Women's Sexual Health
Epidemiology/Models/Classification/Pharmacolog



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# **Disclosures**

I have no disclosures.

# **Objectives**

- •To review prevalence data of female sexual disorders
- •To describe models of female sexual function
- •To review DSM 5 classifications and management of female sexual disorders
- •To discuss FSD Treatments and Pharmacology

# Female Sexual Dysfunction Prevalence

Sexual problems in women are common. Studies support a higher prevalence of SD in women vs males.

Women	Men
43.1%	31%
40% 59.5%	32%
63%	
60%	
	43.1% 40% 59.5% 63%

# **Prevalence of Female Sexual Dysfunction**

PRESIDE

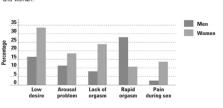
(PREVALENCE OF FEMALE SEXUAL PROBLEMS ASSOCIATED WITH DISTRESS AND DETERMINANTS OF TREATMENT SEEKING)

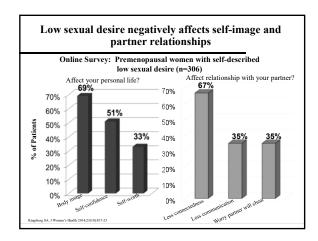


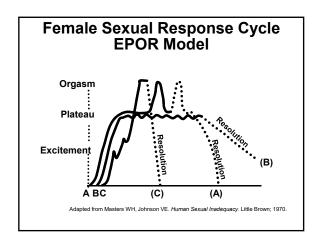
Shifren JL, Monz BU, Russo PA, Segreti A, Johannes CB., (2008). Obstet Gynecol.112(5):970-978.

# PREVALENCE OF SEXUAL **DYSFUNCTION**

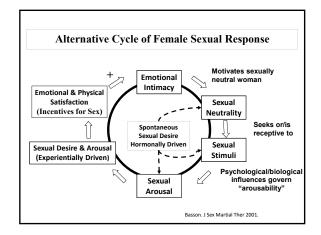
Prevalence of Sexual Dysfunctions: This graph shows the percentage of respondents who reported having sexual difficulties at some time during the previous 12 months. Note the differences in the problems reported by men

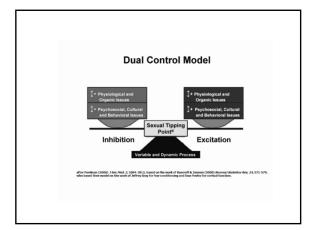


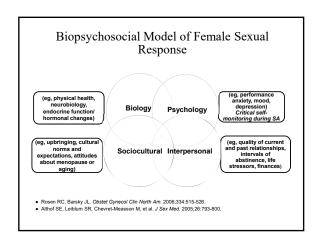




# Linear Progression Model • Excitement → Divided → Arousal • Plateau • Orgasm • Resolution Masters WH, Johnson VE, Human Sexual Response, Boston, Mass: Little Brown; 1966. Kaslan MS, The Man. Sex. Therapa. Nam. York: Bunnear Marca 1977.









# **Sexual Dysfunction: Definition & Diagnosis**

### 1987 (DSM-III-R)

Frequency + Sexual Dysfunction
Persistently or recurrently deficient or absent sexual fantasies and desire for sexual activity

### 2000 (DSM-IV-TR)

Frequency + Sexual Dysfunction + Distress
Persistently or recurrently deficient or absent sexual fantasies and desire
for sexual activity with marked distress or interpressonal difficulty, not
otherwise accounted for by a general medical or psychiatric condition

# 2013 (DSM-5)

Sexual Dysfunction + Distress + Frequency + Duration Lack of sexual interestiarousal as manifested by a presel number of indicators (withhythout a specified frequency) with clinically significant distress, and has persisted a minimum of 6 months, not otherwise accounted for by a general medical or psychiatric condition

Latif EZ, Diamond MP. Fertil Steril. 2013;100:898-904.
 Sungur MZ, Gunduz A. J Sex Med. 2014;11:364-373





