Bone/Joint and Rheumatology

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Learning Objectives

1. Systematically identify patients to screen for osteoporosis and use the screening results to guide the decision on how to treat the patient.
2. Use a STEPS-wise approach for comparing, recommending, and justifying a drug therapy regimen for osteoporosis.
3. Evaluate the severity and prognostic indicators of rheumatoid arthritis to choose the most appropriate initial regimen with disease-modifying antirheumatic drugs (DMARDs).
4. Identify appropriate health maintenance interventions when caring for a patient receiving biologic and nonbiologic DMARD therapy.
5. Select the most appropriate treatment regimen for psoriatic arthritis on the basis of patient limitations because of the disease.
6. Create an algorithm or a stepwise approach to minimize pain and maximize functionality in patients with osteoarthritis.
7. Choose a drug therapy for treating fibromyalgia syndrome, based on drug efficacy and a patient's comorbid conditions.
8. Select follow-up screenings or laboratory tests at correct intervals for patients with systemic lupus erythematous treated with hydroxychloroquine.
9. Formulate a care plan to help patients decrease their uric acid concentrations, gout symptoms, and gouty attacks by using nonpharmacologic and pharmacologic interventions.

Self-Assessment Questions

Answers and explanations to these questions can be found at the end of the chapter.

1. J.T. is a 68-year-old Cuban American woman returning to her primary care practitioner's office to review the results of her most recent dual-energy x-ray absorptiometry (DEXA) scan. Her physician reports that her L1–L4 T-score is −2.1 standard deviations (SDs) (Z-score: −1.1). The physician also reports that J.T. has a WHO (World Health Organization) Fracture Risk Assessment Tool (FRAX) score of 12% for major osteoporotic fracture and 4% for hip fracture. Which is the best action for J.T.'s physician to take in helping preserve her bone density?
   A. Start high-dose vitamin D (50,000 international units) weekly for 8 weeks and then 2000 units daily thereafter.
   B. Start calcium carbonate plus vitamin D (600 mg elemental plus 400 international units) twice daily.
   C. Start alendronate 35 mg weekly plus calcium/vitamin D supplementation.
   D. Start alendronate 70 mg weekly plus calcium/vitamin D supplementation.

2. M.Z. is a 71-year-old Hispanic woman, discharged from the local hospital 2 months ago after a right hip replacement secondary to a fall and fracture. She was prescribed alendronate 70 mg weekly, which she has been taking every Monday morning since discharge, as instructed. At this visit, she reports new symptoms of gastroesophageal reflux that persist for about 48 hours after each dose. Her provider confirmed that she was taking the drug properly, remaining upright for at least 30 minutes after each dose. She discontinues alendronate, and her symptoms subside. Which is the most appropriate way to continue treating M.Z.?
   A. Reinitiate alendronate 70 mg once weekly.
   B. Decrease alendronate to 35 mg once weekly.
   C. Start risedronate 35 mg once weekly.
   D. Start raloxifene 60 mg once daily.

3. C.A. is a 69-year-old woman with rheumatoid arthritis (RA). She is treated with oral methotrexate 15 mg once weekly, prednisone 10 mg once daily, and naproxen 500 mg twice daily as needed. On returning for a follow-up visit with her rheumatologist, she is instructed to continue prednisone 10 mg once daily for another 6 months. A recent DEXA report shows her lumbar spine T-score to be −0.6. According to the American College of Rheumatology (ACR), which approach is best to prevent osteoporosis?
   A. No intervention is required because the patient is premenopausal.
   B. Administer calcium carbonate 500 mg PLUS cholecalciferol 400 units twice daily.
   C. Administer risedronate 150 mg monthly PLUS calcium and cholecalciferol supplementation.
   D. Administer raloxifene 60 mg once daily PLUS calcium and cholecalciferol supplementation.

4. In which situation would the risk of an adverse event most outweigh the benefit of raloxifene to treat postmenopausal osteoporosis?
   A. 56-year-old woman with invasive breast cancer 3 years earlier.
   B. 62-year-old woman with lower extremity venous insufficiency and edema for 6 years.
   C. 58-year-old postmenopausal woman with an intact uterus and ovaries.
   D. 61-year-old woman with a history of an above-the-knee, idiopathic, deep venous thromboembolism 18 months earlier.

5. F.R. is a 62-year-old woman with RA. She is currently using etanercept 50 mg subcutaneously once weekly and ibuprofen 600 mg every 6 hours as needed for pain. At her latest visit to her primary care physician's office, she requested that her immunization history be reviewed and her immunizations be updated. If F.R. requires immunization today, which vaccine is *least* acceptable because of her RA therapy?
   A. Seasonal influenza vaccine (intramuscular).
   B. 23-Valent pneumococcal vaccine.
   C. Tetanus, diphtheria, pertussis (Tdap).
   D. Varicella zoster.

6. Which is the optimal time after diagnosis to start disease-modifying antirheumatic drug (DMARD) therapy?
   A. Less than 12 months.
   B. Less than 9 months.
   C. Less than 6 months.
   D. Less than 3 months.

7. Which agent for treating RA, although not free of risk, is most safe with respect to teratogenicity?
   A. Methotrexate.
   B. Leflunomide.
   C. Sulfasalazine.
   D. Minocycline.

8. G.S. is a 29-year-old unemployed and uninsured man (height 74 inches, weight 85 kg) with a diagnosis of RA and hypertension. His RA was diagnosed 7 months ago. Although he has been treated with methotrexate 20 mg orally once weekly for the past 5 months, he has not achieved low disease activity. His pain has been controlled with systemic corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs), but he requires additional treatment. Before starting methotrexate, he was classified as having high disease activity and had many factors indicative of a poor prognosis. According to the ACR, which is the most appropriate next step for this therapy?
   A. Increase methotrexate weekly dose.
   B. Change to methotrexate injection.
   C. Recommend rituximab now, 2 weeks later, and then every 24 weeks
   D. Recommend rituximab now, 2 weeks later, and then every 24 weeks plus hydroxychloroquine daily.

9. J.P. is a 34-year-old man with a medical history significant for psoriasis. For the past 15 years, he has been treated successfully with hydrocortisone cream and moisturizers, rarely requiring oral systemic corticosteroids. Today, he presents to his primary care physician's office with a worsening joint pain in his hands and hips. He says the pain is minimal (2/10), but annoying. He has been receiving sufficient pain relief from naproxen 500 mg twice daily as needed, but he wonders if he could be doing more. His physician performs some radiographic evaluations and determines that J.P. has symptoms of psoriatic arthritis. Given the patient's presentation, which is the best regimen to treat his arthritic symptoms?
   A. Continue naproxen 500 mg twice daily as needed.
   B. Begin sulfasalazine 1000 mg three times daily.
   C. Begin etanercept 50 mcg twice weekly.
   D. Begin etanercept 50 mcg twice weekly plus sulfasalazine 1000 mg three times daily.

10. J.O. is a 76-year-old woman with bilateral knee osteoarthritis pain that has not been sufficiently controlled with physical therapy, simple analgesics, systemic NSAIDs, or a short trial of opioid combination analgesics. She is unable to perform many activities of daily living because she requires a walker, which considerably impairs her mobility. Which regimen is best to help alleviate the patient's chronic pain?
    A. Glucosamine 1500 mg and chondroitin 1200 mg/day.
    B. Topical diclofenac 1% gel.
    C. Ketorolac 10 mg every 6 hours.
    D. Morphine sulfate extended release 15 mg twice daily.

11. T.Q. is a 29-year-old nonobese woman being treated with hydroxychloroquine for systemic lupus erythematosus (SLE) for the past 3 years. Her current dose is 400 mg once daily (about 5.4 mg/kg). She is speaking with her pharmacist, who asks her whether she has been receiving regular ophthalmologic screenings for patients chronically treated with hydroxychloroquine. The patient reports that she has never had her eyes checked. Which would be the best recommendation for currenth and future ophthalmologic screening for this patient?
    A. Initial screening now and then every 5 years.
    B. Initial screening now and then annually thereafter.
    C. Initial screening now and then annually starting at year 5.
    D. Initial screening now and then every 6 months starting at year 5.

12. R.V. is a 42-year-old woman with a significant history of depression and schizophrenia. Her current drug regimen is ziprasidone 40 mg twice daily and selegiline transdermal 6 mg/24 hours. She has symptoms consistent with fibromyalgia syndrome, but she has been reluctant to start treatment until now because she was afraid it would interfere with her other mental health medications. However, the symptoms have worsened during the past 6 months, and now she is requesting to start therapy. Which medication would be the best for R.V. to begin taking?
    A. Nortriptyline 25 mg once daily in the evening.
    B. Gabapentin 100 mg twice daily.
    C. Pregabalin 75 mg twice daily.
    D. Duloxetine 60 mg once daily.

13. L.L. is a 58-year-old man with chronic tophaceous gout and chronic renal insufficiency (creatinine clearance [CrCl] 32 mL/minute). The patient has 10–12 alcoholic drinks a day and regularly consumes a large amount of meat proteins. In addition to dietary counseling, which therapy below is best to initiate to decrease tophi and prevent gouty attacks in this patient?
    A. No therapy required until he experiences two or more gouty attacks in a 12-month period.
    B. Administer allopurinol 100 mg once daily.
    C. Administer allopurinol 300 mg once daily.
    D. Administer colchicine 0.6 mg three times weekly.

I. OSTEOPOROSIS

A. Clinical Guidelines
   1. 2011 U.S. Preventive Services Task Force (USPSTF)
   2. 2014 National Osteoporosis Foundation (NOF)
   3. 2010 ACR (glucocorticoid-induced osteoporosis)
   4. 2013 National Institute for Health and Care Excellence (NICE)

Table 1. Factors Associated with Decreased BMD and/or Osteoporotic Fractures

Age	Women > 65 years Men > 70 years	
Hormone deficiency	Estrogen deficiency in women Androgen deficiency in men	
Body habitus	Decreased BMI Calorie-restricted weight loss	
Social history	Smoking Alcohol use (>2 drinks per day) 120 mL of wine, 30 mL of liquor, 260 mL of beer High caffeine intake	
Medical history	Rheumatoid arthritis Cardiovascular disease Type 2 diabetes mellitus Celiac disease	Asthma/COPD Autoimmune disorders Hepatic disease History of falls
Drug-induced causes	Antiepileptic agents Immunosuppressants Lithium Proton pump inhibitors Systemic corticosteroids (>5 mg daily of prednisone or equivalent for 3 months or more) Selective serotonin reuptake inhibitors Excessive thyroid hormone supplementation Tricyclic antidepressants Warfarin or heparin (long-term use)	
Sex-specific factors	Women Anorexia nervosa Medroxyprogesterone depot use Excessive vitamin A intake Gastrointestinal malabsorption syndromes Parental history of osteoporosis Men Loop diuretic use Gonadotropin-releasing hormone agonists (prostate cancer) Psoriasis	

BMD = bone mineral density; BMI = body mass index; COPD = chronic obstructive pulmonary disease.

Abbreviated from: National Osteoporosis Foundation. Clinician's Guide to Prevention and Treatment of Osteoporosis. Washington, DC: National Osteoporosis Foundation, 2013.

Patient Case

1. F.R. is a 74-year-old woman with a history of a right hip replacement after a fall and fracture. In addition to her hip fracture, she has a history of type 2 diabetes mellitus (most recent hemoglobin A1C [A1C] reading 7.3%) and hypothyroidism (current thyroid-stimulating hormone concentration [TSH] 0.1 mIU/L), for which she receives treatment. A dual-energy x-ray absorptiometry (DEXA) finding revealed F.R.'s T-score at her femoral neck to be −2.7. The Z-score associated with her femoral neck T-score was −2.1. Her physician believes this was a fracture secondary to drug-induced bone density loss. Which medication most likely contributed to her bone mineral density (BMD) loss and fracture?

   A. Metformin.
   B. Glipizide.
   C. Levothyroxine.
   D. Lovastatin.

Table 2. Fracture Prevention Counseling (all individuals older than 50 years)

Calcium intake	*NOF*: Calcium 1000 to 1200 mg (elemental)/day from diet or supplementation *USPSTF*: 1000 mg (elemental)/day from diet or supplementation Milk, nonfat (1 cup): 300 mg Orange juice, fortified: 350 mg Cereal, fortified: 20–400 mg/serving Cheese (1 oz): 150–300 mg/serving
Vitamin D intake	*NOF*: 800 to 1000 units/day *USPSTF*: 400 units/day Cereals, fortified: 40 units Milk, nonfat (1 cup): 100 units Salmon (3 oz): 530 units Sunlight exposure (bare arms and legs for 15 minutes/day)
Exercise and physical activity	Walking Aerobics (low impact) Strength training
Social habit changes	Smoking cessation/avoidance Limited to moderate alcohol intake (<2 drinks/day) 120 mL of wine, 30 mL of liquor, or 260 mL of beer

NOF = National Osteoporosis Foundation; USPSTF = United States Preventive Services Task Force.

Table 3. Screening Recommendations

National Osteoporosis Foundation (2014)	U.S. Preventive Services Task Force (2011)	American Association of Clinical Endocrinologists (2010)
Women: >65 years Postmenopausal with clinical risk factors Menopausal woman with risk factors (low BMI, previous low-trauma fracture, high-risk medication use)	Women: ≥65 years without known fractures or secondary causes of osteoporosis Age 50–65 years with 10-year major osteoporotic risk (FRAX) > 9.3%	Women: ≥65 years ≤65 years at an increased risk of fracture, based on risk factors
Men: >70 years Age 50–69 years with clinical risk factors	Men: No recommendation	Men: No recommendation
Any adult: Fracture after age 50 years Condition associated with bone loss Use of medication associated with bone loss		

BMI = body mass index; FRAX = Fracture Risk Assessment Tool.

Table 4. Fracture Risk Assessment Tools

WHO FRAX	Available online at www.sheffield.ac.uk/FRAX Developed to assess a 10-year probability for hip or other major osteoporotic fracture For screening, results may be used to identify patients who require diagnostic evaluation with a DEXA scan , but it is not a definitive tool for deciding to treat a patient For treatment, results may be used to determine whether patients with osteopenia need pharmacologic treatment (see Figure 1)
ClinRisk QFracture	Available at http://qfracture.org Developed by ClinRisk Ltd. to assess the 10-year risk of developing an osteoporosis-related fracture in patients from the United Kingdom Consider diagnostic evaluation with a DEXA scan in the following situations: Women's 10-year risk calculated to be ≥8.75% Men's 10-year risk calculated to be ≥2.11%
Peripheral (Calcaneal) DEXA	Useful tool found in many community screenings This method of screening/assessment is useful for identifying individuals with a low BMD, but it should not be used as a diagnostic tool to quantify the severity of bone loss

BMD = bone mineral density; DEXA = dual-energy x-ray absorptiometry; FRAX = Fracture Risk Assessment Tool; WHO = World Health Organization.

