What’s New in Women’s Health 2014: Hormones and Beyond

Presentation Objectives

- Recognize new products and new indications/warnings for existing products that may impact women’s health throughout the lifecycle
- Prescribe medications for women during pregnancy and postpartum period with appropriate consideration of risks and benefits
- Recommend methods of hormonal contraception with consideration of risks/benefits and individual preferences
- Discuss the current evidence and controversies regarding the use of estrogen and estrogen-progestin regimens for the treatment of menopausal symptoms

Young Adulthood and Child-bearing Years
Contraception

- New products
  - New oral contraceptive products
  - Nexplanon®
  - Skyla®
- Treatment issues
  - Hormonal contraceptives and risk of VTE
  - Migraines and OCPs
  - Weight and hormonal contraceptive failures
  - Contraceptive choice and coexisting medical conditions
New Hormonal Contraceptives and Delivery Systems

- Multi-phasic versus monophasic
- Extended cycle
- Folic acid and iron combinations
- Progestin only
  - Once weekly norethindrone contraceptive patch (FDA approval denied 12/2013)

Monophasic vs ‘phasic’ COCs

- Monophasic
  - Same amount of estrogen and progestin per active tablet
- Multi- phasic
  - Progestin and/or estrogen dose varies depending on time in cycle
  - May provide lower total hormone dose per cycle
  - No convincing evidence of any advantages or less adverse effects compared with monophasic COCs

Extended Cycle “Period Optional” Regimens

- May increase efficacy and adherence
- Decrease some OC and menstrual cycle-related side effects
- Commercially available products vary from cycles of 24-84 days to continuous active tablets per cycle
  - Examples: Lo Loestrin-24 Fe®, Seasonique®, Amethyst®
- Can actually use any COC, patch, ring as extended cycle—just skip placebo week
- Can be used for brief manipulation of a cycle (ex., to avoid menses during a vacation)
Extended cycle "Period Optional" COCs

Potential Benefits

- May result in less hormonal fluctuations and shorter menstrual periods
  - may improve mood, headaches, pain scores and reduce general tiredness and irritation
- Long term effects of continuous regimens have not been studied
- Impact of additional days of hormones on thromboembolic risk is unknown
- Effect of prolonged amenorrhea on fertility uncertain

New Oral Contraceptive Products

Lo Loestrin Fe®

- Extended cycle, low dose estrogen, with iron
- 10 mcg ethinyl estradiol/1 mg norethindrone acetate per 24 tablets plus 2 pills with only 10 mcg ethinyl estradiol per tablet and two additional placebo tablets with 75 mg ferrous fumarate (25mg elemental iron)
  - Theoretically less breakthrough bleeding
  - No direct comparisons with other low-dose COCs
  - If iron supplementation required, separate iron containing product is required
  - Place in therapy: women intolerant of estrogen related side effects, nonsmoking perimenopausal women

Beyaz®

- 20 mcg ethinyl estradiol/3 mg drospirenone per 24 tablets
  - Each tab also contains 0.451 mg levomefolate (0.4 mg folic acid); 4 ‘placebo’ tablets also contain levomefolate
  - Adverse effects: hyperkalemia from drospirenone
  - No clinically significant difference between folic acid and levomefolate in physiological activity
  - Product more expensive than traditional monophasic pill plus generic folic acid
  - Also FDA approved to treat symptoms of PMDD and to treat moderate acne in women 14 years and older
New Oral Contraceptive Products

**Natazia®**

- 4 phase COC with estradiol valerate and dienogest
  - Estradiol valerate - metabolized to estradiol
  - Biological effect of 2mg similar to 20 mcg ethinyl estradiol
  - Dienogest – 19-nortestosterone derivative
  - Strong effect on endometrium and antiandrogenic activity
- Dosage: Days 1-2 3mg estradiol alone; days 3-7 2mg/2mg; days 8-24 2mg/3mg; days 25-26 1mg alone; days 27-28 placebo

New Oral Contraceptive Products

**Quartette®**

- 3 month (84 day) extended cycle COC with variable estrogen content combined with 0.15mg levonorgestrel per pill
  - EE 20 mcg x 42 days, 25 mcg x 21 days, 30 mcg x 21 days, then 10 mcg x 7 days
- Stepped estrogen promoted to cause less breakthrough bleeding but no comparison studies with other products
- Significantly more expensive/no more effective than branded generic monophasic pills

New Oral Contraceptive Products

**Nexplanon®**

- Originally marketed as Implanon®
  - Implantable single rod progestin only (etonorgestrel) which provides contraception for up to 3 years
  - Irregular bleeding: most common reason for removal (13%)
- Nexplanon® has preloaded applicator to make insertion easier with more accurate placement
- Nexplanon® is radiopaque which may aid with removal
- Does not appear to be associated with bone loss
- Quicker return to fertility compared with Depo-Provera®
Skyla®

- First new IUD in 12 years
  - T-shaped; smallest of all marketed IUDs
- Releases levonorgestrel 14 mcg/day initially and decreases gradually over 3 years to 5 mcg/day
  - Mirena® releases levonorgestrel 20 mcg/day initially and decreases over 5 years to 10 mcg/day
- No evidence that the lower dose of levonorgestrel translates into lower incidence of progestin-related adverse effects
- Cumulative 3 year pregnancy rate 0.9%

Effectiveness of Emergency Contraception in Overweight Women

- European manufacturer of NorLevo® (levonorgestrel) has recently changed product label to reflect concerns about potential for pregnancy when used by women who are overweight or obese
  - Product same as US product Plan B One-Step®
- Statement to be included “studies suggest NorLevo® is less effective in women over 165 pounds (75 kg) and not effective in women over 175 pounds (80 kg)

Effectiveness of Emergency Contraception in Overweight Women

- Exact mechanism for reduced efficacy not known
  - ? Delay in time to steady state and prolonged half-life
- Alternatives
  - Ulipristal (Ella®) – recent data also indicated increased failure rates in obese women
  - Copper IUD insertion within 5 days of unprotected intercourse
- FDA reviewing the data for potential label changes
- Women should be made aware of information when purchasing emergency contraception
**Ulipristal (Ella®)**

- Progesterone agonist/antagonist structurally similar to mifepristone (RU-486)
- Delays follicular rupture; may interfere with implantation after fertilization
  - Mechanism varies depending on where woman is in menstrual cycle
- Clinical studies indicate ulipristal is more effective than levonorgestrel when taken between 3 and 5 days after unprotected intercourse
  - Effectiveness at 72 hours similar to levonorgestrel

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**Hormonal Contraceptives and Risk of Venous Thromboembolism**

- Are the benefits worth the risk?
- Is risk related to just the estrogen component or does the progestin component play a role?
- Is risk dose dependent?
- Is risk delivery system specific?

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**Oral Contraceptive Use and Risk of Venous Thromboembolism**

- Risk of VTE in current users of COCs 2-3 times the risk of nonusers
  - Absolute risk is low 8-10 events per 10,000 women-years
    - Still lower than increased risk of VTE with pregnancy and postpartum period
  - Risk is higher in the first 6 months to one year of OCP use, particularly among first-time users
  - Increased risk of post-op VTE if OCPs used during month prior to surgery
  - Risk doubled in users of OCPs with higher estrogen doses
  - Risk factors: age, previous personal history of VTE, obesity, trauma, immobility, coagulopathies

Arch Int Med 2004;164:1365-76
Ann Intern Med 2005;143:59705
Oral Contraceptive Use and Risk of Venous Thromboembolism
Is it related to Progestin component?

