Hot Topics in Women’s Health

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The speaker has no actual or potential disclosures to report.
Session Goals – Updates Related to...

- FDA Pregnancy and Lactation Labeling rule
- Teen and OTC contraception
- Cervical cancer prevention and HPV vaccination
- Osteoporosis diagnostic tests and pharmacotherapy monitoring
- Menopausal symptom treatment
Pregnancy and Lactation Labeling Rule

PLLRR
Current pregnancy risk categories introduced in 1979, but multiple issues identified

Updated PLLR approved December 3, 2014 and becomes active June 30, 2015

Includes elimination of risk categories

Section 8.1 - Pregnancy

- Pregnancy registry information, if one exists

- Summary of risks

- Information to assist in making prescribing decisions and in providing patient counseling
  - Disease-associated maternal and fetal risks
  - Dose adjustments
  - Maternal ADRs
  - Fetal/neonatal ADRs
  - Drug impact on labor and/or deliver
Section 8.2 - Lactation

- Summary of risks (on child and on milk production)
- Summary risk-to-benefit statement
- Methods for minimizing drug exposure in child
- Interventions for monitoring and mitigating adverse reactions
Section 8.3 - Females and Males of Reproductive Potential

- Section will only be included if relevant
- Information regarding the need for pregnancy testing and/or contraception before, during, or after use of therapy
- Information regarding impact of drug on fertility
## PLLR Implementation Timeline

<table>
<thead>
<tr>
<th>NDA, BLA, or ES.....</th>
<th>Date of Compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Submitted on or after 06-30-2015</td>
<td>Must be part of application</td>
</tr>
<tr>
<td>Submitted prior to 06-30-2015, but approval pending</td>
<td>By 06-30-2019 or on date approved, whichever is later date</td>
</tr>
<tr>
<td>Approved between 06-30-2001 to 06-29-2002 and between 06-30-2005 to 06-29-2007</td>
<td>By 06-30-2018</td>
</tr>
<tr>
<td>Approved between 06-30-2007 to 06-29-2015</td>
<td>By 06-30-2019</td>
</tr>
<tr>
<td>Approved between 06-30-2002 to 06-29-2005</td>
<td>By 06-30-2020</td>
</tr>
<tr>
<td>Approved prior to 06-30-2001</td>
<td>Not subject to new labeling. Must remove pregnancy category by 2018</td>
</tr>
</tbody>
</table>

NDA = new drug application; BLA = biologics license application; ES = efficacy supplement
Contraception Update

Teens and OTC Status
The Problem...Unintended Pregnancies

- 50% of all pregnancies are unintended (80% teen)

- Unintended pregnancy costs $11.1 billion annually

- Women with unintended pregnancy are...
  - More likely to smoke/drink during pregnancy
  - Less likely to obtain prenatal care
  - Less likely to breastfeed

- Most cited reasons for unintended pregnancy
  - Access
  - Cost
  - Adherence

Solution #1 – Already Implemented
OTC Levonorgestrel only Emergency Contraception

- As of March 2014, truly OTC to all ages and genders

- Remaining issues
  - Labeling still states must use within 72 hours, but can actually be taken up to 120 hours after unprotected sex
  - Lack of understanding regarding mechanism of action may limit recommendations for use from healthcare providers
  - Although safe to use multiple doses in a single cycle, less effective and more expensive than daily contraception
Solution #2 – Partially Implemented
Insurance Coverage of Contraception

- Affordable Care Act has increased access to zero co-pay contraception
- Continuing issues
  - Uninsured patients
  - ACA Exemptions for religious objections
  - OTC products are not covered unless a Rx is acquired
  - Medicaid coverage is still up to each individual State
  - Quantity limits
- Recommendations
  - ACOG, AAFP, and ACCP recommend true OTC coverage by insurance
  - ACOG recommends coverage of 3-12 months supplies
Solution #3 – Improve Teenage Use
New Policy Statement by AAP

- Supports abstinence education, but recognizes limitations
- Encourages pediatricians to counsel on contraceptive choices from those that are most to least effective
- Considers long-acting reversible contraceptives as first-line agents
  - Single-rod implant
  - IUD
- Supports use of DMPA and contraceptive patch despite risks
- Pelvic exam not required before initiation of any method
Solution #4 – OTC Hormonal Contraception

