Disclosures

- Drs. Resman-Targoff and Longyhore declare no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria.

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Learning Objectives

1. Compare and contrast the available biologic and non-biologic DMARDs for RA, and apply to a patient based on his or her characteristics.
2. Formulate a care plan to help patients decrease their uric acid concentration, gout symptoms, and gout attacks using non-pharmacologic and pharmacologic interventions.
3. Evaluate and select medications to prevent fragility fractures from osteoporosis when patients are unable to tolerate or discontinue use of bisphosphonates.
4. Describe a stepwise approach to minimize pain and maximize functionality in patients with osteoarthritis.
5. Provide patients with education to support adherence.

According to the 2015 ACR guideline for treatment of rheumatoid arthritis, if not contraindicated, first line therapy recommended for RA with high disease activity should be:

A. Nonsteroidal antiinflammatory drug
B. Methotrexate monotherapy
C. Combination traditional DMARDs
D. Tumor necrosis factor inhibitor with methotrexate
Urate-lowering therapy is started on a patient who had his 2nd gout attack in the past year. He has no visible tophi. The serum urate goal for him is less than:

A. 3 mg/dL  
B. 5 mg/dL  
C. 6 mg/dL  
D. 7 mg/dL

In studies, the percentage of patients adherent to chronic hyperuricemia therapy is as low as:

A. 18%  
B. 28%  
C. 38%  
D. 48%

Which of the following medications used to treat osteoporosis has a similar serious adverse event profile to the bisphosphonates?

A. Raloxifene  
B. Teriparatide  
C. Denosumab  
D. Calcitonin

When comparing topical NSAIDs to oral NSAIDs, which adverse event is less likely to happen with a topical NSAID?

A. Gastrointestinal upset  
B. Local skin reactions  
C. Heart failure  
D. Renal insufficiency

Rheumatoid Arthritis

- Most common adult autoimmune inflammatory arthritis  
- Prevalence: 1% of population; all populations affected  
- F>M 2-3 fold (less than for lupus)  
- Peak onset 50-75 y, but can occur at any age  
- Joint involvement & extra-articular manifestations  
- Affects quality of life & productivity  
- Can increase mortality  
- Recent progress in understanding disease and new drugs and regimens can prevent deformities, maintain quality of life, and achieve remission

Patient

- A 35-year-old woman presents with a 2-month history of joint pain and swelling in several proximal interphalangeal (PIP) and metacarpophalangeal (MCP) joints bilaterally. Has wrist and knee pain. Takes OTC ibuprofen for pain; denies allergies. Reports morning stiffness of 1 h duration. 20 pack-year smoking history; denies use of alcohol or illicit drugs.  
- PE: soft tissue swelling and tenderness of 2nd and 3rd finger PIPs, tenderness of two MCPs bilaterally, tenderness and effusion of left wrist with decreased range of motion, and effusion in both knees.
Patient

- Labs: Chemistries are normal. Hb 10.8 g/dL, erythrocyte sedimentation rate (ESR) 40 mm/h, C-reactive protein (CRP) 15 mg/L, positive rheumatoid factor at 62 IU/mL, and anti-cyclic citrullinated peptide (anti-CCP) > 250 units.

- Does she have rheumatoid arthritis?

ACR/EULAR 2010 RA Classification Criteria

- Designed for early diagnosis of RA (for use in studies)
- Patients with ≥ 1 swollen joint
- Points assigned in 4 categories
- Score ≥ 6 classifies patient as having definite RA


Patient

- How should our patient be treated?
  A. Hydroxychloroquine
  B. Infliximab
  C. Leflunomide
  D. Methotrexate
  E. Sulfasalazine
  F. Methotrexate-sulfasalazine-hydroxychloroquine

ACR/EULAR 2010 RA Classification Criteria

- Joint involvement
  - # small & large joints involved
- Serology
  - Rheumatoid factor +/- anti-citrullinated peptide antibody
- Acute phase reactant
  - Erythrocyte sedimentation rate (ESR) +/- C-reactive protein (CRP)
- Sx duration
  - < 6 wk vs. ≥ 6 wk
- Our patient’s score: 10 (definite RA)


Patient

- What adjunctive therapy could be added for bridging until her disease-modifying treatment takes effect?
  A. Intramuscular methylprednisolone
  B. Oral naproxen
  C. Oral prednisone
  D. Topical diclofenac

