

Southern California Center for
SEXUAL HEALTH
and SURVIVORSHIP MEDICINE

Desire for Desire

Michael L Krychman MD

Executive Director of the Southern California Center for Sexual Health and Survivorship Medicine

AASECT Certified Sexual Counselor

Associate Clinical Professor UCI

Newport Beach, CA

Disclosures

Speakers Bureau

AMAG, Duchesney, Lupin, Valeant

Consultant /Advisory Board

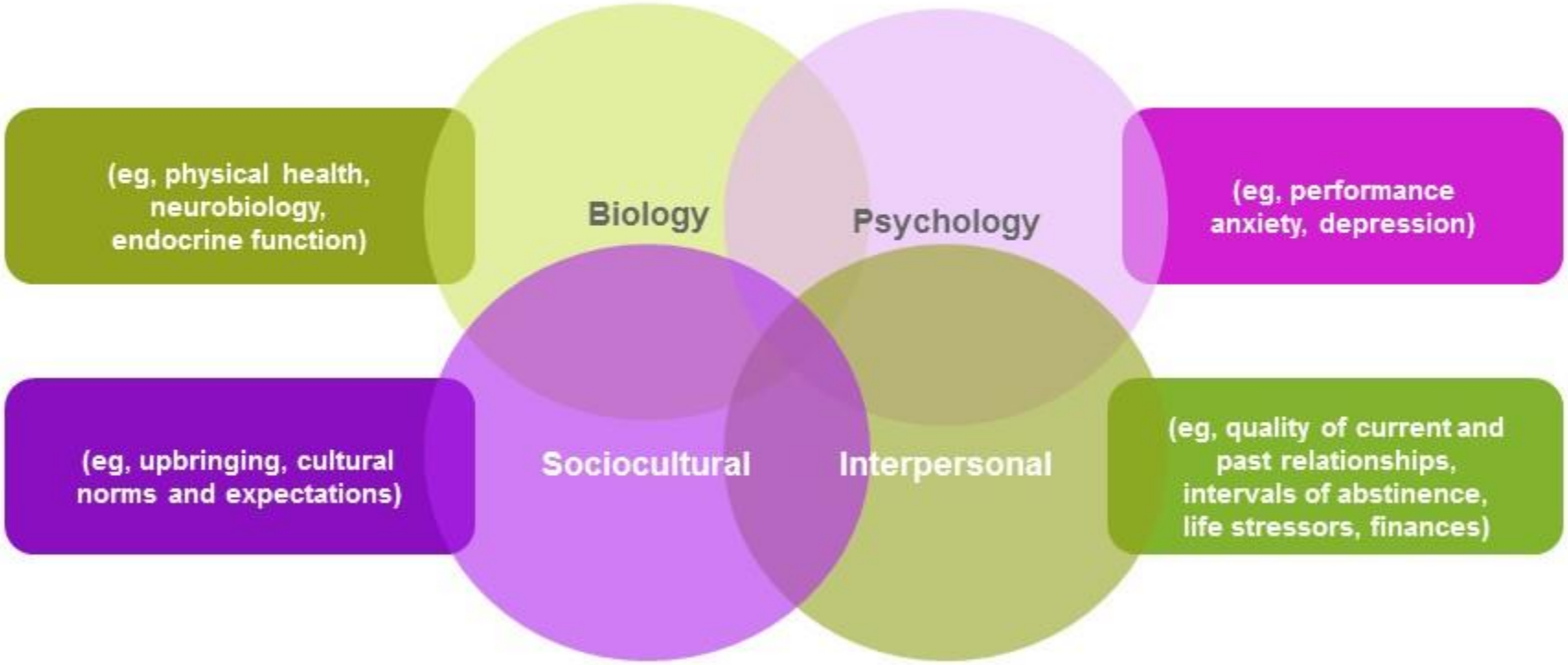
AMAG, Allergan, Lupin Pharmaceuticals, Duchesney, Viveve Medical, Materna, Exeltis, Applied Biology, Palatin Technologies , Valeant Pharmaceuticals, Therapeutics MD

•

Objectives

- Create a differential diagnosis for lowered sexual interest
- Identify some physical facets that influence sexual interest
- Develop a comprehensive treatment paradigm for the treatment of lowered sexual interest

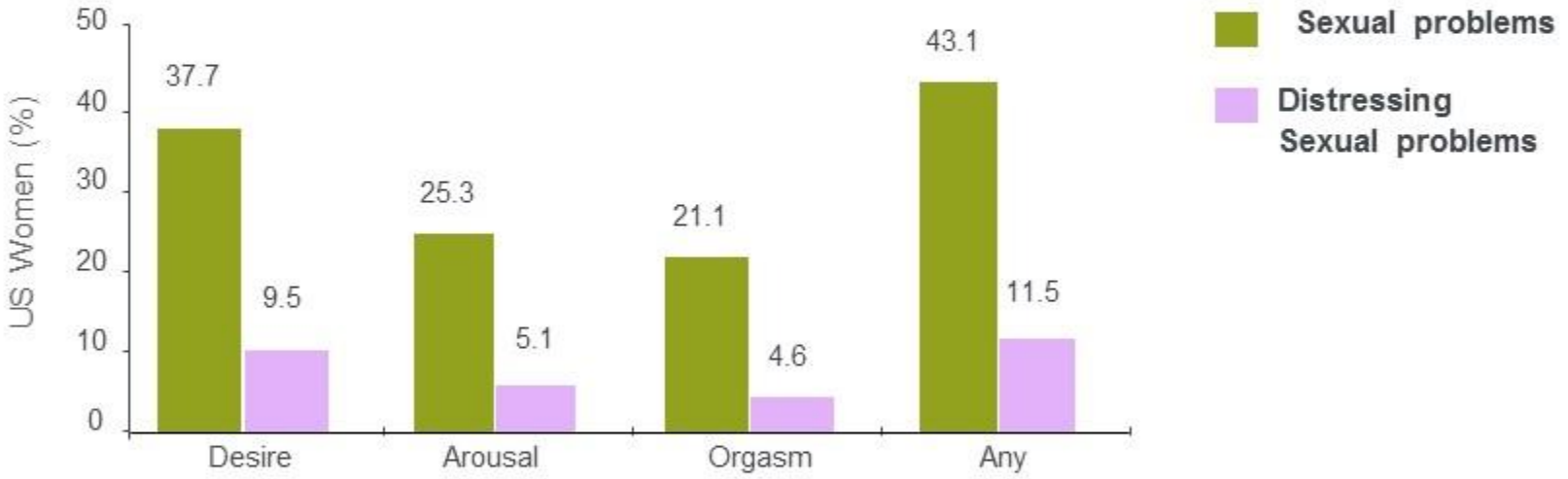
Biopsychosocial Model of Female Sexual Response[1,2]



1. Rosen RC, Barsky JL. *Obstet Gynecol Clin North Am*. 2006;334:515-526 2. Althof SE, Leiblum SR, Chevret-Measson M, et al. *J Sex Med*. 2005;26:793-800.

Prevalence of FSD

PRESIDE Survey

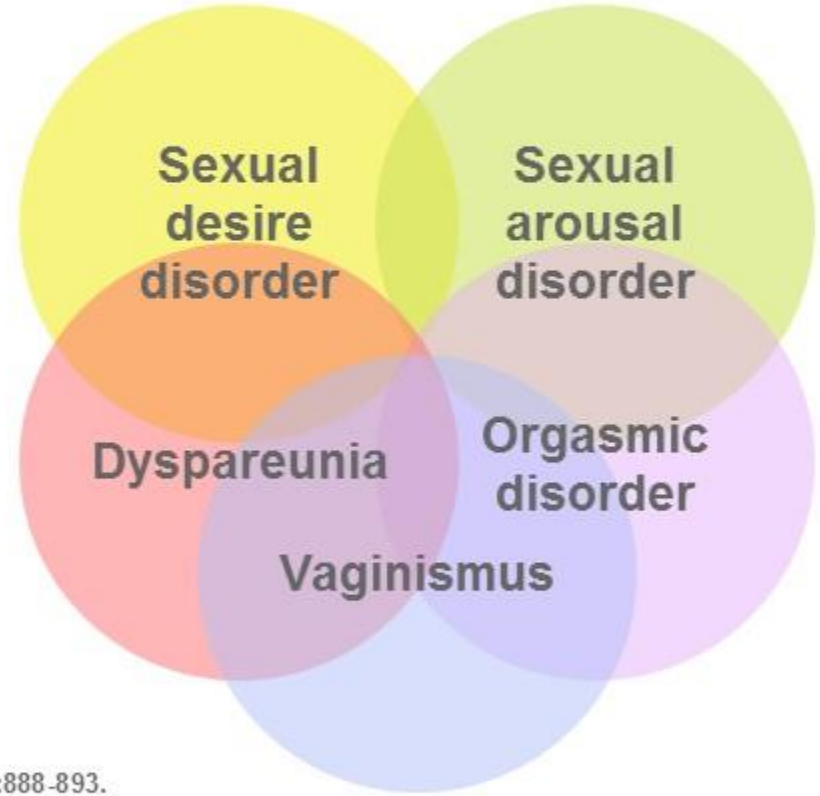


Data are US population age-adjusted.

