

The Treatment of Female Sexual Dysfunction

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Stages of Sexual Response

- Masters and Johnson (1966)
 - First characterized female sexual response
 - Excitement, plateau, orgasmic, resolution
- Kaplan and 3-phase Model (1974)
 - Desire, arousal, orgasm
 - Desire incited the overall response cycle

Libido

- First stage of human sexual response
- Related to desire
- Mediated by mesolimbic dopaminergic reward pathway

Libido – con't

- Dopamine and testosterone promote libido
- Estrogen may also promote libido
- Prolactin reduces libido

Sexual Arousal

- Second stage of human sexual response
- Produces erections in men
- Causes lubrication & swelling in women

Sexual Arousal – con't

- Nitric oxide (NO) and acetylcholine (ACh) promote arousal
- Estrogen may promote arousal in women

Arousal Response

- Genital vasocongestion/clitoral engorgement
 - From increased blood flow
- Vagina lengthens and dilates
 - From smooth muscle relaxation
- Vaginal lubrication
 - From uterine/cervical gland secretions

Similarities between Clitoris and Penis

- | Characteristic | Clitoris | Penis |
|----------------------------------|----------|-------|
| ● Achieves tumescence | Yes | Yes |
| ● Achieves rigidity | No | Yes |
| ● Erection from PGE ₁ | Yes | Yes |
| ● Presence of NO synthase | Yes | Yes |
- Shen et al., J Reprod Med 1999

Orgasm

- Third stage of human sexual response
- Accompanied by ejaculation in men
- Produced by central (spinal) and peripheral reflexes in genitalia

Orgasm – con't

- Norepinephrine (NE) promotes orgasm
- Serotonin (5-HT) inhibits orgasm & ejaculation

Female Sexual Dysfunction (FSD) Prevalence

- U.S. National Health and Social Life Survey of 1749 women aged 18-59
 - 43% prevalence of sexual dysfunction
 - 1/3 decreased libido
 - 1/5 arousal problems (lubrication)
 - 1/4 anorgasmic
- Laumann et al. JAMA 1999;281:537-544

Classification of FSD

- DSM-IV Classification
 - Based on Kaplan's model
 - Limited to psychogenic causes of sexual disorders

Classification of FSD - con't

- American Foundation of Urological Disorders (AFUD) – 1998
 - Interdisciplinary group from 5 countries
 - Based on ICD-10 and DSM-IV
 - Expanded to include psychogenic & organic causes of sexual dysfunction

Hypoactive Sexual Desire Disorder (HSDD)

- Deficiency (or absence) of sexual fantasies or thoughts
- Lack of receptivity to sexual activity (AFUD)
- Causes personal distress
- Sexual Aversion Disorder (Subtype)

Female Sexual Arousal Disorder (FSAD)

- Inability to attain or maintain adequate sexual excitement
 - □ Genital response (lubrication/swelling)
 - □ Subjective excitement (AFUD)
- Causes personal distress

Orgasmic Disorder

- Delay/absence of obtaining orgasm following sufficient sexual stimulation and arousal
- Causes personal distress

Sexual Pain Disorders

- Dyspareunia
 - Pain with intercourse
- Vaginismus
 - Involuntary spasms of vagina with intercourse
- Noncoital Sexual Pain Disorder (AFUD)
 - Vestibulitis

Subtyping of FSD

- Lifelong vs. Acquired type
- Generalized vs. Situational type
- Etiologic origin (organic*, psychogenic, mixed, unknown*)
 - *AFUD

Etiology of FSD

- Vasculogenic
 - Atherosclerotic disease, pelvic surgery
- Neurogenic
 - Spinal cord injury, diabetes
- Hormonal/Endocrine
 - Surgical/natural menopause, hypothyroidism

Etiology of FSD – con't

- Musculogenic
 - Pelvic Pain
- Psychogenic
 - Low self-esteem, body image
 - Depression
 - Relationship difficulties

Androgen Deficiency Syndrome

- Clinical syndrome reported in males
 - Osteopenia, increased fat mass, decreased libido, diminished quality of life
- Possible syndrome occurring in women
 - Oophorectomy
 - Natural menopause

