American College of Clinical Pharmacy

Updates in Therapeutics® 2012:
Ambulatory Care Pharmacy Preparatory Review and Recertification Course

Nephrology
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Conflict of Interest Disclosures

- None

Patient Case 1

- **A 72 yo woman weighing 43 kg who is is 5 feet tall appears to have stable renal function and has a sedentary lifestyle. Her SCr is 0.5 mg/dL. Calculate her CrCl using Cockroft-Gault equation. Which one of the following statement most accurately assesses her estimated CrCl?**
- A. Her calculated CrCl is much lower than what is expected for a woman of her age. She likely has significant renal disease.
- B. Her calculated CrCl is much lower than what is expected for a woman of her age. This is probably a false reading because of her likely reduced muscle mass.
- C. Her calculated CrCl is much higher than what is expected for a woman of her age. She likely has excellent renal function.
- D. Her calculated CrCl is much higher than what is expected for a woman of her age. This is probably a false reading because of her likely reduced muscle mass.

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C. Creatinine

- Byproduct of creatinine metabolism in the muscle.
- Concentration dependent upon muscle mass.
- Freely filtered. Not reabsorbed. Only a small amount secreted.
  - Creatinine clearance overestimates GFR due to secretion clearance.
  - This overestimation greater at lower GFRs.

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C. 4. Several factors affect creatine

- Age – Advanced age associated with lower muscle mass. Partially accounted for in C-G numerator.
- Body mass – High or low muscle mass (outside norm) will affect creatinine. Adipose tissue does not produce creatinine but obese patients have a little more muscle to support additional body weight. Specialize fudge factors and/or equations have been used but are not validated.
- Gender – men typically have more muscle mass than women
- Diet high in meats or protein
- Medications Cimetidine, trimethoprim, probenecid will block renal tubular secretion of creatinine. In patients with a baseline low GFR, there may be a significant increase in serum creatinine (although kidney function is unaltered). Will result in falsely low CrCl concentrations.

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5. Creatinine Standardization

- SCr now standardized across labs.
- MDRD has been modified to adjust for standardization.
- Cockroft and Gault cannot be modified b/c samples are no longer available.
- Difference is “modest”.

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D. Equations to Estimate CrCl and/or GFR

- Assumes kidney function is stable!
- Cockcroft-Gault 1976 (estimates CrCl)
  - Units = mL/min
  - Ideal body weight vs. actual body weight?
  - Most FDA approved drug dosing based on C-G.
- Modification of Diet in Renal Disease Study (MDRD. Estimates GFR.
  - Units = mL/min/1.73 m^2
  - Does not require weight because normalized to BSA.
- CKD-EPI

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Other CrCl estimations

- Jeliffe – Use when height and weight in adults are unavailable
- Salazar-Corcoran - Derived from obese
- Schwartz equation –pediatric method for CrCl

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E. Direct Measurement of Kidney Function

- Urine Collection for CrCl
  - Requires timed urine collection (12-24 hours).
  - Prone to collection errors.
  - Overestimates true GFR because of secretion clearance.
  - If done correctly, most accurate!
- Cystatin C.
- Inulin, Iothalamate

Workbook Page 1-223

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D. Her calculated CrCl is much higher than what is expected for a woman of her age. This is probably a false reading because of her likely reduced muscle mass. Do not "round up" the Scr!

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Stages of CKD

Stage	Description	GFR (mL/min/1.73 m2)	Action
1	Kidney damage with normal or ↑ GFR	≥90	Diagnose and treat Treat comorbid conditions Slow progression CVD risk reduction
2	Kidney damage with mild ↓ GFR	60-89	Estimate progression
3	Moderate ↓ GFR	30-59	Evaluate and treat complications
4	Severe ↓ GFR	15-29	Prepare for renal replacement therapy
5	Kidney failure	<15 (or dialysis)	Replacement (if uremia present)

National Kidney Foundation (NKF). *Am J Kidney Dis.* 2002;39(2 suppl 1):S1-S266.

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Diabetes and CKD

- Annual screening for albuminuria
- Goal BP < 130 / 80 (or lower)
- ACEIs and ARBs should be used in all patients with microalbuminuria, even when normotensive. Monitor potassium and creatinine. Up to 30% elevation in Scr in acceptable!
- ACE/ARBs are standard of care. Often need multiple medications.
- Protein intake of 0.8 g/kg/day.

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Patient Case 4

A 67-year-old patient presents with CKD stage 5 (hemodialysis for past 6 years), hypertension, and insulin-dependent diabetes. Current medications include epoetin alfa 8000 units intravenously 3 times per week, calcium carbonate 650 mg with meals and insulin. Hemoglobin last month was 9.5 mg/dl and today is 9.0 mg/dL. Which one of the following is the most appropriate therapeutic option for this patient?

A. Discontinue water-soluble vitamin.

B. Assess for blood in stool.

C. Change EPO to darbepoetin 60 units/week.

D. Assess serum Ferritin and TSAT saturation at the next blood draw.

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VII. Anemia Management

- Primarily caused by reduced production of erythropoietin in the kidney.
- Anemia can be seen as early as CKD Stage 3, almost universal in Stage 5.
- Generally normochromic, normocytic. Low hemoglobin, low reticulocyte. May have IDA as well.

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Why CKD-5 pts are anemic

- Reduced EPO production
- Reduced iron stores – Especially if on ESAs.
- Chronic inflammation/infection causing ESA resistance.
- Shortened RBC life span (65 days vs. 120 days).
- Blood loss
  - Loss during hemodialysis process itself (20–50 mL of blood lost per hemodialysis treatment)
  - Frequent phlebotomy
  - Reduced platelet function, which increases bleeding propensity
- Unusual/less common
  - Aluminum intoxication (was seen in patients using aluminum-containing phosphate binders)
  - Poor nutritional intake
  - Concomitant medications that suppress erythropoiesis (common in patients with transplants)

Workbook Page 1-228 (same list, just ordered differently) 15

G. Goal of Anemia Management

- Hemoglobin preferred monitoring parameter
- Goal is NOT to "normalize" Hgb!
- Numerous studies shown poor outcomes when Hgb normalized in CKD.
  - CHOIR
    - Death and hospitalization higher in normal-Hgb group
  - CREATE
    - No benefit to higher Hgb.
  - TREAT (DB, R, PC Trial) of placebo versus darbepotein.
    - No difference in death or CV outcomes
    - More strokes

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FDA Label Recommendations

- Patients with CKD on dialysis - Initiate ESA treatment when hemoglobin is less than 10 g/dL. If hemoglobin approaches or exceeds 11 g/dL, reduce or interrupt ESA therapy
- Patients with CKD not on dialysis. Consider initiating epoetin alfa treatment only when the hemoglobin is less than 10 mg/dL and the following applies:
  - The rate of Hb decline indicates the likelihood of an RBC transfusion.
  - Reducing the risk of alloimmunization and/or other transfusion related risk is a goal

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ESA Use and Monitoring

- Epoetin alfa: starting dose 50-150 U/kg TIW (SC or IV)
- Darbepoetin: starting dose 0.45 mcg/kg Qwk
  - Subcutaneous offers no PK advantage over IV
  - Much longer acting, can use Q 2-4 week-dosing
- Monitoring and dose adjustment
  - Hgb every 2 weeks until stable; then monthly
  - Dose adjustments should not be made more often than once monthly and not in increments greater than 25% because of the long lag time between dosing change and observed change in Hgb.

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CKD & Iron Therapy

- Eventually, almost all CKD 5 patients will need iron
  - KDOQI recommends IV iron
  - IV iron easy to give during HD, just inject into line
  - Usually 1 gram LD given in divided doses
  - Often maintenance Q 1-3 weeks
- Iron Targets
  - Ferritin (storage form of iron): 200-500ng/mL
  - Transferring (Transfers iron): >20% saturated

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Patient Case 4

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D. **Assess serum Ferritin and TSAT saturation at the next blood draw.**

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Patient Case 6

A 55-year-old patient with CKD stage 5 & HTN has received HD for the past 5 years. Current medications include EPO 8000 units 3 times/week, calcium carbonate 650 mg with meals. Laboratory values are calcium 9.4 mg/dL, phosphate 6.8 mg/dL, iPTH 677 pg/mL, and albumin 2.5 g/dL. Which one of the following is the best recommendation to manage hyperphosphatemia in this patient?

A. Discontinue calcium carbonate and start calcium acetate 667 mg with meals.

B. Double the calcium carbonate dose.

C. Discontinue calcium carbonate and start sevelamer two 800-mg tablets with meals.

D. Discontinue calcium carbonate and begin aluminum hydroxide 2 tablets with meals.

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VIII. CKD - Mineral and Bone Disorder (CKD-MBD)

A. Pathophysiology – Complex.
- Hyperphosphatemia due to decreased elimination of Phos in kidney. Hyperphosphatemia stimulated PTH secretion. High Phos also reduced calcium through chelation.
- Decreased activation of vitamin D with subsequent hypocalcemia.
- Hypocalcemia also stimulates secretion of PTH.
- Resultant renal osteodystrophy and vascular or other soft-tissue calcification.