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

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

# Hypoactive Sexual Desire Disorder (HSDD)

ISSWSH Nomenclature: ANY of the following for a minimum of 6

- Lack of motivation for sexual activity, manifested by either:
  - Reduced or absent spontaneous desire (sexual thoughts or fantasies)
     Reduced or absent responsive desire to erotic cues and stimulation or inability to maintain desire or interest through sexual activity
- Loss of desire to initiate or participate in sexual activity, including behavioral responses such as avoidance of situations that could lead to sexual activity, not secondary to sexual pain disorders
- AND combined with clinically significant personal distress which includes frustration, grief, incompetence, loss, sadness, sorrow, or worry

# **HSDD: Diagnostic Considerations**

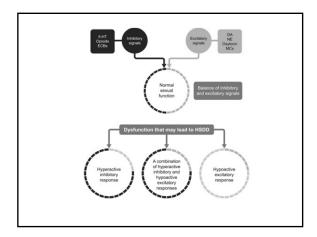
- Diminished desire could be acquired (was normal and now its not) or lifelong(has been there all along) but should be generalized for consideration of pharmacotherapy.
- If the diminished desire is situational, & cause of desire disorder outside the woman, therefore not generalized HSDD
  - Ex: Physical and/or emotional abuse, dissatisfaction with partner, partner's sexual dysfunction, or intrusive life stressors that can be corrected by lifestyle changes
- HSDD should be self-rated as mild, moderate, or severe
- Definition of HSDD incorporates a bio-psycho-social context and can be used in both the somatic and psychiatric diagnostic systems

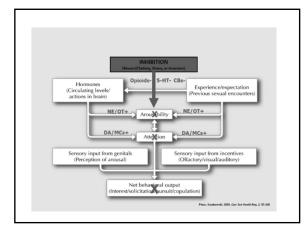
# Sexual Desire is regulated by Key Regions in Brain

- Prefrontal cortex (PFC)
- Locus coeruleus
- Medial preoptic area (mPOA)
- Paraventricular nucleus
- Reward and attention processing centers of the ventral tegmental area and nucleus accumbens

Kingsberg et al. CNS Drugs, 2015

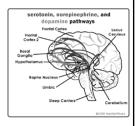
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# How Does This Translate Into Pharmacologic Treatment Options?

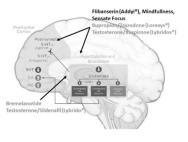
- HSDD is a maladaptation of the brain represented by **dysregulation** of DA, NE, and 5-HT in the PFC
- Correcting the imbalance is the foundation to correcting the maladaptation.
- Similar maladaptation in depression/anxiety (chronic stress alters architecture of neurons changing synaptic interaction)
  - differing in type and magnitude of dysregulation



# mPOA D1 activation is critical for sexual desire and modulating sympathetic outflow Neural excitatory systems Neural excitatory systems Activation for the plant of the pla

# **HSDD Treatment Options**

# **Current treatment options**



# **Melanocortins and Sex**

- POMC peptides, including ACTH, and α-MSH, have pronounced effects on the sexual behavior of female and male rats
- $\bullet \ \alpha\text{-MSH facilitates lordosis in estrogen-primed females and erection in gonadally-intact males }$
- α-MSH levels in anterior hypothalamus increased by estrogen, suggesting that it may be one of several intermediaries of estrogen action

# Melanocortin Receptor Agonist

Slu His Phe Arg Trp Gly Lys Pi

**Bremelanotide:**(tormerly PT-1-141) Ac-NIe-Asp-His-DPhe-Arg-Trp-Lys-OH

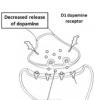
- Binds to MC3R and MC4R in brain Induces erections in healthy men
- Induces erections in healthy rats
- Induces erections in men with mild-to-moderate erectile dysfunction and in men who do not respond well to PDE-5 inhibitors
- Rapid effect in rats (within 5 to 20 min)
- Facilitates solicitations selectively in female rats