- Epidemiologic studies in 1990’s linked third generation progestin desogestrel and gestodene containing pills with increased risk of thromboembolism
  - FDA label includes data from studies; evidence not felt strong enough to remove products from market
- Recent observational studies have also called into question the safety of contraceptives containing drospirenone as well as desogestrel
  - Public Citizen’s Health Group has added drospirenone containing COCs to their “DO Not Use Drug List” due to concerns over hyperkalemia

Drospirenone and VTE Risk

- Six studies have been published which evaluate the relationship of drospirenone and VTE risk
  - results mixed: 4 with variable risk, 2 no increased risk
- FDA has recently concluded that drospirenone-containing birth control pills may be associated with a higher risk for blood clots than other progestin-containing pills
  - Studies reviewed did not provide consistent estimates of the comparative risk of blood clots between birth control pills that contain drospirenone and those that do not.
  - Studies also did not account for important patient characteristics (known and unknown) that may influence prescribing and that likely affect the risk of blood clots.

Putting VTE Risk into Perspective

- Diagram showing VTE risk in different states:
  - Non-Pregnant Non-COC user: Range from 0 to 8
  - COC-user: Range from 0 to 8
  - Pregnancy: Range from 0 to 28
  - Postpartum (12 weeks only): Range from 0 to 28

* Pregnancy data based on actual duration of pregnancy in the reference studies. Based on a model assumption that pregnancy duration is nine months, the rate is 7 to 27 per 10,000 WY.
VTE Risk with Non-oral Hormonal Contraception

- Observational study in Denmark 2001-2010
  - Analyzed data from 1.6 million non-pregnant women 15-49 years of age
- Relative risks of use of patch (compared with non-use) was 7.9, RR 6.5 for ring users, RR 4.2 for pill users
- **Absolute** rates of VTE in patch users was low (9.7 per 10,000 woman years of use), low in vaginal ring users (7.8 per 10,000 woman years of use)

BMJ 2012(May 10);344:e2990

VTE Risk with Non-oral Hormonal Contraception

- It has been hypothesized that continuous, higher exposure to estrogen seen with Ortho Evra® contraceptive patch may increase thromboembolic risk
  - Product labeling indicates potential increased risk
- Using NuvaRing® (which provides low estrogen exposure) can cause a significant increase in sex hormone binding globulin.
  - Thought that the higher the levels of sex hormone-binding globulin, the higher the risk of thrombosis

BMJ 2012(May 10);344:e2990

VTE Risk with Non-oral Hormonal Contraception

- VTE risk associated with implants or levonorgestrel IUDs was similar to non-users of hormonal contraceptives
- Pregnancy/childbirth still carries highest absolute risk of VTE!
Risk of Oral contraceptive use in women with migraines

A database analysis showed that a significantly larger proportion of migraine sufferers with aura who were on combined hormonal contraceptives experienced thrombotic events such as stroke (P<0.001) and deep vein thrombosis (DVT, P≤0.03).

- Analysis based on data from 145,304 women enrolled in the Research Patient Data Registry of the Partners Healthcare System from 2001 to 2012 who were using any hormonal contraceptive
- Evaluated incidence of DVT, myocardial infarction (MI), ischemic stroke, and pulmonary embolism (PE) in women with and without migraine, and with and without aura among women with migraine.

Participants using drospirenone-ethinyl estradiol had significantly higher incidence of DVT (P=0.03), MI (P=0.01), and stroke (P<0.001) among those with migraine with aura compared with those without aura or no migraines. There was no difference between groups in the number of PEs.

- In those taking etonogestrel-ethinyl estradiol vaginal ring, migraine with aura was significantly associated with DVT, PE, and stroke (P<0.001 for all), but not MI (P=0.3).
- For those using norgestromin-ethinyl estradiol transdermal patch, migraine with aura increased incidence of thrombosis, PE, and stroke (P<0.001 for all), but not MI (P=0.2).

Study was limited by lack of adjustment for age, underlying medical conditions, or other confounders.

Further examination of exposure duration and validation of outcomes and temporal relationships to exposure needed.

No comparison with ‘older’ OCPs: levonorgestrel-ethinyl estradiol, norethindrone-ethinyl estradiol or norgestimate-ethinyl estradiol.
Obesity and Contraceptive Effectiveness

- Role of obesity and contraceptive failure is unclear
  - Consider using higher dose estrogen COC or use pill with shorter pill-free interval/extended cycle
  - Injectable and implants not effected by weight
- Recent studies indicate that with consistent use, suppression of ovulation similar in normal weight and obese women
- All forms of contraception acceptable in women with BMI>30 except contraceptive patch (CDC)
- Obesity independent risk factor for VTE
- Bariatric surgery using Roux-en-Y bypass may reduce COC absorption; no effect from gastric banding or sleeve

Contraceptive Choice and Co-existing Medical Conditions

- Risk of pregnancy needs to be weighed against risk of adverse effects of hormonal contraceptive use
- Resources
  - http://www.cdc.gov/reproductivehealth/UnintendedPregnancy/USMEC.htm Color and black/white summary charts of CDC recommendations
  - Prescribers/Pharmacists Letter March 2011, Detail document 27036 (table)

Pregnancy

- Changes in FDA Pregnancy and Lactation Labeling Categories
- Diclegis® for morning sickness
- Tdap recommendation for all pregnant women
- Valproate exposure and adverse outcomes
- Medications and breast-feeding
- Antidepressants during pregnancy and post-partum
Pregnancy and Lactation Labeling

In May 2008, the FDA proposed major revisions to prescription drug labeling to more completely inform the use of medicines during pregnancy and breastfeeding.

The proposed regulations eliminate the current letter risk categories A, B, C, D, and X due to limitations in their ability to accurately and consistently convey risk and benefit.

As of February 2011, the Final Rule is in the writing and clearance process.

FDA Pregnancy and Lactation Categories

<table>
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<tr>
<th>Category</th>
<th>Definition</th>
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<tbody>
<tr>
<td>A</td>
<td>Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote.</td>
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<tr>
<td>B</td>
<td>Animal reproduction studies have not demonstrated a fetal risk, but there are no controlled studies in pregnant women. Alternatively, animal reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).</td>
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<tr>
<td>C</td>
<td>Studies in animals have revealed adverse effects on the fetus (teratogenic, embryocidal, or other) and there are no controlled studies in women; or studies in women and animals are unavailable. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.</td>
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<td>D</td>
<td>There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).</td>
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<tr>
<td>X</td>
<td>Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience or both, and the risk of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.</td>
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Pregnancy and Lactation Labeling

Pregnancy Category C

Animal reproduction studies have shown an adverse effect on the fetus, there are no controlled studies in humans, and the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks;

or

animal studies have not been conducted and there are no controlled studies in humans.
Pregnancy and Lactation Labeling Proposed Changes

- New pregnancy subsection
  - General information
  - Pregnancy exposure registries
  - General statement about background risk
  - Fetal risk summary
  - Clinical considerations
    - Inadvertent exposure
    - Prescribing decisions for pregnant women
      - Risk to pregnant woman and fetus from disease
      - Drug effects during labor and delivery
  - Data


Under the proposed changes by FDA to drug labeling, the current Nursing Mothers section will be replaced by a section called Lactation.