- **Rationale**
  - Improves access
  - Patients can self-screen for contraindications as well as clinicians
  - Women are interested

- **Switch to OTC supported by the**
  - American Medical Association
  - American College of Obstetricians and Gynecologists
  - American Academy of Family Physicians
  - American College of Clinical Pharmacy Women’s Health PRN

- **For further information, see visit ocsotc.org**

ACOG Committee Opinion available in Obstet Gynecol 2012;120:1527-31
AAFP Policy Statement available at [http://www.aafp.org/about/policies/all/otc-oral-contraceptives.html](http://www.aafp.org/about/policies/all/otc-oral-contraceptives.html)
ACCP Women’s Health PRN Opinion available in Pharmacotherapy 2011;31:424-37
Cancer Update

Cervical Cancer Screening and HPV Vaccination
# Quick Review – Cervical Cancer Screening

**USPSTF, ACOG, and ACS 2012**

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 21-65 years</td>
<td>Pap smear q 3 years</td>
</tr>
<tr>
<td>Age 30-65 years</td>
<td>Pap smear q 3 years, or Pap smear + HPV testing q 5 years*</td>
</tr>
<tr>
<td>Age 20 and younger</td>
<td>Do not screen</td>
</tr>
<tr>
<td>Age 66 and older</td>
<td>Do not screen if patient has had adequate prior screening and is not high risk for cancer</td>
</tr>
<tr>
<td>After hysterectomy</td>
<td>Do not screen if cervix removed and no prior history of neoplasia or high-grade lesions</td>
</tr>
</tbody>
</table>

* Method preferred by both ACOG and ACA

Per American Cancer Society data, prevalence of screening is only ~80% nationally.

American Cancer Society Guideline available in CA Cancer J Clin 2015;65:30-54.
Test Your Knowledge
ACIP HPV Vaccine Recommendations

• Which gender(s)

• Ideal age to start series

• Maximum age

• How many doses in series – when are they given?

• What products are on the market and who can receive them?
Status of HPV Vaccination (2013)

Adolescent coverage for ages 13-17

<table>
<thead>
<tr>
<th></th>
<th>At least 1 dose</th>
<th>At least 2 doses</th>
<th>All 3 doses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Girls</strong></td>
<td>57.3%</td>
<td>47.7%</td>
<td>37.6%</td>
</tr>
<tr>
<td><strong>Boys</strong></td>
<td>34.6%</td>
<td>23.5%</td>
<td>13.9%</td>
</tr>
</tbody>
</table>

- **Girls**
  - Not recommended: 13%
  - Lack of knowledge: 15.5%
  - Not needed or necessary: 14.7%
  - Not sexually active: 11.3%
  - Safety concerns: 14.2%

- **Boys**
  - Not recommended: 22.8%
  - Lack of knowledge: 15.5%
  - Not needed or necessary: 17.9%
  - Not sexually active: 7.7%
  - Safety concerns: 6.9%


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What’s New?
HPV9 Vaccine Approved December 2014

Included Serotypes

<table>
<thead>
<tr>
<th>Serotypes</th>
<th>HPV2 (Cervarix)</th>
<th>HPV4 (Gardasil)</th>
<th>HPV9 (Gardasil 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16, 18</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>6, 11</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>31, 33, 45, 52, 58</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

Other high-risk serotypes still absent from all HPV vaccines = 35, 39, 51, 56, 59, 66, and 68

Estimated that by using HPV9 instead of HPV4:
Prevention of cervical cancer will increase from 70 to 90%
Prevention of CIN2/CIN3 will increase from 30 to 80%

October 2014 ACIP Meeting Minutes available at
HPV9 Indications and Side Effects

- Females aged 9-26 and Males aged 9-15

- 3-dose series at 0, 2, and 6 months

- Higher incidence of mild to moderate injection-site reactions as compared to HPV4, otherwise ADR profile similar

