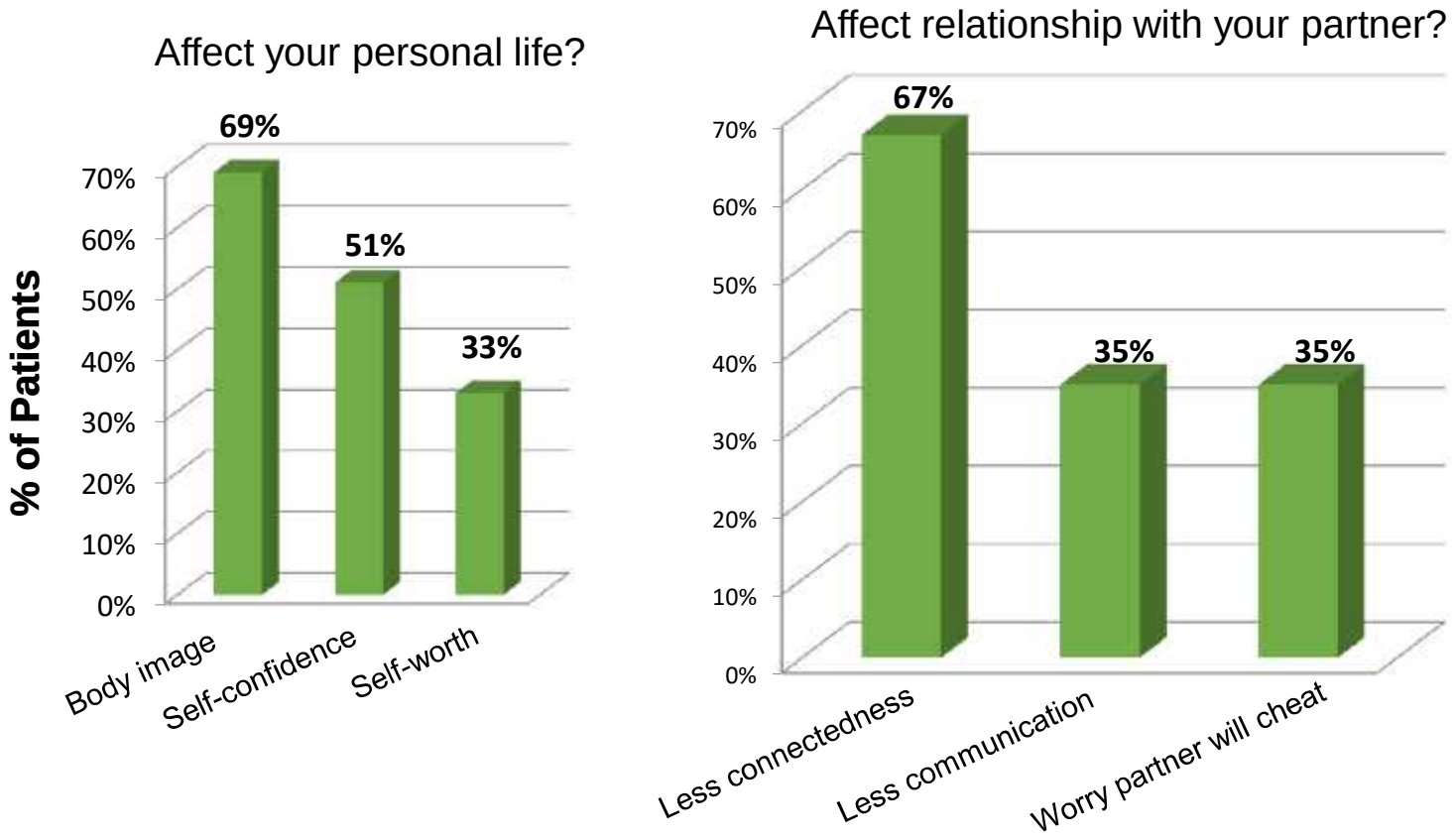
Developmental Issues

- Trauma, abuse, impact of childhood illness or surgery
- Divorce, affairs, abandonment resulting in lack of trust

Body Image

Low Sexual Desire Negatively Affects Self-image and Partner Relationships

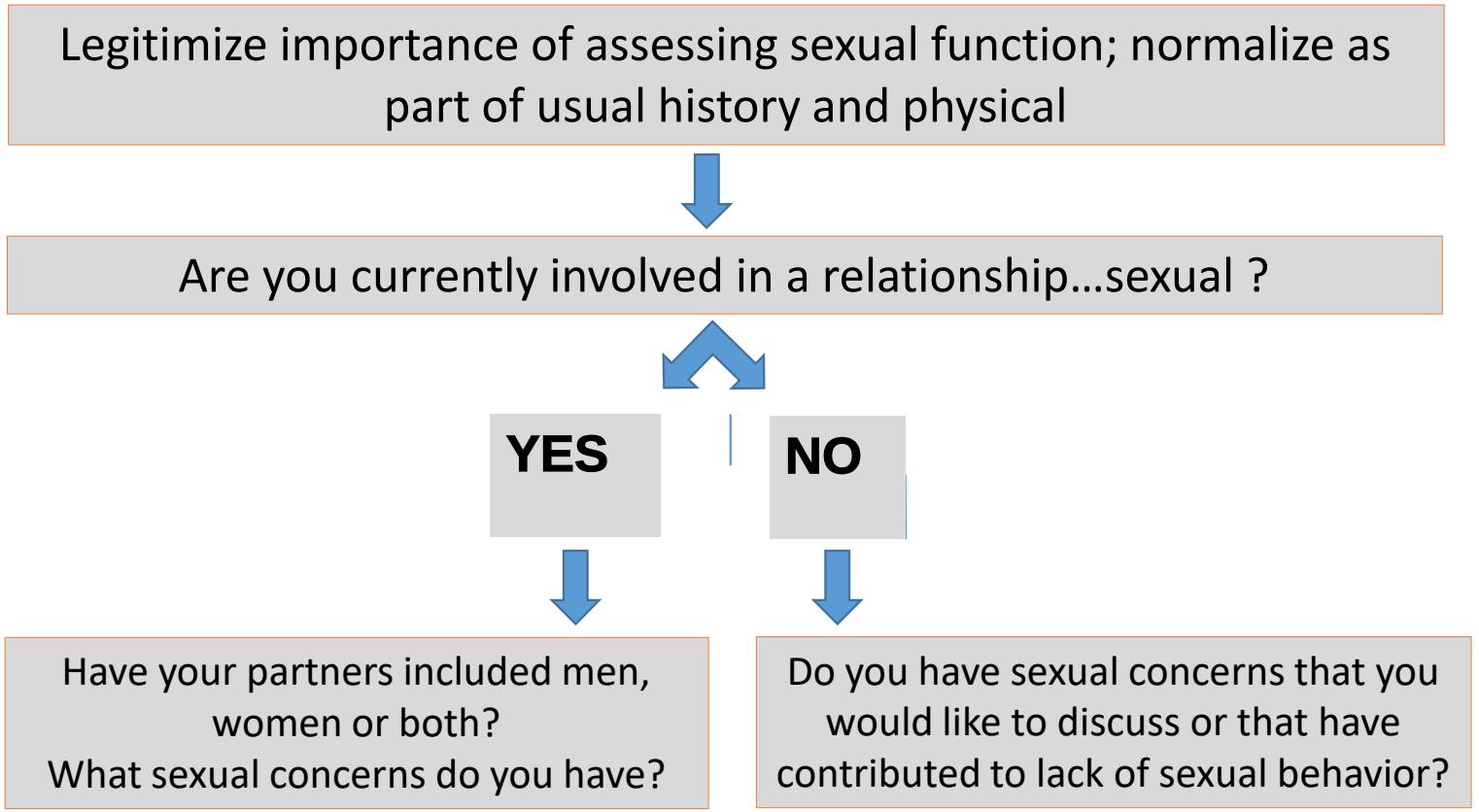
Online Survey: Premenopausal women with self-described low sexual desire (n=306)



Screening for Sexual Problems: When?

1. Written patient intake?
2. During urogenital or gynecological review of systems?
3. Consultation before and follow-up after surgery/medical procedure?
4. Routine visit for yearly exam or care of chronic illness?
5. Major life events (puberty, postpartum, menopause)?

Basic Screening Algorithm for Sexual Function



Screening for Sexual Dysfunction

- Open-ended ubiquity-style question
  - *Many of my female patients develop sexual concerns, what concerns do you have?*
- Higher yield than direct question
- Open-ended questions improve:
  - Assessment of functional impairment
  - Adherence
  - Patient satisfaction

Validated Tools to Assess FSD

Validated Tool	Assessment Area
Decreased Sexual Desire Screener (DSDS)[1]	Brief diagnostic tool for Hypoactive Sexual Desire Disorder (HSDD)
Female Sexual Function Index (FSFI)[2,3*]	Desire, arousal, orgasm, and pain
Female Sexual Distress Scale-Revised (FSDS-R)[4]	Distress

*FSFI questionnaire and scoring key available at: www.fsfi-questionnaire.com.

1. Clayton AH, et al. J Sex Med. 2009;6:730-738. 2. Meston CM. J Sex Marital Ther. 2003;29:39-46. 3. Rosen R, et al. J Sex Marital Ther. 2000;26:191-208. 4. DeRogatis L, et al. J Sex Med. 2008;5:357-364.

Decreased Sexual Desire Screener (DSDS)

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

If "NO" to Q1, 2, 3, or 4 = Not generalized acquired HSDD

If "YES" to all Q1–4 and "NO" to all Q5 factors = clinician to use best judgment to confirm a diagnosis of generalized acquired HSDD

If "YES" to all Q1–4 and "YES" to any Q5 factor = clinician to use best judgment to determine diagnosis*

*Co-morbid conditions such as arousal or orgasmic disorder do not rule out a concurrent diagnosis of HSDD

Clayton AH, Goldfischer ER, Goldstein I, et al. *J Sex Med*. 2009;6(3):730-738.