- The Lactation section of labeling will contain 3 subsections:
  - Risk Summary
    - Summary of what is known about the excretion of the drug into human milk and potential effects on the breastfed infant, as well as maternal milk production.
  - Clinical Considerations
    - Methods to minimize exposure of the breastfed infant to the drug when applicable, as well as information about monitoring for adverse effects
  - Data

Pediatrics 2013;132:e796–e803

Diclegis® for morning sickness

- Drug combination formerly known as Bendectin® approved by FDA again as only drug specifically designated for nausea and vomiting in pregnant women who do not respond to conservative management
  - Initially launched in 1956 but became victim of lawsuits claiming birth defects
  - FDA and courts supported manufacturer but pulled by manufacturer 30 years ago in 1983 due to litigation cost
  - Individual ingredients have been used off-label for years and has been sold as Diclectin® in Canada

Doxylamine/ pyridoxine delayed release tablets (Diclegis®)

- Clinical data
  - 261 women were randomly assigned to receive two weeks of treatment with Diclegis® or placebo
  - The primary efficacy endpoint was the change from baseline at Day 15 in the Pregnancy Unique-Quantification of Emesis (PUQE) score.
    - At baseline, the mean PUQE score was 9.0 in the Diclegis® arm and 8.8 in the placebo arm.
    - There was 0.7 mean decrease (improvement in nausea and vomiting symptoms) from baseline in PUQE at Day 15 with Diclegis® compared to placebo

Doxylamine/ pyridoxine delayed release tablets (Diclegis®)

- Delayed release tablets contain doxylamine succinate 10mg and pyridoxine hydrochloride (Vitamin B6) 10 mg
- Pregnancy Category A
- Dosing: Take two tablets daily at bedtime.
  - If symptoms are not adequately controlled, the dose can be increased to a maximum recommended dose of four tablets daily (one in the morning, one mid-afternoon and two at bedtime)
- Most common adverse effects: somnolence (19%)
- Cost: $570/month
**Tdap vaccine for Pregnant Women**

CDC now recommends giving pregnant women the Tdap vaccine for each pregnancy...preferably between 27 to 36 weeks of gestation.

- Unvaccinated infants have the highest risk of severe disease and death due to a pertussis infection.
- Vaccinating women before pregnancy is not likely to produce high enough maternal antibodies to protect the baby postpartum.
- If not administered during pregnancy, Tdap should be administered immediately postpartum.

2014 ACIP Adult Immunization schedules

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**Valproate contraindicated for migraine prevention in pregnant women**

Pregnancy Risk Category X (change from D)

- Alert is based on the final results of the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study
- NEAD study compared results of IQ tests when children who had been exposed to antiepileptic drugs in utero were 6 years old
- Difference between valproate and other antiepileptics (lamotrigine, phenytoin, carbamazepine) were all statistically significant
- Mean IQs were higher in overall group in children whose mothers reported periconceptional folate use

FDA Drug Safety Communication 5/6/2013

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**Valproate in Pregnancy Possible Link with Autism**

- Data from recent study from Denmark indicated that in utero exposure to valproate was associated with five-fold elevated risk of autism and three-fold elevated risk for autism spectrum disorder
- Absolute risks were 2.5% and 4.4%, respectively
- Study included 655,615 children born in Denmark from 1996 through 2006.
  - National registries indicated autism spectrum disorder diagnoses in 5,437 children through follow-up to a mean age of 8.8 years.
  - 508 children exposed to valproate based on Rx fill data

JAMA 2013;309:1696-1703
JAMA 2013;309:1730-1731
Valproate in Pregnancy link with Autism

- In children of mothers with epilepsy (432 of 508), the risk of autism was 2.9 times higher with valproate exposure, with an absolute risk of 2.95% versus 1.02% among all others in the cohort not exposed to the drug.
- Study limitations: lack of data on valproate dose, whether women actually took the pills that they picked up from the pharmacy, or their alcohol and folic acid supplement use in pregnancy.

Depression/ Antidepressant Use During Pregnancy

- Some findings from recent studies and meta-analyses regarding treatment of depression during the prenatal period are inconsistent with current published APA and ACOG guidelines
- Some current issues of concern:
  - SSRI use and risk of autism
  - Treatment of maternal depression and risk of depression in adolescent offspring
  - First trimester exposure and risk of congenital anomalies

Treatment of Depression During Pregnancy

Effects of SSRIs on Neonates

- Poor Neonatal Adaption (Neonatal behavioral syndrome)
  - Class labeling change required in precaution section of SSRI Package inserts
- Teratogenic effects/ Congenital malformations
  - Paroxetine use in first trimester may increase risk for congenital cardiac malformations – Category D
  - Unclear whether this is class effect with SSRIs
- Persistent pulmonary hypertension
  - Use before 20 weeks not associated with increased risk
  - Use of non-SSRI antidepressants not associated with increased risk
Antidepressants and Breast Feeding/Lactation

- During the postpartum period, up to 85 percent of women experience some type of mood disturbance.
- American Academy of Pediatrics estimates that more than 400,000 infants are born each year to mothers who are depressed.
- Medication exposure significantly less than with transplacental exposure.
- Percentage of maternal doses that approach clinically significant levels (10% or more) have been reported for bupropion, diazepam, fluoxetine, citalopram, lithium, lamotrigine, and venlafaxine.
- No long-term neurobehavioral studies done in infants exposed to SSRIs through breast milk.

Pediatrics 2013;132:e796–e809

Adulthood

- New products for overactive bladder (OAB)
- Recommended dosage reductions for zolpidem products.
- New guidelines for cardiovascular disease prevention, cholesterol, obesity and healthy lifestyles.
- New guideline for stroke prevention in women.
- New pharmacologic options for weight management.

ACA Will Cover Preventive Medicines For Women At High Risk For Breast Cancer

- “Women at increased risk for breast cancer may now get preventive medications without out-of-pocket costs.”
  - HHS Secretary Kathleen Sebelius (1/10/14)
- US Preventive Services Task Force (USPSTF) recommended last September that clinicians give medications such as tamoxifen or raloxifene to such women to reduce their risk of the disease.
  - Under the Affordable Care Act, “items or services rated A or B by the independent review board of physicians and academics must be covered by insurers without a co-pay or deductible.”
Zolpidem (Ambien®)
New warning and Dose reduction

- FDA has recommended label changes because of the known risk of next-morning impairment
- Patients should not drive or engage in other activities that require complete mental alertness the day after taking the drug because zolpidem levels can remain high enough the next day to impair these activities.
  - Zolpidem blood levels above approximately 50 ng/mL appear capable of impairing driving to a degree that increases the risk of a motor vehicle accident.
  - In pharmacokinetic trials of 10 mg Ambien about 15% of women and 3% of men had zolpidem concentrations that exceeded 50 ng/mL approximately 8 hours post-dosing.

