

Module 13: Women's Health

Contraception

General Information

- 5.5 million pregnancies each year
- 42% of pregnancies are unintended
 - Highest in ages 20-24 years old
 - 34% end in abortion
 - 41% occur in people who state they used a method of contraception
- Contraception methods discussed can be used in cis-women and transgender individuals

Epidemiology

- Prevention by 2 methods
 - Inhibiting viable sperm from coming into contact with mature ovum (barriers)
 - Preventing fertilized ovum from implanting in the endometrium
- Failure rates
 - Perfect-use
 - Typical-use

Pregnancy and Continuation Rates for Various Pharmacologic Contraceptive Methods

Method	Pregnancy Typical Use	Pregnancy Ideal Use	Continuation After 1 Year
Combined and progestin-oral contraceptive	7%	<1%	67%
Drospirenone-only contraceptive	4%	-	-
Combined hormonal transdermal contraceptive patch			
Norelgestromin/ethynodiol dihydrogen phosphate	7%	<1%	-
Levonorgestrel/ethynodiol dihydrogen phosphate	3%	-	-

Method	Pregnancy Typical Use	Pregnancy Ideal Use	Continuation After 1 Year
Combined hormonal vaginal contraceptive ring			
Etonogestrel/ethynodiol dihydrogen phosphate	7%	<1%	-
Segesterone/ethynodiol dihydrogen phosphate	3%	-	-
Depo-medroxyprogesterone acetate	4%	<1%	56%
Copper IUD	<1%	<1%	78%
Levonorgestrel IUD	<1%	<1%	80%
Progestin-only implant	<1%	<1%	89%

Menstrual Cycle

- Menstruation cycle begins at menarche
- Cycle ends in menses
- 3 phases of menstrual cycle
 - Follicular
 - Ovulatory
 - Luteal
- Menstrual cycle range 21-40 days

- Hormones involved include FSH and LH

Benefits of Contraception

- Pregnancy prevention
- Prevention of STI/STD (condoms)
- Improves menstrual cycle regularity
- Improves certain health conditions
- Management of perimenopause

Nonpharmacologic Therapy/Methods

- Fertility awareness methods
 - Relatively high pregnancy rates
 - Must avoid intercourse for several days during cycle
- Barrier techniques
 - Male condom
 - Female condom
 - Diaphragm
 - Cervical cap

Pharmacologic Therapy

- Hormonal contraception
 - Combined hormonal contraceptives: combined oral contraceptives, transdermal contraceptives, vaginal rings
 - Progestin only contraceptives: oral, injections, subdermal, implant
 - Intrauterine devices
 - Long-acting reversible contraception
- Spermicides and spermicide-implanted barriers
- Emergency contraception
- Pregnancy termination

Combined Hormonal

Hormonal Contraceptives

- Combination of estrogen and progestin or progestin alone
- Combined hormonal contraceptives (CHC) contain estrogen and progestin
 - Work before fertilization to prevent conception
 - Progestins provide most effect
 - Thicken cervical mucus preventing sperm penetration
 - Slows tubal motility
 - Delays sperm transport
 - Induces endometrial atrophy
- Progestins
 - Block LH surge
 - Inhibits ovulation
 - Suppress FSH release
 - Primary role is stabilizing endometrial lining and providing cycle control

CHC

- Estrogen
 - Ethinyl estradiol (EE)—most commonly used, doses 20-50 mcg
 - Estradiol valerate
 - Estetrol
- Progestin
 - Synthetic progesterone, many available

- Differ in estrogenic, antiestrogenic, and androgenic effects

Combined Oral Contraceptive (COC)

- Monophasic, multiphasic
- Products equally effective
- Extended-cycle tablets and continuous-combination regimens
 - Offer some benefits in adverse effects and convenience
 - 3 additional days of active pills, decreases hormone fluctuation between menstrual cycles
 - Continuous—pills taken for 84 days or longer than 7 days of inactive or estrogen-only pills
- See DiPiro table 104-3 for oral CHC products
- Starting COC
 - Different starting methods
 - First day of cycle bleeding
 - Start COC on first day of menstrual cycle, back up method for at least 7 days
 - First Sunday after cycle begins
 - Start COC on first Sunday after menstrual cycle begins, back up method for at least 7 days
 - Quick start
 - Start COC on day of office visit, back up method for at least 7 days
 - Most successful in getting patients to start COC
- Selection of COC
 - All similarly effective
 - COC with 35 mcg EE or less recommended for patients without coexisting medical conditions
 - Low dose androgenic COC should be given in patients: oily skin, acne, hirsutism
 - Monophasic: may be easier to manage AE or altering timing of cycle
 - Continuous COC eliminate or decrease number of cycles per year
 - Continuous COC products
 - Monophasic COC but skip 7-day placebo tablets
- COC Adverse Effects
 - Adverse effects with early COC use may improve by third cycle
 - Nausea (estrogen effect)
 - Bloating
 - Breakthrough bleeding
 - Continue COC for 2-3 months before changing products unless serious
 - Most common: irregular bleeding
 - Skin breakouts with higher androgenic effects
 - Serious side effects can occur (next slide)

Nature Associated with Combined Hormonal Contraception Symptoms

Symptom	Possible Cause
Serious: Stop Immediately	
Loss of vision, proptosis, diplopia, papilledema	Retinal artery thrombosis
Unilateral numbness, weakness, or tingling	Hemorrhagic or thrombotic stroke
Severe pains in chest, left arm, or neck	Myocardial infarction
Hemoptysis	Pulmonary embolism
Severe pains, tenderness or swelling, warmth or palpable cord in legs	Thrombophlebitis or thrombosis
Slurring of speech	Hemorrhagic or thrombotic stroke
Hepatic mass or tenderness	Liver neoplasm

Symptom	Possible Cause
Potentially Serious: May Continue with Caution While Being Evaluated	
Absence of menses	Cervical endometrial or vaginal cancer
Spotting or breakthrough bleeding	Cholecystitis, cholelithiasis, or liver neoplasm
Breast mass, pain, or swelling	Pituitary adenoma
Right upper-quadrant pain	Cholestatic jaundice
Mid-epigastric pain	B6 deficiency
Migraine headache	Leiomyomata, adenomyosis
Severe nonvascular headache	Depression, sleepiness
Galactorrhea	Uterine size increase
Jaundice, pruritus	

Medication Monitoring for Hormonal Contraception

Medication	Adverse Medication Effect	Monitoring Parameter	Comments
Combined hormonal contraception	Nausea/vomiting Breast tenderness Weight gain Acne, only skin Depression, fatigue Breakthrough bleeding/spotting Application site reaction (transdermal) Vaginal irritation (vaginal ring)	Patient symptoms Weight Visual inspection Depression screening Menstrual symptoms Visual inspection Patient symptoms	Typically improves after two to three cycles; consider changing to lower estrogenic Consider changing to lower androgenic Data are limited and conflicting Consider changing to higher estrogenic
Depo-medroxyprogesterone acetate	Menstrual irregularities Weight gain Acne Hirsutism Depression Decreased bone density	Menstrual symptoms Weight Visual inspection Depression screening Bone mineral density (BMD)	Typically improves after 6 months Data are limited and conflicting Do not routinely screen with dual-energy X-ray absorptiometry (DXA)

Medication Monitoring for Hormonal Contraception (cont.)

Medication	Adverse Medication Effect	Monitoring Parameter	Comments
Levonorgestrel IUD	Menstrual irregularities Insertion-related complications Expulsion Pelvic inflammatory disease (PID)	Menstrual symptoms Cramping, pain, spotting, dyspareunia, missing strings Lower abdominal pain, unusual vaginal discharge, fever	Typically spotting, amenorrhea Prophylactic nonsteroidal anti-inflammatory drugs (NSAIDs) or local anesthetic may reduce occurrence IUD strings should be checked regularly to ensure IUD properly placed Risk of developing is rare, but counseling on STI/STD prevention is important
Copper IUD	See levonorgestrel IUD above	See levonorgestrel IUD above	Menstrual irregularities are typically heavier menses with copper IUD

Medication Monitoring for Hormonal Contraception (cont.)

Medication	Adverse Medication Effect	Monitoring Parameter	Comments
Progestin-only implant	Menstrual irregularities Insertion-site reactions	Menstrual symptoms Pain, bruising, skin irritation, erythema, pus, fever	Typically, well tolerated and resolved without treatment; infection is rare

- COC Medication Interactions
 - Can affect GI absorption, increase intestinal motility, alter metabolism or excretion, alter binding
 - The lower the COC dose, the more likely interactions will affect COC effectiveness
 - Use alternate contraception when medication interaction can affect effectiveness
 - Medications
 - Rifampin
 - Case reports for tetracyclines and penicillin antibiotics
 - Anticonvulsants (phenobarbital, carbamazepine, phenytoin, lamotrigine)
 - HIV antiretrovirals
 - OTC St. Johns Wort
- Eligibility Criteria for Contraceptive Use
 - Know/review table 104-6
 - Category 4: Unacceptable health risk (method not to be used)
 - Category 3: Theoretical or proven risks usually outweigh the advantages
 - Category 2: Advantages generally outweigh theoretical or proven risks
 - Category 1: No restriction (method can be used)
- Patient Instructions with COC
 - Counsel on how the medication works, common and serious adverse medication effects (ACHES), and adverse effect management
 - Discuss benefits of COC, and that they do not protect against STI/STD
 - Detailed instructions on when to start taking the COC should be reviewed

- Emphasize importance of compliance
- Missed Dose Management of COC
 - 1 tablet missed or late: take as soon as remembered and continue the rest of the tablets as prescribed
 - 2 or more COC missed: take 1 missed tablet as soon as remembered, discard other missed tablets and continue the rest of the tablets as prescribed
 - If tablets missed in last week of hormonal tablets, finish remaining active tablets and omit hormone-free interval and start new pack
 - Use additional nonhormonal contraception until active hormone tablets have been taken for 7 consecutive days
- Vomiting or Severe Diarrhea on COC
 - Efficacy can be decreased
 - If symptoms <48 hours, no redosing of COC is needed
 - If symptoms >48 hours, continue tablets; if occurring in last hormonal week then finish tablets, skip hormone-free tablets and begin new pack
 - Use nonhormonal contraception until hormonal tablets have been taken for 7 consecutive days after vomiting/diarrhea subsides

Transdermal Contraceptives

- 2 available patches (Xulane and Twirla)
- Xulane: 35 mcg EE and 150 mcg norelgestromin
 - As effective as COC in patients <90 kg
 - Not recommended as first line in patients >90 kg
- Twirla: 30 mcg EE and 120 mcg levonorgestrel
 - Recommended for BMI <30 kg/m²
 - May have reduced effectiveness with BMI 25-30 kg/m²
- Adverse Effects and Interactions
 - Application-site reactions
 - Other adverse effects similar to COC (breast discomfort, headache, breakthrough bleeding, nausea)
 - EE/norelgestromin manufacturer: people using patch exposed to about 60% more estrogen than from typical COC containing 35 mcg EE, may lead to increased thrombotic risk
 - Medication interactions similar to those with COC
- Patient Instructions
 - Patch provides estrogen and progestin for 7 days
 - Wear only 1 patch at a time
 - Apply to abdomen, buttocks, upper torso, or upper arm
 - Start applying patch at beginning of menstrual cycle
 - Change patch weekly on the same day
 - Apply new patch weekly for 3 weeks then week 4 is a patch free week
- Missed Dose
 - If patch falls off and is <24 hours, reapply patch (old or new), no additional contraception necessary
 - If patch off >24 hours, start new 4-week cycle, apply new patch as soon as possible, use additional contraception until new patch on for 7 consecutive days
 - If delayed application or detachment is in the third patch week, omit the hormone free week and a new patch should be applied immediately