B. Diagnostic Criteria
   1. Dual-energy x-ray absorptiometry
      a. Definitions
         i. T-score: Reports how many standard deviations (SDs) separate a patient's BMD compared with the BMD of a young, healthy adult of the same sex
         ii. Z-score: Reports how many SDs separate a patient's BMD compared with the BMD of another patient matched for age, sex, and ethnicity
      b. Measures the lumbar spine (1–4) and femoral neck of nondominant hip
      c. T-scores are based on the mean BMD for a healthy young man or woman.
         i. "Normal": 0–1 SDs below the mean value
         ii. Osteopenia: 1–2.5 SDs below the mean value
         iii. Osteoporosis: Greater than 2.5 SDs below the mean value
      d. The lumbar spine T-score is reported as the average of L1–L4. Consider a diagnosis of osteoporosis if two individual lumbar spine measurements are greater than 2.5 SDs below the mean, regardless of the lumbar spine average.
      e. If a patient's Z-scores are greater than 2 SDs below the mean, the result is usually indicative of accelerated bone loss unrelated to menopause and/or aging.
   2. Quantitative ultrasonography
      a. Does not measure BMD, but assesses fracture risk by using speed of sound and broadband ultrasound attenuation
      b. Not associated with radiation exposure
   3. Quantitative computed tomography: Able to predict fracture risk, but with greater radiation exposure than DEXA

Table 5. Additional Tests to Consider When Evaluating for Secondary Causes of Osteoporosis

25-Hydroxy-vitamin D	Alkaline phosphatase	Calcium, serum
Creatinine	Phosphate	Thyroid-stimulating hormone
Estradiol	Free testosterone	PTH (PTH intact)
Serum protein electrophoresis		

PTH = parathyroid hormone.

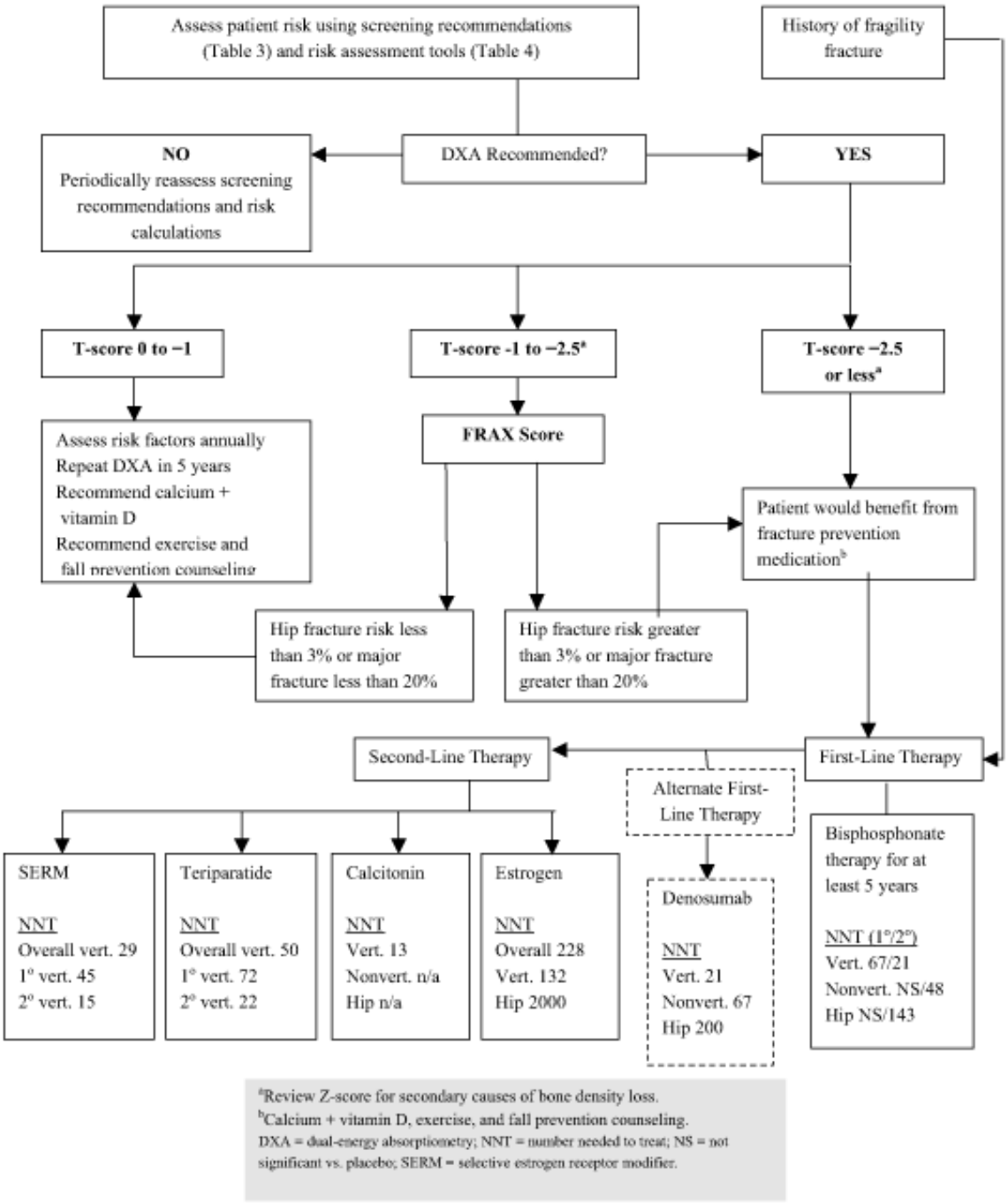

Figure 1. Osteoporosis evaluation and treatment algorithm.

Patient Cases

2. M.J. is a 71-year-old white woman consulting with her pharmacist about the best means to preserve her bone density and prevent a fracture. During the consultation, the pharmacist uses the FRAX tool to determine the patient's 10-year risk of a fracture. The patient weighs 68 kg (150 lb) and is 65 inches tall; her medical history is significant for a maternal hip fracture (age 71 years). Her 10-year risk of a major osteoporotic fracture is estimated at 19% and, for the hip, 6.3%. From these results, which is the best course of action for the pharmacist to take?
   A. Recommend that the patient contact her primary care provider to request a DEXA scan.
   B. Recommend that the patient contact her primary care provider to request a DEXA scan and start calcium plus vitamin D supplementation.
   C. Recommend that the patient contact her primary care provider to request a DEXA scan, start calcium plus vitamin D supplementation, and start taking a bisphosphonate.
   D. Recommend that the patient NOT have a DEXA scan and that she begin calcium plus vitamin D supplementation and start taking a bisphosphonate.

3. O.T. is a 65-year-old woman given a diagnosis of osteopenia after a scheduled DEXA scan. Her other medical conditions include type 2 diabetes mellitus, irritable bowel syndrome, gastroesophageal reflux disease, and migraine headaches. Her medications include metformin, pantoprazole, amitriptyline, and sumatriptan. She is an active woman who regularly participates in aqua aerobics and walking, and she uses laundry detergent bottles to strengthen her upper body. Her dietary calcium intake is limited to one glass of milk (8 oz each) per day. She has not yet started calcium, but she would like to add it to her medications and daily supplements. Which over-the-counter calcium regimen is best to recommend for her?
   A. Calcium carbonate one tablet twice daily with food.
   B. Calcium carbonate two tablets twice daily with food.
   C. Calcium citrate one tablet twice daily.
   D. Calcium citrate two tablets twice daily.

4. E.U. is a 58-year-old woman with a medical history significant for primary progressive multiple sclerosis with severe limitation, for which she spends most of her time in bed or lying on a couch. She attempts to ambulate but is unable to do so without a walker and/or assistance. Her DEXA scan results show that she has osteoporosis of the lumbar spine, and she now requires treatment. She already takes 1200 mg of calcium carbonate daily (600 mg twice daily) and 800 units of vitamin D (400 units twice daily). Which agent is best for E.U. to prevent vertebral fracture?
   A. Zoledronic acid 5-mg infusion once yearly.
   B. Risedronate 150-mg tablet once monthly.
   C. Raloxifene 60-mg tablet once daily.
   D. Calcitonin nasal spray, 1 spray per nostril each day.

Table 6. Nonpharmacologic Interventions[a]

Dietary Changes	Physical Activity	Other Interventions
Adequate intake of calcium-containing foods Adequate intake of vitamin D and exposure to sunlight	Aerobic exercise Low impact Weight bearing Muscle strengthening Balance training	Fall assessments TUG Vision correction Medication review Fall prevention counseling Smoking cessation

[a]See Table 2.

TUG = Timed Up and Go.

C. Pharmacologic Interventions
   1. Calcium supplementation: Available formulations (be aware of whether calcium supplement labels list calcium content as elemental or compound)
      a. Calcium carbonate (40% elemental)
      b. Calcium citrate (21% elemental)

Table 7. Calcium STEPS Analysis

Safety	May increase in risk of myocardial infarction Nephrolithiasis risk slightly increased with calcium carbonate Hypercalcemia in patients with later-stage chronic kidney disease
Tolerability	Constipation GI discomfort
Efficacy	Improves and/or sustains bone mineral density With or without vitamin D, evidence that calcium supplementation reduces fracture risk is not robust; some isolated studies show benefit, but systematic reviews and meta-analyses do not agree whether there is a significant impact
Preference (Pearls)	Calcium citrate preferred in following instances: Chronic gastric acid-suppressive therapy Intolerance of calcium carbonate formulations Calcium citrate formulations usually require two tablets per dose to achieve therapeutic doses Should be used (at a minimum) in patients receiving chronic systemic corticosteroid therapy Should be administered with an appropriate dose of vitamin D
Simplicity	Various formulations available to meet the needs of patients: Tablets (varying sizes) Chewable tablets Soft chews and "gummy" formulations Liquid

GI = gastrointestinal; STEPS = Safety, Tolerability, Efficacy, Preference (Pearls), Simplicity.

   2. Vitamin D: Available formulations
      a. Vitamin D_2 (ergocalciferol)
      b. Vitamin D_3 (cholecalciferol)

Table 8. Vitamin D STEPS

Safety	Annual dosing alternatives (500,000 units) may result in higher rates of falls and fractures in older patients
Tolerability	Hypercalcemia Constipation
Efficacy	Increases BMD Reduces risk of falls in elderly population with low serum vitamin D concentrations
Preference (Pearls)	Unclear whether vitamin D without calcium is effective for fracture prevention In elderly patients with low vitamin D concentrations, daily administration of vitamin D is associated with a reduced fall risk
Simplicity	Coformulated with calcium supplements (200 to 400 units per dose) Administered daily as 400- to 1000-unit tablets/capsules Option for quarterly dosing (100,000 units every 3 months) is available

BMD = bone mineral density; STEPS = Safety, Tolerability, Efficacy, Preference (Pearls), Simplicity.

3. Bisphosphonates: Available agents
   a. Alendronate (Fosamax)
   b. Ibandronate (Boniva)
   c. Risedronate (Actonel, Atelvia [delayed release])
   d. Zoledronic acid (Reclast)

Table 9. Bisphosphonates STEPS

Safety	Concerns regarding osteonecrosis of the jaw with bisphosphonate use are still in question FDA issued warning regarding increased incidence of atypical femur fractures in patients using bisphosphonates (October 2010) More prevalent in patients receiving therapy for >5 years Cautious use in patients with impaired renal function (<30 mL/minute for risedronate and ibandronate or <35 mL/minute for alendronate and zoledronic acid) or low serum calcium concentration In patients with hypocalcemia, resolve low calcium values before starting therapy
Tolerability	Abdominal pain Acute-phase reaction (zoledronic acid and ibandronate infusions) Arthralgias Dyspepsia Cautious use in patients with severe esophageal reflux disease, Barrett esophagus, or esophageal strictures Scleritis and/or uveitis
Efficacy	All bisphosphonates have evidence to support use for preventing vertebral fractures Alendronate, risedronate, and zoledronic acid have proved efficacious for preventing nonvertebral and hip fractures Used in patients taking chronic systemic corticosteroids to prevent BMD loss and subsequent fracture (see Rheumatoid Arthritis, Figure 5 and Figure 6, for assistance when deciding to use a bisphosphonate for corticosteroid-induced BMD loss)
Preference (Pearls)	Most oral doses should be taken with 6–8 oz of water at least 30–60 minutes before food, drink, or other medications (risedronate delayed release should be taken with 4 oz of water right after breakfast) Patients should remain upright for at least 30 minutes after being administered an oral dose (60 minutes with ibandronate) If a patient is unable to tolerate one bisphosphonate, discontinue the agent until the adverse effect resolves, and offer the patient the option to try another available bisphosphonate Questionable efficacy beyond 5 years; may warrant reevaluation and possible discontinuance of therapy
Simplicity	Once-daily, once-weekly, and once-monthly tablets; quarterly and yearly infusions Alendronate: Prevention (5 mg/day or 35 mg/week) and treatment (10 mg daily or 70 mg weekly) Risedronate: Prevention and treatment (5 mg daily, 35 mg weekly, or 150 mg monthly) Ibandronate: Prevention (150 mg monthly) and treatment (150 mg monthly OR 3 mg intravenously every 3 months) Zoledronic acid: Prevention (5 mg intravenously every 2 years) and treatment (5 mg intravenously every year) All dosage forms and intervals are equally effective, so consider the patient's prescription drug coverage (or lack of) when choosing a medication

BMD = bone mineral density; FDA = U.S. Food and Drug Administration; STEPS = Safety, Tolerability, Efficacy, Preference (Pearls), Simplicity.

4. Estrogen replacement therapy

Table 10. Estrogen Replacement STEPS

Safety	Based on information from the WHI trial, the risk of adverse events with hormone replacement therapy exceeds the fracture prevention benefits Hormone replacement therapy is more likely to be associated with the following: Coronary heart disease (estrogen/progesterone only) Stroke Invasive breast cancer (estrogen/progesterone only) Venous thromboembolic event
Tolerability	Breast discomfort GI symptoms Headache disorders Vaginal bleeding Venous thromboembolism
Efficacy	Reduced risk of vertebral fractures Reduced risk of nonvertebral fractures
Preference (Pearls)	Results from the WHI trial showed the benefit of fracture prevention to be similar to or less than the patient's risk of heart disease, stroke, venous embolism, and breast cancer Acts in conjunction with a bisphosphonate to increase BMD more than either agent alone
Simplicity	Once-daily oral dosing Transdermal patch is approved for the prevention of postmenopausal osteoporosis

BMD = bone mineral density; GI = gastrointestinal; STEPS = Safety, Tolerability, Efficacy, Preference (Pearls), Simplicity; WHI = Women's Health Initiative (trial).

5. Selective estrogen receptor modulator (SERM) : Available agents: Raloxifene (Evista)

Table 11. Selective Estrogen Receptor Modulator STEPS

Safety	Increased risk of fatal stroke in women with a history of coronary heart disease Increased risk of venous thromboembolism
Tolerability	Arthralgias Hot flashes/flushes Peripheral edema Sweating
Efficacy	Increased BMD Reduced incidence of clinical vertebral fractures, but not nonvertebral fractures
Preference (Pearls)	The rates of preventing clinical vertebral fractures are similar to rates of venous throboembolisms Evidence to support its use to prevent invasive breast cancer
Simplicity	Fixed-dose, once-daily dosing

BMD = bone mineral density; STEPS = Safety, Tolerability, Efficacy, Preference (Pearls), Simplicity.