FSD, female sexual dysfunction; PRESIDE, Prevalence of Female Sexual Problems Associated With Distress and Determinants of Treatment Seeking.

Shifren JL et al. *Obstet Gynecol.* 2008;112(5):970-978. Reproduced.

Overlap of Female Sexual Dysfunctions



Basson R et al. *J Urol*. 2000;163(3):888-893.

FSDs: DSM-IV-TR Definitions

FSD	DSM-IV-TR Definition
Sexual desire disorders	
Hypoactive sexual desire disorder	Deficiency or absence of sexual fantasies and desire for sexual activity
Sexual aversion disorder	Aversion to and active avoidance of genital sexual contact with sexual partner
Sexual arousal disorder	
Female sexual arousal disorder	Persistent or recurrent inability to attain, or to maintain until completion of sexual activity, adequate lubrication-swelling response of sexual excitement
Orgasmic disorder	
Female orgasmic disorder	Persistent or recurrent delay in, or absence of, orgasm following normal sexual excitement phase
Sexual pain disorders	
Dyspareunia	Genital pain associated with sexual intercourse
Vaginismus	Recurrent or persistent involuntary contraction of perineal muscles surrounding outer third of vagina when vaginal penetration with penis, finger, tampon, or speculum is attempted

DSM-IV-TR, *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition, text revision; FSD, female sexual dysfunction.

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed. Text revision. Washington, DC: American Psychiatric Association; 2000. Reproduced.

Subtypes of Female Sexual Dysfunctions Described by DSM-IV-TR

Defined by Onset	
Lifelong	Sexual dysfunction has been present since the onset of sexual functioning
Acquired	Sexual dysfunction develops only after a period of normal functioning

Defined by Context	
Generalized	Sexual dysfunction is not limited to certain types of stimulation, situations, or partners
Situational	Sexual dysfunction is limited to certain types of stimulation, situations, or partners

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* Fourth Edition, Text Revision. Washington, DC: American Psychiatric Press; 2000.

Female Sexual Disorders: DSM-5[a]

Female Orgasmic Disorder	302.73 (F52.31)	Presence of either on (75%-100%) sexual activity occasions: 1. Marked delay in/infrequency of, or absence of orgasm 2. Marked reduced intensity of orgasmic sensations
Female Sexual Interest/ Arousal disorder	302.72 (F52.22)	Lack of, significantly reduced, or absent, sexual interest/arousal as manifested by 3 of the following: 1. Interest in sexual activity 2. Sexual/erotic thoughts or fantasies 3. Initiation of sexual activity and unreceptive to partner's attempts to initiate 4. Sexual excitement/pleasure during sexual activity in almost all or all (75%-100%) sexual encounters 5. Sexual interest/arousal in response to any internal or external sexual/erotic cues (written, verbal, visual) 6. Genital or nongenital sensations during sexual activity
Genito-Pelvic Pain/ Penetration Disorder	302.76 (F52.6)	Persistent or recurrent difficulties with 1 or more of the following during intercourse of penetration attempts: 1. Vaginal penetration 2. Marked vulvovaginal or pelvic pain 3. Marked fear or anxiety in anticipation of, during, or as a result of vaginal penetration 4. Marked tensing or tightening of the pelvic floor muscles

Symptoms persisted a minimum of 6 months and not better explained by a nonsexual mental disorder or consequence of severe relationship distress or other significant stressors and not due to effects of substance/medication or other medical condition

[a]Can be divided into lifelong vs acquired, generalized vs situational, severity (mild, moderate, severe)

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders,* 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.

Female Sexual Function:
Most Activity Is Above the Neck

Female sexual function appears to be modulated by specific neurotransmitters, several brain structures, and neurohormones

- Dopamine
- Serotonin
- Epinephrine
- Norepinephrine

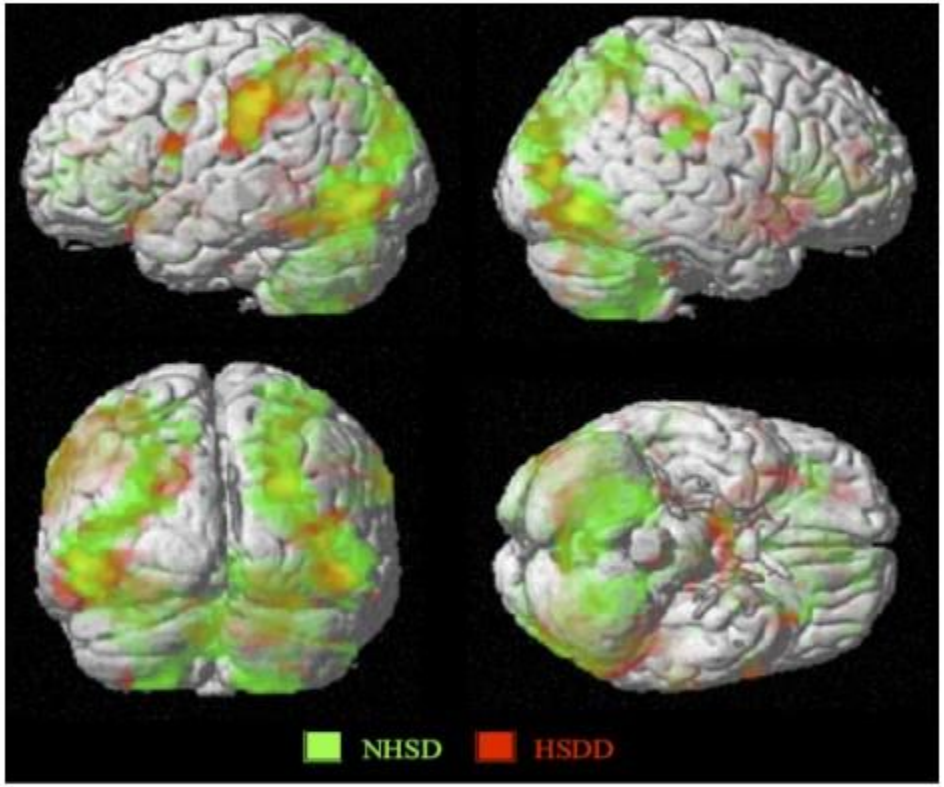
- Basal ganglia
- Amygdala
- Insular cortex
- Caudate nucleus
- Hypothalamus
- Spinal cord
- Pituitary
- Hippocampus
- Ventral tegmental area

- Estrogen
- Testosterone
- Oxytocin
- Endogenous opioids
- Pheromones

Taylor M, et al. *J Affect Disord.* 2005;88:241-254.
Basson R. *N Engl J Med.* 2006;354:1497-1506.

fMRI Imaging Indicates Brain Activation Patterns Differ Between "Never Had Sexual Dysfunction" and HSDD Groups

Overall Pattern of Activation for the Never Had a Sexual Dysfunction (NHSD) and HSDD Groups While Viewing Erotic Compared to Sports Videos (N = 36)[a]



fMRI=functional magnetic resonance imaging; NHSD=never had sexual dysfunction. *Overlap for the NHSD and HSDD groups is in yellow.

