Update in Women’s Health

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Conflicts of Interest: None
Our Systematic Review

• Reviewed all titles published in top journals
  – February 28, 2013 to February 28, 2014
• Evaluated potential impact on internists’ clinical practice
• Top third of abstracts reviewed by all 4 of us
• Consensus reached about those most worthy of your time today
Sources Reviewed

- New England Journal of Medicine
- Journal of the American Medical Association
- Annals of Internal Medicine
- Archives of Internal Medicine
- British Medical Journal
- Lancet
- Obstetrics and Gynecology
- American Journal of Obstetrics and Gynecology
- JGIM
Sources Reviewed

- PLOS Medicine
- American Journal of Public Health
- Circulation
- Cochrane Database of Systematic Reviews
- Guideline Clearing House
- ACP Journal Club
- Journal of Women’s Health
- Journal Watch Women’s Health
- Journal Watch
- Menopause
Plan for today

- Cervical Cancer Screening
- Issues for Reproductive Aged Women
- Breast Cancer
- Menopause and Beyond
- Osteoporosis and Bone Health
Cervical Cancer Screening

Judith M. E. Walsh, MD, MPH
University of California, San Francisco
Ms. Henrietta P. Vee is a 36 year old woman who had her last cervical cancer screening test about 2 years ago. As far as she knows, her tests have always been normal. She has heard that maybe she can be screened less often but is a little nervous about it. What do you tell her about when she should have her next test?
Cervical Cancer Screening

- Dramatic reduction in mortality with routine cervical cancer screening
- HPV is the causative agent in the majority of cases of cervical cancer
  - HPV testing incorporated into new guidelines
- Long latency period for development of cervical cancer
- Many lesions will regress on their own
# Cervical Cancer Screening Guidelines

<table>
<thead>
<tr>
<th>USPSTF 2012</th>
<th>ACS/American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology Joint Guidelines 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pap smear every 3 years in women aged 21-65</td>
<td>Pap every 3 years in women aged 21-29</td>
</tr>
<tr>
<td>For women aged 30-65 who want to lengthen the screening interval, screen with a combination of cervical cytology and HPV testing every 5 years</td>
<td>For women aged 30-65 Pap plus HPV testing is the preferred method Pap every 3 years is acceptable</td>
</tr>
<tr>
<td>Discontinue in women over the age of 65 in whom smears have been consistently normal</td>
<td>Discontinue in women over the age of 65 in whom smears have been consistently normal Continue to screen women diagnosed with cervical pre-cancer</td>
</tr>
<tr>
<td>No HPV screening in women younger than 30</td>
<td>No HPV testing in women less than age 30 unless needed after an abnormal test result</td>
</tr>
<tr>
<td>No screening in women who have had a hysterectomy</td>
<td>No screening in women who have had a hysterectomy and have no history of cervical cancer or pre-cancer</td>
</tr>
</tbody>
</table>
HPV based screening

- Four RCTs have compared HPV based screening with cytology based screening
  - Precursors of cancer were the endpoints in all the trials
  - Lower CIN3 incidence with HPV testing in all studies
- HPV based screening detects persistent high grade CIN before cytology, increasing probability of treatment before invasion
  - Effect similar with different screening protocols
- Relative efficacy of HPV based screening vs cytology for prevention of invasive cancer is not known
The News

• Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials.

• Aim: To evaluate the relative efficacy of HPV-based vs cytology based screening for prevention of invasive cancer in women who undergo regular screening, of modifiers of the relative efficacy and of the duration of protection.
Methods

- 176,464 women aged 20-64 assigned to HPV or cytology based screening in 4 RCTS in 4 countries: Swedescreeen, POBASCAM, ARTISTIC and NTCC
- Mean follow-up 6.5 years
  - (1,214,415 person-years)
- 107 invasive cervical cancers identified
Results: Rate Ratios

- Overall for invasive cervical cancer (HPV vs cytology)
  - 0.60 (0.40-0.89)
- Detection of cervical cancer similar in first 2.5 years but lower after that
  - 0.79 (0.46-1.36) first 2.5 years
  - 0.45 (0.25-0.81) after 2.5 years
- Low rate ratio with negative test at entry
  - 0.30 (0.15-0.60)
- Rate ratio lowest in women aged 30-34
  - 0.36 (0.14-0.94)
Conclusions

- HPV-based screening provides 60-70% greater protection against invasive cervical carcinomas compared with cytology based screening
Take Home Message

• Evidence from these large RCTs supports initiation of HPV based screening at the age of 30 and extension of screening intervals to at least 5 years
Key Article

• 13 year follow-up of Swedescreen RCT
  – CIN3+ vs CIN2+
• At baseline the increased number of CIN2+ lesions detected with HPV screening could reflect over-diagnosis
• After 11 years, cumulative incidence of CIN2+ became similar in both arms
• Increased sensitivity HPV screening for CIN2+ reflects earlier detection rather than over-diagnosis
  – Elfstrom et al. BMJ 2014: 348:g130
Updated Consensus Guidelines for Management of Abnormal Cervical Cancer Screening Tests

- Negative cytology without endocervical cells can be managed without repeat
- Unsatisfactory cytology needs repeat even if HPV negative
- AS-CUS with any HPV type goes to colposcopy
- HPV negative and AS-CUS results should be followed by co-testing at 3 years, not 5 and can’t stop at 65

- ACPG April, 2013
Updated Consensus Guidelines for Management of Abnormal Cervical Cancer Screening Tests

• Negative cytology with positive HPV
  – Repeat co-testing at one year
  – At one year, if HPV positive or cytology AS-CUS or greater, go to colposcopy
  – At one year if both negative, repeat co-testing in three years
  – HPV genotyping acceptable: If HPV 16 or 18, colposcopy and if HPV 16/18 negative, co-testing one year
Back to Henrietta

• Her last normal Pap was two years ago
• If it included HPV testing, she could be screened again in 3 years
• If it did not include HPV testing, she should have her next Pap next year.
Issues for Reproductive Aged Women

Sarah A. Tilstra, MD, MS
University of Pittsburgh
Jennifer

• Jennifer is a 30 yo female who presents to your office to discuss her future pregnancy plans. She has a history of depression with a past suicide attempt in her 20s and has been well controlled on citalopram 40mg since then. Her sister told her that if she continues citalopram during pregnancy, her baby will have autism. She asks for your advice....
Prenatal SSRI Exposure

• Linked to low birth weight, preterm delivery, preeclampsia, HTN, cardiac defects, poor neonatal adaptation and persistent pulmonary HTN of the newborn

• Risks uncontrolled depression >> risk of SSRIs during pregnancy, recommended to continue pre/during/post-partum

Misri et al. UTD Jan 2014.
SSRI Exposure and Autism

• Biologic plausibility:
  – Serotonin dysregulation is linked to development of autism

• Croen et. al 2011:
  – Population case-controlled study, 15/298 cases ASD were exposed to SSRIs
  – Women with a Rx for antidepressant during prenatal period were more than twice as likely to have a child later diagnosed with ASD
• *Parental depression, maternal antidepressant use during pregnancy, and risk of autism spectrum disorders: population based case-control study*  
  – Rai et. al. BMJ April 2013