# Action of melanocortins in the mPOA

Resting (unstimulated) DA release

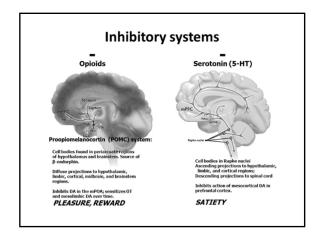
MC4R MC4R

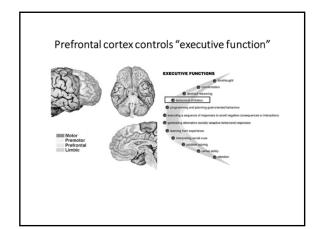
Stimulated DA release MC4R

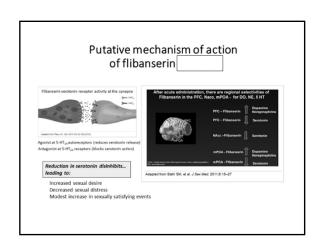


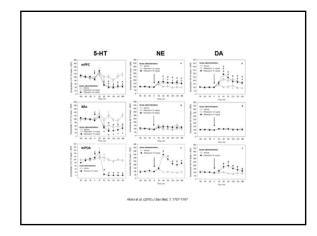
α-MSH or BMT

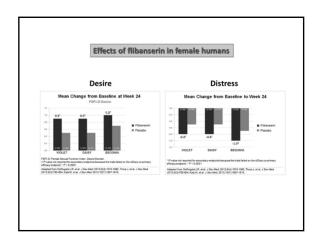
# Effects of bremelanotide in female humans











# Flibanserin 100mg PO qhs Adverse Effects of Flibanserin

# COMMON A/E's

- CNS depression
- Somnolence
- Fatigue
- Dizziness
- Nausea
- Insomnia
- Xerostomia

# SEVERE A/E's

- Hypotension
- Syncope
- Appendicitis
- Mammary tumors (animal studies)

# **Prescribing Considerations**

- · Provider Certification required to prescribe.
- · Requires a Provider-Patient agreement prior to prescribing.
- · Patient cannot consume ETOH while taking Flibanserin.
- If the Patient feels dizzy or faints, she should seek medical help.
- If the patient skips a dose, she does not double up the next day.
- Currently, prescribing only approved for Premenopausal females
- · Flibanserin is to only be taken at bedtime.

# High inhibition, low excitation sexual dysfunction

Dopamine Agonists Buproprion 75mg-150mg/day Cabergoline 0.5mg q M/TH Ropinirole 0.25mg QD-TID

Oxytocin

Oxytocin Lozenge 250IU-One hr prior to sexual activity- may increase up to 3 at one time.

Norepinephrine Agonist Yohimbine HCL 5.4mg-one hour before sexual activity-up to 3 at one time. PDE5 INHIBITORS
Vardenafil- 2.5mg-5mg - ODT
Sildenafil - 12.5mg - 25mg 50mg
Tadalafil - 2.5mg - 5 mg - 10mg

Opioid Antagonists Naltrexone 50mg/day

Serotonin Antagoists Buspirone 10-15mg BID

INCRASE NEUROTRANSMISSION Drugs Dalfampridine ER (10mg/day)

# Female Genital Arousal Disorder (FGAD)

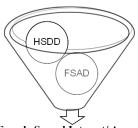
The physiological response of arousal is a <u>physical state</u> arising from both <u>physical & non-physical (emotional)</u> stimuli with increased activity in the central and peripheral (sympathetic) nervous systems resulting in genital (engorgement, lubrication, increased sensitivity) and non-genital (somatic) sexual responses.