Vaginal Rings

- 2 products (NuvaRing, Annovera)
- NuvaRing: flexible ring, releases 15 mcg/day of EE and 120 mcg/day of etonogestrel
 - Use for 3 weeks, then discard
- Annovera: releases 13 mcg of EE and 150 mcg of segesterone acetate
 - Used for 3 weeks at a time, do no discard as it is used for a total of 13 cycles
- Patient Instructions
 - First cycle of use, insert ring on or before 5th day of cycle
 - Ring remains in place for 3 weeks, then remove for 1 week
 - Insert ring on same day of week as previous cycle
 - Precise placement not necessary
 - Do not flush the ring
 - Annovera ring: removed, washed with warm water, put in original container for later use
 - NuvaRing should be refrigerated if not being used promptly, Annovera does not require refrigeration
 - Do not douche, but can use other vaginal products such as antifungal creams and spermicides
- Missed Doses
 - If displaced for < 3 hours for NuvaRing or <2 hours for Annovera, new ring should be inserted as soon as possible, no additional contraception necessary
 - If displaced for > 3 hours for NuvaRing or >2 hours for Annovera, new NuvaRing or current Annovera ring should be inserted immediately and use additional nonhormonal contraception for 7 days
- ADRs and Medication Interactions
 - Adverse effects/precautions/contraindications similar to those for all CHC
 - Specific medication interaction with Annovera includes 1- or 3-day oil-based miconazole suppository
 - Avoid tampons with Annovera until further studies available, NuvaRing okay with tampon use
 - Possibility of increased VTE

Considerations for Combined Hormonal Contraceptive Use

- Complete medical exam and Pap smear are not necessary prior to CHC
- Medical history and BP measurement should be done prior to CHC
- Patients that take COC have reduced risk of ovarian and endometrial cancer after 5 or more years of use
- COC may reduce risk of ovarian cysts, ectopic pregnancy, pelvic inflammatory disease, endometriosis, uterine fibroids, and benign breast disease
- Recommend to use condoms as well to prevent STI/STD

CHC and Patients > 35 yo

- Use is controversial, usually doses <30 mcg estrogen are used
- May improve or decrease chances of developing perimenopausal and menopausal symptoms
- May increase bone mineral density (BMD)
- Increased risk of VTE in this population, especially >40yo
- No increased CV risk if low dose products used in healthy/non-obese
- Increased risk of breast CA in older patients
- Do NOT recommend in >35 yo with migraine (with aura), uncontrolled HTN, smoking, or diabetes with vascular disease

CHC and Smoking

- COC with 50 mcg EE or more—associated with MI in cigarette smokers

- Older patients at higher risk
- CHC contraindicated in patients >35 yo and smoke ≥15 cigarettes per day
- Progestin only or nonhormonal contraception should be considered

CHC and Hypertension

- CHC can cause small increases in BP (6-8 mmHg) for all estrogen doses
- OC associated with increased risk MI and stroke
- Use low dose CHC in patients <35 yo with well controlled and monitored hypertension
- If CHC increases BP, BP usually returns to normal within 3-6 months of D/C of CHC
- Contraindication for CHC: SBP ≥160 mmHg or DBP ≥100 mmHg
- Risk usually outweighs benefit in SBP 140-159 mmHg or DBP 90-99 mmHg
- Increased potassium risk with drospirenone and use with potassium-sparing diuretics, ACE, ARB, or aldosterone antagonists

CHC and Dyslipidemia

- Synthetic progestins may decrease HDL and increase LDL
- Estrogens may decrease LDL and increase HDL and also moderately increase TG
- Most low-dose CHC have no significant impact on HDL, LDL, TG, or TC
- Can use CHC in patients with dyslipidemia

CHC and Diabetes

- Most products available today contain low doses of progestins and do not significantly alter insulin, glucose, or glucagon release
- CHC does not seem to alter hemoglobin A1c levels
- Patients with diabetes and vascular disease (nephropathy, retinopathy, neuropathy, or other vascular disease) or diabetes > 20 years duration should NOT use CHC

CHC and Migraine

- May have decreased or increased frequency of migraine headaches
- Higher risk of stroke in patients with migraine and aura
- Can consider CHC in patients with migraine WITHOUT aura
- CHC can be used in non-migraine headaches
- CHC should NOT be used in patients with migraine WITH aura at any age
 - Consider progestin only products

CHC and Breast Cancer

- Risk may be slightly elevated in CHC use
- Benefits outweigh risks for healthy young patients
- > 40 yo or those with elevated risk of breast CA due to family history or other factors, consider alternatives
- Patients with current or past history of breast CA should NOT use CHC

CHC and Thromboembolism

- Estrogens increase thromboembolic event risk (DVT and PE)
- Risks increased in patients with hypercoagulable states or conditions that predispose to coagulation abnormalities
- Incidence of thromboembolism and mortality increase 3X in current OC users compared to nonusers
- COC with new progestins including third-generation and fourth generation are associated with slightly higher risk of thromboembolism
 - Third generation: desogestrel, norgestimate
 - Fourth generation: drospirenone
- Transdermal patch and vaginal ring have increased thromboembolic risk due to continuous and higher exposure to estrogen

- Progestin only products not found to have significant increases in venous or arterial events per recent systematic review

CHC and Obesity

- Increased hormonal clearance and decreased serum concentrations of CHC
- More adipose tissue, increasing hormonal sequestration, and decreased free hormone serum concentrations
 - Results in lower efficacy
- IUDs, implants, and DMPA have low failure rates and progestin only products considered safe in obese patients
 - Copper IUD most reliable method in obese patients
- Generally, advantages of CHC outweigh risks
- In patients >35 yo and obese, progestin only products may be more appropriate

CHC and Postpartum

- Concern for CHC in postpartum due to hypercoagulability risks and effects on lactation
- Avoid estrogen products in first 21 days postpartum
- Avoid estrogen CHC products if breast feeding for 42 days postpartum and VTE risk factors and for 30 days postpartum without VTE risk factors
- If not breastfeeding, avoid estrogen CHC products for 42 days postpartum and VTE risk factors and for 21 days postpartum without VTE risk factors
- After 42 days postpartum, no restrictions on use of CHC

CHC and Return to Fertility

- CHC do not decrease subsequent fertility
- Return to fertility usually occurs within a few months
- See physician if amenorrhea continues >6 months

Progestin Only

Progestin Only Contraceptives

- Formulations: oral tablets, injections, subdermal implant, IUDs
- Oral tablet Opill (norgestrel) is available OTC
- Patients that may benefit from progestin only:
 - Breastfeeding
 - Intolerant to estrogens
 - Concomitant medical conditions or contraindications to estrogen
- Does not protect against STI/STD

Oral Progestin Only Products

- 3 products: norgestrel (mini pill), norethindrone (mini pill), drospirenone
- Mini pills have similar effectiveness to COC
 - Norethindrone 35 mg and norgestrel 0.075 mg are 28 days of active hormone per cycle
 - Must be taken same time each day for efficacy
 - If taken > 3 hours late, need to use backup method for 48 hours
 - Can be initiated at any day of the cycle
- Drospirenone (Slynd) 4 mg: 24 days of active hormone and 4 days of placebo
 - Not as strict with dose timing, missed dose considered >24 hours after usual time
 - Take missed dose as soon as possible
 - If >2 tablets missed, take last missed tablet as soon as possible and continue 1 tablet daily and use back up method for 7 days
- Adverse Effects
 - Risk of ectopic pregnancy is higher than with CHC
 - Common adverse effects

- Irregular menses
 - Acne
 - Headache
 - Nausea
 - Libido changes
- Drospernone products may have less acne, but need monitoring for thromboembolism, hyperkalemia, and bone loss
- Medication Interactions/Contraindications
 - Phenytoin, carbamazepine, oxcarbazepine, primidone, topiramate, protease inhibitors, St. Johns wort
 - In addition, drospernone can interact with medications that increase potassium (ACE/ARB, potassium sparing diuretics, high dose ibuprofen)
 - Do not use in patients with history of breast CA, unexplained bleeding
 - Caution in patients with current VTE, complicated diabetes, and heart or hepatic disease

Progestin Injections

- Good for patients with adherence issues
- Lower failure rates than CHC
- Depo-Provera (DMPA): administered every 3 months
 - 150 mg/mL IM injection: into gluteal or deltoid muscle
 - 104 mg SubQ injection: into abdomen or thigh
 - Can start anytime of the cycle, if >7 days after start of cycle back up contraception is needed for 7 days
 - Requires medical office visit for administration
 - If administration is >13 weeks between IM injections or >14 weeks for SubQ injections, pregnancy test must be performed
- Mainly suppresses ovulation
- Considerations
 - Do not use until 6 weeks postpartum in breastfeeding patients
 - Can use immediately postpartum in non-breastfeeding patients
 - Contraindicated in current breast CA
 - Use with caution in patients with history of breast CA, vascular/CV/cerebrovascular disease, multiple risk factors for CV disease, lupus
 - Sickle cell disease patients and patients with seizure disorders are good candidates
 - Return to fertility is about 10 months
- Adverse Effects
 - Most frequent: menstrual irregularities including spotting, prolonged bleeding, and amenorrhea
 - These irregularities decrease over time, most common in first year of use
 - Breast tenderness
 - Depression
 - Weight gain
 - Average of 1 kg annually
 - Can resolve 6-8 months after last injection
 - Can still use DMPA in obese patients
 - Monitor weight and BMI
 - Short term bone loss (black box warning)
 - Continue DMPA for >2 years ONLY if other methods are inadequate
 - Bone loss greater with duration of use, may not be completely reversible

- DMPA not recommended for patients requiring long-term corticosteroids

Progestin Subdermal Implants

- Nexplanon: 4 cm long implant, 68 mg of etonogestrel
- Releases at a rate of 60 mcg daily for first month, then average of 30 mcg daily at the end of 3 years
- Recommended duration is up to 3 years
- Placed under skin of upper arm, clinicians inserting must go through training
- Primarily suppresses ovulation
- Efficacy may be decreased in overweight patients weighing >130% of ideal body weight
- Fertility returns within 30 days of removal
- Adverse Effects
 - Irregular menstrual bleeding: spotting, prolonged bleeding, or amenorrhea
 - Potential medication interactions: may need to use alternative product like DMPA or IUDs
 - Rifampin
 - Phenytoin
 - Carbamazepine

Intrauterine Device

Intrauterine Devices (IUDs)

- 5 IUDs available
 - 4 contain levonorgestrel (Mirena, Dkyla, Liletta, and Kyleena)
 - 1 contains copper (ParaGard)
- T-shaped devices implanted/removed by clinician
- MOA: inhibits sperm migration, damages ovum or disrupts transport, possibly damages fertilized ovum; progestin IUD also have endometrial suppression and thickens cervical mucus
- Average time to return to fertility is similar to oral CHC
- Do NOT insert during
 - Current pregnancies
 - Current PID
 - Current STI/STD
 - Postabortion sepsis
 - Cervicitis
 - Undiagnosed abnormal vaginal bleeding
 - Malignancy of genital tract
 - Uterine anomalies or fibroid distorting uterine cavity
 - Wilson's disease (copper IUD)
- Copper IUD
 - Highly effective (99%)
 - Can be in place for 10 years
 - Disadvantage is increased menstrual blood flow and dysmenorrhea
- Levonorgestrel IUD
 - Liletta and Mirena approved for up to 8 years of use, release 20 mcg levonorgestrel daily
 - Kyleena approved for up to 5 years of use, release 17.5 mcg levonorgestrel daily
 - Skyla approved for up to 3 years of use, release 14 mcg levonorgestrel daily
- Systemic absorption of levonorgestrel is minimal
- Insertion pain is minimal, OTC pain medications are effective
- Risk of infection with IUD insertion is minimal
- Screen for STI/STD at time of insertion

