

566 Final Exam Study Guide

Week 5

Prevention of osteoporosis with hormone replacement therapy (p. 433)

Hormone therapy (HT) reduces postmenopausal bone loss & thereby decreases the risk for osteoporosis & related fractures. Unfortunately, when HT is stopped, bone mass rapidly decreases by approximately 12%. Hence to maintain bone health, HT must continue lifelong. As a result, the risk for harm is increased. Accordingly, alternative treatments are preferred. Effective alternatives to HT include raloxifene (*Evista*) & bisphosphonates like alendronate (*Fosamax*), calcitonin (*Miacalcin*), & teriparatide (*Forteo*). All patients should practice primary prevention of bone loss by ensuring adequate intake of calcium & vitamin D, performing regular weight-bearing exercise, & avoiding smoking & excessive alcohol use.

When and when not to use progestin for hormone replacement therapy and why (pp. 430-433)

Goals for noncontraceptive uses of progestins are to counteract endometrial hyperplasia caused by unopposed estrogen during hormone therapy; management of dysfunctional uterine bleeding, amenorrhea, & endometriosis; & support of pregnancy in women with corpus luteum deficiency. Progestins are also used in in vitro fertilization cycles & to prevent prematurity in women at high risk for preterm birth.

Progestins are *contraindicated* in the presence of undiagnosed abnormal vaginal bleeding. *Relative contraindications* include active thrombophlebitis or a history of thromboembolic disorders (DVT, CVA), active liver disease, & carcinoma of the breast. Progestins should not be prescribed for women who have undergone hysterectomy.

Local vs. systemic estrogen options and why one would be chosen over the other (p. 428)

Local estrogen options:

Transdermal: Transdermal estradiol is available in 4 formulations:

- Emulsion (*Estrasorb*): Applied once daily to the top of both thighs & the back of both calves.
- Spray (*Eexamist*): Applied once daily to the forearm.
- Gels (*EstroGel*, *Elestrin*, *Divigel*): Applied once daily to one arm, from the shoulder to the wrist or to the thigh (*Divigel*).
- Patches (*Alora*, *Climara*, *Estraderm*, *Menostar*, *Vivelle-Dot*): Applied to the skin of the trunk (but not the breast).

Intravaginal: Estrogens for intravaginal administration are available as inserts, creams, & vaginal rings. All are used primarily for the treatment of vulval & vaginal atrophy associated with menopause. NOTE: *Femring* is also used for systemic effects to control hot flashes & night sweats.

- Inserts (*Imvexxy*, *Vagifem*, *Yuvaferm*)
- Creams (*Estrace Vaginal*, *Premarin Vaginal*)
- Vaginal rings (*Estring*, *Femring*)

Systemic estrogen options:

Oral: Owing to convenience, the oral route is used more than any other. The most active estrogenic compound—estradiol—is available alone & in combination with progestins.

Parenteral: Although estrogens are formulated for IV & IM administration, use of these routes is rare. IV administration is generally limited to acute, emergency control of heavy uterine bleeding.

Transdermal estrogen therapy has fewer adverse effects (p. 428)

Compared with oral formulations, the transdermal formulations have 4 advantages:

- The total dose of estrogen is greatly reduced (because the liver is bypassed).
- There is less nausea & vomiting.
- Blood levels of estrogen fluctuate less.
- There is a lower risk for DVT, PE, & CVA.

Management of oral contraceptives (OCs)

-How to change patient from one combination oral contraceptive to another. (p. 441)

When one combination OC is being substituted for another, the change is best made at the beginning of a new cycle.

-How to initiate treatment (when in the cycle is it best to start- may vary based on type of contraceptive) (p. 442)

Most 28-day cycle products are taken in a repeating sequence consisting of 21 days of an active pill followed by 7 days on which either no pill is taken, an inert pill is taken, or an iron-containing pill is taken. The sequence is begun on either the first day of the menstrual cycle or the first Sunday after the onset of menses. With the first option, protection is conferred immediately, so no backup contraception is needed. With a Sunday start, which is done to have menses occur on weekdays rather than the weekend, protection may not be immediate, so an alternate form of birth control should be used during the first 7 days of the pill pack. With both options, each dose should be taken at the same time every day (with a meal or at bedtime). Successive dosing cycles should commence every 28 days even if there is breakthrough bleeding or spotting.

Unlike combination OCs, whose administration is cyclic, progestin-only OCs are taken continuously. Use is initiated on day 1 of the menstrual cycle, & one pill is taken daily thereafter. A backup contraceptive method should be used for the first 7 days.

-What teaching needs to be done? (p. 442)

Educate patient on proper protocol for missed doses (depending on medication type & cycle):

For products that use a 28-day cycle, the following recommendations apply:

- If *one or more pills* are missed in the *first week*, take one pill as soon as possible & then continue with the pack. Use an additional form of contraception for 7 days.
- If *one or two pills* are missed during the *second or third week*, take one pill as soon as possible & then continue with the *active pills* in the pack but skip the placebo pills & go straight to a new pack once all the active pills have been taken.
- If *three or more pills* are missed during the *second or third week*, follow the same instructions given for missing one or two pills but use an additional form of contraception for 7 days.

For combination OCs that use an *extended or continuous cycle*, up to 7 days can be missed with little or no increased risk for pregnancy provided that the pills have been taken *continuously for the prior 3 weeks*.

For progestin-only OCs, if one or more doses is missed or taken greater than 3 hours after the scheduled dose, the following guidelines apply:

- If *one pill* is missed, it should be taken as soon as remembered & backup contraception should be used for at least 2 days. The pills should be resumed as scheduled on the next day.
- If *two pills* are missed, the regimen should be restarted & backup contraception should be used for at least 2 days.

- In addition, if two or more pills are missed & no menstrual bleeding occurs, a pregnancy test should be done.

Effectiveness of oral contraceptives can be reduced with some medications, including certain common antibiotics.

-What baseline data is needed? (p. 446)

Assess for history of hypertension, diabetes, thromboembolism, cerebrovascular or cardiovascular disease, breast cancer. Urine pregnancy test.

-Contraindications for OCs (p. 446)

Contraindications to use include current pregnancy, history of thromboembolus, breast cancer, & women over 35 years of age who continue to smoke tobacco. Use with caution in women with diabetes, hypertension, & cardiac disease.

How to achieve an extended cycle with oral contraceptives (p. 442)

Many health care providers recommend taking combination OCs for an extended time rather than following the traditional 28-day cycle because doing so decreases episodes of withdrawal bleeding, with the associated menstrual pain, premenstrual symptoms, headaches, & other problems. Prolonged use of OCs is possible because these drugs suppress endometrial thickening, hence monthly bleeding is not required to slough off hypertrophied tissue. At this time, 14 products are packaged & marketed for prolonged use.

It is important to note that there is nothing special about the estrogen/progestin combinations used in these extended-cycle products. In other words, we could get the same results with other combination OCs, provided they are *monophasic*. To achieve an extended schedule, the user would simply purchase four packets of a 28-day product (each of which contains 21 active pills) & then take the active pills for 84 days straight.

What behaviors would make one birth control method more effective over another? (pp. 437-438)

-Be able to evaluate a patient scenario and suggest an appropriate birth control method (type of prescribed contraception: OC, long-term methods, IUD, etc.

With perfect use, the failure rate for OCs is only 0.3%. However, with typical use, the failure rate is significantly higher: about 8%. Among women of higher weight, efficacy is somewhat reduced. Possible reasons include decreased blood levels of the hormones, sequestration in adipose tissue, & altered metabolism.

Combination OCs should be avoided by women with certain cardiovascular disorders & those older than 35 years who smoke. For women in these categories, an alternative method (diaphragm, progestin-only pill, or IUD) is preferable.

Additional factors that bear on selecting a birth control method include family planning goals, age, frequency of sexual intercourse, & the individual's capacity for adherence. If family planning goals have already been met, sterilization of either the male or female partner may be desirable. For women who engage in coitus frequently, OCs or a long-term method (Nexplanon, Depo-Provera, IUD) are reasonable choices. Conversely, when sexual activity is limited, use of a spermicide, condom, or diaphragm may be more appropriate. Because barrier methods combined with spermicides can offer some protection against STDs, these combinations may be of special benefit to individuals who have multiple partners. If adherence is a problem (as it can be with OCs, condoms, & diaphragms), use of a long-term method (vaginal contraceptive ring, IUD, Nexplanon, Depo-Provera) can confer more reliable protection.

What effect does CYP450 inhibitors or inducers have on OCs? (p. 441)

-Recall examples of CYP450 inhibitors and inducers from NR565 (Chapter 4 in textbook)

-How does this impact prescribing of OCs?

Products that induce hepatic cytochrome P3A4 can accelerate OC metabolism & thereby reduce OC effects. Common drugs that induce CYP450 are phenytoin, carbamazepine, rifampin, alcohol, & sulfonylureas. Women taking OCs in combination with any of these agents should be alert for indications of reduced OC blood levels, such as breakthrough bleeding or spotting. If these signs appear, it may be necessary to either:

1. Increase the estrogen dosage of the OC
2. Combine the OC with a second form of birth control (condom, etc.)
3. Switch to an alternative form of birth control

OCs can decrease the benefits of warfarin & hypoglycemic agents. By increasing clotting factors, OCs can decrease the effectiveness of *warfarin*, an anticoagulant. By increasing levels of glucose, OCs can counteract the benefits of *insulin* & other hypoglycemic agents used in diabetes. Accordingly, when combined with OCs, warfarin & hypoglycemic agents may require increased dosage.

