Updates in Therapeutics® 2015:
The Pharmacotherapy Preparatory Review & Recertification Course
Men’s and Women’s Health
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Conflict of Interest Disclosures

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- No conflicts of interest
- Nothing to disclose for this presentation
Learning Objectives

1. Recommend appropriate treatment options for patients with menopausal symptoms, osteoporosis, infertility and sexual dysfunction.

2. Identify drugs that are considered safe and unsafe in pregnancy and lactation.

3. Modify contraceptive regimens based on estrogen- and progestin-related adverse effects or drug interactions.

4. Devise a pharmacotherapeutic plan for appropriate contraceptive use, misused contraceptive methods, and use of emergency contraception.

5. Identify the common sexually transmitted diseases and recommend appropriate pharmacotherapy.
Agenda

- Menopause
- Osteoporosis
- Pregnancy and Lactation
- Contraception
- Infertility
- Sexually Transmitted Infections
- Sexual Dysfunction in Men
Menopause
Patient Case 1, Question 1

E.L. is a 50-year-old woman with hot flashes and vaginal irritation. Has tried exercise, diet, and antidepressants and is unsuccessful. Otherwise healthy with no history of cancer and no surgeries. States hot flashes are interfering with her daily activities and wants to try hormone therapy.

1. Which one of the following was proved statistically significant with conjugated estrogens and medroxyprogesterone acetate and should be mentioned to E.L.?

A. Increased risk of DVT.
B. Decreased risk of stroke.
C. Decreased risk of MI.
D. Increased risk of fractures.
Signs & Symptoms

Vasomotor
- Hot flashes/flushes*
- Night sweats*

Psychosomatic
- Pressure/tightness in head or body
- Headache
- Muscle/joint pain
- Numbness/tingling in feet/hands
- Dizzy or faint
- Difficulty breathing

Psychological
- Anxiety
- Depression
- Insomnia
- Mood Swings

Vaginal Dryness
- Genitourinary atrophy*

*Directly related to estrogen deficiency
Common Hormone Regimens

- Unopposed estrogen
  - Only if patient does not have a uterus
  - Increased risk of endometrial cancer for those with a uterus

- Estrogen plus cyclic progestogen (progestin)

- Estrogen plus daily progestogen
  - Heart and Estrogen/Progestin Replacement Study (HERS)
  - Women’s Health Initiative (WHI)
    - JAMA. 2002;288:321-33

- Estrogen and intermittent progestogen
<table>
<thead>
<tr>
<th>Risk or Benefit</th>
<th>Relative Risk</th>
<th>Absolute Risk each year</th>
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</thead>
<tbody>
<tr>
<td>Heart attacks</td>
<td>1.29 or 29% ↑</td>
<td>7 more cases in 10,000 women</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>1.26 or 26% ↑</td>
<td>8 more cases in 10,000 women</td>
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<tr>
<td>Strokes</td>
<td>1.41 or 41% ↑</td>
<td>8 more cases in 10,000 women</td>
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<tr>
<td>Blood clots</td>
<td>2.11 or 111% ↑</td>
<td>18 more cases in 10,000 women</td>
</tr>
<tr>
<td>Hip fractures</td>
<td>0.66 or 33% ↓</td>
<td>5 fewer cases in 10,000 women</td>
</tr>
<tr>
<td>Colon Cancer</td>
<td>0.63 or 37% ↓</td>
<td>6 fewer cases in 10,000 women</td>
</tr>
<tr>
<td>Dementia</td>
<td>2.05 or 105% ↑</td>
<td>23 more cases in 10,000 women over 65</td>
</tr>
</tbody>
</table>
Younger women

- In women younger than 60 years old and within 10 years or less of menopause
  - Estrogen alone may decrease CHD and all-cause mortality
  - Progestogen + estrogen shows no difference in this group
- Risk of VTE or ischemic stroke increases with oral HT but absolute risk is low in women younger than 60 years
  - Observational data suggests lower risk with transdermal formulation

de Villers et al. Climacteric 2013; 16:203-204
1. Which one of the following was proved statistically significant with conjugated estrogens and medroxyprogesterone acetate and should be mentioned to E.L.?

A. Increased risk of DVT.
B. Decreased risk of stroke.
C. Decreased risk of MI.
D. Increased risk of fractures.
2. Which one of the following HT treatments should be recommended to E.L.?

A. Estrogen patch (17-ß-estradiol) 0.025 mg; change patch twice weekly

B. Estradiol vaginal cream 0.01 mg/g; apply vaginally once daily

C. Conjugated estrogens 0.3 mg/ medroxyprogesterone acetate 1.5 mg; take 1 tablet daily

D. Ospemifene 20 mg ; take 1 tablet daily
Recommendations – NAMS 2012

- Moderate to severe vasomotor symptoms:
  - Primary indication for HT
  - Recommend lowest effective dose

- Genitourinary syndrome (GSM) encompasses both:
  - Moderate to severe vaginal symptoms:
    - Recommend local ET vs. systemic therapy if treating vaginal symptoms only
  - Urinary health:
    - Systemic HT may worsen stress incontinence, local ET therapy may help with overactive bladder

- Sexual function:
  - HT not recommended for sole treatment of diminished libido

- Osteoporosis:
  - HT indication for prevention, ↓osteoporotic fractures, used only when alternate therapies are not appropriate
Risks

- Venous thromboembolism
- CVD
  - Risk appears higher when HT initiated further from onset of menopause
- Breast cancer
  - Estrogen combined with progestogen appears to have risk with 3-5 years of use
  - Estrogen alone has different risk profile (appears later)
- Cognitive function
- Additional data needed
  - Ovarian cancer
  - Lung cancer
Recommendations