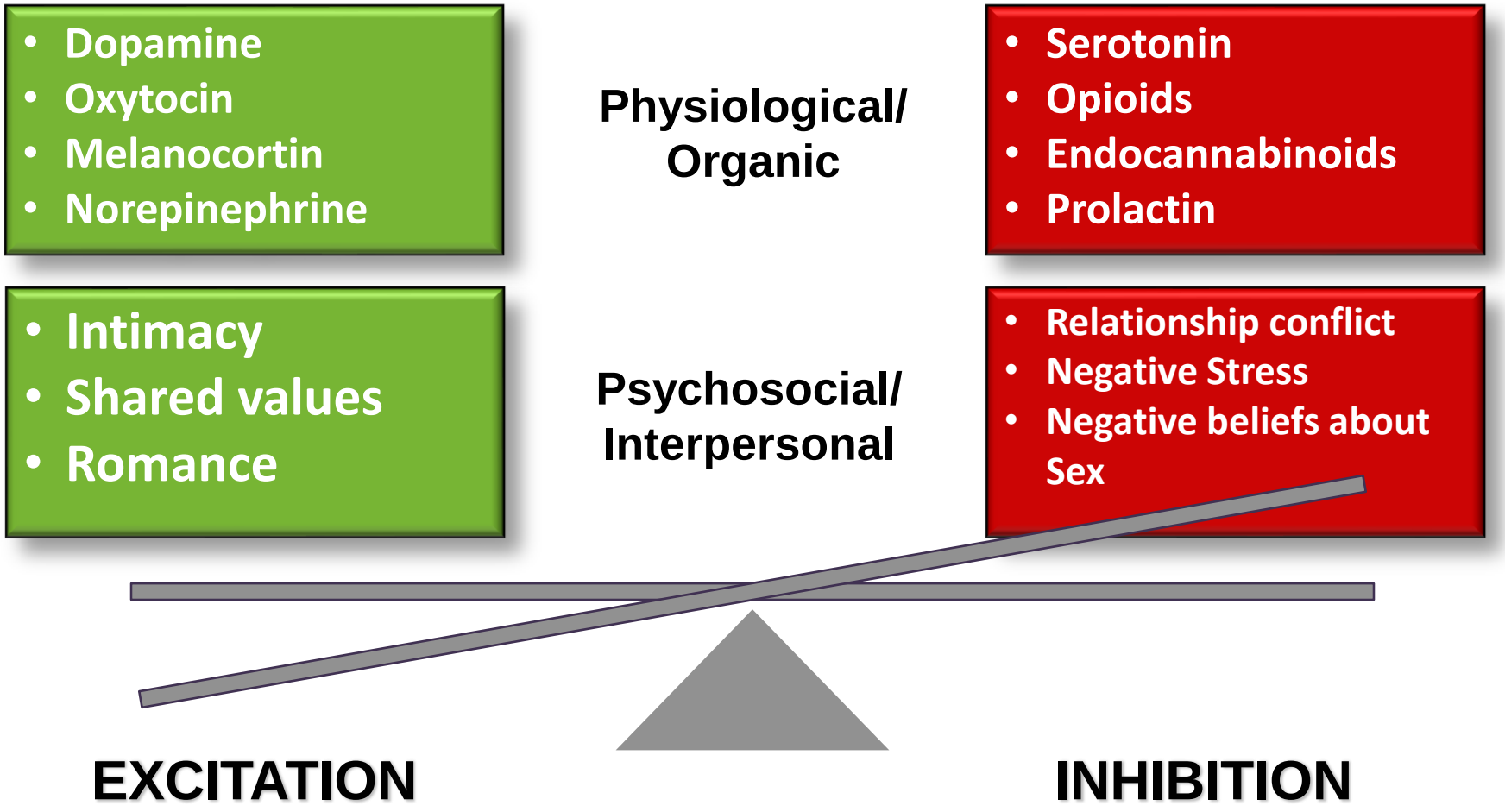
This figure was published in Arnow BA, et al. Women with hypoactive sexual desire disorder compared to normal females: a functional magnetic resonance imaging study. *Neuroscience*. 2009;158(2):484-502; Copyright Elsevier 2009.

Decreased Sexual Desire With Distress Negatively Impacts Women's Lives

- Decreased sexual desire is associated with negative effects including:[1,2]
  - Poor self-image
  - Mood instability
  - Depression
  - Strained relationships with partners

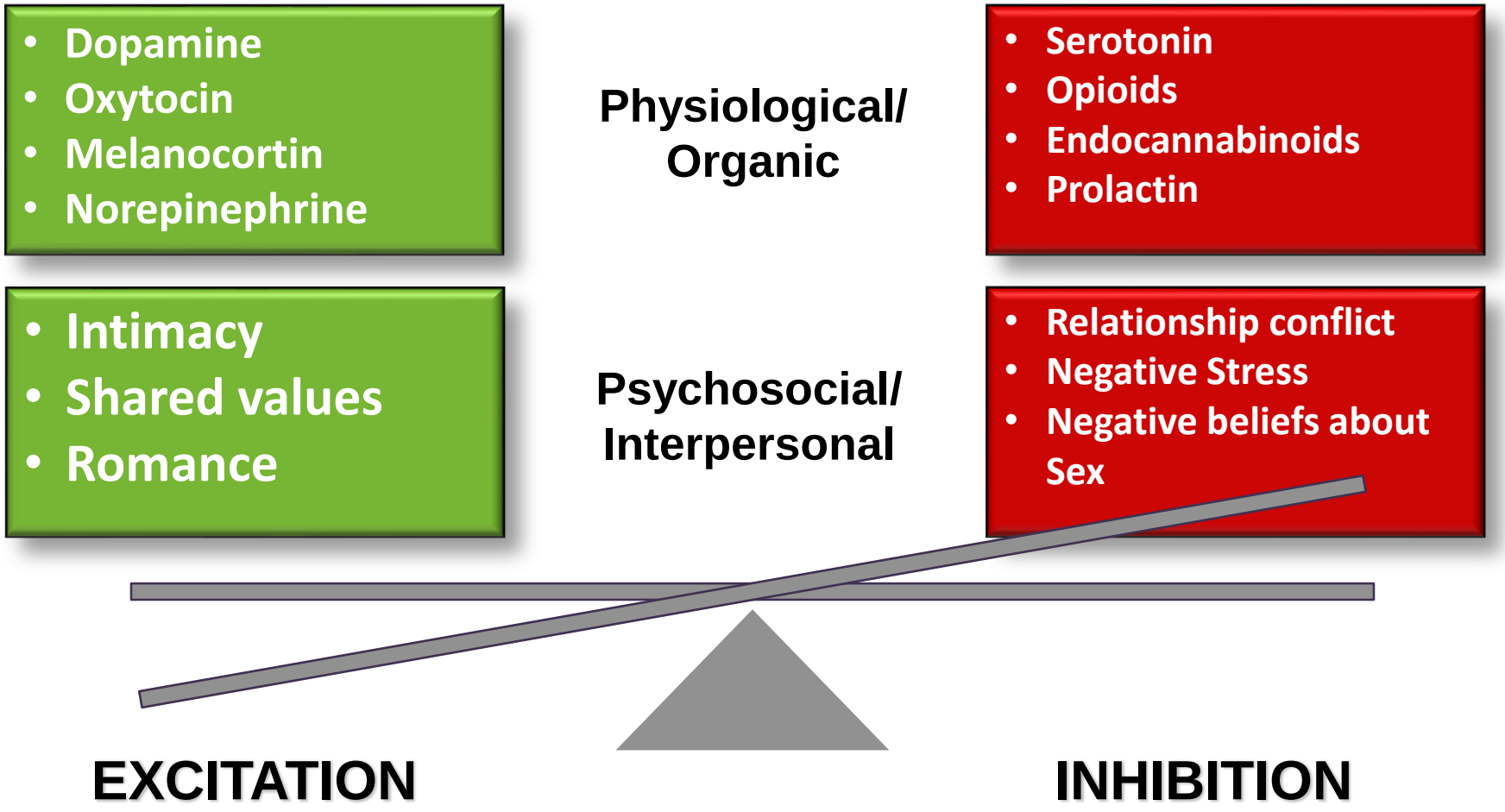
1. Shifren JL, et al. *Obstet Gynecol.* 2008;112(5):970-978. 2. Leiblum SR. *Menopause.* 2006;13(1):46-56.

Current Concepts: Etiology of Female Sexual Dysfunction



Bancroft J, et al. *J Sex Res*. 2009;46:121-142.
Perelman MA. J Sex Med 2009;6:629-32.

Current Concepts: Etiology of Female Sexual Dysfunction



Bancroft J, et al. *J Sex Res*. 2009;46:121-142.
Perelman MA. J Sex Med 2009;6:629-32.

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 = may indicate the presence 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.