Pathophysiology of Sexual Desire and Implications for Treatment

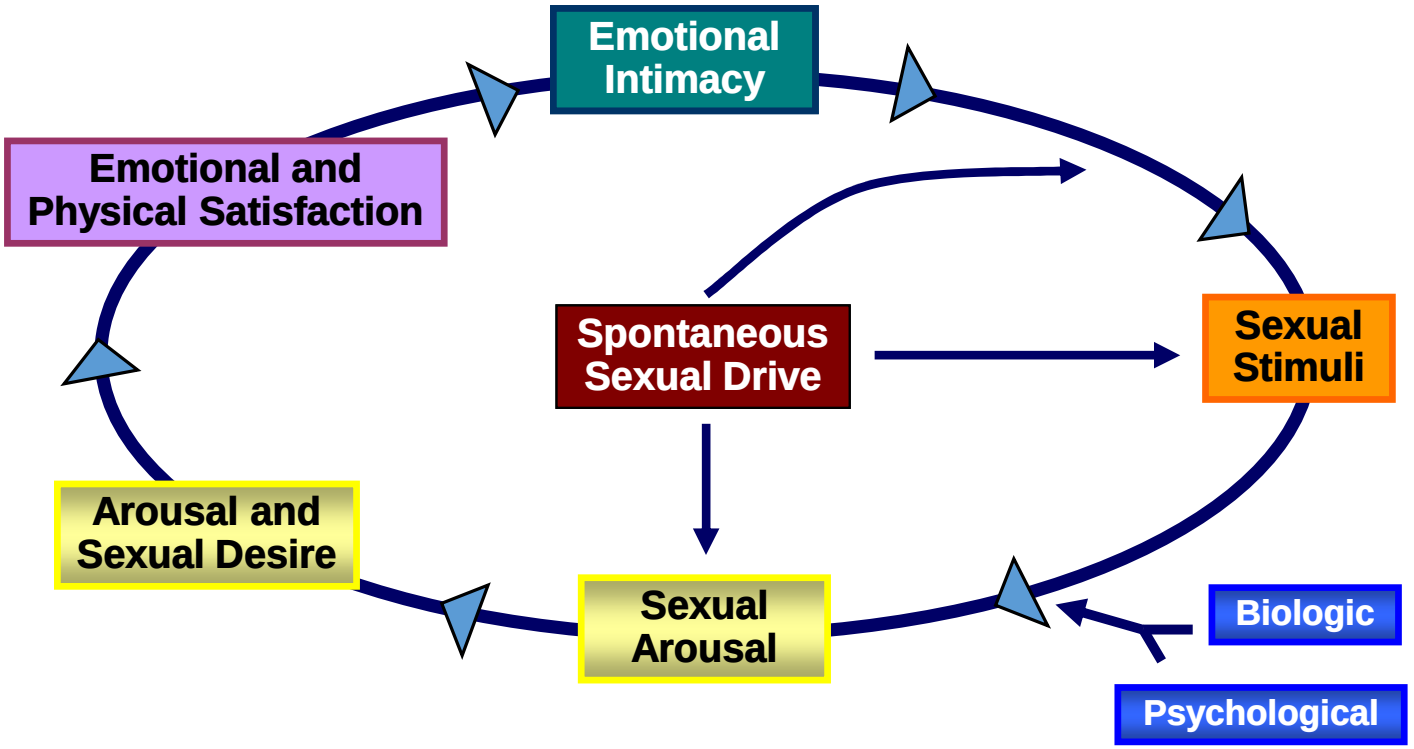
Human Sexual Response: Classic Models

Excitement
Plateau
Orgasm
Resolution

→ **Divided** → **Desire**
→ **Arousal**

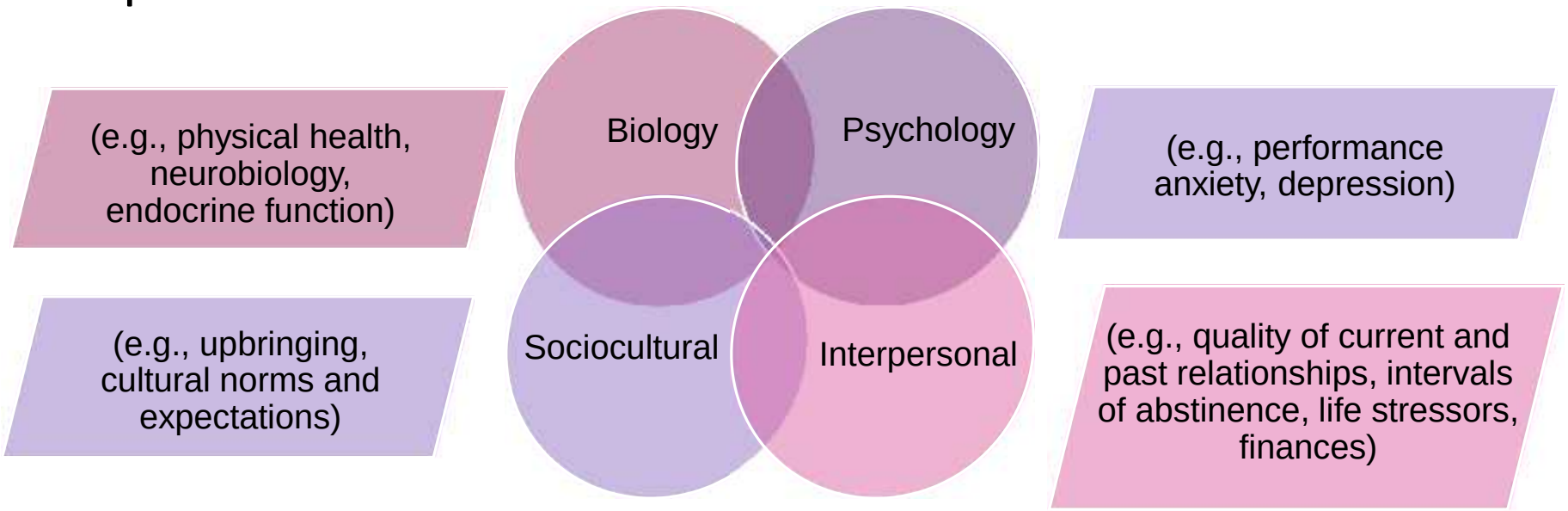
Linear Progression

Basson's Model Non-Linear Model



Basson R. *Med Aspects Hum Sex.* 2001;1:41-42.

Biopsychosocial Model of Female Sexual Response



Rosen RC, Barsky JL. Obstet Gynecol Clin North Am. 2006;334:515-526.

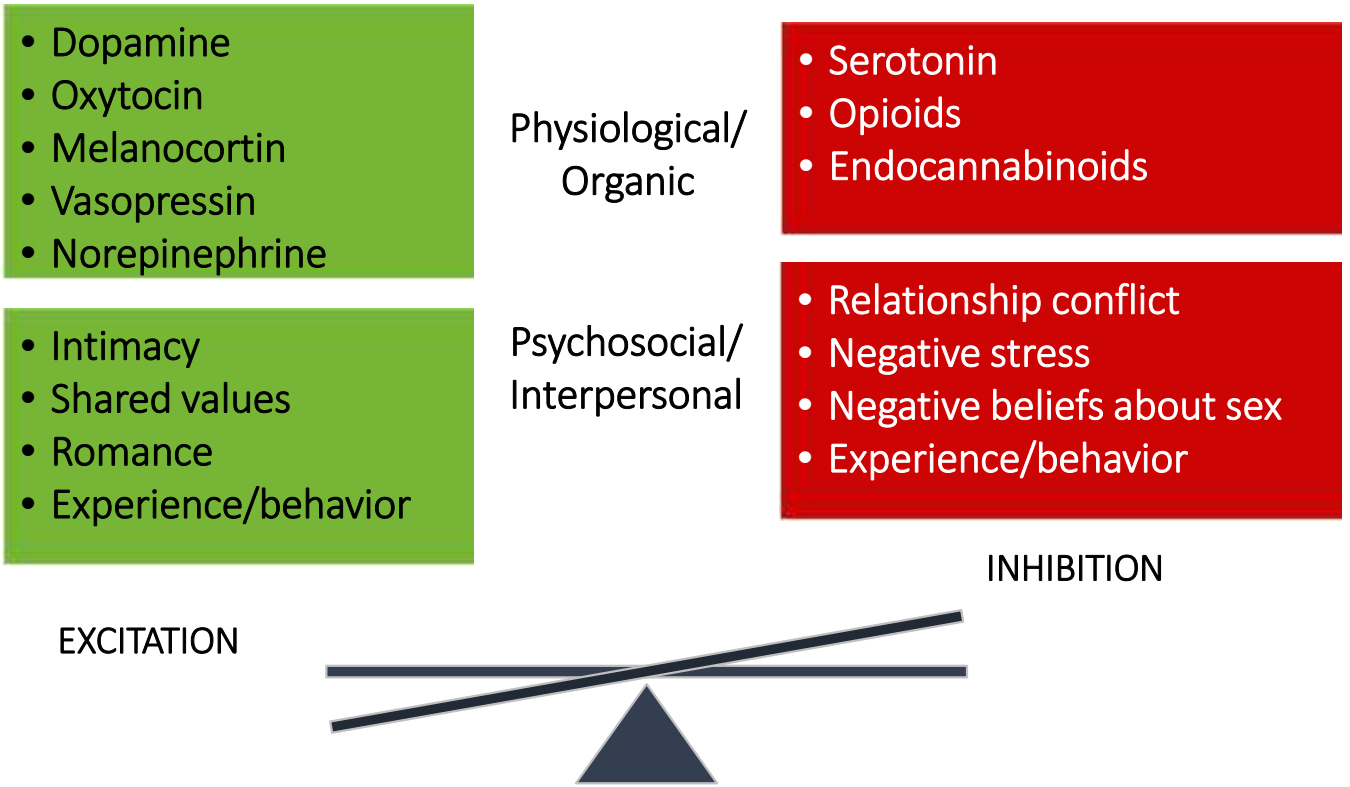
Etiology of HSDD: Imbalance Between Excitation/Inhibition

Norepinephrine and dopamine increase sexual arousal[1]

Serotonin sexual satiety signal and arousal inhibition

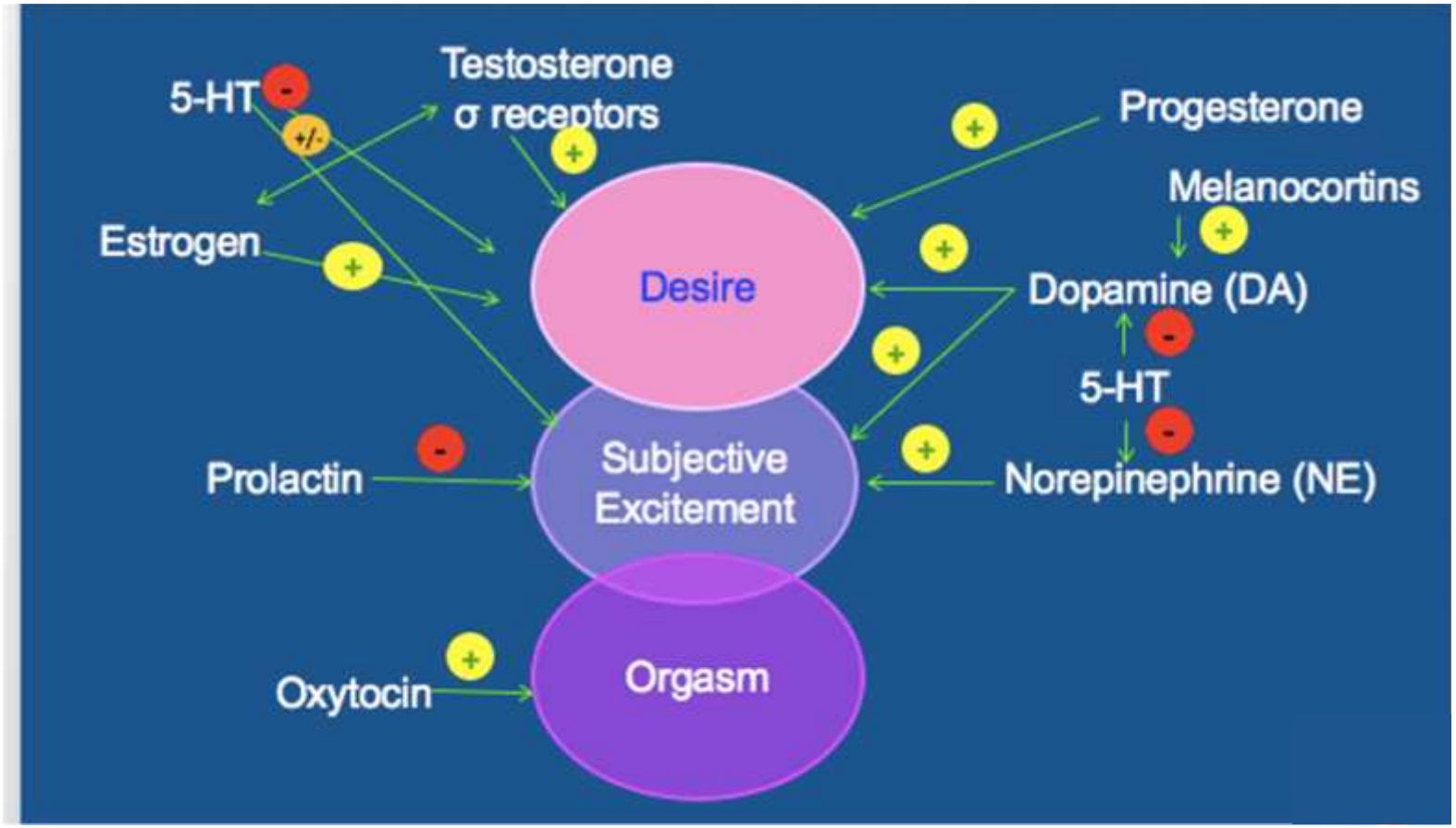
Oxytocin/melanocortins: role in attachment/bonding - ++arousal effects

Hormones (E,T) influence synthesis and storage of neurotransmitters andDeclining levels contribute to decrease in sexual arousal as well as sexual comfort[2]



1. Hull EM et al Hormone neurotransmitter interactions in the control of sexual behavior. Behav Brain Res 1999;105:105–16. 2. Perelman M J Sex Med 2007;4(suppl)280-290.

Physiology of Sexual Function-CNS

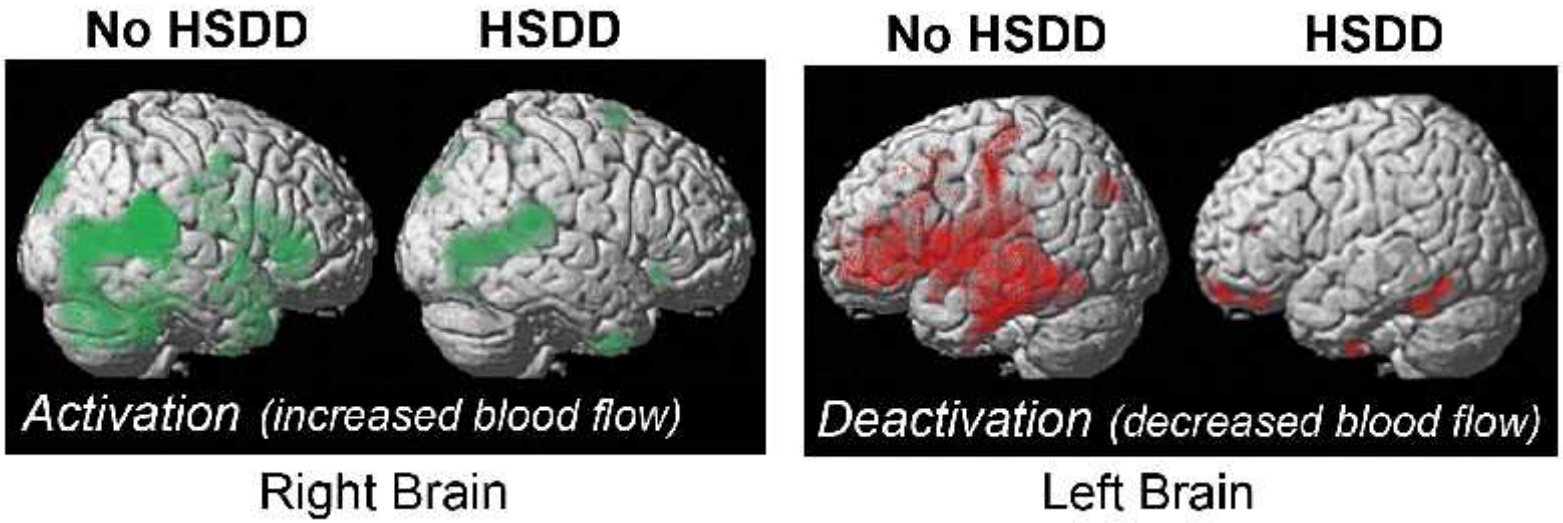


Clayton A, Hamilton D. *Psychiatr Clin N Am.* 2010;33:323-338.