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# FEMALE GENITAL AROUSAL DISORDER

- FGAD: inability to develop or maintain genital arousal for a
- $\geq$  6 months including:
  - Vulvovaginal lubrication
- Engorgement of the genitalia - Sensitivity of the genitalia associated with sexual activity
- Disorder can be the result of:
  - Vascular &/or Neurological injury
- Usually generalized or acquired
- May or may not cause significant intra or interpersonal distress

# DSM-5 (2013) Changes to Nomenclature & Diagnosis



Female Sexual Interest/ Arousal Disorder

# Female Sexual Interest/Arousal Disorder (DSM 5)

Lack of, or significantly reduced, sexual interest/arousal as manifested by 3 of the following:

# Absent/reduced:

- · interest in sexual activity
- sexual/erotic thoughts or fantasies
- initiation of sexual activity & unreceptive to partner's attempts to initiate
- sexual excitement/pleasure during sexual activity in (75%-100%) all almost all or sexual encounters
- sexual interest/arousal in response to any internal or external sexual/erotic cues (written, verbal, visual)
- genital or nongenital sensations during sexual activity (75%-100%) in almost all or all sexual encounters

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# **FSAID Evaluation Treatment** Most Treatments are Off-**Serum Laboratory** Evaluation Label for females. Medication Evaluation · Mindfulness Meditation · Partner coaching Vulvoscopy Biothesiometry Sildenafil • ART · Vaginal pH testing · Vulvar Neuro neuro-• ERT evaluation **Testosterone Replacement Therapy** Recommendations: Androgens are important modulators in Female Sexual Function (FSF). Low T and CFT levels, androstenedione, & dehyroepiandrosterone (DHEA-s) are assoc. w/ low self-reported sexual desire. Consistent evidence that ART influences FSF & transdermal doses are effective for tx. of HSDD in postmenopausal females & women in late reproductive A trial of ART should be considered for treatment of FSAID, $\mbox{\sc HSDD}, \& \mbox{\sc FSOD}.$ Disclaimer: Currently, ART is not approved by the FDA for use in women. It is an off-label medication. Persistent Genital Arousal Disorder (PGAD) •Characterized by persistent, recurrent, unwanted, or intrusive, distressing feelings of genital arousal, or being on the verge of orgasm (genital dysesthesia), not associated with sexual interest, thoughts, or fantasies for a $\geq 6$ months (expert opinion) •Based on case reports - considered rare, but difficult to estimate •May be associated with: - Limited, no resolution, or aggravation of symptoms by SA with or without aversive and/or compromised orgasm - Genital symptoms may be aggravated by certain circumstances (ex: car ride, climbing ladders, or riding a bike) - Despair, emotional lability, catastrophization, and/or suicidality - Inconsistency of genital arousal during symptoms Parish et al. J Sex. Med. In Press.

# **Female Orgasm Disorders**

- Female Orgasmic Disorder (FOD) is characterized by a persistent or recurrent, distressing compromise of orgasm frequency, intensity, timing, and/or pleasure, associated with sexual activity for  $\geq 6$  months.
- Frequency: orgasm occurs with reduced frequency(diminished frequency of orgasm) or is absent of orgasm (anorgasmia).
- Intensity: orgasm occurs with reduced intensity (muted orgasm)
- Timing: orgasm occurs either too late (delayed orgasm) or too early (spontaneous or premature orgasm) than desired by the woman
- Pleasure: orgasm occurs with absent or reduced pleasure (anhedonic orgasm, pleasure dissociative orgasm disorder (PDOD Orgasm without pleasure. expert opinion)

**Diagnosis and Treatment of Orgasmic Disorders** 

# Are there different kinds of Orgasm?

# DSM-5:

FOD is considered a female sexual disorder with the presence of the following "ON ALL OR ALMOST ALL (75% - 100%) OCCASIONS OF SEXUAL ACTIVITY:

- 1. Marked delay in, marked infrequency of, or absence of
- orgasm & 2. Marked reduced intensity of orgasmic sensations." Symptoms persist a  $\geq$  6 months

FOD not better explained by a nonsexual mental disorder or the consequence of severe relationship distress or other significant

FOD not due to effects of substance or medication or other medical conditions.

# **Female Orgasm Disorder**

Female Orgasmic Disorder is characterized by a persistent or recurrent, distressing compromise of orgasm frequency, intensity, timing, and/or pleasure, associated with sexual activity for a minimum of 6 months.

Frequency: orgasm occurs with reduced frequency (diminished or absence of orgasm (anorgasmia).

Intensity: orgasm occurs with reduced intensity (muted orgasm).