6. Parathyroid hormone: Available agent: Teriparatide (biosynthetic parathyroid hormone 1–34) (Forteo)

Table 12. Parathyroid Hormone STEPS

Safety	Avoid use in patients with the following: Alkaline phosphatase elevation (unexplained) Open epiphyses Paget disease Prior skeletal radiation Associated with osteosarcoma (in rats) after about 24 months of therapy (3–60 times the human dose)
Tolerability	Influenza-like symptoms Hypercalcemia Injection site pain and/or rash Urolithiasis
Efficacy	Increases vertebral and total hip BMD Decreased incidence of new or worsening vertebral and nonvertebral fractures Prevents BMD loss and vertebral fractures in patients receiving chronic systemic corticosteroid therapy
Preference (Pearls)	Diminished efficacy if used concurrently with a bisphosphonate After discontinuing teriparatide, adding a bisphosphonate preserves BMD benefits Dropout and discontinuance rates in clinical studies are almost double those of alendronate
Simplicity	Once-daily injection Available as a prefilled (3 mL) pen

BMD = bone mineral density; STEPS = Safety, Tolerability, Efficacy, Preference (Pearls), Simplicity.

Table 13. NICE Recommendations for When to Use Teriparatide as an Alternative to Bisphosphonates for Secondary Prevention of Fragility Fractures

Column 1[a]	**Column 2**[a]
Unable to take a bisphosphonate	65 years or older with a T-score of −4.0 or below
Have an intolerance or contraindication to bisphosphonates or strontium (United Kingdom only)[b]	65 years or older with a T-score of −3.5 or below with more than two fractures
Unsatisfactory response to treatment with a bisphosphonate[c]	55 to 64 years old with a T-score of −4.0 or below with more than two fractures

[a]Patient must meet one criteria from both Column 1 and Column 2.

[b]Intolerance to bisphosphonates is defined as persistent gastrointestinal irritation, severe enough to warrant a change in therapy, despite administering correctly.

[c]Unsatisfactory response is defined as a fracture or decline in BMD to below baseline despite adherence to treatment for at least 12 months.

BMD = bone mineral density; NICE = National Institute for Health and Care Excellence.

7. RANKL antagonist – Denosumab (Prolia)

Table 14. RANKL Antagonist STEPS

Safety	Cellulitis was the most common serious adverse event in clinical trials Osteonecrosis of the jaw Infections
Tolerability	Eczema Flatulence
Efficacy	Decreased incidence of vertebral, nonvertebral, and hip fractures in patients with osteoporosis Increases bone mineral density in the hip and lumbar spine
Preference (Pearls)	NICE in the United Kingdom recommends denosumab for patients at risk of an osteoporotic fracture and unable to adhere to the dosing recommendations or tolerate an oral bisphosphonate
Simplicity	Subcutaneous injection every 6 months

NICE = National Institute for Health and Clinical Excellence; STEPS = Safety, Tolerability, Efficacy, Preference (Pearls), Simplicity.

Table 15. NICE Recommendations for T-Score at Which to Recommend Denosumab as an Alternative to Bisphosphonates

	Number of Independent Clinical Risk Factors for Fracture[a]		
Age, years	0	1	2
65 to 69	Not recommended	−4.5	−4.0
70 to 74	−4.5	−4.0	−3.5
75 and older	−4.0	−4.0	−3.0

[a]Independent clinical risk factors include parental history of hip fracture, more than four alcoholic drinks per day, and rheumatoid arthritis.
NICE = National Institute for Health and Clinical Excellence.

8. Calcitonin (Miacalcin, Fortical)

Table 16. Calcitonin STEPS

Safety	Anaphylactoid and anaphylaxis reactions associated with injection	
Tolerability	Injection GI symptoms Injection site reaction Flushing	Nasal spray Rhinitis Nasal congestion Mucosal irritation
Efficacy	Reduced incidence of recurrent vertebral fractures Beneficial effects on BMD in patients treated with steroid-induced disease	
Preference (Pearls)	Inferior to alendronate for preventing BMD loss May help relieve bone pain associated with fractures but is not an indication to choose as the primary treatment FDA (2013) stated that the lack of effectiveness combined with the increased risk of cancer (oral calcitonin) raises concerns about the overall utility of calcitonin	
Simplicity	Nasal administration in only ONE nostril per day, alternating nostrils each day	

BMD = bone mineral density; FDA = U.S. Food and Drug Administration; GI = gastrointestinal; STEPS = Safety, Tolerability, Efficacy, Preference (Pearls), Simplicity.

D. Follow-up
   1. Dual-energy x-ray absorptiometry
      a. Recheck at about 24 months to evaluate for changes: Do not consider treatment failure if initial, solitary evaluation shows net bone loss.
      b. In patients NOT receiving drug therapy, may recheck DEXA findings every 5 years unless the patient has developed risk factors for osteoporotic fracture
   2. Medication adherence
      a. Review adherence at least every 6 months.
      b. As many as one-half of patients being treated with a bisphosphonate will self-discontinue therapy within the first 6 months, so pharmacists should continually assess for medication adherence.
   3. Patient resources
      a. Various handouts available from the American Family Physician Web site
      b. National Library of Medicine MedlinePlus has patient-oriented educational materials at no cost to provider or patient.
      c. National Osteoporosis Awareness and Prevention Campaign examination room booklets and posters

E. Physician Quality Reporting System 2013 Quality Measures

Table 17. 2015 Physician Quality Reporting System Quality Measures

No.	Category	Criteria
24	Osteoporosis: Communication with the physician managing ongoing care after fracture	Percentage of patients aged 50 years who were treated for a hip, spine, or distal radial fracture with documentation of communication with the physician managing the patient's ongoing care that a fracture occurred and that the patient was or should be tested or treated for osteoporosis
39	Screening or therapy for osteoporosis for women 65 years and older	Percentage of female patients aged 65 years who have had a central DEXA measurement ordered or performed at least once since age 60 years or pharmacologic therapy prescribed within 12 months
40	Osteoporosis: Management after fracture	Percentage of patients aged 50 years with fracture of the hip, spine, or distal radius with a central DEXA measurement ordered or performed or pharmacologic therapy prescribed
41	Osteoporosis: Pharmacologic therapy	Percentage of patients aged 50 years with a diagnosis of osteoporosis who were prescribed pharmacologic therapy within 12 months

DEXA = dual-energy x-ray absorptiometry.

Table 18. Drugs and Doses Reference Table

Medication Name	Brand Name	Dosing
Calcium plus vitamin D	Several OTC formulations	500 mg of elemental calcium PLUS vitamin D 400 international units twice daily
Alendronate	Fosamax	5–10 mg by mouth once daily 35–70 mg by mouth once weekly
Risedronate	Actonel	5 mg by mouth once daily 35 mg by mouth once weekly 150 mg by mouth once monthly

Table 18. Drugs and Doses Reference Table *(continued)*

Ibandronate	Boniva	150 mg by mouth once monthly 3 mg intravenously every 3 months
Zoledronic acid	Reclast	5 mg intravenously every 1–2 years
Denosumab	Prolia	60 mg subcutaneously every 6 months
Raloxifene	Evista	60 mg by mouth once daily
Teriparatide	Forteo	20 mcg subcutaneously once daily
Calcitonin	Miacalcin	100 units intramuscularly every other day 200 units sprayed into one nostril each day

OTC = over-the-counter.

II. RHEUMATOID ARTHRITIS

A. Clinical Guidelines
   1. 2010 RA classification criteria: An American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) collaborative initiative
   2. The EULAR 2013 recommendations for the management of RA with synthetic and biologic disease-modifying drugs
   3. 2012 update of the 2008 ACR recommendations for the use of DMARDs and biologic agents in the treatment of RA

B. Patient Symptom Presentation
   1. Diffuse pain (myalgias, arthralgias, arthritis)
   2. Variable time to symptom onset
   3. Morning joint stiffness (gelling) lasting more than 1 hour
   4. Affected joints are swollen and inflamed.
      a. Elbow
      b. Foot and ankle
      c. Hands and wrists (proximal interphalangeal and metacarpophalangeal joints)
      d. Hip
      e. Knee
      f. Shoulder

C. Other Contributing Factors
   1. Family history of other inflammatory disorders such as the following:
      a. Autoimmune thyroid disease
      b. Multiple sclerosis
      c. Myasthenia gravis
      d. Rheumatoid arthritis
      e. Systemic lupus erythematosus
   2. Smoking is associated with increased disease activity.

D. Evaluation and Diagnosis: 2010 ACR/EULAR Classification Criteria for RA
   1. Test patients who have at least one joint with clinical synovitis not otherwise explained by another disease (e.g., SLE, gout, psoriatic arthritis).

2. Although this tool (Table 19) is not intended to be diagnostic, a score of at least 6 of 10 points classifies patients as having definite RA. (Note: Use the highest score from each category.)
3. Classification criteria score of at least 6 may also be a good guide for identifying individuals with the highest probability of persistent or erosive disease who would benefit from enrolling in clinical trials or DMARD intervention.

Table 19. 2010 ACR/EULAR Classification Criteria for Rheumatoid Arthritis

Classification Criteria	Scoring (points)
Joint involvement	
>10 joints, including at least 1 small joint	5
4–10 small joints	3
1–3 small joints	2
2–10 large joints	1
1 large joint	0
Serology	
Positive RF or positive ACPA test results > 3 times the upper limit of normal	3
Positive RF or positive ACPA test results up to 3 times the upper limit of normal	2
Negative RF and ACPA test results	0
Acute-phase reactants	
Abnormal CRP or ESR test results	1
Normal CRP and ESR test results	0
Duration of symptoms	
At least 6 weeks	1
<6 weeks	0
Total points	

ACPA = anti–citrullinated protein antibody; ACR = American College of Rheumatology; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; EULAR = European League Against Rheumatism; RF = rheumatoid factor.

Patient Case

5. F.T. is a 38-year-old man recently referred by his primary care provider to a rheumatologist for assessment and treatment of RA. During the initial interview, the rheumatologist assesses the patient for various subjective and objective markers of disease activity. Of the four markers used to assess disease activity, which is the most clinically relevant prognostic marker?
   A. Joint involvement (quantity).
   B. Erythrocyte sedimentation rate (ESR).
   C. Rheumatoid factor (RF).
   D. C-reactive protein (CRP).

4. Laboratory and radiographic testing in RA

Table 20. Testing to Consider for Diagnosis and Treatment Decisions in RA

Diagnosing RA	ACR-Suggested Baseline Evaluation	ACR Recommendations for Initiating or Titrating Pharmacotherapy
Laboratory ACPA CBC with differential CRP ESR Liver function tests RF[a] Radiographic Radiography, ultrasonography, or magnetic resonance imaging of affected joints	Laboratory CBC Creatinine CRP ESR Liver function tests Metabolic (Chem) panel Stool guaiac Synovial fluid (to rule out other diseases) Urinalysis Radiographic Radiography, ultrasonography, or magnetic resonance imaging of affected joints	Laboratory CBC Creatinine Hepatitis B and C[b] (nonbiologic and biologic DMARDs) Liver function tests Retinal examination[c] (hydroxychloroquine) Tuberculosis screening[d] (biologic DMARDs)

[a]May repeat at 6–12 months if the initial value is low or negative.

[b]If patient has a high-risk history.

[c]Every 5 years for low-risk patients and annually for high-risk patients.

[d]Screen regardless of history of BCG vaccination.

ACPA = anti–citrullinated protein antibody; ACR = American College of Rheumatology; BCG = bacillus Calmette-Guerin; CBC = complete blood cell count; CRP = C-reactive protein; DMARD = disease-modifying antirheumatic drug; ESR = erythrocyte sedimentation rate; RA = rheumatoid arthritis; RF = rheumatoid factor.

Table 21. Disease Prognosis

Clinically important markers (ACR)	Functional limitations Positive RF or ACPA test results Radiographic evidence of bony erosions Extra-articular disease (Felty syndrome, RA lung disease, RA vasculitis, rheumatoid nodules, secondary Sjögren syndrome)
Disease activity during first 3–6 months of treatment	Lower disease activity (tender or swollen joints) for up to 6 months increases the likelihood of 12-month disease remission Higher disease activity (tender or swollen joints) in first 3 months increases likelihood of presence of symptoms at 12 months

ACPA = anti–citrullinated protein antibody; ACR = American College of Rheumatology; RA = rheumatoid arthritis; RF = rheumatoid factor.

E. Before Initiating Pharmacologic Therapy
   1. Address the entire scope of patient needs with respect to RA.
      a. Discuss potential functional limitations and strategies to overcome and/or compensate.
      b. Involve other health professionals to care for and educate the patient.
         i. Physical therapy
         ii. Occupational therapy
         iii. Social workers and counseling/cognitive services

2. Educate the patient regarding physical conditioning.
   a. Energy conservation
   b. Joint protection
   c. Range-of-motion exercises
   d. Strengthening exercises
3. Tuberculosis screening
4. Immunizations

Table 22. Vaccinations to Consider in Patients Receiving Rheumatoid Arthritis Immunosuppressive Therapy

Vaccination	Recommendations	Before Starting DMARDs	During DMARD Therapy
Influenza vaccine (trivalent, inactivated)	Administer annually to all patients	Yes	Yes
PCV13[a]	Administer to all patients receiving biologic DMARDs, methotrexate, leflunomide, and/or sulfazalazine before PPSV23 or at least 1 year after administering PPSV23	Yes	Yes
PPSV23	Administer to all patients receiving biologic DMARDs, methotrexate, leflunomide, and/or sulfasalazine at least 8 weeks after administering PCV13	Yes	Yes
Hepatitis B vaccine series	Administer to all patients with risk factors and receiving biologic DMARDs, methotrexate, and/or leflunomide	Yes	Yes
Human papillomavirus	Administer to all patients who meet the recommendations from the CDC	Yes	Yes
Herpes zoster	Administer to all patients who meet the recommendations from the CDC	Yes	Yes/no[b]

[a]PCV13 is not included in the ACR 2012 update, but the CDC/ACIP recommendations for iatrogenic immunosuppression apply.

[b]Yes: Patients who are actively being treated with DMARD monotherapy or combination therapy; No: Patients who are actively being treated with an anti-TNF or non-TNF biologic agent.

ACIP = Advisory Committee on Immunization Practices; ACR = American College of Rheumatology; CDC = Centers for Disease Control and Prevention; DMARD = disease-modifying antirheumatic drug; PCV13 = pneumococcal vaccine (13-valent conjugate); PPSV23 = pneumococcal vaccine (23-valent polysaccharide); TNF = tumor necrosis factor.

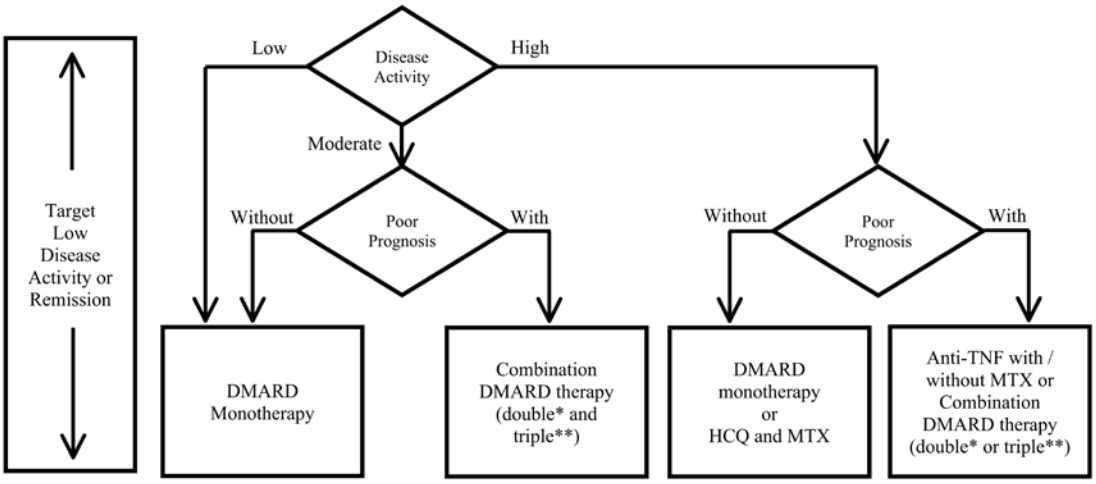

Figure 2. 2012 ACR recommendations for the treatment of RA in patients with disease duration of less than 6 months.