OCs can impair the hepatic metabolism of several agents, including *theophylline*, *tricyclic antidepressants*, *diazepam*, & *chlordiazepoxide*. Because of reduced clearance, these drugs may accumulate to toxic levels. If signs of toxicity appear, the dosages of these drugs should be reduced.

Benefits and drawbacks of progestin-only contraception (p. 442)

Benefits: Because they lack estrogen, “minipills” do not cause thromboembolic disorders, headaches, nausea, or most of the other adverse effects associated with combination OCs.

Drawbacks: Unfortunately, although slightly safer than combination OCs, the progestin-only preparations are less effective & are more likely to cause irregular bleeding (breakthrough bleeding, spotting, amenorrhea, inconsistent cycle length, variations in the volume & duration of monthly flow). Irregular bleeding is the major drawback of these products & the principal reason that women discontinue them.

What are the most effective forms of contraception? (p. 437)

The most effective methods are an etonogestrel implant (Nexplanon), an intrauterine device (IUD), & sterilization. OCs, medroxyprogesterone (Depo-Provera), the contraceptive ring, & the contraceptive patch are close behind. The least reliable methods include barrier methods, periodic abstinence, spermicides, & withdrawal.

Testosterone replacement (pp. 450-453)

Administration

- **Oral:** Only 2 androgens are approved for oral therapy—**fluoxymesterone & methyltestosterone**. Despite the advantage of cost & ease of administration, they are not first-line agents. The androgenic effects of oral androgens are erratic & pose a risk for hepatotoxicity, therefore they should not be used long term.
- **Transdermal patches:** *Androderm*—applied once daily to the upper arm, thigh, back, or abdomen.
- **Transdermal gel:** *AndroGel*, *Testim*, *Fortesta*, *Vogelxo*—applied once daily (preferably in the morning) to clean, dry skin of the shoulders, upper arms, or abdomen. Can be transferred to others by skin-to-skin contact. Wash hands with soap & water after every application, cover the application site with clothing once the gel has dried, wash the application site before skin-to-skin contact with another person, women & children should avoid skin-to-skin contact with application sites on gel users & wash contaminated skin immediately if accidental contact with gel application site occurs.

- **Transdermal topical solution:** **Axiron**—dosing is done by pumping the liquid onto an applicator & then applying the liquid to clean, dry, intact skin of the underarm at the same time every morning. Patients should not swim or bathe for 2 hours after application. If an underarm deodorant/antiperspirant is used, it should be applied before applying the testosterone to avoid contaminating the product.
- **Transdermal nasal gel:** **Natesto**—Pump should be primed before use & excess gel should be removed. Blow nose before administration. Insert pump into nostril with the tip aimed toward the lateral nostril wall. Depress pump slowly until it stops. As the tip is withdrawn, it should be wiped against the lateral nostril wall to ensure that any remaining gel is distributed to the nostril. After administration in both nostrils, the nose should be lightly massaged below the nasal bridge. The patient should avoid blowing or sniffing for at least 1 hour after administration.
- **Implantable pellets:** **Testopel**—implanted subdermally in the hip area or abdominal wall lateral to the umbilicus.
- **Buccal tablets:** **Striant**—tablets are applied to the gum area just above the incisor tooth & are designed to stay in place until removed. To ensure good adhesion, tablets should be held in place (with a finger over the lip) for 30 seconds.
- **Intramuscular esters:** **testosterone cypionate (Depo-Testosterone), testosterone enanthate (Delatestryl)**—IM injection

Patient Teaching

Topical testosterone: To minimize the risk for accidental skin-to-skin transfer, advise users of testosterone gel or testosterone topical solution to:

- Wash their hands after every application
- Cover the application site with clothing after the gel has dried
- Wash the application site before anticipated contact with another person

Also, warn women & children to avoid contact with the user's skin where testosterone was applied & advise them to wash contaminated skin if accidental contact with an application site should occur.

Androgens: Tell female patients about signs of virilization (deepening of the voice, acne, changes in body & facial hair, menstrual irregularities). Instruct them to report if these occur.

Apprise patients of the signs of liver dysfunction (yellow tint to skin & eyes, fatigue, loss of appetite, nausea, dark-colored urine, light-colored stools). Advise them to report the occurrence of these changes.

Inform patients that swelling of the extremities or unusual weight gain may be evidence of salt & water retention. Counsel them to report these events.

Remind patients of child-bearing age that this drug can cause fetal malformations. If the patient is capable of becoming pregnant, emphasize the need for consistent use of reliable contraception.

Treatment of delayed puberty

When is it appropriate to initiate androgen therapy (short course and long-term) (p. 448)

In some boys, puberty fails to occur at the usual age (before 15 years old). Most often, this failure reflects a familial pattern of delayed puberty & does not indicate pathology. Puberty can be expected to occur spontaneously but later than usual. Hence treatment is not an absolute necessity. However, some providers will prescribe a limited course of androgen therapy off label if the psychologic pressure of delayed sexual maturation are causing a boy significant distress. In these cases, a *limited course* of androgen therapy is indicated. Both **fluoxymesterone (Androxy, Halotestin)** & **methyltestosterone (Methitest)** are approved for this purpose.

If delayed puberty is the result of true hypogonadism, *long-term* replacement therapy is indicated.

Androgen therapy

-Effects:

Therapeutic (pp. 448-449)

- Male hypogonadism: A condition in which the testes fail to produce adequate amounts of testosterone. May be hereditary, or it may result from other causes, including pituitary failure, hypothalamic failure, & primary dysfunction of the testes.
- Replacement therapy: When testicular failure occurs in adult males. Treatment restores libido, increases ejaculate volume, & supports expression of secondary sex characteristics. Treatment will NOT restore fertility.
- Delayed puberty: If puberty fails to occur before age 15 years, some providers will prescribe a limited course of androgen therapy off label if the psychologic pressure of delayed sexual maturation are causing a boy significant distress.
- Testosterone therapy in menopausal women: Can alleviate some menopausal symptoms, especially fatigue, reduced libido, & reduced genital sensitivity.
- Cachexia: A wasting of the body associated with severe illnesses such as AIDS, severe trauma, & chronic systemic infections. Testosterone levels often decline in these patients, putting them at risk for wasting & loss of muscle mass. Testosterone therapy decreases this risk.
- Anemias: Sometimes used in men & women to treat anemias that have been refractory to other therapy.

Adverse (p. 450)

- Virilization in women, girls, & boys: The most common complication of androgen therapy. When taken in high doses by women, androgens can cause acne, deepening of the voice, proliferation of facial & body hair, male-pattern baldness, increased libido, clitoral enlargement, & menstrual irregularities. Masculinization can also occur if taken by children (for sports performance enhancement). Boys may experience growth of pubic hair, penile enlargement, increased frequency of erections, & even priapism (persistent erection). Girls can have growth of pubic hair & clitoral enlargement.
- Premature epiphyseal closure: When given to children, androgens can accelerate epiphyseal closure, decreasing adult height. To evaluate androgen effects, radiographic examination of the hand & wrist should be performed every 6 months.
- Hepatotoxicity: Androgens can cause *cholestatic hepatitis* & other disorders of the liver. Clinical *jaundice* may occur but is rare. Androgens may also be carcinogenic: *hepatocellular carcinoma* has developed in some patients after prolonged use of these drugs. (Liver damage is associated primarily with the *17- α -alkylated androgens* (oral androgens).
- Effects on cholesterol levels: Can lower plasma levels of HDL cholesterol & elevate plasma levels of LDL cholesterol, increasing the risk for atherosclerosis & related cardiovascular events.
- Prostate cancer: Do not cause prostate cancer but can promote the growth of this cancer after it occurs.
- Edema: Can result from androgen-induced retention of salt & water. This complication is a concern for patients with heart failure & those with a predisposition to developing edema from other causes.
- Abuse potential: Androgens are frequently misused to enhance athletic performance.
- Risk for thromboembolic events: There have been post marketing reports of thromboembolic events including stroke, MI, DVT, & PE that are believed to have been the result of testosterone's erythropoietic effects.

-Monitoring Needs (p. 452)

Baseline data: Serum testosterone concentration, CBC, lipid panel, liver function, prostate specific antigen (PSA).

Monitoring: Serum testosterone concentration, lipids, liver function, & PSA after 1 year (refer to urologist for evaluation if PSA is greater than 4.0 ng/mL or greater than 1.4 ng/mL above baseline).

-Role of androgens in treating anemia (p. 449)

Androgens are sometimes used in men & women to treat anemias that have been refractory to other therapy. Anemias most likely to respond include aplastic anemia, anemia associated with renal failure, Fanconi anemia, & anemia caused by cancer chemotherapy. Androgens help relieve anemia by promoting synthesis of erythropoietin, the renal hormone that stimulates production of red blood cells, & possibly white blood cells & platelets. With the emergence of other therapies such as erythropoietin-stimulating agents, androgens have fallen out of favor for off-label treatment of anemia.

-Preferred administration route of alprostadil and why (pp. 459-460)

Alprostadil is a nonoral drug for erectile dysfunction (ED) that can be given either by injection into the penis or by insertion into the urethra. Because of this inconvenient method of dosing, this drug is a second-line agent for ED.

Penile fibrosis may develop with the continued use of injections; this complication has not been reported with the pellets inserted into the urethra.