• Aim: Study association between parental depression and maternal antidepressant use during pregnancy with autism spectrum disorders in offspring
• 4429 cases with ASD/43277 controls, Stockholm 2000s
  – nested 1679 cases ASD with maternal data on SSRI use
  – 21/1679 cases ASD exposed to SSRIs
• *Maternal depression* was associated with 50% increase in the risk of ASD (OR 1.49, 1.08-2.08)
• *Strong* association of ASD risk in offspring of mothers who were depressed *and* used antidepressants (but not SSRI alone)
  • OR 3.34 (1.50-7.47)- 9 cases!
• *No* association of ASD risk in offspring of mothers who used antidepressants *without* depression
  • OR 1.61 (0.85-3.06)- 12 cases!
• Conclusion: Antidepressant exposure in utero associated with increase risk of ASD
The News

- **Use of Selective Serotonin Reuptake Inhibitors during Pregnancy and Risk of Autism**
  - Hviid et al. NEJM 2013

- Aim: Quantify the risk of autism spectrum disorders in offspring of mothers exposed to SSRIs during pregnancy
Methods

- Denmark Cohort study all singleton births 1996-2005, f/u through 2009 (630k)
- Linked maternal SSRI (filled Rx) use and ASD in offspring
- Excluded conditions with underlying risk of autism
- Mother’s parity, age of mother, smoking status, country of origin, residence, psych condition, “other meds,” employment status, education
Results

• 1% mothers used SSRIs during pregnancy, “6068 exposed pregnancies”
• SSRI users were less educated, lower SES, more likely to have psych illness, use other meds during pregnancy, and to smoke
## RR of ASD in Offspring Exposed vs. Not Exposed to SSRIs

<table>
<thead>
<tr>
<th>Period of Maternal SSRI Use</th>
<th>Rate Ratio (95% CI) (Crude Rate)</th>
<th>Rate Ratio (95% CI) (fully adjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No use (2 years before pregnancy → delivery)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Use during pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 years before preg → delivery</td>
<td>1.62 (1.23-2.13)</td>
<td>1.20 (0.90-1.61)</td>
</tr>
<tr>
<td>Only during pregnancy</td>
<td>1.50 (1.04-2.21)</td>
<td>1.08 (0.74-1.58)</td>
</tr>
<tr>
<td>During first trimester</td>
<td>1.79 (1.19-2.69)</td>
<td>1.40 (0.92-2.13)</td>
</tr>
<tr>
<td></td>
<td>1.82 (1.33-2.49)</td>
<td>1.35 (0.97-1.87)</td>
</tr>
<tr>
<td>Use 2 years → 6m prior to pregnancy</td>
<td>1.76 (1.42-2.27)</td>
<td>1.46 (1.17-1.81) *</td>
</tr>
</tbody>
</table>

Maternal psych disorders and “other meds” during pregnancy strongly associated with ASD.
Conclusion

• No significant association between maternal use of SSRI during pregnancy and ASD in offspring
Take Home Messages

• Prenatal SSRI exposure does not seem to increase risk of autism in offspring
• Studies that have shown association have been (very) small, case-controlled
• Association seems to be based on indication for SSRI use rather than SSRI use itself
• Many of these women have psych illness that if poorly controlled, could contribute to maternal/fetal morbidity
Back to Jennifer

- Long hx of depression with past suicide attempt, currently well controlled on Citalopram

- Weighing the evidence, benefits of SSRI use and well controlled depression during pregnancy outweigh risk of ASD
Jacque

Jacque is a 32 yo female who presents to you to discuss her birth control (Yaz®). She has been seeing commercials for lawsuits against the company that makes Yaz® and wonders if she should change her birth control pill. She is a nonsmoker, has no personal/family hx of VTE.
The News

• *Different combined oral contraceptives and the risk of venous thrombosis: systematic review and network meta-analysis*
  – Stegeman et al. BMJ 2013

• Aim: Provide overview of the risk of VTE in women using combined oral contraceptives
COCs and VTE

• COC associated VTE is relatively common, given the absolute number of COC users (incidence 3/10,000 person years)
• Since introduction of COCs, estrogen/progestin components have been altered to limit side effects
• Certain combinations have been more (drospirenone) or less (levonorgestrel) associated with VTE risk
Methods

• Network meta-analysis
  – Allows comparisons of interventions even though they have not be directly compared in the articles pooled for the meta-analysis
  – Allows all combinations of specific COCs to be compared with one-another, not just to regimen used in the original trial

• Observation studies: healthy women using COCs with primary outcome DVT/PE
### RR of VTE Compared with Non-Users

<table>
<thead>
<tr>
<th>COC Use</th>
<th>RR of VTE (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any COC use</td>
<td>3.5 (2.9-4.3)</td>
</tr>
<tr>
<td>First-generation progestin</td>
<td></td>
</tr>
<tr>
<td>Lynestrenol, Norethisterone</td>
<td>3.2 (2.0-5.1)</td>
</tr>
<tr>
<td>Second-generation progestin</td>
<td>2.8 (2.0-4.1)*</td>
</tr>
<tr>
<td>Norgestrel, Levonorgestrel</td>
<td></td>
</tr>
<tr>
<td>Third-generation progestin</td>
<td>3.8 (2.7-5.4)*</td>
</tr>
<tr>
<td>Desogestrel, Gestodene, Norgestimate</td>
<td></td>
</tr>
<tr>
<td>Drospirenone</td>
<td>3.9 (2.7-5.5)</td>
</tr>
</tbody>
</table>

*RR 1.3 (1.0-1.8)
Results: VTE Risk Principles Among Top 10 COCs

• Less thrombophilic formulations
  – 20mcg levonorgestrel
  – 20mcg gestodene
  – 30mcg levonorgestrel
  – 35mcg norgestimate

• Desogestrel, cyproterone and drospirenone remain as the “bad actors”

• Higher estrogen component associated with higher risk of VTE, regardless of progestin used
Conclusions

• All COCs are associated with increased risk of VTE

• Effects size depends on progestin used and dose of ethinylestradiol
Take Home Messages

• Consistently start “less thrombophilic” formulations of COCs
• Consider changing women who are on COCs with desogestrel, drospirenone, and cyproterone
• Back to Jacque:
  – Should you change Jacque’s COC? (probably)
Abby

Abby is a 23 yo G3P2 female who presents to your office 3 months post-partum. She is stressed out and does not want any more children. Your medical student states that you should not put Abby on COCs, as they will be less effective in protecting Abby from pregnancy because her BMI is 42.
The News

• **Contraceptive Failures in Overweight and Obese Combined Hormonal Contraceptive Users**
  – McNicholas C et. al. Obstet Gynecol 2013 (CHOICE study)

• **Aim:** Estimate whether contraceptive failure rates among pill/patch/ring users was associated with increasing BMI
Failure Rate of COCs and BMI

- Limited data on effectiveness of contraception in morbidly obese women
- Holt et al 2005 → case-controlled study suggests elevated BMI as risk factor for COC failure (threshold BMI ~27)
  - methods were challenged, recall bias, design flaws
- Biologic plausibility: altered bioavailability of hormones due to volume of distribution/absorption in heavier patients
Methods

• CHOICE study: Prospective cohort study of 9300 reproductive age females in St. Louis, designed to increase access to contraception and decrease cost

• 1500 women chose COC at enrollment, followed at 3m, 6m, then Q6m with telephone interviews

• Primary outcome: contraceptive failure in COC users by BMI class

• Kaplan-Meier failure curves used to estimate failure by BMI group

• Adjusted for women that crossed BMI groups
Results

• Demographically different groups, but failure rate among 3 methods was similar OCP 5.6%, patch 4.6%, ring 3.4% → combined for analysis.

• 128/334 unintended pregnancies attributed to COC failure.