Patterns of Cortical Activation and Deactivation by Erotic Visual Cues

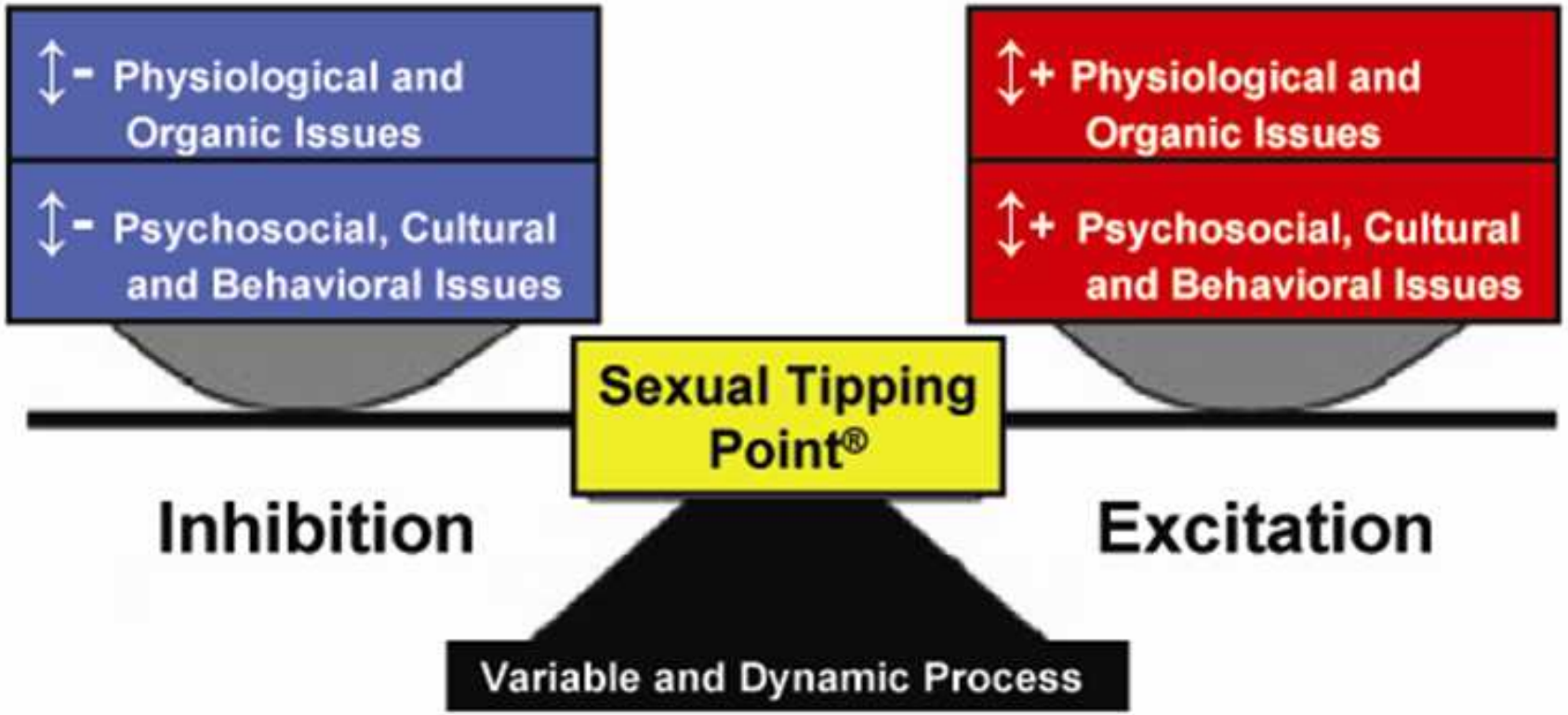
Increased blood flow = activation

Decreased blood flow = deactivation



Goldstein I, Kim NN, Clayton AH et al: Hypoactive Sexual Desire Disorder: International Society for the Study of Women's Sexual Health Expert Consensus Panel Review. Mayo Clinic Proceedings – forthcoming. MRI adapted from Holstege G, How the emotional motor system controls pelvic organs, J Sex Med, in press.

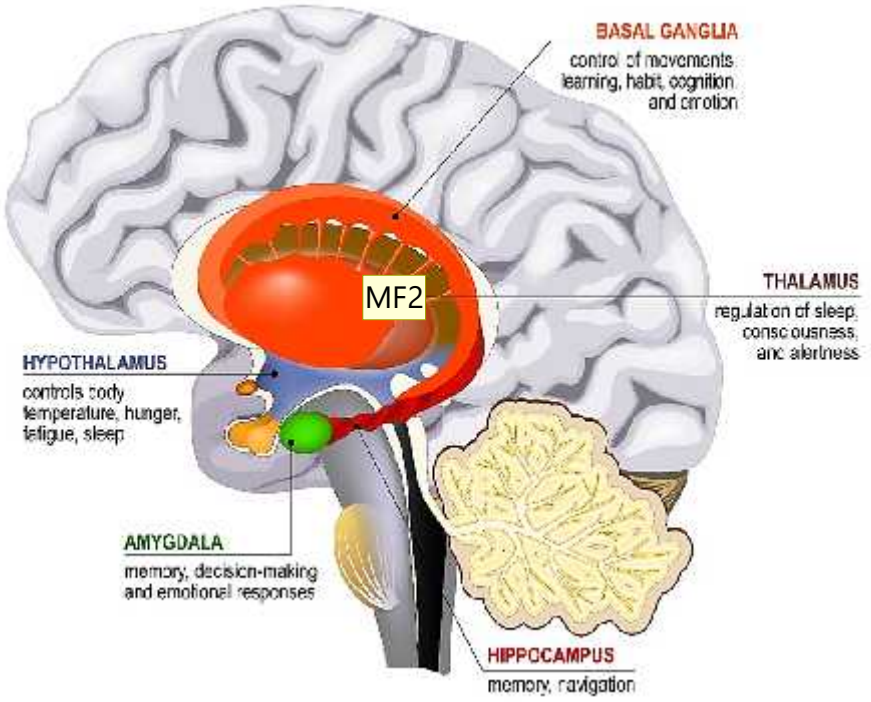
Dual Control Model



after Perelman (2006) J Sex Med, 3, 1004-1012

Female Sexual Function (FSD)

- Sexual function in the female involves both physical and psychological factors.
- Mental stimulation, as well as physical stimulation of the clitoris and female genitalia, are both important components of the female sexual response.
- FSD arises as a result of an issue in one or both of these areas.



[Maruccia Female Sexuality 2017 /p16A]

Slide 30

MF2 New photo highlighting physical and mental factors, maybe diagram of a woman showing the brain and female sexual organs

Michael Fischer, 5/8/2019

Take-Home Messages

- Sexual desire depends critically on the activation of neurochemical systems for sexual excitation by erotic cues, driven by dopamine, noradrenaline, melanocortins, and oxytocin.
- Sexual inhibition is a normal function of satiety, driven by brain opioid, serotonin, and endocannabinoid systems.
- If sexual excitation is too weak, or sexual inhibition too strong, HSDD is likely to occur in response to appropriate and competent appetitive sexual cues.
- Lack of sexual desire can also occur as adaptation of neural systems to a chronic lack of sexual pleasure.

Treatment Options for HSDD

Types of Interventions

- Non-pharmacologic therapies
  - Psychotherapy/counseling
    - Individual
    - Couple
  - OTC products
    - On label
    - Off label
- Pharmacologic therapies
  - FDA approved
  - Evidence-based, off-label

Kingsberg SA, Janata JW. *Urol Clin North Am.* 2007;34:497-506.
Simon JA, Reape KZ, Wininger S, Hait H. *Fertil Steril.* 2008;90:1132-1138.

Nonpharmacologic Treatment Options

Psychological Factor	Recommended Approach
Depression/anxiety	Pharmacotherapy/cognitive behavioral therapy
Poor self/body image	Psychotherapy
Stress/distraction	Cognitive behavioral therapy
History of abuse (physical, sexual, emotional)	Psychotherapy
Substance abuse	Psychotherapy
Self-imposed pressure for sex	Office-based counseling or refer for cognitive behavioral therapy
Religious, personal, cultural or family values, beliefs and taboos	Office-based counseling or refer for cognitive behavioral therapy
Relationship factors	Office-based counseling or refer for individual/couples therapy
Lifestyle factors (e.g., fatigue, sleep deprivation)	Office-based counseling
Sexual factors (e.g., inadequate stimulation)	Office-based counseling

Psychotherapy Goals

- Lessen performance anxiety
- Cognitive restructuring
- Understand HSDD as a metaphor of another issue
- Resolve old issues that interfere with sexual function
- (Re)gain confidence in their sexual performance
- Reconnect to their sensual selves
- Surmount barriers to intimacy
- Resolve interpersonal issues that cause/maintain HSDD
- Increase communication
- Minimize or prevent relapse

Althof, 2016

Sexual Counseling/Therapy

- Psychotherapy with a chief complaint of a sexual problem
  - Based on principles of learning and cognitive processing as the mechanism of change
- Although the stated goal is to correct a sexual problem, sex therapy often does not focus solely on sexual function
- Sexuality is best understood within a biopsychosocial model and treatment follows that model

Heiman JR. Arch Sex Behav. 2002 Oct;31(5):445-50.
Barlow DH. J Consult Clin Psychol. 1986 Apr;54(2):140-8.

Cognitive-Behavioral Psychotherapy for HSDD

- CBT focuses on identifying and altering behaviors (e.g., avoidance of sexual activity) and cognitions (e.g., unrealistic expectations) that contribute to low sexual desire in women.

- Education is also an important component of CBT and can help the woman/couple understand how adequate erotic stimulation and physical stimulation contribute to women's sexual desire and arousal.

- Because cognitive distraction during sexual activity is prevalent among women with sexual dysfunction the application of cognitive challenging strategies (i.e. identifying, challenging, and replacing irrational thoughts) is a mainstay of CBT sex therapy

Nobre P, & Pinto-Gouveia J, *Archives of Sexual Behavior*, 2008;37:652-661.

Mindfulness-based cognitive behavioral sex therapy (MBCST)

- Focus on being present without judgment
- Includes psycho-education about sexual response and cognitive therapy as well as mindfulness
- Involves skills practice of mindfulness practice, body scans, non-masturbatory genital self-stimulation
- Improves attention or focus on bodily sensations
- Theoretically may lead to neuroplastic changes in brain regions related to attention, emotion and self awareness

Brotto L, et. al. *Journal of Sexual Medicine*, 2008;5:1646-1650.

Brotto L,& Goldmeier D, *Journal of Sexual Medicine*, 2015;12:1687–1689.

Mindfulness-Based Therapy

- Based out of Eastern approaches that focus on being present without judgment
- Mindfulness-based cognitive behavioral sex therapy (MBCST) shows effectiveness for improving desire:
  - Includes psycho-education about sexual response and cognitive therapy as well as mindfulness
  - Involves skills practice of mindfulness practice, body scans, non-masturbatory genital self-stimulation
- Can be especially helpful for women who have a disconnect between genital and subjective arousal perhaps due to improving attention or focus on bodily sensations
- Increasing interest in studying the mechanisms underlying the benefits of mindfulness, and there is evidence that mindfulness leads to neuroplastic changes in the structure and function of the brain regions involved in the regulation of attention, emotion and self awareness

Brotto L, et al. *J Sex Med*, 2008; 5: 1646-1650.

Brotto L, Goldmeier D, *J Sex Med*, 2015; 12: 1687–1689.

Psychotherapy/Sex Therapy: Common Themes

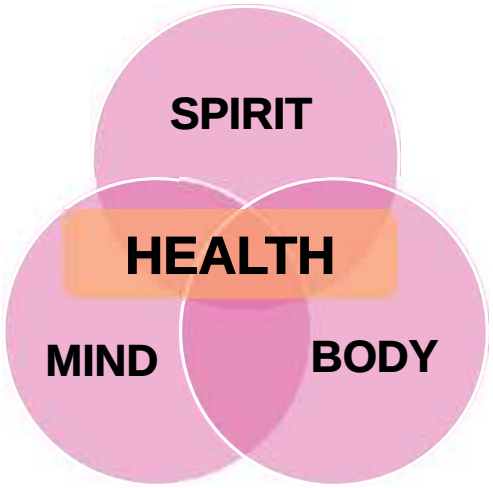
- Relationship conflict (chicken or egg determines if FSD)
- Major life stressor(s)
- Boredom
- Discrepant desire levels between partners
- Cultural/religious prohibitions/guilt
- Subclinical depression/anxiety/body image
- If Axis I condition then FSD may not be the diagnosis

Common Ingredients of Empirically Tested Sex Therapy Techniques

- Brief (5-20 session) solution-focused treatment
- Alter dysfunctional emotions, behaviors and cognitions
- Change the way one thinks/ feels/behave even if the situation does not change
- Homework
- Sex as the legitimate problem and not as a symptom of some underlying psychopathology

Heiman and Meston, 1997

Possible Mechanisms of Action by Which Mindfulness Improves Low Sexual Desire



- Mood enhancer
- Increasing interceptive awareness
- Reduces anxiety
- Increases self compassion
- Reduces distraction

Brotto & Krychman, 2016

Sensate Focus

- Developed by Masters and Johnson, late 1960's
- Series of progressive "sexual" exercises for individuals or couples with 3 general goals:
  1. Decrease avoidance/anxiety
  2. Increase personal and interpersonal awareness of self and partner's experiences/needs
  3. Improve sexual function
- Current use is less formulaic and more individualized

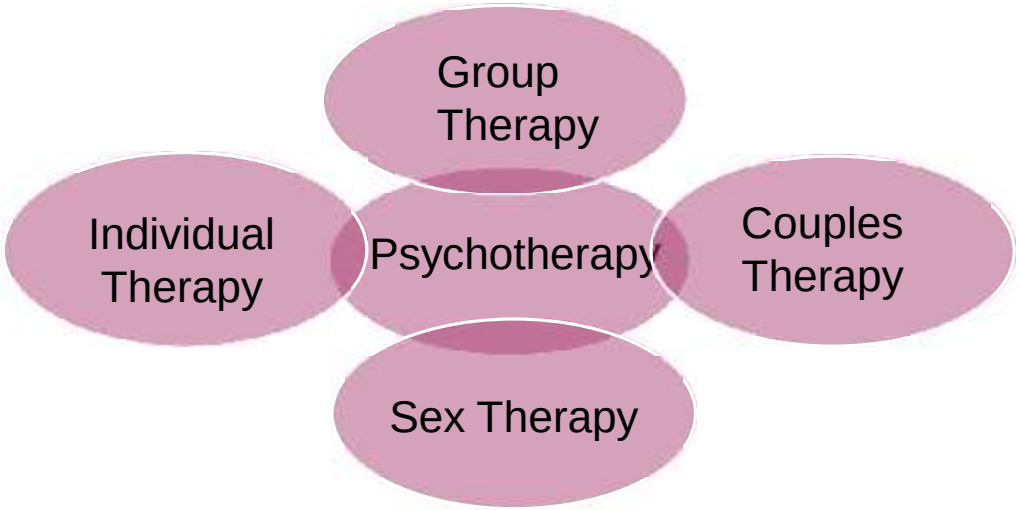
Masters and Johnson, Human Sexual Inadequacy 1970
Weiner L & Avery-Clark C 2017. Sensate Focus in Sex Therapy:The Illustrated Manual. New York, NY: Routledge