Treatment of hypogonadism

-Benefits (p. 448)

Androgen replacement therapy can restore libido, increase ejaculate volume, & support expression of secondary sex characteristics. Treatment will NOT restore fertility.

-Administration methods for transdermal preparations (p. 450)

Testosterone is available in 3 transdermal formulations: patch, gel, & liquid. With all 3 formulations, testosterone is absorbed through the skin & then slowly absorbed into the blood.

Treatment of BPH

-Know examples of drugs in each major drug class (p. 463)

■ **5-α-Reductase Inhibitors:** dutasteride (**Avodart**), finasteride (**Proscar**)

■ **α1 Blockers:**

Selective: silodosin (**Rapaflo**), tamsulosin (**Flomax**)

Nonselective: alfuzosin (**Uroxatral**), doxazosin (**Cardura**), terazosin (**Hytrin**)

■ **Phosphodiesterase-5 Inhibitor:** tadalafil (**Cialis**)

■ **α1a Blocker/5-α-Reductase Inhibitor:** tamsulosin/dutasteride (**Jalyn**)

-Adverse effects of common therapies (p. 463)

■ **5-α-Reductase Inhibitors:** Decreased ejaculate volume & libido. Teratogenic to the male fetus.

■ **α1 Blockers:**

Selective: Abnormal ejaculation (ejaculation failure, reduced ejaculate volume, retrograde ejaculation).

Risk of floppy-iris syndrome during cataract surgery.

Nonselective: Hypotension, fainting, dizziness, somnolence, & nasal congestion (from blocking α1 receptors on blood vessels).

■ **Phosphodiesterase-5 Inhibitor:** Hypotension, priapism.

■ **α 1a Blocker/5- α -Reductase Inhibitor:** Decreased libido & abnormal ejaculation (ejaculation failure, reduced ejaculate volume, retrograde ejaculation).

- Therapeutic Effects

Time to achieve:

■ **5- α -Reductase Inhibitors:** Anticipate symptom improvement after 6-12 months. (p. 464)

■ **α 1 Blockers:** Benefits develop rapidly. (p. 463)

Patient education/Provider response

■ **5- α -Reductase Inhibitors:** Most appropriate for men with very large prostates (mechanical obstruction). Several months are required for a noticeable effect. In 5% to 10 % of patients, it decreases ejaculate volume & libido. Gynecomastia develops in some men. Advise men not to donate blood if taking & for up to 6 months after stopping the drug to avoid the risk of having a pregnant woman as the blood recipient due to teratogenic effects on the male fetus. Dutasteride capsule contents can be irritating to the oropharyngeal mucosa, so they must be swallowed whole with a full glass of water.

■ **α 1 Blockers:** Preferred for men with relatively small prostates (dynamic obstruction). Symptomatic improvement & increased urinary flow develop rapidly. To maintain benefits, they must be taken lifelong. For men undergoing cataract surgery, these medications increase the risk for intraoperative *floppy-iris syndrome*, a complication that can increase postoperative pain, delay recovery, & reduce the hoped-for improvement in vision acuity. In severe cases, the syndrome can cause defects to the iris that may lead to blindness. Men anticipating cataract surgery should postpone α -blocker therapy until after the procedure. Men already taking an α -blocker should be sure to tell their ophthalmologist.

■ **Assessment for therapeutic effect** (p. 463)

■ **5- α -Reductase Inhibitors:** Reduction of dihydrotestosterone (DHT) production causes the prostate to shrink, which reduces mechanical obstruction of the urethra. May also delay BPH progression. Benefits take months to develop.

■ **α 1 Blockers:** Blockade of α -receptors relaxes smooth muscle in the bladder neck, prostate capsule, & prostatic urethra, thereby decreasing dynamic obstruction of the urethra. Benefits develop rapidly.

■ **Phosphodiesterase-5 Inhibitor:** Smooth muscle relaxation in the bladder, prostate, & urethra. Produces a modest decrease in symptoms (urinary frequency, urinary urgency, straining) but does not improve urinary flow rate. Initial improvement is seen in 2 weeks. (p. 465)

National STI/STD Curriculum

-Treatment of STIs/STDs (pp. 764-765)

■ Chlamydia:

Azithromycin, 1 gram PO once OR

Doxycycline, 100 mg PO BID x 7 days

■ Uncomplicated gonococcal urethritis:

Ceftriaxone, 250 mg IM once PLUS Azithromycin, 1 gram PO once

■ Bacterial Vaginosis:

Metronidazole, 500 mg PO BID x 7 days OR

Metronidazole gel (0.75%), 1 full applicator (5 grams) intravaginally once/day x 5 days OR

Clindamycin cream (2%), 1 full applicator (5 grams) intravaginally @ bedtime x 7 days

■ Herpes Simplex Virus:

Aцикловир, 400 mg PO TID x 7-10 days (or longer) OR

Aцикловир, 200 mg PO 5x/day x 7-10 days (or longer) OR

Fамцикловир, 250 mg PO TID x 7-10 days (or longer) OR

Валацикловир, 1 gram PO BID x 7-10 days (or longer)

■ Trichomoniasis:

Метронидазол, 2 grams PO once OR

Тинидазол, 2 grams PO once

■ Syphilis

Adults: Бензатиниум пенициллин G, 2.4 million units IM once

Children: Бензатиниум пенициллин G, 50,000 units/kg IM once (up to a max of 2.4 million units)

Week 6

Management of Parkinson Disease (PD)

-**Early stages** (p. 128)

For patients with mild symptoms, treatment can begin with an MAO-B inhibitor (**расагилайн**, **селигилайн**). MAO-B inhibitors confer mild symptomatic benefit.

For patients with more severe symptoms, treatment should begin with either **леводопа** (combined with **карбидопа**) or a dopamine agonist (**апоморфин**, **прамипексол**, **ропинирол**, **ротиготин**, **бромокриптина**, **каберголин**). Леводопа is more effective than the dopamine agonists, but long-term use carries a higher risk for disabling dyskinesias. Hence the choice must be tailored to the patient: if improving motor function is the primary objective, then леводопа is preferred. However, if drug-induced dyskinesias are a primary concern, then a dopamine agonist would be preferred.

-**Combination therapy** (p. 131)

Because of peripheral metabolism, less than 2% of each dose enters the brain if леводопа is given alone. For this reason, **леводопа** is now available only in combination preparations with either **карбидопа** OR **карбидопа & энтарапоне**. These additional agents decrease the amount of decarboxylation in the periphery so that more of the drug can enter the CNS.

-**Medications used to treat "off" times including "wearing off" experiences** (pp. 128-129)

Acute loss of effect occurs in 2 patterns: gradual loss & abrupt loss.

Gradual loss—"wearing off"—develops near the end of the dosing interval & simply indicates that drug levels have declined to a subtherapeutic value. Wearing off can be minimized in 3 ways:

1. Shortening the dosing interval
2. Giving a drug that prolongs леводопа's plasma half-life (**энтарапоне**—a COMT inhibitor)
3. Giving a direct-active dopamine agonist

Abrupt loss of effect, often referred to as the "on-off" phenomenon, can occur at any time during the dosing interval—even while drug levels are high. Off times may last from minutes to hours. Over the course of treatment, off periods are

likely to increase in both intensity & frequency. Off times can be reduced with 3 types of drugs: dopamine agonist, COMT inhibitors, & MAO-B inhibitors. Evidence of efficacy is strongest for **entacapone** (a COMT inhibitor) & **rasagiline** (an MAO-B inhibitor). The only drug recommended for dyskinesias is **amantadine** (a dopamine releaser).

-**Adverse Effects** (p. 137)

- **Pramipexole (Mirapex):** A nonergot dopamine receptor agonist; used alone is early-stage Parkinson's disease (PD) & is combined with levodopa in advanced-stage PD.

Can produce a variety of adverse effects, primarily by activating dopamine receptors. The most common effects seen when pramipexole is used *alone* are nausea, dizziness, daytime somnolence, insomnia, constipation, weakness, & hallucinations. When the drug is *combined with levodopa*, about 50% of patients experience orthostatic hypotension & dyskinesias, which are not seen when the drug is used by itself. In addition, the incidence of hallucinations nearly doubles.

A few patients have reported *sleep attacks* (overwhelming & irresistible sleepiness that comes on without warning). Sleep attacks should not be equated with the normal sleepiness that occurs with dopaminergic agents.

Pramipexole has been associated with *impulse control disorders*, including compulsive gambling, shopping, binge eating, & hypersexuality. These behaviors are dose related, begin about 9 months after starting the medication, & reverse when the drug is discontinued. Risk factors include younger adulthood, a family or personal history of alcohol abuse, & a personality trait called novelty seeking, characterized by impulsivity, a quick temper, & a low threshold for boredom. Before prescribing pramipexole, providers should screen patients for compulsive behaviors.

Management of seizures

-**Which medication would be the safest choice for someone on an oral contraceptive?** (p. 155)

For women of childbearing age who are not pregnant, it is essential to consider interactions of antiseizure drugs with oral contraceptives. Eight antiseizure drugs decrease the effectiveness of oral contraceptives: **carbamazepine, eslicarbazepine, lamotrigine, oxcarbazepine, phenytoin, phenobarbital, rufinamide, & topiramate**. If it is necessary to prescribe any of these drugs, it is important to advise the patient of the risks & the need for additional contraceptives if pregnancy is not desired.

-**Purpose and timing of serum drug levels** (pp. 152-154)

Safe & effective levels have been firmly established for most antiseizure drugs. Monitoring these levels can help guide dosage adjustments.