- Irregular menstrual bleeding is most common adverse effect
- In levonorgestrel IUD, menstrual flow is decreased
- Liletta and Mirena also have indication for treating heavy menstrual bleeding
- In levonorgestrel IUD, increased spotting in the first 6 months, declines gradually
- Can be used in nulliparous and adolescent patients

Other Contraceptives

Spermicides and Spermicide-Implanted Barriers

- Most contain nonoxynol-9
- Chemical surfactants used to destroy sperm cell walls
- Act as barrier to prevent sperm entering cervical os
- Available: creams, films, foams, gels, suppositories, sponges, tablets
- No STI/STD protection
- Prescription Phexxi
- Contraceptive sponge Today
- Phexxi
 - Prescription
 - Vaginal pH modulator
 - Composed of: lactic acid 1.8%, citric acid 1%, and potassium bitartrate 0.4%
 - Lowers pH and decreases sperm motility
 - Use within 1 hour or immediately before intercourse and with each act
 - Precaution in cystitis
- Today
 - Contains 1g of nonoxynol-9
 - Moisten in water, then insert into vagina up to 6 hours before intercourse
 - Leave in place for at least 6 hours, but no more than 24-30 hours after intercourse
 - Do not reuse, dispose of after use
 - 1 size

Emergency Contraception (EC)

- EC used to prevent unintended pregnancy after unprotected or inadequately protected intercourse
- After intercourse, implantation of fertilized egg usually takes about 5 days
- Progestin-only and progesterone receptor modulator products are approved in US as first line
- Other options include copper IUD insertion or higher doses of COCs
- Controversy regarding decreased efficacy of levonorgestrel and ulipristal in overweight/obese patients
- EC does not disrupt or harm existing pregnancy
- Adverse Effects
 - Nausea
 - Vomiting
 - Irregular bleeding
- No contraindications to therapy for levonorgestrel and ulipristal
- Copper IUD and using higher doses of COC, must adhere to contraindications and precautions
- Consensus: risk of repeated use is low, but should counsel on use of regular ongoing contraception
- Levonorgestrol
 - 1.5 mg tablet for 1 dose, given within 72 hours of unprotected intercourse
 - The earlier given the better the efficacy
 - Inhibits or delays ovulation

- Regimen of choice
 - Availability
 - Improved tolerability
 - Potentially increased efficacy rates
- Available OTC for all ages
- Ulipristal
 - Selective progesterone receptor modulator
 - Primarily delays ovulation
 - Prescription only product
 - Single dose of 30 mg taken within 120 hours (5 days) of unprotected intercourse
 - Data shows non-inferior to levonorgestrel
 - No recommended in breastfeeding patients
 - May interfere with hormonal contraception, barrier method recommended for use in the month that ulipristal is used
 - Avoid using hormonal contraceptive methods or starting new hormonal contraceptive for at least 5 days after ulipristal administration

Pregnancy Termination

- Medications used in early pregnancy ≤70 days:
 - Mifepristone and misoprostol: mifepristone 200 mg day 1, then misoprostol 800 mcg buccally 24-48 hours after mifepristone
 - Efficacy higher when used earlier in pregnancy
 - Works faster than misoprostol alone and is more effective in later gestational ages
 - Misoprostol alone
- Mifepristone BBW include infection and bleeding
- Misoprostol can cause
 - Stomach upset
 - Diarrhea
 - Headache
 - Dizziness
 - Chills
 - Fever
- Misoprostol available as oral, vaginal, buccal, and sublingual
 - Oral not preferred, less effective due to less absorption
- Abdominal cramps and bleeding are common after abortion

Summary

- Selecting agent should be shared decision with patient and clinician
- Consider
 - Effectiveness
 - Presence of medical conditions
 - Other medications
 - Safety
 - Adverse effects
 - Cost
 - Time to return to fertility
 - Patient preference of method
- Can assess efficacy with pregnancy test

Menopause

Menopause

- Menopause = permanent end of menstrual periods from loss of ovarian follicle activity
- A natural life stage, not a disease; everyone with a uterus/ovaries experiences it
- Stages: perimenopause → menopause → post-menopause (≥ 12 months after last menses)
- Average life expectancy ≈ 81 years → over one-third of life in peri/post-menopause
- Induced menopause: before natural onset (surgery, chemo, radiation)
- Symptoms and severity vary → treatment should be individualized

Epidemiology

- Median age of onset in the U.S.: 51.4 years (range 45–56)
- Approximately 1% of individuals experience premature menopause (<40 years)
- 6,000 women/day reach menopause in the U.S.
- By 2025: 1.1 billion post-menopausal individuals worldwide
- Approximately 40% of life spent in postmenopausal stage

Definition of Menopause

- “The permanent cessation of menstrual periods following the loss of ovarian follicular activity, marking the end of a female’s natural reproductive years.”

Diagnosis

- Clinical diagnosis
 - 12 consecutive months of amenorrhea (no menses)
- Perimenopause
 - Irregular cycles, FSH may fluctuate
- Menopause labs
 - FSH elevated (often >40 IU/L), but not required for diagnosis
 - Estradiol decreased (>90% reduction)
- Other tests (to exclude other causes)
 - Thyroid function tests
 - Serum prolactin
 - Iron studies
 - Lipid profile
 - Serum hCG (rule out pregnancy)
- Women with hysterectomy → rely on symptoms (hot flashes, GSM, sleep/mood changes) to estimate timing of menopause onset

Stages

- Perimenopause – begins in the mid-to-late 40s, characterized by irregular cycles and fluctuating hormones
- Menopause – defined retrospectively, after 12 months of amenorrhea
- Post-menopause – the years following menopause, usually accompanied by stabilized low hormone levels
- Induced menopause – before natural onset, caused by surgery (bilateral oophorectomy), chemotherapy, or pelvic radiation

Etiology

- STRAW +10 staging system = gold standard for characterizing reproductive aging
- Natural (Spontaneous) Menopause
 - Normal physiologic aging process
 - Gradual depletion of ovarian follicles → decline in estrogen and progesterone production
- Induced Menopause
 - Surgical: bilateral oophorectomy (removal of both ovaries)

- Iatrogenic: chemotherapy or pelvic radiation leading to ovarian failure
- Premature Menopause
 - Onset before age 40
 - Often due to primary ovarian insufficiency (POI)

Pathophysiology

- Females are born with approximately 2 million follicles; fewer than 500 ovulate, the rest undergo atresia
- Decline in anti-Müllerian hormone (AMH) → marker of reduced ovarian reserve
- Progressive follicular loss leads to a decrease in estrogen and progesterone production
- After menopause, the ovary primarily produces androstenedione
- Loss of normal ovarian negative feedback results in a significant increase in FSH and LH levels
- Menopause is characterized by about a 15-fold increase in FSH, a 10-fold increase in LH, and a greater than 90% decrease in estradiol
- Hormonal fluctuations during perimenopause cause irregular menstrual cycles

Clinical Presentation

- Perimenopause
 - Abnormal uterine bleeding (anovulation)
- Menopause
 - Permanent cessation of menses
- Vasomotor
 - Hot flashes
 - Sweat
 - Night sweats
 - Flash/flush can last 1-30 minutes
- Sleep disturbances, mood changes, impaired memory/concentration
- Fatigue, myalgia/arthritis, headaches, palpitations
- Genitourinary syndrome (GSM)
 - Vaginal dryness
 - Dyspareunia
 - Dysuria
 - Recurrent UTIs
- Sexual dysfunction common (42%–88%)
- Labs
 - FSH >10–12 IU/L (perimenopause, cycle day 2–3)
 - Menopause
 - Sustained ↑FSH (≥ 40 IU/L) (not required for diagnosis)
 - Additional
 - TSH, iron, prolactin, lipid profile, serum hCG

Complications

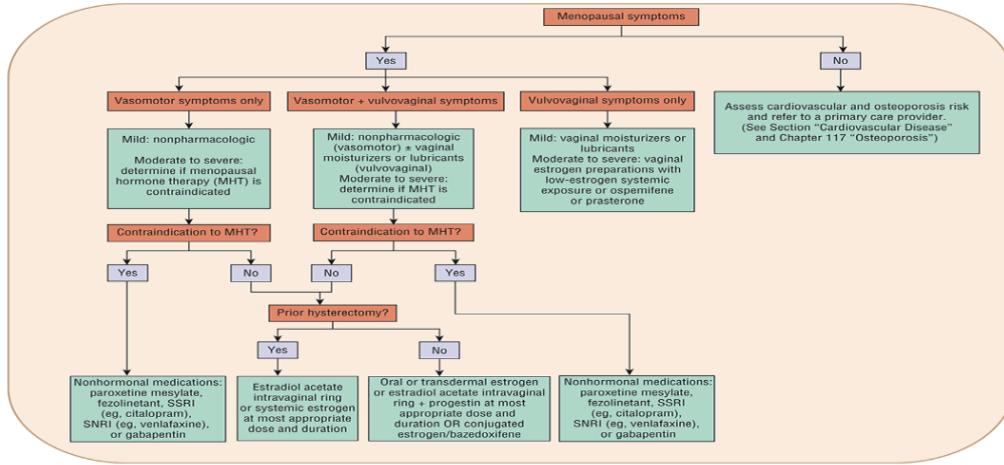
- Estrogen deficiency
 - Cardiometabolic changes
 - ↑visceral fat, central obesity, lipid changes
- Bone loss → osteoporosis risk
- Cognitive complaints (brain fog, memory issues)
- Skin/hair changes (thinning, wrinkles, alopecia, hirsutism)

Treatment

- Relieve symptoms
- Improve quality of life

- Use lowest effective dose, shortest duration
- Reevaluate periodically
- Mild vasomotor → nonpharmacologic
- Moderate–severe → Menopausal hormone therapy (MHT) unless contraindicated
- Vulvovaginal only → topical vaginal estrogen or nonhormonal lubricants

Algorithm for Treatment



Menopause Nonpharmacologic Therapy

Non-pharmacologic Approach

- Smoking cessation (reduces hot flashes, CV risk, osteoporosis)
- Weight loss (associated with less severe vasomotor symptoms)
- Evidence-based
 - Cognitive based therapy (CBT), clinical hypnosis
- Limited data
 - Mindfulness, stellate ganglion block
- Not effective
 - Soy, black cohosh supplements, acupuncture

Nonhormonal Pharmacologic Therapy

- SSRIs/SNRIs (paroxetine, venlafaxine) for vasomotor symptoms
 - Paroxetine (Brisdelle) – only SSRI FDA-approved for hot flashes
 - Venlafaxine, Desvenlafaxine – off-label, effective alternatives
 - **Adverse Effects:** nausea, insomnia, sexual dysfunction, dry mouth
 - **Paroxetine and fluoxetine** could interfere with metabolism of endocrine therapies such as **tamoxifen** so this combination should be avoided
- Fezolinetant (Veozah)
 - Neurokinin receptor 3 antagonist
 - 45 mg daily
 - **Adverse effects:** abdominal pain, diarrhea, insomnia, hot flush, back pain
 - Contraindicated with history of liver cirrhosis, severe renal impairments or end-stage renal disease, and administration with P450 1A2 inhibitors
 - Monitor LFT baseline, monthly for first 3 months, at 6 months, and 9 months after initiation
- **Gabapentin, clonidine** – less effective, alternative if MHT contraindicated