Treatment Pathways: Sexual Complaints



- Treatment of systemic illness
  - Undiagnosed chronic medical illnesses:
    - Hypertension
    - Diabetes
    - Thyroid dysfunction
- Identification of medications/herbs and supplements
  - Many patients are on poly-pharmacy
  - Screen for unnecessary SSRI
  - Sexual Pharmacology

Lifestyle Factors and Sexual Activity

Increased



- Physically active women
- Social support
- Healthy diet



Decreased

- Sleep difficulties
- Inactivity
- Depression
- Obesity



Greendale et al. Journal of Women's Health 1996;5:445-58.

- Structured Sexual Tasks
  - Sensate focusing
  - Guided imagery
  - Relaxation exercise
  - Fantasy exploration
  - Skilled exercises
  - Tantra Sexual Awakening

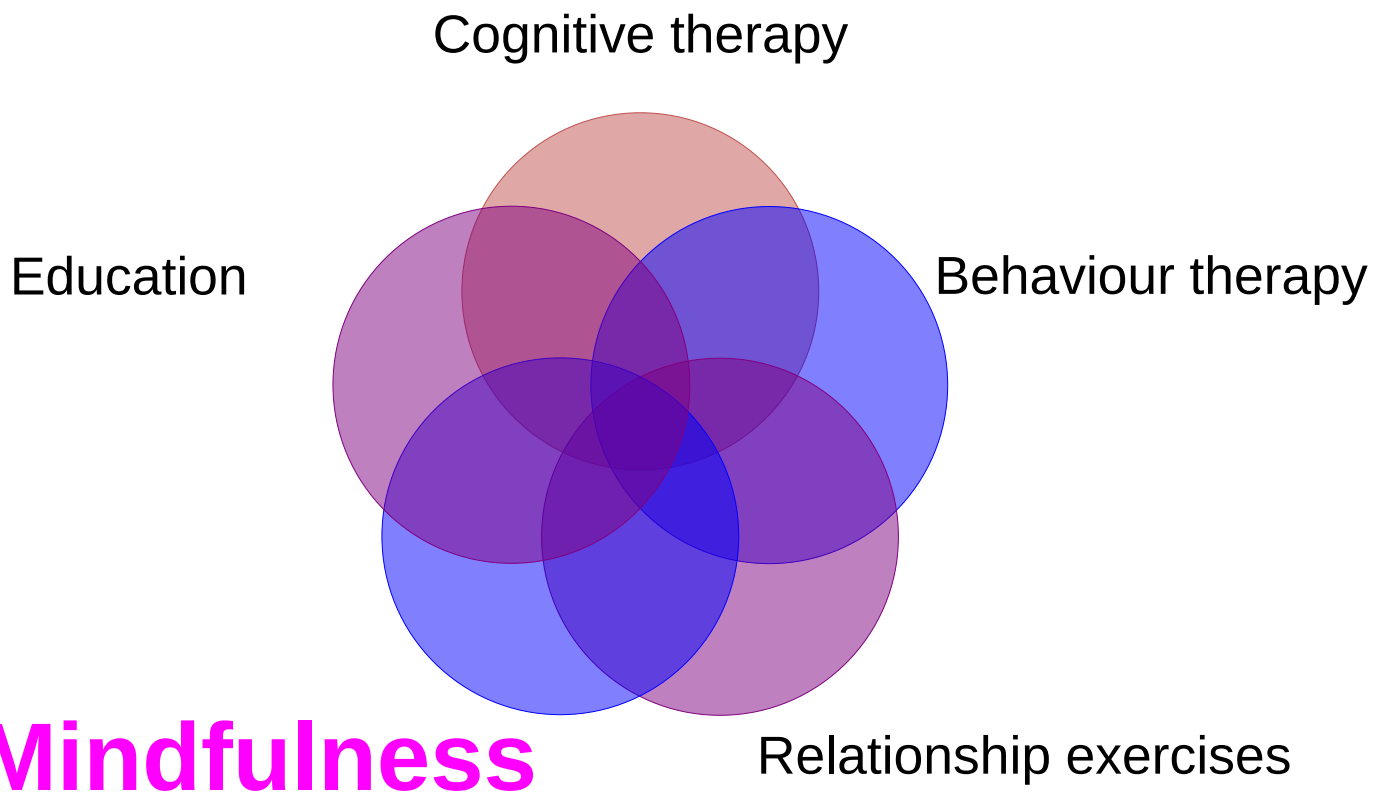




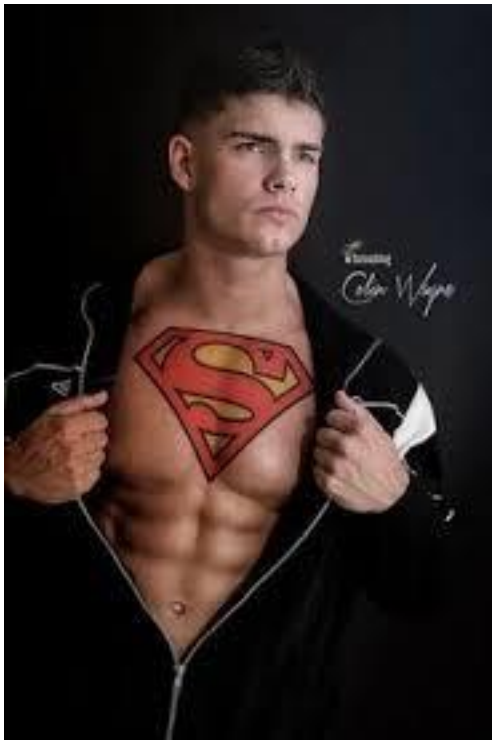
- Sexual Devices/Accessories
  - Self stimulator/vibrators
  - Dilator therapy
  - Sexy lingere
  - Attachable nipples



Psychoeducational Treatments



Assess the Couples Communication





Relearning Skills

Poor Communication

- **Texting**
- **Raised tone**
  - **Yelling from room to room**
- **Non Verbal assumptions**
- **Interuptions**
- **Multi tasking**
- **Post it Discussions**
- **Accusatory**

Good Communication

- Face to face
- Active listening
- Quiet
- Undistracted time
- Uninterupted
- Ground rules
- From a place of “I”

Focus on Novel Activities

- Bring vacation time home again
- Do something novel and exciting
  - Dance in the living room
  - Ride a roller coaster
- Boost adrenaline and increases oxytocin hormones-
  - the love hormone





Lubricants and Moisturizers

- **Lubricants** are considered temporary measures to relieve vaginal dryness during intercourse
  - Short duration of action
  - Must be applied frequently
  - Sexual aid



- **Moisturizers** are promoted as providing long-term relief of vaginal dryness
  - Continuous use- several times a week
  - Everyday aid
- **Both OTC and FDA approved as cosmetics**

Testosterone IS ALL Off Label

- 1% testosterone gels
- Male dose: 5 cc per day
- 1/20th to 1/10th dose: 0.25-0.5 cc per day
  - 250 - 500 mg gel applied
- Measure free T/calc free T/ FAI in 3-4 wks

Efficacy and Safety of Testosterone with Chronic Medical Illness

Barton DL, 2007, JNCI, 99: 672-9

- N = 133 cancer survivors randomized to placebo or T
- No significant T effect (over placebo) on:
- Sexual frequency, Mood, Vitality, Sexual function total score, Sexual function pleasure score

Krychman et al JSM 2008

- Case series 3 breast cancer survivors on testosterone for low desire causing personal distress
- Improved sexual satisfaction by patient report
- Presently over 50 cases

- **Glaser data**: AI and testosterone implants

PDE5 Inhibitors (Off Label)

- If patient complains of slow or no arousal vaginal estrogen and /or 25-50Mg of Sildenafil one hour before intercourse maybe beneficial
- Many increase clitoral vasocongestion
- No change in desire
- Newer data supports the use of PD5 inhibitors with women who suffer from SSRI induced orgasmic complaints of increased latency or decreased intensity or anorgasmia

Current Overview of the Management of Urological Atrophy in Women with Breast Cancer



Pruthi S, Simon JA, Early AP. Breast J. 2011 Jul-Aug;17(4):403-8. doi: 10.1111/j.1524-4741.2011.01089.x.