Mean Steroids Levels (pg/ml)

● Steroid	Pre-meno	Natural	Surgical
● Estradiol	100-150	10-15	10
● Testosterone	400	290	110
● Androstene.	1,900	1,000	700
● DHEA	5,000	2,000	1,800
● DHEAS	3 x 10 ⁶	1 x 10 ⁶	1 x 10 ⁶

Androgen Deficiency in Women

- Clinical Profile
 - Persistent fatigue, blunted motivation
 - Low libido, diminished well-being
- Hormonal Profile
 - Normal estradiol levels
 - □ Total (< 20 pg/dL) & Free (< 0.9 pg/dL) Test.
 - Berman & Goldstein, Urol Clin North Amer, 2001

Evaluation of FSD

- Psychological Exam
- Physical Exam and Pelvic
 - Pain or discomfort during sex
 - Any peri- or postmenopausal woman
 - When pt believes there is a physical cause

Evaluation of FSD - Medications

- CNS Drugs
 - Antidepressants (TCAs, SSRIs)
 - Antipsychotics (Typical, Atypical)
 - Anticholinergics, Anticonvulsants
 - Narcotics, Benzodiazepines

Evaluation of FSD – Medications

- Antihypertensive & CV Agents
 - Centrally acting agents, B-blockers, Ca Blockers, Diuretics, Antilipidemics
- Hormonal Preparations
 - Antiandrogens (cimetidine, spironolactone)
 - Antiestrogens (tamoxifen, raloxifen), OCs

Evaluation - Laboratory Studies

- Follicle stimulating hormone (FSH)
- Luteinizing hormone (LH)
- Estradiol
- Prolactin
- Total and free testosterone
- Sex hormone binding globulin (SHBG)

Treatment – HSDD Estrogen Replacement Therapy

- Improves vaginal dryness & dyspareunia
- May improve clitoral sensitivity and libido
- Sexual complaints occur with estradiol levels < 50 pg/mL

Treatment – HSDD Testosterone Therapy

- Currently no FDA approved preparations for women
- ↑ Clitoral sensitivity, libido
- ↑ Arousal, Vaginal lubrication

Testosterone Therapy – con't

- Oral products
 - Combination product (Estratest)
 - Methyltestosterone (1.25 – 2.5 mg/d)
 - Micronized testosterone (5 mg bid)
- Topical Products
 - 1-2% testosterone/methyltestosterone in petro (3x/wk)
 - Testosterone Gel (_ - _ of 2.5 mg packet 3x/wk)

Testosterone Therapy Adverse Effects

- Early Reversible
 - □ HDL, ↑TG, weight gain
 - ↑ Facial hair, Acne, menstrual irregularities
- Long-term Irreversible
 - Male pattern baldness, voice changes
 - Clitoral enlargement

Testosterone Therapy Contraindications

- Hyperlipidemia
- Cardiac Disease
- Breast Cancer
- Liver disease
- Acne or hirsutism

Testosterone Therapy Monitoring

- Taper to lowest effective dose
- Concurrent HRT if intact uterus
- Monitor symptoms and side effects
- Mammography & Pap Smear (q 12 mo)

Testosterone Therapy Monitoring – con't

- Laboratory (baseline, 3 mo, q 6-12 mo)
 - Testosterone levels
 - Free & total (am level)
 - Upper physiological range of ovulating women
 - Lipid profile
 - Liver enzymes

Phase II/III Testosterone Studies

- Testosterone patches
- Testosterone topical cream
- Surgically/naturally menopausal women
- Does not decrease HDL

Transdermal Testosterone Patches

- 75 oophorectomized women randomized to either 150 or 300 mcg testosterone or PB for 12 weeks
- 300 mcg significantly better than 150 mcg or PB in sexual frequency, pleasure and mood
- Higher dose resulted in testosterone levels at upper limit of normal
 - Shifren et al. NEJM 2000