Timing: orgasm occurs either too late (delayed orgasm) or too early (spontaneous or premature orgasm) than desired by the woman.

Pleasure: orgasm occurs with absent or reduced pleasure (anhedonic orgasm, pleasure dissociative orgasm disorder [PDOD]).

# Female Orgasm Disorder

Classified as: (lifelong or acquired) or (generalized or situational)

Women demonstrate a wide variability of type & intensity of stimulation needed to reach orgasm.

Many women require clitoral stimulation, and fewer women experience orgasm with vaginal penetration. Study: 1055 women, ages 18 to 94

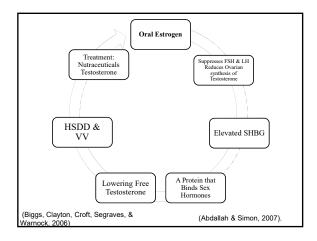
- 18.4% orgasm with vaginal penetration 36.6% Needed clitoral stimulation to orgasm
- 36% Did not need clitoral stim., but clitoral stim. w/penetration produced better orgasms.

\*FOD should not be diagnosed if a woman can achieve a clitoral orgasm but not vaginal penetration orgasm or has had inadequate stimulation.

# **Medications Impacting FSOD**

- SSRIs
- Hypertension medications
- Antipsychotics
- · Antianxiety
- · Chemotherapy
- Birth Control Pill (increases Disulfiram
- gene expression of SHBG)
- · Alpha-blockers
- Clonidine
- · Methyldopa

- chlorpromazine, thioridazine)
- Risperidone
- · Benzodiazepines
- Cimetidine
- Cyproterone acetate
- Finasteride (males w/PFS)
- · Opioid painkillers (i.e. morphine)
- · Spironolactone
- · OTC Appetite Suppressants



Female Orgasmic Illness Syndrome
FOIS is characterized by peripheral and/or central aversive symptoms that occur before, during, or after orgasm not related to a compromise of orgasm quality

# **Central Aversive Symptoms**

- Disorientation
- Confusion
- Impaired judgment
- Decreased Verbal memory
- Anxiety
- Insomnia
- Depression
- (Postcoital Tristesse)
- Seizures(orgasmic epilepsy)
   Headache (Coital Cephalalgia)

### Peripheral Aversive Symptoms

- Diarrhea
- Constipation
- Muscle aches
- Abdominal pain
- Diaphoresis
- Chills
- Hot flashes
- Fatigue
- Akathisia
- Genital pain

Such orgasm-associated symptoms can last for minutes, hours, or days after orgasm and can vary widely among women.

# Female Orgasmic Illness Syndrome (FOIS)

Characterized by peripheral and/or central aversive symptoms that occur prior to, during, or following orgasm not related, to a compromise of orgasm quality.

# Symptoms

- Peripheral: diarrhea, constipation, muscle aches, abdominal pain, diaphoresis, chills, hot flashes, fatigue, akathisia, genital pain
- Central: disorientation, confusion, decreased verbal memory, anxiety, insomnia, depression (post-coital tristesse), seizures, headache (coital cephalalgia)
- ${\bf Orgasm\hbox{-}associated symptoms\ may\ vary\ in\ length\ of\ duration}$ lasting from hours - days.

Farley SJ. Nature Reviews Urology. 2011;8:121.; Waldinger MD, Schweitzer DHJ Sex Marital Ther. 2002;28:251–5. Ashby J, Goldmeier D. J Sex Med. May 2010;7:1976–81.; Rasmussen BK, Olesen J. Neurology, Jun 1992;42:1225–31.

