LECTURE NOTES
ADVANCED PHARMACOTHERAPEUTICS
MUSCULOSKELETAL, PAIN, AND RHEUMATOLOGY SYSTEMS

Learning Outcomes

1. Review Pathophysiology
2. Clinical Pharmacology
3. Mechanism of action
4. PK/PD
5. Medication/Interactions
6. ADR's -Adverse drug reactions
7. RBA (Risk Benefit Analysis)

Acute Pain Management (see supplemental handout)

Osteoporosis Pharmacotherapeutics

8. ASSESSMENT/PLAN:
    a. You have diagnosed both Thoracic and lumbar vertebral compression fractures; this confirms a diagnosis of Osteoporosis, in addition to the results of the most recent DXA scan. Questions
    b. Evaluate the patient's presentation– what are the risk factors and is this a typical presentation of osteoporosis?
    c. You have decided to treat her osteoporosis with an oral bisphosphonate. Is this correct for this diagnosis and patient condition? There are certain factors associated with being able to prescribe a bisphosphonate-what are they and why would this NOT eb a good choice for Betty?

9. Starting Points
    a. Osteoporosis, or low bone mass (osteopenia)
    b. estimated to occur in ~ 54 million Americans > 50 years and older
    c. 80% of whom are women
    d. Women >> men to develop osteoporosis
    e. d/t thinner, lighter bones, changes associated with menopause, and greater longevity than men
    f. National Osteoporosis Foundation (NOF) recommends that health care providers should consider U.S. Food and Drug Administration (FDA)-approved medical therapies for patients at risk for the disease.

10. Definition

a. Osteoporosis is a progressive systemic disease characterized by a decrease in bone mass and microarchitectural deterioration of bone tissue, resulting in bone fragility and increased susceptibility to fractures.

11. Bone fracture is the major cause of mortality and morbidity in patients with osteoporosis.

12. Most Common Fractures of Osteoporosis
    a. Vertebral compression fractures
    b. Fractures of the distal radius
    c. Fractures of the proximal femur

13. Types of Osteoporosis
    a. Type I: Postmenopausal Osteoporosis
        i. Occurs in postmenopausal women between ages 51 and 75.
        ii. Decreased estrogen causes an accelerated rate of bone loss
            1. especially trabecular bone loss.
        iii. The most common fractures are of the vertebrae and distal femur.
        iv. There is also tooth loss.
    b. Type II: Senile Osteoporosis
        i. men & women older than age 70
        ii. proportional loss of cortical and trabecular bone.
        iii. common fractures: hip, pelvic, and vertebral

    c. Type III: Secondary Osteoporosis
        i. Occurs in men & women any age
        ii. Secondary to other conditions such as drug therapy and other diseases

14. Risk Factors for Osteoporosis
    a. Female sex; older age; Asian or White race
    b. Family history; petite stature; low body weight
    c. Amenorrhea, menopause
    d. Sedentary lifestyle; low calcium intake
    e. Excess alcohol intake; smoking; excess caffeine intake
    f. Low testosterone level in men
    g. Certain drugs and disease states

15. Screening for Osteoporosis
    a. All women older than age 65

b. Younger perimenopausal or postmenopausal women and men who have any medical condition or are taking medication associated with bone loss
c. Any adult older than age 50 with a fracture
d. Anyone being treated for osteoporosis
e. Men age 50 and older at risk

16. Diagnostic Tools for Osteoporosis
    a. FRAX
    b. 10 risk factors considered in addition to the BMD T-score: age, gender, fracture history, parental hip fracture history, oral steroid therapy, low body mass index, femoral neck BMD, secondary osteoporosis, current smoking, and alcohol intake.