Dehydroepiandrosterone (DHEA) - HSDD

- Adrenal gland androgen
- Precursor to testosterone & estrogen
- Perimenopausal women have only 50% of peak DHEA levels

DHEA – con't

- 12-wk DB, PB-controlled trial of DHEA (50 mg/d) in 60 perimenopausal women
- DHEA significantly increased DHEA, DHEAS, and testosterone compared to PB
- All subjects improved in perimenopausal symptoms regardless of treatment group
 - Barnhart et al J Clin Endocrinol Metab 1999

DHEA – Monitoring

- Obtain endocrine and lipid parameters
 - Decreases HDL
- Determine content of active ingredient
 - FDA determined DHEA levels in 45 commercial products contained 0-109.5% of declared amount
 - Thompson & Carlson, J AOAC Int, 2000

Bupropion - HSDD

- Inhibits neuronal dopamine reuptake
- 3-wk DB, PB-controlled study of 30 adults on SSRIs with sexual dysfunction received either bupropion SR 150 mg/d or PB
- No significant differences between treatment groups
 - Masand et al, Am J Psychiatry 2001

Apomorphine - FSAD

- Short-acting dopamine agonist
- Effective in erectile dysfunction (Uprima)
- Phase III studies in women
 - SL doses of 1-4 mg
- ADRs
 - N/V, hypotension, syncope

Sildenafil - FSAD

- Selective type 5 (cGMP-specific) phosphodiesterase inhibitor
 - □ Catabolism of cGMP, ↑ NO
- Relaxes clitoral and vaginal smooth muscle
 - ↑ Blood flow to genital area & lubrication

Sildenafil – con't

- DB, crossover, PB-controlled study of 53 women (22-28 yo) with FSAD received 25 mg, 50 mg or PB for three 4-week periods
- Significantly greater arousal with 25 mg & 50 mg of sildenafil compared to PB
 - Caruso et al., Brit J Obstet Gynaecol 2001

Sildenafil – con't

- Case study of sildenafil (50 mg/d) effectively treating fluoxetine-induced FSAD in 38 yo woman who failed trials of cyproheptadine, bupropion, d-amphetamine
- SSRIs inhibit NO synthase
 - Shen et al., J Reprod Med 1999

Sildenafil – con't

- Phase II and III clinical trials in progress
- Adverse effects
 - Facial flushing, dizziness, HA, abnormal vision (greenish-blue halos)
- Contraindications
 - Use of nitrates

Prostaglandin E₁ (Alprostadil) FSAD

- Vasoactive agent
 - Increases vaginal and clitoral blood flow
 - Improves lubrication
- Effective in Erectile Dysfunction
 - MUSE (intraurethral application)

Alprostadil – con't

- Phase I clinical trial of women with FSAD receiving escalating doses of alprostadil cream at 2-week intervals
- Alprostadil enhanced subjective and physiological arousal during visual sexual stimulation
 - J Sex and Mar Ther 2001

Alprostadil – cont'd

- Phase II studies in progress at 12 U.S. sites
- Adverse Effects
 - Vaginal burning
 - Dizziness, HA, light-headedness

Phentolamine - FSAD

- Nonspecific α -adrenergic blocking agent
 - Causes smooth muscle relaxation
- Effective in erectile dysfunction
- Adverse effects
 - Transient drop in BP assoc. with syncope

Phentolamine – con't

- Pilot study in menopausal women with sexual dysfunction demonstrated enhanced vaginal blood flow and subjective arousal
 - Rosen, J Sex Marital Ther, 1999

L-Arginine - FSAD

- Amino acid which is precursor to NO
 - Mediates smooth muscle relaxation
- Preliminary studies in men are promising
- Being investigated currently in women

Yohimbine – Anorgasmia

- Selective α -adrenergic blocker with both central and peripheral effects
 - \uparrow Parasympathetic tone
- Yohimbine 6.75 mg 2-4 hr prior to coitus reversed fluoxetine-induced anorgasmia in women

Conclusions

- FSD is a common disorder among women
- Testosterone appears most promising for libido disorders
- Apomorphine and alprostadil may improve arousal disorders