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KDOQI: Metabolic Bone Disease

KDOQI Goals of Therapy	CKD Stage 3	CKD Stage 4	CKD Stage 5
Calcium (mg/dL)[a]	Normal	Normal	8.4–9.5
Phosphorus (mg/dL)	2.7–4.6	2.7–4.6	3.5–5.5
Calcium x phosphate product	< 55	< 55	< 55
iPTH (pg/mL)	35–70	70–110	150–300

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MBD - Treatment

3 a. Non-Drug Therapy
- Lower Phosphorus intake to 800 mg/day. Difficult diet.
- Dialysis (Phosphorus difficult to dialyze)
- Parathyroidectomy

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MBD - Treatment

b. Drug therapy.
Phosphate binders: (Can combine different binders). Take prior to meals.
- IV. Aluminum-containing phosphate binders Avoid (see notes).
- V. Calcium-containing phosphate binders
  1) Widely used binder. Considered initial binder of choice for stage 3 and 4 CKD. Carbonate is relatively inexpensive
  2) Calcium acetate. Better binder than carbonate, so less calcium given
  3) Use may be limited by development of hypercalcemia.
  4) Total elemental calcium per day = 2000 mg/day (1500-mg binder; 500-mg diet)

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MBD - Treatment

c. Drug therapy.
Phosphate binders: (Can combine different binders).
- VI. Sevelamer: a nonabsorbable phosphate binder
  1) Effectively binds phosphorus.
  2) Indicated especially if calcium-phosphorus factor is greater than 55 mg^2/dL^2.
  3) Decreases cholesterol. As sole binder, may get hypocalemia and acidosis (HCl salt).
  4) Available as sevelamer HCl (Renagel) and sevelamer carbonate (Renvela). Renvela more commonly used now.
- VII. Lanthanum carbonate: chewable wafer. Similar place in therapy as sevelamer.

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Vitamin D Therapy and MBD

- Active Vitamin D analogues:
  - Calcitriol – PO & IV
  - Paracalcitol – PO & IV. Designed to ↓ GI absorption of calcium and phosphate.
  - Doxercalciferol- IV & PO, must be activated by liver

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Parathyroid hormone inhibition

- Cinacalcet HCL: Calcimimetic agent that binds to the calcium receptor on the parathyroid gland. Cinacalcet increases calcium receptor sensitivity, which reduces PTH secretion.
  - Known among clinicians as "chemical parathyroidectomy"
  - Expensive, reserved for patients with high calcium/phosphorus and iPTH concentrations
  - Used in conjunction with vitamin D and phosphate binders (not monotherapy)
  - Caution in patients with seizure disorders, 1% increase in seizure rate. Related to hypocalcemia?
- Metabolized by P450 CYP2D6, CYP3A4 & CYP1A2
  - Ketoconazole increases cinacalcet concentrations 2-fold because ketoconazole inhibits CYP3A4.
- Initial dose is 30 mg/day, dose adjustment q 1–2wks

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Patient Case – not in book

P.P. is a 40-year-old dialysis patient with a history of grand mal seizures. He takes phenytoin 300 mg/day. His albumin concentration is 3.0 g/L. His total phenytoin concentration is 5.0 mg/dL. Which one of the following is the best interpretation of the phenytoin concentrations?

A. The concentration is most likely subtherapeutic, and a dose increase is warranted.

B. The concentration is most likely therapeutic, and no dosage adjustment is needed.

C. The concentration is most likely toxic, and a dose reduction is needed.

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Pharmacokinetic changes in CKD

- Absorption
  - Lowers secondary to drug interactions (antacids and iron with quinolones)
  - Lowers secondary to uremic gastritis, uremic neuropathy, or diabetic gastropathy
  - Lowers secondary to change in gastric pH (more alkaline) (e.g., ketoconazole, itraconazole, iron salts)
  - Lowers secondary to decreased first-pass metabolism by the liver

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Pharmacokinetic changes in CKD

- Distribution
  - Alterations in protein binding (Box 1 page 235)
  - Low albumin (the principal binding protein for acidic drugs)
  - Accumulated uremic byproduct competing for binding sites on albumin
  - Qualitative changes in binding sites
    - Example: Phenytoin
  - Altered tissue binding (e.g., digoxin)

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Pharmacokinetic changes in CKD

- Metabolism by liver & kidney changed
  - Box 3, page 1-236
- Accumulation of active metabolites
  - Morphine – Morphine-6 glucuronide (prolonged analgesia, respiratory depression)
  - Procainamide (class IA) raises *N*-acetyl procainamide (class III) (arrhythmias).
  - Meperidine raises normeperidine (seizures).

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Phenytoin and CKD

b. PK Alterations with Phenytoin. Free fraction of phenytoin in normals is 10%. With uremia and/or hypoalbuinemia, free fraction is elevated (as high as 30%) resulting in lower *total* concentrations despite having normal *free* concentration. Do not need to adjust doses of phenytoin in CKD.

c. There are equations available to "adjust" observed concentrations. More often we now check free levels.

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A. The concentration is most likely subtherapeutic, and a dose increase is warranted.
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C. The concentration is most likely toxic, and a dose reduction is needed.

Can (should) check free phenytoin levels.

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Indications for RRT

- A – Acid/base
- E - Electrolytes
- I - Intoxications
- O – fluid Overload
- U - Uremia
- General rule, dialyze if
  - Azotemia/uremia symptoms
  - BUN >100 mg/dL or S Cr > 10 mg/L

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RRT Choices

- Hemodialysis: TIW, 3-4 hrs per session
  - Solutes removed by diffusion
  - Some ultrafiltration used to achieve "dry" weight
- Common HD complications
  - Intradialytic cramps or hypotension
  - Dialysis dysequilibrium
    - Rapid osmolality and fluid changes
  - Vascular Access site infections

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Increased Dialytic Drug Clearance

- Drug characteristics:
  - Small MW <2000 Daltons
  - Not highly protein bound
  - Highly H_2O soluble
  - Small Vd (drug is in blood, not fat, bone, etc)
- Hemodialysis characteristics:
  - Different membrane types (big pore size & surface area)
    - e.g. conventional membranes (smaller pore sizes & surface areas) does not remove substances with MW>500 Daltons; high-flux (larger pore sizes & surface areas and faster flow rates) can remove larger compounds
  - High blood & dialysate flow rates (these are pretty standard and aren't routinely monitored by pharmacists).
  - Duration of dialysis

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Drug removal by HD - Examples

- Aminoglycosides ~10% of body load lost/hr. Empiric dosing is 1.35 mg/kg after each HD session.
- Vancomycin (MW 1450 Daltons) dependent on the dialyzer type used. High flux dialysis most common now. Multiple regimens used. Will see higher doses if vancomycin given during HD session.
- In general, give home medications after dialysis.

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Peritoneal Dialysis

- Peritoneal Dialysis Technology has changed
- Most PD now is performed with a cycler that performs dialysate exchanges
  - CAPD: Continuous Ambulatory Peritoneal Dialysis
  - CCPD: Continuous Cyclic Peritoneal Dialysis
- CCPD results in superior solute removal because more dialysate used/day
  - Therefore increases drug removal!
- Dialysis membrane = Tenckhoff catheter

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Peritoneal Dialysate

- Usually 1.5%, 2.5%, or 4.25% Dextrose
  - Higher glucose content increases fluid removal
  - Each patient requires a different dextrose content based on their peritoneal membrane.
  - Can be a large source of "dietary" glucose as such, patients may have increased insulin requirements.

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Peritoneal Dialysis Complications

- "Exit site" infections with skin bacteria
- PD-associated Peritonitis
  - Clinical presentation: Cloudy dialysate (98%), abdominal pain (78%), abdominal tenderness (76%), fever (38%), nausea (29%)
  - Elevated dialysate cell count (white blood cell count greater than 100 mm^3, 50% polymorphonuclear neutrophils)
  - Most common organisms = *S. epidermidis* (30%–45%) and *S. aureus* (10%–20%); other organisms: *Streptococcus viridans* (12%–15%), *Enterococcus* (3%–5%), gram-negative organisms (20%–35%), fungi (5%–10%)

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PD-associated Peritonitis Treatment

- Latest guidelines for intraperitoneal antibiotic administration: Perit Dial Int 2010;30:393–423

Peritonitis empiric therapy

- First- and third-generation cephalosporins
- Vancomycin & gentamicin can be used, but ototoxicity and emerging vancomycin resistance are concerns

Drug Administration

- Drugs can be put into dialysate once daily, or in each bag.
- Drugs should be instilled for the longest dwell of day to enhance absorption and contact time with peritoneum.
- Patients with residual renal function need higher antibiotic doses.
- Patients receiving automated PD need higher antibiotic doses.
- In general, IP drug administration is preferred to PO or IV.

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Questions?

Updates in Therapeutics® 2012:
Ambulatory Care Pharmacy Preparatory Review and Recertification Course

Obstetrics and Gynecology

Alicia B. Forinash, Pharm.D., BCPS, BCACP
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Conflict of Interest

Alicia B. Forinash has no conflicts to disclose.