• No difference found in failure rate of COCs across BMI categories.

• Younger age, increased parity and hx of unintended pregnancy remained risk factors for COC failure.
Conclusion

• COC failure rate does not seem to be influenced by BMI

• Back to Abby:
  You remediate your medical student but allow him to discuss contraception methods with Abby. He is advocating for DMPA. Abby asks, “Will depo make me gain weight?”
Key Article

• *Weight change at 12 months in users of three progestin-only contraceptive methods*
  – Vickery et al. Contraception 2013

• Aim: Compared change in body weight over 12 months between etonogestrel implant (nexplanon), levonorgestrel IUD system (mirena), DMPA (depo provera) and copper IUD users
Key Article

• CHOICE study; continuous progestin only users for 11 months, baseline BMI data
• Outcome: change in body weight from baseline to 12 months
• Results:
  – When adjusted for confounders (AGE and RACE), NO association between contraception method and weight gain
  – Overall, black race was a predictor of weight gain, regardless of contraception method
• These data are backed by a recent Cochrane Review (*Progestin-only contraceptives (POCs): effects on weight. July 2013*)
Take Home Messages

• Perceived weight gain is a deterrent of effective contraception (notably DMPA)
• There is a subset of women that will gain weight on progestin only contraception methods (DMPA) but hard to predict
• Use these studies to help inform your patients (average weight gain <5lbs)
• Any weight gain that could be attributed to contraception is WAY LESS than weight gain associated with pregnancy!
Key Article
Effective Contraception


- Aim: To evaluate pregnancy rates with 84/7, 21/7, 24/4 COC regimens
Key Article

- **Methods**: retrospective study using insurance claims database, 84/7 users were matched 1:1 with 24/4 and 21/7 users
- **Results**: Statistically significant higher rates of pregnancy reported in the 24/4 and 21/7 groups compared to 84/7 group
- **Conclusion**: 84/7 regimen may prevent pregnancy more effectively than 21/7 and 24/4 regimens (also data that it’s more cost-effective)
Back to Abby

• Abby chooses to decline any birth control for now and go home and “think about” the options that you presented to her

• She calls the office 6 weeks later, 2 days after having unprotected intercourse, asking for “that pill that prevents pregnancy.” Her LMP was 2 weeks ago
Emergency Contraception

- EC available for 15 years
- Plan B One-Step ~ $40-50, no ID to buy, 72hrs
- Plan B generics- coming soon, $35-45, need to be 17yo to buy
- Ella is Rx only, can buy through online pharmacy with shipping, $42, 120hrs
- Must be taken ASAP after unprotected sex to prevent ovulation
Emergency Contraception

- Ella has been shown to be >50% more effective in preventing pregnancy than Plan B
- Glasier et al, *Contraception 84* (2011)
  - Identified risk factors for EC failure Plan B/Ella
  - Obesity increased risk of failure by >3
    (OR 3.60; 95% CI, 1.96–6.53; p<.0001)
  - Threshold where EC not effective more than placebo
    - Plan B: 70kg, BMI >26
    - Ella: 88kg, BMI >35
The News

• *Ulipristal acetate prevents ovulation more effectively than levonorgestrel: analysis of pooled data from three randomized trials of emergency contraception regimens* – Brache et al. Contraception 2013

• Aim: Estimate and compare the ability of Ella and Plan B One-Step to inhibit ovulation
Methods

• Pooled data from 3 previous randomized, double-blind, placebo-controlled crossover studies (same authors)
  – Plan B One-step
  – Plan B One-step + Meloxicam 15mg
  – Ella 30mg
  – Placebo

• Outcome: effect of drug regimen on follicular rupture in the 5 days post-treatment, visualized by daily TVUS

• Serum LH levels starting at 15mm were used to follow LH surge

• All participants treated when follicle ≥18mm
Proportion of Unruptured Follicles at 5 days Post-Tx According to LH Status

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=50)</th>
<th>Plan B (n=48)</th>
<th>Plan B + meloxicam (n=31)</th>
<th>Ella (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx before LH surge</td>
<td>0% (0/16)</td>
<td>25% (3/12)</td>
<td>56% (5/9)</td>
<td>100% (8/8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P = .0026</td>
</tr>
<tr>
<td>Tx after LH surge, before peak</td>
<td>10% (1/10)</td>
<td>14% (2/14)</td>
<td>39% (5/13)</td>
<td>79% (11/14)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P = .0018</td>
</tr>
<tr>
<td>Tx after LH peak</td>
<td>4% (1/24)</td>
<td>9% (2/22)</td>
<td>22% (2/9)</td>
<td>8% (1/12)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>nonsignificant</td>
</tr>
<tr>
<td>% Unruptured Follicles at 5 days</td>
<td>4%</td>
<td>15%</td>
<td>39%</td>
<td>59%</td>
</tr>
</tbody>
</table>
Conclusions

- Ella is more effective at delaying follicle rupture than Plan B when given during the late follicular phase
- Plan B is no more effective than placebo in delaying follicular rupture when given during the late follicular phase
- Why? Ella may have a direct effect on the progesterone pathways that contribute to ovulation
- Adding meloxicam to Plan B doubles the proportion of unruptured follicles at 5 days
Take Home Messages

- Data show that Ella is superior to Plan B in preventing follicular rupture and pregnancy
- But, Plan B isn’t that bad… prevented 70%-85% of pregnancies in studies
- Likely more to prevention of pregnancy than just inhibition of ovulation
Back to Abby

- Ella (or copper IUD!) should be used for any patient at high-risk for pregnancy > Plan B
- Obese women are more likely to fail any emergency contraception, but Ella is more effective with higher BMI
- Abby needs Ella!
Angelina

Angelina is a healthy 37 yo women who presents to you to discuss her risk of breast cancer. Her mother was diagnosed with breast cancer in her 40s and ovarian cancer in her 50s. She recently passed away. Her maternal grandmother died from ovarian cancer and her aunt died from breast cancer.
BRCA1 and BRCA2

- Incidence: 1/300-500, 2.1% of all Ashkenazi Jewish women
- Inheritance is autosomal dominant
- 50-85% lifetime risk of breast cancer
- 15-40% lifetime risk of ovarian cancer
- Appropriately managing women with BRCA mutations decreases Br Ca incidence by 80-95%
- Goal:
  - Identify women at high risk for BRCA mutations or other patterns of inherited breast cancer
  - Refer for genetic counseling
  - Testing & Treatment

# USPSTF Guidelines

## Population

Asymptomatic women not diagnosed with BRCA-related cancer

## Recommendation

<table>
<thead>
<tr>
<th>Grade B</th>
<th>Screen women whose family hx may be associated with potential BRCA mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade D</td>
<td>Do not recommend genetic counseling/BRCA testing whose family hx is not significant for BRCA risk</td>
</tr>
</tbody>
</table>

## Risk Assessment

- *(known BRCA+ mutation in the family)*
- Breast cancer <50 years old
- Bilateral breast CA
- Family hx of breast and ovarian cancer *(same side of family)*
- Male breast cancer
- Multiple cases of breast cancer *(≥2 same side of family)*
- >1 family member with 2 primary types of BRCA related cancer
- Ashkenazi Jewish ethnicity *with family hx of breast cancer*
## USPSTF Guidelines

| Risk Assessment Tools | Ontario Family History Assessment Tool  
Manchester Scoring System  
Referral Screening Tool  
Pedigree Assessment Tool  
FHS-7 |
|-----------------------|--------------------------------------------------|
| Screening Tests        | Genetic counseling  
Testing for BRCA |
| Treatment             | Earlier and more frequent screening for breast/ovarian Ca  
Risk reduction (lifestyle/medications)  
Risk-reducing surgery (mastectomy/BSO) |
| Balance of Benefits/Harms | Net benefit of BRCA+ is MODERATE  
Net risk of women BRCA- is MINIMAL |
Updates in Breast Cancer: Screening, Prevention, and Treatment

Megan C. McNamara, MD, MSc
Louis Stokes Cleveland VAMC
Case Western Reserve University
School of Medicine
Kimberly

- Kimberly is 43 year old healthy female who has been getting annual mammograms since the age of 40. She is a non-smoker, drinks alcohol occasionally, and exercises regularly. She has no family history of cancer.