Monitoring plasma drug levels is especially helpful when treating major convulsive disorders (tonic-clonic seizures). Because these seizures can be dangerous, & because delay of therapy may allow the condition to worsen, rapid control of seizures is desirable. However, because these seizures occur infrequently, a long time may be needed to establish control if clinical outcome is relied on as the only means of determining an effective dosage. By adjusting initial doses on the basis of plasma drug levels (rather than on the basis of seizure control), we can readily achieve drug levels that are likely to be effective, thereby increasing our chances of establishing control quickly.

Measurements of plasma drug levels are less important for determining effective dosages for absence seizures. Because absence seizures occur very frequently (up to several hundred a day), observation of the patient is the best means for establishing an effective dosage: if seizures stop, dosage is sufficient; if seizures continue, it is likely that more drug is needed.

In addition to serving as a guide for dosage adjustment, knowledge of plasma drug levels can serve as an aid to:

1. Monitoring patient adherence
2. Determining the cause of lost seizure control
3. Identifying causes of toxicity, especially in patients taking more than one drug

Patient teaching & Drug Interactions

▪ **Phenytoin (Dilantin):** The most widely used antiseizure drug; active against partial seizures as well as primary generalized tonic-clonic seizures; of historical importance because it was the first drug to suppress seizures without depressing the entire CNS. (p. 155)

Drug interactions: (p. 158)

Induction of hepatic drug-metabolizing enzymes: Stimulates synthesis of multiple hepatic drug-metabolizing enzymes, & as a result it can decrease the effects of other drugs, including *oral contraceptives*, *warfarin* (an anticoagulant), & *glucocorticoids* (anti-inflammatory & immunosuppressive drugs). Because avoiding pregnancy is desirable while taking antiseizure medications, & because phenytoin can decrease the effectiveness of oral contraceptives, the provider may need to increase the contraceptive dosage, or a switch to an alternative form of contraception may need to be made.

Drugs that increase plasma levels of phenytoin: Because the therapeutic range of phenytoin is narrow, slight increases in phenytoin levels can cause toxicity. Caution must be exercised when phenytoin is used with drugs that can increase its level. Drugs known to elevate phenytoin levels include *diazepam* (an antianxiety agent & antiseizure drug), *isoniazid* (a drug for TB), *cimetidine* (a drug for gastric ulcers), & *alcohol* (when taken acutely). These agents increase phenytoin levels by reducing the rate at which phenytoin is metabolized. *Valproic acid* (an antiseizure drug) elevates levels of free phenytoin by displacing phenytoin from binding sites on plasma proteins.

Drugs that decrease plasma levels of phenytoin: *Carbamazepine*, *phenobarbital*, & *alcohol* (when used chronically) can accelerate the metabolism of phenytoin, decreasing its level. Breakthrough seizures can result.

Central nervous system depressants: The depressant effects of *alcohol*, *barbiturates*, & other CNS depressants will add with those of phenytoin. Advise patients to avoid alcohol & all other drugs with CNS-depressant actions.

Enteral tube feedings: Tube feedings decrease phenytoin absorption & can lead to subtherapeutic serum levels. For patients receiving continuous tube feedings, hold the feeding for 1 to 2 hours before & after phenytoin administration.

Patient teaching: (p. 162)

- Explain that finding the optimal dose takes time & that the medication regimen may require tweaking over the next several appointments.
- To promote adherence, educate patients about the importance of taking antiseizure drugs exactly as prescribed. Inform them that, after a safe & effective dosage has been established, small deviations in dosage can lead to toxicity or to loss of seizure control.
- Inform patients about the dangers of abrupt drug withdrawal & instruct them never to discontinue drug use without consulting the prescriber. Advise patients who are planning a trip to carry extra medication to ensure an uninterrupted supply in the event they become stranded where medication is unavailable. Explain the need to obtain refills on time so that they do not run out of drugs.
- Teach the patient (or family member) to maintain a seizure frequency chart, indicating the date, time, & nature of all seizure events. They should bring this with them to all clinic appointments.
- If the drug requires periodic measurement of drug levels or other laboratory studies, explain the purpose & the importance of keeping those appointments.
- Advise patients to avoid potentially hazardous activities (driving, operating dangerous machinery) until seizure control is achieved. It may be necessary to explain laws concerning this risk. Also, because

- seizures may recur after they are largely under control, advise patients to carry some form of identification (Medic Alert bracelet) to aid in diagnosis & treatment if a seizure occurs.
- Forewarn patients about CNS depression that can occur as a drug side effect. Advise them to avoid driving & other hazardous activities if CNS depression is significant. To prevent additive CNS depressant effects, warn patients against using alcohol & other CNS depressants.
 - To reduce the risk for neural tube defects, advise women to take folic acid supplements before & throughout pregnancy.
 - Educate patients, families, & caregivers about signs that may precede suicidal behavior (increased anxiety, agitation, mania, or hostility) & advise them to report these immediately.

Management of Migraines

-1st line therapy

- **Preventative:** Beta-blockers are first-line drugs for migraine prevention. Of the available beta-blockers, **propranolol** is used most often, although **metoprolol** is now deemed to be just as effective. Other beta-blockers that can also be used to prevent migraines are **timolol**, **atenolol**, & **nadolol**. (p. 199)
- **Abortive:** The serotonin receptor agonists, also known as *triptans*, are first-line drugs for terminating a migraine attack. These agents relieve pain by constricting intracranial blood vessels & suppressing release of inflammatory neuropeptides. **Sumatriptan (Imitrex)** was the first triptan available & will serve as the prototype for the group. (p. 196)

-When to use abortive therapy and when to use preventive therapy

Abortive therapy: The objective of abortive therapy is to eliminate headache pain & suppress associated nausea & vomiting. Treatment should commence at the earliest sign of an attack. Because migraines cause GI disturbances, oral therapy may be ineffective after an attack has begun. Hence, for treatment of an established attack, a drug that can be administered by injection, nasal spray, or rectal suppository may be best. Two types of drugs are used: nonspecific analgesics & migraine-specific agents. (pp. 195-196)

Nonspecific Analgesics:

- NSAIDs & NSAID Combinations: Aspirin, Naproxen, Diclofenac; Excedrin Migraine (acetaminophen + aspirin + caffeine)
- Opioid Analgesics: Butorphanol nasal spray

Migraine-Specific Drugs:

- Triptans: almotriptan (Axert), eletriptan (Relpax), frovatriptan (Frova), naratriptan (Amerge), rizatriptan (Maxalt), sumatriptan (Imitrex), zolmitriptan (Zomig)
- Ergot Alkaloids: dihydroergotamine intranasal spray (Migranal), ergotamine sublingual (Ergomar), ergotamine + caffeine (Cafergot, Migergot)

Preventive therapy: Prophylactic therapy can reduce the frequency, intensity, & duration of migraine attacks & can improve responses to abortive drugs. Preventive treatment is indicated for patients who have frequent attacks (3 or more a month), attacks that are especially severe, or attacks that do not respond adequately to abortive agents. Preferred drugs for prophylaxis include **propranolol**, **divalproex**, & **amitriptyline**. All 3 are effective & well tolerated, & the benefits take 4-6 weeks to develop. (p. 199)

- Beta-Blocking Agents: propranolol (*Inderal*), metoprolol (*Lopressor*)
- Antiepileptic Drugs: divalproex (*Depakote ER*), topiramate (*Topamax*)
- Tricyclic Antidepressants: amitriptyline (*Elavil*)

▪ **Contraindications for drugs**

- **Sumatriptan:** All triptans are contraindicated for patients with ischemic heart disease, prior MI, or uncontrolled hypertension. Also contraindicated in pregnancy due to the risk for birth defects. (p. 198)

-Alternative preventative medication options (p. 200)

- Estrogens (for Menstrually Associated Migraine): estrogen gel, estrogen patch (*Alora, Climara, Vivelle-Dot*)
- Calcitonin Gene-Related Peptide Receptor Antagonist: erenumab (*Aimovig*)
- Botulinum toxin: injections of botulinum toxin A (*Botox*)

Management of Alzheimer Disease

-Administration Considerations

- **Memantine (Namenda):** Dosage adjustment is required for patients with renal impairment having creatinine clearance of less than 30 mL/min. Avoid in patients with severe hepatic impairment as a precaution due to inadequate studies & in patients with corneal conditions as these have worsened during treatment. Use caution with prescribing to patients with a history of cardiovascular disease. (p. 149)
- **Rivastigmine (Exelon):** Should be prescribed cautiously for patients with a history of respiratory or peptic ulcer disease. Exercise caution when prescribing for patients with bradycardia or first-degree heart block; benefits may not be worth the risks. Avoid prescribing to patients with higher degrees of heart block. (p. 147)

-Dosing considerations (p. 146)

- **Donepezil (Aricept):**
 - Mild to moderate AD: 5 mg daily. After 4-6 weeks, may increase to 10 mg daily
 - Severe AD: 10 mg daily. After 3 months, may increase to 23 mg daily
- **Memantine (Namenda):** Increase gradually using the following schedules for IR & ER formulations:
 - IR tablets & oral solution:
 - 5 mg/day (5 mg once a day) for 1 week or more
 - 10 mg/day (5 mg twice a day) for 1 week or more
 - 15 mg/day (5 & 10 mg in separate doses) for 1 week or more
 - 20 mg/day (20 mg twice a day) for maintenance
 - ER capsules:
 - 7 mg once daily for 1 week or more
 - 14 mg once daily for 1 week or more
 - 21 mg once daily for 1 week or more
 - 21 mg once daily for maintenance

*Reduce dosage in patients with moderate renal impairment & discontinue in patients with severe renal impairment.