Learning Objectives

1. Recommend contraceptive products, infertility, menstrual disorders, endometriosis, and post-menopausal therapy based on patient-specific information.
2. Recommend treatment of common acute and chronic conditions in pregnancy.
3. Educate patients regarding medication use during pregnancy and lactation, contraception, infertility, menstrual disorders, endometriosis, and post-menopausal therapy.
4. Identify resources for additional information for health care providers and patients for contraception, infertility, pregnancy and lactation, menstrual disorders, endometriosis, postmenopausal therapy, and patient assistance programs.

Case 1

Page 1-252

A 39yo woman is requesting hormonal contraception. She plans to start attempting conception in about 12 mo. She is currently 6 wk postpartum and is formula feeding the infant. Is concerned about losing her pregnancy weight. ***PMH:*** *gestational DM, HTN, and hyperthyroidism.* ***Medications:*** *propylthiouracil 100 mg TID, lisinopril 10 mg/day, HCTZ 25 mg/day, PNV 1 tablet/day.* ***Social history: (-)*** *tobacco/illegal drug use, EtOH socially. Height: 5'5"; Today: 290lb (pre-pregnancy: 230lb). BP: 178/96 (188/102 2 weeks ago). Which one of the following is the most appropriate hormonal contraceptive recommendation?*

- ***A.*** *Depo-Provera (medroxyprogesterone acetate)*
- ***B.*** *Ortho-Evra (ethinyl estradiol and norelgestromin)*
- ***C.*** *Yaz (ethinyl estradiol and drospirenone)*
- ***D.*** *Micronor (norethindrone)*

Page 1-254

Estrogen-Progestin Advantages

- Table 1 (pg 1-251 and 1-252)
- High efficacy if taken as instructed
- Improves menstrual symptoms
  - Lighter and decreased length of menstrual bleeding
- ↓ risk of ectopic pregnancies
- Safe throughout reproductive years
- Readily reversible
- Cycle manipulation (extended interval dosing pg 2-156)
- ↓ incidence and severity of PID
  - ↓ menstrual blood loss which can act as medium for bacterial growth

Page 1-254

Estrogen-Progestin Advantages

- ↓ risk of
  - Ovarian and endometrial cancer
  - Functional ovarian cysts
  - Fibrocystic breast disease
- Helpful for patients with PCOS
  - Decrease stimulation of androgen production
  - Decrease free testosterone due to ↑ SHBG
- ↓ Acne

Page 1-254

Estrogen-Progestin Disadvantages

- No protection for sexually transmitted infections
- Pills require daily administration
- ↑ blood pressure
  - ↑ angiotensinogen
  - Sodium and water retention
  - Drospirenone
- ↑ risk for CVA and MI
  - Mainly with 50mcg EE and concomitant risk factors
  - Smokers ≥35 years old

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Estrogen-Progestin Disadvantages

- ↑ risk for
  - Thromboembolic disorders
  - Glucose intolerance
  - Chlamydia infections
    - Cervical ectopy
    - Pelvic inflammatory disease is not increased
  - Gallbladder disease

Page 1-254-5

Progestin Only Pills

Advantages

- Can use if contraindicated to estrogen
- Intolerable ADRs from estrogen
- Less risk for MI if >35 years old
- Breastfeeding

Disadvantages

- Daily administration
- Irregular menses and ↑ BTB and spotting
- ↑ Ectopic pregnancy risk
- ↑ need for compliance
  - Backup method x48h if pill is ≥ **3 hours** late
- ↑ risk for ovulation

Page 1-255

Depot Medroxyprogesterone Advantages

- Same as Progesterone only pills
- ↓ user error with less frequent administration
- Scant-to-light menses with continued use
- ↓ risk of
  - Anemia, menstrual bleeding, Menstrual cramps, Mittelschmerz
  - Endometrial and ovarian cancer
  - PID
- Useful for patients with endometriosis
- No drug interactions

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Depot Medroxyprogesterone Disadvantages

- Delayed return of ovulation
- Menstrual irregularities with first several injections
- Weight gain
- Increased risk of bone loss
- ↓ HDL

Page 1-255

Progestin IUD Advantages

Advantages

- Progestin only pill advantages
- Can be left in place for 5 years
- Provides 2 mechanisms of action
- 20% have amenorrhea at year 1

Disadvantages

- Need to check daily for strings
- Avoid if patient has a history or increased risk for PID
- Heavy menstrual bleeding and cramping after placement

Case 1

Page 1-252

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Case 1

Page 1-252
Answer: 1-296

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Case

A 21yo woman has been taking contraceptive X for 8 months. She calls today because she has been experiencing BTB for 2 days then her menses begin 4-5 days later. She states it is bothersome to have so much bleeding in the past 2 cycles. PMH: dysmenorrhea.

Which of the following is the best recommendation?

Product	Estrogen	Progestin	Androgen
X	++	++	++
A	++	+++	++
B	+++	++	++
C	+	++	++
D	++	+	++

- **A.** *A*
- **B.** *B*
- **C.** *C*
- **D.** *D*

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Adjusting Products

- Identify whether adverse event is related to hormone deficiency/excess
  - Rule out that adverse event is related to incorrect use or administration timing (i.e., nausea with morning dose)
  - Table 3 (page 1-256) lists symptoms with hormone excess/deficiency
- Select a product with more or less activity than the hormone abnormality.
- Dickey Managing Contraceptive Pill Patients tables.

Page 1-256

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- **C.** C
- **D.** D

Page 1-256
Answer: 1-296

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- **A. A**
- **B.** B
- **C.** C
- **D.** D

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Product Initiation

- Interview the patient
  - Preferences (personal, religious, etc), plans for future pregnancy
  - History with previous products
  - Purpose for product (contraceptive, STI protection, cycle control)
  - Reversibility
  - Adherence and partner(s) support
  - Cost

Page 1-260

Review Patient Specific Factors

- Use adverse event table to help (table 3, pg 1-256)
  - If heavy menses, use mod-high progestin activity
- Contraindications (table 4, page 1-257-8)
- Drug Interactions (table 5, pg 1-259)

Page 1-260

Education

- Purpose
- Proper use
  - Initiate 1st day menses, 1st Sunday, or day prescribed
  - Administration time
- Potential Adverse Events
  - Common symptoms
  - Wait until after 3 cycles

Page 1-260

Education

- Serious
  - Warrant ED visit
  - A: Abdominal pain
  - C: Chest pain (severe), cough, SOB
  - H: Headaches (severe), dizziness, weakness, numbness
  - E: Eye problems (vision loss/blurring), speech problems
  - S: Severe Leg pain

Page 2-164

Education

- Missed doses (table 6, pg 1-261)
- Back-up methods
  - Initiation: minimum 7 days (9 days for Natazia)
  - Drug interactions that decrease efficacy
    - During med and 7-9 days afterwards
  - Severe diarrhea and/or vomiting
  - If progestin only pill is >3h later, use x48h
  - Missed doses

Page 1-262

Case 3

A 17 yo is crying in the waiting room, saying she needs help. The front desk asks you to talk to her. She states that a condom broke during intercourse 4d ago and that she wants to use EC. The pharmacy refused to provide plan B and told her she should not have sex until she is older. Unable to tolerate the vomiting with Yuzpe method for EC in the past. PMH: PID (treated and resolved 2 months ago), multiple sexual partners.

Which one of the following is the best action to take?

- ☐ **A.** *Refer her to another pharmacy to get OTC Levonorgestrel 1.5mg Q12h x2 doses.*
- ☐ **B.** *Recommend that her physician insert an IUD.*
- ☐ **C.** *Have her physician prescribe ulipristal 30mg x1.*
- ☐ **D.** *Refuse EC because it has been too long.*

Page 1-263

Emergency Contraception

- Table 7 (pg 1-263)
  - New Product: Ulipristal (Ella)
- Contraindication: Pregnancy
- Education
  - Purpose
  - Proper use
  - Potential ADR (Yuzpe > progestin > SPRM)
    - Nausea (50% >23%>12%), bloating, menstrual cramps, headache
    - Metoclopramide 10mg, Meclizine 50mg, other 1h before

Page 1-263

Menstrual Changes

- Start date and amount of loss varies
  - Pre-ovulation: early onset (3-7d)
  - Post-ovulation: normal to late onset
  - Ulipristal: extends cycle by mean of 2.5 days
- ACOG recommends a pregnancy test if no menses
  - Within 21 days
  - >1 week than expected

Page 1-263

Restarting Regular Contraceptives

- Barrier Methods: Immediately
- Hormonal contraception
  - Progestin only/Yuzpe: Day after finishing
  - Ulipristal: Next cycle

Page 1-262

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Page 1-262
Answer: 1-296

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Page 1-265

Case 4

A 42-year-old woman and her husband are trying to conceive but have been unsuccessful after 6 months. PMH: amenorrhea. Current medications: PNV daily and clomiphene 25 mg/day on cycle days 5–9. She states she was instructed to check for ovulation.

Which one of the following is the best method for detecting ovulation?

- ***A.*** *Cervical mucus monitoring.*
- ***B.*** *Basal body temperature.*
- ***C.*** *Urine LH kits.*
- ***D.*** *Ultrasound.*

Page 1-265

Case 5

The patient does not respond to clomiphene, so she is initiated on FSH and LH. What should you educate her about regarding monitoring for ovarian hyperstimulation?