- She notes that her mammograms are quite painful and fairly inconvenient. She has been called back twice for “minor abnormalities” which necessitated additional images (all of which were negative).

- She recently read an article in The New York Times which stated that mammograms may be less beneficial than previously thought. She wonders if she needs her mammogram this year.
Background

• Several trials have shown that mammography reduces breast cancer mortality, although their results may be affected by the adequacy of randomization.

• Mammography may also be associated with significant harms, including false-positives and over-diagnosis.

The News

- Twenty five year follow-up for breast cancer incidence and mortality of the Canadian National Breast Screening Study: randomised screening trial.

- Aims:
  - 1. To evaluate the benefit of annual breast physical exam and screening mammography among women aged 40-49 compared with usual care.
  - 2. To evaluate the risk/benefit of adding mammography to breast physical examination among women aged 50-59.
Women aged 40-59 who were non-pregnant, had no diagnosis of breast cancer and no mammography in prior 12 months
N= 89,835

Breast examination by examiner

Women aged 40-49  N= 50,430

Randomization by study coordinator

Mammography + breast exam  N= 25,214

Usual care  N = 25,216

Women aged 50-59  N= 39,405

Randomization by study coordinator

Mammography + breast exam  N= 19,694

Breast exam Alone  N = 19,694

Screening period: 5 yrs

Outcome: Breast cancer mortality
### Results: Years 1-5 (screening phase)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Arm (usual care, annual breast exam) N = 524</th>
<th>Mammogram Arm N = 666</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at diagnosis (years)</td>
<td>52.6</td>
<td>52.5</td>
</tr>
<tr>
<td>Died from breast cancer (%)</td>
<td>171 (32.6)</td>
<td>180 (27.0)</td>
</tr>
<tr>
<td>Tumor size (cm)*</td>
<td>2.1 (0.2-7.0)</td>
<td>1.9 (0.2-9.0)</td>
</tr>
<tr>
<td>Lymph node status positive (%)**</td>
<td>170 (32.4)</td>
<td>204 (30.6)</td>
</tr>
<tr>
<td>Estrogen receptor status (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>85 (16.2)</td>
<td>102 (15.3)</td>
</tr>
<tr>
<td>Equivocal</td>
<td>41 (7.8)</td>
<td>41 (6.2)</td>
</tr>
<tr>
<td>Positive</td>
<td>261 (49.8)</td>
<td>312 (46.9)</td>
</tr>
</tbody>
</table>

*p = 0.01  
**p = 0.53
Breast cancer specific mortality, by assignment to mammography or control arms (all participants).

All cause mortality, by assignment to mammography or control arms (all participants).

Overdiagnosis = 22%
Potential limitations

– **Selection bias**
  - Exclusion of prevalent breast cancers did not change results
  - Equal proportions of women in both groups were diagnosed with breast cancer after screening was complete (mammogram arm: 5.8%, control arm: 5.9%)

– **Contamination**
  - 26% of usual care group received mammograms
  - Adjustment for outside mammography did not change results

– **Mammography after end of screening phase**
  - Unlikely that screening after the study was differential between study arm participants or masked a benefit from screening during the study
Comparison with Other Trials

• Swedish Two-County Trial
  – 30% breast cancer mortality reduction
  – Randomization was by county
    • Possible selection bias?
  – Analysis was based on invitation to screen
    • Possible selection bias?

• Review of data from SEER
  – 31% overdiagnosis rate
    • Wider age range included

Conclusions

• In this randomized study, mammography did not reduce breast cancer mortality; moreover, 22% of cancers were over-diagnosed

• *Taken in context*…
  – Prior trials may not have had adequate randomization
  – Benefit may be related to improvements in treatment rather than screening
How Should I Counsel Kimberly?
Key Article

• *Quantifying the Benefits and Harms of Screening Mammography*

• Aim: To use all available data to quantify the benefit-risk trade-off for screening mammography among women ages 40-69

• Outcomes assessed:
  – Reduction in breast cancer deaths
  – False-positive results
  – Over-diagnosis
## How do I counsel Kimberly?

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Among 1000 40-year old women screened with annual mammography for 10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benefits</strong></td>
<td>0.1-1.6 will avoid dying from breast cancer*</td>
</tr>
<tr>
<td><strong>Harms</strong></td>
<td>510-690 women will have a false-positive result</td>
</tr>
<tr>
<td></td>
<td>60-80 will have a false-positive biopsy recommendation</td>
</tr>
<tr>
<td></td>
<td>Up to 11 women will be over-diagnosed and potentially receive unnecessary treatment</td>
</tr>
</tbody>
</table>

*Range of benefits include data from the Canadian National Breast Cancer Screening Studies and Swedish Two-County trials*
Take-Home Message

• Decisions regarding mammographic screening should be highly individualized and take into account the range of possible benefits and risks.
Lynn

- Lynn is a 52 year old healthy post-menopausal female who presents for routine follow-up.
- Several members of her family have been diagnosed with breast cancer; her calculated 5-year and lifetime Gail risk scores are significantly elevated.
- We discussed the most recent USPSTF guidelines, which recommend consideration of chemoprophylaxis for women at high risk for breast cancer.
**USPSTF Guidelines**

<table>
<thead>
<tr>
<th>Population</th>
<th>Asymptomatic women aged &gt;35 <em>without</em> a prior diagnosis of breast cancer who are at increased risk for the disease</th>
<th>Asymptomatic women aged &gt;35 <em>without</em> a prior diagnosis of breast cancer who are not at increased risk for the disease</th>
</tr>
</thead>
</table>
| Recommendation | Engage in shared decision-making  
Offer risk-reducing medications if appropriate **Grade B** | Do not prescribe risk-reducing medications  
**Grade D** |
| Risk Assessment | Consider: age, ethnicity, age at menarche, age at first live birth, personal history of DCIS/LCIS, family history, history of breast biopsy, BMI, menopause status, breast density, estrogen/progestin use, smoking, EtOH use, physical activity,diet | |
| Preventive Medications | The SERMs tamoxifen and raloxifene have been shown to reduce the incidence of invasive breast cancer in women at increased risk. Tamoxifen has been approved in women age >35, raloxifene has been approved in postmenopausal women. Tamoxifen is dosed at 20mg and raloxifene is dosed at 60mg for 5 years. | |
**USPSTF Guidelines**

<table>
<thead>
<tr>
<th>Population</th>
<th>Asymptomatic women aged &gt;35 <em>without</em> a prior diagnosis of breast cancer <em>who are at increased risk for the disease</em></th>
<th>Asymptomatic women aged &gt;35 <em>without</em> a prior diagnosis of breast cancer <em>who are not at increased risk for the disease</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Balance of Benefits and Harms</strong></td>
<td>There is moderate net benefit from use of tamoxifen and raloxifene to reduce the incidence of invasive breast cancer in women who are at increased risk for the disease.</td>
<td>The potential harms of tamoxifen and raloxifene outweigh the potential benefits for breast cancer risk reduction in women who are not at increased risk for the disease.</td>
</tr>
</tbody>
</table>

Potential harms include thrombembolic events, endometrial cancer, and cataracts.