- Therapy duration –
  - Lowest dose for least amount of time
  - Check after 3 months to 1 year if asymptomatic; if symptoms occur, treat for an additional 3 months
  - Best to keep less than 5 years of treatment

- Contraindications:
  - Breast cancer, CVD, stroke, history of blood clots
Alternatives for Vasomotor Symptoms

- **Serotonin reuptake inhibitors**
  - Paroxetine (Brisdelle®) 7.5 mg orally daily
    - Has FDA labeling for postmenopausal hot flashes
  - Fluoxetine (Prozac®) 20 mg orally daily
  - Paroxetine (Paxil®) 20 mg orally daily
  - Venlafaxine (Effexor®) 75 mg orally daily (SNRI)

- **Others**
  - Clonidine
  - Megestrol
  - Gabapentin
  - Natural products

Alternatives for Vasomotor Symptoms
Selective Estrogen Receptor Modulators (SERMS)

- Conjugated estrogens 0.45 mg plus bazedoxifene 20 mg oral tablet orally daily (Duavee®)
  - Indicated for treatment of moderate to severe vasomotor symptoms, prevention of osteoporosis
  - Bazedoxifene may be used instead of a progestin, may be used in women with intact uteruses
  - Common adverse effects: Muscle spasms, nausea/vomiting, throat, neck and/or upper abdominal pain, and indigestion
  - Similar contraindications as other SERMs
Alternatives for Vaginal Atrophy
Selective Estrogen Receptor Modulators (SERMS)

- **Ospemifene 60 mg oral tablet daily (Osphena®)**
  - Indicated for the treatment of moderate to severe dyspareunia caused by vulvar and vaginal atrophy owing to menopause
  - Affects uterine endometrium; women with a uterus *may* require a progestin in addition to ospemifene though studies did not include a progestin
  - Adverse reactions (>1%):
    - Hot flashes, muscle cramps, vaginal discharge, hyperhidrosis
Alternative Therapies - Ospemifene

- **Contraindications**
  - Similar to those of estrogen (e.g. history of estrogen-dependent cancer, DVT, undiagnosed vaginal bleeding)
  - Pregnancy, nursing, pediatrics
  - Hepatic impairment

- **Drug interactions**
  - CYP 3A4 inhibitors or inducers
    - Rifampin may decrease levels
    - Fluconazole and ketoconazole may increase levels
  - Highly protein bound: around 99%; may affect other medications that are protein bound
  - Should not be given with estrogen products
E.L. is a 50-year-old woman with hot flashes and vaginal irritation. Has tried exercise, diet, and antidepressants and is unsuccessful. Otherwise healthy with no history of cancer and no surgeries. States hot flashes are interfering with her daily activities and wants to try hormone therapy.

2. Which one of the following HT treatments should be recommended to E.L.?

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References

- The 2012 Hormone Therapy Position Statement of The North American Menopause Society (NAMS)
  - Available at http://www.menopause.org/psht12.pdf

  - Menopause 2013;20(9): 888-902
  - Available at http://www.menopause.org/docs/default-source/2013/vva-position-statement.pdf?sfvrsn=0
Osteoporosis
Patient Case 2, Question 3

R.K. is a 71-year-old white woman with a history of rheumatoid arthritis who smokes ½ pack/day. She takes calcium 1200 mg per day in divided doses and vitamin D 600 IU orally per day. She is 63 in. (160cm) and weighs 140 lbs. (63kg). Her BMD T-score is −2.6 at the hip and −2.1 at the spine. Her FRAX score is 10-year major fracture risk of 22% and 10-year hip fracture risk of 11%.

3. Which one of the following statements best describes the correct diagnosis for R.K.?

A. Normal BMD of the spine.
B. She has low bone mass (osteopenia) of the hip.
C. She has osteoporosis of the hip.
D. She has severe osteoporosis of the spine.
Osteoporosis Definitions

World Health Organization Definitions

- **Normal** = BMD within 1 standard deviation (SD) of the young adult mean

- **Osteopenia** = BMD between $-1$ SD and $-2.5$ SD below the young adult mean

- **Osteoporosis** = BMD at least $-2.5$ SD
Risk Factors

- Female
- White race
- Poor nutrition, long-term low-calorie intake
- Early menopause (before age 45) or prolonged amenorrhea
- Estrogen deficiency
- Drugs:
  - Glucocorticoids
  - Heparin
  - Anticonvulsants
  - Excessive levothyroxine
  - GnRH agonists
  - Lithium
  - Cancer drugs

- Low body mass index (BMI) or low weight
- Family history of osteoporosis
- Low calcium and vitamin D intake
- Sedentary lifestyle, decreased mobility
- Cigarette smoking
- Alcoholism
- Dementia
- Impaired eyesight despite adequate correction
- Previous fractures
- History of falls
Risk Assessment

- FRAX® Score – platform created to calculate 10-year fracture risk
  - Available at http://www.shef.ac.uk/FRAX/ or http://www.nof.org
  - Includes 10 risk factors: age, sex, weight, height, femoral neck BMD, parental history of fractures, tobacco use, glucocorticoids, rheumatoid arthritis, alcohol use, other secondary causes

- Bone mineral density (BMD) testing
  - Dual-energy x-ray absorptiometry (DXA)- gold standard
Screening Recommendations

- **BMD Measurements in Women**
  - All women 65 years and older
  - Postmenopausal women with medical causes of bone loss (hyperparathyroidism, steroid use, etc.)
  - Postmenopausal women age 50 and older with risk factors:
    - Fracture after menopause
    - Wt <127 lbs or BMI <21 kg/m²
    - Smoker
    - Parent w/ hip fracture
    - Rheumatoid arthritis
    - Alcohol > 2 units/day
  - Postmenopausal women with fragility fracture
Screening Recommendations

- **BMD Measurements in Men**
  - All men older than 70 years of age
  - Men ages 50-70 with risk factors or previous fractures
Lifestyle Modifications

Recommendations

- Advise patient to avoid smoking and to consume only moderate amounts of alcohol.