Psychotherapy Trials for HSDD

- Paucity of randomized trials evaluating efficacy of psychotherapy
- Mindfulness-based treatments show promise
- 3 CBT trials and 2 MMT trials superior to wait-list control[1]
- Insufficient data to conclude efficacy due to
- Lack of hierarchy of endpoints and preplanned primary endpoints
- Lack of randomization
- Lack of adequate control/placebo
- Nocebo Effect: A negative placebo effect
- Waiting list may be a nocebo condition in psychotherapy trials[2]

1. Pyke R. Clayton A. JSM 2015;12:2451-2458.
2. Furukawa et al. Acta Psychiatr Scan 2014;130(3):180-192

Psychological Interventions Alone



Combined Medical and Psychology Therapy

Althof S. Sex therapy in the age of pharmacotherapy. Ann Rev Sex Res; 2006;17:116-132.
Brotto L, Frontiers in Neuroendocrinology 2017;45: 11-17

Female Erogenous Zones

1. Clitoris
2. Vagina
3. Mouth/lips
4. Nape of neck
5. Breasts
6. Nipples
7. Inner thigh
8. Back of neck
9. Ears
10. Pubic hairline
11. Buttocks
12. Head & hair
13. Stomach
14. Hips
15. Sides
16. Shoulders
17. Perineum
18. Upper back
19. Hands
20. Back of thigh

Turnbull, et al., 2014

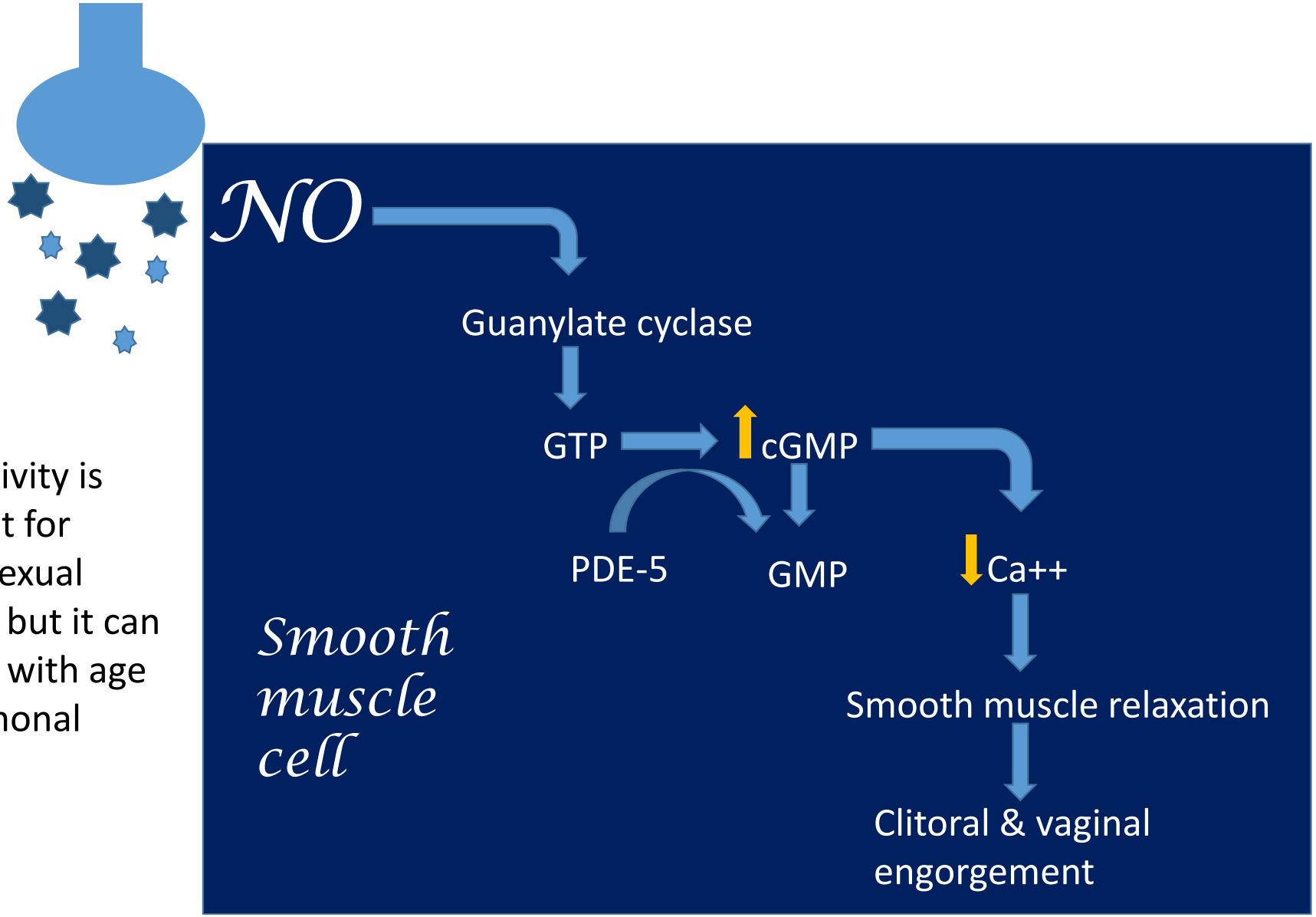
Amino Acid Complexes

The Role of NO in Female Sexual Arousal

- During the female sexual response, the body produces Endothelial Nitric Oxide Synthase (eNOS), an enzyme that converts arginine and citrulline into nitric oxide (NO)
- This increase in eNOS-NO leads to vasodilation, transudation (lubrication), and relaxation of the smooth muscle cells in the vagina
- eNOS activity is important for healthy sexual function, but it can decrease with age and hormonal changes
- NO may be involved in nipple erection during sexual response as well

Musicki, et al., 2009; Tezer, et al., 2012
Fitzpatrick D, et al. J Cardiol Pharmacol. 1998;32:509-515

eNOS activity is important for healthy sexual function, but it can decrease with age and hormonal changes.



Amino Acid Mechanism of Action for Sexual Functioning: Increases overall and regional blood flow

Blood flow is vital for women to experience sexual comfort and pleasure.

- Lower levels of estrogen cause a decrease in blood flow to the vagina.
- Lack of blood flow to the genital areas can lead to:
  - Reduced sensitivity to touch
  - Reduced receptivity to physical arousal
  - Reduced vaginal lubrication
  - painful or uncomfortable intercourse and reduced sexual desire.
- Sexual dysfunction is common in peri and post-menopausal women and may be caused by the decline in nitric oxide and estrogen levels, both strong vasodilators.

Berman 2005, Frank, 2008, Nishioka, 2007

The enhancement of female sexual function with ArginMax, a nutritional supplement, among women differing in menopausal status.

Premenopausal women: improvement in sexual desire (72%; p = 0.03) satisfaction with overall sex life (68%; p = 0.007) frequency of intercourse (56% p = 0.01)

Perimenopausal women: improvements frequency of intercourse (86%; p = 0.002), satisfaction with sexual relationship (79%; p = 0.03), vaginal dryness and arousal (64%; p = 0.03)

Postmenopausal women: increased in sexual desire,51% showing improvement, compared with 8% placebo group (p = 0.008).

Supplement Facts

Serving Size: 6 tablets Servings Per Container: 30

Amount per serving		% DV*
Vitamin A (as retinyl palmitate)	5000 IU	100%
Vitamin C (as ascorbic acid)	60 mg	100%
Vitamin E (as natural d-alpha-tocopherol succinate)	30 IU	100%
Thiamin (as thiamin mononitrate)	1.5 mg	100%
Riboflavin	1.7 mg	100%
Niacin (as niacinamide)	20 mg	100%
Vitamin B-6 (as pyridoxine hydrochloride)	2 mg	100%
Folate (as folic acid)	400 mcg	100%
Vitamin B-12 (as cyanocobalamin)	6 mcg	100%
Biotin	300 mcg	100%
Pantothenic acid (as calcium d-pantothenate)	10 mg	100%
Calcium (as calcium carbonate)	500 mg	50%
Iron (as ferrous gluconate)	9 mg	50%
Zinc (as zinc gluconate)	7.5 mg	50%
Proprietary Blend		
L-Arginine	2500 mg	†
Korean Ginseng (Panax Ginseng) – root extract (aerial part and root)	100 mg	†
Ginkgo Biloba – extract (leaf)	50 mg	†
Damiana (Turnera Aphrodisiaca) – leaf	50 mg	†

* Percent Daily Values (%DV) are based on a 2000 calorie diet
† Daily Value not established
NO ARTIFICIAL FLAVOR, COLOR OR PRESERVATIVES

J Sex Marital Ther. 2006 Oct-Dec;32(5):369-78.
Ito TY1, Polan ML, Whipple B, Trant AS.

METHODS

- 77 women with sexual dysfunction
- Enrolled consecutively
- Two groups randomly assigned active or placebo in a double blind fashion
- Baseline & 4 weeks medical history, physical examination, BP measurement, and assessment using FSFI
- Daily regimen of ArginMax for 4 weeks

DISCUSSION

Our study evaluated the role of nutritional supplementation in female sexual health. Proposed mechanism is through up-regulation of the nitric oxide (NO) pathway resulting in smooth muscle relaxation, vascular dilatation, and enhancement of peripheral circulation, resulting in improved clitoral engorgement and vaginal lubrication.

Role of nutritional supplements for sexual health is an infrequently discussed yet extremely important subject which warrants in-depth research.

CONCLUSION

Based on the findings of this study, there appears to be a **clinically important role for nutritional supplementation in sexual health and female sexual function**. The expansion of the current study protocol is expected to exceed several hundred patients.

RESULTS

(Based on FSFI assessment):

- **70.6% improved in sexual desire level** - (placebo=41.9%), ($p<0.01$)
- **73.5% improved in satisfaction with sex life** - (placebo=37.2%), ($p<0.01$)
- **61.8% improved in sexual relationship with partner** - (placebo=34.9%), ($p<0.01$)
- **47.1% improved in frequency of orgasms** - (placebo=30.2%), ($p<0.07$)
- **52.9% improved in clitoral sensation to stimulation** - (placebo=34.9%), ($p<0.06$)

Side Effects

No significant change in blood pressure. No reports of headaches, nausea, stomach upset, chest pain, dizziness, vision disturbance, or cardiovascular complications.

Subject Group Profile

	ArginMax	Placebo
Total # of subjects	34	43
Age range, mean	24-71, 44.5	22-68, 41.0

N=60. Stronvivo 6 tabs/d supports endothelium function, boosts nitric oxide production.

PRE-POSTMW studies: after 90 use = significant improvements in all areas of sexual functioning on FSFI including desire, arousal, orgasm and lubrication while also experiencing significant improvements in mood.

- L Arginine
- L Citruline
- L-Carnitine
- Magnesium
- Zinc

Journal of Sexual Medicine July 2015, Vascoe.J et al

RISTELA

General

- RISTELA is a new, non-hormonal, non-prescription dietary supplement.
- Ristela has been shown to improve overall sexual function and sexual satisfaction in 3 clinical trials with a safety/tolerability profile comparable to placebo.

Formulation

- Each daily dose (2 tablets) of RISTELA contains the following active ingredients:
  - 80 mg of Pycnogenol® (proprietary French maritime pine bark extract)
  - 200 mg of Rosvita® (branded rose hips extract)
  - 800 mg of L-arginine
  - 800 mg of L-citrulline

Ristela Clinical Trials

1

Peri-menopause

PACR improves emotional, physical health and sexual function in peri-menopausal women.

R Stanislavov and P Rohdewald. *J Women's Health Care* 2014; 3:1-6

8-week, randomized, double-blind, placebo-controlled study conducted in 80 peri-menopausal women ages 40-50.

2

Post-menopause

Lady Prelox improves sexual function in post-menopausal women.

A Bottari, G Belcaro, A Ledda, et al. *Panminerva Medica* 2012;54:3-9

8-week, randomized, single-blind, placebo-controlled study in 83 post-menopausal women ages 45-55

3

Pre-menopause

Lady Prelox® improves sexual function in generally healthy women of reproductive age.

A Bottari, G Belcaro, A Ledda, et al. *Minerva Ginecologica* 2013;65:435-444

8-week, active-controlled lifestyle study in 100 pre-menopausal women ages 37- 45

Mechanism of Action

The ingredients in Ristela are designed to increase blood to the female genitals, improving overall sexual function and satisfaction.

Pycnogenol®

Ristela contains Pycnogenol, a French maritime pine bark extract which has been shown in preclinical studies to increase production of eNOS.

Arginine & Citrulline

Ristela also contains 800mg each of arginine and citrulline, providing an ample supply of substrate with which eNOS can produce nitric oxide.