- Used for women at risk for breast cancer or CV disease
- Gabapentin
 - Used for nocturnal hot flashes
 - **Adverse Effects:** dizziness, somnolence, fatigue
- Clonidine
 - Central alpha-2 agonist, modest benefit for vasomotor symptoms
 - **Adverse Effects:** dry mouth, constipation, drowsiness, hypotension

Goals of Therapy

- Relieve vasomotor and genitourinary symptoms
- Improve sleep, mood, and quality of life
- Prevent long-term complications (e.g., bone loss, fractures)
- Use lowest effective dose for the shortest duration
- Reassess need for therapy annually

Evidence-Base Hormone Therapy Guidelines for Menopausal Symptom Management

Recommendation	Level
Hormone therapy remains the gold standard for relief of vasomotor symptoms. <ul style="list-style-type: none"> • Estrogen-alone therapy can be used for symptomatic individuals without a uterus. • For symptomatic individual with a uterus, estrogen plus progesterone therapy or a tissue-selective estrogen complex protects against endometrial hyperplasia. 	1
The appropriate, often lowest, effective dose of systemic estrogen therapy consistent with treatment goals that provides benefits and minimizes risks for the individual women should be the therapeutic goal.	3
The appropriate formulation, dose, and routes of administration of progestogen are needed to counter the proliferative effects of systemic estrogen on the endometrium.	1
Different hormone therapy doses, formulations, and routes of administration may have different effects on target organs, potentially allowing options to minimize risk.	2
Low-dose vaginal estrogen therapy preparations are effective and safe for the treatment of GSM, with minimal systemic absorption, and are preferred over systemic therapies when estrogen therapy is used only for genitourinary symptoms.	1

Recommendation	Level
For survivors of breast cancer with GSM, low-dose vaginal estrogen therapy or DHEA may be considered in consultation with their oncologists if bothersome symptoms persist after a trial of nonhormone therapy. There is increased concern with low-dose vaginal estrogen therapy for individuals on aromatase inhibitors.	3
For individuals with GSM, low-dose vaginal estrogen therapy may be considered for use at any age and for extended duration, if needed.	3
For healthy symptomatic individuals aged younger than 60 years or within 10 years of menopause onset, the favorable effects of hormone therapy on CHD and all-cause mortality should be considered against potential rare increase in risks of breast cancer, venous thromboembolism, and stroke.	1
Individuals who initiate hormone therapy aged older than 60 years or more than 10 or 20 years from menopause onset are at higher absolute risks of CHD, venous thromboembolism, and stroke than individuals initiating hormone therapy in early menopause.	1
Periodic reassessment of the need for ongoing use of hormone therapy should be individualized on the basis of an individual's menopause symptoms, general health and underlying medical conditions,	3

Recommendation	Level
The absolute risks reduced for all-cause mortality, fractures, diabetes mellitus (EPT and estrogen therapy), and breast cancer (estrogen therapy) in individuals aged younger than 60 years.	1
Long-term use of hormone therapy, including for individuals aged older than 60 years, may be considered in healthy individuals at low risk of CVD and breast cancer with persistent vasomotor symptoms or at elevated risk of fractures for whom other therapies are not appropriate.	3
Hormone therapy does not need to be routinely discontinued in individuals aged older than 60 or 65 years. Longer durations or extended use beyond age 65 should include periodic reevaluation of comorbidities with consideration of periodic trials of lowering or discontinuing hormone therapy.	3
The effect of hormone therapy on breast cancer risk may depend on the type of hormone therapy, duration of use, regimen prior exposure, and individual characteristics.	2
Progestogen therapy is not required with low-dose vaginal estrogen therapy but randomized controlled trial data are lacking beyond 1 year.	2
Mitigation of risks through use of the lowest effective dose and potentially with nonoral route of administration becomes increasingly important as individuals age and with longer duration of therapy.	3

Recommendation	Level
Compounded bioidentical hormone therapy presents safety concerns, such as minimal government regulation and monitoring, overdosing and underdosing, presence of impurities and lack of sterility, lack of scientific efficacy and safety data, and lack of a label outlining risks.	1

Menopause – Pharmacologic Therapy

FDA-Labeled Indications and Contraindications for Menopausal Hormone Therapy with Estrogens and Progestins

Indications	
For systemic use	Treatment of moderate-to-severe vasomotor symptoms (ie, moderate-to-severe hot flashes)
For intravaginal use (low systemic exposure)	Treatment of moderate-to-severe symptoms of genitourinary syndrome of menopause (ie, moderate-to-severe vaginal dryness, dyspareunia, and atrophic vaginitis)

Contraindications	
Absolute contraindications	Undiagnosed abnormal genital bleeding Known, suspected, or history of breast cancer Known or suspected estrogen – or progesterone-dependent neoplasia Active deep vein thrombosis, pulmonary embolism, or a history of these conditions Thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency) Active or recent (e.g. within the past year) arterial thromboembolic disease (e.g. stroke, myocardial infarction) Liver dysfunction or disease

Contraindications	
Relative contraindications	Elevated blood pressure Hypertriglyceridemia Impaired liver function and past history of cholestatic jaundice Hypothyroidism Fluid retention Severe hypocalcemia Ovarian cancer Exacerbation of endometriosis, asthma, diabetes mellitus, migraine, systemic lupus erythematosus, epilepsy, porphyria, hepatic hemangioma, and gallbladder disease

Pharmacologic Approach

- **Menopausal Hormone Therapy (MHT)** = Most effective treatment for moderate to severe vasomotor and genitourinary symptoms
- MHT consists of an estrogen plus a progestogen, or a tissue-selective estrogen complex (TSEC)
- Women with an intact uterus → require estrogen + progestogen or a tissue-selective estrogen complex (TSEC); decreases risk of **endometrial cancer** (**MUST** use progestogen with estrogen)
- Women without a uterus → estrogen alone
- Local vaginal estrogen → preferred for genitourinary syndrome of menopause (GSM) only

FDA-approved Indications

- Vasomotor symptoms (hot flashes, sweats)
- Genitourinary syndrome (vaginal dryness, dyspareunia)
- Prevention of postmenopausal osteoporosis

MHT Benefits

- Most effective for vasomotor symptoms (↓ by ~75%)
- Improves sleep, mood, and vaginal health
- Prevents postmenopausal bone loss and fractures
- Transdermal formulations: lower VTE and CV risk than oral medications
- Low-dose regimens effective for most symptoms

MHT Risks and Precautions

- **Breast cancer**
 - Risk ↑ with estrogen + progestogen, not estrogen alone
- **VTE, stroke**
 - Higher with oral formulations
- **Endometrial cancer**
 - Risk ↑ with unopposed estrogen; must add progestogen or TSEC if uterus present
- **CV disease**
 - Not for prevention; avoid starting after age 60 or >10 years post-menopause

Summary of North American Menopause Society Position Statement on Menopausal Hormone Therapy

Symptom/Condition	Summary Statement(s)
Vasomotor symptoms	Estrogen therapy (\pm progestogen) is the most effective therapy, including consequences of vasomotor symptoms such as sleep quality and quality of life.
Genitourinary syndrome of menopause (GSM)	Estrogen therapy is the most effective treatment for moderate-to-severe GSM symptoms. Local therapy is recommended for sole vaginal symptoms; progestogen generally not indicated for low-dose vaginal estrogen therapy. Individuals at risk of endometrial cancer may warrant endometrial surveillance. No data to support initial use of combined systemic and vaginal estrogen for severe GSM.
Sexual function	Low-dose local estrogen therapy may improve lubrication, blood flow, sensation of vaginal tissues and sexual function in postmenopausal women with GSM; however, systemic hormone therapy is not recommended as treatment for other problems of sexual function (e.g. libido, orgasmic response). If sexual function or libido are concerns in women with menopausal symptoms, transdermal estrogen therapy may be preferable over oral estrogen therapy because of minimal effect on sex hormone-binding globulin and free testosterone levels.

Symptom/Condition	Summary Statement(s)
Cognition	Hormone therapy is not recommended at any age to prevent or treat decline in cognitive function or dementia. Initiating hormone therapy in women aged older than 65 years increase the risk of dementia.
Depression	There is some evidence that estrogen therapy enhances mood and improves well-being in nondepressed postmenopausal women. Initial evidence suggests that transdermal estradiol with intermittent progestin may prevent the onset of depressive symptoms in euthymic perimenopausal women.
Breast cancer	Potential differences on the effects of estrogen therapy, EPT, and conjugated estrogen plus BZA on breast tissue may exist. Different types of estrogen and progestogen therapy, and patient characteristics, may play a role in the effect of hormone therapy on the breast. In the WHI, estrogen-alone therapy (conjugated estrogen) had a significant reduction in breast cancer risk compared to placebo after 20 years of follow-up. However, individuals who received daily estrogen plus medroxyprogesterone therapy experienced risk. Systemic use of hormone therapy in survivors of breast cancer is not recommended.

Symptom/Condition	Summary Statement(s)
Osteoporosis	Standard-dose MHT reduces postmenopausal osteoporotic fractures (hip, vertebral, and nonvertebral), and many systemic MHT products are approved of osteoporosis. MHT is not indicated for treatment. Benefits of MHT dissipate when discontinued; however, no excess fractures were seen in WHI after discontinuation.
Diabetes mellitus	Hormone therapy is not contraindicated in otherwise healthy women with preexisting type 2 diabetes mellitus and may be beneficial in terms of glycemic control when used for menopausal symptom management. However, MHT is not approved to reduce new-onset type 2 diabetes.
Stroke	Increased risk of ischemic stroke (not hemorrhagic) exists with estrogen only and estrogen only and estrogen + progestogen use. On the basis of observational studies, lower doses of either oral estrogen or transdermal estrogen may confer less risk of stroke.

Symptom/Condition	Summary Statement(s)
Venous thromboembolism (VTE)	Increased risk of VTE with oral MHT across all ages. Risk increases with personal risk factors including obesity, previous history of VTE, and the presence of Factor V Leiden mutation. The type of progestogen may impact risk; micronized progesterone may be less thrombogenic than other progestins. Transdermal formulations have not been associated with VTE risk in observational studies and may have lower VTE risks than oral formulations.
Coronary heart disease	The effects of hormone therapy on CHD may vary depending on when hormone therapy is initiated in relation to a woman's age or time since menopause. Observational data and meta-analyses show reduced risk of CHD in women who initiate therapy when aged younger than 60 years or within 10 years of menopause onset. Women who initiate hormone therapy aged older than 60 years or more than 10 or 20 years from menopause onset are higher absolute risk of CHD, VTE, and stroke than women initiating hormone therapy in early menopause. MHT is not recommended any time for primary or secondary cardio protection.