17. "WHO Fracture Risk Assessment Tool"
    a. National Osteoporosis Foundation (NOF) Recommendations: Drug Therapy
    b. Low bone mass
        i. T-score –1.0 to –2.5 at the femoral neck, total hip, or spine
        ii. 10-year probability of hip fracture of 3% or more
        iii. 10-year probability of any major osteoporosis-related fracture of 20% or more
        iv. T-score of -2.5 or less at the femoral neck, total hip, or spine after appropriate evaluation to exclude secondary causes.
    c. Low bone mass (T-score from –1.0 to –2.5 at the femoral neck, total hip, or spine) and secondary causes associated with high fracture risk (such as glucocorticoid use or immobilization)

    d. Other prior fractures and low bone mass (BMD T-score from –1.0 to –2.5 at the femoral neck, total hip, or spine)

18. Goals of Drug Therapy for Osteoporosis
    a. Minimizing bone loss

    b. Delaying the progression of osteoporosis

    c. Preventing fractures and fracture-related morbidity and mortality
19. Recommended Order of Prevention and Treatment for Osteoporosis
    a. First line
        i. Prevention: raloxifene, alendronate, ibandronate, zoledronic acid, or risedronate
    b. plus, calcium and vitamin D
        i. Treatment: raloxifene, alendronate, risedronate, ibandronate, zoledronic acid, or calcitonin
    c. Second line

i. Addition of hormone modifiers or calcitonin if not being taken

20. Bisphosphonates

a. Alendronate (Fosamax)
    i. Prevention: 5 mg/d or 35 mg once a week
    ii. Treatment: 10 mg/d or 70 mg once a week
b. Risedronate (Actonel)
    i. 5 mg/d or 35 mg once a week
c. Ibandronate (Boniva)
    i. 2.5 mg PO daily or 150 mg PO once a month
    ii. 3 mg/3 mL IV every 3 months
d. Zoledronic acid (Reclast)
    i. 5 mg/100 mL IV once yearly

21. Drug information
a. Bisphosphonates should be taken with 8 ounces of water, and the patient should remain upright for 30 minutes after administration.
b. Lifestyle/nutritional changes
c. Well-balanced diet and weight-bearing exercises
d. Complementary and alternative therapy
e. Supplemental calcium and vitamin D

22. MOA:
a. inhibits osteoclast activity, reducing bone resorption and turnover
b. Attach to hydroxyapatite on bony surfaces
c. Prevent osteocyte and osteoblast apoptosis

23. Alendronate/FOSAMAX
a. Monitoring Parameters
    i. Cr at baseline
    ii. Ca at baseline, then if hypocalcemia risk cont.
    iii. Ca, Mg, PO4 periodically
a. Metabolism: none
    i. CYP450: none
b. Excretion:
    i. urine 50%
c. Half-life:
    i. >10y
    ii. accumulates in bone

d. IMPORTANT admin directions:

i. give w/ water
ii. 30min before first food/drink/med
iii. avoid lying down x30min
iv. calcium and vitamin D supp recommended if inadequate dietary intake
v. periodically reassess need for Tx
vi. may consider drug holiday if stable after Tx 5y (low-mod risk pt.) or x6-10y (high risk pt.
vii. optimal holiday duration not defined, consider resuming Tx in pts w/ fracture or significant BMD loss

24. OTHER Agents: Osteoporosis

a. Selective Estrogen Receptor Modulators
    i. Raloxifene (Evista*) 60 mg qd

b. RANK Ligand Inhibitor:
    i. Denosumab (Prolia): 60 mg subq q 6 months

c. Calcitonin (Miacalcin*)
    i. 200 U (1 spray) daily 100 U IM or SC daily

d. Hormone Modifiers:
    i. Teriparatide (Forteo*) 20 mcg daily SC

Osteoarthritis Pharmacotherapeutics

25. Osteoarthritis (OA)
a. progressive disease that can results in:
b. chronic pain
c. restricted range of motion
d. muscle weakness
e. especially if a weight-bearing joint is affected.
f. The joints commonly affected
    i. knees, hips
    ii. cervical and lumbar spine
    iii. distal interphalangeal (DIP) joints, and the carpometacarpal joint at the base of the thumb

26. Forms of OA
a. Defined as:
b. Primary, or idiopathic:

i. Arises from physiologic changes that occur with normal aging

c. Secondary:
   i. Usually results from traumatic injuries or inherited conditions and may present as hemochromatosis, chondrodystrophy, or inflammatory OA.