- Encourage regular weight-bearing and muscle-strengthening exercise.

- Encourage adequate intake of calcium (at least 1000 mg/day) and vitamin D (600–800 IU/day). For older than 70 years – 800 IU/day.

- Assess fall risks.
R.K. is a 71-year-old white woman with a history of rheumatoid arthritis who smokes ½ pack/day. She takes calcium 1200 mg per day in divided doses and vitamin D 600 IU orally per day. She is 5’3” (160cm) and weighs 140 lbs. (63kg). Her BMD T-score is −2.6 at the hip and −2.1 at the spine. Her FRAX score is 10-year major fracture risk of 22% and 10-year hip fracture risk of 11%.

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4. Which one of the following is the best therapy for R.K.?

A. No further treatment is required; continue calcium 1200 mg/vitamin D 600 IU orally daily.

B. Teriparatide 20 mcg SQ daily, calcium 1200 mg orally in divided doses, vitamin D 600 IU orally daily.

C. Miacalcin nasal spray 1 spray (200 IU) in one nostril daily, calcium 1200 mg orally in divided doses and increasing vitamin D to 800 IU orally daily.

D. Risedronate 35 mg PO every week, calcium 1200 mg orally in divided doses and increasing vitamin D to 800 IU orally daily.
Initiating Pharmacotherapy

- Based on NOF, AACE, and NAMS recommendations:
  - Hip or spine fracture
  - T-score -2.5 or below at hip, spine, or femoral neck
  - T-score between -1.0 and -2.5 with a 10-year probability of a hip fracture $\geq 3\%$ OR a 10-year probability of a major osteoporosis-related fracture $\geq 20\%$ based on the FRAX® tool (US-adapted WHO algorithm)
Current Treatments

- Bisphosphonates (1\textsuperscript{st} line)
- Selective estrogen receptor modulators (SERMs)
- Calcitonin
- Teriparatide
- Denosumab
- Hormone therapy
Bisphosphonates

- Inhibit osteoclasts, reduce bone resorption
- Reduce risk of vertebral fractures by 40-70%
- Reduce risk of non-vertebral fractures (hip) by 20-35%
- Adverse effects: Oral agents → most common is esophageal/gastric irritation
- Must be taken on an empty stomach and remain upright for at least 30 min. (60 min for ibandronate), Risedronate sodium (delayed release) should be taken after breakfast
- Only use in patients with GFR of > 30mL/min (see individual agents)
- Additional risks: osteonecrosis of jaw, atypical fractures, afib?
Bisphosphonates

- Alendronate (Fosamax®) PO daily or weekly
  - Also available with vitamin D 2800 or 5600 IU with weekly dose
  - Effervescent tablet (Binosto®)
- Risedronate (Actonel®) PO daily, weekly, monthly
  - Also with calcium 1250 mg days 2-7 with 35 mg weekly dose
- Risedronate (Atelvia®) PO weekly (delayed release, take after breakfast, avoid PPI/antacid use)
- Ibandronate (Boniva®) PO daily, monthly or IV Q 3 months
- Zolendronic acid (Reclast®) IV yearly or Q 2 years for prevention
- Etidronate (approved in Canada for osteoporosis)
Other Therapies - SERMs

- Raloxifene (Evista®) 60 mg orally daily
  - Approved for prevention and treatment of osteoporosis
  - ↓risk of vertebral fracture by 55% (MORE data) in women with T-score < -2.5 and by 30% in women with low T-scores
  - No effect observed for non-vertebral (hip) fracture
  - Adverse Effects: ↑VTE events, may cause hot flashes or leg cramps
Other Therapies - SERMs

- Conjugated estrogens 0.45 mg plus bazedoxifene 20 mg (Duavee®) orally daily
  - Approved for prevention of osteoporosis in postmenopausal women
  - Significantly increased total hip BMD at 24 months by 1.96% in women who had been postmenopausal 1 to 5 years
  - Increased total hip BMD by 1.73% in women postmenopausal for more than 5 years
  - Significantly increased mean lumbar spine BMD by 1.51% at 12 months in women who had been postmenopausal between 1 and 5 years
  - Adverse reactions, contraindications discussed in hormone therapy section
Other Therapies

- **Calcitonin (Miacalcin®, Fortical®)** 200 IU daily intranasally
  - Approved for treatment, usually alternative if other agents cannot be used
  - Effective for reducing risk of vertebral fractures only, may help with bone pain from compression fractures
  - Adverse effects (nasal): rhinitis, epistaxis
  - Also available as SubQ and IM inj.

- **Teriparatide (Forteo®)**: recombinant human PTH
  - Subcutaneous injection 20 mcg/day for up to 24 months
  - Rare risk of osteosarcoma (seen in animal studies)
Other Therapies

- **Denosumab (Prolia®)**
  - Inhibits osteoclast-mediated bone resorption, monoclonal antibody binds to RANKL (receptor activator of nuclear factor κβ ligand)
    - cytokine essential for formation, function, survival of osteoclasts
  - Dose 60 mg subcutaneously every 6 months
  - Increased BMD hip (6%) and spine (9%)
  - Reduced spinal fracture risk by 68%, hip fracture risk by 40%
  - Safety issues
    - Possible infections
    - Hypocalcemia

- **Hormone therapy**
  - Approved for prevention only
Patient Case 2, Question 4

R.K. is a 71-year-old white woman with a history of rheumatoid arthritis who smokes ½ pack/day. She takes calcium 1200 mg orally in divided doses and vitamin D 600 IU orally daily. She is 63 in. (160 cm) and weighs 140 lbs. (63 kg). Her BMD T-score is −2.6 at the hip and −2.1 at the spine. Her FRAX score is 10-year major fracture risk of 22% and 10-year hip fracture risk of 11%.