Contraindications to MHT

- Absolute Contraindications
 - Breast cancer
 - Estrogen/progesterone-dependent tumors, VTE/PE
 - Thrombophilia
 - Arterial thromboembolism
 - Liver disease
 - Undiagnosed vaginal bleeding
- Relative Contraindications
 - HTN
 - Hypertriglyceridemia
 - Hypothyroidism
 - Migraines
 - SLE
 - Gallbladder disease

Estrogen Products

- **Oral**
 - Conjugated equine estrogens (Premarin), estradiol (Estrace)
- **Transdermal**
 - Estradiol patches (Climara, Vivelle-Dot)
- **Vaginal**
 - Creams, rings, tablets (Estrace, Estring, Vagifem)
- **Adverse Effects**
 - Nausea, bloating, breast tenderness
 - Headache, leg cramps
 - Increased triglycerides (oral only)
 - Increased risk of VTE, stroke, breast tenderness (dose and route dependent)
 - Vaginal forms have minimal systemic effects

Estrogen Formulations—Comparison

- **Oral Estrogens**
 - Examples: Conjugated equine estrogens (Premarin®), Estradiol (Estrace®)
 - Doses:
 - Conjugated quine estrogens: 0.3-1.25mg daily
 - Estradiol: 0.5-2 mg daily

- Advantages: Effective for vasomotor symptoms
 - Disadvantages: Increases triglycerides; higher risk of VTE and stroke
- **Transdermal Estrogens**
 - Examples: Estradiol patches (Climara®, Vivelle-Dot®); once to twice weekly
 - Advantages: Lower risk of VTE; bypasses first-pass hepatic metabolism
 - Disadvantages: May cause local skin irritation
- **Vaginal Estrogens**
 - Examples: Creams, rings, tablets (Estrace®, Estring®, Vagifem®)
 - Advantages: Most effective for genitourinary syndrome of menopause (GSM); minimal systemic absorption

Progesterin Products

- **Purpose:** Protect endometrium from unopposed estrogen stimulation
- **Common Agents**
 - Medroxyprogesterone acetate (Provera)
 - Micronized progesterone (Prometrium)
 - Norethindrone acetate (Aygestin)
- **Adverse Effects**
 - Bloating, mood swings, irritability
 - Breast tenderness, headache
 - Breakthrough bleeding or spotting
 - Weight gain and fatigue (with medroxyprogesterone)
 - Sedation with micronized progesterone (take at bedtime)

Common Progestogen Regimens

- **Medroxyprogesterone acetate (Provera®)**
 - Dose: 2.5–10 mg orally once daily
 - Can be used in a continuous or cyclic regimen
 - Commonly combined with estrogen for endometrial protection
- **Micronized progesterone (Prometrium®)**
 - Dose: 100 mg orally once daily, or 200 mg at bedtime for cyclic use
 - Fewer mood changes compared to synthetic progestins
 - May cause drowsiness — best taken at bedtime
- **Norethindrone acetate (Aygestin®)**
 - Dose: 0.35–5 mg orally once daily
 - Provides endometrial protection
 - May cause mild androgenic effects (e.g., acne, weight gain)

Tissue-Selective Estrogen Complex (TSE)

- Definition: Combines estrogen (conjugated estrogens) with bazedoxifene (a selective estrogen receptor modulator)
- Product Example: Duavee®
 - Indicated for vasomotor symptoms and osteoporosis prevention in women with a uterus
 - Bazedoxifene replaces the need for a progestogen
- Adverse Effects
 - Muscle spasms, nausea, diarrhea, abdominal pain
 - Thromboembolic events (rare)
 - Contraindicated in women with a history of VTE or estrogen-dependent cancers

Vaginal Estrogen and Local Therapies

- **Local Estrogen Products (for GSM only)**
 - Creams: Estrace®, Premarin®

- Vaginal ring: Estring®
 - Vaginal tablet: Vagifem®
- **Adverse Effects**
 - Mild vaginal irritation, discharge, spotting
 - Minimal systemic absorption → safe for long-term use
- **Nonhormonal Alternatives**
 - Vaginal moisturizers (Replens®, K-Y Liquibeads®)
 - Lubricants (water- or silicone-based)

Selective Estrogen Receptor Modulators (SERM)

- **Ospemifene (Ospheena®)**
 - Oral SERM for dyspareunia and vaginal dryness
- **Dose**
 - 60 mg PO once daily with food
- **Adverse Effects**
 - Hot flashes, vaginal discharge, muscle spasms
- **Warnings**
 - Risk of VTE, stroke, and endometrial hyperplasia (estrogenic uterine effects)

Intravaginal DHEA (Prasterone, Intrarosa®)

- Converted locally into active estrogens and androgens
- **Dose**
 - 6.5 mg intravaginally nightly
- **Indication**
 - Moderate–severe dyspareunia from GSM
- **Adverse Effects**
 - Vaginal discharge, abnormal Pap smear, irritation
- No need for progestogen co-therapy

Monitoring and Follow-Up

- **Symptom Relief**
 - Decrease frequency/severity of hot flashes, improve sleep and vaginal health
- **Adverse Effects**
 - Bloating, breast tenderness, mood changes, vaginal bleeding
- **Labs**
 - Lipids, LFTs if on oral therapy, bone density every 2–3 years
- **Stop MHT if**
 - VTE, MI, stroke, or new estrogen-dependent cancer emerges

Discontinuation and Tapering

- Gradually taper over 3–6 months to minimize recurrence of hot flashes
- Switch to transdermal or lower-dose before stopping if symptomatic
- Maintain vaginal estrogen or moisturizers if GSM persists

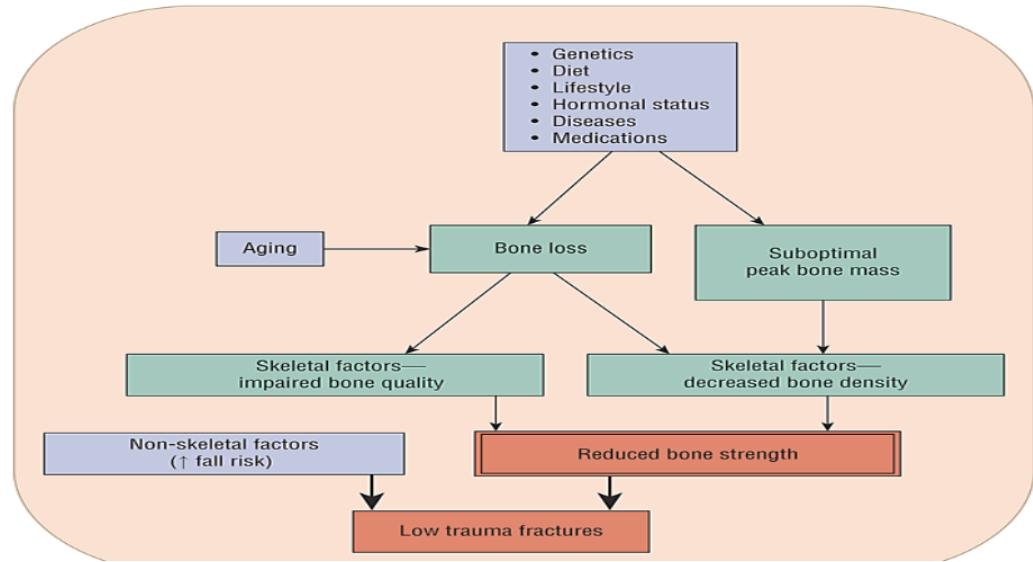
Osteoporosis

General Information

- DiPiro definition: “..bone disorder characterized by low bone density, impaired bone architecture, and compromised bone strength that predisposes a person to increased fracture risk.”
- 50% of patients >50 yo will develop osteoporosis
 - Prevalence increases with age, more in women than men
 - Highest fragility fracture rates in women: white American (17%) and Hispanic American (14%), then Black American (6%)

- Bone healthy lifestyles are important
- Underdiagnosed and undertreated
- Fragility wrist and vertebral fractures common throughout adults
- Hip fractures more common in older adults
- 70% of osteoporosis fractures occur in women, 30% in men
- Hip fractures are the most costly due to associated morbidity

Etiology of Osteoporosis Fractures



Risk factors for Osteoporosis and Osteoporotic Fractures

- Low bone mineral density
- Female sex
- Advanced age
- Race/ethnicity
- History of a previous fragility fracture including radiographic vertebral fracture as an adult
- Osteoporotic fracture in a first-degree relative
- Low body weight or body mass index
- Premature menopause
- Secondary osteoporosis
- Rheumatoid arthritis
- Past or Present systemic oral glucocorticoid therapy (prednisolone 5mg daily or more for >3 months)
- Current smoking
- Alcohol intake of 2 or more drinks/day
- Low calcium intake
- Low physical activity or immobilization
- Vitamin D insufficiency and deficiency
- Recent falls
- Cognitive impairment
- Impaired vision

Low Bone Density

- Bone Mineral Density (BMD) is major predictor of fracture risk

- Benefit of increasing peak bone mass in younger years
- Low BMD occurs
 - Failure to reach normal peak bone mass
 - Bone loss
 - Both of above
- Genetics can account for 50-85% of variability in peak bone mass
- Bone loss
 - Occurs when bone resorption exceeds bone formation
- Lose bone mass starting in third to fourth decade of life
- Perimenopause and menopause
 - Bone loss usually due to increased bone resorption

Falls

- 90% of hip fractures occur from falls in older patients
- Fall care is costly
- Risk factors for falls overlap with risk factors for osteoporosis and fractures
- Environmental factors also play a role
 - Electric cords
 - Rugs
 - Poor lighting

Bone Physiology

- 2 types of bone
 - Cortical: most of skeleton (80%) and mostly in long bones
 - Trabecular: mostly in vertebrae and ends of long bones
- Bone composed of collagen and minerals
 - Collagen: gives bone flexibility and energy-absorbing qualities
 - Mineral: mostly calcium and phosphorus, gives bone stiffness and strength (50-70% of bone mass)
- Peak bone mass by age 18-25 yo
- Medical conditions associated with osteoporosis can be found in table 112-2 of DiPiro chapter

Select Medications Associated with Increased Bone Loss and/or Fracture Risk

Medications	Comments
Antiseizure therapy (phenytoin, carbamazepine, phenobarbital, and valproic acid)	↓BMD and ↑ fracture risk; ↑ vitamin D metabolism leading to low 25(OH) vitamin D concentrations
Aromatase inhibitors (e.g. letrozole and anastrozole)	↓BMD and ↑ fracture risk; ↓ estrogen concentrations
Calcineurin inhibitors (e.g. cyclosporine and tacrolimus)	↓BMD and ↑ fracture risk; ↑ osteoclast activity
Glucocorticoids (long-term oral therapy)	↓BMD and ↑ fracture risk; ↓ bone resorption and ↓ bone formation, and ↓ calcium absorption and reabsorption; dose and duration dependent
Gonadotropin-releasing hormone agonists (e.g. leuprolide and goserelin) or analogs (ganirelix)	↓BMD and ↑ fracture risk; ↓ sex hormone production
Heparin (unfractionated, UFH) or low molecular weight heparin (LMWH)	↑BMD and ↑ fracture risk (UFH>>LMWH) with long-term use (e.g. >6 months); ↓ osteoblast replication and osteoclast function

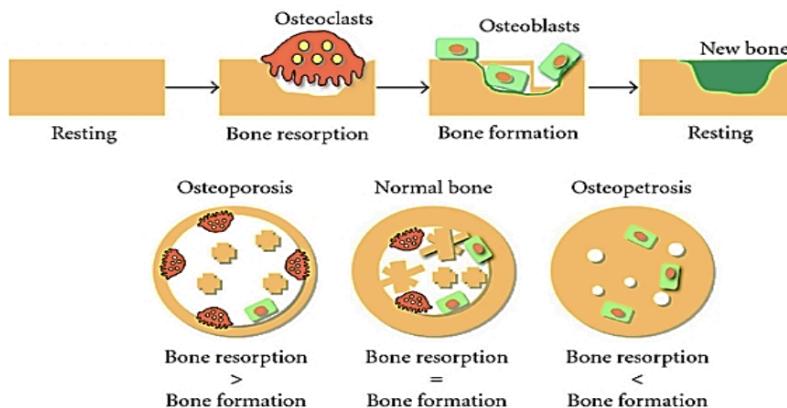
Medications	Comments
Loop diuretics (e.g. furosemide)	↓fracture risk; ↑ calcium renal elimination
Medroxyprogesterone acetate depot administration	↓BMD, ↑ fracture risk unknown; possible BMD recovery with discontinuation; ↓ estrogen concentrations
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) (tenofovir disoproxil fumarate > other NRTIs)	↓BMD, fracture risk unknown; greater risk when combined with pharmacological boosters
Proton pump inhibitor therapy (long-term therapy)	↓BMD and ↑ fracture risk; possible calcium malabsorption secondary to acid suppression for calcium carbonate salts
Selective serotonin reuptake inhibitors	↓BMD and ↑ fracture risk; ↓ osteoclast activity
Sodium glucose cotransporter 2 (SGLT2) inhibitors (canagliflozin; class effect uncertain)	↓BMD and ↑ fracture risk; alteration in calcium and phosphate homeostasis; bone resorption
Thiazolidinediones (pioglitazone and rosiglitazone)	↓BMD and ↑ fracture risk; ↓ osteoblast function