*Double therapy: Methotrexate PLUS hydroxychloroquine, leflunomide, OR sulfasalazine; sulfasalazine PLUS hydroxychloroquine.

**Triple therapy: Methotrexate PLUS hydroxychloroquine PLUS sulfasalazine.

ACR = American College of Rheumatology; RA = rheumatoid arthritis.

Reprinted with permission from: Singh JA, Furst DE, Bharat A, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res 2012;64:625-39.

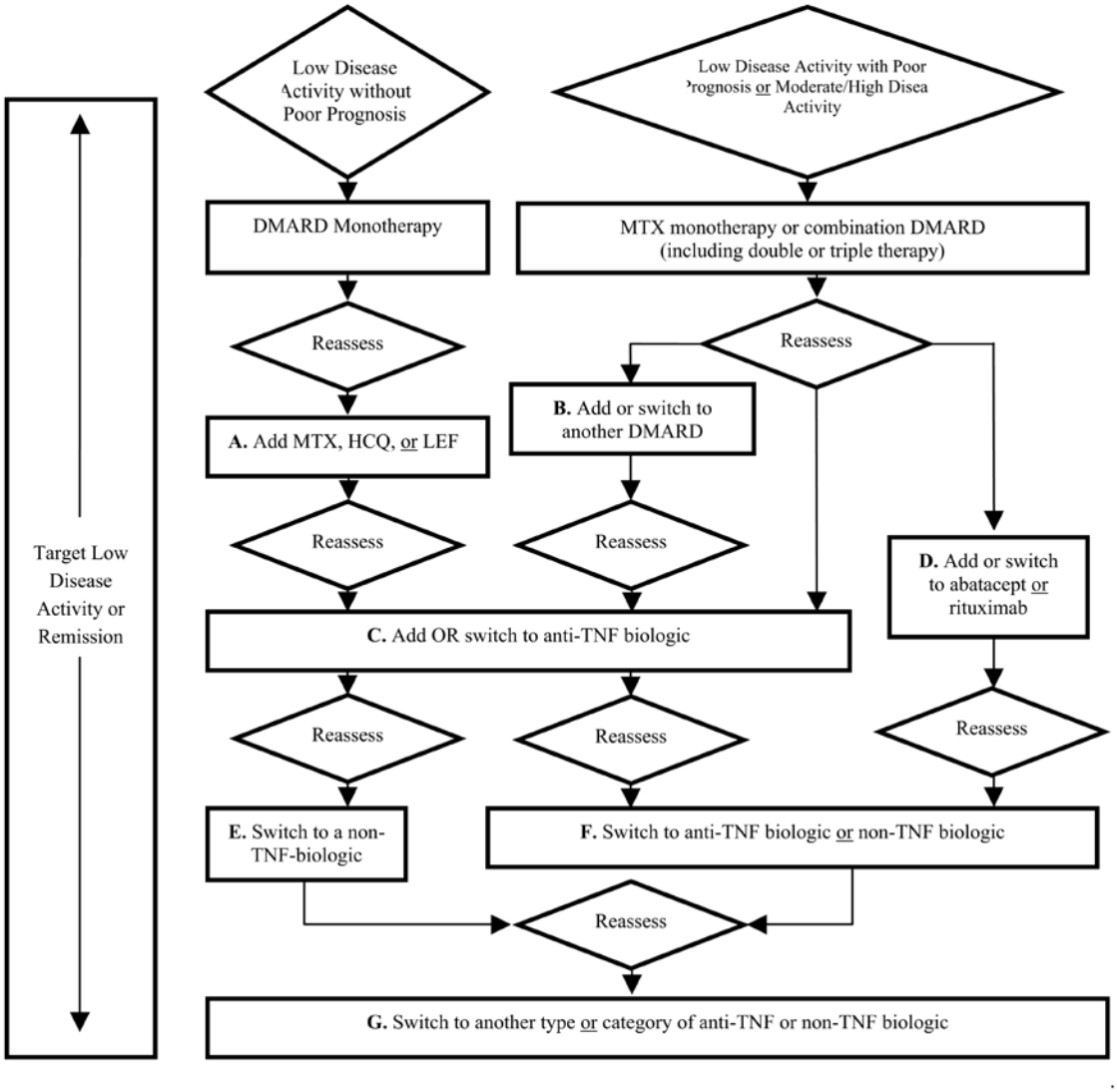

Figure 3. 2012 ACR recommendations for the treatment of RA in patients with disease duration of greater than 6 months.

ACR = American College of Rheumatology; RA = rheumatoid arthritis.

Reprinted with permission from: Singh JA, Furst DE, Bharat A, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res 2012;64:625-39.

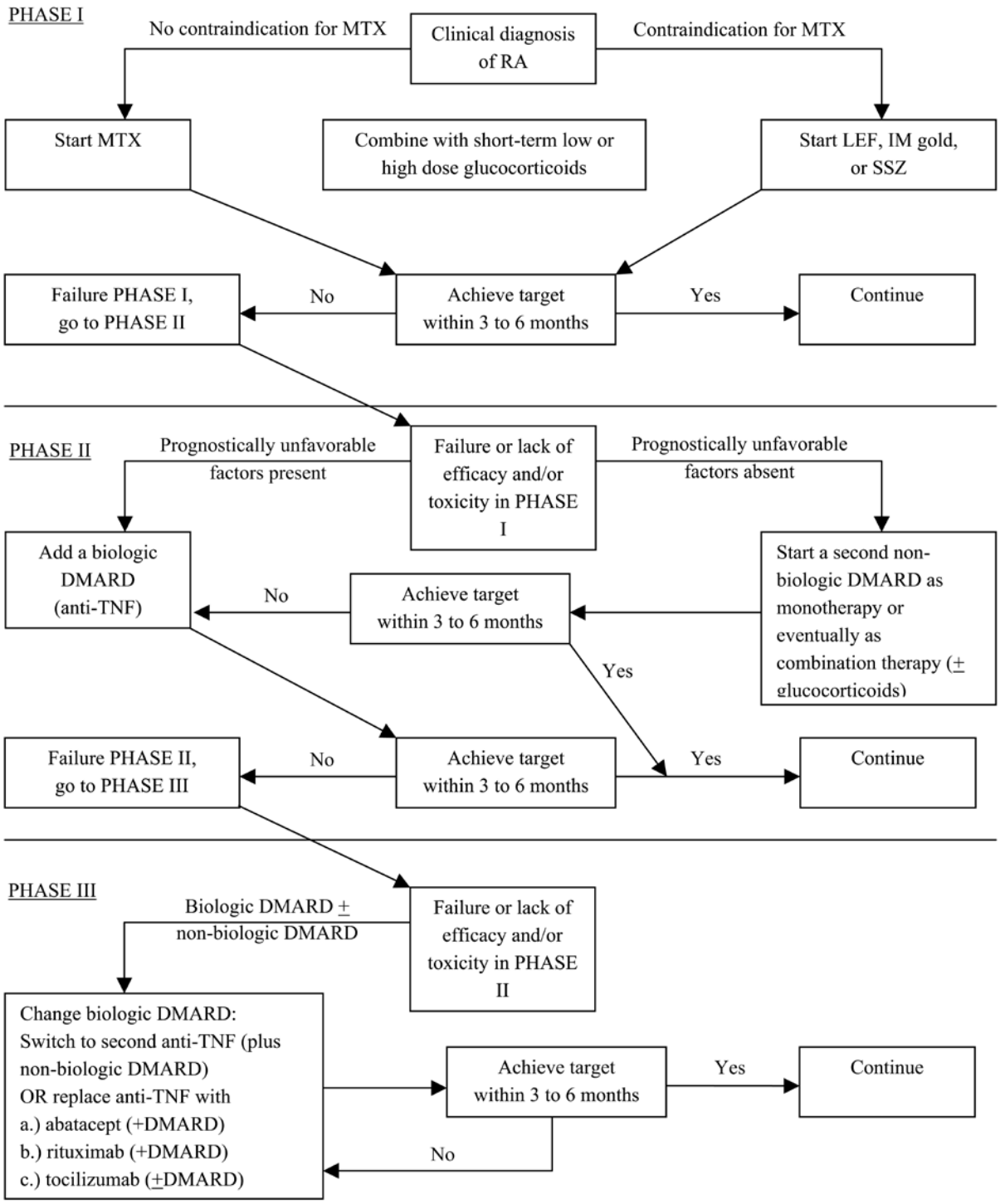

Figure 4. EULAR-recommended use of nonbiologic and biologic DMARDs.

DMARD = disease-modifying antirheumatic drug; EULAR = European League Against Rheumatism.

Reprinted with permission from: Smolen JS, Landewé R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis. 2014 Mar;73(3):492-509

F. Guideline Recommendations
   1. American College of Rheumatology (2012 update)
      a. Symptomatic pain control achieved with the following:
         i. Nonsteroidal anti-inflammatory drugs
         ii. Low-dose systemic steroids (ACR defines as 10 mg of prednisone per day or less)
         iii. Local steroid injections (not more frequent than every 3 months)
      b. DMARDs should be initiated within the first 3 months of diagnosis as monotherapy or combination therapy, depending on the patient's prognosis and disease activity.
      c. ACR recommendations consider a patient's ability to pay for therapy as self or through a third party.
   2. European League Against Rheumatism (2013 update)
      a. Initiate synthetic DMARDs early as soon as the patient's condition is diagnosed (see Figure 4 for EULAR's recommended treatment algorithm).
         i. Methotrexate is preferred.
         ii. Consider leflunomide, sulfasalazine, or injectable gold (gold sodium thiomalate) when methotrexate is contraindicated for or not tolerated by the patient.
      b. In treatment-naive patients with a poor prognosis or for patients who have not responded to synthetic DMARDs, adding a biologic DMARD (tumor necrosis factor [TNF] antagonist or selective T-cell antagonist) is appropriate.
      c. Consider changing synthetic and biologic DMARDs if patient has an inadequate response to therapy.
      d. In patients who show evidence of persistent remission, consider the following:
         i. Tapering the dose of corticosteroids
         ii. Tapering biologic DMARDs
         iii. Decreasing the dose of nonbiologic DMARDS to the lowest efficacious dose

G. Supportive Care Medications
   1. NSAIDs: Systemic and/or topical

Table 23. NSAID STEPS

Safety	In patients at risk of or with existing cardiovascular disease, NSAIDs may increase the risk of a fatal or nonfatal event All NSAIDs carry the risk of causing changes in renal function Patients at greater risk of GI toxicity include the following: Elderly patients Patients with a history of GI bleed Patients concurrently using anticoagulants, antiplatelet drugs, and/or systemic corticosteroids
Tolerability	Dyspepsia Prolonged bleeding Dermatologic reactions
Efficacy	Available NSAIDs are equally effective, but individuals' responses to agents will vary NSAIDs will reduce joint pain and swelling to some degree, but they will not modify the destruction or progression of RA

Table 23. NSAID STEPS *(continued)*

Preference (Pearls)	Celecoxib has fewer GI adverse events than other NSAIDs; however, it is no more effective at reducing pain and inflammation Adding misoprostol to an NSAID will decrease the risk of GI ulceration Adding a proton pump inhibitor to an NSAID will decrease nonulcerative symptoms If a patient does not respond to NSAID therapy (after an appropriate 14- to 28-day trial), providers should consider trying other NSAIDs before concluding therapeutic failure
Simplicity	Widely available prescription and over-the-counter agents Once-daily formulations allow continuous analgesia

GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug; RA = rheumatoid arthritis; STEPS = Safety, Tolerability, Efficacy, Preference (Pearls), Simplicity.

2. Corticosteroids: Oral or intra-articular injections

Table 24. Corticosteroid STEPS

Safety	Increased risk of osteoporosis and fracture Risk of symptoms of a psychiatric disturbance with increasing doses of corticosteroids <40 mg of prednisone per day (1%–2% incidence) >40 mg of prednisone per day (5% incidence) >80 mg of prednisone per day (20% incidence)	
Tolerability	Cataracts Dyslipidemia (high dose) Glaucoma Hirsutism Hyperglycemia	Hypertension (high dose) Hypothalamic-pituitary-adrenal axis suppression Osteoporosis Pancreatitis (high dose) Weight gain
Efficacy	Short-term (weeks), low-dose (<10 mg of prednisone daily) corticosteroids are effective for symptoms flare Early initiation of corticosteroids and continuance at a low dose reduce joint destruction and increase likelihood of clinical remission Higher corticosteroid doses may be warranted to treat symptoms of severe or advanced disease (e.g., presence of vasculitis) Intra-articular injections may be beneficial, but limit injections in joint to no more often than every 3–4 months	
Preference (Pearls)	Start appropriate calcium and vitamin D supplementation in all patients taking corticosteroid therapy See Figure 5 and Figure 6 for recommendations for using bisphosphonates in patients receiving chronic corticosteroid therapy	
Simplicity	Once-daily fixed dose appears to be effective for symptom control and possibly slowing disease progression	

STEPS = Safety, Tolerability, Efficacy, Preference (Pearls), Simplicity.

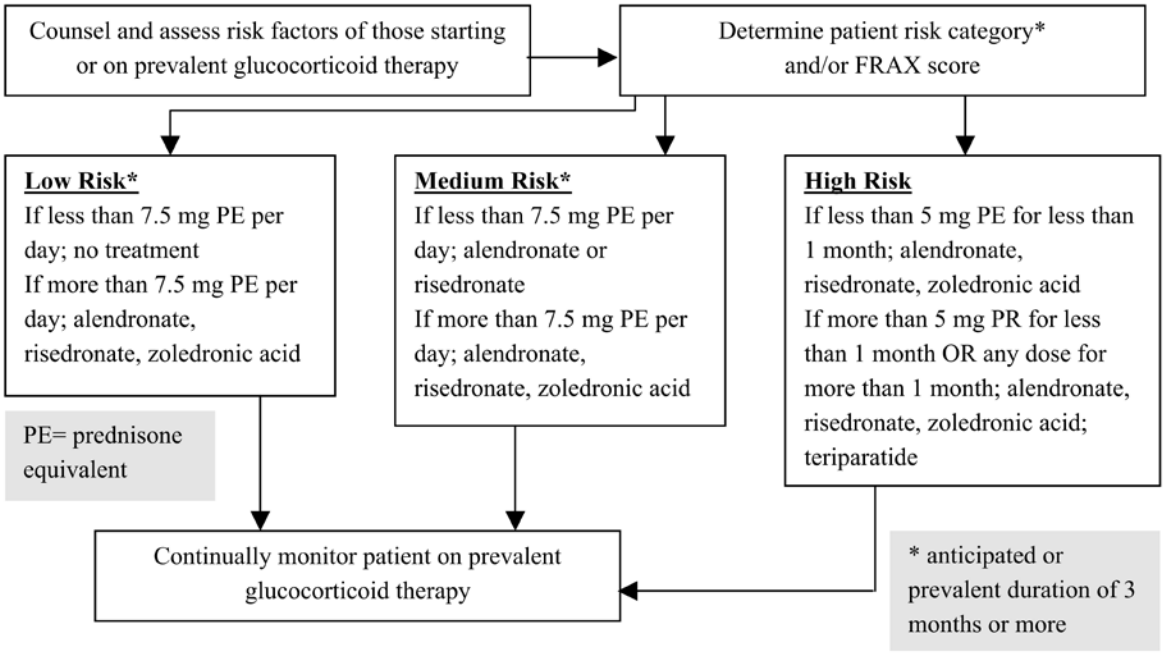

Figure 5. Preventing corticosteroid-induced BMD loss in postmenopausal women and men older than 50 years.

