Women Getting Better with Age

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Objectives

- Advancing Health after Hysterectomy
- Review CV benefits and risks of HT
- Discuss “designer estrogens” SERMs
- Review use, indications of Flibanserin/Addyi
AHAH!

Advancing Health After Hysterectomy

Disclosure

- Philip Sarrel, M.D. is the Founder and President of The Advancing Health After Hysterectomy Foundation, Inc. (a non-profit corporation registered in Connecticut).
- The Foundation does not receive funding from the pharmaceutical industry.
- I am an unpaid Advisor, Warrior, and I have a chip on my shoulder.
Objectives

Evaluate the evidence that supports the mission statement that post TH Estrogen is
ONLY therapy that: Treats symptoms,
Prevents disease and Decreases mortality.

• Review aftermath of the Women’s Health Initiative 13.5 years later.
• Examine the risk/benefit ratios related to cardiovascular disease and other outcomes in women with respect to Hormone Therapy.
• Understand the increased risk for CV disease in women with total hysterectomy (with or without oophorectomy) and the significance of early intervention with estrogen for CV risk reduction.
Health Outcomes After CEE: WHI

LaCroix AZ, Chlebowski RT, Manson JE, et al. JAMA 2011;305(13):1305-1314
Hysterectomy in the United States

• After Cesarean Section, hysterectomy is the most common major surgery performed on women.

• More than 6 million hysterectomies have been performed in the last 10 years. Ovaries removed in 54%.
  – More than 600,000/year

• Most common age group = 40–44 y, followed by 35–39 y, 46.1 is the average age for hysterectomy. 20% are age 35 or younger.

• By age 50-54 1/3 women in USA have had a hysterectomy.

• By age 55-59, the rate is just over 40%.

• More than 15 million women under age 60 have had a hysterectomy.

MTEA = Mortality Toll of Estrogen Avoidance

MTEA: Study Variables

- Excess Mortality Rate: 0.0013 per year.
- Population year by year: 17,307,862 to 21,933,149.
- Hysterectomy Rate: 33% to 40%.

MTEA : Annual Calculations and Best Point Estimates

• “Reasonable range of all assumptions: 40,292 to 48,835 excess deaths between 2002 and 2011”

• Sarrel PM, Njike V, Vinante V, Katz DL. AJPH. 2013;103:1583-88. July 18, 2013:e1-e6
ET Reduces Mortality: Literature Review

WHI-CEE trial, 11 years: reduction = 27%
DOPS, 16 years: reduction = 46%
Tuomikoski P, 1-8 years: reduction = 43%-54%
Salpeter SR, et al. reduction = 27%
  – 8 prospective observational studies-212,717 women followed for 2,935,495 women-years.
  – 19 RCTs, mean age of 54.5-83,043 woman year.

Explaining How Estrogen Therapy Reduces Mortality

• Cardiovascular Effects: Reduced CHD and MI.

• Other Estrogen Actions:
  – Reduced breast cancer mortality: WHI (63% reduction in mortality from invasive breast cancer); DOPS (62%)
  – Reduced psychiatric, osteoporotic, and colon cancer related mortality.
Causes of Death in Women

- Cardiovascular: 53%
- Other Causes: 25%
- Other Cancers: 18%
- Breast Cancer: 4%
CV Risk in women from hormonal perspective

- At each age from 40 to 54 years, postmenopausal women have a 2-4 fold greater risk of CVD than premenopausal women.
- The perceived differences between observational studies and randomized trials is explained by the timing hypothesis.
- HT appears to be beneficial when underlying vascular tissue is healthy and neutral or detrimental when initiated in women with diseased vasculature – a “dual effect of HT.”
- Timing, that is, early initiation of HT relative to menopause reduces CHD and total mortality.
Game Changer: DOPS Oct 2012 and long term WHI data 10/2013

- 10 year study Danish women
- Oral EPT 10 yrs.
- “Effect of HRT on CV events in recently postmenopausal women: a randomized trial”
- Reduced death rate, reduced MI CHF and no increase in cancer or VTE on HRT users compared to placebo.

The Elite Trial: IMS 2014

- Findings presented by Dr. Howard Hodis (PI)
- NIH-funded, prospective trial using oral estradiol and vaginal progesterone.
- Women < 6 years vs women > 10 Years Post-Menopause.
- Measures: Carotid artery IMT; CCT: coronary artery Ca++ and lesions.
- Confirms the “Timing Hypothesis” i.e. there is about a 10 year window in which HT intervention leads to cardio-protection

Clinical Trials.gov/ELITE:Early vs Late Intervention Trial with Estradiol: AHA, Nov 18, 2014
Women’s Health Initiative (WHI) 2002: The Headlines
Incremental Direct and Indirect Cost of Untreated Vasomotor Symptoms (VMS)

- Employer-based health insurance records 13 million individuals.
- 69 U.S. Fortune 500 companies.
- Case Cohorts: Untreated VMS vs non-VMS (Control) N= 252,273; mean age = 56 years.
- Measures: Number of health care visits and work loss costs for 12 months from index date.