Ristela

- Increased genital circulation
- Improved sexual function
- More satisfying sexual experiences

Berman 2005
Frank 2008
Doshi 2013
Farhat 1996
Rohdewald, 2016

Pharmacologic Treatments

2 FDA approved Pharmacologic Treatments for HSDD in Premenopausal Women

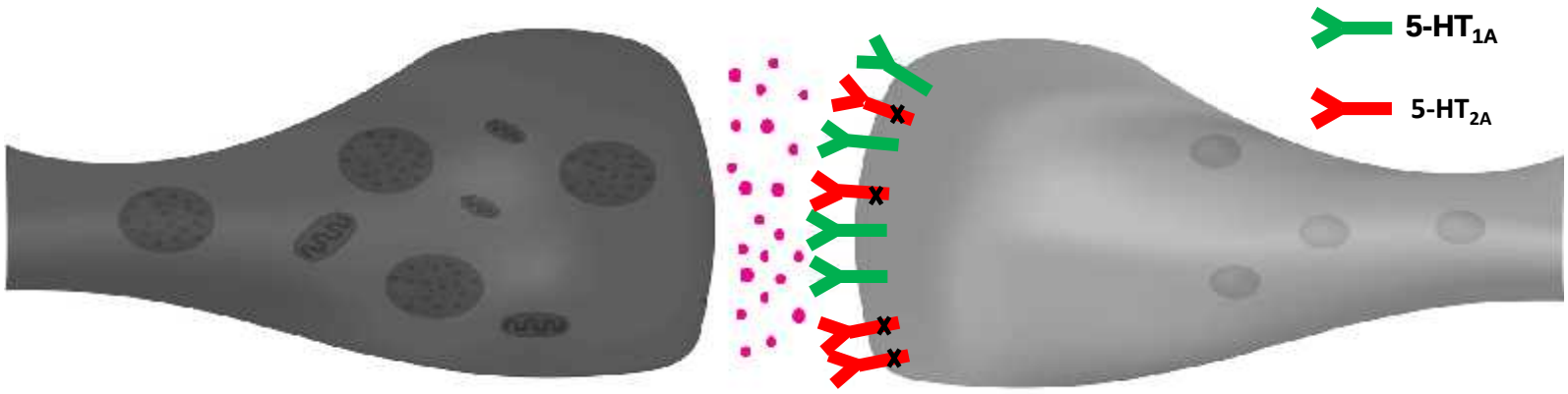
* 0 FDA approved pharm txmts for HSDD in POSTMENOPAUSAL women

Flibanserin

- Mixed post-synaptic 5HT1A agonist and 5HT2A antagonist
- 5HT1A agonists could have pro-sexual effects
- 5HT2A antagonists could have pro-sexual effects
- Has activity at dopamine D4 receptors as well as moderate affinity for 5HT2B and 5HT2C receptors
- Thought to produce region-specific elevations in dopamine and norepinephrine which offset inhibitory serotonergic activity = increased desire pathways
- Serotonin may have a role in low desire by acting as a sexual satiety signal

Flibanserin Serotonin Receptor Activity

- Flibanserin, a centrally-acting central nervous system agent, is thought to act mainly on serotonin receptors in the brain.
- Its exact mechanism of action in treating HSDD is unknown



Flibanserin Serotonin Receptor Activity at the Synapse

Phase 3 Pivotal Clinical Trials of Safety and Efficacy of flibanserin 100 mg at Bedtime

Study population:

- Premenopausal women with acquired, generalized HSDD for 6 months
- 88.6% Caucasian
- Mean age: 36 years (19-55 yrs)
- Mean duration of HSDD: ?5 years
- Mean duration in monogamous, heterosexual relationship: 11 years

Study 1: VIOLET	Study 2: DAISY	Study 3: BEGONIA
Flibanserin (N = 280)	Flibanserin (N = 365)	Flibanserin (N = 532)
Placebo (N = 290)	Placebo (N = 372)	Placebo (N = 536)

Flibanserin: Three 24-Week Pivotal Trials Involving >2,300 Premenopausal Women[1-3]

Key efficacy measures examined change from baseline in sexual desire, satisfying sexual events, and sexual distress in randomized, double-blind, placebo-controlled trials

	Co-Primary Endpoints	Secondary Endpoints
Studies I & II	Mean change from baseline at Week 24 in: ▪ Monthly sexual desire score (eDiary)[1,2] ▪ Number of monthly satisfying sexual events (SSEs)[5]	Mean change from baseline at Week 24 in: ▪ FSFI-D ▪ Female Sexual Distress Scale-Revised Item 13 (FSDS-R-Q13)[6,7]
Study III	Mean change from baseline at Week 24 in: ▪ Female Sexual Function Index-Desire Domain (FSFI-D)[4] ▪ Number of monthly SSEs[4]	Mean change from baseline at Week 24 in: ▪ FSDS-R-Q13

Safety measures focused on incidence of adverse events

1. Derogatis LR, et al. *J Sex Med*. 2012;9(4):1074-1085. 2. Thorp J, et al. *J Sex Med.* 2012;9(3):793-804. 3. Katz M, et al. *J Sex Med*. 2013;10(7):1807-1815. 4. Gerstenberger EP, et al. *J Sex Med*. 2010;7(9):3096-3103. 5. Kingsberg SA, Althof SE. *J Sex Med*. 2011;8(12):3262-70. 6. Derogatis LR, et al. *J Sex Marital Ther*. 2002;28(4):317-330. 7. Derogatis LR, et al. *J Sex Med*. 2008;5(2):357-364.

What defines a Satisfying Sexual Event (SSE)?

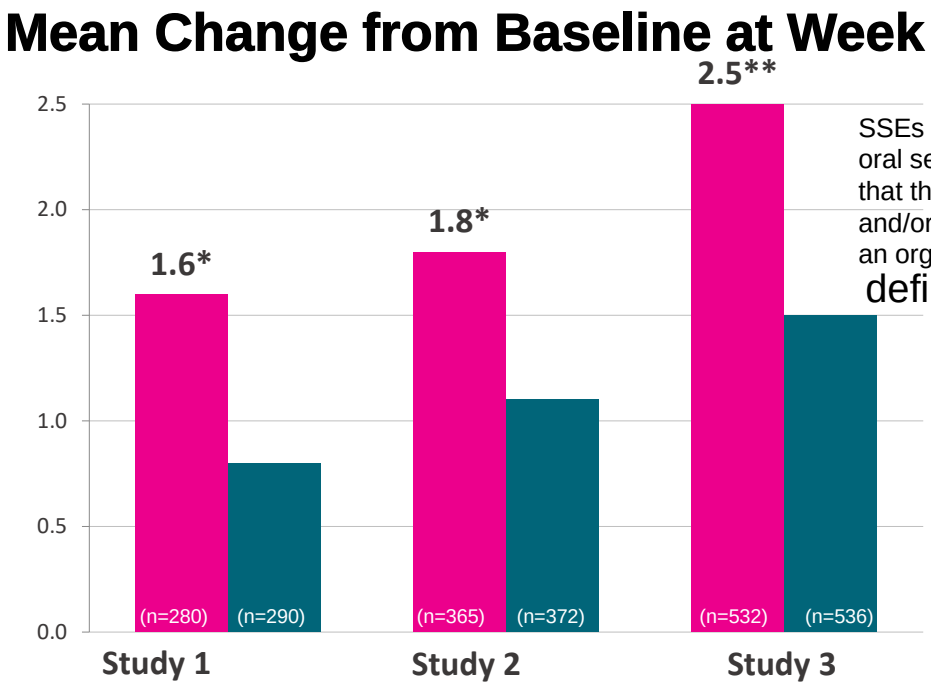
- Number of monthly SSEs
- Women indicated daily if they had experienced a sexual event
- If a sexual event occurred, the SSE primary endpoint was measured by the eDiary question: "Was the sex satisfying for you?"
- Standardized to a 28-day period as follows:
- Total monthly count of SSEs= 28 x (sum of the number of SSE entered)/(sum of number of days entered)

Did you have a sexual event?
Sexual intercourse, oral sex, masturbation, or genital stimulation by the partner

Was the sex satisfying to you?
Gratifying, fulfilling, satisfactory, and/or successful—irrespective of whether women had an orgasm or whether the event was satisfying for the partner

1. Derogatis LR, et al. *J Sex Med.* 2012;9(4):1074-1085. 2. Thorp J, et al. *J Sex Med.* 2012;9(3):793-804. 3. Katz M, et al. *J Sex Med*. 2013;10(7):1807-1815. 4. Flibanserin [package insert]. Raleigh, NC: Sprout Pharmaceuticals; 2015

Women Taking Flibanserin Reported Significantly More SSEs vs Placebo



SSEs are of satisfying sexual events: sexual intercourse, oral sex, masturbation, or genital stimulation by the partner that the patient reported as gratifying, fulfilling, satisfactory, and/or successful, irrespective of whether the woman had an orgasm

defined as the number

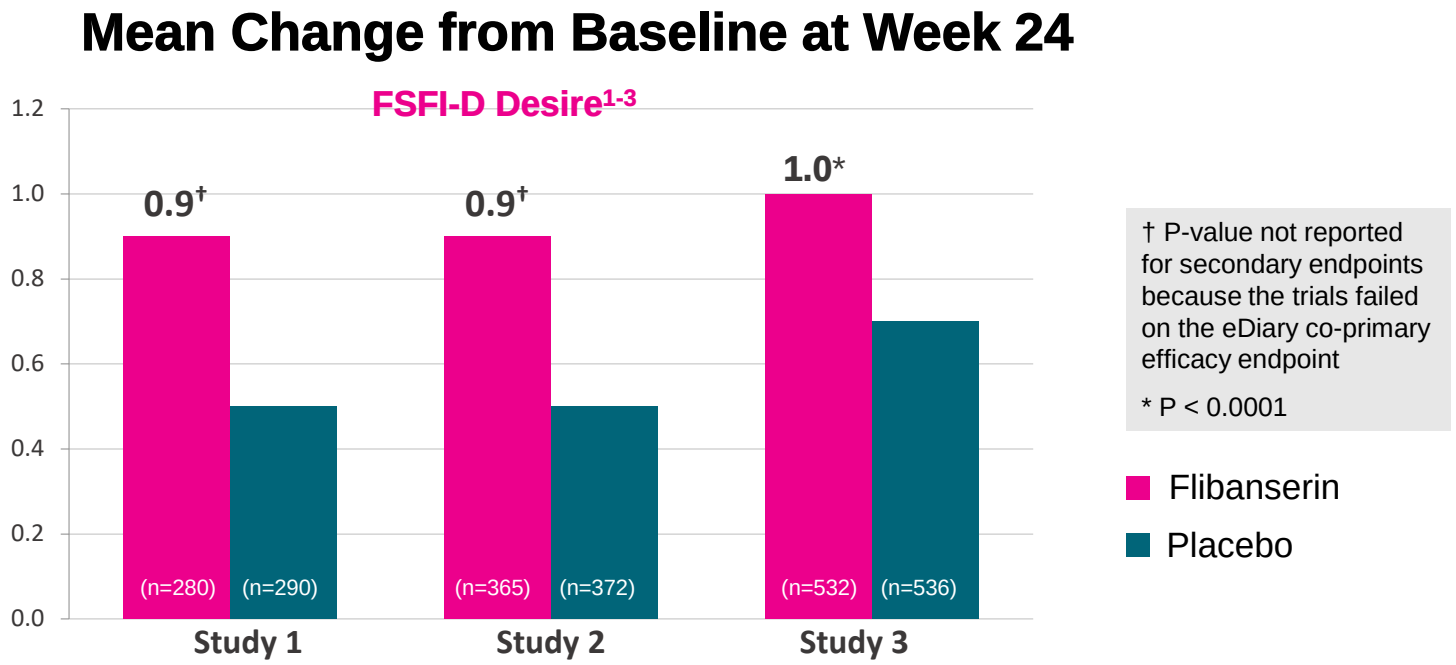
*P < 0.01 versus placebo
**P < 0.0001 versus placebo

Flibanserin

Placebo

1. Derogatis LR, et al. *J Sex Med*. 2012;9(4):1074-1085. 2 . Thorp J, et al. *J Sex Med*. 2012;9(3):793-804. 3. Katz M, et al. *J Sex Med*. 2013;10(7):1807-1815.

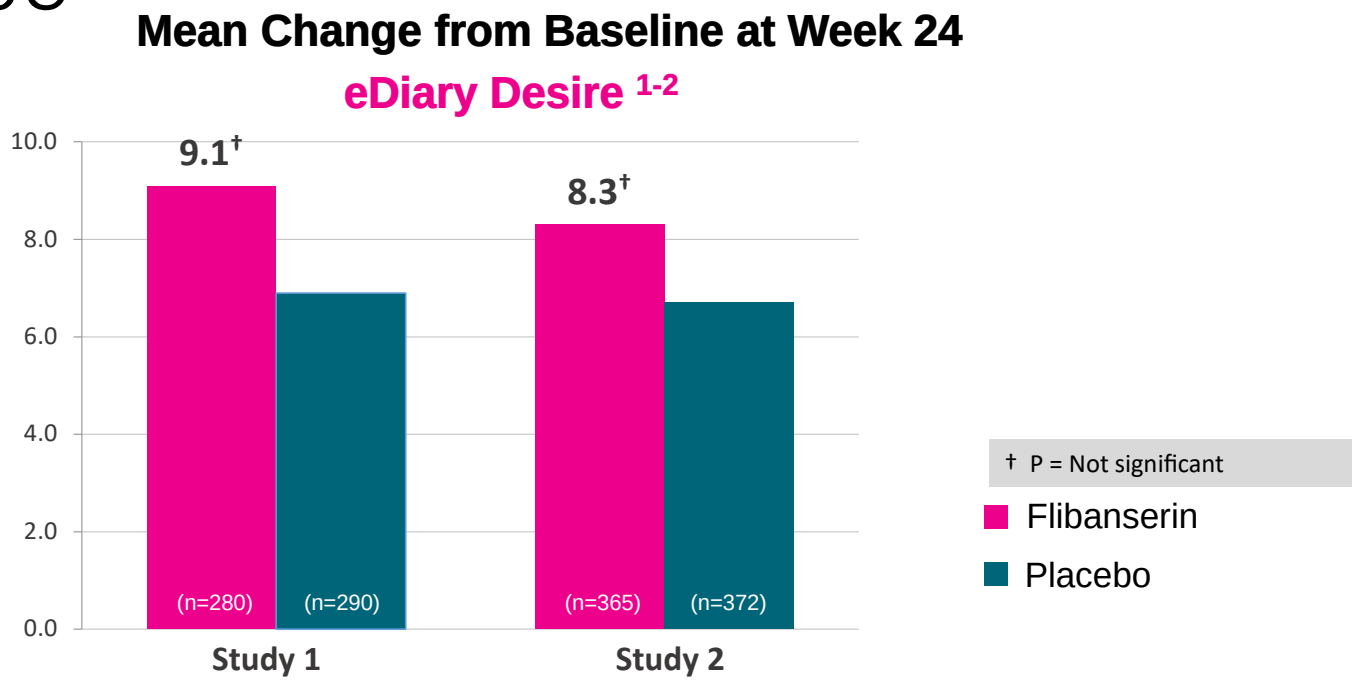
Flibanserin Consistently Improved Sexual Desire vs. Placebo