27. Risk factors:
   a. Modifiable
      i. Obesity; prior joint injury
      ii. Occupations requiring excessive mechanical stress or heavy lifting
   b. Nonmodifiable
      i. Gender, age, race, genetics

28. Diagnostics
   a. Hand: Pain, aching, or stiffness and three of the following:
      i. Hard tissue enlargement of >2 joints; Hard tissue enlargement of >2 DIP joints; <3 swollen MCP joints; Deformity of >1 selected joint

   b. Hip: Pain and two of the following:
      i. ESR <20 mm/h; Radiographic femoral or acetabular osteophytes; Radiographic joint space narrowing
   c. Knee: Knee pain and three of the following:
      i. >50-year-old; Stiffness <30 minutes; Crepitus; Bony tenderness
      ii. Bony enlargement; no palpable warmth

29. Goals of Therapy for OA
   a. Physical therapy
   b. Reduce pain
   c. maintain functional
   d. Improve motion
   e. Pharmacotherapy
      i. Maintain function
      ii. Prevent further joint damage
      iii. Diminish associated pain

30. Order of Treatment for OA:

31. Hand
   a. ACR Initial Treatment Options: topical capsaicin; topical NSAIDs; oral NSAIDs
   b. EULAR:
      i. 1st line: topical NSAIDs, capsaicin
      ii. 2nd line: APAP
      iii. 3rd line: NSAIDs
      iv. IA steroids for painful flares

32. Hip
    a. ACR Initial Treatment Options: APAP; oral NSAIDs; Tramadol; IA steroids
    b. EULAR:
        i. 1st line: APAP
        ii. 2nd line: NSAIDs +/- gastroprotection
        iii. 3rd line: opioid +/- APAP
        iv. IA steroids for flares unresponsive to analgesia and NSAIDs

33. Knee
    a. ACR Initial Treatment Options: APAP; oral NSAIDs; topical NSAIDs; Tramadol; IA steroids

    b. EULAR:
        i. 1st line: APAP, topical NSAIDs, capsaicin
        ii. 2nd line: NSAIDs +/- gastroprotection
        iii. 3rd line: opioid +/- APAP
        iv. IA steroids for flares with effusions

34. First-Line Pharmacotherapy for OA
    a. Geared toward analgesia
        i. Specifically, with acetaminophen (Tylenol)
        ii. Due to acetaminophen's cost-effectiveness and safety, it is currently the first-line treatment recommended in guidelines by the ACR, the European League against Rheumatism (EULAR), and others.
        iii. recommended dose =
            a. 650 mg q 4 to 6 hours
                i. _OR_
            b. 1,000 mg every 6 to 8 hours around the clock

35. Diclofenac topical
    a. Apply to clean, dry, intact skin
    b. do not apply to open wounds, eyes, or mucous membranes
    c. Do not cover with occlusive dressings
    d. DO not apply heat, sunscreens, cosmetics, lotions, moisturizers, insect repellents, or other topical medications to affected area
    e. Showering/bathing should be avoided for ≥1 hour following application
    f. Wash hands immediately after application (unless hands are treated joint, then wait ≥1 hour to wash hands)
    g. Avoid sunlight to exposure areas.
    h. Avoid wearing clothes or gloves for ≥10 minutes after application

36. Capsaicin topical
    a. Mechanism of Action
       exact mechanism of action unknown
    b. selectively binds nerve membrane TRPV1 receptors, initially stimulates then desensitizes and degenerates cutaneous nociceptive neurons
    c. substance P depletion may also reduce pain impulse transmission to the CNS

37. SalonPAs

38. Nonpharmacologic Therapies
    a. Moist heat to help diminish muscle spasm and relieve stiffness
    b. Weight loss if the patient is overweight
    c. Reduce joint stress
    d. Exercises to strengthen the muscles surrounding the involved joint(s)
    e. fitness program to maintain flexibility involved joint through swimming, walking, cycling, and isometric exercises
    f. Use of assistive devices to help with ambulation and activities of daily living

39. NSAIDS
    a. 6 major classes Nonsteroidal Anti-Inflammatory Agents
        i. Salicylates
        ii. Propionic acid derivatives
        iii. Acetic acid derivative s
        iv. Enolic acid derivatives
        v. Anthranilic acid derivatives
        vi. Selective COX-2 inhibitors
    b. Acetic Acid NSAIDs
        i. Etodolac (Lodine):
        ii. Indomethacin (Indocin):
        iii. Nabumetone (Relafen):
        iv. Sulindac (Clinoril):
        v. Tolmetin (Tolectin):
    c. Enolic acid NSAID
        i. Piroxicam (Feldene): 10–20 mg/d PO
    d. Fenamic acid NSAID
        i. Meclofenamate (Meclomen): 200–400 mg/d PO 3–4 dose
    e. Phenylacetic acid NSAIDs
        i. Diclofenac sodium (Voltaren):
            1. OA: 100–150 mg/d PO in 2–3 divided doses
        ii. Diclofenac potassium (Cataflam):
            1. RA: 100–200 mg/d PO in 2–4 divided doses