Testing Procedures: Neurologic, Hormonal, and Vascular

# Nerve injuries cause **Neurologic Sexual Dysfunction**

Neurologic sexual dysfunction: hypothesized to result, in part, from abnormal (excess/reduced) sensory afferent/motor efferent information from various injuries to:

- **Peripheral Dorsal nerve**
- Perineal nerve
- **Pudendal nerve**
- Pelvic nerve
- Hypogastric nerve
- &/or Sacral (S2, S3, S4) Spinal nerve root pathologies



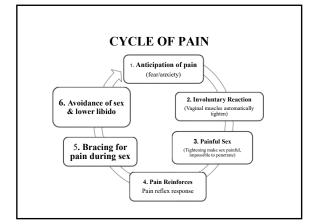
# **Causes of Vaginal Penetration Pain** Differentiate Pain.... • Initial Penetration Deep Penetration **Superficial Physical Conditions Associated** With Chronic Vaginal Penetrative Pain · Vulvitis, vulvovaginitis **Vulvar Vestibulitis** Syndrome · Bartholinitis Scarring Condylamata (warts) Partner's penis size (penile implants in the aging) Atrophy Dermatologic diseases Urethritis, cystitis Noninfectious inflammations . Anatomic variations **Epithelial defects** · Hymenal remnants · Large labia minora · Episiotomy neuroma Heim L. Am Fam Phys. 2001;63:1535-1544. **Deep Physical Conditions Associated With Chronic** Genito-Pelvic Pain Penetration Disorder · Estrogen deficiency · Fixed inverted uterus · Vaginitis • Uterine Fibroid · Chronic Pelvic Ovarian tumor **Inflammatory Disease** Ovarian remnant syndrome · Foreshortened vagina · Chronic abdominal pain · Scarification · Abdominal wall pain Endometriosis · Irritable bowel syndrome · Vaginal septum · Hemorrhoids · Urethritis, cystitis Heim L. Am Fam Phys. 2001;63:1535-1544.

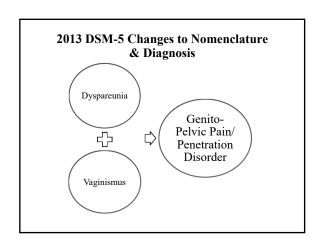
# Vaginismus

### Defined as:

Persistent difficulty to allow vaginal entry of a penis, finger or any object despite the express wish to do so

- Nor is it necessarily a "pain" disorder
- $\bullet$  Prevalence rates range from 1%-6%
- Vaginismus may include:
  - Problems with muscle tension
  - Anticipatory fear of pain
  - $A voidance\ behavior$





# DSM-5 Genito-Pelvic Pain/Penetration Disorder Persistent or recurrent difficulties with <u>at least one</u> of the following:

- i. Vaginal penetration during intercourse
- ii. Marked vulvovaginal pain or pelvic pain during intercourse or penetration
- iii. Marked fear or anxiety about vulvovaginal or pelvic pain in anticipation of, during, or as a result of vaginal penetration
- iv. Marked tensing or tightening of the pelvic floor muscles during attempted vaginal penetration

American Psychiatric Association DSM 5, 2013

# Vulvovaginal Atrophy (VVA)/Atropic Vaginitis Genitourinary Syndrome of Menopause (GSM)

New nomenclature for VVA , Genitourinary syndrome of menopause (GSM)

- Characterized by many symptoms including vaginal dryness, dyspareunia, irritation, dysuria, burning
- Affects up to 69% of postmenopausal women and has a deleterious effect on QoL & sexual function
- Most women do not seek medical treatment for their GSM symptoms

Poetman DJ, Gass ML. Climacteric 2014;17:557-563.
 Mac Bride MB, et al. Mayo Clinic Proceed 2010:85: 87-94.
 Cumming GP, et al. Menopause Int 2007;13:79-83.
 Parish SJ, et al. Int J Women's Health 2013;5437-447.
 Nappi RE, Kokot-Kierepa M. Mantriaz 2016;27:32-328.