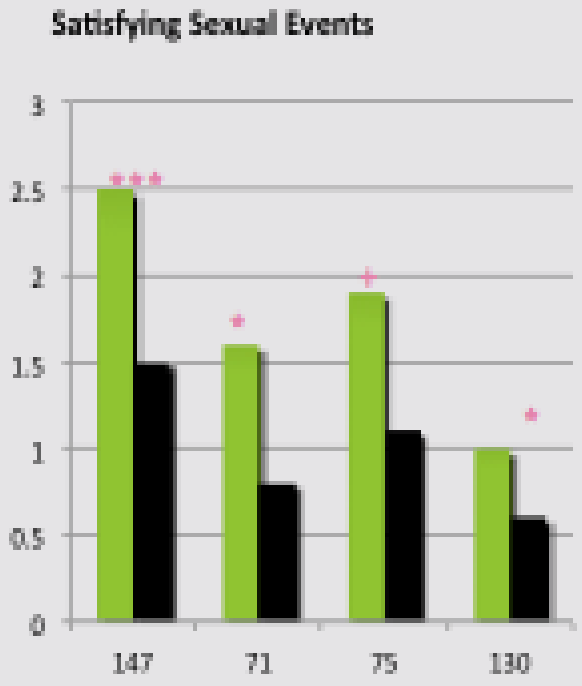
Table 1. Estradiol Preparations and Maximum Annual Delivered Dose

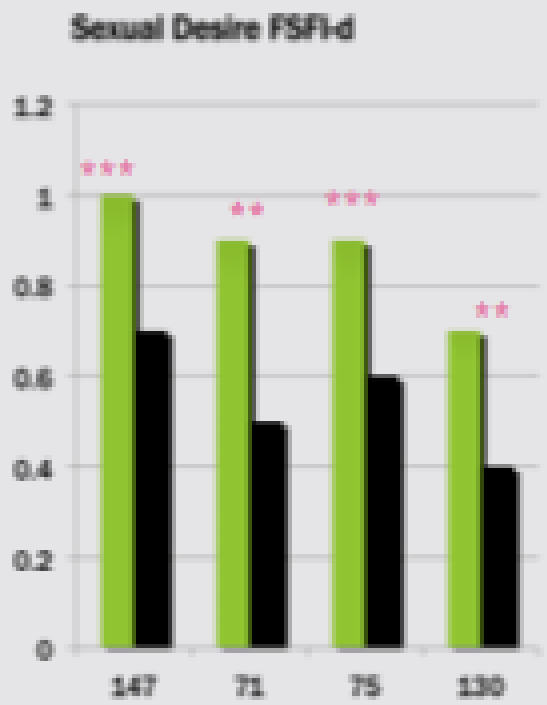
Product name	Route/Type of administration	Typical regimen	Nominal daily delivery rate or administered lowest approved dose (mg/day)	Typical serum level (pg/mL)	Maximum annual delivered dose (mg)[1]
Vaginal estradiol					
Vagifem	Vaginal tablet	1 Tablet daily × 14 then 2 × weekly	10 μg	4.6	1.14
Estring	Vaginal ring	1 Ring vaginally q 3 months	7.5 μg	8.0	2.74
Estrace	Vaginal cream	1 g cream vaginally q week[2]	variable[2]	NA	7.1
FemRing	Vaginal ring	1 Ring vaginally q 3 months	0.05 mg	40.6	18.25
Oral estradiol					
Estrace tablets and generics	Oral tablet	1 Tablet p.o. qd	0.5 mg	55.4	182.5
Transdermal estradiol					
Divigel[3]	Gel	0.25 mg packet qd	0.003	9.8	1.09
Estrogel	Gel	0.75 mg/pump qd	0.035	28.3	12.78
Evamist[3]	Spray	1.53 mg spray qd	0.021	19.6	7.67
Climara[4]	Patch	1 Patch weekly	0.025	22	9.13
Menostar	Patch	1 Patch weekly	0.014	13.7	5.11
Vivelle-Dot[5]	Patch	1 Patch twice weekly	0.0375	34	12.78

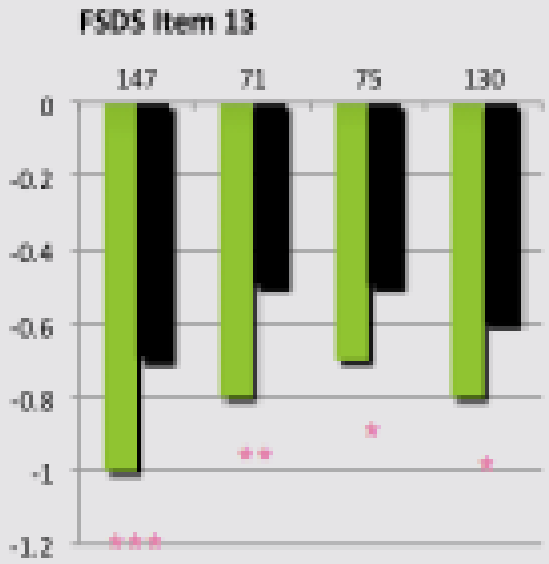
Flibanserin/ Addyi ®

- Novel, non-hormonal therapy that works on key sexual pathways in the brain
- Over 11,000 women studied in trials to date
- Once daily pill taken at bedtime
- Demonstrated efficacy on measurements of desire, distress and satisfying sexual events (SSEs)
- Most common side effects – dizziness, nausea, fatigue and somnolence
- Re-submission to FDA with 14 new trials and a validation
- June 2015 FDA meeting 18-6 **APPROVED**

Consistent Efficacy:
4 Different US Phase III Clinical Trials*





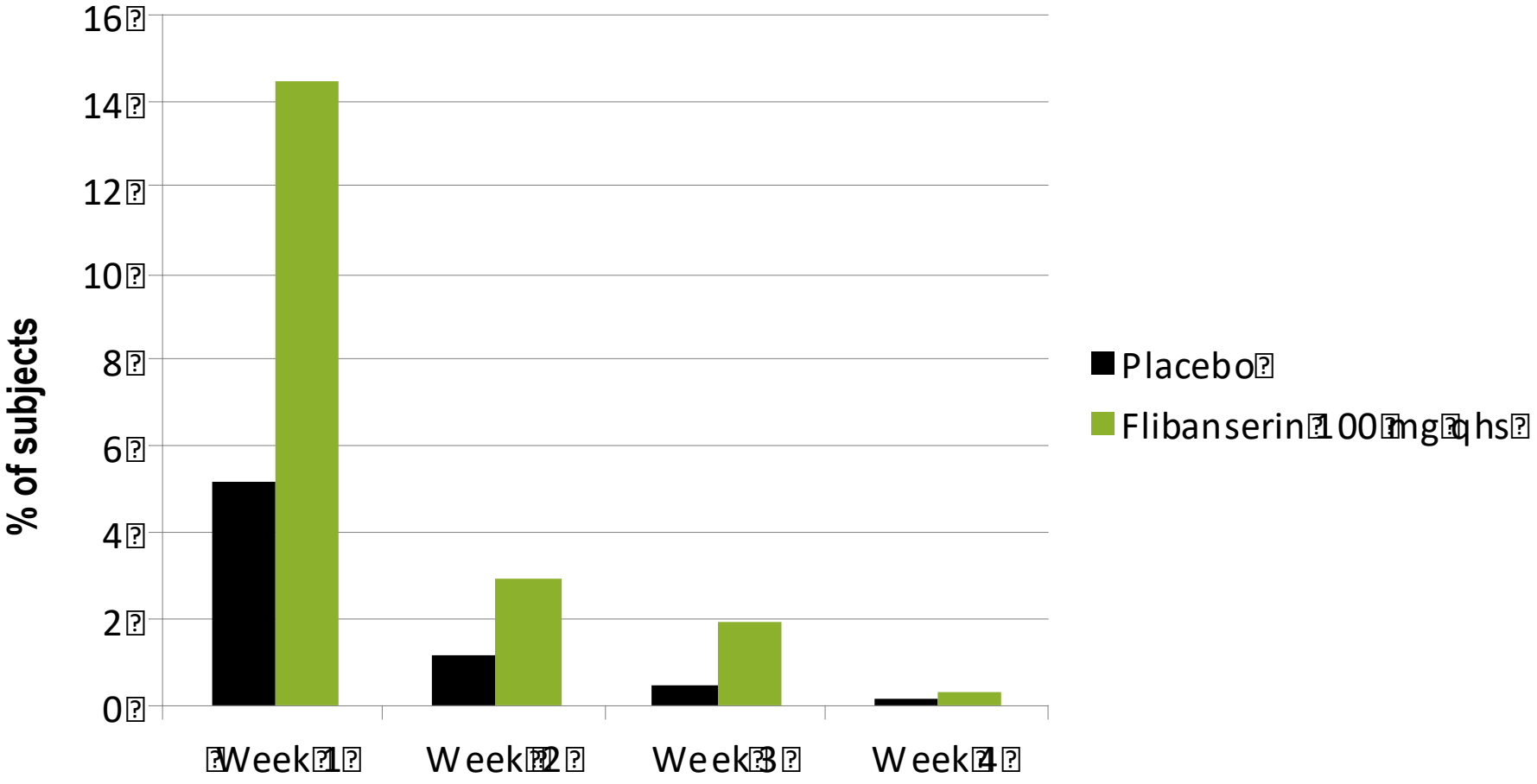


FLIBANSERIN

PLACEBO

147–M. Katz, L. DeRogatis, R. Ackerman, P. *Sex Med* 2012 (In press).;
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.;
130–Simon JA, Kingsberg SA, Shumel B, et. al. *Menopause* 2012 (under review)