f. Propionic acid NSAIDs
    i. Fenoprofen (Nalfon):
        1. 800–3,200 mg/d PO in 3–4 divided doses
    ii. Ibuprofen (Motrin):
        1. 1,200–3,200 mg/d PO in 3–4 divided doses
    iii. Naproxen (Naprosyn):
        1. 500–1,500 mg/d PO in 2 divided doses
g. Salicylic acid NSAIDs
    i. Diflunisal (Dolobid): 500–1,500 mg/d PO in 2–3 doses
    ii. Aspirin: 2.4–3.6 g/d PO in 4–6 divided doses
        1. max daily dose is 5.4 g
h. COX-2 selective NSAIDs
    i. Celecoxib (Celebrex): 200–400 mg/d PO in 2 divided doses

i. **Important factors for Prescribing

40. Nonacetylated Salicylates

a. Diflunisal
b. Sodium salicylate
c. Choline salicylate
d. Magnesium salicylate
e. Choline magnesium trisalicylate
f. Salsalate

41. GOUT Pharmacotherapeutics
a. Gout Starting points
    i. Gout is the most common form of inflammatory arthritis in the United States
        1. incidence of gout in America has increased over the last 20 years
        2. estimated to affect 8.3 million Americans (4%)
        3. due to the improved diagnosis
        4. but also the increasing number of patients with obesity, hypertension, thiazide diuretic use, and alcohol intake.
    ii. most common joint affected >>is the metatarsophalangeal joint; also, midtarsal joints, ankles, knees, fingers, wrists, and elbows.

b. Defined as:

i. inflammatory condition that results from monosodium urate crystals precipitating in the synovial fluid between joints due to hyperuricemia.
ii. monosodium urate crystals form due to hyperuricemia either from over production or under excretion of uric acid.

Risk factors	Prevention
Obesity, dietary factors, ETOH intake HTN, HLD, CVD, DM Chronic kidney dz of any levels Age, gender, ethnicity Genetic variants	Limit ETOH excessive dietary purine containing foods Correct vitamin deficiency B12 Drug induced hyperuricemia Diuretics (both loop and thiazide) Low dose salicylates Others_____

42. Acute vs Recurrent RX

acute gout	recurrent gout
nonsteroidal anti- inflammatory drug (NSAID) colchicine Corticosteroid Halt the inflammatory cascade	2-3 weeks post-acute episode suppressive therapy +allopurinol Or febuxostat lesinurad probenecid intravenous pegloticase

43. Combination Therapy: Acute Gouty Arthritis
    a. Colchicine + NSAID
    b. Oral corticosteroid + colchicine
    c. Intra-articular steroid + (NSAID OR colchicine OR oral corticosteroid)

44. Colchicine/Colcrys
    a. Antigout agent
    b. Mechanism of Action
        i. exact mechanism unknown
        ii. in gout, concentrates in PMN cells and inhibits microtubule polymerization, preventing neutrophil migration and activity related to gout sx
    c. Narrow therapeutic index

i. Drug accumulation is associated with severe, including fatal, consequences
ii. During use, close monitoring for signs/symptoms of colchicine toxicity

d. **Factors contributing to colchicine accumulation
   i. hepatic/renal function or concomitant interacting medications, are essential to be aware of
   ii. Especially important when titrating the dose upwards and with prolonged or repeated courses

e. Metabolism: liver
   i. CYP450: 3A4 substrate
f. Excretion:
   i. urine 40-65%, bile
g. Half-life:
   i. 26.6-31.2h

h. Baseline/Monitoring Parameters
   i. Cr at baseline
   ii. CBC if long-term use

i. Common reactions:
   1. N/V/D
   2. Abdominal pain and cramping
   3. Fatigue
   4. Headache
   5. Pharyngolaryngeal pain
   6. Serious reactions
   7. Myelosuppression
   8. Rhabdomyolysis
   9. Hepatic or nephro toxicity

j. Drug interactions
   1. cyclosporine; nefazodone; tipranavir
   2. clarithromycin or telithromycin
   3. itraconazole or ketoconazole
   4. HIV/AIDS medicines
   5. Digoxin
   6. cholesterol-lowering meds
   7. liver disease or kidney disease
   8. Myelosuppression effects
   9. Avoid/limit _____

ii. Able to use in pregnancy
iii. Caution for lactation/breastfeeding
iv. Caution on elderly or debilitated patients