Flibanserin showed consistent improvement in desire using the validated FSFI-D instrument in all three studies

1. Derogatis LR, et al. *J Sex Med.* 2012;9(4):1074-1085. 2. Thorp J, et al. *J Sex Med.* 2012;9(3):793-804. 3. Katz M, et al. *J Sex Med*. 2013;10(7):1807-1815. 4. Flibanserin [package insert]. Raleigh, NC: Sprout Pharmaceuticals; 2015

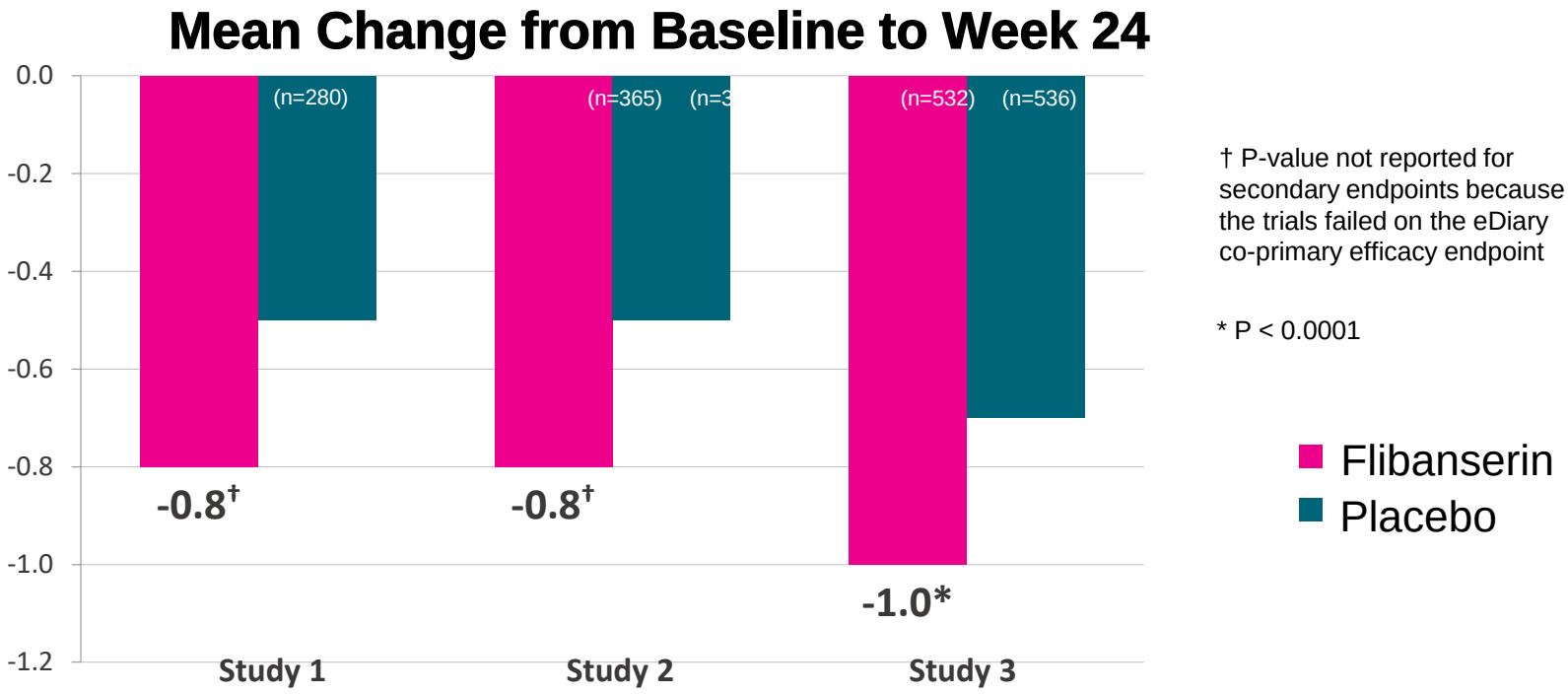
Flibanserin Increased Sexual Desire vs Placebo



While subjects responding to Flibanserin showed an increase in sexual desire as measured by the eDiary, the difference did not reach statistical significance

Derogatis LR, et al. *J Sex Med*. 2012;9(4):1074-1085. Thorp J, et al. *J Sex Med*. 2012;9(3):793-804.

Flibanserin Showed a Decrease in Distress vs. Placebo Across All 3 Studies



Derogatis LR, et al. *J Sex Med*. 2012;9(4):1074-1085. Thorp J, et al. *J Sex Med*. 2012;9(3):793-804. Katz M, et al. *J Sex Med*. 2013;10(7):1807-1815.

Responder Analysis

Percentage of patients reporting improvement across each efficacy endpoint			
	Sexual desire (FSFI-D)	**Satisfying sexual events (SSEs)**	**Decreased distress FSDS-R, Q13**
Patients taking flibanserin (n=1177)	43%–51%	44%–48%	50%–60%
Patients taking placebo (n=1198)	31%–39%	33%–36%	41%–48%
Absolute difference flibanserin vs placebo	12%-13%	10%-15%	9%-12%

PGI-I responders were defined as being at least minimally improved (responses of 1, 2, or 3 were considered “improved” on a 1-7 scale)

Derogatis LR, et al. *J Sex Med*. 2012;9(4):1074-1085. Thorp J, et al. *J Sex Med*. 2012;9(3):793-804. Katz M, et al. *J Sex Med*. 2013;10(7):1807-1815.

Flibanserin Adverse Reactions

Adverse reactions reported in clinical trials in ≥2% of patients receiving 100 mg of flibanserin at bedtime and at a higher incidence than placebo-treated patients

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

The majority of these adverse reactions began within the first 14 days of treatment

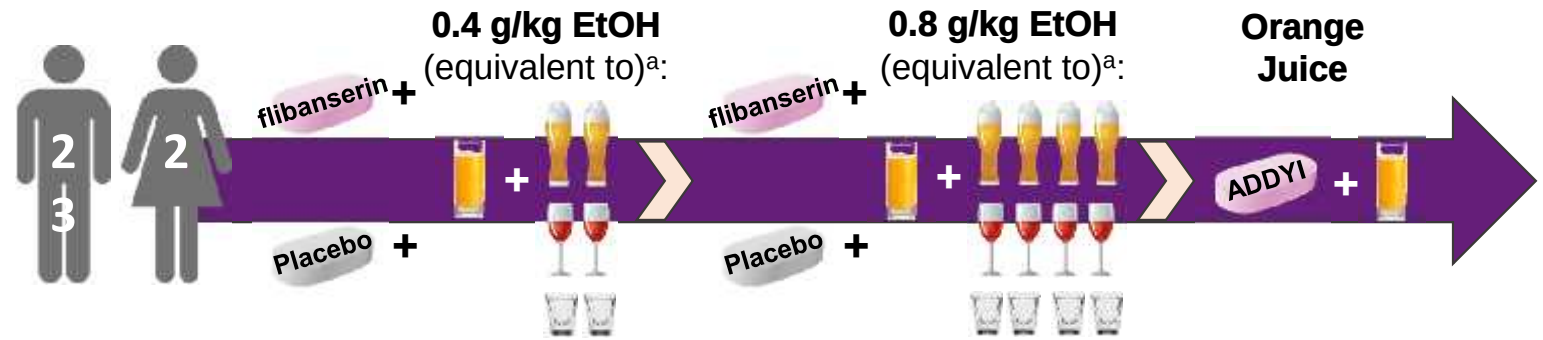
- Adverse reactions leading to discontinuation of ≥1% of patients receiving flibanserin 100 mg at bedtime and at a higher incidence than placebo-treated patients were: dizziness, nausea, insomnia, somnolence, and anxiety
- Discontinuation rate due to adverse reactions was 13% for flibanserin 100 mg and 6% for placebo

Contraindications

- Flibanserin is contraindicated:
- With concomitant use with moderate or strong CYP3A4 inhibitors
- In patients with hepatic impairment
- NO LONGER CONTRAINDICATED WITH ETOH! (Sept, 2019)

PHASE 1 ALCOHOL CHALLENGE STUDY[1]

Subjects received each of the 5 treatments in randomized order:



25 Subjects
Mean age: 31 years (21-52)
Fasted for 10 hours
Ate a light breakfast

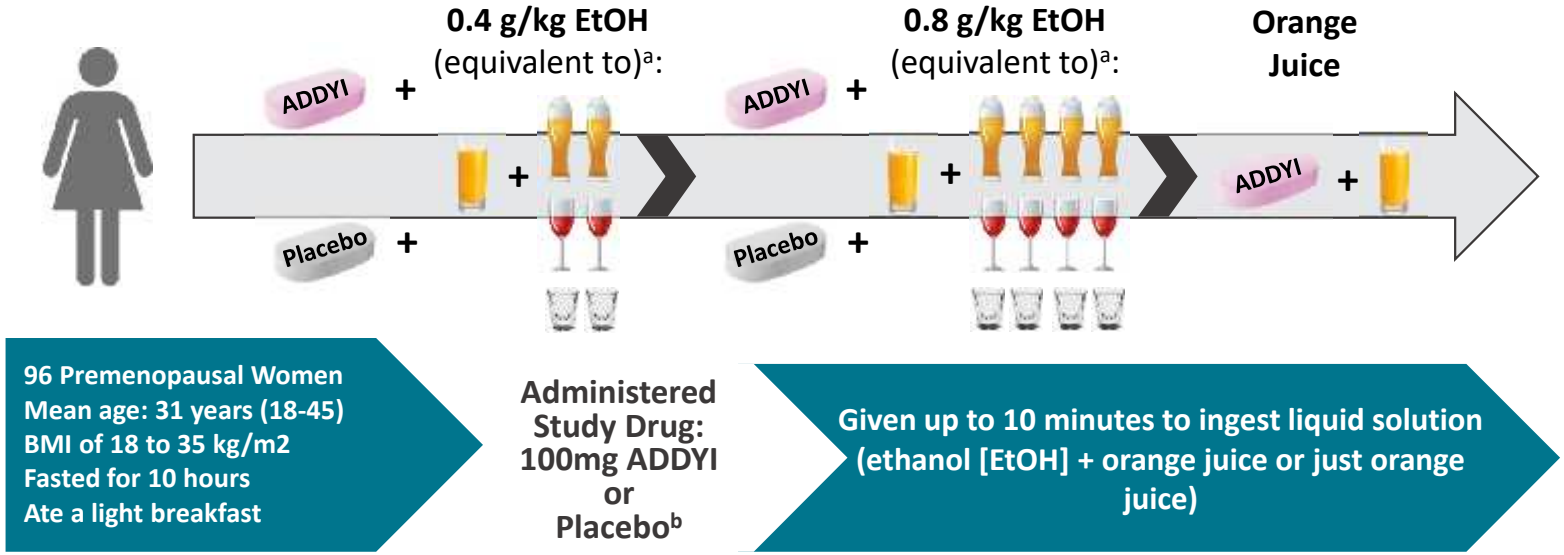
Administered Study Drug: 100mg flibanserin or Placebo[b]

Given up to 10 minutes to ingest liquid solution (ethanol [EtOH] + orange juice or just orange juice)

[a]equivalents in a 70 kg (~154 lb) person: 12 oz of beer containing 5% alcohol content; 5 oz of wine containing 12% alcohol content; 1.5 oz of 80-proof spirit. [b]Study consisted of 5 single dose study periods; subjects received each of the 5 treatments

Effects of Alcohol Administered with Flibanserin in Healthy Premenopausal Women

- In this large, 7-treatment, 12-sequence, crossover study, administration of alcohol with flibanserin was not associated with an increased risk of hypotension and syncope
- 1 Subject in the ADDYI + 0.4 g/kg EtOH group experienced hypotension
- The adverse event profile for concomitant administration of mild (0.2 g/kg) or moderate (0.4 g/kg) quantities of ethanol with flibanserin was similar to that of flibanserin alone
- Increased drowsiness following administration of flibanserin (with or without ethanol) in this study supports the recommended (bedtime) dosing