Rate of First Onset of Most Common Side Effects in all trials



***Somnolence, fatigue, or sedation in phase III placebo controlled trials (%)**

Data on file Sprout Pharmaceuticals.

Side Effect Profile

Phase 3 clinical trial program,

*60% of women studied mild to moderate drinkers.

*This is in line with the general population

*Alcohol consumption was not excluded from trials in women.

*This study required participants to drink the alcoholic equivalent of a half to full bottle of wine within 10 minutes on a nearly empty stomach before taking the drug.

*More men than women enrolled for the challenge trial with body weights and consumption capability that likely made them less likely to vomit than women



- Cialis is an example of a drug where a similar study was conducted - the outcomes are much like flibanserin's.

- Their prescription labeling warns not to take Cialis if you have had 5 or more drinks

Flibanserin & Hypotension/Syncope (low blood pressure and fainting)

•FDA identified 6 cases of hypotension and/or syncope in the Flibanserin Phase 3 trials – a combined incidence of 0.5%. The placebo incidence was 0.3%.

- Hypotension specifically was 0.2%
- Syncope specifically was 0.3%

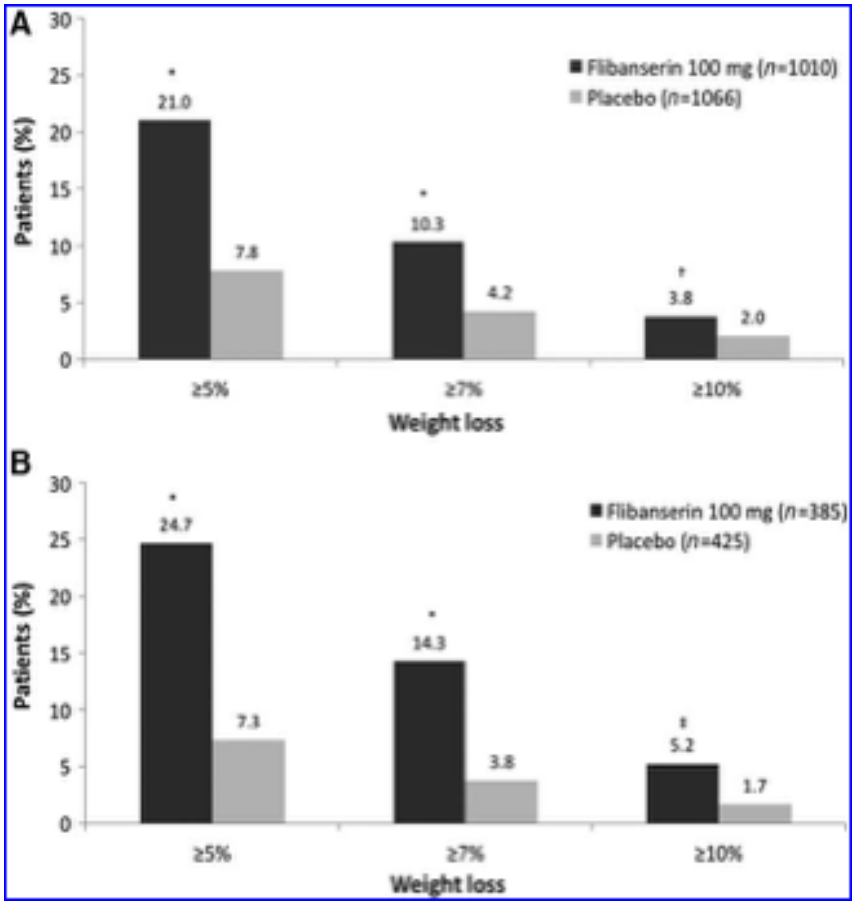
•Bupropion, a drug commonly used off-label to treat HSDD today in the absence of an FDA approved treatment option, has a much higher incidence of both.

•Buproprion

- hypotension is 2.5%, or **12x** the Flibanserin rate
- syncope is 1.2%, or **4x** the Flibanserin rate

Flibanserin and Weight Loss





- Pooled analysis of 5 studies
- HSDD patients were not attempting to loose weight and did not receive ancillary therapies provided in weight loss studies such as nutritional counseling, exercise counseling
- Hormonal Contraception, SSRI/SNRI, smoking status, treatment responder status did not demonstrate a significant effect on weight.
- Weight loss was sustained at 12 and 18 months

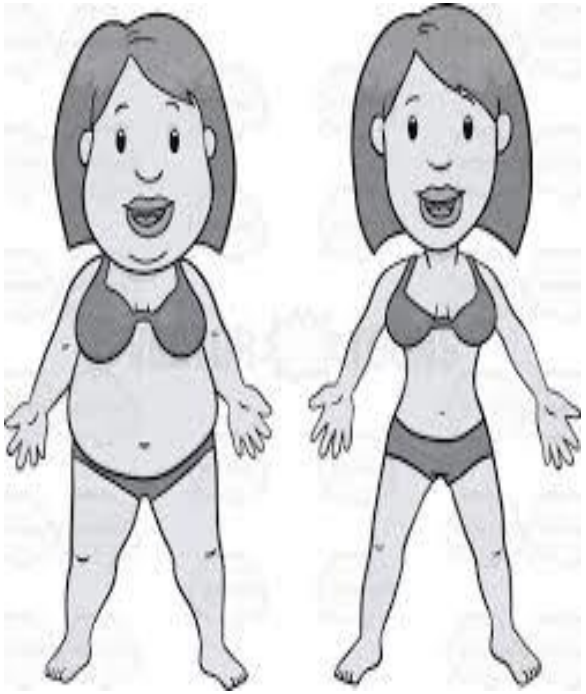
A= pre-menopausal

B= post-menopausal

Kornstein et al JWH 2017.