*Risk is defined in Figure 2 of the ACR guidelines as follows: Low risk (<10%), medium risk (10%–20%), or high risk (>20%).

ACR = American College of Rheumatology; BMD = bone mineral density.

Reprinted with permission from: Grossman JM, Gordon R, Ranganath VK, et al. American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Care Res 2010;62:1515-26.

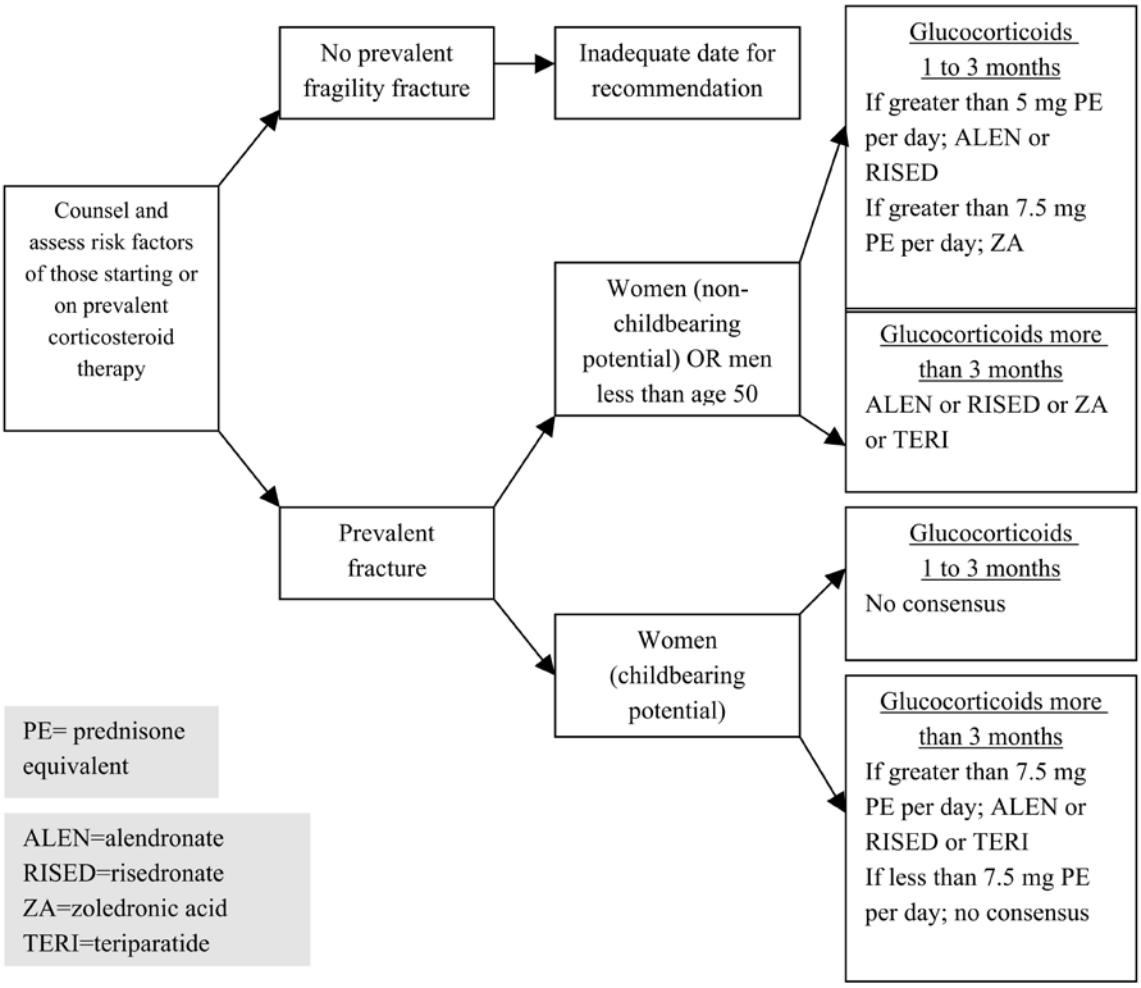

Figure 6. Preventing corticosteroid-induced BMD loss in premenopausal women and men younger than 50 years.

BMD = bone mineral density.

Reprinted with permission from: Grossman JM, Gordon R, Ranganath VK, et al. American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Care Res 2010;62:1515-26.

Patient Case

6. K.W. is a 27-year-old female executive with RA (diagnosed 3 months ago), type 2 diabetes mellitus, and hypertension who smokes cigarettes. Her basic metabolic profile and complete blood cell count (CBC) are all within normal limits. Her RF is about 4 times the upper limit of normal; she has elevated anticyclic citrullinated peptide antibody values and ESR (high disease activity). Her radiographs show evidence of bony erosions. During the 2 months before her diagnosis, she experienced severe functional limitation, sometimes missing work because she was unable to prepare herself in a timely fashion. According to the ACR recommendations, which medication regimen is best for K.W.?

   A. Hydroxychloroquine 400 mg once daily.
   B. Methotrexate 10 mg once weekly.
   C. Methotrexate 10 mg once weekly plus infliximab 3 mg/kg every 8 weeks.
   D. Methotrexate 10 mg once weekly plus anakinra 100 mg daily.

H. Synthetic DMARDs
1. Methotrexate

Table 25. Methotrexate STEPS

Safety	Contraindicated in pregnancy and breastfeeding; pregnancy should be avoided for at least 3 months with men and at least one ovulatory cycle for women after discontinuing methotrexate Significantly diminishes ability to generate an immune response Increased incidence of the following: Any malignancy Lung cancer Melanoma Non-Hodgkin lymphoma Avoid in patients with the following: CrCl < 30 mL/minute Platelet count < 50,000/mm^3 White blood cell count < 3 x 10^3 cells/mm^3 Liver transaminase concentrations > 2 times the upper limit of normal Avoid concurrent use of NSAIDs in patients before or actively using high-dose methotrexate	
Tolerability	Abdominal cramping Anorexia Bone marrow suppression Hypersensitivity pneumonitis	Increased aminotransferases Infections Nausea Stomatitis
Efficacy	Intense treatment strategy and dose may result in an increased chance of disease remission, but also an increased likelihood of having an adverse event or discontinuing therapy Consider changing to subcutaneous methotrexate in patients with an inadequate response to oral therapy (secondary to increased bioavailability of the injectable formulation) and unable to use biologic DMARDs Proposed benefit of decreased risk of cardiovascular mortality	
Preference (Pearls)	Considered first choice for nonbiologic DMARD therapy in both ACR and EULAR recommendations Adding a folic acid supplement decreases adverse events (folic acid daily or folinic acid weekly)	
Simplicity	Dosed as one subcutaneous injection or one oral dose weekly (5 to 20 mg)	

ACR = American College of Rheumatology; CrCl = creatinine clearance; DMARD = disease-modifying antirheumatic drug; EULAR = European League Against Rheumatism; NSAID = nonsteroidal anti-inflammatory drug; STEPS = Safety, Tolerability, Efficacy, Preference (Pearls), Simplicity.

2. Leflunomide (Arava)

Table 26. Leflunomide STEPS

Safety	Stevens-Johnson syndrome and toxic epidermal necrolysis May decrease defenses against malignancy Women who wish to become pregnant or men who wish to father children should discontinue leflunomide use and use cholestyramine to achieve plasma (leflunomide) active metabolite concentrations < 0.02 mg/L Patients with preexisting liver disease or aspartate aminotransferase/alanine aminotransferase values > 2 times the upper limit of normal should not receive leflunomide	
Tolerability	Alopecia Debilitating diarrhea	Rash Severe hepatotoxicity

Table 26. Leflunomide STEPS *(continued)*

Efficacy	Available evidence shows leflunomide is comparable to methotrexate therapy May be added to methotrexate therapy to further improve symptoms, but at risk of hepatic toxicity
Preference (Pearls)	An alternative for patients unable to tolerate or not responding to methotrexate therapy
Simplicity	100 mg by mouth daily for 3 days (loading dose) and then 20 mg by mouth once daily Dosage may be reduced (10 mg daily) for patients unable to tolerate full dose Loading dose can be omitted for patients at high risk of hepatic or hematologic toxicities

STEPS = Safety, Tolerability, Efficacy, Preference (Pearls), Simplicity.

3. Sulfasalazine (Azulfidine)

Table 27. Sulfasalazine STEPS

Safety	"Probably" safe for use in pregnancy; has not demonstrated abnormal/adverse fetal outcomes Avoid use in patients with the following: Platelet count < 50,000/mm^3 Liver transaminase concentrations > 2 times the upper limit of normal Acute hepatitis B/C Chronic hepatitis B, not receiving therapy Chronic hepatitis B, Child-Pugh class C Chronic hepatitis C, Child-Pugh class B or C
Tolerability	GI effects (may be lessened with enteric-coated tablets) A lupus-like syndrome has been reported in patients taking sulfasalazine
Efficacy	Available data suggest that sulfasalazine is effective at modifying rheumatic disease activity, but data are less supportive of its effects on radiologic progression
Preference (Pearls)	May be an alternative for women who are (or planning to become) pregnant
Simplicity	Twice- to thrice-daily dosing May require 2–4 tablets per dose

GI = gastrointestinal; STEPS = Safety, Tolerability, Efficacy, Preference (Pearls), Simplicity.

4. Other considerations: Routine monitoring of complete blood cell count (CBC), hepatic transaminases, and creatinine concentration when starting or adjusting DMARD therapy (methotrexate, leflunomide, sulfasalazine)
    a. Every 2–4 weeks for the first 3 months
    b. Every 8–12 weeks until month 6
    c. Every 12 weeks thereafter
5. Additional agents to consider
    a. Low disease activity and no poor prognostic factors
        i. Hydroxychloroquine
        ii. Minocycline (diagnosis less than 6 months)
    b. Not recommended by the ACR
        i. Azathioprine
        ii. Cyclophosphamide
        iii. Cyclosporine
        iv. D-penicillamine
        v. Gold salts

Patient Case

7. T.D. is a 28-year-old, uninsured graduate student meeting with a rheumatologist regarding worsening RA symptoms. She currently takes methotrexate 20 mg by mouth weekly, folic acid 1 mg by mouth daily, and naproxen 500 mg by mouth twice daily as needed for pain. Her symptoms have been increasingly worse during the past 3 months, and she has been using naproxen around the clock for the past 30 days. Which is the best strategy to help T.D. control her symptoms?

   A. Recommend that she change to subcutaneous, injectable methotrexate.
   B. Increase methotrexate to 30 mg weekly.
   C. Replace methotrexate with adalimumab 40 mg subcutaneously every other week.
   D. Replace methotrexate with infliximab 3 mg/kg intravenously every 8 weeks.

I. Biologic DMARDs
   1. TNF inhibitors
      a. Adalimumab (Humira)
      b. Certolizumab pegol (Cimzia)
      c. Etanercept (Enbrel)
      d. Golimumab (Simponi)
      e. Infliximab (Remicade)

Table 28. TNF Inhibitors STEPS

Safety	Increased risk of serious bacterial and/or fungal infections Associated with reactivation of tuberculosis May increase risk of malignancy, including melanoma, leukemia, and lymphoma Linked with new or worsening heart failure and possibly death in patients with heart failure
Tolerability	Headache Abdominal pain Injection site reactions Upper respiratory tract infection Infusion reactions (infliximab)
Efficacy	First-line choice for biologic DMARDs on the basis of their ability to improve physical function and delay radiographic changes Superior to synthetic DMARDs with respect to radiographic outcomes Combination with methotrexate yields better outcomes than using TNF inhibitors as monotherapy

Table 28. TNF Inhibitors STEPS *(continued)*

Preference (Pearls)	The ACR generally recommends biologic DMARDs after insufficient response to nonbiologic DMARDs or for patients with high disease activity and features of poor prognosis The EULAR recommends biologic DMARDs after insufficient response to methotrexate or other nonbiologic DMARDs All patients receiving biologic DMARDs should be tested for (and treated for) TB before starting RA therapy (see Figure 7 for TB screening recommendations) Treatment is expensive for patients without insurance or suboptimal coverage Infliximab should only be used in combination with methotrexate
Simplicity	Doses may be given subcutaneously weekly (etanercept), every other week (adalimumab), or every 4 weeks (golimumab) Certolizumab is dosed subcutaneously every other week when initiating therapy and may be extended to every 4 weeks for maintenance therapy Infliximab is dosed intravenously every 8 weeks after completing induction therapy at 0, 2, and 6 weeks; interval may be decreased to every 4 weeks if necessary

ACR = American College of Rheumatology; DMARD = disease-modifying antirheumatic drug; EULAR = European League Against Rheumatism; RA = rheumatoid arthritis; STEPS = Safety, Tolerability, Efficacy, Preference (Pearls), Simplicity; TB = tuberculosis; TNF = tumor necrosis factor.

2. Abatacept (Orencia)

Table 29. Abatacept STEPS

Safety	In patients with COPD, abatacept has been linked with more adverse pulmonary effects Increased risk of developing serious infections
Tolerability	Acute infusion reactions Upper respiratory tract infections
Efficacy	Should not be used in combination with other biologic DMARDs Effective for improving RA symptoms but should not be introduced until failure of at least one TNF inhibitor Combination with methotrexate results in higher rates of remission than methotrexate monotherapy
Preference (Pearls)	The ACR recommendations suggest abatacept as an option for patients with moderate to severe disease for >6 months or low disease activity with poor prognostic features who have not responded to methotrexate or another synthetic DMARD
Simplicity	IV regimen: After initial infusion, administer again at 2 weeks and then at 4 weeks; then begin administering every 4 weeks Subcutaneous regimen: Initial IV infusion; then subcutaneous injection within 24 hours; and then weekly thereafter

ACR = American College of Rheumatology; COPD = chronic obstructive pulmonary disease; DMARD = disease-modifying antirheumatic drug; IV = intravenous; RA = rheumatoid arthritis; STEPS = Safety, Tolerability, Efficacy, Preference (Pearls), Simplicity; TNF = tumor necrosis factor.

3. Rituximab (Rituxan)

Table 30. Rituximab STEPS

Safety	Acute renal failure Cardiac arrhythmias Linked to fatal infusion-related adverse reactions Mucocutaneous reactions Progressive multifocal leukoencephalopathy Tumor lysis syndrome
Tolerability	Arthralgias Hematologic effects may include lymphopenia, neutropenia, leukopenia, thrombocytopenia, and anemia Hyperphosphatemia Hypertension Hyperuricemia
Efficacy	Has shown efficacy as monotherapy or as add-on therapy to methotrexate
Preference (Pearls)	Avoid use in patients who have not had an adequate trial with a TNF inhibitor Avoid administering live vaccines 3 months before or during treatment with rituximab
Simplicity	A two-dose therapeutic course (separated by 14 days) every 24 weeks (may be readministered every 16 weeks, if needed) Consider using acetaminophen and antihistamine before infusion

STEPS = Safety, Tolerability, Efficacy, Preference (Pearls), Simplicity; TNF = tumor necrosis factor.