-Side Effects

- **Cholinesterase Inhibitors:** (p. 147)
 - Most adverse effects (nausea, diarrhea, insomnia) are dose related & can be decreased by starting with lower doses & increasing gradually. These symptoms usually abate in 2-3 weeks.
 - Falls are more likely to occur as a result of bradycardia & other cardiac changes. Initiate fall precautions if hospitalized & teach patient & family how to prevent falls at home.
 - To prevent weight loss, encourage nutritional supplements (*Boost*) & snacks between meals. Schedule an appointment with a registered dietitian.
 - *The most common cholinergic effects are N/V/D, abd pain, tremors, & anorexia. By enhancing cholinergic transmission, it can intensify symptoms in patients with peptic ulcer disease, bradycardia, sick sinus syndrome, & constipation.*

syndrome, urinary obstruction, & lung disease. Can cause bradycardia, fainting, falls, & fall-related fractures.

Additional Notes

*If phenytoin is administered in doses only slightly greater than those needed for therapeutic effects, the liver's capacity to metabolize the drug will be overwhelmed, causing plasma levels of phenytoin to rise dramatically. This unusual relationship between dosage and plasma levels is illustrated in Fig. 21.1A. As you can see, after plasma levels have reached the therapeutic range, small changes in dosage produce large changes in plasma levels. As a result, small increases in dosage can cause toxicity, and small decreases can cause therapeutic failure. This relationship makes it difficult to establish and maintain a dosage that is both safe and effective. For this reason, serum drug levels and trough levels are often used, along with assessments of seizure control, to determine dosage.

- Examples: If a patient is taking phenytoin 300mg daily for seizures and their serum concentration is 8 mg/L and they experience a considerable increase in seizure activity, their dose would only need to increase to 350mg daily.

*When on medications for Alzheimer's Disease (AD) and symptoms increase, it is better to increase the AD medication than to add things like herbal medications, vitamins, or NSAIDs

Week 7

Management of Bipolar Disorder (BPD)

-Drugs from other classes that can be used to treat BPD

BPD is treated with 3 major groups of drugs: mood stabilizers, antipsychotics, & antidepressants. In addition, benzodiazepines are frequently used for sedation. (p. 229)

- **Mood stabilizers:** Drugs that relieve symptoms during manic & depressive episodes, prevent the recurrence of manic & depressive episodes, & do not worsen symptoms of mania or depression or accelerate the rate of cycling. The principle mood stabilizers are *lithium* & 2 drugs originally developed for epilepsy: *divalproex sodium (valproate)* & *carbamazepine*. *Lamotrigine (Lamictal)* is another antiepileptic drug indicated for long-term maintenance therapy of BPD. (pp. 230-232)
- **Antipsychotics:** Drugs given in BPD to help control ACUTE symptoms during severe manic episodes, even if psychotic symptoms are absent. They are also given LONG TERM to help stabilize mood. Although they can be used alone, they are usually employed in combination with a mood stabilizer. The 2nd generation (atypical) antipsychotics (*olanzapine*, *risperidone*) are generally preferred to the 1st generation (conventional) agents (*haloperidol*) because they carry a lower risk for extrapyramidal side effects, including tardive dyskinesia. (Currently, only 3 atypical agents are approved for long-term use to prevent the recurrence of mood episodes: *ariPIPrazole*, *olanzapine*, & *ziprasidone*. (p. 233)
- **Antidepressants:** In patients with BPD, antidepressants are almost always combined with a mood stabilizer because of the long-held belief that when used alone they may elevate mood so much that a hypomanic or manic episode will result. Among clinicians with extensive experience in BPD, the following are considered antidepressants of choice: *bupropion (Wellbutrin)*, *venlafaxine (Effexor XR)*, & the serotonin reuptake inhibitors (SSRIs) such as *fluoxetine (Prozac)* & *sertraline (Zoloft)*. NOTE: The use of tricyclic antidepressants (TCAs) appears to promote more incidents of mania, therefore they are not recommended in the treatment of BPD. (pp. 229-230)

-Drug Interactions (pp. 231-232)

- **Lithium:**

Diuretics: Diuretics promote sodium loss & can thereby increase the risk for lithium toxicity. Toxicity can occur because renal excretion of lithium is reduced in the presence of low sodium, causing lithium levels to rise.

NSAIDs: NSAIDs can increase lithium levels by as much as 60%. By suppressing prostaglandin synthesis in the kidney, NSAIDs can increase renal reabsorption of lithium (& also sodium), causing lithium levels to rise.

(EXCEPTION: Aspirin & Sulindac do NOT increase lithium levels!)

Anticholinergics: Anticholinergic drugs can cause urinary hesitancy. Coupled with lithium-induced polyuria, this can result in considerable discomfort. Accordingly, patients should avoid drugs with prominent anticholinergic actions (antihistamines, phenothiazine antipsychotics, TCAs).

-Monitoring (pp. 230-231)

▪ **Lithium:** Lithium has a low therapeutic index. As a result, toxicity can occur at blood levels only slightly greater than therapeutic levels. Accordingly, the monitoring of lithium levels is mandatory & an essential component of treatment. **Lithium levels must be kept below 1.5 mEq/L--levels greater than this can produce significant toxicity.** Lithium levels should range from 0.4 to 1 mEq/L. Generally levels should be between 0.6 & 0.8 mEq/L as these levels are effective for most patients. Levels of 0.8 to 1 mEq/L may be more effective but carry a greater risk of adverse effects. Blood for lithium determinations should be drawn in the morning, 12 hours after the evening dose. Lithium levels should be measured every 2-3 days during initial therapy & every 3-6 months during maintenance.

BLACK BOX WARNING: Lithium toxicity is closely related to serum lithium levels & can occur at doses close to therapeutic levels. Facilities for prompt & accurate serum lithium determinations should be available before initiating therapy.

Signs of Lithium Toxicity:

Less than 1.5 mEq/L: N/V/D, thirst, polyuria, lethargy, slurred speech, muscle weakness, fine hand tremor.

1.5-2 mEq/L: Persistent GI upset, coarse hand tremor, confusion, hyperirritability of muscles, EKG changes, sedation, incoordination.

2-2.5 mEq/L: Ataxia, giddiness, high output of dilute urine, serious EKG changes, fasciculations, tinnitus, blurred vision, clonic movements, seizures, stupor, severe hypotension, coma, death (usually secondary to pulmonary complications).

More than 2.5: Symptoms may progress rapidly to generalized convulsions, oliguria, & death.

Management of Major Depressive Disorder (pp. 214-216)

Drugs are the primary therapy for major depression. However, benefits are limited mainly to patients with severe depression. In patients with mild to moderate depression, antidepressants have little or no beneficial effect.

Available antidepressants fall into 5 major classes:

***selective serotonin reuptake inhibitors (SSRIs)**

***serotonin-norepinephrine reuptake inhibitors (SNRIs)**

***tricyclic antidepressants (TCAs)**

***monoamine oxidase inhibitors (MAOIs)**

***atypical antidepressants**

ALL OF THESE CLASSES ARE EQUIALLY EFFECTIVE, AS ARE ALL THE INDIVIDUAL DRUGS WITHIN EACH CLASS. Differences among these drugs relate mainly to side effects & drug interactions.

-Know example drugs

▪ **SSRIs:** The most commonly prescribed antidepressants, they are indicated for major depression as well as several other psychological disorders. Compared with the TCAs & MAOIs, they are equally effective, better tolerated, & much safer. They work by blocking 5-HT reuptake & thereby increase 5-HT in the synapse. (pp. 216-219)

Citalopram (Celexa)

Escitalopram (Lexapro)
Fluoxetine (Prozac)
Paroxetine (Paxil)
Sertraline (Zoloft)
Vortioxetine (Trintellix)

-Adverse Effects

- **Venlafaxine (Effexor XR):** The 1st serotonin-norepinephrine reuptake inhibitor (SNRI) available & the prototype drug for this class of antidepressants. (pp. 219-220)

Venlafaxine can cause a variety of adverse effects. The most common is **nausea** (37% to 58%), followed by **headache, anorexia, nervousness, sweating, somnolence, & insomnia**. Dose-dependent **weight loss** may occur secondary to anorexia. It can also cause dose-related sustained **diastolic hypertension**, so blood pressure should be monitored. **Sexual dysfunction** may also occur. Some patients experience sustained **mydriasis**, which can increase the risk for eye injury in those with elevated intraocular pressure or glaucoma. Like the SSRIs, venlafaxine can cause **hyponatremia**, especially in older adult patients taking diuretics. Like all other antidepressants, it may **increase the risk for suicide**, especially in children & young adults.

The combined use of venlafaxine with MAOIs & other serotonergic drugs increases the risk for **serotonin syndrome**, a potentially fatal reaction. Because of this, use with an MAOI is contraindicated. MAOIs should be withdrawn at least 14 days before starting venlafaxine. When switching from venlafaxine to an MAOI, venlafaxine should be discontinued 7 days before starting the MAOI.

As with the SSRIs, the use of venlafaxine late in pregnancy can result in a **neonatal withdrawal syndrome**, characterized by irritability, abnormal crying, tremor, respiratory distress, & possibly seizures. Symptoms can be managed with supportive care & generally abate within a few days.