Lynn is agreeable to considering therapy, but is very concerned about the risks of these serious adverse effects. She wonders if there are any other treatments which might be safer but just as effective?
The News

- **Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind randomised placebo-controlled trial**

- **Aim:** To evaluate the efficacy and safety of anastrozole for the prevention of breast cancer among high-risk women.
Background

- SERMs (tamoxifen and raloxifene) reduce the risk for invasive breast cancer but are associated with an increased risk for thromboembolic disease.

- Aromatase inhibitors significantly reduce the synthesis of estrogen, may have similar benefits as SERMs, and are potentially better tolerated.
  - Exemestane decreased the risk of invasive breast cancer by 65% at a median follow-up of 35 months.

Methods

P: 3864 women aged 40-70 at increased risk for invasive breast cancer (relative risk 1.5x-4x higher) (N=3864)

I: 1mg oral anastrozole daily for 5 years (N=1920)

C: placebo daily for 5 years (N=1944)

O: Invasive breast cancer and non-invasive DCIS

Details: all study personnel, participants, and clinicians were blinded; analysis was done on an intention-to-treat basis; mammograms were done at least every 2 years; follow-up continued up to 7 years
## Results: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Anastrozole group N = 1920</th>
<th>Placebo group N = 1944</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59.5</td>
<td>59.4</td>
</tr>
<tr>
<td>Prior use of HT</td>
<td>47%</td>
<td>47%</td>
</tr>
<tr>
<td>Two or more 1\textsuperscript{st} degree relatives with breast or ovarian cancer</td>
<td>50%</td>
<td>48%</td>
</tr>
<tr>
<td>One 1\textsuperscript{st} degree relative with breast cancer diagnosed at age 50 or younger</td>
<td>35%</td>
<td>34%</td>
</tr>
<tr>
<td>One 1\textsuperscript{st} degree relative with bilateral breast cancer</td>
<td>9%</td>
<td>7%</td>
</tr>
<tr>
<td>LCIS or atypical hyperplasia</td>
<td>8%</td>
<td>10%</td>
</tr>
<tr>
<td>ER positive DCIS treated with mastectomy</td>
<td>8%</td>
<td>9%</td>
</tr>
<tr>
<td>10-year Tyrer-Cuzick risk</td>
<td>7.6%</td>
<td>7.8%</td>
</tr>
</tbody>
</table>
### Results

**Table:**

<table>
<thead>
<tr>
<th>Number of women</th>
<th>Hazard ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anastrozole group (n=1920)</td>
<td>Placebo group (n=1944)</td>
</tr>
<tr>
<td>All invasive cancers</td>
<td>32 (2%)</td>
<td>64 (3%)</td>
</tr>
<tr>
<td>Invasive ER-positive cancers</td>
<td>20 (1%)</td>
<td>47 (2%)</td>
</tr>
<tr>
<td>Invasive ER-negative cancers</td>
<td>11 (1%)</td>
<td>14 (1%)</td>
</tr>
<tr>
<td>Ductal carcinoma in situ</td>
<td>6 (&lt;1%)</td>
<td>20 (1%)</td>
</tr>
<tr>
<td>All</td>
<td>40 (2%)</td>
<td>85 (4%)</td>
</tr>
</tbody>
</table>

- Moderate arthralgia, carpal tunnel syndrome, joint stiffness, and dry eyes were more common in the treatment group.

- There were no between-group differences in the number of fractures or thromboembolic, CVA, or MI events.
Conclusions

• Treatment with anastrozole for 5 years significantly reduces the incidence of non-invasive and invasive breast cancer among high-risk women (NNT = 36).

• Anastrozole demonstrates similar efficacy as tamoxifen and raloxifene with fewer serious adverse effects.
Back to Lynn

• She may be willing to consider anastrozole for chemoprevention because of its more favorable side-effect profile, and you and she plan to stay tuned…
Take Home Message

- Chemoprophylaxis significantly reduces the risk of invasive and non-invasive breast cancer among high-risk women.
- Since most women starting therapy will be healthy and feeling well, the choice of specific therapy may be guided by the potential for adverse events, which can be serious and affect quality of life.
Debbie

- Debbie is a 53 year old female who was diagnosed with estrogen and progesterone-receptor positive breast cancer 5 years ago.

- She underwent a right breast lumpectomy and sentinel-node biopsy and was subsequently treated with chemotherapy, radiation, and tamoxifen.

- Debbie was excited about the possibility of discontinuing her tamoxifen this year, until her oncologist brought up the results of a new study…
The News

• Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial.

• Aim: To assess the relative benefits and risks of continuing tamoxifen therapy for 10 years after diagnosis of invasive breast cancer
Background

• Among women with ER+ breast cancer, treatment with 5 years of tamoxifen significantly reduces the risk of breast cancer recurrence and mortality over 10-15 years of follow-up.

• It is unclear what additional benefit, if any, might accrue with longer durations of tamoxifen therapy.

Methods

15,244 women with early stage breast cancer, randomized to:
• Continue tamoxifen for another 5 years, n=7629
  • Stop tamoxifen immediately, n = 7615

12,894 included in analysis of side effects
  (median prior tamoxifen duration: 5 years)

6846 with ER+ breast cancer included in efficacy analysis
• 3428 continued tamoxifen for another 5 years
  • 3418 stopped tamoxifen immediately

Outcomes:
All cause mortality
Breast cancer recurrence
Breast cancer mortality

36 countries, trial years 1996-2005

2350 excluded because prior treatment with tamoxifen was less than 4 years

6048 excluded because ER status was unknown or negative

Responsible clinicians provided information on outcomes; “death certificates were also sought.” Outcome assessor was not blinded to treatment assignment.
Breast cancer recurrence

Breast cancer mortality

Absolute recurrence reduction 3.7%

Absolute mortality reduction 2.8%

## Results

<table>
<thead>
<tr>
<th>ER-Positive Patients Who Experienced…</th>
<th>Continued tamoxifen to 10 years N= 3428</th>
<th>Stopped tamoxifen at 5 years N= 3418</th>
<th>Event rate ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any death</td>
<td>639</td>
<td>722</td>
<td>0.87 (0.78-0.97)</td>
<td>0.01</td>
</tr>
<tr>
<td>Death with recurrence</td>
<td>331</td>
<td>397</td>
<td>0.83 (0.72 –0.96)</td>
<td>0.01</td>
</tr>
<tr>
<td>Death without recurrence</td>
<td>308</td>
<td>325</td>
<td>0.91 (0.78-1.06)</td>
<td>0.24</td>
</tr>
<tr>
<td>Stroke</td>
<td>130</td>
<td>119</td>
<td>1.06 (0.83-1.36)</td>
<td>0.63</td>
</tr>
<tr>
<td>Pulmonary embolus</td>
<td>41</td>
<td>21</td>
<td>1.87 (1.13-3.07)</td>
<td>0.01</td>
</tr>
<tr>
<td>Ischemic heart dz</td>
<td>127</td>
<td>163</td>
<td>0.76 (0.60-0.95)</td>
<td>0.02</td>
</tr>
<tr>
<td>Endometrial CA</td>
<td>116</td>
<td>63</td>
<td>1.74 (1.30-2.34)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Cataract</td>
<td>72</td>
<td>63</td>
<td>1.11 (0.79-1.56)</td>
<td>0.54</td>
</tr>
</tbody>
</table>
Conclusions

• Among women with ER+ breast cancer, continuing tamoxifen for a total of 10 years, as compared to 5 years, further reduces the risk of breast cancer recurrence and mortality during 10-15 years of follow-up.