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   C. Miacalcin nasal spray 1 spray (200 IU) in one nostril daily, calcium 1200 mg orally in divided doses and increasing vitamin D to 800 IU orally daily.
   D. Risedronate 35 mg PO every week, calcium 1200 mg orally in divided doses and increasing vitamin D to 800 IU orally daily.
References

  - Available at http://www.nof.org/


  - Available at http://www.menopause.org/PSosteo10.pdf

- 2010 AACE Medical Guidelines for Clinical Practice for the Diagnosis and Treatment of Postmenopausal Osteoporosis
  - Available at http://www.aace.com
Pregnancy and Lactation
Patient Case 3, Question 5

S.E. is a 28-year-old woman who would like to get pregnant soon. Her medical history includes hypertension and seasonal allergies. Her drugs include lisinopril, nasal saline spray, and folic acid.

5. Which one of the following is best to treat her hypertension while she is pregnant or trying to conceive?

A. Continue lisinopril.  
B. Discontinue lisinopril and all other medications.  
C. Discontinue lisinopril and start methyldopa.  
D. Continue lisinopril and add atenolol.
Drug Use in Pregnancy

General approaches

- Folic acid (at least 400 mcg daily) prior to conception to prevent neural tube defects
- Assess current drug use if trying to conceive
  - Teratogen: drug or environmental agent that has potential to cause abnormal fetal growth and development.
- Consider trimester and timing of medication administration.
- Assess drug safety versus benefit.
FDA Pregnancy Risk Classifications

Summary (See Table 9, page 1-270):
- A: Controlled studies show no risk
- B: No evidence of risk in humans
- C: Risk cannot be ruled out (no studies in humans)
- D: Positive evidence of risk
- X: Contraindicated in pregnancy, definite risk
FDA New Labeling for Pregnancy and Lactation

- New labeling – Effective June 30, 2015
  - Fetal risk summary
  - Clinical considerations
  - Data section
  - Information for exposure registries
Known Teratogens

- Isotretinoin
- Methotrexate
- Alcohol
- Mercury
- Thalidomide
- Androgens
- Cocaine
- Tetracycline
- Vitamin A
- Statins
- ACE inhibitors
- Diethylstilbestrol
- Warfarin
- Lead
- Carbamazepine
- Topiramate
- Phenytoin
- Valproate
- Lithium
Conditions in Pregnancy– Key Concepts

- GI (nausea and vomiting)
  - Options include vitamin B6, antihistamines, ondansetron, metoclopramide

- Headache
  - Acetaminophen recommended first-line
  - Avoid use of NSAIDs, ASA (consider trimester), triptans, ergot derivatives

- Coagulation disorders
  - Heparin/LMWH preferred for anticoagulation; AVOID warfarin

- Diabetes
  - Insulin preferred; sulfonylureas/metformin studied

- Hypertension
  - AVOID ACE-I/ARBs; methyl dopa, labetalol, nifedipine are 1st line (may use certain CCBs, beta-blockers [atenolol risk of intrauterine growth retardation])
Patient Case 3, Question 5

S.E. is a 28-year-old woman who would like to get pregnant soon. Her medical history includes hypertension and seasonal allergies. Her drugs include lisinopril, nasal saline spray, and folic acid.

5. Which one of the following is best to treat her hypertension while she is pregnant or trying to conceive?

A. Continue lisinopril.
B. Discontinue lisinopril and all other medications.
C. Discontinue lisinopril and start methyldopa.
D. Continue lisinopril and add atenolol.
Drug Use in Lactation

- Consider risk vs. benefit
- “Pump and Dump” milk
- Choose drugs with shorter half-lives
- Drugs enter human milk if they are:
  - Highly lipid soluble
  - In high concentration in the mother’s plasma
  - Low in molecular weight (<500)
  - Low in protein binding
- Also need to consider mother’s genotype
General Recommendations from American Academy of Pediatrics

  - Pain medications (best to avoid narcotics, short term use of NSAIDs may be okay)
  - Vaccine use (small pox and yellow fever contraindicated)
  - Diagnostic imaging agents
  - Galactagogues
  - Common herbals
  - Drugs for treating alcohol, tobacco, substance abuse
Contraception
Patient Case 4, Question 6

K.R. is a 22-year-old woman initiated on Mircette 4 months ago for contraception. She has breakthrough bleeding at the start of her active pills that lasts a few days before resolving. The physician wants to change the OC.

6. Which one of the following OCs on her formulary is the best for the physician to prescribe?
   A. Continue on Mircette (desogestrel 0.15 mg/ethinyl estradiol 20 mcg) for another 3 months.
   B. Change to Ortho-Cept (desogestrel 0.15 mg/ethinyl estradiol 30 mcg).
   C. Change to Loestrin 21 (norethindrone acetate 1.5 mg/ethinyl estradiol 30 mcg).
   D. Change to Lessina (levornogestrel 0.1 mg/ethinyl estradiol 20 mcg).
## Patient Case 4, Question 6

<table>
<thead>
<tr>
<th>Name of OC</th>
<th>Estrogen Property</th>
<th>Progestin property</th>
<th>Androgen property</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mircette (desogestrel 0.15mg /EE 20mcg)</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Ortho-Cept (desogestrel 0.15mg /EE 30 mcg)</td>
<td>Intermediate</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Lessina (levonorgestrel 0.1mg/EE 20mcg)</td>
<td>Low</td>
<td>Low</td>
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</tr>
<tr>
<td>Loestrin 21 (norethindrone acetate 1.5 mg/ 30 mcg)</td>
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Contraceptive Methods