- *A. Constipation.*
- *B. Polyuria.*
- *C. Double vision.*
- *D. More than 2.25-kg weight gain.*

Page 1-266

Infertility

- Infertility is a challenge for the COUPLE
  - Infertility involves 40%–50% of male partners.
- Evaluation begins after 12 months unless the woman
  - 35 years or older
  - Has a history of oligomenorrhea/amenorrhea
  - Has known/suspected uterine/tubal disease
  - Has endometriosis
  - Has a subfertile partner

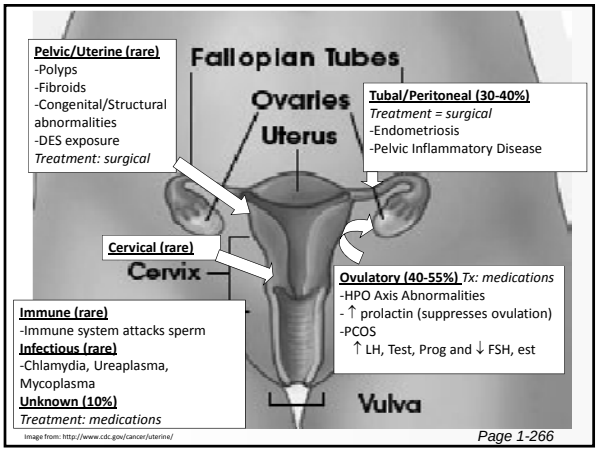

Image from: http://www.cdc.gov/cancer/uterine/

Page 1-266

Page 1-267

Treatment Risks

- Multiple gestation
- Ovarian Hyperstimulation (2% assisted)
  - Risk with high dose gonadotropins or GnRH
  - Exact MOA unknown
  - Sx begin 3-10 days after ovulation or hCG injection
    - Weight gain >2.25 kg and increased abdominal girth
    - Abdominal or pelvic pain
    - N,V,D
    - Dyspnea, Dizziness
    - Oliguria

Page 1-267

Role of Hormones

- FSH = mature egg
- LH = ovulation
  - Gonadotropin products: FSH/LH, FSH >>LH
- hCG = structurally similar to LH
  - Products: hCG
  - Used with FSH only products
- Progesterone = luteal support or induce menses

Page 1-267

Infertility Medications

Ovulation Induction Level 1
Clomiphene, Metformin, Letrozole, Anastrazole, or Combination

Ovulation Induction Level 2
FSH/LH or FSH + hCG

Suppress endogenous HPO
Continuous GnRH, GnRH antagonist

Then Ovulation Induction Level 2: FSH + hCG

Page 1-267-8

Infertility Medications

- Luteal Support
  - Progesterone
  - Required with FSH/LH, FSH + hCG, pulsatile GnRH
- Hyperprolactinemia
  - Bromocriptine
  - Cabergoline
- Assistive Technologies
  - Artificial insemination, in-vitro fertilization, embryo transfer, gamete/zygote intra-fallopian transfer

Page 1-269

Role of Pharmacists: Education

- Ovulation Detection
  - Cervical mucus monitoring
  - Basal body temperature monitoring
  - Urine LH kits
  - Ultrasound monitoring
- Medications
  - Purpose/Proper Use/Potential ADR

Page 1-270

Role of Pharmacists: Education

- When to notify MD
  - Abnormal increase in abdominal circumference
  - Nausea
  - Pelvic pain
  - Decreased urine output
  - Weight gain greater than 2.25 kg
  - Dizziness
  - Shortness of breath
- Support groups (RESOLVE) and counseling

Case 4

Page 1-265

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Which one of the following is the best method for detecting ovulation?

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Case 4

Page 1-265
Answer: 1-296

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Page 1-265
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- C. Double vision.
- D. **More than 2.25-kg weight gain.**

Page 1-270

Pregnant Patient Interactions

- Establish trust
  - Do not impose your values on the patient with drug and disease treatment during pregnancy.
  - Actively listen to the patient.
  - Teratogenicity (72% idiopathic, 25% genetic, and 3% medications)
  - May seek treatment with other medications, herbals, or illicit drugs
  - May never take prescribed therapy because believe all medications are harmful

Page 1-270

Evaluating Meds in Pregnancy

- Evaluate risks of med
  - Specific percentage, incidence/prevalence, etc.
- General risk of the same abnormality
  - Specific percentage, incidence/prevalence, etc.
- **Stage of development**
  - Determine critical time for development
  - Compared with patient's current gestational age

Page 1-270

Educating on Meds in Pregnancy

- Purpose
- Proper use
- Potential adverse events
  - Maternal and Fetal
- Potential risks of untreated conditions
  - Incorporate specific information when possible.
  - Timing (using gestational week)
  - Present risk in understandable terms (percentage)

Page 1-271

Principles of Meds in Pregnancy

- Factors influencing teratogenicity
  - Stage at the time of exposure*
  - Maternal and fetal genotypes
  - Dose
  - Specificity of the agent
  - Other simultaneous exposures (other drugs or environmental agents)

Page 1-271

Principles of Meds in Pregnancy

- Possible complications of medication exposure
  - No effect
  - Premature or delayed labor
  - Spontaneous abortion
  - Malformations—Major or minor
  - Altered fetal growth
  - Functional deficit
  - Carcinogenesis
  - Mutagenesis

Page 1-271

Drug Transfer in Pregnancy

- Simple diffusion (most drugs)
  - Molecular weight (low > high)
  - Lipid solubility (lipophilic > hydrophilic)
  - Ionization (nonionized > ionized)
  - Protein binding (free > low > high)
  - Maternal and fetal bloodflow (high > low)
  - Placental diffusion distance (thin > thick)
  - Placental villi exchange area (large > small)
  - Efflux proteins (no activity > high activity)

Page 1-271

Drug Transfer in Pregnancy

- Facilitated diffusion (glucose)
- Active transport (some vitamins, amino acids
- Pinocytosis (immune antibodies)
- Breaks between cells (erythrocytes)

	Physiology Changes	**P-kinetic Changes**	**Potential Effects**
Metabolic	↑hepatic metabolism ↓hepatic metabolism	↑metabolism ↓ metabolism	↓ drug conc. ↑ drug conc.
Placental	thinning of barrier	↑ distribution	↓ mom conc. ↑ fetal conc.
Renal	↑ renal blood flow	↑GFR and elimination	↓ concentration
Volume	↑ blood volume ↓ protein levels ↑ Body fat	↑ distribution ↓Protein binding ↑ Vd lipophilic	↓concentration ↑free drug conc ↓ conc. Lipoph.
GI	↓ motility and ↑intestinal blood flow	↑ absorption	↑concentration

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FDA Pregnancy Categories

A	Well-controlled studies in pregnant women have not shown risk
B	-Animal = no risk; Human = no controlled studies -Animal = risk; Human = controlled studies have no risk
C	-Animal = risk; Human = no controlled studies -No available studies in women or animals
D	Benefit of medication > risk
X	Risk > Benefit

Medication Use in Pregnancy

- Acute Conditions (pg 1-272-4)
  - Ask your patients about symptoms
  - Risk vs. Benefit
  - Nonpharm treatments
- Chronic Conditions (pg 1-274-8)
  - Balance risk of untreated condition vs. risk of Med

Page 1-276

Case

A patient (18 weeks gestation) is here for her prenatal visit. You discover that she has not been taking her lamotrigine because of a fear of birth defects. Last seizure was 6mo ago. Which one of the following represents the best way to educate the patient on the risk of birth defects?

- ☐ *A. Risk is <u>low</u> because she is past the stage of development for cleft palate/lip.*
- ☐ *B. Risk is <u>low</u> because intrauterine growth restriction is similar to uncontrolled epilepsy.*
- ☐ *C. Risk is <u>high</u> because cardiac abnormalities develop during second trimester.*
- ☐ *D. Risk is <u>high</u> because of neurodevelopment delays with exposure during second and third trimesters.*

Page 1-275

Diabetes Mellitus

	Any MCM	Cardiac	Neural Tube Defects	Macrosomia	Other
PG rate	1-3%	0.8%	0.2%	10%	-CNS abnormalities -Still birth -Respiratory distress -Intrauterine growth restriction -Polyhydraminos -Progression of retinopathy
Risk Time	---	***0-12 weeks***	***0-5 wks***	2nd/3rd trimesters	
Uncontrolled DM	**18.4%**	**8.5%**	**1%**	**12-35%**	

Diabetes in Pregnancy

Page 1-275

Place in tx	Drug	Notes
1st line	Regular, Lispro, Aspart NPH	-Does not cross placenta
	Glargine Determir	*Limited data in pregnancy* Pregnancy category changed to B (April 2012)
Alternative	Glyburide	-Initiate after 12 weeks gestation -no drug detected in cord blood samples -no difference in A1c, birth wt or length -Clinical use: only for mild hyperglycemia
	Other sulfonylureas	*Associated with fetal and neonatal hypoglycemia*
Alternative	Metformin	-Appears safe -Less efficacious than insulin and glyburide
	Pioglitazone, Rosiglitazone	*Limited human data, Animal data showed risk of fetal death and IUGR*