• These benefits must be weighed against potential harms, including a 2-5% risk of endometrial cancer at year 15.
Back to Debbie…

• She had experienced multiple episodes of vaginal bleeding while on tamoxifen and had undergone 2 endometrial biopsies. She was very concerned about her risk for endometrial cancer and wanted to avoid further procedures. She elected not to continue on tamoxifen.
Take Home Message

• While continuing treatment with tamoxifen to 10 years after diagnosis is associated with clear benefits, the decision to do so must be highly individualized, and take into account the potential harms of therapy.
Key Article

- *Risk of Ischemic Heart Disease in Women After Radiotherapy for Breast Cancer*

- Aim: To investigate the association between radiotherapy for breast cancer and the risk for ischemic heart disease
Methods/Results

- Case-control study
- Women with breast cancer who received radiotherapy between 1958-2001
- Rate of major coronary events increased by 7.4% for each 1 Gray increase in mean radiation dose to the heart. Increase started within 5 years and continued for at least 20 years.

**Take-Home Message:**
Women who previously received breast radiotherapy may be at increased risk for coronary events. Current radiotherapy techniques are different from those used in the study; however, the risks of radiotherapy may be more carefully weighed in women with significant cardiac risk factors.
Issues for the Menopausal Woman

Rachel A. Bonnema, MD, MS
University of Nebraska Medical Center
Marcia

- Marcia is a 52 year old woman with a history of hypertension well controlled on lisinopril. She has intolerable hot flashes and is interested in some sort of treatment for her symptoms. She would like to hear your thoughts on hormones and whether they are a safe option for her.

- What do you tell her?
WHI trials designed to determine benefit/risk of hormone therapy when taken for chronic disease prevention

- Primary efficacy outcome: CHD
- Primary safety outcome: invasive breast cancer

Combination trial stopped early due to increased breast cancer risk and unfavorable risk-to-benefit ratio
The News

• *Menopausal Hormone Therapy and Health Outcomes During the Intervention and Extended Poststopping Phases of the Women’s Health Initiative Randomized Trials*

• Aims:
  – Provide a comprehensive, integrated overview of findings from the 2 WHI hormone therapy trials with extended post-intervention follow-up and stratification by age and other important variables
Methods

- Post-intervention follow up through Sept 30, 2010 based on 81.1% surviving participants
- Utilized time to event methods based on intention-to-treat, global index calculated
  - CHD, invasive breast cancer, stroke, PE, colorectal cancer, endometrial cancer, hip fracture, and death
**Methods**

**Intervention**
- 1993-2002
- (2004 CEE alone)

**Original trial completion date**

**Instructed to stop study medication**

**Extension phase**
- 2005-2010

**Data in this study**

**Initial WHI:** Randomized to CEE/MPA (or CEE alone) or placebo

**Post-intervention**

**Post-stopping WHI:** Follow up for those providing additional consent
Results

<table>
<thead>
<tr>
<th>Post-Intervention</th>
<th>CEE + MPA</th>
<th>Diff/10,000 PY</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td></td>
<td>2</td>
<td>1.04 (0.89-1.23)</td>
<td>0.61</td>
</tr>
<tr>
<td>Breast CA</td>
<td></td>
<td>10</td>
<td>1.32 (1.08-1.61)</td>
<td>0.007</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td></td>
<td>0</td>
<td>1.01 (0.91-1.11)</td>
<td>0.90</td>
</tr>
<tr>
<td>Global index</td>
<td></td>
<td>4</td>
<td>1.03 (0.95-1.11)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

- Global index HR was not modified by age (p>0.99 for trend)
  - Absolute risks of adverse events were lower in younger than older women
Results

<table>
<thead>
<tr>
<th>Post-Intervention</th>
<th>CEE Alone</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diff/10,000 PY</td>
<td>HR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>CHD</td>
<td>-4</td>
<td>0.96</td>
<td>(0.77-1.19)</td>
</tr>
<tr>
<td>Breast CA</td>
<td>-7</td>
<td>0.80</td>
<td>(0.58-1.11)</td>
</tr>
<tr>
<td>All-cause Mortality</td>
<td>-7</td>
<td>0.96</td>
<td>(0.84-1.10)</td>
</tr>
<tr>
<td>Global index</td>
<td>-6</td>
<td>1.00</td>
<td>(0.90-1.12)</td>
</tr>
</tbody>
</table>

- Women in 50s had fewer events per 10,000 PY compared with women in 70s (p for trend, 0.02)
Conclusions

• Neither CEE + MPA nor CEE alone significantly affected all-cause mortality during or after the intervention phase
  – HT has a harmful effect on CHD risk among older women, results in younger women are inconclusive

• Risk–benefit ratio of HT is most favorable when initiated in younger menopausal women
  – Most risks and benefits from hormone therapy dissipate after stopping
Key Article

- Management of Menopausal Symptoms, ACOG Practice Bulletin #141, January 2014
  - ACOG. Obstet Gyne. 2014

- Level A Evidence:
  - Systemic HT is the most effective therapy for vasomotor symptoms, low dose has better side effect profile
  - Risks of combined systemic HT include VTE and breast cancer
  - It is recommended that providers individualize care and treat women with lowest effective dose for the shortest duration needed to relieve vasomotor symptoms
Take Home Messages

• For women early in menopause, risks are lowest for hormone therapy and once therapy is stopped these risks wane

• Marcia is young and healthy and would be a candidate for hormone therapy for her vasomotor symptoms; would recommend revisiting the use of hormones annually for her
Marcia, continued…

• Marcia decides she wants to use hormone therapy and asks what she should start. You have heard that transdermal methods might be safer, but are not entirely sure what to recommend beyond that…
Background

• No RCT comparisons of differing HT regimens and clinical CVD outcomes are available

• Transdermal HT delivery avoids first pass liver metabolism
  – Decreased effect on serum coagulation factors, triglycerides, CRP
  – More physiologic ratio of estradiol to estrone
The News

• *Hormone therapy dose, formulation, route of delivery, and risk of cardiovascular events in women: findings from the Women’s Health Initiative Observational Study*

• Aims
  – Compare different estrogen dose/formulation and risks for major CHD, stroke, CVD mortality, total CVD and all-cause mortality
Methods

• Prospective cohort study of 93,676 postmenopausal women aged 50-79
  – Clinic visit at baseline and 3 years
  – Annual mailed self-administered questionnaires
  – CVD events confirmed by medical record review

• Mean follow up time, 10.4 years

• Adjusted for age, race, smoking, activity, BMI, HTN, diabetes, use of lipid-lowering medication, hysterectomy, oophorectomy, education, income
## Results