FDA Drug Safety Communication 5/14/2013
FDA Drug Safety Communication 1/10/2013

Zolpidem (Ambien®)
New warning and Dose reduction

- Inform patients that impairment from sleep drugs can be present despite feeling fully awake.
- The recommended dose of zolpidem for women should be lowered from 10 mg to 5 mg for immediate-release products (Ambien, Edluar, and Zolpimist) and from 12.5 mg to 6.25 mg for extended-release products (Ambien CR).
  - The recommended doses of Intermezzo, a lower dose zolpidem product approved for middle-of-the-night awakenings, are not changing.
  - At the time of Intermezzo’s approval in November 2011, the label already recommended a lower dosage for women than for men.

FDA Drug Safety Communication 1/10/2013

Overactive Bladder (OAB)

- Definition: presence of urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of a urinary tract infection or other obvious cause
- The International Continence Society
- First-line therapy is behavioral therapy,
  - bladder training, bladder control strategies, Kegel exercises, pelvic floor muscle training, and fluid management
- Antimuscarinic agents considered pharmacologic treatment of choice

Clinical Management of Urinary Incontinence in Women
Am Fam Phys 2013(May);87(5)
Drugs for Overactive Bladder

- Botox (onabotulinumtoxinA)
  - for patients who cannot tolerate or have inadequate response to anticholinergic drugs
  - 100 units by intradetrusor injection during cystoscopy
- Mirabegron (Myrbetriq®)
  - Beta 3 adrenergic agonist
- Oxybutynin patch (Oxytrol for Women®)
  - Recently FDA approved for nonprescription (OTC) use by women

Am Fam Phys 2013;87(9)

Mirabegron (Myrbetriq®)

- Beta-3 adrenergic agonist
  - Consider as alternative in patients who cannot tolerate adverse effects of antimuscarinic agents
- First new mechanism for OAB in 30 years
  - relaxes detrusor smooth muscle during storage phase of fill-void cycle by activation of beta-3 receptors which increases bladder capacity
- Demonstrates modest clinical effectiveness
  - Reduces number of incontinence episodes and number of micturitions per day by 1-2 from baseline
  - No comparison data on clinical effectiveness with currently marketed products

Mirabegron (Myrbetriq®)

- Can increase Blood Pressure (7.5%):
  - Not recommended in patients with severe uncontrolled hypertension (SBP>180 or DBP>110mm Hg)
- Additional evaluation of CV outcomes and new malignant events being required by FDA
- Drug interactions: CYP 2D6 inhibitor
  - Increased levels of metoprolol, desipramine
  - Use caution with flecainide, propafenone, thioridazine
  - Increased digoxin levels
- Urinary retention if used in combination with anticholinergic agents
Mirabegron (Myrbetriq®)

- Most common side effects (from clinical trials):
  - Hypertension, UTIs, nasopharyngitis, headache
- Low risk of dry mouth (3%)
  - Oxybutynin 50-60%
  - Tolterodine (Detrol®) 40%
  - Fesoterodine (Toviaz®) 20-34%
  - Trospium (Sanctura®) 20%
  - Solifenacin (Vesicare®) 10-20%
  - Darifenacin (Enablex®) 10-20%

Oxybutynin patch (Oxytrol for Women®)

- 2013 FDA approved for nonprescription treatment of overactive bladder in women 18 years and older
  - Marketed for women who have had at least 2 of the following symptoms for at least 3 months...urinating more often than usual, having an urgent need to urinate, or not being able to control the urge to go.
- Will remain prescription only for men
  - May cause urinary retention with enlarged prostate or symptoms of prostate disease may be mistaken for OAB
  - Available as transdermal patch that delivers 3.9 mg drug every day (same as Rx product); must be applied every 4 days ****$30 per month vs $200 with Rx

New Guidelines for Cardiovascular Disease Prevention

- 2013 ACC/AHA guideline on the assessment of cardiovascular risk
- 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults
- 2013 ACC/AHA guideline on lifestyle management to reduce cardiovascular risk
- 2013 ACC/AHA/TOS guideline for the management of overweight and obesity in adults

Circulation November 12, 2013
http://Circ.ahajournals.org
AHA/ASA Guidelines for Prevention of Stroke in Women

- In US each year, 55,000 more strokes occur in women than in men
- Stroke is fifth leading cause of death for men but third leading cause for women
- Recognition that certain risk factors for stroke are unique to women or much more common in women
- Guidelines call for stroke risk score specific to women

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<th>Risk Factor</th>
<th>Sex-specific Risk Factor</th>
<th>Sex-specific or identical</th>
<th>Identical to men</th>
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<td>Pregnancy</td>
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<td>Preeclampsia</td>
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<td>Oral contraceptive use</td>
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<td>Postmenopausal hormone use</td>
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<td>Psychosocial stress</td>
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Adapted from Stroke Feb 6, 2014 online
AHA/ASA Guidelines for Prevention of Stroke in Women

Recommendations focus on
- Pre-eclampsia
- Hypertension during and after pregnancy
- Central venous thrombosis
- Oral contraceptives
- Menopause and hormone replacement
- Migraine with aura
- Obesity, metabolic syndrome and lifestyle factors
- Atrial fibrillation

Prevention of Preeclampsia
1. Women with chronic primary or secondary hypertension or previous pregnancy-related hypertension should take low-dose aspirin from the 12th week of gestation until delivery (Class I; Level of Evidence A).
2. Calcium supplementation (of ≥1 g/d, orally) should be considered for women with low dietary intake of calcium (<600 mg/d) to prevent preeclampsia (Class I; Level of Evidence A).

Treatment of Hypertension in Pregnancy and Post Partum
1. Severe hypertension in pregnancy should be treated with safe and effective antihypertensive medications, such as methyldopa, labetalol, and nifedipine, with consideration of maternal and fetal side effects (Class I; Level of Evidence A).
2. Consideration may be given to treatment of moderate hypertension in pregnancy with safe and effective antihypertensive medications, given the evidence for possibly increased stroke risk at currently defined systolic and diastolic BP cutoffs, as well as evidence for decreased risk for the development of severe hypertension with treatment (although maternal-fetal risk-benefit ratios have not been established) (Class IIa; Level of Evidence B).
3. Atenolol, angiotensin receptor blockers, and direct renin inhibitors are contraindicated during pregnancy and should not be used (Class III; Level of Evidence C).
4. After giving birth, women with chronic hypertension should be continued on their antihypertensive regimen, with dosage adjustments to reflect the decrease in volume of distribution and glomerular filtration rate that occurs after delivery. They should also be monitored carefully for the development of postpartum preeclampsia (Class IIa; Level of Evidence C).
AHA/ASA Guidelines for Prevention of Stroke in Women

Recommendations – Preeclampsia and Pregnancy Outcomes

Prevention of Stroke in Women With a History of Preeclampsia

1. Because of the increased risk of future hypertension and stroke 1 to 30 years after delivery in women with a history of preeclampsia (Level of Evidence B), it is reasonable to (1) consider evaluating all women starting 6 months to 1 year post partum, as well as those who are past childbearing age, for a history of preeclampsia/eclampsia and document their history of preeclampsia/eclampsia as a risk factor, and (2) evaluate and treat for cardiovascular risk factors including hypertension, obesity, smoking, and dyslipidemia (Class IIa; Level of Evidence C).