- Anticipated that HPV4 will be discontinued in 12-18 months

- Vote anticipated by ACIP regarding HPV9 recommendations at next week’s meeting

Gardasil 9 Package Insert

What’s New?
Two-dose Schedules

- Already being used in Europe if first dose prior to age 15
- Most studies giving at 0 and 6 months
- Data suggests 2-dose schedule is non-inferior to 3-dose schedule
- No current submissions to FDA to consider 2-dose schedule for any product – not anticipated that ACIP will act upon this issue yet

Osteoporosis Update

Screening and Monitoring
Role of DXA

Types

• Peripheral DXA (pDXA) – screening
  • Central DXA (cDXA) – diagnosis
    • L2-L4
    • Hip (total hip and femoral neck)

Interpretation: BMD converted to scores

• T-score
  (SD of BMD from young adult, sex-matched, reference population)

• Z-score
  (SD of BMD from age, sex, and ethnicity matched reference population)

If hip or spine not able to be measured, one-third radius site may be used for diagnosis
Role of Vertebral Imaging

- Vertebral fractures highly prevalent, yet often asymptomatic
- Radiographically confirmed fractures are sign of poor bone quality and strength, and strongly predict future fractures
- Only mechanism to diagnose such fractures is via imaging
- Can be performed in conjunction with DXA
# National Osteoporosis Foundation Testing Guidelines

## Central DXA

- Women ≥ age 65 and men ≥ age 70 regardless of clinical risk factors
- Younger postmenopausal women, women in menopausal transition, and men aged 50-69 with clinical risk factors
- Adults who have any fracture after age 50
- Adults with a condition or taking a medication associated with low bone mass or bone loss

## Vertebral Imaging

- Women ≥ age 70 and men ≥ age 80 if T-score < -1 at any site
- Women aged 65-69 and men aged 70-79 if T-score ≤ -1.5 at any site
- Any woman or man ≥ age 50 if one of the following present:
  - Low trauma fracture
  - Historical height loss of ≥ 1.5 inches (4 cm)
  - Prospective height loss of ≥ 0.8 inches (2 cm)
  - Recent or ongoing long term glucocorticoid treatment

Repeat Testing

cDXA

• Repeat testing for screening only needed “when medically appropriate”

• Repeat testing if placed on pharmacologic therapy is q 2 years

Vertebral imaging – no need to repeat unless:

• Prospective height loss documented

• New back pain or postural change noted

• Chest x-ray findings suggest vertebral change

Updates in Menopause
### Scope of the Problem

<table>
<thead>
<tr>
<th>Vasomotor Symptoms</th>
<th>Vulvovaginal Atrophy Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>75% of all women</td>
<td>50% of all women</td>
</tr>
<tr>
<td>Symptoms peak at time of menopausal transition, then diminish over time</td>
<td>Symptoms are progressive</td>
</tr>
</tbody>
</table>

- Hot flashes
- Poor sleep quality
- Irritability
- Difficulty concentrating
- Diminished QOL
- Dryness
- Irritation
- Dysuria
- Vaginal discharge
- Painful intercourse

Side note – NAMS is recommending use of the term “genitourinary syndrome of menopause” (GSM) instead of vulvovaginal atrophy
Timeline of Hormone Therapy

ET use for symptom relief

1960s

Observational studies show CHD, osteoporosis, and dementia protection. Endometrial protection by progestin discovered.

ET/EPT used for chronic disease prevention

1980s

1990s

HERS data published – harm for secondary CHD prevention

1998

EPT arm of WHI stopped early due to breast CA, CHD, and CVA

2002

ET arm of WHI stopped early due to CVA

2004
Problems with the WHI Study

- **Study Objectives**
  - NOT menopausal symptoms
  - Goal: primary prevention of CHD

- **The Patients**
  - Average age 65
  - Only 15% age 50-54 and 20% age 55-59

- **The Treatment**
  - Only one product/route (CEE +/- MPA)
  - Speculation that safety profile may differ among products and routes
Serious ADRs

• CHD – likely related to timing of initiation
  • *Benefit* if started therapy within 10 yrs of menopause
  • *Harm* if started therapy more than 10 yrs after menopause