Abrupt discontinuation can cause an intense **withdrawal syndrome**. Symptoms include anxiety, agitation, tremors, headache, vertigo, nausea, tachycardia, & tinnitus. Worsening of pretreatment symptoms may also occur. Withdrawal symptoms can be minimized by tapering the dosage over 2 to 4 weeks. Warn patients not to stop venlafaxine abruptly.

▪ **Monoamine Oxidase Inhibitors (MAOIs): Isocarboxazid (Marplan), Phenelzine (Nardil), Tranylcypromine (Parnate), Selegiline (Emsam)** Are 2nd or 3rd choice antidepressants, because although as effective as the SSRIs & TCAs, they are more hazardous. At this time, MAOIs are drugs of choice **ONLY** for atypical depression. (pp. 222-224)

Central nervous system stimulation: MAOIs cause direct CNS stimulation (in addition to their antidepressant effects). Excessive stimulation can produce **anxiety, insomnia, agitation, hypomania, & even mania**.

Orthostatic hypotension: MAOIs reduce blood pressure when administered in usual therapeutic doses. Patients should be informed about signs of hypotension (**dizziness, lightheadedness**) & advised to sit or lie down if these occur. This can be minimized by moving slowly when assuming an erect position.

Hypertensive crisis from dietary tyramine: Although the MAOIs normally produce hypotension, they can be the cause of severe hypertension if the patient eats food that is rich in tyramine, a substance that promotes the release of norepinephrine (NE) from sympathetic neurons. Hypertensive crisis is characterized by **severe headache, tachycardia, hypertension, nausea, vomiting, confusion, & profuse sweating--possibly leading to stroke & death**.

-Food & Drug Interactions

- **Monoamine Oxidase Inhibitors (MAOIs):** (pp. 223-225)

Food Interactions: *Dietary tyramine can produce a life-threatening hypertensive crisis when taken with MAOIs.* In the absence of MAO inhibition, dietary tyramine is not a threat.

1. Inhibition of neuronal MAO augments NE levels within the terminals of sympathetic neurons that regulate cardiac function & vascular tone.
2. Inhibition of intestinal & hepatic MAO allows dietary tyramine to pass directly through the intestinal wall & liver, & then enter the systemic circulation intact.

3. On reaching peripheral sympathetic nerves, tyramine stimulates the release of the accumulated NE, thereby causing massive vasoconstriction & intense stimulation of the heart.

Foods That Contain Tyramine

Vegetables: Avocados; fermented bean curd; fermented soybean; soybean paste

Fruits: Figs; bananas (in large amounts)

Meats: Meats that are fermented, smoked, or otherwise aged; spoiled meats; liver (unless very fresh)

Sausages: Fermented varieties: bologna, pepperoni, salami, others

Fish: Dried or cured fish; fish that is fermented, smoked, or otherwise aged; spoiled fish

Milk/Milk Products: Practically all cheeses

Foods with Yeast: Yeast extract

Beer/Wine: Some imported beers, Chianti wine

Other Foods: Protein dietary supplements; soups (may contain protein extract); shrimp paste; soy sauce

Foods That Contain Nontyramine Vasopressors

Chocolate, Fava beans, Ginseng, Caffeinated beverages

Drug Interactions:

Indirect-acting sympathomimetic agents: Drugs that promote the release of NE from sympathetic nerves. Patients should be instructed to avoid all sympathomimetic drugs, including **ephedrine, methylphenidate, amphetamines, & cocaine**. Sympathomimetic agents may be present in cold remedies, nasal decongestants, & asthma medications--all of these should be avoided unless approved by the prescriber.

Interactions secondary to inhibition of hepatic monoamine oxidase: Inhibition of MAO in the liver can decrease the metabolism of several drugs, including **epinephrine, norepinephrine, & dopamine**. These drugs must be used with caution because their effects will be more intense & prolonged.

Tricyclic antidepressants: The combination of a **TCA** with an MAOI may produce hypertensive episodes or hypertensive crisis. As a result, this combination of antidepressants is not employed routinely. However, although potentially dangerous, the combination can benefit certain patients. If concurrent use is employed, caution must be exercised.

Serotonergic drugs: Combining MAOIs with **SSRIs & other serotonergic drugs** poses a risk for serotonin syndrome. Accordingly, these combinations should be avoided.

Antihypertensive drugs: Combined use of MAOIs & **antihypertensive agents** may result in excessive lowering of blood pressure.

-Suicide Risks and Considerations for Major Depressive Disorder (pp. 215-216)

Time Course of Response: With all antidepressants, symptoms resolve slowly. Initial responses develop in 1 to 3 weeks; maximum responses may not be seen until 12 weeks. Because therapeutic effects are delayed, antidepressants cannot

be used PRN & a therapeutic trial should not be considered a failure until a drug has been taken for at least 1 month without success.

Drug Selection: Because all antidepressants have nearly equal efficacy, selection among them is based largely on tolerability & safety. Additional considerations are drug interactions, patient preference, & cost. The usual drugs of first choice are SSRIs, SNRIs, bupropion, & mirtazapine. Older antidepressants (TCAs & MAOIs) have more adverse effects & are less well tolerated than the first-line agents, & hence are generally reserved for patients who have not responded to the first-line drugs.

In some cases, the side effects of a drug, when matched to the right patient, can actually be beneficial. Here are some examples:

- For a patient with fatigue, choose a drug that causes CNS stimulation (fluoxetine, bupropion).
- For a patient with insomnia, choose a drug that causes substantial sedation (mirtazapine).
- For a patient with sexual dysfunction, choose a drug that enhances libido (bupropion).
- For a patient with chronic pain, choose a drug that can relieve chronic pain (duloxetine or a TCA).

Managing Treatment: After a drug has been selected for initial treatment, it should be used for 4 to 8 weeks to assess efficacy. As a rule, dosage should be low initially (to reduce side effects) & then gradually increased (see Table 27.1). If the initial drug is not effective, we have 4 major options:

- Increase the dosage
- Switch to another drug in the same class
- Switch to another drug in a different class
- Add a 2nd drug, such as an atypical antidepressant

After symptoms are in remission, treatment should continue for at least 4 to 9 months to prevent a relapse. Patients should be encouraged to continue the medication, even if they are symptom free. When antidepressant therapy is discontinued, dosage should be gradually tapered over several weeks because abrupt withdrawal can trigger withdrawal symptoms.

BLACK BOX WARNING: Patients with depression often think about or attempt suicide. During treatment with antidepressants, especially early on, the risk for suicide may actually increase. Concerns about antidepressant-induced suicide apply mainly to children, adolescents, & adults younger than 25 years old.

▪ Safety measures

To reduce the risk for suicide, patients taking antidepressants should be observed closely for suicidality, worsening mood, & unusual changes in behavior. Close observation is especially important during the first few months of therapy & whenever antidepressant dosage is changed (either increased or decreased). Ideally, the patient or caregiver should meet with the prescriber at least weekly during the first 4 weeks of treatment, then biweekly for the next 4 weeks, then once 1 month later, & periodically thereafter. Phone contact may be appropriate between visits. In addition, family members or caregivers should monitor the patient daily, being alert for symptoms of decline (anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, hypomania, emergence of suicidality). If these symptoms are severe or develop abruptly, the patient should see their prescriber immediately.

Because antidepressant drugs can be used to commit suicide, prescriptions should be written for the smallest number of doses consistent with good patient management.

What should be done if suicidal thoughts emerge during drug therapy, or if depression is persistently worse while taking drugs? One option is to switch to another antidepressant. However, the risk for suicidality appears equal with all antidepressants. Another option is to stop antidepressants entirely. However, this option is probably unwise because the

long-term risk for suicide from untreated depression is much greater than the long-term risk associated with antidepressant drugs. If the risk for suicide appears high, temporary hospitalization may be the best protection.

-Administration and Cessation of Medication Considerations

▪ Selective serotonin reuptake inhibitors (SSRIs)

- **What do patients need to know about starting and stopping SSRIs?** (pp. 216-219)

SSRIs are indicated for major depression as well as several other psychological disorders. Characteristic side effects are nausea, agitation & insomnia, & sexual dysfunction (especially anorgasmia). Like all other antidepressants, SSRIs may increase the risk for suicide.

Abrupt discontinuation of SSRIs can cause a withdrawal syndrome. Symptoms include dizziness, headache, nausea, sensory disturbances, tremor, anxiety, & dysphoria. These begin within days to weeks of the last dose & then persist for 1 to 3 weeks. Resumption of drug use will make symptoms subside. The withdrawal syndrome can be minimized by tapering the dosage slowly.

▪ MAOIs

- **What patient type would be appropriate for MAOIs?** (pp. 222-223)

MAOIs are equal to SSRIs & TCAs for relieving depression. However, because MAOIs can be hazardous, they are generally reserved for patients who have not responded to SSRIs, TCAs, & other safer drugs. At this time, MAOIs are the drugs of choice only for atypical depression. As with other antidepressants, beneficial effects do not reach their peak for several weeks.

-Baseline data needed to prescribe & strategies to minimize adverse effects for the following: (you will use each option only one on the exam)

▪ SSRI/SNRI: (p. 220)

Baseline data: Serum sodium should be checked in older adults & patients on diuretic therapy.

Minimizing adverse effects: Educate patients that abrupt cessation of these drugs is not recommended. Patient should also report thoughts of suicide or self-harm immediately.