2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis

Disease-Modifying Antirheumatic Drugs Approved For RA (Nonbiologic) 2015 Guideline

- Included
  - Hydroxychloroquine
  - Leflunomide
  - Methotrexate
  - Sulfasalazine

- Not included
  - Azathioprine
  - Cyclosporine
  - Minocycline
  - Gold

Biologic & Targeted Synthetic Drugs Approved For RA Included in 2015 Guideline

- Non-TNF Biologics (Target)
  - Abatacept (T cell costimulation)
  - Tocilizuab (IL-6)
  - Rituximab (B cells)

- Small Molecule
  - Tofacitinib (Janus kinase)

ACR Rheumatoid Arthritis Treatment

- Disease-Modifying Antirheumatic Drug (DMARD)-naïve
- Early (< 6 months duration) or established (≥ 6 months)
- Low or moderate-high disease activity
- DMARD monotherapy preferred over combination
  - Methotrexate preferred
- Consider low dose (< 10 mg prednisone or equivalent), short-term (< 3 months) corticosteroid if moderate-high disease activity when DMARD initiated and for flares
  - Lowest possible dose & shortest duration

According to the 2015 ACR guideline for treatment of rheumatoid arthritis, if not contraindicated, first line therapy recommended for RA with high disease activity should be:

A. Nonsteroidal antiinflammatory drug
B. Methotrexate monotherapy
C. Combination traditional DMARDs
D. Tumor necrosis factor inhibitor with methotrexate

Rheumatoid Arthritis Treatment Goal

REMISSION

Low Disease Activity
Rheumatoid Arthritis Treatment Goal
Disease Activity Measures

- Clinical Disease Activity Index
- Disease Activity Score with 28-joint counts (erythrocyte sedimentation rate or C-reactive protein)
- Patient Activity Scale (PAS)
- Patient Activity Scale-II (PAS-II)
- Routine Assessment of Patient Index Data with 3 measures (RAPID-3)
- Simplified Disease Activity Index


Rheumatoid Arthritis Treatment Goal
Patient Concerns

- Consider personal goals
  - Work productivity
  - Daily routines
  - Social & leisure activities
  - Emotional well-being
  - Daily pain & fatigue
- Surveys
  - Good Days Fast
  - Getting to Your Destination Faster


Rheumatoid Arthritis Treatment Goal
Remission

- Each of the following ≤ 1:
  - Tender joint count
  - Swollen joint count
  - C-reactive protein concentration (mg/dL)
  - Patient global assessment


Patient

- What vaccines should be considered for our patient?
  A. Hepatitis B
  B. Herpes zoster
  C. Influenza
  D. Pneumococcal

Immunizations - Considerations

- Administer vaccines before starting immunosuppressive drugs if possible
- Give pneumococcal & annual flu vaccines regardless of therapy
- Give other inactivated vaccines as warranted


Immunizations - Considerations

- Live vaccines contraindicated in patients receiving biologics or tofacitinib
  - Or prednisone-equivalent doses >20 mg/day for >2 weeks
  - Or high doses of other immunosuppressive drugs
- Live vaccines: measles-mumps-rubella, varicella, zoster, intranasal influenza, BCG, and yellow fever
  - Up to 61% increased risk herpes zoster in patients taking TNF inhibitors
  - Herpes zoster vaccine should be given before biologic or tofacitinib for patients aged ≥ 50 years
- Give live vaccines at least 2 weeks before biologic or tofacitinib or 1-3 months after stopping


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**Methotrexate**

- Screen for hepatitis, alcohol use before starting
- Screen for pregnancy; counsel about pregnancy & contraception
- Counsel about smoking cessation
- Monitoring complete blood count, liver transaminases, serum creatinine at baseline and:
  - Every 2-4 weeks up to 3 months
  - Every 8-12 weeks from 3-6 months
  - Every 12 weeks after 6 months


**Methotrexate**

- Label vial with day of week based on patient preference
- Give with folic acid
- Increase dose
- Split oral dose over 15 mg, give 8 h apart
  - Decreased absorption due to saturation of reduced folate carrier
- Consider changing from oral to subcutaneous route
- Over 1/3 patients will respond to methotrexate monotherapy


**Patient**

- Her oral methotrexate dose is increased over three months and she still has moderate disease activity. What should be tried next?