4. Tocilizumab (Actemra)

Table 31. Tocilizumab STEPS

Safety	Serious bacterial, fungal, and viral infections reported with use All patients should receive monitoring for tuberculosis before and after starting tocilizumab therapy GI perforation reported with concomitant use of tocilizumab and NSAIDs, corticosteroids, and/or methotrexate Avoid use in patients with the following: Absolute neutrophil count < 2000/mm^3 Platelet count < 100,000/mm^3 Aminotransferase concentrations > 1.5 times the upper limit of normal
Tolerability	Dyslipidemias reported Hypersensitivity reactions starting with the second to fourth infusion Neutropenia or thrombocytopenia Transaminase elevations Upper respiratory tract infections
Efficacy	Effective treatment option for patients not responding, or inadequately responding, to methotrexate therapy Used in combination with methotrexate therapy
Preference (Pearls)	FDA approved for patients with an inadequate response to one or more TNF inhibitors
Simplicity	Intravenous infusion every 4 weeks

FDA = U.S. Food and Drug Administration; GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug; STEPS = Safety, Tolerability, Efficacy, Preference (Pearls), Simplicity; TNF = tumor necrosis factor.

5. Anakinra (Kineret)

Table 32. Anakinra STEPS

Safety	Increased risk of neutropenia when combined with TNF inhibitors High doses are associated with an increased risk of serious infection
Tolerability	Diarrhea Influenza-like reaction Injection site reactions
Efficacy	Effective for decreasing RA symptoms, but not as effective as TNF inhibitors
Preference (Pearls)	Do not administer live vaccines to patients receiving anakinra Not included in the ACR recommendations because of limited data available in the literature and not recommended in the EULAR guidelines because of lesser clinical efficacy in trials
Simplicity	Once-daily subcutaneous injection

ACR = American College of Rheumatology; EULAR = European League Against Rheumatism; RA = rheumatoid arthritis; STEPS = Safety, Tolerability, Efficacy, Preference (Pearls), Simplicity; TNF = tumor necrosis factor.

J. Janus-associated kinase inhibitor - Tofacitinib (Xeljanz)

Table 33. Tofacitinib STEPS

Safety	Bone marrow suppression Gastrointestinal perforation in those with a history or at risk Hepatotoxicity Malignancy Tuberculosis	
Tolerability	Increased risk of infection Diarrhea	Headache Upper respiratory tract infections
Efficacy	Effective to reduce symptoms of RA Most studies evaluate efficacy by using ACR20 (20% improvement in RA symptoms), but others use ACR50 (50%) or ACR70 (70%) to assess symptom improvement	
Preference (Pearls)	The medication is too new (approved November 2012) to be included in ACR EULAR recommends using tofacitinib after other biologic treatments fail to control the disease	
Simplicity	Oral therapy, dosed twice daily Price (per month) is comparable to that of most biologic DMARDs	

ACR = American College of Rheumatology; DMARD = disease-modifying antirheumatic drug; EULAR = European League Against Rheumatism; RA = rheumatoid arthritis; STEPS = Safety, Tolerability, Efficacy, Preference (Pearls), Simplicity.

K. Other Considerations with Biologic DMARDs
   1. Tuberculosis

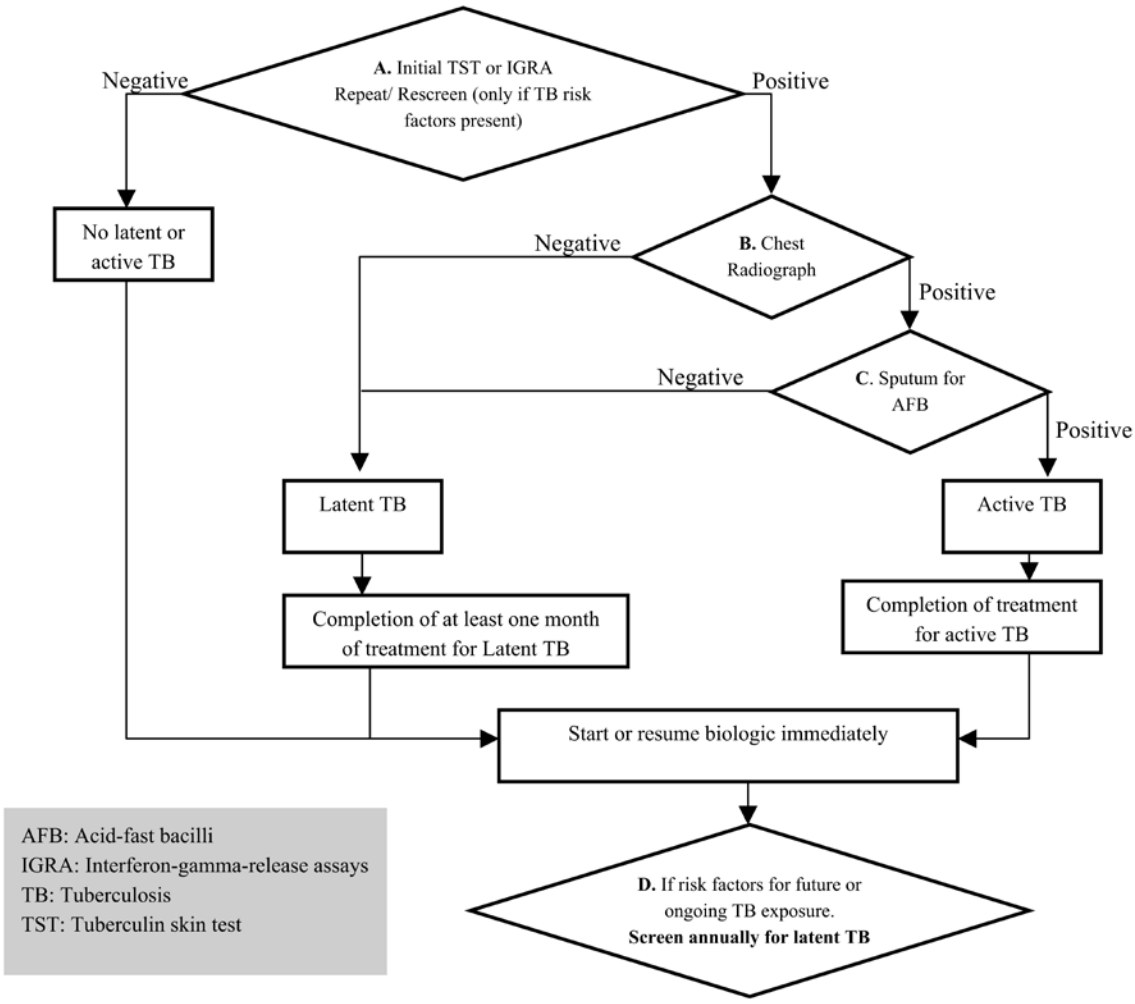

Figure 7. 2012 ACR recommendations for TB screening in patients using biologic DMARD therapy.

ACR = American College of Rheumatology; DMARD = disease-modifying antirheumatic drug; TB = tuberculosis.

Reprinted with permission from: Singh JA, Furst DE, Bharat A, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res 2012;64:625-39.

   2. Medication assistance programs (www.needymeds.com) are available for those who qualify on the basis of financial need.
   3. Many pharmacy insurance providers require prior authorization paperwork before paying for biologic DMARD therapy.
   4. Support groups are available, but patients who have used support groups have not shown significant improvements in disease or outcomes.
      a. Local group meetings
      b. Online chat or message boards
      c. Social networking groups

Patient Case

8. D.K. is a 37-year-old woman with RA for the past 8 years. She is currently treated with methotrexate and etanercept, but she returns to the rheumatology office today with worsening RA symptoms (classified as moderate to severe disease). Her concerns were the same 6 months ago, but she was given a course of oral corticosteroids in the hope that they would cause her symptoms to remit. However, her symptoms are still present and worsening. Which is the best next step to help control the patient's RA and symptoms?

   A. Start another course of prednisone, but increase the dose to 20 mg daily and continue indefinitely.
   B. Add another anti-TNF agent to the patient's regimen, such as adalimumab.
   C. Discontinue etanercept and initiate abatacept therapy for the patient.
   D. Continue etanercept and initiate abatacept therapy for the patient.

5. Patient resources
   a. Patient handouts from American Family Physician
   b. Online information from The Arthritis Foundation (www.arthritis.org)
   c. Online information from the ACR

L. Physician Quality Reporting System 2012 Quality Measures

Table 34. 2015 Physician Quality Reporting System Quality Measures

Number	Category	Criteria
108	RA: DMARD therapy	Percentage of patients ≥18 years who received a diagnosis of RA and were prescribed, dispensed, or administered at least one ambulatory prescription for a DMARD
176	RA: Tuberculosis screening	Percentage of patients ≥18 years with a diagnosis of RA who have documentation of a TB screening performed and results interpreted within 6 months before receiving a first course of therapy using a biologic DMARD
177	RA: Periodic assessment of disease activity	Percentage of patients ≥18 years with a diagnosis of RA who have an assessment and classification of disease activity within 12 months
178	RA: Functional status assessment	Percentage of patients ≥18 years with a diagnosis of RA for whom a functional status assessment was performed at least once within 12 months
179	RA: Assessment and classification of disease prognosis	Percentage of patients ≥18 years with a diagnosis of RA who have an assessment and classification of disease prognosis at least once within 12 months
180	RA: Glucocorticoid management	Percentage of patients ≥18 years with a diagnosis of RA who have been evaluated for glucocorticoid use and, for those taking prolonged doses of prednisone ≥10 mg daily (or equivalent) with improvement or no change in disease activity, documentation of glucocorticoid management plan within 12 months

DMARD = disease-modifying antirheumatic drug; RA = rheumatoid arthritis; TB = tuberculosis.

Table 35. Drugs and Doses Reference Table

Medication Name	Brand Name	Dosing
Methotrexate		5–20 mg by mouth once weekly
Leflunomide	Arava	10–20 mg by mouth once daily
Sulfasalazine	Azulfidine	1–3 g by mouth once or twice daily
Tofacitinib	XELJANZ	5 mg by mouth twice daily
Hydroxychloroquine	Plaquenil	200–600 mg by mouth once daily
Minocycline		100 mg by mouth twice daily
Adalimumab	Humira	40 mg subcutaneously every other week
Certolizumab	Cimzia	200–400 mg subcutaneously every other week (or every 4 weeks)
Golimumab	Simponi	2 mg/kg intravenously at weeks 0 and 4; then every 8 weeks thereafter 50 mg subcutaneously once monthly
Etanercept	Enbrel	50 mg subcutaneously once weekly or 25 mg twice weekly
Infliximab	Remicade	3 mg/kg intravenously at weeks 0, 2, and 6 and then every 8 weeks thereafter
Abatacept	Orencia	Initial weight-based infusion and then: IV at weeks 2 and 4 and then every 4 weeks thereafter 125 mg subcutaneously within 24 hours of infusion and then 125 mg subcutaneously every week thereafter
Rituximab	Rituxan	1000 mg intravenously at days 1 and 15 and then repeated every 24 weeks
Tocilizumab	Actemra	4–8 mg/kg intravenous every 4 weeks
Anakinra	Kineret	100 mg subcutaneously once daily

IV = intravenously.

III. PSORIATIC ARTHRITIS

A. Clinical Guidelines
   1. 2009 Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA)
   2. 2008 American Academy of Dermatology guidelines on management of psoriasis and psoriatic arthritis

B. Clinical Presentation
   1. Subtypes
      a. Arthritis mutilans – Progressive disease with "telescoping digits"
      b. Distal interphalangeal disease (DIP arthritis) – Classic symptoms presentation
      c. Oligoarticular – Asymmetric arthritis, typically with dactylitis (sausage digits)

d. Polyarticular – Symmetric arthritis
e. Spondyloarthropathy – Symptoms predominantly in vertebrae, hip, and shoulder

2. History and physical findings
   a. Articular pain, discomfort, and/or malformation
   b. Ocular inflammation
   c. Psoriatic lesions on body
   d. Skin and fingernail symptoms (e.g., fingernail begins to separate from nail bed)

C. Risk Factors
1. Presence of psoriasis, specifically at sites such as the scalp, nails, and/or gluteus and perineum
2. Environmental exposures – Trauma (Koebner effect) or infectious origin
3. Genetic predisposition – First-degree relative with disease increases risk.

D. Disease Complications
1. Rarely as severe as RA and not usually as debilitating (still painful and debilitating)
2. May result in premature cardiovascular damage or pulmonary fibrosis

Patient Case

9. E.M. is a 35-year-old woman presenting to her primary care physician for a routine follow-up. She has no significant findings in her medical history and is usually without any health concern. However, today, she reports to her physician a 2- to-3 month history of worsening pain in her fingers, hands, hips, and knees. On physical examination, she has "thick" swollen fingers; brittle, pitted nails; and several small scaly lesions on her arms and lower back. The physician performs several blood tests and finds that she has a negative antinuclear antibody (ANA) and RF finding, but a slightly elevated high-sensitivity (hs)–CRP concentration (6.4 mg/dL). From the patient's presentation, physical examination, and laboratory tests, which evidence is the most useful for the physician to use to diagnose psoriatic arthritis in this patient?

   A. Dermatologic findings and hs-CRP concentration greater than 5 mg/dL.
   B. Dactylitis, nail dystrophy, psoriatic-like lesions, and negative RF finding.
   C. Swollen fingers, psoriatic-like lesions, and hs-CRP concentration greater than 5 mg/dL.
   D. Nail dystrophy, negative ANA finding, and negative RF finding.