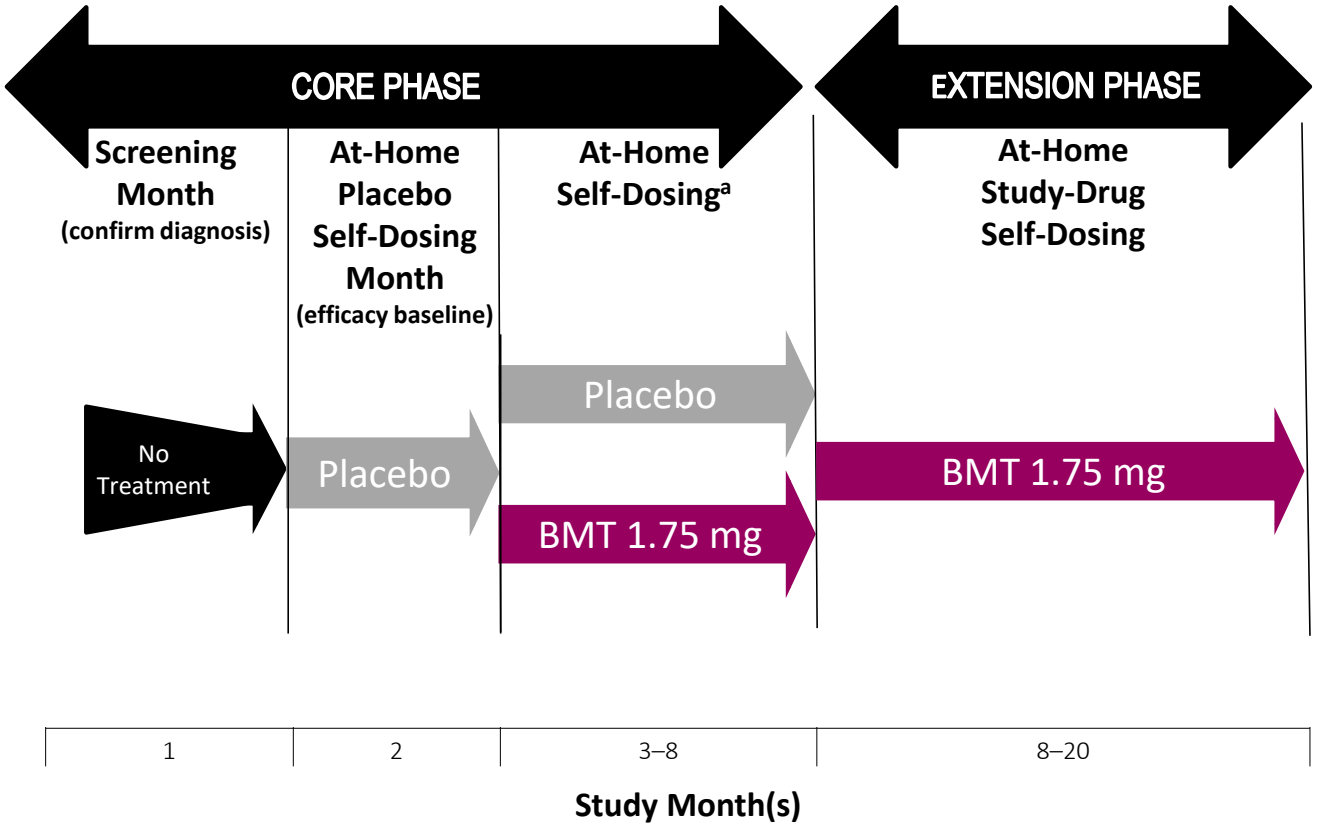
[a]equivalents in a 70 kg (~154 lb) person: 12 oz of beer containing 5% alcohol content; 5 oz of wine containing 12% alcohol content; 1.5 oz of 80-proof spirit. [b]Study consisted of 5 single dose study periods; subjects received each of the 5 treatments

1. Sicard, E; Effects of Alcohol Administered with Flibanserin on Dizziness, Syncope, and Hypotension in Healthy Premenopausal Women

Bremelanotide (BMT)

- BMT is a novel cyclic 7-amino acid melanocortin-receptor agonist, with high affinity for the type-4 melanocortin receptor, and an analog of α-melanocyte-stimulating hormone (MSH)
- BMT is delivered via an auto-injector on an “as desired” basis
- The RECONNECT study comprises 2 randomized, double-blind, placebo-controlled, phase 3 studies of BMT administered as-desired for the treatment of HSDD in premenopausal women

Bremelanotide: Study Design



Study Population

- Healthy, premenopausal, nonpregnant women, ≥18 years of age, currently in a stable (≥6 months) relationship
- Diagnosed with HSDD (with/without decreased arousal) for ≥6 months
- Experienced “normal” sexual function in the past for ≥2 years
- Willing to engage in sexual activities ≥1X/month during the study
- Had ALL of the following at screening:
- Patient Health Questionnaire-9 total score <10 and a score of 0 on question 9
- Female Sexual Function Index (FSFI) total score ≤26 (if diagnosed with HSDD with/without symptoms of decreased arousal) OR
- FSFI desire domain (FSFI-D) score ≤5 (if diagnosed with HSDD without decreased arousal) regardless of total FSFI score
- Female Sexual Distress Scale-Desire/Arousal/Orgasm (FSDS-DAO) total score >18

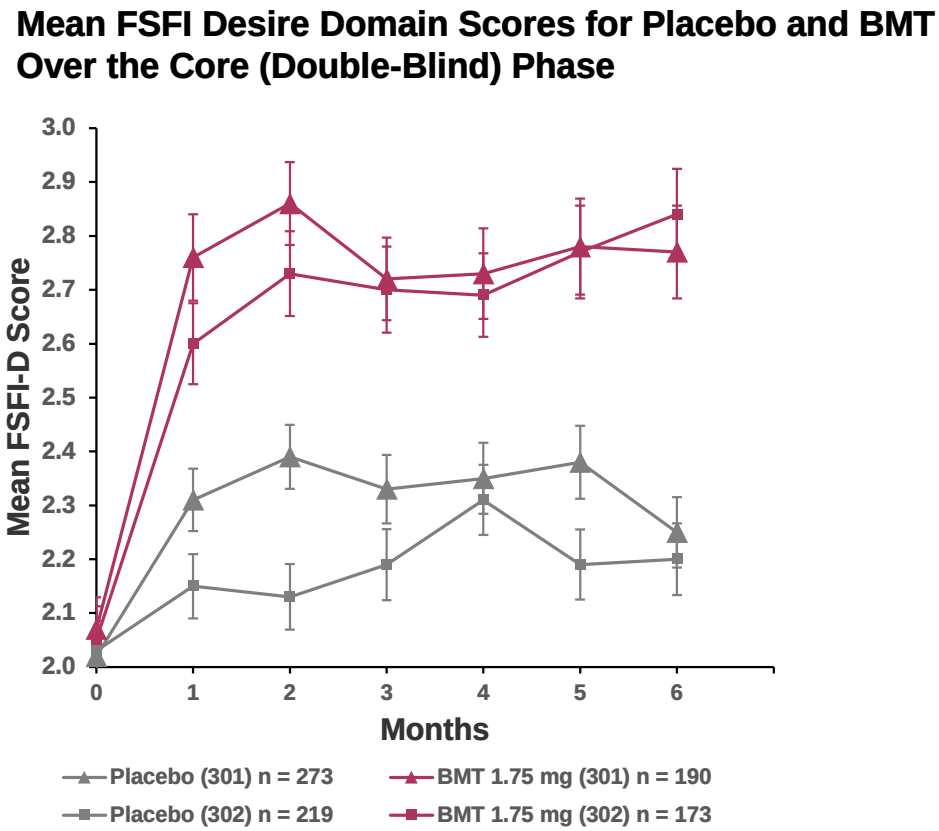
All data presented at ISSWSH annual meeting Feb 2017 by Simon, J.

Key Outcome Measures

- Coprimary Efficacy Endpoints
  - Change in the FSFI-D and FSDS-DAO Item 13 scores among women who completed the double-blind treatment phase of the RECONNECT study
- Responder Analysis Based On
  - Participants self-reporting a score of ≥5 (on a 7-point Likert scale) in response to question 3 on the General Assessment Questionnaire “To what degree do you think you benefited from taking the study drug?”
  - The proportion of participants meeting or exceeding the following predefined minimal clinically important differences (MCIDs)
    - FSFI-D score (MCID=0.6)
    - FSDS-DAO Item 13 score (MCID=-1.0)

Efficacy Results: FSFI-D (Completers)

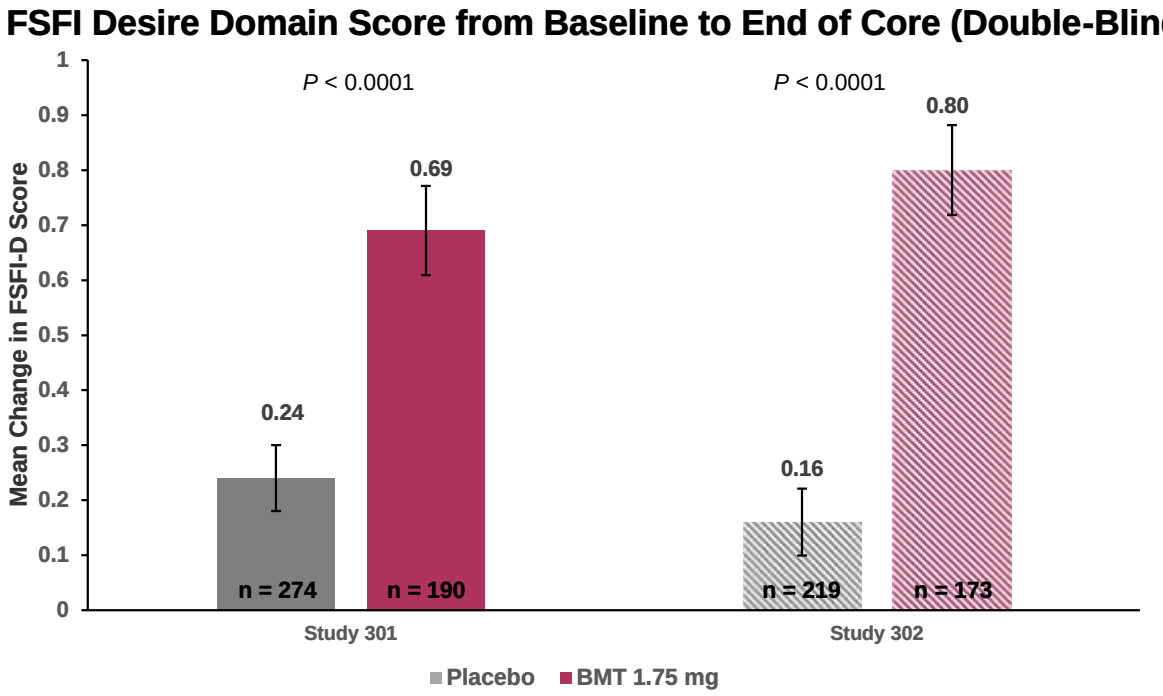
- Relative to placebo, the FSFI-D score increased in women using BMT 1.75 mg from the first month of double-blind treatment
- Following a sensitivity analysis that assumed all dropouts were treatment failures, the effect size decreased but results still showed statistically significant improvement in comparison to placebo



BMT, bremelanotide; FSFI-D, Female Sexual Function Index desire domain.

Efficacy Results: FSFI-D (Completers)

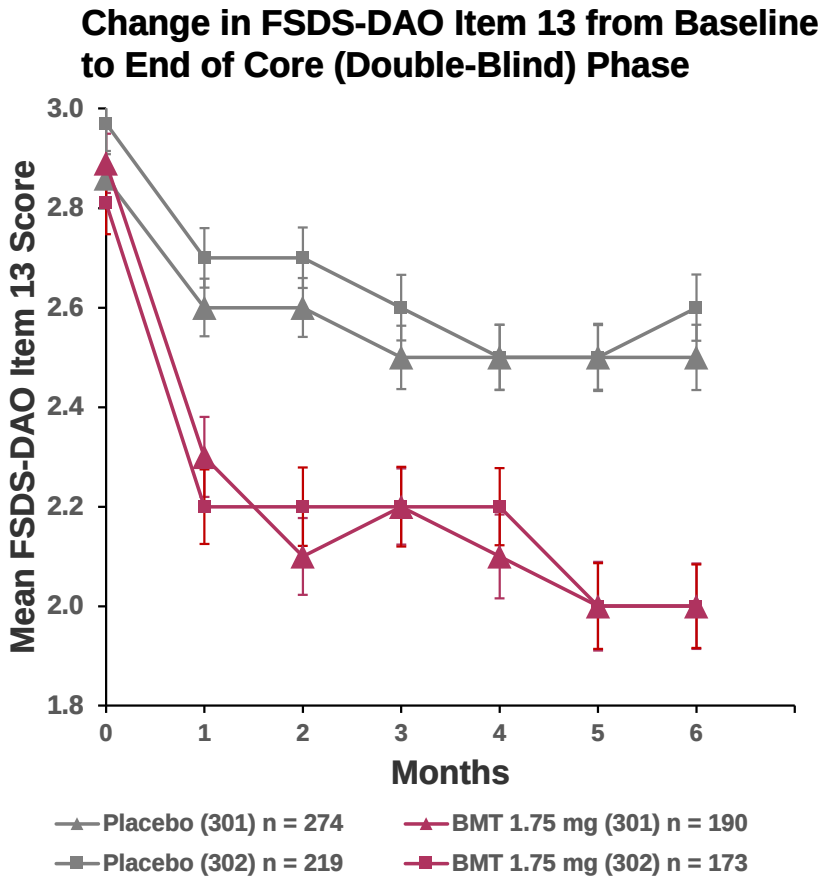
Compared with those taking placebo, women taking BMT had significantly increased scores on the desire domain of the FSFI at 6 months, indicating an increase in desire



BMT, bremelanotide; FSFI-D, Female Sexual Function Index desire domain.

Efficacy Results: FSDS-DAO Item 13 (Completers)

Relative to placebo, FSDS-DAO Item 13 score decreased in women taking BMT 1.75 mg from the first month of double-blind treatment

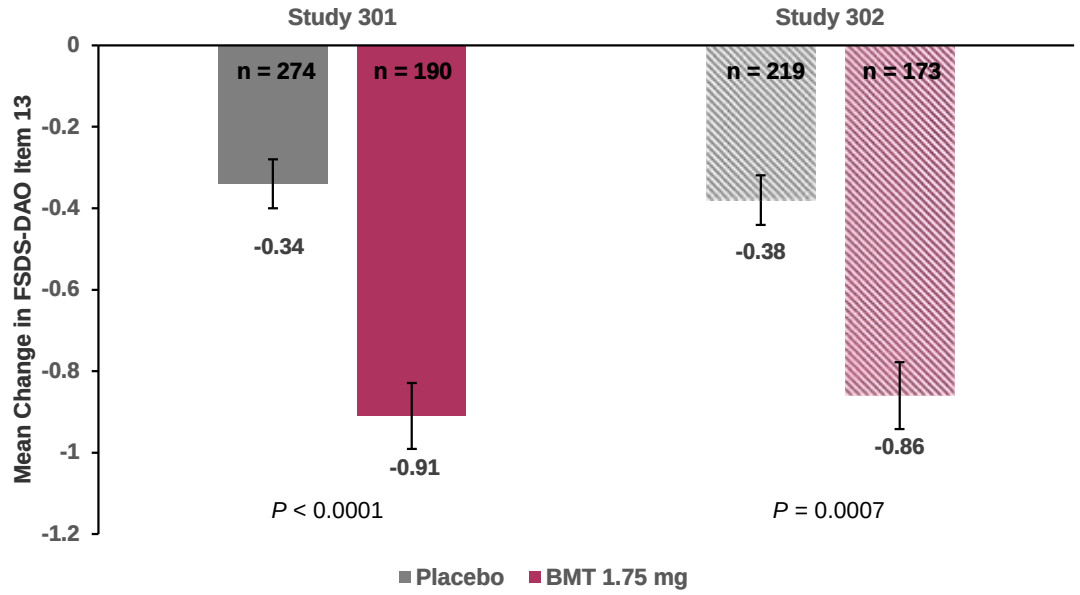


Error bars are standard error of the mean.
BMT, bremelanotide; FSDS-DAO, Female Sexual Distress Scale-Desire/Arousal/Orgasm.