AHA/ASA Guidelines for Prevention of Stroke in Women

Recommendations – Oral Contraceptives

1. OCs may be harmful in women with additional risk factors (eg, cigarette smoking, prior thromboembolic events) (Class III; Level of Evidence B).
2. Among OC users, aggressive therapy of stroke risk factors may be reasonable (Class IIb; Level of Evidence C).
3. Routine screening for prothrombotic mutations before initiation of hormonal contraception is not useful (Class III; Level of Evidence A).
4. Measurement of BP before initiation of hormonal contraception is recommended (Class I; Level of Evidence B).

AHA/ASA Guidelines for Prevention of Stroke in Women

Recommendations – Menopause and Postmenopausal hormone therapy

1. HT (CEE with or without medroxyprogesterone) should not be used for primary or secondary prevention of stroke in postmenopausal women (Class III; Level of Evidence A).
2. Selective estrogen receptor modulators, such as raloxifene, tamoxifen, or tibolone, should not be used for primary prevention of stroke (Class III; Level of Evidence A).
AHA/ASA Guidelines for Prevention of Stroke in Women
Recommendations – Migraine with Aura

1. Because there is an association between higher migraine frequency and stroke risk, treatments to reduce migraine frequency might be reasonable, although evidence is lacking that this treatment reduces the risk of first stroke (Class IIb; Level of Evidence C).

2. Because of the increased stroke risk seen in women with migraine headaches with aura and smoking, it is reasonable to strongly recommend smoking cessation in women with migraine headaches with aura (Class IIa; Level of Evidence B).

AHA/ASA Guidelines for Prevention of Stroke in Women
Recommendations – Obesity, Metabolic Syndrome and Lifestyle Factors

1. A healthy lifestyle consisting of regular physical activity, moderate alcohol consumption (<1 drink/d for nonpregnant women), abstention from cigarette smoking, and a diet rich in fruits, vegetables, grains, nuts, olive oil, and low in saturated fat (such as the DASH [Dietary Approaches to Stop Hypertension] diet) is recommended for primary stroke prevention in women with cardiovascular risk factors (Class I; Level of Evidence B).

2. Lifestyle interventions focusing on diet and exercise are recommended for primary stroke prevention among individuals at high risk for stroke (Class I; Level of Evidence B).

AHA/ASA Guidelines for Prevention of Stroke in Women
Recommendations – Atrial Fibrillation

1. Risk stratification tools in AF that account for age and sex-specific differences in the incidence of stroke are recommended (Class I; Level of Evidence A).

2. Considering the increased prevalence of AF with age and the higher risk of stroke in elderly women with AF, active screening (in particular of women >75 years of age) in primary care settings using pulse taking followed by an ECG as appropriate is recommended (Class I; Level of Evidence B).

3. Oral anticoagulation in women aged 565 years with AF alone (no other risk factors; women with CHA2DS2-VASc=0 or CHA2DS2-VASc=1) is not recommended (Class III; Level of Evidence B). Antiplatelet therapy is a reasonable therapeutic option for selected low-risk women (Class IIa; Level of Evidence B).

4. New oral anticoagulants are a useful alternative to warfarin for the prevention of stroke and systemic thromboembolism in women with paroxysmal or permanent AF and prespecified risk factors (according to CHA2DS2-VASc) who do not have a prosthetic heart valve or hemodynamically significant valve disease, severe renal failure (creatinine clearance 15 mL/min), lower weight (<50 kg), or advanced liver disease (impaired baseline clotting function) (Class I; Level of Evidence B).
AHA/ASA Guidelines for Prevention of Stroke in Women

- Society of Maternal-Fetal Medicine has expressed concerns regarding new AHA guidelines because of differences with the recent 2013 ACOG Hypertension in Pregnancy guidelines.
- The ACOG and AHA guidelines have “different diagnostic criteria for pre-eclampsia, differing recommendations for the use of low-dose aspirin for the prevention of pre-eclampsia and the threshold for initiating antihypertensive medications for pregnant patients with chronic hypertension.”

Obesity / Weight Management

- More than one-third of U.S. adults (35.7%) are obese.
- In 2008, medical costs associated with obesity were estimated at $147 billion.
- Non-Hispanic blacks have the highest age-adjusted rates of obesity (49.5%).
- Higher income women are less likely to be obese than low-income women.
- Obesity ranks ahead of smoking as major preventable cause of numerous chronic medical conditions.

Prevalence of Self-Reported Obesity Among U.S. Adults BRFSS, 2011

- Colorado 20.7% (Least) vs. Mississippi 34.9% (highest)
2013 AHA/ACC/TOS Guideline for the management of Overweight and Obesity in Adults

Recommendations:

- Identifying Patients Who Need to Lose Weight
- Matching Treatment Benefits With Risk Profiles
- Diets for Weight Loss
- Lifestyle Intervention and Counseling
- Selecting Patients for Bariatric Surgical Treatment for Obesity

Pharmacotherapy options for weight management not addressed

2013 AHA/ACC/TOS Guideline for the management of Overweight and Obesity in Adults

Identifying Patients Who Need to Lose Weight

- Measure height and weight and calculate BMI at annual visits or more frequently.
- Use the current cutpoints for overweight (BMI >25.0 - 29.9 kg/m²) and obesity (BMI ≥30 kg/m²) to identify adults who may be at elevated risk of CVD and cutpoints for obesity (BMI ≥30) to identify adults who may be at elevated risk of mortality from all causes.
- Advise overweight and obese adults that the greater the BMI and waist circumference, the greater the risk of CVD, type 2 diabetes and all-cause mortality

2013 AHA/ACC/TOS Guideline for the management of Overweight and Obesity in Adults

Matching Treatment Benefits With Risk Profiles

- Counsel obese and overweight adults with CV risk factors (high BP, hyperlipidemia and hyperglycemia), that lifestyle changes that produce even modest, sustained weight loss of 3%-5% produce clinically meaningful health benefits, and greater weight losses produces greater benefits.
- Sustained weight loss of 3%-5% is likely to result in clinically meaningful reductions in triglycerides, blood glucose, HbA1C, and the risk of developing type 2 diabetes.
- Greater amounts of weight loss will reduce BP, improve LDL–C and HDL–C, and reduce the need for medications to control BP, blood glucose and lipids as well as further reduce triglycerides and blood glucose.
2013 AHA/ACC/TOS Guideline for the management of Overweight and Obesity in Adults

**Diets for Weight Loss**

- Prescribe one of the evidence-based diets that restricts certain food types (such as high-carbohydrate foods, low-fiber foods, or high-fat foods) in order to create an energy deficit by reduced food intake.

- Prescribe a calorie-restricted diet, for obese and overweight individuals who would benefit from weight loss, based on the patient's preferences and health status and preferably refer to a nutrition professional* for counseling. A variety of dietary approaches can produce weight loss in overweight and obese adults.

- Prescribe a diet to achieve reduced calorie intake for obese or overweight individuals who would benefit from weight loss, as part of a comprehensive lifestyle intervention. Any 1 of the following methods can be used to reduce food and calorie intake:
  - Prescribe 1,200–1,500 kcal/day for women and 1,500–1,800 kcal/day for men (kcal levels are usually adjusted for the individual's body weight);
  - Prescribe a 500 kcal/day or 750 kcal/day energy deficit; or
  - Prescribe one of the evidence-based diets that restricts certain food types (such as high-carbohydrate foods, low-fiber foods, or high-fat foods) in order to create an energy deficit by reduced food intake.