• CVA (ischemic) – likely related to age at initiation
  • *No effect* if started therapy age 50-59
  • *Harm* if started therapy age 60 or older

• VTE – increased risk, but
  • Highest risk in first 1-2 years, then diminishes
  • EPT risk greater than ET risk
  • Low overall risk if < age 60

Breast cancer – possibly related to use of progestin and timing of initiation

- Most harm seen in EPT users. In some studies, ET users had breast cancer reduction.
- Most harm observed when therapy started within 5 yrs of menopause. If started later, risk seems negligible.
- Most harm seen after 3 years of EPT use.
- Data starting to suggest that sequential progestin might confer lower risk than continuous progestin.

None of these risks exist with vaginal ET therapy!
What About Compounded Bio-identical Therapy?

Expert organizations and FDA recommend *against* use

- No evidence to support superiority claims
- No evidence to support use of salivary, serum, or urinary testing
- Lack of safety data
- Concerns over variances in potency and purity
- FDA-approved products include “natural” hormone options

So What’s New?

New Clinical Trials
New(er) Drugs
New Guidelines
Recently Completed Trial – KEEPS

Kronos Early Estrogen Prevention Study

• EPT started within 3 years of menopause
• [CEE 0.45 mg oral vs. 50 mcg patch vs. placebo] plus cyclic oral micronized progestin
• Four years duration, n = 727
• Outcomes = efficacy and safety
• Initial results presented at 2012 NAMS meeting
  • Good symptom relief
  • No increases in CHD, VTE, CVA or breast cancer

http://www.menopause.org/annual-meetings/2012-meeting/keeps-report
Recently Completed Trial – ELITE

Early Versus Late Intervention Trial with Estrogen

- Early (< 6 yrs) vs. Late (> 10 yrs) starters on EPT
- [Estradiol 1 mg oral vs. placebo] plus cyclic vaginal progestin gel
- Six years duration, n = 643
- Outcomes = cardiovascular and neurocognitive
- Initial cardiovascular results presented at 2014 AHA meeting
  - Reduced carotid artery intima media thickness in early start group
  - No change in late start group

http://circ.ahajournals.org.une.idm.oclc.org/content/130/Suppl_2/A13283.abstract?sid=db1333ab-d4bb-4508-b0ba-ac7ddc1f522f
Ongoing Trials
Data found on clinicaltrials.gov

• A Phase 3 Safety and Efficacy Study of the Combination of Estradiol and Progesterone to Treat Vasomotor Symptoms in Women with and Intact Uterus (REPLENISH)
  • [Estradiol + oral micronized progesterone] vs. placebo
  • 12 months duration
  • Outcomes = vasomotor symptoms and endometrial safety

• Effects of Estradiol and Soy on Menopausal Symptoms (RISE)
  • Estradiol-medroxyprogesterone vs. Novasoy® vs. Placebo
  • 18 weeks duration
  • Outcome = quality of life
## Available Pharmacologic Modalities

### Vasomotor
- ET/EPT
- ET/SERM combo
  - CE/bazedoxifene (Duavee)
- SSRI
  - Paroxetine (Brisdelle)
- Non-FDA approved
  - Other SSRIs/SNRIs
  - Clonidine
  - Gabapentin
  - Black cohosh
  - Soy isoflavones

### Vulvovaginal Atrophy
- ET/EPT
- ET/SERM combo
  - CE/bazedoxifene (Duavee)
- SERM
  - Ospemifene (Osphena)
Paroxetine for Vasomotor Symptoms
Brisdelle®

- Approved July 2013
- Mechanism of action = increased serotonin activity at 2c receptors which helps to inhibit thermoregulatory center release of heat
- Dose = 7.5 mg po capsule at bedtime
- Two placebo-controlled trials led to approval (12- and 24-weeks)
  - Both studies showed statistical reductions in hot flash frequency and severity
  - In 24-week study, % responders (≥ 50% reduction in frequency of moderate to severe hot flashes) was 47.5% paroxetine vs. 36.3% placebo
  - Side effects meaningfully greater than placebo = nausea, fatigue, and dizziness

Clinical pearl – “responders” to hormone therapy using above definition usually > 80%