Medications	Comments
Thyroid – excessive supplementation	↓BMD and ↑ fracture risk associated with suppressed serum TSH; possible ↑ bone resorption
Vitamin A – excessive chronic intake (> 10,000 units of retinol form)	BMD and ↑ fracture risk; osteoblast activity and osteoclast activity

Bone Remodeling

- Occurs continuously throughout life
- Supports calcium homeostasis, releases calcium into the bloodstream when needed
- Osteoclasts resorb bone during the resorptive phase and osteoblasts form bone during the formation phase
- Decreases in BMD occur when remodeling is unbalanced, and bone resorption surpasses bone formation or if bone resorption occurs without adequate formation

Bone Remodeling Cycle



- Hormones can influence the bone remodeling steps
- Estrogen produces positive effects on bone remodeling in both males and females
 - Act to maintain normal bone resorption rate, suppress osteoclast proliferation and increases osteoclast apoptosis
- Testosterone has direct and indirect affects on osteoblasts
 - Metabolizes to estradiol, leading to above estrogen effects
 - Increases osteoblast proliferation, increases muscle strength

Postmenopausal Osteoporosis

- Estrogen deficiency leads to bone density loss
 - Increases proliferation and activation of new osteoclasts
 - Prolongs survival of mature osteoclasts
- Estrogen loss leads to increased calcium excretion and decreases calcium absorption in the stomach
- Increased/accelerated bone loss (mass and strength) begins in perimenopause and continues up to 10 years after menopause
- Leads to predominantly vertebral and wrist fractures

Male Osteoporosis

- Lower risk of osteoporosis and fractures due to larger bone size, greater peak bone mass, fewer falls, and shorter life expectancy
- Less testosterone with aging, therefore less conversion to estrogen
- Mortality rate post-fracture greater in men than women
- Most common risk factors for osteoporosis in men
 - Smoking
 - Alcohol abuse
 - Low body weight
 - Weight loss
 - Age
 - Long-term glucocorticoid use
 - Androgen deprivation therapy
 - Low testosterone concentrations

Age-related Osteoporosis

- Occurs in older adults due to accelerated bone turnover rate and reduced osteoblast bone formation
- Causes
 - Changes/deficiencies in hormones
 - Calcium and vitamin D deficiencies
 - Decreased body water
 - Less exercise
- Increased risk of hip fracture with aging
- Falls cause 87% of fractures in older adults

Clinical Presentation of Osteoporosis – Symptoms

- General
 - Many patients are unaware they have osteoporosis until testing or fracture
 - Fractures can occur after bending, lifting, or independent of any activity
- Symptoms
 - Frequently asymptomatic
 - Pain
 - Immobility
 - Depression, fear, and low self-esteem from physical limitations and deformities
- Signs
 - Shortened stature (> 1.5in loss from maximum height; > 0.8in loss in 1 year), Kyphosis, or lordosis
 - Fragility (low-trauma) vertebral, hip, wrist, or forearm fracture
- Laboratory tests
 - Routine tests

- Comprehensive metabolic profile
 - 25(OH) vitamin D
 - Thyroid-stimulating hormone
 - Complete blood count
 - Total Testosterone (for men)
 - 24-hour urine calcium and creatinine concentrations
- Bone turnover markers (e.g. serum NTX, serum CTX, and serum PINP) are sometimes used, especially to determine if high bone turnover exists
- Additional testing if the patient's history, physical examination, or initial laboratory and/or diagnostic tests suggest a specific secondary cause
- Other diagnostic tests
 - Spine and hip bone density measurement using central dual-energy x-ray absorptiometry (DXA)
 - Vertebral fracture assessment (VFA) with DXA technology
 - Radiograph ordered for other reasons that shows low bone density
 - Radiograph to confirm fracture
 - Balance and mobility tests

Consequences

- Leads to fragility or low-trauma fractures
 - Defined as fracture resulting from a fall from standing height or less or with minimal/no trauma
- Major osteoporotic fractures
 - Vertebrae, hip, forearm, humerus
 - Lead to decreased quality of life, increased morbidity/mortality
 - Other fractures not considered osteoporosis related
- Pain and physical deformity common with these fractures
- Severe kyphosis can lead to respiratory problems/GI complications
- Depression
- Hip fracture—greatest increase in morbidity and mortality
 - Men have higher 1 year mortality rate than women
- Wrist fractures more common in younger postmenopausal women
- Risk of subsequent fracture increases exponentially
 - Vertebral fractures major predictor of future fracture
 - Hip fracture has 2-10% chance of second hip fracture

Patient Assessment

- Lab tests (see table 112-4)
- Height annually
- Radiographs
- Tests for secondary causes
- Physical exam
- QOL questionnaires, risk factor assessment tools, DXA

Risk Factor Assessment

- Goal - Identify patients at risk for osteoporosis and osteoporotic fractures
- Most used tool is fracture risk assessment (FRAX)
 - Another option is Garvan tool
- FRAX tool uses 11 risk factors
 - Age
 - Sex

- Race/ethnicity
 - Previous fracture
 - Body mass index
 - Glucocorticoid use
 - Current smoking
 - Rheumatoid arthritis
 - Parent history of hip fracture
 - Alcohol of ≥ 3 drinks per day
 - Secondary causes of osteoporosis
- FRAX calculates patient's percent probability of any major osteoporotic fracture and hip fracture in next 10 years

Screening Tools

- Peripheral DXA
- Quantitative ultrasonography (QUS)
 - Better fracture predictor than peripheral DXA
- These are not used for diagnosis or to monitor therapy

BMD Measurements

- Measurements done at the hip and spine to assess risk of fracture, diagnose osteoporosis, determine severity of osteoporosis, and confirm osteoporosis after a low-trauma fracture
- Techniques available
 - DXA
 - Central DXA most widely used and preferred for therapeutic decision making
 - Measurements at lumbar spine, femoral neck, and total hip recommended
 - Forearm can be used as alternative site
 - Quantitative computed tomography (QCT)
 - Digital x-ray radiogrammetry
 - Radiographic absorptiometry
- Central BMD recommended in
 - All women ≥ 65 yo
 - All men ≥ 70 yo
 - Postmenopausal women < 65 yo
 - Men 50-69 yo with risk of fracture
 - Have secondary cause for bone loss

Central DXA

- Reports bone density value, T-score, and Z-score
- T-score used for diagnosis
- Follow-up BMD is recommended every 1-3 years in some guidelines and every 5 years in other guidelines
- Many insurance providers cover BMD testing every 2 years

Diagnosis

- Low bone mass (osteopenia)
 - T-score between -1 and -2.5
- Osteoporosis
 - T-score at or below -2.5

Desired Outcome of Treatment

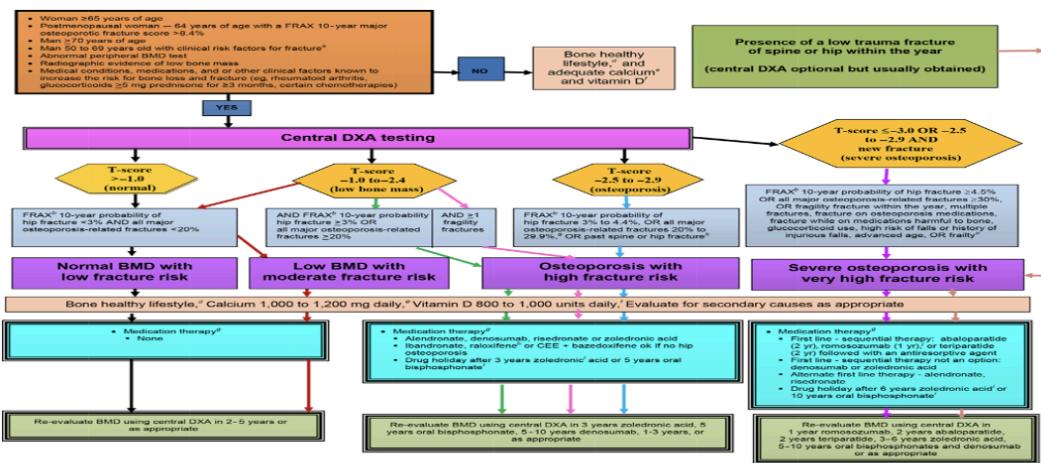
- Primary goal is osteoporosis prevention
- Once low bone mass occurs

- Objective is to improve or stabilize bone mass and strength in addition to preventing fracture
- In patients with fracture
 - Goal is to reduce pain and deformity, improve functional capacity, improve quality of life, reduce future falls and fractures

Treatment: General

- Bone-healthy lifestyle throughout life
- Supplements and medications used when lifestyle is suboptimal, osteoporosis has developed, or fracture has occurred
- Prescription therapy should be considered
 - Postmenopausal women or a man ≥ 50 yo with
 - Hip or vertebral fracture
 - T-score -2.5 or lower at the femoral neck, total hip, or spine
 - T-score -1 to -2.5 with FRAX 10-year risk of hip fracture 3% or more or major osteoporosis related fracture of 20% or more

Algorithm for Osteoporosis Management in Postmenopausal Women and Men ≥ 50 yo



Sources: Joseph T. Dipiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod,
L. Michael Posey; *Ottrino's Pharmacotherapy: A Pathophysiologic Approach*, 12e
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Osteoporosis – Nonpharmacologic Therapy

Nonpharmacologic Therapy

- Bone healthy lifestyle
 - Proper nutrition
 - Moderation of alcohol
 - Smoking cessation
 - Exercise
 - Fall prevention
- Decreases falls and fragility fractures

Diet

- Balanced nutrients and minerals
- Limited salt
- Limited alcohol
- Limited caffeine

- Adequate calcium and vitamin D
- Protein
 - 0.8 g/kg body weight in adults, 1-1.2 g/kg in older adults, and up to 1.5 g/kg in some chronic illnesses
- Magnesium, boron, and vitamin K
 - Insufficient data for prevention/treatment
- Eating disorders lead to increased bone loss and fractures

Calcium

- Adequate calcium is important
 - Bone development during growth
 - Bone maintenance throughout life
- Calcium intake recommendations based on age and gender
- Higher than RDA may be necessary with certain diseases or medications
- Preferred calcium sources for daily requirements: ingesting calcium containing/fortified foods and beverages
 - Dairy products highest per serving
 - Carbs increase calcium absorption
- Average diet in many children and adults is insufficient in calcium
- If cannot achieve recommended calcium intake in diet, supplements are needed
- Most common adverse effect is constipation
 - Treat with increased water intake, dietary fiber, and exercise
- Calcium carbonate can cause gas and stomach upset
- Calcium citrate causes less GI side effects
- Calcium + vitamin D supplementation can cause kidney stones, increase fluid intake to help
- Calcium carbonate interacts with PPI and H2RA to decrease the absorption of the calcium, choose calcium citrate in these patients
- Calcium can decrease absorption of iron, bisphosphonates, and thyroid supplements
- Calcium absorption is dose limited: max single doses of 500-600 mg elemental calcium recommended
- Calcium carbonate is salt of choice: highest elemental calcium and least expensive
 - Take with meals for better absorption
- Calcium citrate can be taken any time of day, without or without food
- Dosage forms: tablets, chewable tablets, dissolvable tablets, liquid