**Lifestyle Intervention and Counseling**

- Advise overweight and obese individuals who would benefit from weight loss to participate for ≥6 months in a comprehensive lifestyle program that assists participants in adhering to a lower calorie diet and in increasing physical activity through the use of behavioral strategies.

- Prescribe on site, high-intensity (i.e., ≥14 sessions in 6 months) comprehensive weight loss interventions provided in individual or group sessions by a trained interventionist.†
## 2013 AHA/ACC/TOS Guideline for the management of Overweight and Obesity in Adults

### Lifestyle Intervention and Counseling
- Electronically delivered weight loss programs (including by telephone) that include personalized feedback from a trained interventionist may be prescribed for weight loss but may result in smaller weight loss than face-to-face interventions.
- Some commercial-based programs that provide a comprehensive lifestyle intervention can be prescribed as an option for weight loss, provided there is peer-reviewed published evidence of their safety and efficacy.
- Advise overweight and obese individuals who have lost weight to participate long-term (≥1 year) in a comprehensive weight loss maintenance program.

### Selecting Patients for Bariatric Surgical Treatment for Obesity
- Advise adults with a BMI ≥40 or BMI ≥35 with obesity-related comorbid conditions who are motivated to lose weight and who have not responded to behavioral treatment with or without pharmacotherapy with sufficient weight loss to achieve targeted health outcome goals that bariatric surgery may be an appropriate option to improve health and offer referral to an experienced bariatric surgeon for consultation and evaluation.
- For individuals with a BMI <35, there is insufficient evidence to recommend for or against undergoing bariatric surgical procedures.

### Weight loss Options Prior to 2012

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Comments</th>
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<tr>
<td>Phentermine</td>
<td>Sympathomimetic</td>
<td>Short term 12 week use only; adverse effects and potential for misuse</td>
</tr>
<tr>
<td>Diethylpropion</td>
<td>Sympathomimetic</td>
<td>Short term 12 week use only; adverse effects and potential for misuse</td>
</tr>
<tr>
<td>Benzphetamine</td>
<td>Sympathomimetic</td>
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<td>Phendimetrazine</td>
<td>Sympathomimetic</td>
<td>Short term 12 week use only; adverse effects and potential for misuse</td>
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<td>Fenfluramine</td>
<td>Inhibition of CNS 5-HT uptake and release of 5-HT</td>
<td>Removed from market 1997 due to increased risk of valvulopathy and pulmonary hypertension</td>
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<tr>
<td>Dexfenfluramine</td>
<td>Inhibition of CNS 5-HT uptake and release of 5-HT</td>
<td>Removed from market 1997 due to increased risk of valvulopathy and pulmonary hypertension</td>
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<tr>
<td>Orlistat</td>
<td>Lipase inhibitor that reduces absorption of dietary fat</td>
<td>Substantial GI effects: steatorrhea, loose oily stools, abdominal cramping</td>
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<tr>
<td>Sibutramine</td>
<td>Noradrenaline and 5-HT reuptake inhibitor</td>
<td>Removed from market 2010 due to increase in adverse cardiovascular effects</td>
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<tr>
<td>Rimonabant</td>
<td>Cannabinoid-1 receptor antagonist</td>
<td>Never FDA approved; substantial risk of psychiatric side effects</td>
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</table>
FDA approval requirements for new pharmacologic options for weight loss

New drug must show a statistically significant placebo-subtracted weight loss of greater than 5% of baseline weight at 1 year or that more than 35% of treated patients achieve a greater than 5% weight loss that must also be at least twice that produced by treatment with placebo.

Drug must also significantly improve obesity-related metabolic abnormalities, including blood pressure, lipid and blood glucose levels.

Pharmacologic Options for Weight Management

Recently FDA approved Products

- Lorcaserin (Belviq®)
  - First new agent approved in 13 years for weight loss
  - Similar to fenfluramine; selective agonist of 5-HT2c receptors

- Phentermine-Topiramate ER (Qysmia®)
  - Indicated for chronic weight management in combination with a reduced-calorie diet, increased physical activity in patients with BMI ≥ 30 kg/m2 or BMI ≥ 27 with (hypertension, dyslipidemia, type 2 diabetes)

Lorcaserin Clinical Trial Results

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<th>BLOOM</th>
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<th>BLOOM-DM</th>
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<td>Mean weight loss (% of baseline) -&lt;5 kg</td>
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<tr>
<td>Lorcaserin 10mg BID</td>
<td>5.8</td>
<td>5.8</td>
<td>4.5</td>
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<tr>
<td>Lorcaserin 10 mg QD</td>
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<td>Placebo</td>
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<td>5% or greater weight loss (% of baseline)</td>
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<td>Lorcaserin 10mg BID</td>
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<td>Lorcaserin 10mg BID</td>
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<td>Placebo</td>
<td>7.7</td>
<td>9.7</td>
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*lorcaserin statistically significant at all comparison points*
Lorcaserin (Belviq®)

- No increase in risk of valvulopathy noted in clinical trials (8000 patients)
  - Fenfluramine and dexfenfluramine activated serotonin 2B receptors
  - FDA requiring 6 post-marketing studies to assess long term effect on heart
- FDA requiring further study...
  - Linked to a number of mammary tumors in rats... prolonged high levels of prolactin?
- Schedule C-IV substance
  - Human abuse potential study in recreational drug abusers rated responses similar to zolpidem

Lorcaserin (Belviq®)

- Adverse effects
  - Headache (15-17%)
  - Upper Respiratory Infection (14%)
  - Nausea (8-9%)
  - Dizziness (8%)
  - Hypoglycemia (specific to diabetics) (29%)
  - Priapism

- Drug interactions
  - CYP2D6 inhibitor
  - Serotonin syndrome or neuroleptic malignant syndrome
  - Do not use in combination with other potent serotonergic or antidopaminergic agents

Lorcaserin (Belviq®)

Clinical Effectiveness

- Approved labeling recommends that drug be discontinued in patients who fail to lose 5% of body weight after 12 weeks of treatment, as they are unlikely to achieve clinically meaningful weight loss with continued treatment
- Dose: 10 mg twice daily
- Cost:
Phentermine-topiramate combination clinical trial data

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<tr>
<td>Phentermine 15 mg-topiramate 92 mg daily</td>
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<td>Phentermine 7.5 mg-topiramate 46 mg daily</td>
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<td>Phentermine 3.75 mg-topiramate 23 mg daily</td>
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5% or greater weight loss (% of baseline) Mean weight loss (% of baseline) -8-10kg

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<td>Phentermine 7.5 mg-topiramate 46 mg daily</td>
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<tr>
<td>Phentermine 3.75 mg-topiramate 23 mg daily</td>
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<td>NA</td>
</tr>
<tr>
<td>Placebo</td>
<td>17.3</td>
<td>21</td>
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10% or greater weight loss (% of baseline)

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<td>NA</td>
</tr>
<tr>
<td>Placebo</td>
<td>7.4</td>
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</tbody>
</table>

**Phentermine + topiramate ER (Qsymia®)**

- **Adverse Effects** (dose-related)
  - Dry mouth: 21%
  - Paresthesia: 21%
  - Constipation: 17%
  - Mood/sleep disorder 20.6%
  - Impaired cognition: 10%
  - Dysgeusia: 10%
  - Increased heart rate:
    - >100BPM 56% of patients
    - >20BPM in 20% of patients at max dose
  - Anxiety-related adverse events: 8%
  - Nephrolithiasis, hypokalemia

- **Pregnancy Category X**
  - Risk Evaluation and Mitigation Strategy (REMS) required
  - Baseline and one month pregnancy test required

- **Schedule C-IV**
  - Available only from certified retail or mail order pharmacies

Lancet. 2011;377(9774):1341-1352.