- Combined hormonal contraceptives
  - Oral tablet
  - Patch
  - Vaginal ring
- Progestin-only
  - Oral tablet
  - Injection
  - Implant
  - Intrauterine system
- Non-hormonal
Combined Contraceptives: Contraindications (Category 4)

- Less than 3-6 wks postpartum
- Smoker ≥ 35 yrs old
- Multiple risk factors for CVD
- BP >160/100
- Vascular disease
- Current or history of DVT/PE
- Complicated diabetes
- Presence of liver tumors, severe cirrhosis, or active viral hepatitis

- Major surgery with prolonged mobilization
- Known thrombogenic mutations
- Current or history of ischemic heart disease
- Stroke (history of CVA)
- Complicated valvular heart disease
- Migraine headache with aura or migraine without aura if ≥ 35 yrs old
- Current breast cancer


(US Medical Eligibility Criteria http://www.cdc.gov/reproductivehealth/unintendedpregnancy/USMEC.htm)
Combined Contraceptives: Side Effects

Estrogenic
- Nausea, vomiting
- Bloating, edema
- Irritability
- Cyclic weight gain
- Cyclic headache
- Hypertension
- Breast fullness, tenderness

Progestational and Androgenic**
- Headaches
- Increased appetite
- Increased weight gain
- Depression, fatigue
- Changes in libido
- Hair loss, hirsutism**
- Acne, oily skin**
Managing Side Effects

- **Nausea**
  - Usually related to estrogen content
  - Take at bedtime or with food

- **Acne**
  - Choose less androgenic formulation or higher estrogen activity

- **Breakthrough bleeding and spotting**
  - If unexpected bleeding occurs, use additional contraception until bleeding completely ceases
  - Rule out potential causes (e.g., pelvic inflammatory disease)
  - Encourage continuation if first few cycles
Managing Side Effects

- Breakthrough bleeding and spotting (cont’d)
  - **When switch is indicated:**
    - **Increase estrogen dose**
      - If bleeding begins during first 14 days
      - If absence of withdrawal menses
      - If menses continues into active pill cycle
    - **Change progestin**
      - If bleeding begins after 14 days (late in the cycle)
      - Progestin should have higher progestational and/or androgenic activity
    - **Increase both estrogen and progestin**
      - If bleeding occurs midcycle
K.R. is a 22-year-old woman initiated on Mircette \textbf{4 months ago} for contraception. She has breakthrough bleeding at \textbf{the start of her active pills} that lasts a few days before resolving. The physician wants to change the OC.
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C. Change to Loestrin 21 (norethindrone acetate 1.5 mg/ethinyl estradiol 30 mcg).

D. Change to Lessina (levonorgestrel 0.1 mg/ethinyl estradiol 20 mcg).
L.M. is a 37-year-old woman, going to get married, needs birth control pills for now, wants children in a year. PMH: hypertension x 2 years, GERD, admits to 2 glasses of wine/week and smokes ½ pack per day. Meds: HCTZ 25 mg PO daily, Lotrel 5/20 (amlodipine/benazepril) PO daily, Prilosec 20 mg (omeprazole) PO daily, and occasional ibuprofen. She is 67 in., Weight: 210 lbs. (95kg).

7. Which one of the following contraceptive products is best to recommend for L.M.?

A. Transdermal contraceptive patch
B. Oral tablet ethinyl estradiol/drospirenone
C. Oral tablet norethindrone
D. Depot medroxyprogesterone acetate injection
Combined Contraceptives: Drug Interactions

**Common hepatic enzyme inducers (may reduce contraceptive effectiveness)**

- Rifampin - significant risk of failure
  - Continue back-up method for 3 weeks after discontinuation
- Anticonvulsant agents: phenobarbital, phenytoin, topiramate, carbamazepine, primidone
  - **Levels of lamotrigine decreased by CHC use**
- St. John’s wort
- Protease inhibitors

**Management**

- Use another contraceptive method
- Use different therapeutic agent (i.e. anticonvulsant)
- Use contraceptive with higher estrogen doses
Combined Contraceptives: Drug Interactions

- **Drospirenone** (progestin with antiandrogenic properties)
  - Interacts with NSAIDs, ACE Inhibitors, may increase serum potassium
  - Increased risk of VTE – FDA statement

- **Antibiotics** (broad-spectrum)
  - Reported cases in the literature of contraceptive failure; not possible to identify women who may be at risk of OC failure.
  - Recent WHO/CDC eligibility criteria do not recommend alternate contraception.
  - Counsel about the additional use of nonhormonal contraception or alternate methods:
    - Those not comfortable with risk of interaction
    - Those with previous failures or who develop breakthrough bleeding during use of antibiotics
Combined Contraceptives

- Unique oral formulations (select examples)
  - Quadriphasic
    - Natazia® (estradiol valerate/dienogest)
  - Contain levomefolate calcium
    - Safyral® (ethinyl estradiol 30 mcg /drospirenone 3 mg)
    - Beyaz® (ethinyl estradiol 20 mcg /drospirenone 3 mg)
  - Low estrogen
    - Lo Loestrin Fe® (ethinyl estradiol 10 mcg/ norethindrone acetate 1 mg)

- Extended regimen
  - 3 month formulations (Quartette- ethinyl estradiol 20-30 mcg/levonorgestrel 0.15 mg --newest addition)
  - 1 year formulations
  - Breakthrough bleeding common
Combined Contraceptives