  A. Subcutaneous methotrexate
  B. Methotrexate-sulfasalazine-hydroxychloroquine
  C. Etanercept monotherapy
  D. Adalimumab-methotrexate

**ACR Rheumatoid Arthritis Treatment**

- Early or established RA with moderate or high disease activity despite monotherapy
  - Combination traditional DMARDs
  - Tumor necrosis factor (TNF) inhibitor +/- methotrexate (MTX)
  - Non-TNF biologic +/- MTX
- Established RA:
  - Alternative: Tofacitinib +/- MTX


**Combination Traditional DMARDs**

- About 1/3 patients will respond to triple therapy for RA after failing MTX
- Lower cost than biologics
- No evidence that delay in starting biologics has long-term disadvantages
- Sulfasalazine - laboratory monitoring as with methotrexate
- Hydroxychloroquine
  - Baseline ophthalmologic exam
  - If at low risk, repeat after 5 years
  - If at high risk, repeat annually


**Response**

Response

• Response at 3 months predicts 6 & 12-month response
  – Data from 7 studies analyzed
  – Patients who improve at 3 months continue to improve
  – Can be used to modify therapy (or not)

• Simplified Disease Activity Index or Clinical Disease Activity Index assessed at 3 months
  – If change of 58% noted, 80% sensitive for achieving low disease activity (LDA) at 6 months
  – If < 50% SDAI response (minor), low negative likelihood ratio (LR) 0.28 for LDA, 0.07 for remission at 6 months
  – If SDAI 85% response (major), LR 9.2 for LDA, 6.2 for remission at 6 months


Patient

• She does not adequately respond to combination traditional DMARDs and her therapy will be changed to adalimumab and methotrexate.
• What needs to be done before starting the new regimen?
  A. Chest x-ray
  B. Tuberculin skin test
  C. Interferon-gamma release assay blood test
  D. Sputum for acid-fast bacilli

Patient

• With adalimumab and methotrexate, her rheumatoid arthritis goes into remission that is sustained for 6 months.
• Can her drugs be stopped?

Tuberculosis Screening

• Tuberculin skin test or IGRA blood test
  – IGRA = interferon gamma release assay
  – IGRA preferred if prior BCG vaccine
  – QuantiFERON-TB Gold or T-Spot TB
  • If positive, get chest x-ray
    – If negative, treat for latent Tb (> 1 month)
    – If positive, get sputum for AFB; if positive, treat for active Tb
  • If at risk, screen annually


Withdrawal of Treatment

• Tapering more likely to be successful than discontinuation of all therapy
• Reducing TNF inhibitor dose to half had 20% risk of flare vs. 50% when stopping
• May have better success if RA in remission vs LDA
• Better success if LDA for ≥ 6 consecutive months
• Average time to flare when deescalating biologic 14.7 mo
• Overall, > 1/3 patients with LDA or remission can taper or stop DMARD/biologic treatment therapy without flare in 1st yr
• Can lower costs and decrease risk of adverse events


Adherence

• Remission and low disease activity possible in RA
• Adherence to therapy and monitoring essential
• Must identify target and modify therapy to achieve
• Pharmacist counseling and ensuring timely refills essential
• Pharmacists may participate in monitoring and adjusting therapy
Key Points - Rheumatoid Arthritis
• Initiate therapy early
• Give appropriate immunizations
• Screen for tuberculosis before initiating biologics/tofacitinib
• Identify goal and adjust therapy to achieve it
• Use corticosteroids for flares
• Consider tapering therapy
• Control of inflammation through adherence to therapy can prevent deformities

Gout and Hyperuricemia
• Gout is the most common inflammatory arthritis
• 8.3 million in US (3.9% adults) have gout
• Gout cost is $27.4 million/year
• Prevalence increasing
  – Hypertension, obesity, metabolic syndrome, diabetes mellitus 2, renal disease, diuretic and low-dose aspirin use
• “Curable” (or at least controllable)
• One of chronic diseases with lowest adherence rates

Patient
• A 57-year-old man is hospitalized for left leg deep vein thrombosis. One morning on rounds, he reports that severe right great toe pain awakened him during the night. He has not had similar episodes previously. He has a history of hypertension. His medications include enoxaparin, warfarin, and hydrochlorothiazide. He reports no allergies. He drinks a 6-pack of beer daily.
• PE: Ht 5’7”, wt 195 lb. First metatarsophalangeal joint is red, swollen, & very tender. He can’t put weight on it. He has no visible tophi.
• Labs: CrCl is 95 mL/min; serum urate is 7.2 mg/dL.
• Does he have gout?