# Genito-Urinary Syndrome of Menopause (GSM)

# Symptomatology

- pH > 5.0 Alkaline Vaginal environment
- · Absence of Rugosity
- · Color: Pallor/friability
- Inelasticity: Introital Stenosis
- · Urethra: telescoped/prolapsed
- · Vestibule: erythema, dry
- Posterior fourchette bridging and possible mid-line fissures
- · Clitoral Phimosis
- · Labia Minora: Resorption
- · Recurrent UTI's


Treatment Options  • None Hormonal Treatment  • Estrogen replacement	
options: therapy:  -Coconut oil -Vaginal estradiol	
-Cocontit on - Vaginal estraction  -Olive oil » Creams	
-Alvocado oil » Pearls  National » Rings	
-Lubricants  Vaginal Moieturizors  » Gels	
- Vaginal Moisturizers » Tablets - Vaginal Lasers – DHEA	
-PRP	
*Oral Estrogens cause a first pass effect in the liver causing an elevation in SHBC which can lead to a binding of sex hormones. SHBC has a hierarchial affinity for Dihydrotestosterone, Testosterone , and Estradiol.	-
Personal lubricants	
Provides temporary lubrication	
• Reduces friction during vaginal	
penetration	
Types:	
-Water-based	
-Silicone-based	
-Oils	
	_
Water-based Lubricants	
Most widely available     Ingredients: deionized     water, glycerin, prophylene	
condoms, sex toys	
• Tend to dry up  • Available in glycerin-free options	-
quickly • Glycerin may promote	
-reactivate with vaginal inflammation and water yeast infection	
• Do not stain	
Rarely cause     irritation	
n rication	

### Silicone-based lubricants

- Longer lasting than water-based lubricants
- · Can be used in water
- Safe to use with latex condoms, diaphragms, non-silicone toys
- Available in glycerinfree options
- Can be used as a massage oil
- More expensive than water-based lubricants
- Harder to wash off sheets and clothing

# Oil-based lubricants

# Petroleum-based:

- Petroleum jelly, mineral oil, baby oil
- May promote vaginal inflammation/irritation
- Not for use with latex condoms

-Can reduce both the effectiveness of latex items and prevention of STDs

# Natural oils:

- Coconut, Avocado, corn, olive, & peanut
- · Non-irritating
- Should not be used with latex items

# Cutaneous lysate cream: Provoked vestibulodynia

Randomized crossover study

Cutaneous lysate cream vs placebo

N=30 women w/provoked vestibulodynia w/visible vulvar erythema

BID application for 12 weeks, 1 week washout, 12 week crossover

Result: tolerability same with placebo & cutaneous lysate; significant decrease in dyspareunia and erythema after 4 and 12 weeks with cutaneous lysate only;

Donders GG, Bellen G. Cream with cutaneous fibroblast lysate for the treatment of provoked vestibulodynia: a double-blind randomized placebo-controlled crossover study. J Low Genit. Tract is. 2012 Oct; 16(4): 427-36

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# **Low Dose Vaginal Estradiol**

- Metabolized liver; CYP450: 3A4 (partial) substrate
- Info: enterohepatically recirculated; converted to active estrogen metabolites including estrone.
- Excreted mainly in urine; Half-life 1-2hrs, 4-18h (estrone)
- Extended absorption may produce longer half-lives (transdermal, topical, or inj.)
- · Mechanism of action: binds to E2 receptors,

## **Take-home Messages**

- 1. Sexual desire depends critically on the activation of neurochemical systems for sexual excitation by erotic cues (such as DA, NE, melanocortins, & oxytocin). These are set up by the actions of ovarian estradiol and testosterone.
- 2. Sexual inhibition is a normal function of satiety states. This is driven by brain opioid, serotonin, and endocannabinoid systems.
- 3. 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.
- 4. Lack of sexual desire is normal in response to incompetent sexual cues.

However it can also occur as a physiological effect of hypoactive excitation or hyperactive inhibition, or as a neural systems adaptation to a chronic lack of sexual pleasure.

### **Summary**

- Start the conversation.
- Sexual Health is a vital part of a woman's quality of life and well being.
- Don't be afraid to ask.
- If you do not feel confident in treating your patient's sexual dysfunction, refer!
- I can help!

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References  - American Psychiatric Association, (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Washington, D.C Ahrisi S, Baldasvarre N, Lambertini M, et al. Sexuality and psychopathological aspects in premenopausal women with metabolic syndrome. J Sex Med 2014;11:2020-2028.	
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