E. Diagnostic Evaluation
1. CASPAR (Classification criteria for Psoriatic Arthritis) criteria are both highly sensitive and specific for the diagnosis of psoriatic arthritis.
2. Requires a score of at least 3 (of possible 6) points plus established articular inflammation
   a. Current (2 points) or history of (1 point) psoriasis
   b. Dactylitis (1 point)
   c. Juxta-articular new bone formation (1 point)
   d. Negative RF finding (1 point)
   e. Nail dystrophy (1 point)
3. Negative prognostic indicators
   a. More than 5 actively inflamed joints
   b. Increased acute phase reactants
   c. Evidence of progressive radiographic changes
   d. Previous treatment with glucocorticoids
   e. Functional decline (or loss thereof)
   f. Deteriorated quality of life

F. Treatment Recommendations

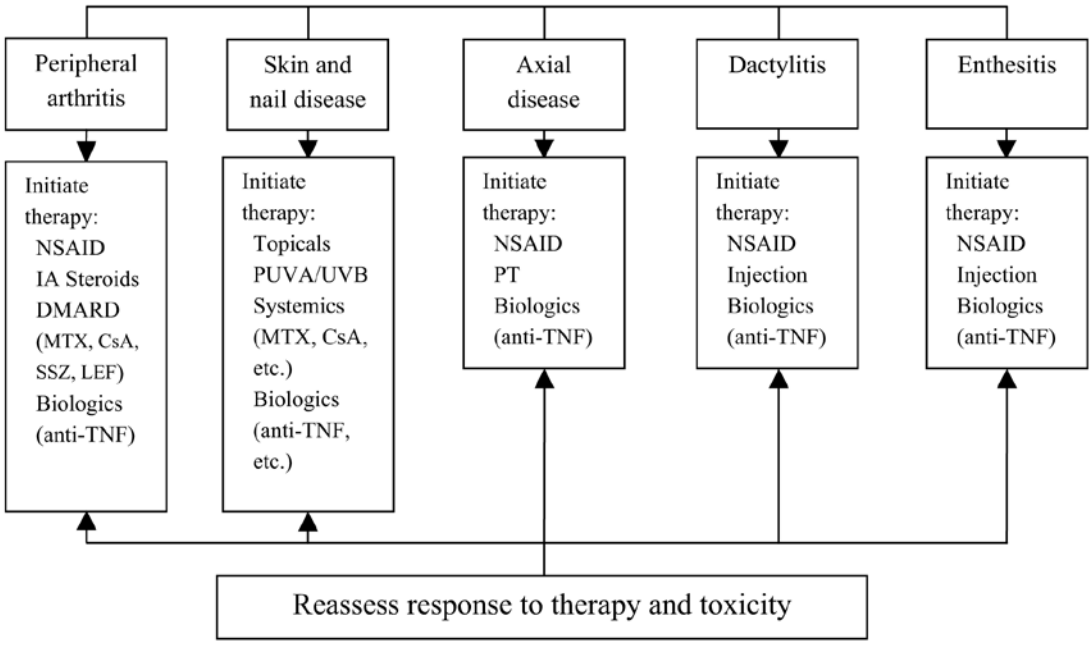

Figure 8. GRAPPA treatment guidelines for psoriatic arthritis.

Anti-TNF = antitumor necrosis factor; CsA = cyclosporine A; DMARD = disease-modifying antirheumatic drug; GRAPPA = Group for Research and Assessment of Psoriasis and Psoriatic Arthritis; IA = intra-articular; LEF = leflunomide, MTX = methotrexate; NSAID = nonsteroidal anti-inflammatory drug; PT = physical therapy; PUVA = psoralen ultraviolet A; SSZ = sulfasalazine; UVB = ultraviolet B.

Reprinted with permission from: Ritchlin CT, Kavanaugh A, Gladman DD, et al. Treatment recommendations for psoriatic arthritis. Ann Rheum Dis 2009;68:1387-94.

1. Treatment is based on agents for psoriasis and type of arthritis.
2. Initial therapy is determined by level of severity (mild, moderate, or severe).

Table 36. ACR Recommendations for Classification and Treatment of Psoriatic Arthritis[a]

Classification	Impact on Quality of Life	Therapy Choice(s)
Mild	Minimal	NSAID
Moderate	Affects daily tasks of living and physical/mental functions Lack of response to NSAID	DMARD Anti-TNF
Severe	Cannot perform major daily tasks without pain or dysfunction Large impact on physical/mental functions Lack of response to either DMARD or TNF blockers as monotherapy	DMARD plus anti-TNF or other biologic therapy

[a]See Rheumatoid Arthritis section for information about the safety, tolerability, and simplicity of the medications listed below to treat psoriatic arthritis.

ACR = American College of Rheumatology; DMARD = disease-modifying antirheumatic drug; NSAID = nonsteroidal anti-inflammatory drug; TNF = tumor necrosis factor.

Patient Case

10. T.M. is a 42-year-old man with a medical history significant for psoriasis and psoriatic arthritis. His current medications include topical betamethasone/calcipotriene and diclofenac extended release 150 mg daily. His psoriatic arthritis symptoms have been progressively worsening during the past 12 months, and he has been reluctant to use anything more than an NSAID. He has extreme debilitation more days than not and has some periods when he requires assistance with tasks such as dressing and simple cleaning. If he chooses to intensify his therapy, which would be the best approach to his treatment?
    A. Prednisone 10 mg once daily for 6 weeks.
    B. Methotrexate 10 mg once weekly.
    C. Golimumab 50 mg once monthly.
    D. Methotrexate 10 mg once weekly plus golimumab 50 mg once monthly.

3. Nonsteroidal anti-inflammatory drugs

Table 37. Efficacy and Preference/Pearls for NSAIDs in Psoriatic Arthritis

Efficacy	Monotherapy with NSAID is as effective as combination therapy with dual-NSAID or non-NSAID analgesic plus NSAID for pain associated with psoriatic arthritis
Preference (Pearls)	NSAIDs may worsen dermatologic symptoms/skin lesions in some patients

NSAID = nonsteroidal anti-inflammatory drug.

4. Nonbiologic DMARDs

Table 38. Efficacy and Preference/Pearls for Nonbiologic DMARDs in Psoriatic Arthritis

Efficacy	Methotrexate, leflunomide, and sulfasalazine all appear effective for reducing dermatologic and peripheral arthritic symptoms
Preference (Pearls)	May be used as first-line therapy in patients with moderate to severe psoriatic arthritis and/or an insufficient response to NSAID therapy

DMARD = disease-modifying antirheumatic drug; NSAID = nonsteroidal anti-inflammatory drug.

5. Biologic DMARDs

Table 39. Efficacy and Preference/Pearls for Biologic DMARDs in Psoriatic Arthritis

Efficacy	All agents (TNF inhibitors, T-cell inhibitor, and IL-12/IL-23 inhibitor) are effective for reducing the symptoms of psoriatic arthritis
Preference (Pearls)	Consider for first-line therapy in patients with moderate to severe symptoms and functional limitations with psoriatic arthritis May consider use in combination with a nonbiologic DMARD for severe or refractory cases of psoriatic arthritis

DMARD = disease-modifying antirheumatic drugs; IL = interleukin; TNF = tumor necrosis factor.

6. Alefacept (Amevive)

Table 40. Alefacept STEPS

Safety	HIV-infected patients should avoid because this medication actively reduces CD4+ counts Increased risk of malignancy Liver failure Lymphopenia and infectious complications including the following: Abscesses Cellulitis Pneumonia Toxic shock syndrome Herpes infection
Tolerability	Injection site reaction Shivering Myalgias
Efficacy	Effective as an add-on for patients with psoriatic arthritis with continued symptoms while treated with methotrexate
Preference (Pearls)	In clinical trials, alefacept was superior to placebo, when added to methotrexate, only in the ACR20 criteria and not the ACR50 or ACR70 criteria
Simplicity	Once weekly intramuscular injection

ACR = American College of Rheumatology; HIV = human immunodeficiency virus; STEPS = Safety, Tolerability, Efficacy, Preference (Pearls), Simplicity.

7. Apremilast (Otezla)

Table 41. Apremilast STEPS

Safety	Depression and suicidal ideations
Tolerability	Unintentional weight loss Nausea Diarrhea
Efficacy	As monotherapy, demonstrated improvements in patients' arthritic symptoms and quality of life
Preference (Pearls)	Dose reduction required in patients with CrCl less than 30 mL/minute Dose titration required to help patients with gastrointestinal tolerance In clinical research, improvements over placebo were noted when using both the ACR20 and ACR50 response criteria
Simplicity	Oral medicine dosed once (renally impaired) to twice daily

ACR = American College of Rheumatology; CrCl = creatinine clearance; STEPS = Safety, Tolerability, Efficacy, Preference (Pearls), Simplicity.

8. Ustekinumab (Stelara)

Table 42. Ustekinumab STEPS

Safety	Infections reported in ≥27% of patients Severe infections (2%–3%) such as sepsis, tuberculosis, or opportunistic infections Hypersensitivity reactions Malignancy (Rare) neurotoxicity Many (potentially) significant drug-drug interactions	
Tolerability	Headache Fatigue Arthralgia	
Efficacy	Has demonstrated efficacy in patients with psoriatic arthritis	
Preference (Pearls)	Provide all necessary immunizations before starting therapy If necessary, may administer inactivated vaccines during therapy, but avoid all live vaccines May be used together or in combination with methotrexate In clinical research, improvements vs. placebo are noted in the ACR20 and ACR50 response criteria	
Simplicity	Intravenous administration every 12 weeks First two doses are administered 4 weeks apart	

ACR = American College of Rheumatology; STEPS = Safety, Tolerability, Efficacy, Preference (Pearls), Simplicity.

9. Several agents in the pipeline including brodaulmab
10. Surgery may be necessary for patients whose condition does not respond sufficiently to pharmacotherapy or who have progressive loss of joint function.
11. Psoralen ultraviolet A/ultraviolet B therapy may be helpful for patients with both (extensive) skin and articular disease.

G. Patient Information - only a few resources are dedicated specifically to psoriatic arthritis because most originate from "arthritis" advocacy and information groups.
   1. The Arthritis Foundation (www.arthritistoday.org)
   2. The American College of Rheumatology (www.rheumatology.org)
   3. The Mayo Clinic (www.mayoclinic.com)

Table 43. Drugs and Doses Reference Table

Medication Name	Brand Name	Dosing
Methotrexate		5–20 mg by mouth once weekly
Leflunomide	Arava	10–20 mg by mouth once daily
Sulfasalazine	Azulfidine	2–3 g by mouth once or twice daily
Adalimumab	Humira	40 mg subcutaneously every other week
Golimumab	Simponi	50 mg subcutaneously once monthly
Etanercept	Enbrel	50 mg subcutaneously twice weekly for 3 months; then 25 mg twice weekly
Infliximab	Remicade	5 mg/kg intravenously at weeks 0, 2, and 6; then every 8 weeks thereafter

Table 43. Drugs and Doses Reference Table *(continued)*

Medication Name	Brand Name	Dosing
Abatacept	Orencia	Initial weight-based infusion and then: IV at weeks 2 and 4; then every 4 weeks thereafter 125 mg subcutaneously within 24 hours of infusion; then 125 mg subcutaneously every week thereafter
Alefacept	Amevive	15 mg intramuscular injection each week
Apremilast	Otezla	10 mg once daily on DAY 1 10 mg twice daily on DAY 2 10 mg in the morning and 20 mg in the evening on DAY 3 20 mg in the morning and 20 mg in the evening on DAY 4 20 mg in the morning and 30 mg in the evening on DAY 5 30 mg twice daily thereafter
Ustekinumab	Stelara	45 mg subcutaneously at weeks 0 and 4; then every 12 weeks thereafter

IV = intravenously.

IV. OSTEOARTHRITIS

A. Treatment Guidelines
   1. Michigan Quality Improvement Consortium 2007 (updated 2011)
   2. National Institute for Health and Clinical Excellence
   3. American College of Rheumatology 2012

B. Common Sites
   1. Knees
   2. Hips
   3. Small joints of the hand
   4. Low back
   5. Ankle
   6. Elbow

C. Risk Factors
   1. Many risk factors are reversible and/or avoidable.
   2. Risk factors for developing disease are not always risk factors for clinical progression (e.g., a high bone density may be a risk factor for developing osteoarthritis, but a low bone density increases the chance of clinical progression).

Table 44. Factors Associated with Developing Osteoarthritis

Biomechanical	Joint injury Occupational/recreational use Joint laxity	Reduced muscle strength Joint malignancy
Constitutional	Ageing Obesity	Female sex High bone density
Genetic	40%–60% of hand, knee, and hip osteoarthritis is inherited through unknown genes	

Table 45. Clinical Findings in Osteoarthritis by Joint

	Back (chronic low back pain)	Knee	Hand (metacarpophalangeal)
Patient concerns	Low back pain for >3 months	Activity related Instability or buckling Morning stiffness <30 minutes Recurrent pain	Thumb or radial hand pain Difficulty with manual dexterity Gelling with inactivity <10 minutes Morning stiffness <30 minutes
Physical findings	Pain with straight leg raise examination (30–70 degrees)	Bony enlargement Crepitus Limited range of motion	Localized tenderness Limited range of motion
Imaging	Radiography is not routinely recommended for nonspecific back pain Consider MRI or CT for patients only if they are candidates for surgery	Radiography findings may be normal and are only adjunct to diagnosis CT or MRI is not indicated	Radiography (for staging)
Laboratory evaluation	Only in the presence of "red flags"[a]	Erythrocyte sedimentation rate (<40 mm/hour) Rheumatoid factor < 1:40 Synovial fluid aspiration unremarkable	Aspirate evaluation if suspected infection

[a]Red flags = age at onset > 50 years, pain unrelenting at night or unrelated to activity, widespread symptoms, progressive motor or sensory deficit, unexplained weight loss, fevers/chills/infection, significant trauma, indications of nerve root problem, history of cancer, human immunodeficiency virus, steroids, osteoporosis, or substance abuse.

CT = computed tomography; MRI = magnetic resonance imaging.

D. Nonpharmacologic Interventions
   1. Education about expectations for therapy, importance of nonpharmacologic management strategies, and cognitive behavioral therapy (chronic low back pain)
   2. Weight loss (at least 5%)
   3. Low-impact exercise
   4. Physical therapy (mixed results as beneficial in the short term, but may lessen as patients provide self-care at home after stopping therapy)
   5. Support braces, orthotics, and assistive devices also have mixed results and are not strongly recommended by the American Academy of Orthopedic Surgeons (AAOS).

Patient Case

11. T.W. is a 67-year-old man with severe degenerative joint disease of his right knee. His medical history is significant for coronary artery disease (myocardial infarction 6 years earlier), heart failure (ejection fraction 32%), hypertension, erectile dysfunction, and gastroesophageal reflux disease. He takes lovastatin 40 mg daily, fosinopril 20 mg daily, carvedilol 12.5 mg twice daily, aspirin 81 mg daily, calcium carbonate chewable tablets as needed (around three times weekly), and sildenafil 25 mg as needed. His knee pain causes significant physical limitations, and he is embarrassed to use an electronic cart when he shops at grocery and department stores. He would like to be more active but has difficulty even with the activities of daily living. Given this information, which is the best initial choice for this patient's knee osteoarthritis?

    A. Take acetaminophen 650 mg two tablets every 6 hours as needed for pain.
    B. Take ibuprofen 400 mg one tablet every 6 hours as needed for pain.
    C. Take naproxen 500 mg one tablet every 12 hours as needed for pain.
    D. Apply diclofenac 1% gel to affected knee up to four times daily.