Primary Care Gout Diagnostic Rule
For Monoarthritis without Joint Fluid Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>2.0</td>
</tr>
<tr>
<td>Previous patient-reported arthritis attack</td>
<td>2.0</td>
</tr>
<tr>
<td>Onset within 1 day</td>
<td>0.5</td>
</tr>
<tr>
<td>Joint redness</td>
<td>1.0</td>
</tr>
<tr>
<td>First metatarsophalangeal (MTP) involvement</td>
<td>2.5</td>
</tr>
<tr>
<td>Hypertension or ≥ 1 cardiovascular disease</td>
<td>1.5</td>
</tr>
<tr>
<td>Serum uric acid &gt; 5.88 mg/dL</td>
<td>3.5</td>
</tr>
</tbody>
</table>

[Predictive values: positive 0.64, negative 0.87]
Our patient’s risk: 0.84

2015 ACR/EULAR Gout Classification Criteria
• Points assigned in categories (maximum 23 points)
  – Most considered positive if ever present
  – ≥ 8 points classifies patient as having gout for studies
• If sufficient criterion not met:
  – Clinical
    • Involvement pattern
    • Characteristics of symptomatic episode
    • Time course
    • Clinical evidence of tophus

2015 ACR/EULAR Gout Classification Criteria
• For qualifying for studies
• Identifies patients with acute or intercritical gout
• Sensitivity 92%, specificity 89%
• Entry criterion: ≥ 1 episode swelling, pain, or tenderness in peripheral joint or bursa
• Sufficient criterion: monosodium urate crystals in symptomatic joint, bursa, or tophus

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2015 ACR/EULAR Gout Classification Criteria

- If sufficient criterion not met:
  - Laboratory
    - Serum urate (4 points subtracted if < 4 mg/dL)
    - Synovial fluid analysis (2 points subtracted if no MSU)
  - Imaging
    - Evidence of urate deposition
    - Evidence of gout-related joint damage (erosions)
- Our patient’s score: 7

http://goutclassificationcalculator.auckland.ac.nz/

Patient

- How should our patient be treated?
  A. Anakinra
  B. ACTH
  C. Colchicine
  D. Indomethacin
  E. Intraarticular triamcinolone hexacetonide
  F. Prednisone

Patient

Acute Gout Attack Treatment

- Suppress inflammation
- Treat pain

2012 American College of Rheumatology Guidelines for Management of Gout


Pharmacologic Treatment - Gout

- Nonsteroidal antiinflammatory drugs
- Colchicine
- Corticosteroids (systemic, intraarticular)
- ACTH
- If refractory, intolerant, or others contraindicated - interleukin-1 inhibitor (off label) - anakinra, canakinumab


Nondrug Treatment - Gout

- Topical ice
- Rest inflamed joint(s) 1-2 days

Colchicine Mechanism

- Inhibits neutrophil function & inflammatory response to urate crystals
- Persists in neutrophils 10 d after dose

![Neutrophil Diagram](image)

Colchicine Dosing

- Start within 36 h of attack onset
- Two 0.6 mg tab then one after 1 h
  - Previously dosed until:
    - Pain relief
    - Diarrhea, nausea, vomiting occur
    - 4-6 mg ingested
  - Screen for drug interactions; adjust dose if needed
  - Monitor for GI effects
  - Baseline CBC, BUN/Cr, LFTs
  - CBC & CK within 6 months of initiation if still being given

Patient

- What urate-lowering therapy should be started?
  A. Allopurinol
  B. Febuxostat
  C. Lesinurad
  D. Probenecid
  E. Pegloticase
  F. None

When to Treat Hyperuricemia

- Confirmed gouty arthritis diagnosis and
  - 2 or more gout attacks/year
  - Tophi
  - Chronic kidney disease stage 2 or worse
  - Past urolithiasis

Nondrug Treatment - Hyperuricemia

- Weight loss
- Diet
  - Avoid organ meats, alcohol overuse or any during gout flare
  - Limit alcohol (especially beer), red meats, sardines, shellfish, naturally sweet fruit juices, sugar, salt, high fructose corn syrup-sweetened drinks, energy drinks
  - Encourage low-fat or non-fat dairy products, vegetables
- Diet & fitness decrease serum urate by 10-18%
- Cherry juice concentrate/cherries??
- Stop drugs that increase serum urate (e.g., diuretics)