<table>
<thead>
<tr>
<th></th>
<th>Bone</th>
<th>Breast</th>
<th>Vagina</th>
<th>Uterus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bazedoxifene</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Ospemifene</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>neutral</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>neutral</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
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</table>
Ospemifene for Vulvovaginal Atrophy
Osphena™

- Approved March 2013
- Dose = 60 mg po once daily with food
- Three placebo-controlled trials led to approval
  - Symptom improvement measured using Likert scale for bothersome moderate-to-severe symptoms of vaginal dryness or dyspareunia (0 = no symptoms, 1 = mild, 2 = moderate, 3 = severe)
  - Baseline scores typically in moderate to severe range
  - Vaginal dryness scores decreased about 0.4 pts greater than placebo
  - Dyspareunia scores decreased about 0.2-0.3 pts greater than placebo
  - Side effects = hot flashes, vaginal candidiasis, and UTI

Conj. Estrogens-Bazedoxifene for Vasomotor Sx
Duavee®

• Approved October 2013
• Dose = 0.45/20 mg po once daily
• SMART-1 and SMART-2
  • 12-week trials
  • Improvement in hot flashes, dyspareunia, and menopause-specific QOL scores
  • Adverse effects similar to placebo, no endometrial issues

Clinical pearl – also indicated for prevention of postmenopausal osteoporosis

NAMS 2013 – Position Statement on Treating Vulvovaginal Atrophy

• First-line for symptomatic patients = Nonhormonal lubricants and sexual activity +/- long-acting vaginal moisturizers
• Moderate to severe symptoms or first-line failure = Estrogen therapy
• Alternate option = Ospemifene
• Concurrent progestin not indicated for vaginal products
• Vaginal ET and ospemifene may be continued indefinitely
Global Consensus Statement Recommendations

- Benefits outweigh risks if age < 60 and within 10 years of menopause
- Most effective treatment available for vasomotor symptoms
- ET may decrease CVD risk and all-cause mortality in this population
- EPT shows no significant increase in CVD in this population
- Although oral therapy increased CVA and VTE, absolute rates are very low in this population
- Breast cancer is related to progesterone and duration of use
- If only vaginal symptoms, use local therapy
- EPT recommended in those with premature ovarian insufficiency until average age of natural menopause (~51 years)
- Compounded bio-identical hormone therapy should be avoided
NAMS Decision Algorithm

Moderate-to-severe hot flashes and/or night sweats? (and inadequate response to behavioral/lifestyle modifications)

No

Genitourinary symptoms such as vaginal dryness or pain with intercourse/sexual activity?

Yes

Free of breast cancer, endometrial cancer, venous thromboembolism, CHD, stroke/TIA, and other contraindications to HT and interested in considering HT?

Yes

Free of breast cancer, endometrial cancer, and other hormone-sensitive cancers?

Avoid HT

No

Prior Hysterectomy?

Yes

No

Consider low-dose paroxetine or other well-studied SSRIs/SNRIs (venlafaxine, escitalopram, others) if no contraindications.

No

Avoid SSRIs/SNRIs. Consider gabapentin, pregabalin, or clonidine.

Vaginal lubricants and/or moisturizers.

Vaginal lubricants and/or moisturizers. Consider low-dose vaginal estrogen if response is inadequate. Osanifemone may be an option for women who prefer a non-estrogen oral treatment, if no contraindications.

CVD Risk Over 10 Years

ACC/AHA Risk prediction score

Low (<5%)

Moderate (5% to 10%)

High (>10%)

HT OK (choose transdermal)

HT OK (choose transdermal)

Avoid HT

HT OK

HT OK

Avoid HT

Avoid HT

Avoid HT

Avoid HT

Assess CVD risk and time since menopause onset

Years Since Menopause Onset

≤5

6 to 10

>10

Adequate control of hot flashes?

Yes

No

Continue low-dose paroxetine or other SSRIs/SNRIs.

Adjust dose or consider gabapentin, pregabalin, or clonidine.

Decision about duration of use: continued moderate-to-severe symptoms; patient preference; weigh baseline risks of breast cancer, CVD, and osteoporosis.