Page 1-276

Risk of Uncontrolled Epilepsy

- Maternal:
  - Pre-term labor
  - Anemia
  - HTN
  - UTI
  - N/V
  - Vaginal bleeding
- Fetal:
  - Placental abruption or detachment
  - Premature membrane rupture
  - Significant fetal heart rate decelerations
  - Decreased IQ with 5 seizures during gestation

Page 1-276

Epilepsy

- If recurrent epilepsy on medications
  - 90% of having a normal child
  - Risk of congenital abnormalities and mental retardation (2x risk of general population)
  - Monotherapy is preferred

Page 1-276

Epilepsy Care

Preconception
- If >2yr since last seizure, trial off x 6mo
- If <2yr, continue therapy

Prevention
- Folic Acid 4mg Qday
- Vitamin K last month of pregnancy and delivery
- Calcium and Vitamin D

Therapy
- Continue therapy. Monotherapy preferred
- Avoid phenobarbital, phenytoin, and VPA in women childbearing age, if possible (2009 Guideline)

	Major Malformations	Neural Tube Defects	Cleft Palate/lip	Cardiac	Neurodevelop-ment delay
Pregnancy	1-3%	0.2%	0.14%	0.5-0.8%	
Risk Time	---	***0-5 wks***	***0-9 wks***	***0-12 wks***	***2/3rd trimesters***
PHY	**3.67-4.7%**	0	**1.2%**	**1.2%**	No
PHB, PRI	**6.5%**			**1.1%**	
CBZ, OXC	**2.2-4.5%**	**0.2-1%**	0.4%	**0.7-0.9%**	No
VPA*	**6.2-17.1%**	**1-2%**	**1.5%**	**0.7-0.9%**	**Yes**
GAB	**3.2%**				
TOP **(D)**	**7.1-9%**		**2.2%**		
LAM	**2.8-3.2%**	0.2%	**0.2%**	0.6%	No
LEV	2%				
FEL	*Unknown*	*Only 10 reported exposures in literature*			
ZON	*Unknown*	*Only 28 reported exposures in literature*			
TIA	*Unknown*	*Only 23 reported exposures in literature*			
ETH	*Unknown*	*Only 18 reported exposures in literature*			

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	Major Malformations	**Anticonvulsant Syndrome**	**Other** *Page 1-277*
Pregnancy	*1-3%*	0%	
Risk Time	---	***Any***	
PHY	***3.67-4.7%***	**11%**	
PHB, PRI	***6.5%***	**6.5%**	
CBZ, OXC	***2.2-4.5%***	**4%**	
VPA*	***6.2-17.1%***	**>4%**	IUGR, hernia, hypospadia
GAB	***3.2%***	Possible	
TOP	***7.1%***		hirsutism, third fontanelle, hypospadia
LAM	***2.8-3.2%***		↓ Levels
LEV	*2%*		↓ Birth weight, ↓ levels
FEL	*Unknown*	*Only 10 reported exposures in literature*	
ZON	*Unknown*	*Only 28 reported exposures in literature*	
TIA	*Unknown*	*Only 23 reported exposures in literature*	
ETH	*Unknown*	*Only 18 reported exposures in literature*	

Case 6

Page 1-276

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Case 6

Page 1-276
Answer: 1-296

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Case 7

Page 1-286

A 44 yo woman is experiencing vasomotor symptoms that disrupt her ability to complete work activities and get a good night's sleep. PMH: Hyperlipidemia and TAH/BSO (2 months ago). Labs: Total cholesterol 198, triglycerides 225, and HDL 44.

Which one of the following products is most appropriate?

A. Estinyl tablet (ethinyl estradiol) 0.02 mg/day.
B. Vivelle patch (17b estradiol) 0.025 mg/day.
C. Prempro tablet (conjugated equine estrogens + medroxyprogesterone) 0.45/1.5mg/day.
D. Estratest tablet (esterified estrogens + testosterone) 0.625/1.25 mg/d.

Menopause

Page 1-286

Estrogen (ET) and Estrogen plus Progestin (HT or E+P)

- Indications
  - Moderate to severe symptoms associated with menopause
  - Moderate to severe vulvar and vaginal atrophy associated with menopause
  - Prevention of postmenopausal osteoporosis

Benefits

Page 1-286

- Vasomotor symptoms: Systemic estrogens
- Urogenital symptoms: Estrogens administered by any route is the most effective treatment.
  - Urogenital atrophy
  - Vaginal dryness
  - Dyspareunia
- ↓ risk of urinary tract infections
  - Only local estrogen

Page 1-286

Benefits

- Osteoporosis prevention
- Quality of life
  - Mood stability
  - Fatigue
  - Insomnia

Page 1-286

Risks

- Cardiovascular risk
  - HT primary prevention (WHI)
    - No overall increase in CV events or death
    - HR 1.29 (95% CI 1.02–1.63)
    - Absolute risk: 7 per 10,000 person-years
  - HT secondary prevention (HERS)
    - Increased risk of myocardial infarction during first year of use (HR 1.52 [95% CI, 1.01–2.29])
    - No overall difference. HR 0.99 (95% CI, 0.80–1.22)

Page 1-286

Risks

  - ET primary prevention (WHI-ET)
    - No overall increase in CV events or death
    - HR 0.91 (95% CI, 0.75–1.12)
- Factors to consider
  - Timing
    - Age
    - Years since onset of menopause

Page 1-286

Risks

- Cerebrovascular risk
  - HT (WHI)
    - Increased risk with HR 1.41 (95% CI, 1.07–1.85)
    - Absolute risk of 8 per 10,000 person-years
  - ET (WHI-ET)
    - Increased risk HR 1.39 (1.10–1.77).
    - Absolute risk of 12 per 10,000 person-years

Page 1-286-7

Risks

- Thromboembolism
  - Estrogen ↑ vitamin K–dependent clotting factors.
  - ↑ risk of DVT by 2–3.5, but the absolute risk is relatively small (20 per 100,000 cases)
- Breast cancer
  - HT (WHI):
    - Nonsignificant ↑ 15% with use <5 years of use
    - Significant ↑54% with ≥ 5 years of use
  - ET: ↑ after 10–15 years of use.
    - New data: 23% decreased risk after 10 years (JAMA 4/6/11)

Page 1-287

Risks

- Endometrial cancer
  - Endometrial cell mitosis and hyperproliferation.
  - Increased risk after 1 year
  - Progestins (medroxyprogesterone acetate 5–10 mg/day or equivalent) 10–14 days/month
- Gallbladder dysfunction

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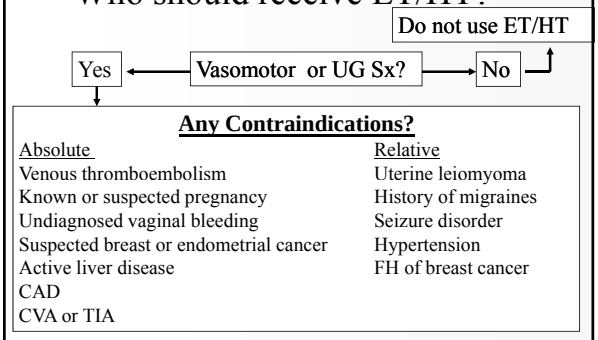
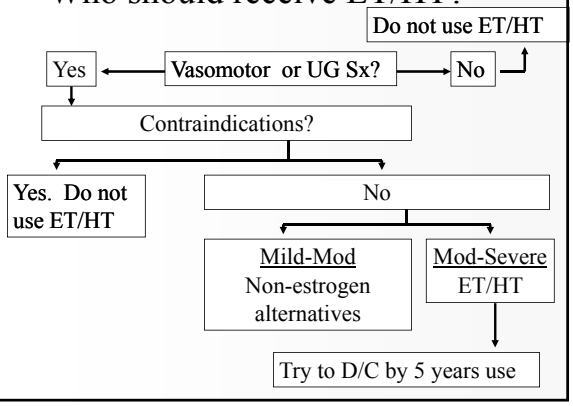
Risks

- Cognitive decline (WHIMS)
  - HT: ↑ risk for dementia in women ≥65 years.
  - HR 2.05 (95% CI, 1.21–3.48)
  - Absolute risk of 12 per 10,000 person-years
- Ovarian cancer
  - Meta-analysis, case-control, and cohort trials show ↑ risk with estrogen and estrogen-progestin therapy
  - 1 RCT did not show increased risk.