▪ Tricyclic Antidepressants: (p. 222)

Baseline data: EKG should be checked, especially in patients with known dysrhythmias or patients older than 40 years of age.

Minimizing adverse effects: Educate patients regarding orthostatic hypotension & anticholinergic effects, including dry mouth, blurred vision, constipation, & urinary hesitancy.

▪ MAOIs: (p. 225)

Baseline data: Baseline blood pressure should be obtained.

Minimizing adverse effects: Educate patient on foods containing tyramine & to report signs of hypertensive crisis (nausea, vomiting, profuse sweating, severe headache) immediately.

Management of Panic Disorder (pp. 244-245)

Panic disorder is characterized by recurrent, intensely uncomfortable episodes known as *panic attacks*—an abrupt surge of intense fear or discomfort during which 4 or more of the following are present:

--palpitations, sweating, trembling/shaking, SOB, feeling of choking, CP, nausea, dizziness, chills or heat sensations, paresthesias, derealization/depersonalization, fear of losing control or going crazy, fear of dying.

Symptoms reach a peak in a few minutes & then dissipate within 30 minutes. Panic disorder is a common condition that affects 1.6% of Americans at some time in their lives.

-Medications used to treat

Panic disorder responds well to all 4 classes of antidepressants: SSRIs, SNRIs, TCAs, & MAOIs. With all classes, full benefits take 6 to 12 weeks to develop. Owing to better tolerability, SSRIs are generally preferred.

The SSRIs are first-line drugs for panic disorder. At this time, only 3 SSRIs are approved for this condition: **fluoxetine (Prozac)**, **paroxetine (Paxil)**, & **sertraline (Zoloft)**.

- **Exam will note mg in choices but if you know the med, the mg will be irrelevant.**

Fluoxetine (Prozac) 10 mg PO daily (initial), 20 mg PO daily (usual range)

Paroxetine (Paxil) 10 mg PO daily (initial), 20-40 mg PO daily (usual range)

Sertraline (Zoloft) 25 mg PO daily (initial), 50-200 mg PO daily (usual range)

Management of social anxiety disorder (SAD) (p. 246)

SAD is characterized by an intense, irrational fear of situations in which one might be scrutinized by others or might do something that is embarrassing or humiliating. Exposure to the feared situation almost always elicits anxiety. As a result, the person avoids the situation of, if it can't be avoided, endures it with intense anxiety (manifestations include blushing, stuttering, sweating, palpitations, dry throat, & muscle tension/twitches).

There are 2 principal forms: generalized & performance only. In the generalized form, the person fears nearly all social & performance situations. In the performance only form, fear is limited to speaking or performing in public.

-What medications can be used on a routine basis versus on an as needed basis

Routine: **SSRIs** are considered first-line drugs for most patients. Only 2 SSRIs are approved for this condition: **paroxetine (Paxil)** & **sertraline (Zoloft)**. Initial effects take about 4 weeks to develop; optimal effects are seen in 8 to 12 weeks.

PRN:

Benzodiazepines can provide rapid relief & can be used PRN. Accordingly, these drugs are well suited for people whose fear is limited to performance situations & who must face those situations only occasionally. The usual dosage is **clonazepam (Klonopin)** 1 to 3 mg/day & **alprazolam (Xanax)** 1 to 4 mg/day.

Beta-blockers can benefit patients with performance anxiety. When taken 1 to 2 hours before a scheduled performance, they can reduce symptoms caused by autonomic hyperactivity (tremors, sweating, tachycardia, palpitations). **Propranolol (Inderal)** 10 to 80 mg.

Management of anxiety (pp. 243-244)

Generalized anxiety disorder (GAD) is a chronic condition characterized by uncontrollable worrying. The hallmark of GAD is unrealistic or excessive anxiety about several events or activities that lasts 6 months or longer. Other psychological

manifestations include vigilance, tension, apprehension, poor concentration, & difficulty fall or staying asleep. Somatic manifestations include trembling, muscle tension, restlessness, & signs of autonomic hyperactivity, such as palpitations, tachycardia, sweating, & cold clammy hands.

-Long term treatment options

Both SSRIs & SNRIs are considered first-line treatment for GAD. At this time, only 4 antidepressants are approved for GAD: **venlafaxine (Effexor XR)**, **duloxetine (Cymbalta)**, **paroxetine (Paxil)**, & **escitalopram (Lexapro)**.

Buspirone (Buspar) is also considered a first-line treatment for GAD. For treatment of anxiety, buspirone is as effective as the benzodiazepines & has 2 distinct advantages: it has no abuse potential & does not intensify the effects of CNS depressants (benzos, alcohol, & barbiturates). Because it lacks depressant properties, buspirone is an attractive alternative to benzodiazepines in patients who require long-term therapy but cannot tolerate benzo-induced sedation & psychomotor slowing.

NOTE: Benzodiazepines are first-choice drugs for acute anxiety. Long-term use carries a risk for physical dependence. Withdrawal symptoms include panic, paranoia, & delirium. To minimize withdrawal symptoms, they should be tapered gradually over a period of several months. The benzos most commonly prescribed for anxiety are **alprazolam (Xanax)** & **lorazepam (Ativan)**.

-Recommended duration of treatment

Because GAD is a chronic disorder, initial drug therapy should be prolonged, lasting at least 12 months & possibly longer. Unfortunately, even after extended treatment, drug withdrawal frequently results in relapse. Hence, for many patients, drug therapy must continue indefinitely.

Side effects of both 1st generation and 2nd generation antipsychotics (pp. 204-211)

Traditional (1st generation) Antipsychotics: **chlorpromazine, haloperidol (Haldol)**

Side effects:

Extrapyramidal symptoms:

--Acute dystonia: (EARLY REACTION) spasm of muscles of tongue, face, neck, & back; oculogyric crisis (involuntary upward deviation of the eyes); opisthotonus (tetanic spasm of the back muscles causing the trunk to arch forward while the head & lower limbs are thrust backward). *Severe cramping can cause joint dislocation. Laryngeal dystonia can impair respiration.*

--Parkinsonism: (EARLY REACTION) bradykinesia, mask-like facies, tremor, rigidity, shuffling gait, drooling, cogwheeling, stooped posture.

--Akathisia: (EARLY REACTION) compulsive, restless movement; symptoms of anxiety & agitation

--Tardive dyskinesia: (LATE REACTION) oral-facial dyskinesias, involuntary choreoathetoid (twisting, writhing, worm-like) movements of the tongue & face, may also present with lip-smacking movements & their tongues may flick out in a "fly catching" motion. *Involuntary movements that involve the tongue & mouth can interfere with chewing, swallowing, & speaking. Eating difficulties can result in malnutrition & weight loss.*

Other adverse effects:

--**Neuroleptic malignant syndrome**: "lead pipe" rigidity, sudden high fever, sweating, autonomic instability (dysrhythmias & fluctuations in blood pressure), level of consciousness may rise & fall, may appear confused or mute, seizures or coma may develop. Death can result from respiratory failure, cardiovascular collapse, dysrhythmias, & other causes.

--**Anticholingeric effects**: dry mouth, blurred vision, photophobia, urinary hesitancy, constipation, tachycardia.

--**Orthostatic hypotension**

--**Sedation**

--**Neuroendocrine effects**: gynecomastia (breast growth), galactorrhea (milky nipple discharge)

--**Seizures**: can reduce seizure threshold

--**Sexual dysfunction**: suppress libido & impair the ability to achieve orgasm, erectile dysfunction

--**Agranulocytosis**

--**Severe dysrhythmias**: prolongation of the QT interval which can increase the risk for torsades de pointes that can progress to fatal ventricular fibrillation.

Atypical (2nd generation) Antipsychotics: aripiprazole (**Abilify**), lurasidone (**Latuda**), olanzapine (**Zyprexa**), quetiapine (**Seroquel**), risperidone (**Risperdal**), ziprasidone (**Geodon**)

Side effects:

Common adverse effects include sedation & weight gain (from blocking H₁ receptors); orthostatic hypotension (from blocking α-adrenergic receptors); & dry mouth, blurred vision, urinary retention, constipation, & tachycardia (from blocking muscarinic cholinergic receptors).

Neuroendocrine effects (galactorrhea, gynecomastia, amenorrhea) & interference with sexual function are minimal. Compared with 1st generation antipsychotics, 2nd generation antipsychotics carry a low risk for extrapyramidal effects, including tardive dyskinesia (TD).

--**Agranulocytosis**

--**Metabolic effects**: weight gain, diabetes, & dyslipidemia

--**Seizures**

--**Extrapyramidal symptoms**: parkinsonism, acute dystonia, akathisia, TD

--**Orthostatic hypotension**

--**Effects in older adult patients with dementia**: Approximately double the rate of mortality when used off-label to treat dementia-related psychosis in older adults.

Management of Insomnia (pp. 240-241)

Insomnia can be defined as an inability to sleep well. Some people have difficulty falling asleep, some have difficulty maintaining sleep, some are troubled by early-morning awakening, & some have sleep that is not refreshing. Insomnia is transient for some people & chronic for others.

Hypnotics should be used only when insomnia cannot be managed by other means. Before resorting to drugs, nondrug measures should be implemented & any pathology that may underline inadequate sleep should be treated.

Drug therapy of transient insomnia should be short term (just 2 to 3 weeks) & the patient should be reassessed on a regular basis to determine whether drug therapy is still needed. To minimize drug-dependency insomnia, hypnotics should be employed judiciously—in the lowest effective dosage for the shortest amount of time required.