<table>
<thead>
<tr>
<th></th>
<th>Transdermal HT vs Oral CEE</th>
<th>Oral estradiol vs Oral CEE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Major CHD</td>
<td>0.63 (0.37-1.06)</td>
<td>1.13 (0.79-1.61)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.87 (0.55-1.38)</td>
<td>0.64 (0.40-1.02)</td>
</tr>
<tr>
<td>Total CVD</td>
<td>0.82 (0.59-1.14)</td>
<td>0.93 (0.71-1.23)</td>
</tr>
<tr>
<td>CVD mortality</td>
<td>0.94 (0.50-1.74)</td>
<td>1.33 (0.84-2.12)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1.06 (0.78-1.44)</td>
<td>1.09 (0.83-1.43)</td>
</tr>
</tbody>
</table>
Conclusions

• CVD risk did not differ substantively among different formulations/routes of administration
  – Overall absolute risk of CVD in younger women was lower as compared with older

• Only a small percentage of women were using transdermal estrogen—not powered to fully see differences
Key Article #1

- **Lower Risk of Cardiovascular Events in Postmenopausal Women Taking Oral Estradiol Compared with Oral Conjugated Equine Estrogens**

- Retrospective case-control study comparing CV event risk associated with current CEE compared with estradiol use in a large HMO

<table>
<thead>
<tr>
<th>Event</th>
<th>Adjusted Odds Ratio (95% CI) [reference: estradiol use]</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE</td>
<td>2.08 (1.02-4.27)</td>
<td>0.045</td>
</tr>
<tr>
<td>MI</td>
<td>1.87 (0.91-3.84)</td>
<td>0.09</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.13 (0.55-2.31)</td>
<td>0.74</td>
</tr>
</tbody>
</table>
Key Article #2

• ACOG Committee Opinion: Postmenopausal Estrogen Therapy: Route of Administration and Risk of Venous Thromboembolism
  – ACOG Committee Opinion #556, April 2013

• Prothrombotic effect of estrogen is possibly related to high concentrations of estrogen in the liver due to first pass effect

• Transdermally administered estrogen has little or no effect in elevating prothrombotic substances
Take home messages

• Observational data suggest an increase in risk of MI with CEE compared with estradiol use
  – Did not reach statistical significance

• Transdermal estrogen has decreased risks of VTE compared with oral forms

• For Marcia, transdermal estrogen is safest, and it may be better to recommend estradiol over CEE
  – And she needs a progestin as she still has a uterus
Donna

• Donna is a 67 year old woman with significant vaginal atrophy. She has not been sexually active for some time and when asked if this is bothersome to her she admits it causes difficulties in her relationship with her husband. She is very hesitant to use hormones in any form because she reads a lot of articles about them and doesn’t think they are safe. She has significant pain with intercourse, no other major symptoms.

• What recommendations do you have?
Background

- VVA is associated with physical discomfort, sexual dysfunction, emotional distress, and reduced quality of life
- Incidence of VVA can be ~60%
- Current treatment options are only estrogen or vaginal moisturizer
The News

• *Ospemifene, a novel selective estrogen receptor modulator for treating dyspareunia associated with postmenopausal vulvar and vaginal atrophy*

• Aims
  – Assess the efficacy and safety of ospemifene for the treatment of dyspareunia
Methods

P: 605 women aged 40-80 postmenopausal women who self-reported mod-severe dyspareunia as most bothersome symptom
I: 60mg oral ospemifene daily for 12 weeks (N=303)
C: placebo daily for 12 weeks (N=302)
O: Change from baseline in:
  – % parabasal cells and % superficial cells in maturation index
  – Vaginal pH
  – Severity of dyspareunia

• Details: all study personnel, participants, and clinicians were blinded; analysis was done on an intention-to-treat basis (took at least 1 dose); vaginal exam done at week 4 and 12 along with symptom questionnaire
Results

**ITT**

<table>
<thead>
<tr>
<th>OSP</th>
<th>PBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1.5 (1.1)</td>
<td>0</td>
</tr>
</tbody>
</table>

**PP**

<table>
<thead>
<tr>
<th>OSP</th>
<th>PBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1.6 (1.1)</td>
<td>0</td>
</tr>
</tbody>
</table>

- NNT: 4
- NNT: 3
Results

- All 4 endpoints showed statistically significant improvement in both ITT and PP analysis.
- Severity of vaginal pain improved by 2-3 levels in 52.8% of ospemifene, 38.8% of placebo.

<table>
<thead>
<tr>
<th>Treatment-emergent AE</th>
<th>Ospemifene (n=303)</th>
<th>Placebo (n=302)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot flushes</td>
<td>20 (6.6)</td>
<td>13 (4.3)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>17 (5.6)</td>
<td>11 (3.6)</td>
</tr>
<tr>
<td>Vaginal candidiasis</td>
<td>14 (4.6)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Vaginal discharge</td>
<td>14 (4.6)</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Vulvar/vaginal mycotic infection</td>
<td>13 (4.3)</td>
<td>1 (0.3)</td>
</tr>
</tbody>
</table>
Conclusions

- Ospemifene induced beneficial improvement in vaginal epithelium and vaginal pH
  - Superior efficacy in reducing vaginal pain associated with sexual intercourse

- Hot flushes were the most common AE
  - only 4.6% in treatment group discontinuing due to AE
Key Article #1

• One-year long-term safety extension study of ospemifene for the treatment of vulvar and vaginal atrophy in postmenopausal women with a uterus

• 40wk extension after a 12wk Phase 3 efficacy and safety trial
  – 180 women enrolled
  – Most common adverse event was hot flushes (7.2%)
  – No cases of VTE or endometrial hyperplasia occurred in the study
Key Article #2


• <10% of women report their provider initiated a conversation about VVA

• 1st line therapy: lubricant with intercourse and vaginal moisturizer [Level A]

• Mod-severe VVA: low dose vaginal estrogen or ospemifene [Level A]
Take Home Messages

• Screen women for dyspareunia and VVA—it’s common and distressing for women

• Ospemifene is a SERM with apparent positive effects on VVA without endometrial or VTE events
  – Vasomotor symptoms are the most common side effect
  – Not for use in women with a history of breast cancer
  – FDA approved for mod-severe dyspareunia
Donna

• Donna took your advice and started ospemifene with significant improvement in her dyspareunia. Intercourse is no longer painful for her, however she now admits she has no libido and “is just not interested in it”.

• What options do you have to offer Donna now?
Background

• Low sexual desire among postmenopausal women is 6-10%
• Neurotransmitters help regulate sexual response
  – Serotonin inhibits sexual desire
• Flibanserin is believed to improve balance of systems that regulate sexual desire
  – 3 RCTs in premenopausal women have shown improvement in satisfying sexual events (SSE) and desire, a decrease in sexual distress, and was well-tolerated
The News

• *Efficacy and safety of flibanserin in postmenopausal women with hypoactive sexual desire disorder: results of SNOWDROP trial.*

• Aims:
  – Investigate efficacy and safety of flibanserin in naturally postmenopausal women with HSDD
Methods

**P**: 949 heterosexual women, any age, with naturally occurring menopause and a diagnosis of HSDD lasting 6 months

**I**: 100mg oral flibanserin qhs for 24 weeks (N=468)

**C**: placebo daily for 24 weeks (N=481)

**O**: change from baseline in number of SSE and in Female Sexual Function Index-desire score

- Details: e-Diary prompted daily entry re: SSE; analysis approach based on FDA protocol for therapies for HSDD
Results

Change in number of SSE
Results

Change in Female Sexual Function Index - desire domain
Conclusions

• First non-hormonal treatment to show effectiveness in treating HSDD in postmenopausal women
  – Most common side effects were dizziness, somnolence, nausea, and headache

• Study limited to women in a stable heterosexual relationship with a sexually functional partner without any other psychiatric d/o (including depression)
Take Home Messages

- Flibanserin is a novel non-hormonal therapy for HSDD…
  that is not yet FDA-approved.