45. Allopurinol/ZYLOPRIM
    a. xanthine oxidase inhibitor
    b. Mechanism of Action
        i. inhibits xanthine oxidase, interfering w/ conversion of hypoxanthine and xanthine to uric acid
        ii. reduces the production of uric acid
    c. It should not be started during an acute attack as it might prolong the attack or precipitate more attacks.
    d. Goal =
        i. reduce uric acid level <6 mg/dL to prevent supersaturation and crystal formation
        ii. serum urate target level of 6 mg/dL
    e. Adjust dose to reach targets
    f. Genetic polymorphism
        i. AA & Asian & Pacific Islander HLA-b5801
        ii. Caution usage
    g. Baseline/monitoring parameters
        i. BUN/Cr at baseline
        ii. then if decr. renal fxn or concurrent illness affecting renal fxn cont. periodically
        iii. LFTs during early Tx if hepatic dz
    h. Renal:
        i. Crcl 10-50: 50% dose reduction
        ii. Crcl <10: 70% dose reduction
        iii. may titrate dose based on serum uric acid levels
    i. Hepatic: no defined dosing changes

46. ADR's
    a. Common
        i. Rash, diarrhea, nausea, pruritis, urticaria, drowsiness
        ii. LFTs elevation
        iii. Eosinophilia
        iv. Gout exacerbation
    b. Serious
        i. Severe skin reactions
        ii. Myelosuppression

47. Important information

a. Medication interactions
    i. Cyclosporine, ampicillin or amoxicillin, coumadin/warfarin or Jantoven
    ii. Diuretic pill
    iii. Better choice than febuxostat for patients with CV disease

48. Foods and Beverages
    a. Red meat:
        i. specifically, organ meat: Kidney; liver; sweetbreads
    b. Seafood:
        i. Sardines; shellfish
    c. High-fructose corn syrup:
        i. Sodas or sports drinks; foods containing high levels
    d. Alcohol:
        i. Especially beer; also, wine and spirits

49. Rheumatoid Arthritis Starting points
    a. In 2008, approximately 0.6% of the adult population in the United States had RA
    b. with the prevalence in women about twice of that in men (Helmick et al., 2008).
    c. New onset of RA is seen throughout the life span
        i. including infancy; most cases occur in the fifth or sixth decade.
        ii. higher rate of disability and mortality compared to patients of similar age without RA.
    d. With increasing use of DMARDs, especially early in the disease process, these risks appear to have normalized (Kroot et al., 2000).\
    e. Defined as
        i. Chronic autoimmune inflammatory disease characterized by symmetric polyarthritis and joint changes, including erythema, effusion, and tenderness.
        ii. The course of RA is characterized by remissions and exacerbations.
        iii. RA can affect several organs, but it usually involves synovial tissue changes in the freely movable joints (diarthroses)
    f. Goals of treatment
        I. Control Synovitis
        II. Prevent joint injury
        III. Achieve low disease activity, maintain remission, by using DMARDS early in disease state
        IV. Require specialized treatment by rheumatologist
    g. General information
        i. Pretreatment evaluation
        ii. CBC, BUN/creat, ESR, CRP, LFT's
        iii. Serology_____
        iv. Ophthalmologic eval
        v. TB testing

vi. DMARDS: methotrexate (MXT), hydroxychloroquine (HCQ), sulfasalazine (SSZ)
vii. Corticosteroids and NSAIDS

h. Nonpharmacological RA treatments

i. Included as a component of treatment for patients with rheumatoid arthritis

ii. Patient education about the disease process

iii. Psychosocial interventions

iv. Rest, exercise, and PT/OT

v. Nutritional and dietary counseling

i. WHAT the NP needs to know
i. Hepatitis B and C status
ii. purified protein derivative (PPD)
iii. CBC
iv. LFTs
v. ***need to be checked before starting DMARDs or biologic agents****
vi. ****Refer to the rheumatologist ****