EFFICACY RESULTS: FSDS-DAO ITEM 13 (COMPLETERS)

Compared with those taking placebo, women using BMT had a significant reduction in their FSDS-DAO Item 13 score at 6 months, indicating a reduction in distress related to low sexual desire

Figure 4. Change in FSDS-DAO Item 13 from Baseline to End of Core (Double-Blind) Phase



Responder Analysis

% Responders Based on Self-Assessment of Benefit	Study 301	Study 302
GAQ question 3 (”How often do you feel bothered by low sexual desire?”) score ≥5 (% responders BMT 1.75 mg SC)	59%	58%
Responder Analysis Based on MCIDs	**Study 301**	**Study 302**
FSFI-D (MCID=0.6)	*P*=0.0002	*P*<0.0001
FSDS-DAO Item 13 (MCID=–1.0)	*P*<0.0001	*P*=0.0419

Error bars are standard error of the mean.

BMT, bremelanotide; FSDS-DAO, Female Sexual Distress Scale-Desire/Arousal/Orgasm; FSFI-D, Female Sexual Function Index desire domain; GAQ, General Assessment Questionnaire; MCID, minimal clinically important difference; SC, subcutaneous

Safety

- Bremelanotide has a favorable safety profile
- Most AEs were mild or moderate in nature
- TEAEs led to treatment discontinuation/interruption in approximately 18% of women taking bremelanotide (vs. 2% in placebo)
- Most of the bremelanotide AEs causing withdrawal were gastrointestinal (11.1% in Study 301 and 7.6% in Study 302)
- Bremelanotide's safety profile was consistent with prior clinical experience; no new or unusual safety issues were identified

Off-Label Pharmacologic Options

Off-label use of on-label prescription options

Osphena

Results

Ospemifene 60 mg/day demonstrated a significantly greater FSFI total score improvement vs. placebo at Week 4 ($p <$ 0.001). Improvement in FSFI scores continued to Week 12 ($p <$ 0.001). At Week 4, the FSFI domains of Sexual Pain, Arousal, and Desire were significantly improved with ospemifene vs. placebo; at Week 12, improvements in all domains were significant ($p < 0.05$). Changes in serum hormones were minor and uncorrelated with changes in sexual functioning

LET

Bachmann, and others: vaginal epithelial health restoration with estrogen results in increased vaginal compliance, decreased vaginal pH, increased vaginal blood flow and lubrication. Changes in vaginal fluids and electrolytes have been noted with one month of therapy and in pH, blood flow and vaginal electropotential in 18-24 months. Women subsequently report decreased vaginal irritation, pain, dryness and burning during intercourse, which may lead to increased sexual desire, arousal and improved quality of life.

Intrarosa

Prasterone showed significant increase over placebo on the Female Sexual Function Index questionnaire in terms of desire, arousal, lubrication, orgasm, satisfaction, and pain at sexual activity.[4] An open-label study suggested that the benefit of prasterone is maintained for 52 weeks.[5]

Sildenafil

J Womens Health Gend Based Med. 2002 May;11(4):357-65.

The enhancement of vaginal vasocongestion by sildenafil in healthy premenopausal women.

Laan E[1], van Lunsen RH, Everaerd W, Riley A, Scott E, Boolell M.

⊕ Author information

Abstract

OBJECTIVE: This study examined the effect of a single oral dose of sildenafil citrate (Viagra, Pfizer, Inc., New York, NY) on vaginal vasocongestion and subjective sexual arousal in healthy premenopausal women.

METHODS: Twelve women without sexual dysfunction were randomly assigned to receive either a single oral 50 mg dose of sildenafil or matching placebo in a first session and the alternate medication in a second session. Subjective measures of sexual arousal were assessed after participants had been exposed to erotic stimulus conditions. Vaginal vasocongestion was recorded continuously during baseline, neutral, and erotic stimulus conditions. At the end of each session, subjects were also asked to specify which treatment they suspected they had received.

RESULTS: Significant increases in vaginal vasocongestion were found with sildenafil treatment compared with placebo. There were no differences between treatments on subjective sexual arousal experience. Analyses by suspected treatment received found that significantly stronger sexual arousal and vaginal wetness were reported for the treatment that was believed to be sildenafil vs. the treatment that was believed to be placebo. The suspected treatment sequence was incorrect for half of the women. Sildenafil was well tolerated, with no evidence of significant adverse events.

CONCLUSIONS: Sildenafil was found to be effective in enhancing vaginal engorgement during erotic stimulus conditions in healthy women without sexual dysfunction but was not associated with an effect on subjective sexual arousal.

Bupropion

J Sex Marital Ther. 2000 Jul-Sep;26(3):231-40.

Effect of bupropion-SR on orgasmic dysfunction in nondepressed subjects: a pilot study.

Modell JG[1], May RS, Katholi CR.

⊕ Author information

Abstract

The objective of this study was to determine whether the aminoketone antidepressant bupropion has beneficial effects in orgasmic dysfunction.

DESIGN: Single-blind, sequential treatment order of three weeks each: placebo, bupropion-SR 150 mg/day, bupropion-SR 300 mg/day.

SUBJECTS: Nondepressed women (n = 20) and men (n = 10) having nonphysiologic orgasmic delay or inhibition.

MAIN OUTCOME MEASURES: Reported difficulty or delay in achieving orgasm, satisfaction with orgasm and erectile function, and subjective impressions of drug effect.

RESULTS: In the women, there were significant improvements relative to baseline ($p < .01$) on both doses of bupropion-SR in all measured aspects of sexual function, and significant improvements relative to placebo ($p < .05$) in overall sexual satisfaction on both doses and satisfaction with intensity of orgasm on 150 mg/day (300 mg/day, $p = .10$). In the men, significant improvements over baseline ($p < .01$) were observed with both doses in overall sexual satisfaction, ability to achieve an erection, and delay in reaching orgasm/ejaculation; significant improvements relative to placebo ($p < .05$) were observed in overall sexual satisfaction on both doses, ability to achieve erection on 150 mg/day, and delay in orgasm/ejaculation on 150 mg/day. Seventy percent of subjects reported improvement in libido, arousal, or orgasmic function during bupropion administration.

CONCLUSIONS: Bupropion-SR may be a useful agent for treating orgasmic delay and inhibition, and possibly disorders of sexual arousal. The results argue against bupropion's apparent prosexual effect in depressed patients being simply a result of its antidepressant activity.

PMID: 10929571 DOI: 10.1080/00926230050084623

References

ADDYI (package insert). Raleigh, NC: Sprout Pharmaceuticals, Inc. 2015.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders (5th ed. [DSM-5]). 2013; Arlington, VA: American Psychiatric Publishing.

Annon JS. The PLISSIT model: a proposed conceptual scheme for the behavioral treatment of sexual problems. J Sex Ed & Ther. 1976;2(2):1-15.

Bachman G. Female sexuality and sexual dysfunction are we stuck on the learning curve? J Sex Med. 2006;3(4):639-645.

Bachmann GA, Leiblum SR, Grill J. Brief sexual inquiry in gynecologic practice. Obstet Gynecol. 1989:73(3 Pt 1):425-427.

Clayton AH, Goldfischer ER, Goldstein I, et al. Validation of the Decreased Sexual Desire Screener (DSDS): a brief diagnostic instrument for generalized acquired female hypoactive sexual desire disorder (HSDD). J Sex Med. 2009;6(3):730-738.

Clayton AH, Goldstein I, Kim NN, et al. The International Society for the Study of Women's Sexual Health Process of Care for Management of Hypoactive Sexual Desire Disorder in Women. Mayo Clin Proc. 2018;93(4):467-487.

Croft HA. Understanding the role of serotonin in female hypoactive sexual desire disorder and treatment options. J Sex Med. 2017;14(12):1575-1584.

References

DeRogatis LR, Clayton AH, Goldstein A, et al. eDiary and Female Sexual Distress Scale© in evaluation distress in hypoactive sexual desire disorder (HSDD). J Sex Res. 2011;48(6):565-572.(c)

DeRogatis L, Clayton A, Lewis-D'Agostino D, Wunderlich G, Fu Y. Validation of the Female Sexual Distress Scale-Revised for assessing distress in women with hypoactive sexual desire disorder. J Sex Med. 2008;5(2):357-364.(b)

DeRogatis LR, Rosen R, Leiblum SR, et al. The Female Sexual Distress Scale (FSDS): initial validation of a standardized scale for the assessment of sexually related personal distress in women. J Sex Marital Ther. 2002;28(4):317-320.(a)

FDA approves new treatment for hypoactive sexual desire disorder in premenopausal women. June 21, 2019. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-hypoactive-sexual-desire-disorder-premenopausal-women. Accessed July 19, 2019.

Gerstenberger EP, Rosen RC, Brewer JV, et al. Sexual desire and the female sexual function index (FSFI): a sexual desire cutpoint for clinical interpretation of the FSFI in women with and without hypoactive sexual desire disorder. J Sex Med. 2010;7(9): 3096-3103.

Goldstein I, Lines C, Pyke R, Scheld JS. National differences in patient-clinician communication regarding hypoactive sexual desire disorder. J Sex Med. 2009;6(5):1349-1357.

Harsh V, McGarvey EL, Clayton AH. Physician attitudes regarding hypoactive sexual desire disorder in a primary care clinic: a pilot study. J Sex Med. 2008;5(3):640-645.

References

Kingsberg SA. Attitudinal survey of women living with low sexual desire. J Women's Health. 2014;23(10):817-23.

Kingsberg SA, Rezaee RL. Hypoactive sexual desire in women. Menopause. 2013;20(12):1284-1300.

Leiblum SR, Koochaki PE, Rodenberg CA, Barton IP, Rosen RC. Hypoactive sexual desire disorder in postmenopausal women: US results from the Women's International Study of Health and Sexuality (WISHeS). Menopause. 2006;13(1):46-56.

Leiblum SR, Symonds T, Moore J, et al. A methodology study to develop and validate a screener for hypoactive sexual desire disorder in postmenopausal women. J Sex Med. 2006;3(3): 454-455.

Meston CM. Validation of the Female Sexual Function Index (FSFI) in women with female orgasmic disorder and in women with hypoactive sexual desire disorder. J Sex Marital Ther. 2003;29(1):39-46.

Parish SJ, Goldstein AT, Goldstein SW, et al. Toward a more evidence-based nosology and nomenclature for female sexual dysfunctions–Part II. J Sex Med. 2016;13(12):1888-1906. (a)

Parish SJ, Hahn SR. Hypoactive sexual desire disorder: A review of epidemiology, biopsychology, diagnosis, and treatment. Sex Med Rev. 2016;4(2):103-120. (b)

Rosen R, Brown C, Heiman J, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther. 2000;26(2):191-208.

References

Rosen RC, Connor MK, Miyasato G, et al. Sexual desire problems in women seeking healthcare: a novel study design for ascertaining prevalence of hypoactive sexual desire disorder in clinic-based samples of U.S. women. J Womens Health (Larchmt). 2012;21(5):505-515. 13 14 15.

Rust J, Derogatis L, Rodenberg C, et al. Development and validation of a new screening tool for hypoactive sexual desire disorder: The Brief Profile of Female Sexual Function (B-PFSF). Gynecol Endocrinol. 2007;23:638-644.

Segraves R, Woodard T. Female hypoactive sexual desire disorder: History and current status. J Sex Med. 2006;3(3):408-418.

Shifren JL, Johannes CB, Monz BU, et al. Help-seeking behavior of women with self-reported distressing sexual problems. J Womens Health (Larchmt). 2009;18(4):461-468.

Shifren JL, Monz BU, Russo PA, Segreti A, Johannes CB. Sexual problems and distress in United States women: prevalence and correlates. Obstet Gynecol. 2008;112(5):970-978.

Sobecki JN, Curlin FA, Rasinski KA, Lindau ST. What we don't talk about when we don't talk about sex: results of a national survey of U.S. obstetrician/gynecologists. J Sex Med. 2012;9(5): 1285-1294.

Stahl SM, Sommer B, Allers KA. Multifunctional pharmacology of flibanserin: Possible mechanism of therapeutic action in hypoactive sexual desire disorder. J Sex Med. 2011;8(1):15-27.

References

Tsimtsiou Z, Hatzimouratidis K, Nakopoulou E, et al. Predictors of physicians' involvement in addressing sexual health issues. J Sex Med. 2006;3(4):583-588.

Taylor JF, Rosen RC, Leiblum SR. Self-report assessment of female sexual function: psychometric evaluation of the Brief Index of Sexual Functioning for Women. Arch Sex Behav. 1994;23(6): 627-643.

Van Nes Y, Bloemers J, van der Heijden PGM, et al. The Sexual Event Diary (SED): Development and validation of a standardized questionnaire for assessing female sexual functioning during discrete sexual events. J Sex Med. 2017;14(11):1438-1450.