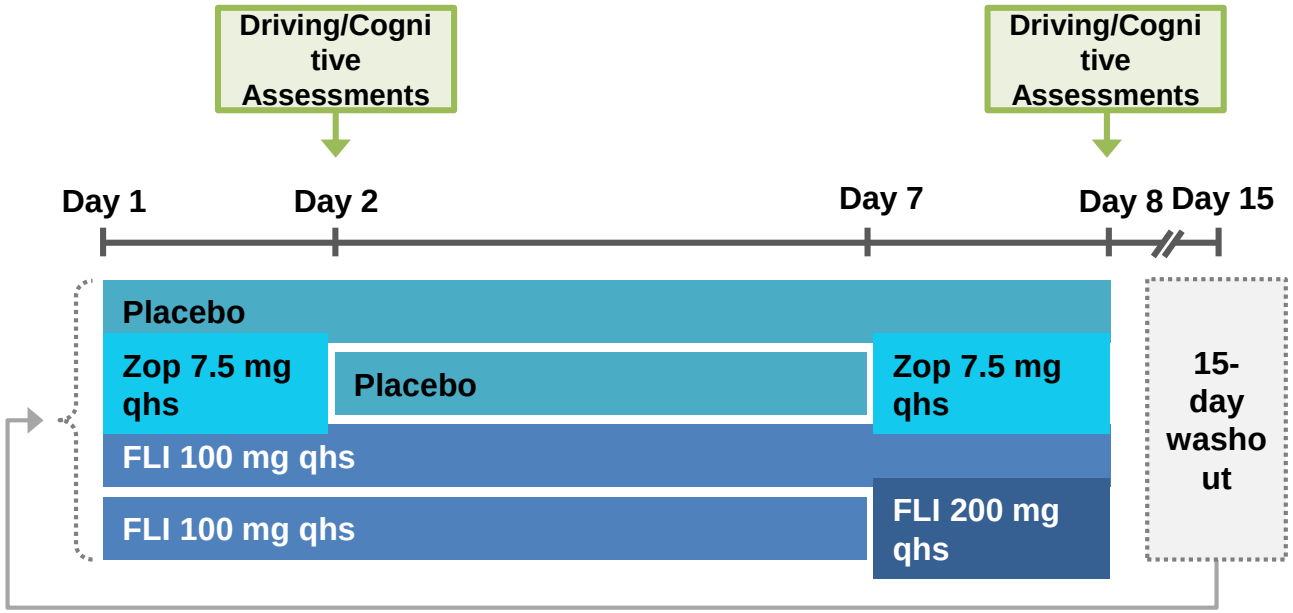
Mechanism

- Serotonin neurons play a complex role in the regulation of weight and metabolism
- Pharmacological agents with serotonin activity have been shown to increase or decrease body weight
- 5HT1A agonist activity and 5HT2A antagonist activity result in the inhibition of glutamate neurons reducing serotonin release in prefrontal cortex
- **Mirtazapine**
  - atypical antidepressant
  - 5HT1A agonist activity and 5HT2A antagonist activity
  - Causes weight gain
- **Lorcaserin**
  - 5HT 2C receptor agonist (like flibanserin)
  - Approved weight loss drug
- Typically
  - Serotonin based process yet to be discovered
  - Non Serotonin related mechanism
    - ? Enhanced cortical norepinephrine release



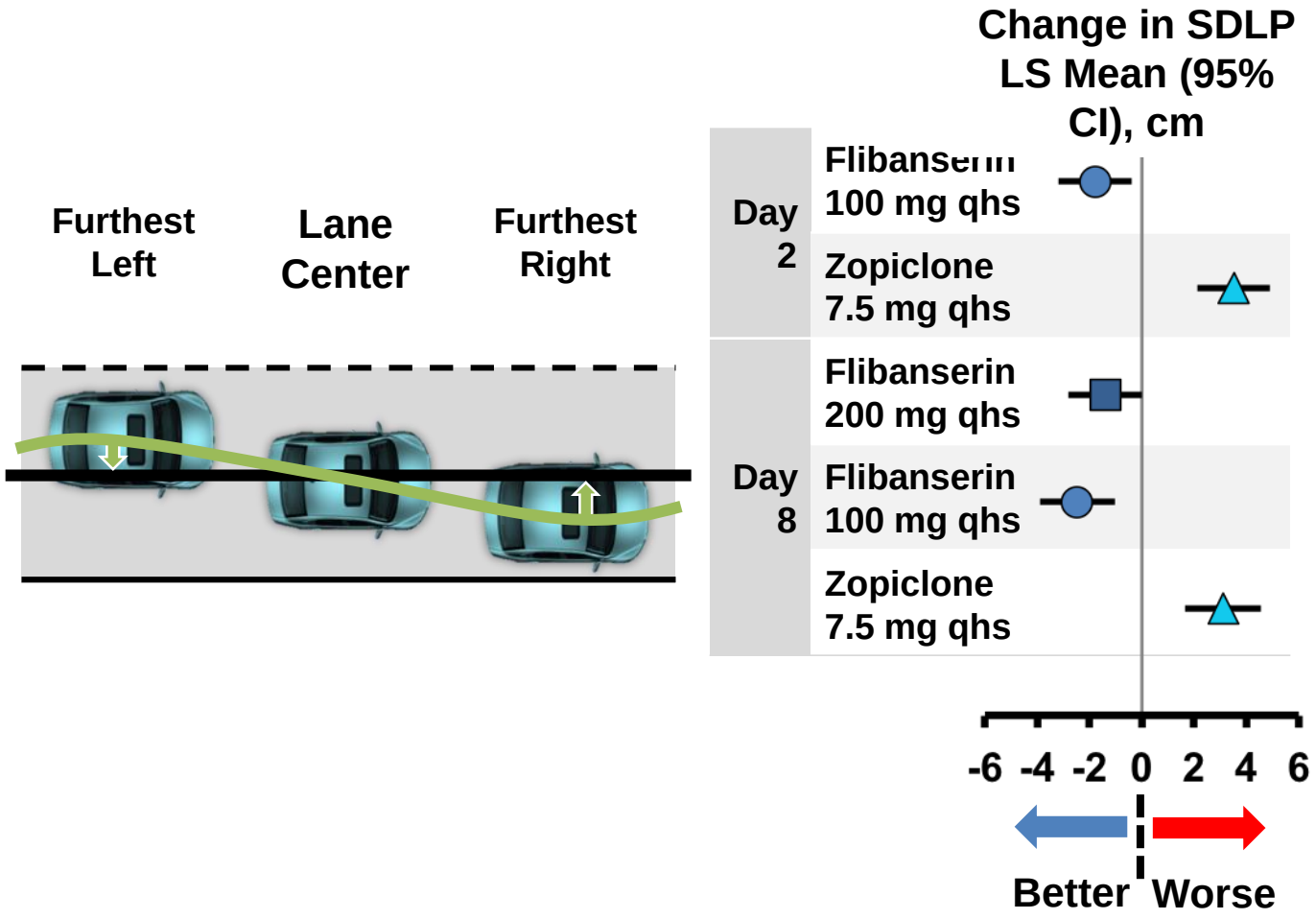
Driving and Cognition Study

- **Objective**
  - Evaluate potential next-day residual effects of flibanserin the morning after bedtime dosing in healthy premenopausal women
- **Design**
  - Randomized, double-blind, placebo-controlled, 4-way crossover study
- **Primary endpoint:** standard deviation of lateral position



Zop=zopiclone.

Standard Deviation of Lateral Position (SDLP)
Driving and Cognition Study



LS=least squares.

Summary of Results from the Dedicated Driving Study

- No evidence of worsening of driving performance with either acute or steady state administration of flibanserin 100 mg or acute administration of 200 mg

- No evidence of impaired cognitive performance

REMS Program

- Certification and more information

- https://www.addyirems.com

Boxed Warning:

Use of ADDYI and alcohol increases the risk of severe hypotension and syncope; therefore, alcohol use is contraindicated. Before prescribing ADDYI, assess the likelihood of the patient abstaining from alcohol.

Counsel patients prescribed ADDYI about the importance of abstaining from alcohol.

ADDYI is available only through a restricted program called the ADDYI REMS Program. (5.2)

Severe hypotension and syncope can occur when ADDYI

- is used with moderate or strong CYP3A4 inhibitors or in patients with hepatic impairment; therefore, ADDYI use in these settings is contraindicated.



Medications and Alcohol

- Loratadine
- Hydroxyzine
- Diphenhydramine
- Lorazepam
- Buspirone
- Clonazepam
- Diazepam
- Alprazolam
- Trazodone
- Warafin
- Cimetidine
- Naproxen
- Mirlazapine
- verapamil
- Paroxetine
- Desvenlafaxine
- Mirtazapine
- Risperidone
- Nefazodone
- Fluoxetine
- Bupropion
- Sertraline
- Gabapentin
- Glyberide
- Phenytoin
- Lamotrigine
- Ibuprofen
- clonidine
- Amphetamine
- Atorvastatin
- Simivastin
- Nitrofurantonin
- Metronidazole
- Ketoconazole
- Tinidazole
- Azithromycin
- Lithium
- Naproxen
- Phenytoin
- Zolpidem
- Eszapiclone
- Doxylamine