Disease-Modifying Antirheumatic Drugs

50. Preferred csDMARDs
a. Methotrexate (Rheumatrex):
i. 7.5 mg/wk in single dose, up to 25 mg/wk
b. Sulfasalazine (Azulfidine):
i. 500–1,000 mg/d in divided doses; may increase up to maximum 3 g/d
c. Hydroxychloroquine (Plaquenil):
i. 400–600 mg/d in divided doses
d. Leflunomide (Arava):
i. 100 mg PO daily for 3 days; 20 mg daily thereafter

51. Nonpreferred csDMARDs
a. d-penicillamine (Depen, Cuprimine):
i. 125 mg/d as single dose; may increase at monthly intervals to maximum daily dose of 1.5 g
b. Azathioprine (Imuran):
i. 50–100 mg in single daily dose; can increase after 6–8 wk; 3.5 mg/kg is maximum daily dose

c. Cyclophosphamide (Cytoxan, Neosar):
    i. 1 mg/kg/d increased to 2 mg/kg/d after 6 wk
d. Cyclosporine A (Sandimmune, Neoral):
    i. 5 mg/kg/d divided into 2 doses

52. tsDMARD
a. Tofacitinib (Xeljanz): 5 mg PO twice a day

53. Biologic DMARDs
a. Etanercept (Enbrel):
    i. 25 mg SQ twice weekly or 50 mg SQ weekly
b. Infliximab (Remicade):
    i. 3 mg/kg IV infusion at baseline, 2 wk, 6 wk, then every 8 wk thereafter
c. Adalimumab (Humira):
    i. 40 mg SQ every other week; 40 mg weekly as monotherapy
    ii. Close monitoring related to easy side effect and toxicity profile (narrow therapeutic windows)
    iii. Multiple lab and radiologic testing while on therapy
    iv. Will vary at onset of treatment, within treatment and evaluating for side effects via H&P
    v. Concern for any infectious symptomology

d. Methotrexate
    i. admin. only under supervision of physician experienced w/ antimetabolite tx
    ii. use only in life-threatening neoplastic dz or for severe, recalcitrant, disabling psoriasis or RA not responsive to other tx
    iii. deaths reported w/ use in malignancy, psoriasis, and RA
    iv. closely monitor for bone marrow, liver, lung, and kidney toxicities
    v. caution w/ high dose osteosarcoma regimens, high dose regimens for other neoplastic dz are investigational w/o demonstrated therapeutic advantage

54. adalimumab/HUMERA
a. TNF blocking agent
b. Interaction Characteristics:
c. immunosuppressive effects
d. Other Info
    i. caution advised w/ narrow therapeutic index drugs
    ii. chronic inflammatory conditions may alter metabolic enzyme formation
    iii. tx w/ immune modulators may reverse this effect, resulting in altered levels of concomitant drugs
e. CONTRAINDICATED

i. Any live or attenuated vaccine

f. Monitoring Parameters
   i. HBsAg at baseline
   ii. active HBV infection s/sx at baseline, during and for several months after D/C tx if HBV carrier
   iii. TB test at baseline, then periodically; active TB s/sx
   iv. dermatologic exams, especially if incr. skin CA risk

g. Metabolism:
   i. Unknown
   ii. CYP450: unknown

h. Excretion:
   i. Unknown

i. Half-life:
   i. 2wk

j. Mechanism of Action: binds and inhibits tumor necrosis factor alpha, reducing inflammation and altering immune response

1. 40 mg/0.8 mL (1 box, 2 trays): $3,617.02
2. 40 mg/0.8 mL (1 box, 2 trays): $3,710.92
3. 20 mg/0.4 mL (1 box, 2 trays): $5,329.48

55. Special Populations: Geriatric
   a. Caution should be used when starting elderly patients on NSAIDs due to the increased risk of GI hemorrhage.

   b. Many elderly patients have decreased renal function, and NSAIDs may contribute to a decline in this function.

   c. Several DMARDs and some immunomodulators are renally excreted, and doses should be adjusted in the elderly due to decreased renal function.

56. Patient Education
   a. Drug information
   b. Necessary blood work
   c. Patient-oriented information sources
   d. Nutrition/lifestyle changes
   e. Complementary and alternative medications