Patient

- 5 years later, the same patient comes into your pharmacy and asks for something to treat his hot, swollen, painful wrist. He tells you about his prior gout episode, but doesn’t think this is gout because it involves his wrist. He admits to not following lifestyle changes and not following up with his provider.
- You notice tophi on his ears and fingers.
- You refer him to his provider and he receives treatment for an acute gout attack. His CrCl is 45 mL/min and his serum urate is 8 mg/dL.
Patient
- What urate-lowering therapy should be started?
  A. Allopurinol
  B. Febuxostat
  C. Lesinurad
  D. Probenecid
  E. Pegloticase
  F. None

Hyperuricemia Management
- Lower serum urate to target
- Prevent gout flare

Why Treat Hyperuricemia
- Hyperuricemia = serum urate > 6.8-7 mg/dL
  - When fluids supersaturated, crystals precipitate
- Prevent acute gout attacks/chronic gouty arthritis
- Prevent/eliminate tophi/chronic tophaceous gouty arthropathy
- Prevent/eliminate urate nephrolithiasis
- Prevent chronic interstitial nephropathy due to monosodium urate (MSU) deposition in renal medulla
- Role in cardiovascular/metabolic comorbidities?

Reasons for Not Achieving Goal
- Lack of monitoring
- Not treating to goal
- Fear of increasing drug doses
  - Especially with chronic kidney disease
- Experiencing attack when starting urate-lowering drug
- Lack of patient education
  - Patient confusion about drugs to relieve vs. prevent acute flares
- Not recognizing underlying cause of hyperuricemia

Consider Causes of Hyperuricemia
- Overproduction
  - Inherited - HGPRT deficiency (Lesch-Nyhan syndrome), PRPP synthetase overactivity
  - Psoriasis
  - Myeloproliferative disease, tumor lysis syndrome
  - Ethanol, diet
- Underexcretion
  - Lead intoxication (“Saturnine” gout)
  - Medications (e.g., diuretics, calcineurin inhibitors, niacin)
  - Ethanol

Drug Treatment - Hyperuricemia
- Xanthine oxidase inhibitor (allopurinol, febuxostat)
- Alternative if CrCl ≥ 50 mL/min, probenecid
- If dose-optimized xanthine oxidase inhibitor inadequate, add uricosuric drug [probenecid, lesinurad, or (off-label) fenofibrate or losartan]
- Severe refractory disease - uricase (pegloticase)
  - Very expensive; may develop antibodies - limit future use
- Start urate lowering therapy when on effective treatment or after acute attack subsides
- If on urate-lowering therapy, continue during attack

**Xanthine Oxidase Inhibitors**

- Hypoxanthine
- Xanthine
- Uric acid

**Allopurinol**

- Starting dose 100 mg/d
  - For chronic kidney disease stage 4 or worse, start at 50 mg/d
- Maximum dose 800 mg/d
  - Split dose if > 300 mg/d
  - < 50% patients reach goal if dose ≤ 300 mg/d
  - < 5% patients receive doses > 300 mg/d
  - Educate & monitor patients on > 300 mg/d for rash, pruritus, ↑ LFTs
- Consider HLA-B*5801 testing in patients at high risk for allopurinol hypersensitivity reactions
  - Koreans with stage 3 or worse CKD, Han Chinese, Thai

**Uricosurics**

- URAT1
- OAT4
- URAT1 = uric acid transporter 1
- OAT = organic anion transporter

**Uricase**

- Uric acid
- Allantoin
Serum Urate Goal

Urate-lowering therapy is started on a patient who had his 2nd gout attack in the past year. He has no visible tophi. The serum urate goal for him is less than:

A. 3 mg/dL  
B. 5 mg/dL  
C. 6 mg/dL  
D. 7 mg/dL

Patient

• What prophylaxis should our patient receive when starting urate-lowering therapy?

A. Colchicine  
B. Naproxen  
C. Prednisone  
D. None

Prophylaxis

• Lowering uric acid can precipitate gout flare  
• Start prophylaxis before or when initiating urate-lowering  
• First line: low dose NSAIDs or colchicine  
• Second line: low dose prednisone/prednisolone

Prophylaxis

• Continue for greater of:  
  – 6 months or  
  – 3 months after target urate achieved & no initial tophi or  
  – 6 months after target urate achieved & initial tophi are gone
Adherence

- May be assessed by proportion of days covered (PDC)
  - Degree of prescription filling in a specified time
  - Adherent = PDC 80%
  - Partially adherent = PDC 20-79%
  - Nonadherent = PDC < 20%
- Pharmacy dispensing studies
  - Good adherence (≥ 80%) observed in 18-44% of patients
  - NOT GOOD!!!!!!