Vitamin D

- 3 main sources of vitamin D
 - Sunlight
 - Diet
 - Supplements
- Vitamin D3
 - Oily fish
 - Eggs
 - Fortified dairy products
- Vitamin D2
 - Fungi
 - Eggs
- Low vitamin D
 - Higher rates in patients >60yo
 - Minorities

- Lower education levels
 - Obese
 - Inactive
 - Current smokers
- Low vitamin D results from
 - Insufficient intake
 - Dietary fat malabsorption
 - Decreased sun exposure
 - Decreased skin production
 - Decreased liver
 - Renal metabolism
- Most people require vitamin D supplements to achieve recommended intake (especially older adults)
- Guidelines for osteoporosis recommend to treat to serum vitamin D level of at least 20 ng/mL or 30-50 ng/mL
- 700-800 units/day reduces incidence of hip and nonvertebral fractures
- Vitamin D absorption can be decreased by cholestyramine, colestipol, orlistat, and mineral oil
- Vitamin D can increase absorption of aluminum, so aluminum products should be avoided
- Vitamin D₃ and vitamin D₂ can both be used for prevention and treatment, but guidelines prefer vitamin D₃
- Usually, doses of 1,000-2,000 units daily is recommended for osteoporosis
- Vitamin D levels can be assessed every 3 months when indicated

Calcium and Vitamin D Recommended Dietary Allowances and Tolerable Upper Intake Levels

Group and Ages	Elemental Calcium RDA (mg)	Calcium Tolerable Upper Intake Level (mg)	Vitamin D RDA (units)	Vitamin D Tolerable Upper Level (units)
Birth to 6 months	200	1,000	400	1,000
7-12 months	260	1,500	400	1,500
1-3 years	700	2,500	600	2,500
4-8 years	1,000	2,500	600	3,000
9-18 years	1,300	3,000	600	4,000
19-50 years	1,000	2,500	600	4,000
51-70 years (men)	1,000	2,000	600	4,000
51-70 years (women)	1,200	2,000	600	4,000
>70 years	1,200	2,000	800	4,000

Antiresorptive Medications – Nutritional Supplements

Medication	Brand Name	Dose	Comments
Calcium	Various	Adequate daily intake: IOM: 200-1,200mg/day, varies per age; supplement dose is the difference between required adequate intake and dietary intake. Immediate-release doses should be <500-600mg	Recommend food sources first to achieve goal intake. Available in different salts including carbonate and citrate, absorption of other salts not fully quantified. Different formulations including chewable, liquid, gummy, softgel, drink, and wafer; different combination products. Review package to determine number of units per serving size and desired amount of elemental calcium. Give calcium carbonate with meals to improve absorption.

Medication	Brand Name	Dose	Comments
Vitamin D D3 (cholecalciferol) D2 (ergocalciferol)	Over the counter <ul style="list-style-type: none"> Tablets, 400, 1,000, and 2,000 units Capsules, 400, 1,000, 2,000, 5,000, and 10,000 units Gummies, 300, 500, and 1,000 units Drops, 300, 400, 1,000, and 2,000 units/ml or drop Solution, 400 and 5,000 units/ml Spray, 1,000 and 5,000 units/spray Creams and lotions, 500 and 1,000 units per 1/4 	Adequate daily intake: IOM: 400-800 units/day to achieve adequate intake; guidelines: 800-2,000 units orally daily; if low 25(OH) vitamin D concentrations, malabsorption, or altered metabolism higher doses (>2,000 units daily) might be required. Vitamin D deficiency: 5,000 units or higher daily preferred over 50,000 units orally once to twice weekly for 8-12 weeks; repeat as needed. Higher doses until therapeutic concentrations reached.	Vegetarians and vegans need to read label to determine if the vitamin D source is plant-based. Slight advantage of D3 over D2 for increasing serum 25(OH) vitamin D concentrations. For drops, make sure measurement is correct for desired dose. Ability of sprays, lotions, and creams to resolve deficiencies or maintain adequate intakes is unknown.

Smoking

- Independent risk factor for osteoporosis
- Increased risk for fracture at all fracture sites
- Due to decreased intestinal calcium absorption and lower vitamin D concentrations
- Smoking has effects on physical function and balance, increasing risk of falls
- Counsel patients on smoking cessation

Exercise

- Exercise is part of nonpharmacologic approach to care
- Increases bone mechanical strain, stimulates osteocytes leading to bone resorption and then new stronger bone formation
- Weight-bearing exercise is important, increases muscle and bone mass
- Decreases risk for falls
- Important early in life

- Most beneficial: moderate-intensity weight-bearing activities, plyometric activities, and resistance activity
- 3-4 times per week for 30-40 minutes per session

Fall Prevention

- Risk of falls increases with age
- Older adults more likely to experience hip or pelvic fractures
 - Fall backward
 - Sideways instead of forward
- Assess falls annually in older patients, many assessment tools available
- Review medication profiles for drugs that may affect cognition and balance
- Counsel on proper footwear, safe home environments

Osteoporosis – Pharmacologic Therapy

Pharmacologic Therapy

- Important table: Table 112-7 Medications in Osteoporosis
- Calcium and Vitamin D are part of osteoporosis treatment, please see above slides for information regarding this therapy
- Nonpharmacologic therapy alone usually insufficient to prevent or treat osteoporosis
- Combine medications with bone healthy lifestyles

First Line Therapies

- Alendronate, risedronate, zoledronic acid, and denosumab decrease hip and vertebral fracture risk
- Abaloparatide, ibandronate, raloxifene, romosozumab, and teriparatide decrease vertebral fracture risk, but not hip
- Estrogen and testosterone not used as osteoporosis treatment, but have positive bone effects when used for other indications
- Sequential therapy is recommended: bone formation medication followed by antiresorption medications, especially with very high risk for fracture but these medications come with high cost
- Guideline recommendation: bisphosphonates first, then denosumab as second line when bisphosphonates cannot be used
- Combine prescription therapy with adequate calcium and vitamin D
- Type of fracture risk (spine, hip, both) help to determine medication choice

Antiresorptive Therapies

- Calcium
- Vitamin D
- Bisphosphonates
- Denosumab
- Estrogen agonists/antagonists
- Tissue selective estrogen complexes
- Estrogen
- Testosterone

Bisphosphonates

- Alendronate, risedronate, and IV zoledronic acid approved by FDA for postmenopausal women and men
- IV and oral ibandronate indicated only for postmenopausal osteoporosis
- MOA: mimic pyrophosphate, an endogenous bone resorption inhibitor
- Oral bioavailability is <1%, and decreased with concomitant food and beverages
- Bisphosphonates are incorporated into bone, so have long biologic half-lives up to 10 years

- Zoledronic acid has greatest bone absorption and longest bone retention
- Ibandronate is not considered first line therapy as it lacks decreased hip fracture data
- BMD increases and decreased fracture risk occur within first 6-12 months of therapy
 - Greater in spine compared to hip
- Increases in BMD continue for 4-5 years, then plateau
- After discontinuing the medication, increased BMD is sustained for prolong period
 - Drug holiday can be considered
- Bisphosphonates are only FDA indicated to increase BMD and not to reduce fracture risk in men
- Adverse effects
 - Do NOT take bisphosphonates if
 - CrCl <30-35 mL/min
 - Serious GI conditions
 - Pregnant
 - Common AE
 - GI complaints (heartburn/dyspepsia) is common reason for discontinuation
 - Can cause musculoskeletal pain
 - Rare AE
 - Esophageal erosion
 - Ulcer
 - GI bleed
 - Osteonecrosis of the jaw
 - Subtrochanteric femoral fracture
 - IV zoledronic acid or ibandronate can be used in patients with GI contraindications or intolerances to oral therapy
 - Fever
 - Flu-like symptoms
 - Myalgia
 - Arthralgias can occur with IV therapy
- Oral Administration
 - Bioavailability is poor
 - Take oral tablets with at least 6 oz of plain water 30 minutes (60 for ibandronate) before any food, supplements, or medications
 - Remain upright (sitting or standing) for at least 30 minutes (60 for ibandronate)
 - If swallowing difficulties, can use effervescent tablet of alendronate dissolved in 4 oz room temperature water
 - Delayed release risedronate is administered immediately after breakfast with at least 4 oz plain water
- IV Administration
 - Serum calcium must be normal before IV therapies are used
 - Monitor Scr before each zoledronic acid dose
 - IV medications administered by healthcare provider
 - Acetaminophen can be given to minimize AE
- Duration of Therapy
 - Ideal duration is currently not known
 - Deposited into bone and continue to suppress bone turnover after medication is discontinued
 - Some recommend a drug holiday

- One study showed drug holiday after therapy with alendronate for 5 years and zoledronic acid after 3 years had continued fracture benefit
- Experts say can have drug holiday after 5 years of oral therapy or 3 years of IV therapy
- In women with very high fracture risk, recommended to continue therapy for 10 years for oral therapy and 6 years for IV therapy
- Monitor during drug holiday, restart therapy if fractures occur or have significant BMD losses

Antiresorptive Prescription Medications

Bisphosphonates			
Alendronate	Fosamax Fosamax Plus D Binosto (effervescent tablet)	Treatment: 10mg orally daily or 70mg orally weekly Prevention: 5mg orally daily or 35mg orally weekly	Generic available, effervescent tablet is brand only. 70mg dose is available as a tablet, effervescent tablet, solution, or combination tablet with 2,800 or 5,600 units of vitamin D3. Administered in the morning on an empty stomach with 6-8 ounces of plain water. Do not eat and remain upright for at least 30 minutes following administration. Do not coadminister with any other medications or supplements, including calcium and vitamin D. Caution if CrCl <35ml/min
Ibandronate	Bonvia	Treatment: 150mg orally monthly, 3mg intravenous quarterly Prevention: 150mg orally monthly	Generics available Administrations same as alendronate, except must delay eating and remain upright for at least 60 minutes. Caution if CrCl <30ml/min

Bisphosphonates			
Risedronate	Actonel Atelvia (delayed-release)	Treatment and prevention: 5mg orally daily, 35mg orally weekly, 150mg orally monthly	Generics available. 35mg dose is also available as a delayed-release product. Administration instructions same as for alendronate, except delayed-release product is taken immediately following breakfast with at least 120ml of plain water. Caution if CrCl <30ml/min.
Zoledronic acid	Reclast	Treatment: 5mg intravenous infusion yearly Prevention: 5mg intravenous infusion every 2 years	Generics available. Can premedicate with acetaminophen to decrease infusion reactions. Contraindicated if CrCl <35ml/min Also marketed under the brand name Zometa (4mg) with different dosing for oncology-related indications.