**Phentermine + topiramate ER (Qsymia®) Clinical effectiveness**

- Start treatment with 3.75mg/23mg once daily in morning for 14 days; after 14 days increase to recommended dose of 7.5mg/46mg once daily
  - Evaluate weight loss after 12 weeks; if patient has not lost at least 3% of baseline body weight discontinue as it is unlikely to achieve meaningful weight loss
  - Can escalate with 11.25mg/69mg daily for 14 days followed by max of 15mg/92mg daily
  - Discontinue slowly if at least 5% of body weight not lost after additional 12 weeks at max dose
  - Data indicates improved CVD/metabolic parameters
    - Clinically significant improvement in systolic blood pressure and HDL-cholesterol
Pharmacologic Options for Weight Management

Drugs in clinical trials or awaiting FDA approval

- Bupropion SR-naltrexone SR (Contrave®)
  - 180mg[B] plus 8-16mg N] BID
- Liraglutide (Victoza®)*
  - 8% weight loss with 3mg daily in patients with and without diabetes
- Exenatide (Byetta®, Bydureon®)

Pharmacologic Options for Weight Management

Off Label Study and Use

- Metformin
- Fluoxetine
- Bupropion
- Zonisamide
- Pramlintide

New weight management options

Questions yet to be answered

- Cost and insurance coverage for products and weight management interventions
  - Proposed SC Medicaid coverage of obesity management
- Comparison with existing weight loss drugs
- Long term benefit and risks of weight-loss interventions
- Role of bariatric surgery procedures
Too Good to be True???
- Claims to “trick” body metabolism to waste energy
- “Miracle breakthrough”, “secret formula”
- Claims “fast” and “easy” weight loss
- Uses ‘experts’ or celebrities to tout benefits
- Addresses taking product only without a focus on lifestyle or exercise change

Peri-Menopause and Menopause
- Women’s Health Initiative (WHI) study 10 years later… postintervention followup
- More individualized approaches to estrogen/hormone therapy
  - Time of initiation
  - Dose
  - Duration
  - Formulation/type of hormone/delivery system
- Compounded/Bioidentical hormones
- Nonhormonal options for relief of vasomotor symptoms

Women’s Health Initiative (WHI) trials
- Purpose of trials
  - Determine the benefits and risks of postmenopausal hormone therapy when taken for chronic disease prevention
    - Primary efficacy and safety outcomes were coronary heart disease (CHD) and invasive breast cancer
  - Two related trials evaluated the impact of diet modification and supplementation with vitamin D and calcium on cardiovascular disease, breast cancer/colorectal cancer and fractures
Women’s Health Initiative (WHI) Trials

Treatment groups
- Women with intact uterus
  - 16,608 women, mean age at screening 63 years, only third of participants between 50-59 years of age, 36% less than 10 years since menopause
  - Prempro® – conjugated equine estrogens 0.625mg plus medroxyprogesterone 2.5mg daily
- Women with prior hysterectomy
  - 10,608 women, 80% greater than 20 years since menopause, 48% current or past estrogen use
  - Premarin® - conjugated equine estrogens 0.625mg daily

Women’s health Initiative (WHI) Overview of findings

Conclusions and Relevance
- “Menopausal hormone therapy has a complex pattern of risks and benefits. Findings from the intervention and extended postintervention follow-up of the 2 WHI hormone therapy trials do not support use of this therapy for chronic disease prevention, although it is appropriate for symptom management in some women.”

JAMA 2013;310(13):1353-1368

Women’s Health Initiative (WHI) trials

Overview of findings – Estrogen plus progestin

- Increased risk of CHD and MI
- Increased risk of stroke
- Increased risk of pulmonary embolism
- Increased risk of breast cancer
- Reduced risk of colorectal cancer
- Reduced risk of hip fracture
- No protection against mild cognitive impairment
- No impact on all-cause mortality

JAMA 2013;310(13):1353-1368
Women’s Health Initiative (WHI) trials

Overview of findings – Estrogen only

- Increased risk of stroke
- Increased risk of pulmonary embolism
- Uncertain effects on risk of breast cancer
- Reduced risk of hip fracture
- No difference in risk for CHD and MI
- No difference for risk of colorectal cancer
- No impact on all-cause mortality

JAMA 2013;310(13):1353-1368

Women’s Health Initiative (WHI)

Overview of findings

- Findings from the diet modification trial
- Findings from the calcium and vitamin D trial
- Additional findings and observations

JAMA 2013;310(13):1353-1368

Estrogen/Hormone Therapy

FDA Position on Hormone Therapy

- FDA believes the risks attributable to combination product in WHI study are applicable to all HT products
- When prescribing medication to prevent osteoporosis, PCP should consider all non-estrogen preparations first
- When prescribing ET/HT, PCP should prescribe smallest dose for shortest amount of time to achieve treatment goals
- PCP should prescribe ET/HT products only when benefits are believed to outweigh risk for specific patient
Consensus Statement (published 3/13)
American Society for Reproductive Medicine, Asia Pacific Menopause Federation, the Endocrine Society, European Menopause and Andropause Society, International Menopause Society, International Osteoporosis Foundation, and North American Menopause Society

- Among women younger than 60 or within 10 years after menopause, estrogen-alone HRT at standard doses "may decrease coronary heart disease and all-cause mortality." Mortality benefits of estrogen plus progestogen in this group are less clear with no increase or decrease in cardiovascular risk.

- For women whose only menopause symptom is vaginal dryness or discomfort during intercourse, low-dose topical estrogen is preferred.

- Estrogen-only HRT is preferred in women after hysterectomy; other women should receive estrogen plus progestogen.

- Venous thromboembolism and ischemic stroke risk increases with oral HRT but the absolute risk remains low in women younger than 60. Such risks may be smaller with transdermal therapy.

- HRT is not recommended in breast cancer survivors.

- Custom-compounded "bioidentical" hormone therapy is not recommended.

- Breast cancer "complex issue" [statement did not provide specific recommendations on HRT types or durations to minimize the risk].

Individualizing hormone therapy

Use the lowest effective dosage for shortest possible duration with periodic reevaluation
- Consider desired outcomes from use of HT
- Attempts to wean hormone therapy should be considered annually after 3-5 years
- Combined therapy with progestin indicated for women with intact uterus
  - Consider novel dosing strategies
- Low dose: 0.3mg for oral conjugated and esterified estrogens; 0.5 mg oral estradiol, 0.025mg transdermal estradiol patches
  - Ultra low dose Menostar does not require concomitant progestin
New Transdermal HT options
Does the type, route of administration, or dose of estrogen make a difference?