In studies, the percentage of patients adherent to chronic hyperuricemia therapy is as low as:

A. 18%
B. 28%
C. 38%
D. 48%


Pharmacist Gout Management

- Kaiser Permanente feasibility telephone study
  - 100 patients referred
  - Pharmacist provided educational and diet information
  - Protocol followed for initiation and titration of urate-lowering therapy
    - with lab assessment every 2 weeks until at target (≤ 6 mg/dL)
    - Began with allopurinol 100 mg/d, maximum 600 mg/d
    - Febuxostat or probenecid if allergy or adverse reaction
  - All received prophylaxis with colchicine 0.6 mg/d
    - 0.3 mg/d if eGFR < 30 mL/min
    - If still at target after 3 months, discharged from program


Pharmacist Gout Management

- Results
  - 78 of 95 patients achieved two consecutive SUA ≤ 6 mg/dL 3 months apart; 4 still in program
  - 4% completed program on 100 mg/d; 68% with 300 mg/d
  - Flares often associated with nonadherence
  - Pharmacist time to manage about 90 patients - 6-8 h/week
  - Rheumatologist time for oversight & assistance - ≤ 30 min/week
- Similar study with specialist nurse addressing lifestyle changes and dose titration (by phone or in person)
  - 96% of 106 patients achieved target SUA


Key Points - Gout/Hyperuricemia

- Acute gout treatment targets inflammation
- Hyperuricemia treatment must be monitored and have specific serum urate goal
- Gout prophylaxis should be given when starting urate-lowering therapy
- Adherence to urate-lowering therapy must be stressed

Osteoporosis

- PMH: Hypertension, (mild) stress incontinence, (intermittent) restless leg syndrome, and GERD
- Meds: amlodipine 10 mg, Benazepril 10 mg, chlorothalidone 25 mg, carbidopa/levodopa 10/100, famotidine 10 mg
Osteoporosis

"I just don't want to take alendronate. It makes me uncomfortable thinking about all the bad reactions and conditions people develop when they take that drug... or any drug like it."

Guidelines for treatment and/or prevention of osteoporosis

National Osteoporosis Foundation (NOF;2014)
United States Preventative Services Task Force (USPSTF; 2011/2013)
American Academy of Clinical Endocrinologists (AACE;2010)
North American Menopause Society (NAMS;2010)
American College of Physicians (ACP;2008)
American College of Obstetrics & Gynecology (ACOG;2012)

Who should be screened?

<table>
<thead>
<tr>
<th>Category</th>
<th>BMD</th>
<th>T-score</th>
<th>Antiresorptive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Within 1 SD of the mean of reference population</td>
<td>0 to -1</td>
<td>None</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>Between 1 and 2.5 SD below mean</td>
<td>-1 to -2.5</td>
<td>Yes if FRAX is &gt;20% or &gt;3%/</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>More than 2.5 SD below mean</td>
<td>At/Below -2.5</td>
<td>Yes</td>
</tr>
<tr>
<td>Severe Osteoporosis</td>
<td>More than 2.5 SD below mean with fracture(s)</td>
<td>At/Below -2.5 with fracture(s)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

What do the results mean?

- SD = standard deviation
- * >20% 10-year risk of major osteoporotic fracture; >3% 10-year risk of hip fracture

What do we need to consider?

What's the best?

<table>
<thead>
<tr>
<th>Medication</th>
<th>Absolute decrease in fracture incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Verterbral</td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td>5%</td>
</tr>
<tr>
<td>Raloxifene (ERA/A)</td>
<td>1.5%</td>
</tr>
<tr>
<td>Teriparatide (biosynthetic PTH)</td>
<td>10%</td>
</tr>
<tr>
<td>Denosumab (RANKL inhibitor)</td>
<td>2%</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>8%*</td>
</tr>
</tbody>
</table>

* %: 10-year risk of major osteoporotic fracture. -%: 10-year risk of hip fracture

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Are Janice’s concerns valid?