Denosumab

- FDA approved for postmenopausal women and men at high risk for fracture, and in men receiving androgen deprivation therapy for nonmetastatic prostate CA and women on aromatase inhibitor therapy for breast CA at high risk for fracture
- Fully human monoclonal antibody that binds to RANKL, inhibiting osteoclastogenesis and increasing osteoclast apoptosis
- Administered via subQ injection, peak concentrations occur in 10 days
- Concentration slowly declines over 4-5 months

- No renal dose adjustment necessary, no studies in hepatic impairment
- Decreased vertebral fracture, nonvertebral fracture, and hip fractures over 3 years
- Increases in BMD continue with long-term treatment over 10 years
- Not incorporated into bone and therefore drug holiday not recommended
- After discontinuation, loss of protection against vertebral fractures occurs so if high fracture risk therapy should be continued
- If discontinued, bisphosphonate therapy should be started
- ADRs
 - Generally, well tolerated
 - Rarely osteonecrosis of the jaw and atypical fracture
 - Hypocalcemia can occur, correct calcium level prior to use
 - Monitor serum calcium, magnesium, and phosphorus within 14 days of administration in patients with CrCl <30 mL/min
- No drug interactions found
- Administration and Duration
 - Administration
 - SubQ in upper arm, upper thigh, or abdomen by healthcare professional
 - Store in fridge, room temp up until 14 days before administration
 - Duration
 - After 5-10 years of therapy, reevaluate for medication continuation, discontinuation, or switch to another medication

RANK Ligand Inhibitor

RANK Ligand Inhibitor			
Denosumab	Prolia	Treatment: 60mg subcutaneously every 6 months	Administered by healthcare practitioner. Correct hypocalcemia before administration. Also marked under the brand name Xgeva (70mg/ml) with different dosing for treatment of hypercalcemia of malignancy, multiple myeloma, bone metastases from solid tumors, and giant cell tumor of bone.

Estrogen Agonist/Antagonists (EAA)

- Raloxifene is second-generation mixed estrogen agonist/antagonist (EAA) FDA approved for prevention and treatment of postmenopausal osteoporosis
- Bazedoxifene is third generation EAA that is combined with conjugated equine estrogen (CEE) FDA approved for prevention of postmenopausal osteoporosis and vasomotor menopausal symptoms
- Food has nonsignificant effects on absorption
- Both EAAs decrease vertebral but not hip fractures
- EAAs increase spine and hip BMD, but less than bisphosphonates
- Medication effect of EAA is lost when the medication is discontinued
- Hot flushes are common with raloxifene, but bazedoxifene with CEE decreases hot flushes
- Raloxifene rarely causes endometrial thickening/bleeding, bazedoxifene decreases these effects so progestogen therapy is not needed when combined with CEE
- EAAs cause leg cramps and muscle spasms
- Raloxifene has black box warning for slight increase in fatal stroke

- Medication interactions: warfarin, cholestyramine, rifampin, phenytoin, carbamazepine, and phenobarbital
- EAA administered orally daily
- Contraindicated in active or past history of venous thromboembolic disease, pregnancy, or childbearing potential
- Stop therapy if patient will have extended immobility
- Women high risk for stroke or coronary events and with known CAD, PVD, Afib, or history of cerebrovascular events may not be best candidates for EAA therapy
- Use with caution in patients with severe liver impairment or mod-severe renal impairment (lack of data in this population)

Estrogen Agonist/Antagonist

Estrogen Agonist/Antagonist and Tissue Selective Estrogen Complex			
Raloxifene	Evista	60mg daily	Generic available
Bazedoxifene with conjugated equine estrogens (CEE)	Duavee	20mg plus 0.45mg CEE daily	For postmenopausal women with a uterus; no progestogen needed. Bazeoxifene monotherapy available in some countries.

Parathyroid Hormone Analogs (PTH Therapy)

- Abaloparatide and teriparatide
- FDA approved for treatment of postmenopausal women with osteoporosis at high risk for fracture (multiple risk factors for fracture, history of osteoporotic fracture, or failed or intolerant to other therapies)
- FDA approved to increase bone mass in men at high risk of fracture or failed/intolerant to other osteoporosis medications
- Good candidates for therapy
 - Very high fracture risk
 - History of osteoporotic fracture
 - Low bone density (T-score <-3.5)
 - Failed or intolerant to previous bisphosphonate therapy
- Teriparatide
 - Recombinant human product
 - Increases bone formation with a minor increase in bone resorption
- Abaloparatide
 - Synthetic analog
 - Demonstrates less of an effect on activating bone resorption and remodeling compared to teriparatide
- Both products improve bone mass
- No dose adjustments needed in renal insufficiency, no studies done in hepatic impairment
- 2 years of teriparatide or abaloperotide reduces vertebral and nonvertebral fracture risk in postmenopausal women
- Teriparatide shows similar fracture benefit in men, no fracture data for abaloperotide in men
- Discontinuing the medication results in decrease in BMD
- AE

- Transient hypercalcemia, less with abaloperitide
 - Black box warning against use in patients at increased baseline risk for osteosarcoma (only seen in rats to date)
- Interactions
 - Can increase calcium concentration with digoxin therapy
- Therapy Administration
 - Both available as prefilled pen for daily SubQ injection, rotation of sites
 - Teriparatide
 - Injection sites: abdominal area, thigh
 - Abaloperitide
 - Injection site: abdominal area
 - First dose should be given either sitting or lying down in case of orthostatic hypotension
 - Both should be stored in fridge until first use
 - Duration of therapy limited to 2 years of lifetime use due to theoretical risk for osteosarcoma
 - Do NOT use in patients
 - Hypercalcemia
 - Metabolic bone diseases other than osteoporosis
 - Metastatic or skeletal cancers
 - Previous radiation therapy
 - Premenopausal women of childbearing potential

Human Parathyroid Hormone-Related Peptide

Formation Medications			
Abaloparatide	Tymlos	80mcg subcutaneously daily for up to 2 years	First dose sitting or lying. Refrigerate before use then keep at room temperature. Use new needle with each dose. Inject in abdomen. Discard after 30 days.

Recombinant Human Parathyroid Hormone

Formation Medications			
Teriparatide	Forsteo Bonsity	20mcg subcutaneously daily	First dose sitting or lying. Refrigerate before and after each use. Use new needle with each dose. Inject in thigh or abdomen. Discard after 28 days or if cloudy. Forsteo and Bonsity not interchangeable.

Romosozumab

- FDA approved for postmenopausal women at high risk for fracture
 - High risk of fracture defined as

- Multiple risk factors for fracture
 - History of osteoporotic fracture
 - Failed/intolerant to other therapies
- May be anabolic osteoporosis medication of choice for patients with previous radiation therapy and those at risk for osteosarcoma and hypercalcemia
- Is a humanized monoclonal antibody binding to sclerostin to prevent inhibition of bone formation and decrease bone resorption
- Peak serum concentrations occur within 3-4.5 days of SubQ administration
- After 1 year of therapy, vertebral fractures decreased by 73% in postmenopausal women
- May be better at preventing hip fractures compared to abaloparatide and teriparatide
- AE
 - Most common: headache and arthralgia
 - Hypercalcemia
 - Mild injection site irritation
 - Low incidence of serious cardiovascular events
 - Black box warning for MI, stroke, and CV death
 - Rarely osteonecrosis of the jaw and atypical femoral fractures
- **Romosozumab should NOT be used within 1 year of MI or stroke and benefit risk evaluation should be done in patients at risk for these conditions or a history of these conditions**
- Interactions: none reported
- Available as 2 prefilled syringes
- Require refrigeration until administered by healthcare provider
- Each syringe injected into 2 different sites during same visit

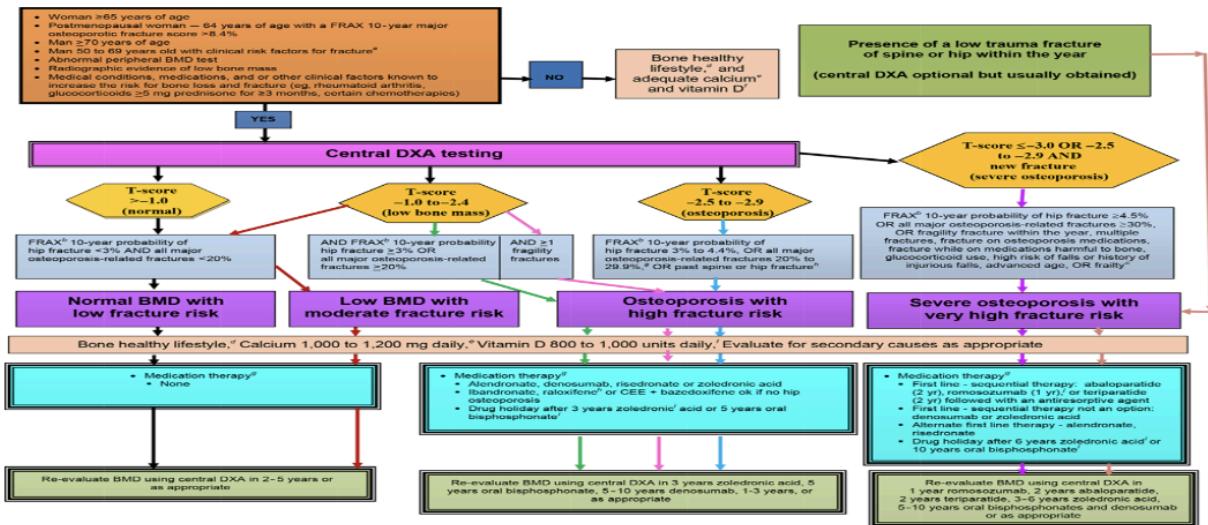
Sclerostin Inhibitor

Formation and Antiresorptive Medication			
Romosozumab	Evenity	210mg subcutaneously monthly for 1 year; administered as two single use 205mg/ 1.17ml prefilled syringes	Correct hypocalcemia before administration. Refrigerate. Leave at room temperature for at least 30 minutes before use. Provider administration, exploring patient self- administration. Inject in abdomen, thigh, or upper arm, preferably each injection at a different site.

Sequential and Combination Therapy

- Sequential therapy
 - Anabolic agent given first to increase bone remodeling units and bone mass, followed by antiresorptive agent to continue bone formation
 - Recommended in guidelines, but in practice usually reserved for patients with severe osteoporosis due to cost
 - Starting teriparatide after antiresorption therapy not preferred and it led to lower BMD
 - Small BMD increases shown when switching from oral bisphosphonate to denosumab (can be done during bisphosphonate drug holiday)
- Combination therapy
 - Rarely used due to lack of documented fracture benefit, increased cost, concern for dual suppression of bone turnover, and potential for increased adverse effects

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Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach*, 12e
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Special Populations

- Premenopausal Women
 - Clinically significant bone loss and fracture rare
 - With prior fracture, risk for postmenopausal osteoporotic fracture is higher
 - Use pharmacologic therapy with caution; efficacy and safety not yet demonstrated
- Older Adults
 - Falls more common
 - Osteoporosis underdiagnosed in this population
 - Bone healthy lifestyle, calcium and vitamin D supplements when needed
 - When using prescription medications, consider
 - Remaining lifespan
 - Ability to take and afford medications
 - Cognitive function
 - Swallowing ability
 - GI disorders
 - Polypharmacy
 - Desire to avoid additional medications
 - Regimen complexity
- Chronic Kidney Disease
 - Low BMD and fractures occur in CKD (GFR <60 mL/min), chronic dialysis, and/or kidney transplant patients
 - DXA results can underestimate fracture risk in this population
 - Fractures occur earlier and have greater 1 year mortality rates
 - Studies for pharmacologic therapy in this patient population are lacking
 - Denosumab is not renally eliminated so can be used, monitor serum calcium
 - Zoledronic acid contraindicated if CrCl <30/35 mL/min
 - Raloxifene not suggested for patients with severe renal impairment

Monitoring

- Assess adherence and tolerability of pharmacologic treatment
- AACE/ACE guidelines recommend central DXA every 1-2 years after medication initiation until BMD is stable
- Endocrine Society recommends waiting 3 years for zoledronic acid, 5 years for other bisphosphonates, and 5-10 years for denosumab