- As of February, 2014 the FDA again denied the approval of flibanserin and requested 3 more safety studies.

- Continue to utilize a multifactorial approach to improving libido and HSDD including lifestyle, cognitive-behavioral therapy, attention to relationship, etc.
Bone Health

Judith M.E. Walsh, MD, MPH
University of California,
San Francisco
Bonnie Bony

• Bonnie Bony is a 72 year old woman who wants to know when she should have her next bone mineral density test. Her last BMD was 2 years ago and showed osteopenia with a t score of -1.8. What do you tell her?
USPSTF Recommendations

• Screen all women age 65 and older
  – Evidence for screening is indirect
• Screen younger women whose fracture risk is equal to or greater than a 65 year old white woman who has no additional risk factors
• “Evidence is lacking about optimal intervals for repeated screening”
  – A minimum of 2 years may be needed to reliably measure a change in BMD
  – Longer intervals may be needed to improve fracture risk prediction

» USPSTF 2011
BMD testing

- Medicare pays for BMD every two years regardless of baseline BMD
- Is repeat BMD useful?
- Does change in BMD provide additional information about fracture risk?
Monitoring Guidelines

• All recommend follow-up monitoring but no consensus on site and frequency
• What is “treatment failure?”
• ISCD: DEXA spine and hip when expected change in BMD exceeds LSC expected on bone densitometer
  – Typically every 1-2 years
  – Less often once stable
• AACE: DEXA spine and hip every 1-2 years until stability
• NAMS: DXA hip every 2 years
• Question: What are you going to do?
The News

• *Repeat bone mineral density screening and prediction of hip and major osteoporotic fracture.*

• *Aim:* To determine whether BMD changes after 4 years provide additional information on fracture risk and to quantify the change in fracture risk classification after a second BMD measure.
Methods

• Framingham Osteoporosis Study population based cohort of 310 men and 492 women
  – Two BMD measures from 1987 to 1999
• Outcome: risk of hip or major osteoporotic fracture through 2009 or 12 years after second BMD measure
• Net Reclassification Index (NRI):
  – Quantifies change in risk classification after a second BMD measure
  – High risk: Risk of hip fracture 3% or greater or major osteoporotic fracture 20% or greater (vs low risk)
Results

- Mean age 74.8 years
- Mean BMD change -0.6% per year
- Median follow up 9.6 years
- NRI increased proportion classified as high risk by 3.9% and decreased the proportion defined as low risk by 2.2%
- Adding BMD change to a model that included baseline BMD did not improve performance of the ROC curve
  - AUC baseline 0.71 (0.65-0.67) vs 0.72 (0.66-0.79)
ROC Curves for Hip and Major Osteoporotic Fractures

Figure Legend:
Receiver Operating Characteristic Curves for Models Investigating Fracture in Older Adults From the Framingham Osteoporosis Study. BMD indicates bone mineral density. All models are adjusted for age, sex, body mass index, weight loss (per pound), and history of fracture measured at the time of the second BMD test. Models are defined in the Methods section.
Conclusion

- In untreated men and women with a mean age of 75, a repeat BMD after 4 years did not meaningfully improve the prediction of major hip or osteoporotic fracture.
Take home message

• Repeating a BMD after 4 years to improve fracture risk prediction may not be necessary in adults of this age untreated for osteoporosis.
Bea Brittle

• Bea Brittle is a 68 year old woman whom you started on alendronate three years ago for a hip BMD t score of -2.8. She keeps hearing bad things about the bisphosphonates and wonders if she should switch to a different drug. What do you tell her?
Osteoporosis Treatment

• Bisphosphonates are considered first line therapy
• Continued concern about some of the rare side effects of bisphosphonates
  – Osteonecrosis of the Jaw
  – Atypical femoral fractures
• What about other treatment options or combinations
  – To date there has been no evidence to suggest that combination therapy is beneficial
The News

• *Denosumab compared with ibandronate in postmenopausal women previously treated with bisphosphonate: a randomized open-label trial*
  – Recknor et al. Obstetrics and Gynecology June 2013

• Aim: To compare the efficacy and safety of denosumab to ibandronate in postmenopausal women with low BMD previously treated with a bisphosphonate
Methods

- Randomized open-label study
- Post-menopausal women received 60 mg denosumab subQ every 6 months vs ibandronate 150 mg a month
- 12 month follow-up
- Outcomes changes in BMD and serum C-telopeptide
Results

• Average duration prior bisphosphonate use was 16.8 months

• BMD increased more in women on denosumab
  – Total hip (2.3 vs 1.1%: p<0.001)
  – Lumbar Spine (4.1% vs 2.0%: p<0.001)
  – No fracture outcomes

• Higher rate of serious adverse events in denosumab group
  – 9.5% vs 5.4%: p=.046
  – Not clustered in any organ system
  – No new safety risks
The News

• *Romosozumab in postmenopausal women with low bone mineral density*
  – Mcclung et al. NEJM Jan 2014

• Aim: To evaluate the efficacy and safety of romosozumab in postmenopausal women with low bone mass
Background

- Sclerostin is an osteocyte-derived inhibitor of osteoblast activity
- Individuals with hereditary deficiency of sclerostin have high bone mass and resistance to fractures
- Monoclonal antibody romosozumab binds to sclerostin and increases bone formation
Methods

• 419 post-menopausal women with low BMD randomized to one of 8 treatment arms
  – Placebo and two active comparators

• Primary endpoint was percentage change in BMD at lumbar spine at 12 months
Study Schema to 12 Months.

Placebo (N=52 [every 3 mo, N=22; monthly, N=30])
Romosozumab 140 mg every 3 mo (N=54)
Romosozumab 210 mg every 3 mo (N=53)
Romosozumab 70 mg monthly (N=51)
Romosozumab 140 mg monthly (N=51)
Romosozumab 210 mg monthly (N=52)
Alendronate 70 mg weekly (N=51)
Teriparatide 20 μg daily (N=55)

Results: BMD Changes

Adverse events similar except for mild injection-site reactions with romosozumab

Conclusion

• In postmenopausal women with low bone mass, romosozumab is associated with increased bone mineral density and bone formation
The News

• *Teriparatide and denosumab, alone or combined, in women with postmenopausal osteoporosis: the DATA study randomised trial.*
  – Tsai et al. Lancet July 2013

• Aim: To compare combined teriparatide and denosumab with either agent alone
Methods

• RCT of 100 postmenopausal women with “high fracture risk”
  – T score -2.5 or less
  – T score -2.0 or less with one other risk factor
  – T score -1.0 or less with history of fragility fracture

• Treatments
  – 20 µg teriparatide daily
  – 60 mg denosumab every 6 months
  – Both

• Main outcome is BMD at 6 months
Results

Bone Mineral density at multiple sites increased significantly more with combined treatment than with either agent alone.
Conclusion

• Combined teriparatide and denosumab increased BMD more than either agent alone and more than has been reported with other approved therapies
Take home message

- New therapeutic options for osteoporosis are promising but limited by lack of fracture outcomes
- May be appropriate for selected high risk women
- Although previous studies of combined therapy have not suggested benefit, the combination of teriparatide and denosumab is promising and deserves further study
Back to Bea......

• There is currently no compelling reason for her to switch from a bisphosphonate to any other osteoporosis therapy
Questions?