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo: 0-2 per 10,000</th>
<th>Bisphos: 0.67 to 1.27%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteonecrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-term bisphosphonate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious atrial fibrillation</td>
<td>Placebo: 0.66%</td>
<td>Bisphos: 0.67 to 1.27%</td>
</tr>
<tr>
<td>Sharma S et al. Chest 2013;144:1231-1233</td>
<td></td>
<td></td>
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<tr>
<td>Sharma S et al. Am J Cardiol 2014;114:1815-1821</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femur Fracture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical Femur Fracture</td>
<td>Bisphos (&lt;2 yrs): 1.8 per 100,000</td>
<td>Bisphos (8-9 yrs): 113 per 100,000</td>
</tr>
<tr>
<td>Cancer (esophagus)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of esophageal CA</td>
<td>Bisphos: 0.44 per 1,000 PYR</td>
<td>Bisphos: 0.48 per 1,000 PYR</td>
</tr>
<tr>
<td>Cardwell CR et al. JAMA 2015;304:607-63</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PYR: Person Years of Risk

Let’s evaluate other options.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonates</td>
<td>Esophageal cancer, osteonecrosis, femur fracture, atrial fibrillation</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>Prevent breast cancer in high risk women; DVT risk</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>Builds bone density; daily injections; will require antiresorptive therapy after it is discontinued</td>
</tr>
<tr>
<td>Denosumab</td>
<td>Injection once every 6 months; similar efficacy and risk profile as compared to bisphosphonates</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>Intranasal application; the most limited effect data</td>
</tr>
</tbody>
</table>

Which of the following medications used to treat osteoporosis has a similar serious adverse event profile to the bisphosphonates?

A. Raloxifene
B. Teriparatide
C. Denosumab
D. Calcitonin

Denosumab education

What is the medicine doing?
Denosumab works to inhibit the receptor activator involved in osteoclast formation (RANKL).

Slow the process by which the body resorbs bone

How (and where) is the medicine given?
1. Prescribed by a licensed prescriber
2. Provided by a pharmacy
3. Administered as a subcutaneous injection by a healthcare professional

Does the patient need any special directions or advice?
Single use prefilled syringe (needle attached). Pick up the medicine the day before you are scheduled to receive the injection. Do not use if it has been more than 14 days since the medicine was removed from the refrigerator. Set a reminder or schedule subsequent injections during your visit.
Janice had osteoporosis that required treatment, but she refused the traditional first-line medicine. Of the available options, denosumab was the best option for her based on her needs and preferences.

Key Points (Osteoporosis)

- Though the serious adverse events related to bisphosphonates are valid concerns for patients, they may not be clinically relevant given their scarce incidence.
- Denosumab has demonstrated a clinical effect on vertebral, nonvertebral, and hip fractures similar to that of the bisphosphonates.

Case 2

Fernando G. (Age 62)

PMH: Type 2 diabetes, CAD (DES 5 years prior), hypertension, gout, osteoarthritis of knees (bilateral), depression, and alcoholism

Meds: metformin 1000 mg, sitagliptin 100 mg, aspirin 81 mg, fosinopril 20 mg, atorvastatin 80 mg, amlodipine 5 mg, allopurinol 100 mg, escitalopram 10 mg

“My family doc, my cardiologist, my endocrinologist, and my wife keep nagging on me to exercise so I can lose weight. I know what I am supposed to do, but my knees hurt when I walk. I have enough trouble going shopping, let alone walking for exercise.”

Guidelines for osteoarthritis treatment

American Academy of Orthopaedic Surgeons (AAOS;2015)

American College of Rheumatology (ACR;2012)

What are the recommendations?

ACR 2012 Recommendations for Knee Osteoarthritis

We conditionally recommend that patients with knee OA should use one of the following:
- Acetaminophen
- Oral NSAIDs
- Topical NSAIDs
- Tramadol
- Intra-articular corticosteroid injections

We conditionally recommend that patients with knee OA should not use the following:
- Chondroitin sulfate
- Glucosamine
- Topical capsaicin

We have no recommendations regarding the use of intra-articular hyaluronates, duloxetine, and opioid analgesics.
**What do we need to consider?**

**What options are available?**

- Acetaminophen
- Oral NSAIDs
- Topical NSAIDs
- Tramadol
- Corticosteroid Injections

**Do NSAIDs & CV disease matter?**

*U.S. Department of Health and Human Services*

**U.S. Food and Drug Administration**

Protecting and Promoting Your Health

FDA Drug Safety Communication: FDA strengthens warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) can cause heart attacks or strokes