Who should receive ET/HT? Page 1-288



Who should receive ET/HT? Page 1-288



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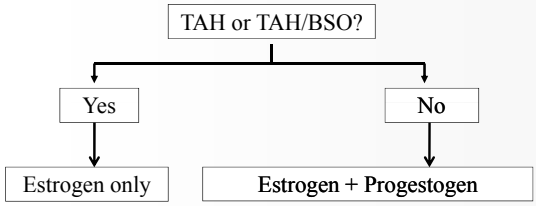
Step 1: Deciding on ET or HT



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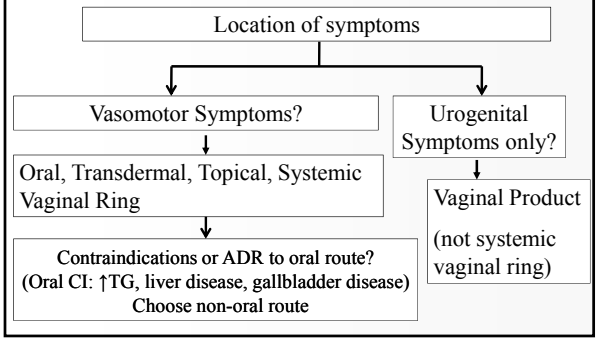
Step 2: Deciding a Route



Page 1-290-1

Alternatives

- Cannot or do not want ET/HT
- Antidepressants
  - venlafaxine, sertraline, paroxetine, fluoxetine, citalopram
- Antihypertensives
  - clonidine
  - ;β-blockers: blocks sympathetic stimulation of sweat glands

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Alternatives (cont.)

- Miscellaneous
  - Gabapentin
  - Megesterol
- Herbals
  - Soy
  - Black Cohosh- Not efficacious in breast cancer patients

Page 1-286

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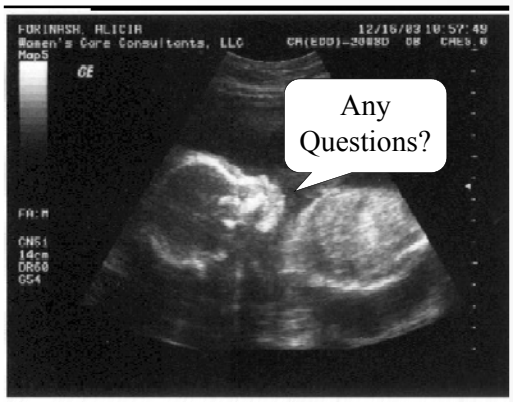

American College of Clinical Pharmacy

Updates in Therapeutics® 2012:
Ambulatory Care Pharmacy Preparatory Review and Recertification Course

Men's and Women's Health

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University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences

Conflict of Interest Disclosures

Dr. Linnebur has no conflicts of interest.

Learning Objectives

1. Describe risk factors and clinical signs/symptoms for benign prostatic hyperplasia (BPH), urinary incontinence, and erectile dysfunction (ED).
2. Differentiate the type of urinary incontinence on the basis of subjective complaints, physical examination, and simple urodynamic evaluations.
3. Evaluate and manage drug-induced causes of urinary incontinence and ED.

Learning Objectives

4. Evaluate pharmacologic and nonpharmacologic interventions for BPH, urinary incontinence, and ED.
5. Using patient-specific information, formulate treatment strategies for BPH, urinary incontinence, and ED.
6. Provide pertinent education for patients and prescribers regarding pharmacologic agents for BPH, urinary incontinence, and ED.

Patient Case # 1

- HPI: 75 year-old man presents with new-onset urinary symptoms (nocturia, decreased force of stream, hesitancy, incomplete emptying). He has no complications associated with his LUTS. He desires drug therapy.
- PMH: enlarged prostate
- What items of information are critical in your decision to recommend an α_1-antagonist, a 5-ARI, or the combination?

Workbook Page 1-308

Benign Prostatic Hyperplasia (BPH)

- Clinical presentation and assessment
  - Lower urinary tract symptoms (LUTS)
    - Obstructive/voiding symptoms
    - Irritative/storage symptoms
  - AUA symptom score
    - 0-7 = mild
    - 8-19 = moderate
    - 20-35 = severe

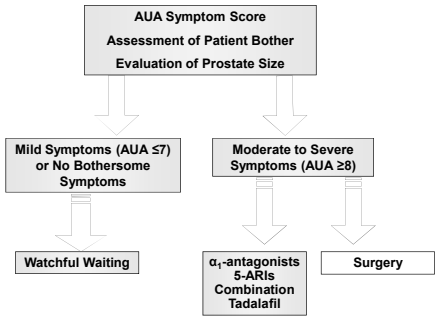
Workbook Page 1-303

Benign Prostatic Hyperplasia (BPH)

- Clinical presentation and assessment
  - Enlarged prostate: DRE, or ultrasound
    - Rule out prostate cancer
    - Estimation of prostate size: "Large" typically characterized as > 40 mL
  - PSA: normal to slightly elevated levels
    - Controversial assessment
    - Rule out prostate cancer
    - Reasonable to skip if age >75 yrs, < 10 years life expectancy, or will not change treatment plan

Workbook Page 1-303

Initial Treatment of BPH



Initial Treatment of BPH

- Watchful waiting
  - Appropriate for patients with mild symptoms or without bothersome symptoms
- α_1-antagonists
  - 1st line therapy for patients with moderate to severe symptoms without complications
  - Improve urinary flow and symptoms
  - Onset of action: days to weeks
  - Generic drugs available
- Tadalafil
  - Approved as monotherapy for BPH and BPH/ED
  - Improves irritative and obstructive symptoms

Workbook Page 1-304-305, 307

Initial Treatment of BPH

- 5-α-reductase inhibitors (5-ARIs)
  - 1st line therapy for patients with moderate to severe symptoms
  - Most effective in patients with prostate size > 40 mL
  - Reduce prostate size, BPH progression, prevent complications and improve urinary symptoms
  - Onset of action: 3-6 months
  - Generic drug available
- Combination 5-ARIs and α_1-antagonists
  - 1st line therapy for men with moderate to severe symptoms or with prostate size > 40 mL
  - More effective than monotherapy
- Surgery: for severe symptoms or complications

Workbook Page 1-306-308

Patient Case # 1

- HPI: 75 year-old man presents with new-onset urinary symptoms (nocturia, decreased force of stream, hesitancy, incomplete emptying). He has no complications associated with his LUTS. He desires drug therapy.
- PMH: enlarged prostate

Workbook Page 1-308

Patient Case #1

Which one of the following items of information is most critical in your decision to recommend an α_1-antagonist, a 5-ARI, or the combination?

A. His AUA symptom score

B. His PSA result

C. The approximate size of his prostate

D. His insurance coverage of the medications

Workbook Page 1-308; Answer: Page 1-328

Patient Case # 2

- HPI: 72 year-old man presents with uncontrolled symptoms of BPH and ejaculatory dysfunction
- Medications: tamsulosin 0.4 mg daily for 1 month, finasteride 5 mg daily for 6 months
- What medication changes would be appropriate to treat his symptoms?

Workbook Page 1-308

Treatment of BPH

- α_1-antagonists
  - Dosing
    - Doxazosin 1-8 mg daily; XL 4-8 mg daily
    - Terazosin 1-10 mg daily
    - Tamsulosin 0.4-0.8 mg daily
    - Silodosin 4-8 mg daily
    - Alfuzosin 10 mg daily
  - Adverse effects with all: dizziness, asthenia, headache, edema, fatigue, nasal congestion, floppy iris syndrome
  - Adverse effects with non-selective agents: hypotension, syncope, dyspnea
  - Abnormal ejaculation: tamsulosin, silodosin

Workbook Page 1-304-5

Treatment of BPH

- 5-α-reductase inhibitors (5-ARIs)
  - Dosing: finasteride 5 mg daily, dutasteride 0.5 mg daily
  - Adverse effects: decreased libido, ejaculatory disorder, ED, breast changes
- Combination
  - Dosing consistent with above
  - One combination product commercially available (dutasteride 0.5 mg/tamsulosin 0.4 mg)
  - Adverse effects: combination of those above
- Tadalafil
  - Dosing: 2.5-5 mg daily
  - Adverse effects: dizziness, headache, flushing, rhinitis, dyspepsia, hypotension, back pain

Workbook Page 1-306-7

Patient Case # 2

- HPI: 72 year-old man presents with uncontrolled symptoms of BPH and ejaculatory dysfunction
- Medications: tamsulosin 0.4 mg daily for 1 month, finasteride 5 mg daily for 6 months

Workbook Page 1-308

Patient Case #2

Which one of the following medication changes is most appropriate to treat his symptoms?

A. Increase tamsulosin to 0.8 mg daily

B. Increase finasteride to 10 mg daily

C. Change tamsulosin to alfuzosin

D. Change finasteride to dutasteride

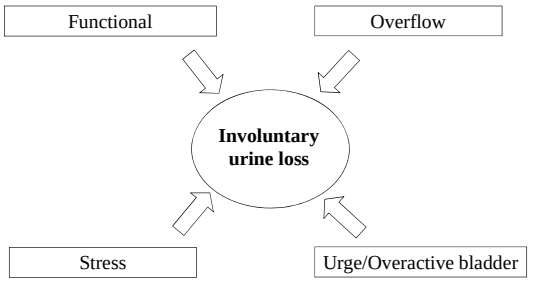
Workbook Page 1-308; Answer: Page 1-328

Patient Case #3

- HPI: 88 year-old woman has been experiencing urinary urgency, frequency, and moderate involuntary losses of urine. She is incontinent 3-4 times each night.
- PMH: stroke
- SH: living in an assisted living facility
- Objective data: negative urinalysis, normal pelvic and rectal evaluations, PVR = 75 mL urine
- What therapy will likely help her symptoms the most?