- Non-oral Formulations
  - Transdermal patch (Ortho-Evra®)
    - Increased exposure to estrogen, 60% more estrogen than in women taking 35 mcg of ethinyl estradiol
    - Increased risk of VTE, cardiovascular and cerebrovascular events?
    - Less effective in women > 198 lbs. (90kg)
  - Vaginal ring (NuvaRing®)
    - Insert vaginally and leave for 3 weeks, one week off, then repeat
    - Consider correct administration technique, specific recommendations for expulsion
Contraceptive Methods

- Combined hormonal contraceptives
  - Oral tablet
  - Patch
  - Vaginal ring

- Progestin-only
  - Oral tablet
  - Injection
  - Implant
  - Intrauterine system

- Non-hormonal
Progestin-Only Contraceptives

- Progestin-only “mini-pills” (POPs)
  - Take one pill at the **SAME TIME** daily until end of pack. Start next pack the next day.
  - **More than a 3 hour delay** is considered to be a “missed dose”
  - If a pill is missed, take missed pill(s) and use backup for 48 hours.
Progestin-Only Contraceptives

- Depot medroxyprogesterone acetate (Depo-Provera®, DMPA) injection
  - Injection administered every 11-13 weeks
  - Side effects
    - Weight gain
    - Mood issues, other progestin related effects
    - Long return to fertility
    - Possible decrease in BMD, especially in younger women with use > 5 years
  - Recommend calcium supplements with use
Progestin-Only Contraceptives

- Levonorgestrel intrauterine system (Mirena®, Skyla®, Liletta®)
  - Releases 20 mcg/day of levonorgestrel (Mirena), 10-14 mcg/day (Skyla), 12-18 mcg/day (Liletta)
  - Mirena effective for 5 years, Skyla and Liletta for 3 years
  - Risks include infections and expulsion (patient counseling points)
  - Quick return to fertility

- Implantable rod (etongestrel- Implanon/Nexplanon®)
  - Effective for 3 years
  - Insertion-site reactions, Nexplanon – radiopaque
  - Concern with weight and effectiveness
Patient Case 5, Question 7

L.M. is a 37-year-old woman, going to get married, needs birth control pills for now, wants children in a year. PMH: hypertension x 2 years, GERD, admits to 2 glasses of wine/week and smokes ½ pack per day. Meds: HCTZ 25 mg PO daily, Lotrel 5/20 (amlodipine/benazepril) PO daily, Prilosec 20 mg (omeprazole) PO daily, and occasional ibuprofen. She is 5’7”, Weight: 210 lbs. (95kg).

7. Which one of the following contraceptive products is best to recommend for L.M.?

A. Transdermal contraceptive patch
B. Oral tablet (ethinyl estradiol/drospirenone)
C. Oral tablet (noretindrone)
D. Depot medroxyprogesterone acetate injection
Emergency Contraception

- Indications
  - Unprotected intercourse in the past 120 hours (OTC products labeled for use within 72 hours)
  - Contraceptive failure
    - Condom breaks
    - Missed oral contraceptive pills
    - Expulsion of IUD or vaginal ring
    - Patch fell off for long period of time
    - Displacement of barrier method (diaphragm)
  - Sexual assault
  - Exposure to teratogen
Emergency Contraception

- **Yuzpe Regimen** – high dose estrogen + progestin
- **Levonorgestrel** – progestin only
  - Generic forms (0.75 mg, 2 tablets in package), tablets may be taken 12 hours apart or together at one time.
  - **OTC for 17 years and older**
  - MyWay®, Next Choice One Dose®, Plan B One-Step®, Take Action® (1.5 mg, 1 tablet taken as soon as possible after unprotected intercourse).
  - **OTC for all ages**
- **Ulipristal acetate** – Selective Progesterone Receptor Modulator (SPRM)
  - ella® 30 mg, 1 tablet taken as soon as possible after unprotected intercourse, labeled for use within 120 hours
  - Prescription-only
- **Copper IUD** - Use within 5 days of unprotected intercourse
Emergency Contraception – add weight issues

- Levonorgestrel
  - Not recommended for those with a BMI of 26 or greater
- Ulipristal acetate
  - May be used for those with a BMI of up to 30
- Copper IUD
  - May be used by all
  - Recommended for those who have BMI of 30 or greater
<table>
<thead>
<tr>
<th>Product Name</th>
<th>Formulation</th>
<th>Availability and recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ella®</td>
<td>Ulipristal acetate 30 mg single dose</td>
<td>Prescription only, labeled for up 120 hours post-coitus</td>
</tr>
<tr>
<td>Levonorgestrel generic,</td>
<td>Levonorgestrel 0.75 mg x 2 doses</td>
<td>OTC for those older than 17 years old, labeled for 72 hours post-coitus*</td>
</tr>
<tr>
<td>Plan B One-Step®, My Way®,</td>
<td>Levonorgestrel 1.5 mg single dose</td>
<td>OTC for all, labeled for 72 hours post-coitus*</td>
</tr>
<tr>
<td>Next Choice One Dose®,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Take Action®</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Labeled for 72 hours but studies suggest use up to 120 hours post-coitus
Infertility
8. L.L. is a 26-year-old woman who has been trying to conceive for 13 months. She is 61 in. (155 cm) and weighs 172 lb (78 kg); her BMI is 32, and she has moderate acne and hirsutism. Her menstrual cycle is fairly regular at 26-27 days. Her husband’s medical exam is normal and semen exam are normal. Her ultrasonography shows polycystic ovaries. Her insulin/glucose ratio is high. Which is the best first-line agent to recommend to L.L. that might help her to ovulate?
Patient Case 6, Question 8