**Do NSAIDs & CV disease matter?**

Versus placebo for major vascular events

<table>
<thead>
<tr>
<th>Drug</th>
<th>RR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coxib</td>
<td>1.37 (1.14-1.66)</td>
<td>0.0009</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>1.41 (1.12-1.78)</td>
<td>0.0036</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>1.44 (0.89-2.33)</td>
<td>0.14</td>
</tr>
<tr>
<td>Naproxen</td>
<td>0.93 (0.69-1.27)</td>
<td>0.66</td>
</tr>
</tbody>
</table>

Versus placebo for heart failure

<table>
<thead>
<tr>
<th>Drug</th>
<th>RR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coxib</td>
<td>2.28 (1.62-3.20)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>1.20 (0.94-1.54)</td>
<td>0.015</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>2.49 (1.19-5.20)</td>
<td>0.0155</td>
</tr>
<tr>
<td>Naproxen</td>
<td>1.87 (1.10-3.16)</td>
<td>0.0197</td>
</tr>
</tbody>
</table>

**Do NSAIDs & CV disease matter?**

Versus COXIB for major vascular events

<table>
<thead>
<tr>
<th>Drug</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac</td>
<td>1.27 (0.84-1.72)</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>0.92 (0.85-1.58)</td>
</tr>
<tr>
<td>Naproxen</td>
<td>1.40 (1.06-1.83)</td>
</tr>
</tbody>
</table>

Versus COXIB for heart failure

<table>
<thead>
<tr>
<th>Drug</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac</td>
<td>1.23 (0.87-1.73)</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>0.83 (0.42-1.64)</td>
</tr>
<tr>
<td>Naproxen</td>
<td>1.17 (0.76-1.79)</td>
</tr>
</tbody>
</table>

**What about the topical NSAIDs?**

Several available commercially as gel or “packs”
- diclofenac
- ketoprofen
- ibuprofen
- piroxicam

Topical NSAIDs are expensive when compared to traditional, systemic NSAIDs.

Topical agents are **AS effective as systemic with LESS GI adverse events, but MORE** local skin reactions.

*B: commercially available gel
#prepackaged compounded product


Derry S et al. Cochrane Database Syst Rev. 2012;CD007400

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What about the topical NSAIDs?

Percent of patients meeting clinical outcomes using topical versus oral NSAID therapy.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Topical</th>
<th>Oral</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical success</td>
<td>479 / 877</td>
<td>462 / 858</td>
<td>1.02 (0.94-1.11)</td>
</tr>
<tr>
<td>Local reactions</td>
<td>182 / 846</td>
<td>47 / 805</td>
<td>3.74 (2.76-5.06)</td>
</tr>
<tr>
<td>GI reactions</td>
<td>167 / 1011</td>
<td>248 / 950</td>
<td>0.66 (0.56-0.77)</td>
</tr>
<tr>
<td>Trial withdrawals</td>
<td>121 / 1011</td>
<td>140 / 950</td>
<td>0.85 (0.68 – 1.06)</td>
</tr>
</tbody>
</table>

When comparing topical NSAIDs to oral NSAIDs, which adverse event is less likely to happen with a topical NSAID?

A. Gastrointestinal upset  
B. Local skin reactions  
C. Heart failure  
D. Renal insufficiency

Topical NSAID education

The delivery vehicle is important...
- Gel: may cause dry skin, erythema, itching
- Cream: may leave sticky film on the skin

Be cautious of how the medicine may be affected...
- Heating pads
- Occlusive dressings
- Sun (cold or wind) exposure

Price of topical preparations is significantly greater than that of oral preparations.

Case 2 conclusion

Fernando deals with (intermitent) osteoarthritis of his knee, which limits his ability to be physically active.

A topical NSAID may be his best option for as needed pain prevention/relief because it will provide the effect he desires with less adverse events.

Key Points (Osteoporosis)

- Though the serious adverse events related to bisphosphonates are valid concerns for patients, they may not be clinically relevant given their scarce incidence.
- Denosumab has demonstrated a clinical effect on vertebral, nonvertebral, and hip fractures similar to that of the bisphosphonates.

Key Points (Osteoarthritis)

- Vascular complications should be discussed with patients when recommending NSAIDs for chronic pain conditions.
- Naproxen may be the better option for reducing pain in osteoarthritis while minimizing the risk of vascular events.
- Topical NSAIDs offer the same pain relief (clinical success) as the oral NSAIDs, with less GI adverse events and more local skin reactions.