Workbook Page 1-317

Types of Urinary Incontinence (UI)



Types of UI

- Functional
  - Inability to reach the toilet in time
  - Symptoms: Loss of urine on the way to the toilet and in the early morning
- Stress
  - Urethral sphincter and/or bladder neck weakness/instability leading to involuntary transient loss of small amounts of urine when intra-abdominal pressure increases
  - Symptoms: incontinence when sneezing, coughing, laughing, bending, lifiting; often no incontinence while sleeping

Workbook Page 1-309

Types of UI

- Overflow
  - Involuntary loss of urine, often large volumes, when intravesicular pressures exceed intraurethral pressures
  - Symptoms: lower abdominal fullness/pain, hesitancy, straining, decreased force of stream, incomplete bladder emptying, frequency, urgency, increased post-void residual (normal = 25-50 mL)
- Urge/overactive bladder
  - Involuntary loss of urine of small or large volumes typically related to uninhibited detrusor contractions
  - Symptoms: urgency, frequency (> 8 voids/day), nocturia (> 1 voids/night), enuresis
- Mixed: multiple types of urinary incontinence

Workbook Page 1-309

Treatment of UI Based on Type

- Functional
  - Remove/treat precipitating factors
  - Schedule bathroom visits, bedside commode
  - Assist patient with functional disabilities
- Stress
  - Remove precipitating factors
  - Pelvic floor exercises
  - Topical estrogens
  - Adrenergic agonists (e.g. pseudoephedrine)
  - Duloxetine
  - Surgery to improve stability of bladder neck

Workbook Page 1-312-3

Treatment of UI Based on Type

- Overflow
  - Remove precipitating factors
  - Treat BPH
  - Bethanechol
  - Catheterization
- Urge/Overactive bladder
  - Remove precipitating factors
  - Pelvic floor exercises
  - Anti-muscarinic agents
- Drug treatments should be combined with behavioral interventions

Workbook Page 1-313-7

Patient Case #3

- HPI: 88 year-old woman has been experiencing urinary urgency, frequency, and moderate involuntary losses of urine. She is incontinent 3-4 times each night.
- PMH: stroke
- SH: living in an assisted living facility
- Objective data: negative urinalysis, normal pelvic and rectal evaluations, post-void residual (PVR) = 75 mL urine

Workbook Page 1-317

Patient Case #3

Which one of the following therapies is likely to help her symptoms the most?

A. Oxybutynin

B. Estrogen vaginal cream

C. Bethanechol and bladder training

D. Tolterodine and scheduled bathroom visits

Workbook Page 1-317; Answer: Page 1-328

Patient Case #4

- HPI: 84 year-old woman presents with moderate urinary incontinence, urgency, frequency, and nocturia
- PMH: mild dementia, atrial fibrillation, HTN, insomnia, osteoporosis
- SH: accompanied by daughter who lives with her
- MEDS: donepezil 10 mg/d, warfarin 2 mg/d, digoxin 0.125 mg every other day, metoprolol 50 mg BID, amlodipine 5 mg/d, nortriptyline 25 mg/d, alendronate 70 mg/wk
- Objective data: normal PVR, urinalysis, and physical examinations
- What therapy is most appropriate for her urinary incontinence?

Workbook Page 1-317

Drug Causes of UI

- Functional
  - Diuretics, opioids, benzodiazepines, alcohol, antipsychotics, anticholinergic agents
- Stress
  - Diuretics, α_1-antagonists, ACE-inhibitors
- Overflow
  - Diuretics, adrenergic agonists, beta-blockers, calcium channel blockers, anticholinergic agents, TCAs, vincristine, skeletal muscle relaxants, cyclobenzaprine, cyproheptadine
- Urge/overactive bladder
  - Diuretics, bethanechol, cholinesterase inhibitors

Workbook Page 1-311

Patient Case #4

Which one of the following recommendations is most appropriate for this patient for her urinary incontinence symptoms at this time?

A. Discontinue nortriptyline

B. Reduce the dose of donepezil

C. Initiate darifenacin

D. Initiate oxybutynin gel

Workbook Page 1-317; Answer: Page 1-328

Patient Case #5

- HPI: 67 year-old woman presenting for patient education regarding fesoterodine and non-pharmacologic recommendations for urinary incontinence
- PMH: urge incontinence
- Medication: fesoterodine

- What education points are important to include in your discussion with her?

Workbook Page 1-318

Non Pharmacologic Options for UI

- Dietary changes
  - Avoid aspartame, spicy/citrus foods, caffeine, carbonated beverages
- Scheduled/timed voiding
- Assistance with functional difficulties
- Pelvic floor exercises (Kegels) can benefit patients with stress, urge, and mixed UI
- Biofeedback
- Vaginal weight training
- Bladder training to increase interval between voids
- Pessaries/bladder neck support prostheses

Workbook Page 1-311

Anti-muscarinic Agents for UI

- Reduce or eliminate uninhibited detrusor muscle contractions
  - Reduce incontinence episodes by 50%
  - Reduce frequency by 20%
  - May reduce urgency and nocturia
- Major side effects: dry mouth, dry eyes, constipation, urinary retention, cognitive impairment, dizziness, vision changes, HA, thirst
- Cognitive impairment can be affected by:
  - Receptor specificity in the CNS: M_3 selective is best
  - Lipophilicity, P-glycoprotein active efflux transport
  - Charge/polarity, molecular weight

Workbook Page 1-313-7

Anti-muscarinic Agents for UI: Efficacy

Table 3. Direct Comparison of Efficacy Among Antimuscarinic Agents on Voids per Day

	Oxybutynin, ER	Oxybutynin, IR	Tolterodine, ER	Tolterodine, IR	Solifenacin	Darifenacin	Trospium, ER	Trospium, IR	Fesoterodine	Oxybutynin, TDS
Oxybutynin, ER										
Oxybutynin, IR										
Tolterodine, ER	O >T*									
Tolterodine, IR	O >T*	=	=							
Solifenacin			=	=						
Darifenacin		=								
Trospium, ER										
Trospium, IR		=								
Fesoterodine			=							
Oxybutynin, TDS			=							

ER = extended release, IR = immediate release, TDS = transdermal system.
Source: Treatment of overactive bladder in women. AHRQ Publication No. 09-E017. 8/09.

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Anti-muscarinic Agents for UI: ADRs and Cost

Table 4. Comparison of the Incidence of Adverse Effects and Approximate Monthly Drug Cost Among Antimuscarinic Agents[a]

Drug	Dry Mouth (%)	Constipation (%)	Dizziness (%)	Vision Changes (%)	Price
Oxybutynin	88	32	38	22	$4
Oxy ER/XL	68	9	11	3	$90
Oxy TDS	10	5	4	2	$228
Oxy gel	8	1	3	?	$167
Tolterodine IR, ER	50, 39	10, 10	4, 3	8, 6	$197, $169
Fesoterodine	99	14	2	4	$157
Trospium	33	11	7	3	$172
Solifenacin	34	19	1	7	$170
Darifenacin	59	28	0	4	$164

[a]Highest reported incidence of the adverse effect is listed.
ER = extended release, IR = immediate release, Oxy = oxybutynin, TDS = transdermal system, XL = extended release.
Sources: Table 19. Treatment of Overactive Bladder in Women. AHRQ Publication No. 09-E017. 8/09, product labeling for Gelnique (oxybutynin gel), and www.drugstore.com for drug costs – 30 day supply. Accessed September 27, 2011.

Workbook Page 1-317

Patient Case #5

- HPI: 67 year-old woman presenting for patient education regarding fesoterodine and non-pharmacologic recommendations for urinary incontinence
- PMH: urge incontinence
- Medication: fesoterodine

Workbook Page 1-318

Patient Case #5

Which one of the following education points is most important to include in your discussion with her?

A. Fesoterodine is a generic drug that should be relatively inexpensive for her
B. Fesoterodine is better tolerated than tolterodine ER
C. Eating spicy foods may help reduce some of her incontinence symptoms
D. Pelvic floor muscle exercises may improve some of her incontinence symptoms

Workbook Page 1-318; Answer: Page 1-328

Patient Case #6

- HPI: 68 year-old man presents to his PCP for ED treatment.
- PMH: ED, obesity, HTN, dyslipidemia, BPH, insomnia
- Vitals: BP = 140/87 mm Hg
- Based on the patient's cardiovascular risk, what is appropriate treatment for him at this time?