Philip Sarrel; Patrick Lefebvre; Marie-Hélène Lafeuille Jonathan Gravel; Mei Sheng Duh; Peter M. Aupperle; David Portman. Menopause:The Journal of NAMS. 2015

Incremental Direct and Indirect Cost of Untreated Vasomotor Symptoms (VMS): Important Findings

- 1.5 million more outpatient visits (12 months) by women with untreated VMS.
- Cost per-patient-per-year of direct healthcare costs and indirect work loss cost (PPPY)=$2,000.00 more for women with untreated VMS.
- Total cohort cost (252, 273 women in each group): almost $400,000,000 more for women with untreated VMS.
Tissue Selective Estrogen Complex (TSEC) Duavee

- SERM-Bazedoxifene coupled with CE at 0.45 with 20mg BZD
  - effective and safe Tx for menopausal Sx in women with intact uterus in the SMART trial
  - FDA approved to prevent osteoporosis
- Bazedoxifene competitively inhibits binding of 17B–estradiol

SERMs
Estrogen Agonists Estrogen Antagonists
- Clomiphene/Clomid
- Tamoxifen/Nolvadex
- Raloxifene/Evista
- Ospemifene/Osphena
- Bazedoxifene (BZD) coupled w CE/Duavee
Treatment of high risk women

Treat CV condition first; once stabilized
Can use ET/HT if indicated-in women over age 60 combo HT/statin best


What are the harms of menopausal hormone therapy when used for the primary prevention of chronic conditions?

- VTE is the major risk of HT EPT greater than ET
- Increase risk for breast cancer diagnosis with over 5 years of oral estrogen/progestin-(specifically MPA) however, the WHI-EPT arm still showed mortality reduction for women on HT with a uterus who took HT for at least 5 years and started within 10 years of menopause. Consider “designer” HT.
- Increase risk for gallstones and increase in triglyceride level in some women with oral HT.
- Increase in uterine cancer in unopposed estrogen in women with a uterus.
- Increased risk MI/stroke esp women under age 60 when taken off HT. Mikkola TS, Tuomikoski P, Lyytinen H, et al “Increased Cardiovascular Mortality Risk in Women Discontinuing Postmenopausal Hormone Therapy” *JCEM* 2015; http://dx.doi.org/10.1210/jc.2015-1864

Males and Females are Different

Addyi

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HSDD and the “little pink pill”

Most common type of FSD.

– First in class Flibanserin (Addyi) 100mg at night approved for pre-menopausal women
– Have to be “certified” and instruct women not to ingest
ETOH www.AddyiREMS.com

R/O other co-existing medical, hormonal, psychiatric or Relationship issues
CONTRAINDICATED with Moderate or Strong CYP3A4 inhibitors (eg Fluconazole)

Overlap of Female Sexual Dysfunctions

Sexual desire disorder  Sexual arousal disorder  Dyspareunia  Orgasmic disorder  Vaginismus

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hardesire.net
### FSDs: DSM-IV-TR Definitions

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

<table>
<thead>
<tr>
<th>Defined by Onset</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Lifelong</td>
<td>Sexual dysfunction has been present since the onset of sexual functioning</td>
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<tr>
<td>Acquired</td>
<td>Sexual dysfunction develops only after a period of normal functioning</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Defined by Context</th>
<th></th>
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<tbody>
<tr>
<td>Generalized</td>
<td>Sexual dysfunction is not limited to certain types of stimulation, situations, or</td>
</tr>
<tr>
<td></td>
<td>partners</td>
</tr>
<tr>
<td>Situational</td>
<td>Sexual dysfunction is limited to certain types of stimulation, situations, or partners</td>
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</tbody>
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herdesire.net
FOD + HSDD = FSIAD

• Female Sexual Interest Arousal Disorder
• F52.22

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

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Physiology of Sexual Function

**Desire**
- Excitatory: dopamine, norepinephrine, testosterone, estrogen
- Inhibitory: serotonin, prolactin

**Arousal**
- Excitatory: dopamine, norepinephrine, testosterone, estrogen, nitric oxide, acetylcholine
- Inhibitory: serotonin, prolactin


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Physiology of Sexual Function

**Central Nervous System**

![Diagram](Diagram.png)


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Addyi for Pre-Menopausal women

- Get certified www.addyi.com
- WHladdyi-smart phrase
- 100mg at night with NO ETOH for 12 weeks
- Pharmacist has to be certified
- HSDD is real NOT a Flibanserin Deficiency Disorder
- Side effects of hypotension, syncope, headache, gi distress minimized by taking at HS and less than or similar to other drugs in the CNS class of meds.

Flibanserin Q’s

• Why is ETOH contraindicated with Addyi?
  a. Hepatotoxicity, b. Teratogenicity, c. Hypotension d) Hypersensitivity

• What is the purpose of the Addyi REM pt-provider agreement?
  a. For MDs to counsel, b. For charting c. For safety d. For pharmacist to counsel e. All of the above

• How often must pharmacists counsel pts about need to avoid ETOH?
  a. Never b. Only if pts asks about ETOH c. With 1st script d. With every script

• What is the primary counseling message for the pt?
  a. Do not drink ETOH until you know how it will affect you b. Limit your ETOH while taking Addyi
c. Do NOT drink any ETOH d. Do not drink ETOH at night at the time you take Addyi
Off Label Therapies and Future Therapies

- Bupropion (Wellbutrin) for patients who have trouble climaxing after arousal esp in women on SSRIs
- PDE5I like Sildenafil (Viagra) or Tadalafil (Cialis) in women on SSRIs or women with vasculogenic arousal problems (DM, MS)
- 1% vaginal DHEA (phase 3 study in vaginal ring)
- Bremelanotide (under study-taken on as needed basis)
- Lybrido (T/sildenafil)

Anorgasmia

- Anorgasmia is the medical term for regular difficulty reaching orgasm after ample sexual stimulation, causing personal distress.
  - Fewer than one third of women consistently have orgasms with sexual activity.
  - Orgasms often change with age, medical issues or medications.
  - “ClitGva”
  - OTC Zesta lotion to genitals
- Off label vaginal DHEA 1%
It’s all in the eye of the beholder
Be Strong, Be Healthy, and Be in Charge!