A. Lose weight and start metformin.
B. Continue trying to conceive; make no recommendations at this time.
C. Start FSH injections.
D. Start hCG injections.
Infertility Potential Causes

85% of couples conceive in 1 year, 15% infertile

- Men (male factor)
  - Endocrine
  - Anatomic
  - Sexual dysfunction

- Women (female factor)
  - Ovulatory
  - Cervical
  - Pelvic

- Medical conditions
  - Polycystic ovary syndrome
  - Endometriosis
  - Pelvic inflammatory disease
  - Uterine fibroids
  - Idiopathic
Fertility Agents

1. Clomiphene citrate
2. Human menopausal gonadotropin (hMG)
3. Follicle-stimulating hormone (FSH)
4. Human chorionic gonadotropin (hCG)
5. Gonadotropin-releasing hormone analogs (GnRH)
6. Metformin
7. Aromatase inhibitors
Patient Case 6, Question 8

8. Which is the best first-line agent to recommend to L.L. that might help her to ovulate?

A. Lose weight and start metformin.
B. Continue trying to conceive; make no recommendations at this time.
C. Start FSH injections.
D. Start hCG injections.
Sexually Transmitted Diseases/Infections
Sexually Transmitted Infections/Diseases

- Available at www.cdc.gov/std/treatment/
- 2014 Guidelines will be available in summer 2014
Herpes Simplex Virus (HSV)

- Therapy can help control symptoms but does not affect risk, frequency or severity of recurrences (50-80% recur)
- Virus remains latent in sacral dorsal root ganglia
- Initial HSV infection
  - Acyclovir 400 mg orally 3 times/day for 7–10 days
  - Acyclovir 200 mg orally 5 times/day for 7–10 days
  - Famciclovir 250 mg orally 3 times/day for 7–10 days
  - Valacyclovir 1 g orally 2 times/day for 7–10 days
 HSV

- Recurrent HSV infection
  - If treatment is initiated within 1 day of lesion onset, patients with recurrent infections may benefit.
  - See page 1-156 for regimens of acyclovir, famciclovir, and valacyclovir

- Suppressive therapy
  - Recommended in patients with six or more episodes yearly (reassess annually the need for suppressive therapy)
    - Acyclovir 400 mg orally 2 times/day
    - Famciclovir 250 mg orally 2 times/day
    - Valacyclovir 500 mg/day orally
    - Valacyclovir 1000 mg/day orally
Patient Case 7, Question 9

D.H. is a 21-year-old woman who presents with genital itching and vesicles on her vulva. She is sexually active with one partner who has a history of herpes. Her partner does not always use a condom. She is initiated on acyclovir for this initial herpes simplex infection.

9. Which of the following statements is best to mention to D.H. regarding treatment of her herpes infection?

A. Treatment will decrease the risk of recurrent herpes infections.
B. Treatment will shorten the duration of symptoms and infectivity of the initial infection.
C. Treatment will decrease the severity of recurrent herpes infections.
D. Treatment will prevent the virus from remaining latent in the dorsal root ganglia.
10. D.H. returns to the clinic 10 months after her initial herpes infection. She is troubled by all of the recurrences she is having (seven to date). Which is best to recommend?

A. Valacyclovir 500 mg orally 2 times/day to be used for 5 days whenever she notices a recurrence beginning.
B. Acyclovir 400 mg orally 3 times/day to be used for 10 days whenever she notices a recurrence beginning.
C. Suppressive therapy with famciclovir 250 mg orally 3 times/day.
D. Suppressive therapy with valacyclovir 500 mg/day orally.
Sexually Transmitted Infections

- **Syphilis (primary)**- Benzathine penicillin G 50,000 units/kg up to 2.4 million units IM (adults), doxycycline 100 mg PO BID x 2 weeks

- **Chlamydia** – Azithromycin 1 gm in a single dose or doxycycline 100 mg 2 times/day for 7 days

- **Gonorrhea** – **Ceftriaxone 250 mg IM or** cefixime 400 mg orally—all as a single dose **PLUS** treatment of chlamydia if not ruled out
  - Fluoroquinolones not recommended because of resistance

- Abstain from sexual intercourse for at least 7 days and until sexual partners are adequately treated.

- Complications:
  - Urethritis, Prostatitis, Pelvic Inflammatory Disease
M.A. is a 24-year-old woman with severe abdominal pain, fever, dysuria, and a vaginal discharge. She is sexually active with multiple male partners. PMH unremarkable except for recurrent genital herpes (one or two episodes per year). Medications: oral contraceptive, fluticasone nasal spray as needed. Temp. 101.2°F (38°C), HR 92, RR 15, BP 117/75 mm Hg. M.A. has adnexal tenderness, cervical motion tenderness, and a vaginal discharge.

11. Which one of the following is the best empiric therapy?

A. Ampicillin/sulbactam 2 g IV every 6 hours for 14 days.
B. Metronidazole 500 mg IV 3 times/day for 7 days.
C. Cefotetan 2 g IV every 12 hours with doxycycline 100 mg orally every 12 hours for 14 days.
D. Ceftriaxone 125 mg IM × 1 with doxycycline 100 mg IV 2 times/day for 7 days.
Pelvic Inflammatory Disease

- Parenteral treatment:
  - Discontinued 24 hours after clinical improvement and switched to oral therapy for 14 days.
  - Regimen A: cefotetan 2 g intravenously every 12 hours or cefoxitin 2 g intravenously every 6 hours **PLUS** doxycycline 100 mg intravenously or orally every 12 hours
  - Regimen B: clindamycin 900 mg intravenously every 8 hours **PLUS** gentamicin intravenously/intramuscularly 2-mg/kg loading dose; then 1.5 mg/kg every 8 hours (or once-daily therapy)
Pelvic Inflammatory Disease