Investigational Medications in the Pipeline

Single Drugs

- Bremelanotide
- Femprox
- Intranasal Testosterone

Combination Drugs

- Lybrido
- Lybridos
- Lorexys

Bupropion Treatment for HSDD

Bupropion versus placebo

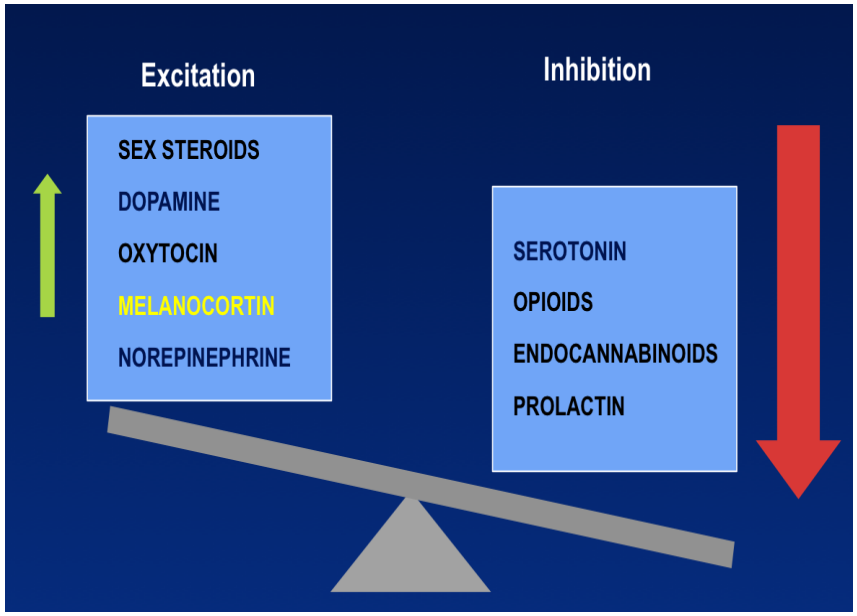
- Increased desire
- Frequency of sexual activity correlated with total testosterone, baseline and during treatment

Depressed minority switched from SSRI to Buproprion SR

- 150-300 mg; CSFQ improved desire, arousal, orgasm

Seagraves et al. J Clin Psychopharmacology 2004;24:339-342
Dobkin et al. J Clin Psychopharmacol 2006;26:21-6.

Bremelanotide



- Melanocortin receptor 4 agonist (MCR4 agonist) for treatment of HSDD and/or FSAD.
- Was initially delivered as a nasal spray and Phase II - adverse effects on BP.
- The drug reformulated in a lower dose for SQ injection.
- Phase IIb study is completed in premenopausal women with HSDD and or FSAD

Results:

1.25 and 1.75 mg SC was effective in decreasing distress, increasing arousal and desire and increasing the number of SSE with robust dose response and consistency of effect across all key endpoints.

1.Stephen B. Levine, MD;1 Candace Brown, MSN, PharmD;2 Eileen Palace, PhD;3 Steven Fischkoff, MD;4 Christine Schnorrbusch, Phase 2B., Bremelanotide Study in Pre and Post Menopausal Women with Female Sexual Arousal Disorder BS4. Poster Presentation. ACOG Annual Meeting. Annual Clinical Meeting. New Orleans LA. Poster 56. May 2008.

Lorexys ®

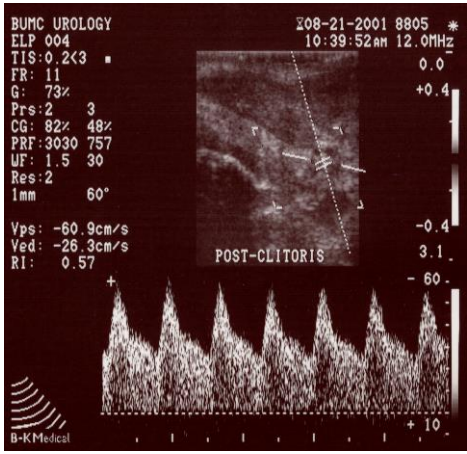
- Lorexys is designed to restore the balance of three neurotransmitters –
  - dopamine, serotonin and norepinephrine
  - that are known to regulate sexual inhibition and sexual excitation.

- An oral, non-hormonal, fixed-dose combination of two antidepressants,
  - **Bupropion and Trazodone**
  - Lorexys is formulated with a ratio that is precisely balanced to neutralize the side effects of its individual components and maximize efficacy.

Lorexys has completed a Phase 2a clinical study that evaluated its Safety Tolerability and Pro-sexual efficacy

Femprox

- RCT Stage III trial of topical alprostadil 0.4% cream with a skin penetration enhancer (DDAIP) an ester of N, N dimethylalanine and dodecanol
- 900 mg dose showed statistically significant and clinically relevant improvements in primary and secondary efficacy outcomes
  - Primary endpoint: arousal success
    - (yes to #3 of Female Sexual encounter profile)
  - Secondary endpoints: FSFI and Global Assessment Questionaire and Sexual Distress Scale.
    - Goldstein et al J Sex Med 2012 9: supl 1 22

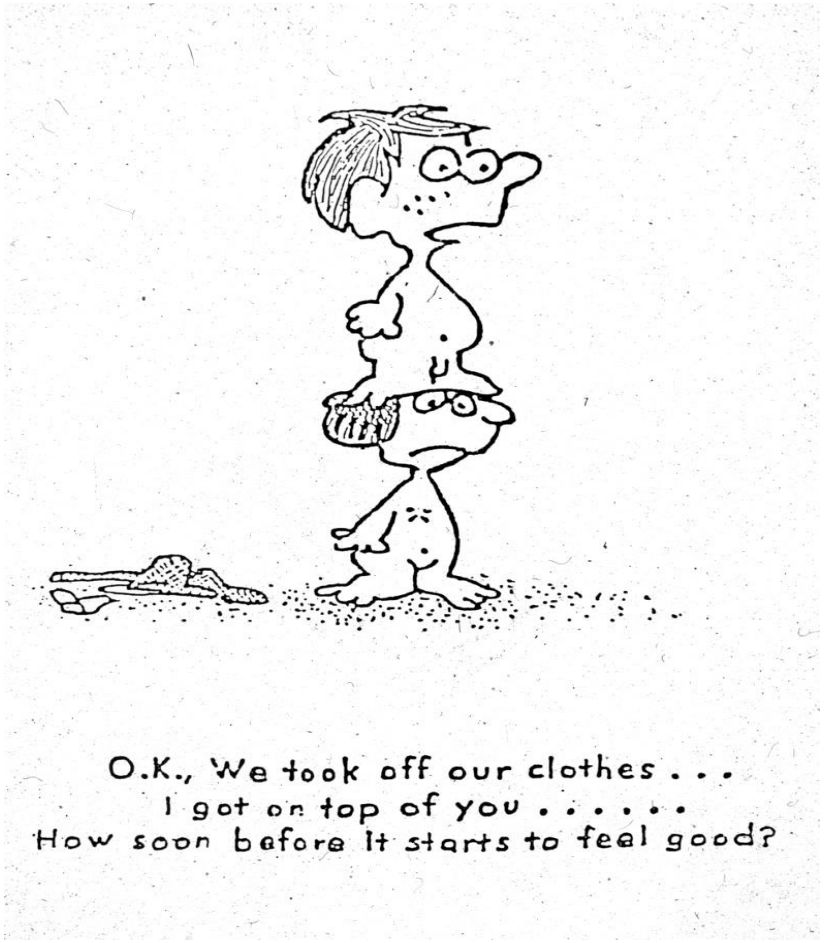


Is Sex Medically Necessary?

- Enhances intimacy
  - Longevity, chronic illness
- Decreases pain/Increases oxytocin and endorphines
  - pair bonding/cuddle hormone
- May increase overall happiness by decreasing stress
- Sex improves cardiovascular health and stamina
  - Sexually active men had lowered rates of stroke
- Sex burns calories (85 calories per act)
  - 42 sessions of 30 minutes each is 3570 calories or a pound
- Sex improves immunity
  - Increased IgA antibodies
- Sex improves sexual self esteem
- Sex Reduces cancer risk
  - Prostate cancer reduced with more than 21 ejaculations per month
- Sex strengthens pelvic floor
- Sex improves sleep
  - Oxytocin release

Education in Sexual Medicine

- Myths and Mysteries
  - Locker room syndrome
  - Self esteem issues
  - Size issues
- Anatomy
- G spot
- Orgasms
  - Vaginal Vs Clitoral
- Alternative forms of sexual positioning and expression
- Sexual devices/accessories
- Bibliotherapy
- Books/ Videos/ DVD
- Safe non-spam websites
- Internet links
- Sexual Health Organizations



QUESTIONS & ANSWERS

Michael L Krychman MD

Southern California Center for
SEXUAL HEALTH
and SURVIVORSHIP MEDICINE

mkrychman@icloud.com

949-764-9300

Follow me on
Twitter
@mkrychman