-**What type of patient scenario would be appropriate for administration of the following drugs?**

- **Trazodone:** An atypical antidepressant with strong sedative actions, it can decrease sleep latency & prolong sleep duration without causing tolerance or physical dependence. It is especially useful for treating insomnia resulting from use of antidepressants that cause significant CNS stimulation (fluoxetine, bupropion).
- **Zaleplon (Sonata):** A benzodiazepine-like drug, it is an ultrashort duration medication useful for helping patients to fall asleep but not helpful for maintaining sleep.
- **Flurazepam:** A benzodiazepine with a long duration, it is useful for helping patients with both difficulty in falling asleep & staying asleep. (Because of its long duration of action, this drug is not generally recommended).
- **Zolpidem (Ambien):** A benzodiazepine-like drug used for short-term management of insomnia. It can be useful for helping patients to fall asleep, reducing sleep latency & awakenings, & prolong sleep duration.

-**Know examples for the major drug classes** (p. 241)

- **Benzodiazepine:** triazolam (*Halcion*), flurazepam, estazolam, quazepam (*Doral*), temazepam (*Restoril*)
- **Benzodiazepine-Like Drug:** eszopiclone (*Lunesta*), zolpidem (*Ambien*, *Ambien CR*, *Intermezzo*, *Edluar*, *Zolpimist*), zaleplon (*Sonata*)
- **Zolpidem:**
 - Extended-release tablets: (*Ambien CR*)
 - Immediate-release tablets: (*Ambien*)
 - Sublingual: (*Intermezzo*), (*Edluar*)
 - Oral spray: (*Zolpimist*)
- **Melatonin Receptor Agonist:** Ramelteon (*Rozerem*)

For the following herbal medications, you will need to know how they interact with conventional drugs and common problems that can happen with each one.

-**Kava:** Used to relieve anxiety, promote sleep, & relax muscles. In the USA, it has been promoted as a natural alternative to benzos for treating anxiety & stress. (p. 649)

Adverse effects: Kava can cause serious liver injury, leading the FDA to issue a public warning in March 2002. The CDC also issued a report on kava-related hepatotoxicity, discussing 11 cases of hepatotoxicity in which the patients required a liver transplant due to severe liver failure. Because of these concerns, kava sales have been restricted in some countries, but not yet in the USA.

-**Ginkgo biloba:** Used primarily to improve memory, halt progression of dementia, & decrease intermittent claudication. Less common uses include treatment of erectile dysfunction & other conditions associated with decreased perfusion. (pp. 644-645)

Adverse effects: Generally well tolerated. In some patients it causes stomach upset, headache, dizziness, or vertigo, all of which can be minimized by avoiding rapid increases in dosage. There have been case reports of spontaneous bleeding, although no bleeding was observed in a large placebo-controlled trial study. There have been reports of people eating raw or roasted ginkgo seeds. Unlike ginkgo leaves, the seeds contain significant amounts of toxins & can cause seizures & fatalities.

Interactions w/conventional drugs: May suppress coagulation, so it should be used with caution in patients taking antiplatelet drugs (aspirin) or anticoagulants (warfarin & heparin). There is a concern that ginkgo may promote seizures, so it should be avoided by patients at risk for seizures, including those taking drugs that can lower the seizure threshold as well as some antipsychotics, antidepressants, cholinesterase inhibitors, decongestants, 1st generation antihistamines, & systemic glucocorticoids.

-**Echinacea:** Administered orally & topically. Taken orally to stimulate immune function, suppress inflammation, & treat viral infections, including influenza & the common cold. Used topically to treat wounds, burns, eczema, psoriasis, & herpes simplex infections. (p. 642)

Adverse effects: Very few adverse effects have been reported. The most common complaint is unpleasant taste. Fever, nausea, & vomiting occur infrequently. Rarely, it causes allergic reactions, including acute asthma, urticaria, angioedema, & anaphylaxis. There is concern that although short-term exposure can stimulate immune-function, long-term exposure may actually suppress immune function, so use in patients with autoimmune diseases (lupus, RA, HIV) should be avoided.

Interactions w/conventional drugs: By stimulating the immune system, it can oppose the effects of immunosuppressant drugs. In long-term use, by suppressing the immune system, it can compromise drug therapy of TB, cancer, & HIV infection.

-**St. John's wort:** Used primarily for oral therapy of mild to moderate depression. Has also been used topically to manage local infection & orally to relieve pain & inflammation. (p. 648)

Adverse effects: Generally well tolerated. Allergic skin reactions may occur, especially in people allergic to ragweed & daisies. May cause CNS effects (insomnia, vivid dreams, restlessness, anxiety, agitation, & irritability) as well as GI discomfort, fatigue, dry mouth & headache. High-dose therapy may pose a risk for phototoxicity, so patients should minimize exposure to sunlight, wear protective clothing, & apply a sunscreen to exposed skin.

Interactions w/conventional drugs: Known to interact adversely with many drugs. 3 mechanisms are involved—induction of cytochrome P450 enzymes, induction of P-glycoprotein, & intensification of serotonin effects.

Induction of 3A4 isoenzymes of cytochrome P450 can accelerate the metabolism of many drugs, thereby decreasing their effects. This mechanism appears to be responsible for breakthrough bleeding & unintended pregnancy in women taking oral contraceptives, transplant rejection in patients taking cyclosporine (an immunosuppressant), reduced anticoagulation in patients taking warfarin, & reduced antiretroviral effects in patients taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors.

P-glycoprotein is a transplant protein found in cells that line the intestine & renal tubules. By increasing P-glycoprotein synthesis, St. John's wort can accelerate elimination of drugs & reduce their effects. This is the mechanism by which it greatly reduces levels of digoxin, a drug for heart failure. Other drugs whose levels can probably be reduced by this mechanism include calcium channel blockers, steroid hormones, protease inhibitors, & certain anticancer drugs.

Combining St. John's wort with certain drugs can intensify serotonergic transmission to a degree sufficient to cause potentially fatal *serotonin syndrome*. St. John's wort should not be combined with such drugs, including amphetamine, cocaine, & many antidepressants, including MAOIs, SSRIs, certain TCAs (amitriptyline & clomipramine), & duloxetine, nefazodone, & venlafaxine.

-**Ginger root:** Used primarily to treat vertigo & to suppress nausea & vomiting associated with motion sickness, morning sickness, seasickness, & general anesthesia. It also has anti-inflammatory & analgesic properties that may help people with arthritis & other chronic inflammatory conditions. Some practitioners use it for URIs, although proof of efficacy is lacking. (p. 644)

Adverse effects: Very well tolerated. Severe toxicity has not been reported, although excessive doses (above 5 grams/day) have the potential to cause CNS depression & cardiac dysrhythmias. Excessive doses may also cause GI disturbances.

Interactions w/conventional drugs: It can inhibit production of thromboxane by platelets, suppressing platelet aggregation, so it can increase the risk for bleeding in patients receiving antiplatelet drugs (aspirin) or anticoagulants (warfarin & heparin) or other drugs that inhibit clotting such as the direct thrombin & factor xa inhibitors. Ginger can lower blood sugar & may potentiate the hypoglycemic effects of insulin & other drugs for diabetes.

-**Flaxseed:** Used to treat constipation & dyslipidemia. Because it is a phytoestrogen, some women use it to combat hot flashes associated with menopause. It also represents a vegetarian source of omega-3 fatty acids. (p. 643)

Adverse effects: Similar to other sources of dietary fiber, it can cause adverse GI effects, including bloating, flatulence, & abdominal discomfort.

Interactions w/conventional drugs: Flaxseed may reduce the absorption of conventional medications, therefore it should be taken 1 hour before or 2 hours after these drugs.

-**Black cohosh:** Used for treating symptoms of menopause, including hot flashes, vaginal dryness, palpitations, depression, irritability, & sleep disturbance. (p. 640)

Adverse effects: Some women have developed liver inflammation that in some instances has led to liver failure. Until more is known, it may be wise to check baseline liver function with periodic rechecks. Less serious & more common adverse effects include rash, headache, dizziness, & abdominal discomfort.

Interactions w/conventional drugs: May potentiate the hypotensive effects of antihypertensive drugs as well as the hypoglycemic effects of insulin & other drugs for diabetes. May potentiate the effects of estrogens used for hormone therapy. Because it may cause liver inflammation, may increase the risk for liver damage when taken with other drugs that may harm the liver.

Prescription Writing

Medications you will need to know for the prescription writing questions include:

-Azithromycin:

For chlamydia, gonorrhea, & nongonococcal urethritis:

Azithromycin, 1 gram PO once

-Erythromycin:

For chlamydia infection in children & newborns:

Erythromycin base/ethylsuccinate, 12.5 mg/kg PO 4x/day x 14 days

For gonorrhea infections in newborns:

Erythromycin 0.5% ophthalmic ointment in each eye at birth

-Tinidazole:

For trichomoniasis:

Tinidazole, 2 grams PO once

-Benzathine Penicillin:

For syphilis in adults:

Benzathine penicillin G, 2.4 million units IM once

For syphilis in children:

Benzathine penicillin G, 50,000 units/kg IM once (up to a max of 2.4 million units)

-Acyclovir:

For genital herpes simplex virus infections:

Acyclovir, 400 mg PO 3x/day x 7-10 days (or longer) OR

Acyclovir, 200 mg PO 5x/day x 7-10 days (or longer)