- Transdermal delivery of HT may have more favorable effects than oral estrogen on markers for cardiovascular risk
  - Avoids first-pass metabolism in liver; permits use of lower doses
  - Transdermal estrogen does not impact lipids and may decrease insulin resistance
  - Hypertriglyceridemia not affected by transdermal estrogen

- Products available in variety of delivery systems:
  - Patches, gels, metered-dose sprays

Bioidentical Hormone Therapy (BHT)

- Treatment with medications that contain hormones that have the same chemical formula on a molecular level as those made naturally in the body
- Many FDA approved treatments are structurally identical or similar to endogenously produced hormones
- More evidence regarding the use of and advantages/disadvantages of compounded BHT is needed

Components of HT Products

**Estrogens**
- Bioidentical
  - Compounded
    - Estrone, estradiol, estriol
  - Commercially available
    - 17-beta estradiol, estradiol acetate, estradiol hemihydrate
- Manufactured
  - Conjugated estrogens
  - Esterified estrogens
  - Conjugated equine estrogens

**Progestogens**
- Bioidentical
  - Compounded
    - Progesterone
  - Commercially available
    - Micronized progesterone
- Manufactured
  - Medroxyprogesterone acetate
  - Norethindrone acetate
  - Levonorgestrel
  - Drospirenone
Compounded Bioidentical Hormone Therapy (CBHT)

Key discussion points for Patient Education

- Bioidentical does not necessarily mean natural.
- Custom-compounded hormone therapy is not the same as bioidentical hormone therapy.
- Products approved by the FDA offer advantages over custom-compounded preparations such as ingredient and dose consistency.
- The concept of an "absolutely safe" hormone is a myth.
- Conventional or traditional hormone therapy is a broad term that includes both bioidentical and nonbioidentical hormones.
- Benefits of individualization and monitoring with testing hormone concentrations have not been established.
- Estriol is a weak estrogen but not a benign estrogen.
- Bioidentical progesterone and synthetic progestins are structurally and functionally different in nonendometrial tissues.
- The use of dehydroepiandrosterone and testosterone therapy among women is controversial.
- Adrenal fatigue does not mean adrenal insufficiency.

Adapted from ACCP Women's Health PRN opinion paper
Compounded bioidentical hormone therapy in menopausal women. Pharmacotherapy January 2014

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonidine</td>
<td>0.1-0.4 mg total daily dose (give qd or bid) May also use TTS patches</td>
<td>Reduction in hot flash severity, frequency and duration</td>
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<tr>
<td></td>
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<td>Useful with tamoxifen induced hot flashes</td>
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<tr>
<td>Venlafaxine</td>
<td>37.5-75 mg XR (no additional benefit with increased dose)</td>
<td>Most studies were conducted in breast cancer, not postmenopausal patients</td>
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<td></td>
<td></td>
<td>Side effects: decreased appetite, dry mouth</td>
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<tr>
<td>SSRIs</td>
<td>F 10-20 mg qd P-CR 12.5-25mg qd F 20 mg qd</td>
<td>Paroxetine appears to be most effective SSRI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Response with low doses within 1 week</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Side effects: headache, nausea, insomnia</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Titrate up to 300 mg TID May increase to 1800mg</td>
<td>Effective in breast cancer, tamoxifen and postmenopausal hot flashes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Benefit noted within first week of therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Side effects: somnolence, dizziness, rash</td>
</tr>
</tbody>
</table>

Non-Hormonal Drug Options for Menopausal Symptoms

- Paroxetine mesylate (Brisdelle)
  - Recent FDA approval for hot flashes indication
- Gabapentin (Sefelsa)
  - FDA approval denied in 2013
Non-Hormonal Products for Relief of Vasomotor Symptoms

**Paroxetine mesylate (Brisdelle®)**

- Approved as first nonhormonal products to treat the hot flashes associated with menopause
- Clinical efficacy
  - Lowered the frequency of hot flashes per day by 0.9 and 1.7 after 12 weeks in two randomized, controlled trials versus placebo (n=1174)
  - Hot flash severity also decreased
  - In 12 week continuation trial, proportion of women who achieved a ≥50% reduction in frequency of moderate-to-severe hot flashes from baseline to week 24 was 48% with paroxetine and 36% with placebo
- Can be used by women who cannot or will not consider hormone therapy
  - No impact on vaginal atrophy, BMD

**Paroxetine mesylate (Brisdelle)**

- Adverse effects (>2%):
  - Headache, fatigue/malaise/lethargy, nausea/vomiting
- Drug interactions:
  - Strong CYP2D6 inhibitor
    - Decrease analgesic effect of codeine
    - Decrease efficacy of tamoxifen
- Available as 7.5 mg capsule
- Cost $135 per month

**Gabapentin (Sefelsa®)**

- FDA approval for gabapentin (Sefelsa) denied
  - Company will no longer pursue approval
- Gabapentin failed to reduce the severity and frequency of hot flashes in statistically significant levels after 12 weeks in any of the three randomized, blinded, placebo-controlled trials of involving 1700 postmenopausal women
  - Did experience between 1.5 and 1.6 fewer hot flashes per day than patients on placebo after 4 weeks, which was statistically significant
  - Severity of hot flashes dropped by 0.20, 0.29, and 0.18 after 12 weeks compared with placebo on an ad-hoc, 3-point scale of severity (P=0.047, P=0.003, and P<0.001 respectively).
Additional Pharmacologic Options for Menopausal Symptoms

- **Progesterone**
  - Small Canadian clinical trial indicates Micronized progesterone 300mg/day alone effective in women with recent onset of menopausal symptoms

- **Duexave®**
  - combination of conjugated estrogens with the selective estrogen receptor modulator (SERM) bazedoxifene

Herbal Therapies for Menopausal Symptoms

- Possibly effective or inconsistent data
  - Soy protein from diet
  - Flaxseed
  - Black cohosh
  - DHEA

- Not effective
  - Red clover
  - Chasteberry
  - Dong quai
  - Hops, kudzu, wild yam
  - Ginseng
  - Ginkgo
  - Evening primrose oil
  - Vitamin E

Non-hormonal Therapies for Hot Flashes

- Systematic review and meta-analysis of 70 randomized controlled clinical trials (48 studies involving biological entities)

- Results:
  - Data are insufficient to support effectiveness of any CAM therapy for menopausal symptoms
  - Studies with phytoestrogens do not support benefit
  - Data with black cohosh is inconsistent
  - Several alternative therapies have not been adequately studied (yoga, massage, aromatherapy)

Arch Int Med 2006;166:1453-11465
References and Resources

- Comparison of Oral Contraceptives and Non-Oral Alternatives. Prescribers/Pharmacists Letter detail document #290322
  - The transfer of drugs and therapeutics into human breast milk: an update on selected topics. Pediatrics 2013;132:e796-e809
  - Ling H et al. Reducing the risk of obesity: defining the role of weight loss drugs. Pharmacotherapy 2013
  - McBane et al. Use of compounded bioidentical hormone therapy in menopausal women: an opinion statement of the women’s health practice and research network of the American College of Clinical Pharmacy. Pharmacotherapy 2014 (Jan).