Workbook Page 1-325

Cardiovascular Evaluation for ED

- Sexual activity may cause CV event
  - Increases in BP and HR increase MI risk
  - CVD is often a comorbidity with ED
- Assessment should occur before ED treatment
  - Walking 2 miles/hr requires about 2 metabolic equivalent of energy (METs)
  - Sexual activity requires at least 3-4 METs
- Princeton Consensus Panel Guidelines

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Table 6. Cardiovascular Risk Assessment in Patients with Erectile Dysfunction

Grade of Risk	Definition	Management
Low risk	Asymptomatic, <3 major risk factors for CAD excluding gender; controlled HTN; mild, stable angina; post-successful coronary revascularization; uncomplicated past MI (>6–8 weeks); mild valvular disease; LVD/CHF (NYHA Class I)	Primary care management Consider all first-line therapies Reassess at 6 to 12 month intervals
Intermediate risk	3 or more major risk factors for CAD, excluding gender; moderate, stable angina; recent MI (>2, <6 weeks); LVD/CHF (NYHA Class II); noncardiac sequelae of atherosclerotic disease (e.g. CVA, peripheral vascular disease)	Specialized cardiovascular testing (e.g. Exercise tolerance test, echocardiogram) Restratification into high risk or low risk based on the results of the cardiovascular assessment
High risk	Unstable or refractory angina; uncontrolled HTN; LVD/CHF (NYHA class III/IV); recent MI (<2 weeks); CVA; high-risk arrhythmias; hypertrophic obstructive and other cardiomyopathies; moderate/severe valvular disease	Priority referral for specialized cardiovascular management Treatment for sexual dysfunction to be deferred until cardiac condition stabilized and dependent on specialist recommendations

*Risk factors for CAD: age, hypertension, diabetes, obesity/sedentary lifestyle, smoking, dyslipidemia.
CAD = coronary artery [illegible] = hypertension; LVD = left ventricular dysfunction; MI = myocardial infarction; NYHA = New York Heart Association.
Used with permission from: Am J Cardiol 2000;86:175–81.

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Patient Case #6

Based on the patient's cardiovascular risk, which one of the following is the most appropriate treatment for him at this time?

A. Initiate sildenafil

B. Initiate alprostadil suppository

C. Defer ED treatment for further cardiovascular testing (e.g. exercise tolerance test)

D. Defer ED treatment until his cardiovascular disease can be stabilized by a specialist.

Workbook Page 1-325; Answer: Page 1-329

Patient Case #7

- HPI: 60 year-old man presents to his PCP with complaints of ED. He requests medical therapy for his symptoms and is determined to be physically fit for sexual activity.
- PMH: ED, chronic stable angina (well-controlled), HTN, GERD, obesity
- Medications: lansoprazole, HCTZ, metoprolol, nitroglycerin SL prn chest pain (no use in several months)
- What treatments would be appropriate to treat his ED?

Workbook Page 1-325

ED Treatment

- 1st Line Therapy
  - PDE-5 inhibitors: sildenafil, vardenafil, tadalafil
  - Testosterone replacement
- 2nd Line Therapy
  - Vacuum constriction device
  - Intraurethral alprostadil
- 3rd Line Therapy
  - Injected vasodilators
- Unapproved agents
  - Supplements

Workbook Page 1-321-5

ED Treatment: PDE-5 Inhibitors

- Well studied, well tolerated, least invasive therapy
  - All effective, but tadalafil may be slightly more effective and offer more flexibility
- Improves ability to obtain and maintain an erection with sexual stimulation
- Overall ≈ 65% effective
  - Adequate trial requires at least 5-8 doses
  - If inadequate response, can trial another PDE-5 inhibitor

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ED Treatment: PDE-5 Inhibitors

Table 8 PDE-5 Inhibitors for ED

	Sildenafil	Vardenafil	Tadalafil
Tablet strength	25, 50, 100 mg	2.5, 5, 10, 20 mg	2.5, 5, 10, 20 mg
Starting PRN dose	50 mg	10 mg	10 mg
Daily use dose			2.5–5 mg/day
Low dose indicated	Patients taking CYP3A4 inhibitors (e.g., erythromycin, protease inhibitors) Hepatic impairment Renal impairment (sildenafil, tadalafil) Age older than 65 years (sildenafil, vardenafil)		
Onset of action	30–60 minutes		30 minutes to 6 hours
Duration of action	4 hours		24–36 hours
Best absorption	Empty stomach		No difference
Effects of concomitant alcohol	No effect		More than five drinks increases risk of hypotension, dizziness, headache, and tachycardia
Metabolism	CYP3A4 enzyme system		
Half-life	4 hours		18 hours

CYP = cytochrome P450; ED = erectile dysfunction; PDE-5 = phosphodiesterase-5; PRN = as needed up to every 24 hours.

Workbook Page 1-322

ED Treatment: PDE-5 Inhibitors

- Contraindications/warnings
  - Use of any type of nitrate due to risk of hypotension
    - 24 hours with sildenafil & vardenafil; 48 hours with tadalafil
  - Concomitant α_1-antagonist therapy
    - Use uroselective α_1-antagonist to avoid hypotension
    - When adding either drug, consider using lowest dose and separating dosing

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ED Treatment: PDE-5 Inhibitors

- Common adverse effects
  - Induced by vasodilation: headache, flushing, rhinitis, dyspepsia, hypotension, dizziness
  - Back/limb pain: tadalafil
- Rare adverse effects
  - Sudden hearing loss ± tinnitis/dizziness
  - Vision changes
    - Reversible blue-green color discrimination and light sensitivity (sildenafil & vardenafil)
    - Irreversible nonarteritic anterior ischemic optic neuropathy (any PDE-5 inhibitor)

Workbook Page 1-323

Patient Case #7

- HPI: 60 year-old man presents to his PCP with complaints of ED. He requests medical therapy for his symptoms and is determined to be physically fit for sexual activity.
- PMH: ED, chronic stable angina (well-controlled), HTN, GERD, obesity
- Medications: lansoprazole, HCTZ, metoprolol, nitroglycerin SL prn chest pain (no use in several months)

Workbook Page 1-325

Patient Case #7

Which one of the following treatments is most appropriate to treat his ED?

A. Sildenafil 50 mg/day as needed

B. Vardenafil 2.5 mg/day as needed

C. Yohimbine 5.4 mg 3 times/day

D. Vacuum pump as needed

Workbook Page 1-325; Answer: Page 1-329

Patient Case #8

- HPI: 52 year-old man presents to PCP with symptoms of ED. He states they have been mild for years, but are now more bothersome. His SHIM score is in the mild-moderate range.
- PMH/SH: ED, OA, cigarette smoking 2 packs/d, drinks alcohol socially
- Medications: acetaminophen as needed, glucosamine/chondroitin daily
- What additional laboratory information is appropriate to evaluate this man's ED?

Workbook Page 1-326

Assessment of ED

- Risk factors
- Medical and surgical history
- Medications
- Laboratory
- Sexual history
- Psychosocial history
- Physical examination
- Cardiovascular evaluation

Workbook Page 1-318-9

Laboratory Assessment of ED

Not standardized

Should evaluate for underlying cause of ED

- Serum testosterone
- Complete blood count
- Urinalysis
- Serum creatinine
- Glucose
- Fasting lipid panel
- Thyroid-stimulating hormone
- Prostate-specific antigen (PSA)

Workbook Page 1-318

Patient Case #8

- HPI: 52 year-old man presents to PCP with symptoms of ED. He states they have been mild for years, but are now more bothersome. His SHIM score is in the mild-moderate range.
- PMH/SH: ED, OA, cigarette smoking 2 packs/d, drinks alcohol socially
- Medications: acetaminophen as needed, glucosamine/chondroitin daily

Workbook Page 1-326

Patient Case #8

Which one of the following additional laboratory information is most appropriate to further evaluate this man's ED?

A. Serum creatinine level

B. Fasting lipid panel

C. Free thyroxine level

D. Follicle-stimulating hormone level

Workbook Page 1-326; Answer: Page 1-329

Patient Case #9

- HPI: 62 year-old man presents requesting treatment of his ED. He is also interested in making changes to improve his health.
- PMH: HTN, dyslipidemia, diabetes, depression, obesity, COPD
- SH: occasional alcohol socially, smoking 1 ppd X 20 yrs
- Objective data:
  - LDL cholesterol = 85 mg/dL
  - BP = 132/78 mm Hg
  - BMI = 33 kg/m^2
  - HR 78 beats/minute
- What lifestyle changes/risk modifications could positively affect his ED?

Workbook Page 1-326

Lifestyle Changes/Risk Modification for ED

- Implicated medications should be modified
- Weight loss is effective to resolve ED in ≈ 1/3
- Smoking cessation
- Pelvic floor exercises (Kegels)
  - Should focus on the bulbocavernosus and ischiocavernosus muscles
- Discontinuing alcohol and drug use
- Improving chronic diseases: diabetes, HTN, dyslipidemia, thyroid disorders, hypogonadism, depression, anxiety

Workbook Page 1-320-1

Patient Case #9

- HPI: 62 year-old man presents requesting treatment of his ED. He is also interested in making changes to improve his health.
- PMH: HTN, dyslipidemia, diabetes, depression, obesity, COPD
- SH: occasional alcohol socially, smoking 1 ppd X 20 yrs
- Objective data:
  - LDL cholesterol = 85 mg/dL
  - BP = 132/78 mm Hg
  - BMI = 33 kg/m^2
  - HR 78 beats/minute

Workbook Page 1-326

Patient Case #9

Which one of the following lifestyle changes/risk modifications is most likely to affect his ED?

A. Improve his LDL cholesterol

B. Improve his blood pressure

C. Suggest exercise and weight loss

D. Discontinue alcohol

Workbook Page 1-326; Answer: Page 1-329

Questions?