- **Alternative regimens:**
  - Ampicillin-sulbactam 3 g intravenously every 6 hours plus doxycycline 100 mg intravenously **or** orally every 12 hours
  - Ceftriaxone 250 mg intramuscularly once (other third-generation cephalosporins also acceptable) **or** cefoxitin 2 g intramuscularly plus probenecid 1 g orally once
    - **PLUS** doxycycline 100 mg 2 times/day for 14 days with or without metronidazole 500 mg orally 2 times/day for 14 days
- **Sexual partners of patients with PID within the past 60 days** should be tested and treated.
M.A. is a 24-year-old woman with severe abdominal pain, fever, dysuria, and a vaginal discharge. She is sexually active with multiple partners. PMH unremarkable except for recurrent genital herpes (one or two episodes per year). Medications: oral contraceptive, fluticasone nasal spray as needed. Temp. 101.2°F (38°C), HR 92, RR 15, BP 117/75 mm Hg. M.A. has adnexal tenderness, cervical motion tenderness, and a vaginal discharge.

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C. Cefotetan 2 g intravenously every 12 hours with doxycycline 100 mg orally every 12 hours for 14 days.
D. Ceftriaxone 125 mg intramuscularly × 1 with doxycycline 100 mg intravenously 2 times/day for 7 days.
Vaginal Infections

- **Bacterial Vaginosis**
  - Metronidazole or clindamycin
  - Malodorous vaginal discharge
  - Treatment of sexual partners is unnecessary

- **Trichomoniasis**
  - Metronidazole
  - Malodorous yellow-green vaginal discharge
  - **All sexual partners should be treated**

- **Vulvovaginal Candidiasis**
  - OTC/Rx vaginal antifungals (1, 3, and 7 day regimens- see Table 23) and oral fluconazole
  - Intense itchiness and beige, milky vaginal discharge
  - Recurrent (4 or more episodes/year) may require longer treatment, maintenance therapy
Male Sexual Dysfunction
A 65-year-old man presents to his physician complaining of symptoms determined to be erectile dysfunction (ED). He has a history of hyperlipidemia, GERD, and glucose intolerance. His current medications include atorvastatin 20 mg PO daily, omeprazole 20 mg PO daily, and aspirin 81 mg as tolerated. He states that he heard of medications to help with his symptoms but does not want to have to plan out his intimate moments.

13. Which of the following drugs would work best for this patient?

A. Tadalafil
B. Avanafil
C. Yohimbine
D. Bupropion
Male Sexual Dysfunction

- Reduced libido from organic or psychological causes
  - Low serum testosterone concentrations
  - Increased concentrations of serum prolactin

- Ejaculation
  - Premature
  - Retarded
  - Absent
  - Retrograde

- Erectile dysfunction
  - Psychological
  - Organic
  - Mixed
  - Other causes (drugs)
Male Sexual Dysfunction

- Treat underlying cause, if possible
- Control risk factors
- Non-pharmacological: vacuum pump devices, venous constriction rings
- Pharmacological:
  - Testosterone replacements: injection, patch, gel, topical solution, buccal system, pellet
    - Specific application instructions
    - Avoid in patients with prostate cancer
    - Monitor for liver toxicity, increased lipids/BP, enlarged prostate
  - Yohimbine
  - Alprostadil injection or pellets
  - **SSRIs- for premature ejaculation
Male Sexual Dysfunction

- Phosphodiesterase Type 5 Inhibitors:
  - Generally, 1\textsuperscript{st} line therapy for ED
  - Contraindicated with nitrate use, caution with cardiovascular disease
  - Drug interactions – CYP3A4 inhibitors (macrolides, azole antifungals, protease inhibitors), can increase levels of the PDE-5s and may require PDE-5 dose decrease
  - Concurrent use with alpha-antagonists may cause hypotension
  - May require hepatic or renal dose adjustments
  - Vardenafil may cause QT prolongation, avoid with Class Ia and Class III antiarrhythmics
<table>
<thead>
<tr>
<th>Name</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil (Viagra)</td>
<td>50 mg PO 1 hr. prior to intercourse (Dose range 25-100 mg)</td>
<td>May require hepatic and renal dose adjustments, take on empty stomach</td>
</tr>
<tr>
<td>Vardenafil (Levitra)</td>
<td>10 mg PO 1 hr prior to intercourse (Dose range 5-20 mg)</td>
<td>May require hepatic dose adjustment, fatty meal delays onset</td>
</tr>
<tr>
<td>Vardenafil oral disintegrating tablet (Staxyn)</td>
<td>10 mg PO 1 hr prior to intercourse</td>
<td>Not recommended with hepatic issues, do not use with CYP3A4 inhibitors</td>
</tr>
<tr>
<td>Tadalafil (Cialis)</td>
<td>5 mg PO up to 36 hours prior to intercourse (Dose range 5-20 mg), 2.5 – 5 mg PO daily for daily dosing</td>
<td>May require hepatic or renal dose adjustments, food has no effect on onset</td>
</tr>
<tr>
<td>Avanafil (Stendra)</td>
<td>100 mg PO 30 min. prior to intercourse, (Dose range 50-200)</td>
<td>Fatty food may delay onset</td>
</tr>
</tbody>
</table>
A 65-year-old man presents to his physician complaining of symptoms determined to be erectile dysfunction (ED). He has a history of hyperlipidemia, GERD, and glucose intolerance. His current medications include atorvastatin 20 mg PO daily, omeprazole 20 mg PO daily, and aspirin 81 mg PO daily as tolerated. He states that he heard of medications to help with his symptoms but does not want to have to plan out his intimate moments.

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B. Avanafil
C. Yohimbine
D. Bupropion
Questions