Table 46. Pharmacologic Interventions

Class/Agent	Comments
Topical applications	Capsaicin, NSAIDs Topical NSAIDs have proved short-term efficacy, but there is insufficient information to comment on long-term use (>12 weeks), and they are markedly more expensive than oral NSAIDs Topical NSAIDs are recommended over oral NSAIDs for patients >75 years Topical capsaicin should reduce pain in about 2 weeks
Acetaminophen	Recommended as the first-line pharmacologic agent for pain associated with (mild) osteoarthritis (Exception: Acetaminophen is not recommended by the ACR for hand OA) Maximal dose of 4 g daily is still acceptable, though much more likely to see transaminase elevations with higher doses Most research finds acetaminophen more effective than placebo for osteoarthritis pain, but less effective than NSAIDs
NSAIDs	Naproxen, ibuprofen NSAIDs are more effective than acetaminophen at reducing pain, but their adverse event profile is less favorable No single NSAID is preferred to another, though the ACR does not recommend ibuprofen for patients using aspirin for cardiovascular disease prevention because of FDA documentation that ibuprofen interferes with aspirin activity The selective COX-2 inhibitor agent celecoxib may also be considered an alternative to nonselective NSAIDs; efficacy profile is the same as that for traditional NSAIDs, but with fewer reports of adverse GI events, and COX-2 agents do not affect platelet function For patients with a history of GI ulceration, a COX-2 inhibitor or an NSAID with a proton pump inhibitor is recommended as primary therapy For patients with a GI bleed in the past 12 months, the ACR recommends using a COX-2 inhibitor with a proton pump inhibitor

Table 46. Pharmacologic Interventions *(continued)*

Class/Agent	Comments
Controlled opioid analgesics	Opioid analgesics may be useful, but they should not be used routinely to treat pain associated with osteoarthritis Patients may respond to therapy, but limit use to patients with severe pain that is inadequately controlled with previously mentioned therapies Likelihood of adverse event similar to that of NSAIDs NOT routinely recommended for osteoarthritis because risk and severity of adverse events outweigh benefit potential
Glucosamine and chondroitin	Delayed onset of effects, cannot be used for immediate pain relief Trials that evaluate the use of glucosamine (with or without chondroitin) are usually small and of variable quality, resulting in highly heterogeneous conclusions in meta-analyses and systematic reviews NOT routinely recommended by the ACR
Low-dose corticosteroids	May help with short-term pain reduction and increased mobility for patients with moderate to severe osteoarthritis of the knee

ACR = American College of Rheumatology; COX-2 = cyclooxygenase-2; FDA = U.S. Food and Drug Administration; GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug; OA = osteoarthritis.

E. Tramadol (Con Zip, Rybix, Ryzolt, Ultram, Ultram ER [extended release])

Table 47. Tramadol STEPS

Safety	Avoid use (Rybix, Ultram, Ultram ER) in any situation where opioids are not indicated, including acute intoxication with alcohol, hypnotics, opioids, or psychotropic drugs Avoid use (Con Zip, Ryzolt) in patients with severe/acute asthma, hypercapnia, or severe respiratory depression in the absence of resuscitative equipment Contraindicated within 14 days of monoamine oxidase inhibitor therapy Seizures: As monotherapy or with greater risk when combined with other agents that lower the seizure threshold Limit immediate-release dose to 50 mg every 12 hours in patients with cirrhosis Avoid extended-release formulations in severe hepatic impairment (Child-Pugh class C) Cautious use in patients with mild to moderate renal impairment and avoid extended-release formulations in severe renal impairment (CrCl < 30 mL/minute) Risk of serotonin syndrome in patients concurrently using agents that act on the serotonin system	
Tolerability	CNS depression Constipation Dizziness Dyspepsia Flushing	Headache Nausea Postural hypotension Pruritus Somnolence
Efficacy	Provides small degree of pain relief	
Preference (Pearls)	Consider as an alternative in patients who do not receive adequate pain relief from acetaminophen and cannot tolerate it or for whom NSAID therapy is contraindicated	
Simplicity	May administer dose as needed up to four times daily (maximum 100 mg per dose) Classified by the DEA as Schedule IV in August 2014	

CNS = central nervous system; CrCl = creatinine clearance; DEA = Drug Enforcement Agency; ER = extended release; NSAID = nonsteroidal anti-inflammatory drug; STEPS = Safety, Tolerability, Efficacy, Preference (Pearls), Simplicity.

F. Invasive Interventions
   1. Intra-articular corticosteroids may be effective for short-term pain relief (less than 4 weeks), but there is usually diminishing benefit beyond that time.
      a. Joint injections should not be performed more often than every 3 months.
      b. Osteoarthritis symptoms requiring regular use of corticosteroid injections (three or four a year) should be considered for surgical intervention.
   2. Intra-articular hyaluronic acid may be as effective as intra-articular corticosteroids for some patients, but with benefits observed up to 6 months.
      a. Benefits over corticosteroids not observed until 4 weeks after injections
      b. Much more costly alternative to intra-articular corticosteroids
      c. More frequent injections because many regimens require weekly injections for 3–5 consecutive weeks

G. Surgery
   1. Total arthroplasty (joint replacement)
   2. Arthroscopic debridement
   3. Arthroscopic lavage

H. Alternative Treatments
   1. S-adenosylmethionine (SAMe) may decrease pain and improve functional limitations in patients with osteoarthritis.
   2. Avocado/soybean unsaponifiables appear to help reduce pain in patients with osteoarthritis, but few trials with questionable supportive bias
   3. Devil's claw (*Harpagophytum procumbens*) has been associated with pain reduction in osteoarthritis in several low-quality clinical trials.

I. Patient Resources
   1. Patient handouts from American Family Physician
   2. Online information from The Arthritis Foundation

Table 48. 2015 Physician Quality Reporting System Quality Measures

No.	Category	Criteria
109	OA: Function and pain assessment	Percentage of patient visits for patients ≥21 years with a diagnosis of OA with assessment for function and pain

OA = osteoarthritis; OTC = over-the-counter.

V. FIBROMYALGIA

A. Clinical Guidelines
   1. 2004 American Pain Society (APS) guideline on the management of fibromyalgia syndrome
   2. 2008 EULAR evidence-based recommendations for the management of fibromyalgia syndrome
   3. 2010 ACR preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity

B. Patient Presentation and Symptoms
   1. Patients will experience the following:
      a. Physical symptoms (weakness, fatigue, decrements in physical function, morning stiffness, heat or cold disturbances, swelling in extremities)
      b. Psychological symptoms (mood disturbances)
      c. Cognitive problems (difficulty concentrating, diminished mental clarity, memory problems)
      d. Photophobia, phonophobia, and/or osmophobia

Patient Case

12. M.F. is a 32-year-old woman presenting to her primary care physician's office with fatigue, "pain all over," and headaches for the past 4 weeks. She has a history of major depression, but she has been successfully treated with regular counseling. She reports having a dull, aching pain most days in her shoulders and upper arms (bilateral), hips (bilateral), neck, and lower back. She says that she has fatigue daily (cannot play with children), difficulty sleeping 2 or 3 nights per week, and chronic headaches. She heard from a friend that she has all the symptoms of fibromyalgia and would like to be treated. Which is the best response for the physician to provide to the patient?

    A. Her symptoms do not meet the fibromyalgia diagnosis criteria.
    B. Her fibromyalgia would benefit most from tai chi.
    C. Her fibromyalgia requires drug therapy.
    D. Her fibromyalgia will require treatment with a two-drug regimen.

   2. Diagnostic tools
      a. Widespread pain index (WPI): Award 1 point for each location a patient has experienced pain in the past 7 days.

Shoulder girdle, left	Shoulder girdle, right	Upper arm, left	Upper arm, right	Lower arm, left
Upper leg, left	Upper leg, right	Hip (buttock, trochanter), left	Hip (buttock, trochanter), right	Lower arm, right
Lower leg, left	Lower left, right	Jaw, left	Jaw, right	Chest
Abdomen	Upper back	Lower back	Neck	

      b. Symptom severity scale (SSS): Award 0–3 points for each level of severity of fatigue, waking unrefreshed, cognitive symptoms, and somatic symptoms.
         i. 0 = no problem/symptoms
         ii. 1 = slight or mild problems/few symptoms
         iii. 2 = moderate or considerable problems/moderate number of symptoms
         iv. 3 = severe, pervasive, life-disturbing problems/great deal of symptoms
      c. ACR updated the diagnosis in 2010 to include the following:
         i. Symptoms for more than 3 months PLUS
            (a) WPI of 7 or higher and an SSS of 5 or higher -OR-
            (b) WPI of 3–6 and an SSS of 9 or higher
         ii. Absence of other disorders that could cause the same symptoms

C. Professional Treatment Recommendations (APS and EULAR)
   1. Educate patients about pain management and self-management.
   2. Cognitive behavioral therapy will help reduce pain, improve function, and enhance self-efficacy.
   3. Exercise programs should be of "moderate" intensity.
      a. High-intensity exercise will make symptoms of fibromyalgia worse.
      b. Exercise recommendations state the patient should exercise two to three times per week to a target of 60%–75% of his or her age-adjusted maximum heart rate (210 minus patient age).
      c. Patients should stretch before exercise to the point of mild resistance to reduce exercise-induced pain and injury.
   4. Other nonpharmacologic treatments
      a. Acupuncture
      b. Biofeedback
      c. Chiropractic manipulation
      d. Heated pool treatments (with or without exercise)
      e. Hypnosis
      f. Osteopathic manipulation
      g. Therapeutic massage
   5. Pharmacologic treatment strategy
      a. Tricyclic antidepressants, particularly amitriptyline, are the first-line treatment for reducing pain and symptoms associated with fibromyalgia.
      b. If patient has a contraindication to, cannot tolerate, or does not respond to therapy with a tricyclic antidepressant (at target does), consider therapy with an alternative agent.
      c. Additional classes with efficacy (vs. placebo) include the following:
         i. α2δ Ligands (gabapentin, pregabalin)
         ii. Dopamine D_3 receptor agonists (pramipexole)
         iii. Selective serotonin reuptake inhibitors (fluoxetine, paroxetine)
         iv. Serotonin and norepinephrine dual reuptake inhibitors (duloxetine, milnacipran)
         v. Nonopioid μ-receptor antagonist (tramadol)
   6. Tricyclic antidepressants
      a. Amitriptyline
      b. Cyclobenzaprine
      c. Nortriptyline

Table 49. Tricyclic Antidepressant STEPS

Safety	FDA warns that antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults with major depressive disorder Orthostatic hypotension Use with caution in patients with a history of cardiovascular disease, diabetes, hepatic impairment, mania/hypomania, renal impairment, seizure disorders, or thyroid dysfunction Patients should discontinue tricyclic antidepressants before general elective surgery that requires anesthesia	
Tolerability	Anticholinergic effects Anorexia Dizziness Hypertension/hypotension Insomnia Numbness	Paresthesia Syncope Tachycardia Urticaria Weight gain

Table 49. Tricyclic Antidepressant STEPS *(continued)*

Efficacy	Tricyclic antidepressants, particularly amitriptyline, are the best medication intervention for improving the symptoms of fibromyalgia Have been proved to decrease symptoms of pain, fatigue, sleep, and depressed mood
Preference (Pearls)	Target dose of amitriptyline or cyclobenzaprine is 10–30 mg in the evening before sleep Likelihood of experiencing pain relief is about the same as the likelihood of experiencing an adverse event
Simplicity	Once-daily dosing in the evening, before sleep, to decrease adverse event severity

FDA = U.S. Food and Drug Administration; STEPS = Safety, Tolerability, Efficacy, Preference (Pearls), Simplicity.

Patient Case

13. S.E. is a 39-year-old woman with a medical history significant for minor depressive disorder. She is presenting to a medication management clinic after having initiated amitriptyline therapy for fibromyalgia. She raised the dose to 50 mg during the past 4 weeks and reports that she has not experienced a significant change in her symptoms. However, she does report that her negative feelings have lessened and that her sleep is much improved, but the pain and discomfort associated with her fibromyalgia remain. She is requesting a new medication to help control her symptoms. Which medication would be best to replace amitriptyline?

A. Gabapentin titrated to 800 mg three times daily.
B. Pregabalin 75 mg twice daily.
C. Duloxetine 60 mg once daily.
D. Tramadol 50 mg every 6 hours as needed for pain.

7. Selective serotonin reuptake inhibitors
   a. Fluoxetine
   b. Paroxetine

Table 50. Selective Serotonin Reuptake Inhibitor STEPS

Safety	See above for FDA warning about suicidal ideations with anitdepressants Allergic skin reactions May increase bleeding risk when used in conjunction with antiplatelet or anticoagulation therapy Use with caution in patients with a history of cardiovascular disease, diabetes, mania/hypomania, hepatic effects, renal impairment, and/or seizure disorders	
Tolerability	Anticholinergic effects Diarrhea Dizziness Dyspepsia	Headaches Insomnia Nausea Sexual dysfunction
Efficacy	Evidence is available to support use in fibromyalgia, but strength of recommendation is not as strong as with tricyclic antidepressants The combination of a selective serotonin reuptake inhibitor and a tricyclic antidepressant is better than either class alone	
Preference (Pearls)	Fluoxetine and paroxetine are the most often studied agents to have an effect in patients with fibromyalgia symptoms Small clinical trial with citalopram vs. placebo did not show significantly reduced symptoms	
Simplicity	Once-daily dosing	

FDA = U.S. Food and Drug Administration; STEPS = Safety, Tolerability, Efficacy, Preference (Pearls), Simplicity.

8. Serotonin and norepinephrine dual reuptake inhibitors
   a. Duloxetine
   b. Milnacipran

Table 51. Serotonin and Norepinephrine Dual Reuptake Inhibitor STEPS

Safety	See above for FDA warning about suicidal ideations with antidepressants Increased risk of bleeding when used with antiplatelet or anticoagulation therapy Severe skin reactions have been reported with duloxetine Blood pressure and heart rate may be increased with milnacipran	
Tolerability	Anticholinergic effects Dizziness Headache Hyperhidrosis Insomnia	Nausea Hot flashes (milnacipran) Sexual dysfunction
Efficacy	Agents equally improve pain, sleep, depressed mood, and quality of life in patients with fibromyalgia Duloxetine 60 mg or 120 mg daily is effective for treating fibromyalgia syndrome Milnacipran's target dose is 50 mg twice daily (start with 12.5 mg twice daily and titrate every 7 days to target dose) Class efficacy is equal to that of pregabalin, but assumed from indirect comparisons of all three agents	
Preference (Pearls)	Both duloxetine and milnacipran are FDA approved for treating fibromyalgia syndrome Duloxetine requires dose adjustments when creatinine clearance is <30 mL/minute	
Simplicity	Agents are dosed once or twice daily and have a relatively quick onset of effect	

FDA = U.S. Food and Drug Administration; STEPS = Safety, Tolerability, Efficacy, Preference (Pearls), Simplicity.

9. α2δ Ligand
   a. Gabapentin
   b. Pregabalin

Table 52. α2δ Ligand STEPS

Safety	Safety concerns are relatively rare, but still present: Angioedema Visual field disturbances have been reported Use with caution in patients with cardiac disease, particularly heart failure, because of the risk of edema	
Tolerability	Dizziness Edema (peripheral)	Somnolence Weight gain
Efficacy	Both gabapentin and pregabalin are effective for improving pain, sleep, fatigue, and quality of life Poor tolerability reported in clinical trials	
Preference (Pearls)	Target dose: Gabapentin 2400 mg daily Pregabalin 300–450 mg daily Dosage adjustments are required in patients with renal impairment Pregabalin is registered as a schedule V substance (euphoria)	
Simplicity	Pregabalin is dosed twice daily Titration schedule for gabapentin is relatively difficult and requires thrice-daily dosing	

STEPS = Safety, Tolerability, Efficacy, Preference (Pearls), Simplicity.

10. Nonopioid μ-receptor antagonist (tramadol)
    a. See STEPS analysis and Osteoarthritis section.
    b. The APS recommends using tramadol when all other pain relief therapies have been exhausted.
11. Dopamine D_3 receptor agonists (pramipexole): One small clinical trial (60 patients) reported at least a 50% improvement in symptoms in significantly more patients using pramipexole titrated to 4.5 mg daily than with placebo.

D. Patient Information
    1. Medications are effective for symptom relief, but all professional organizations advocate for education and cognitive behavioral therapy as the root of all treatments.
    2. Most clinical trials evaluate and report symptom improvement and not complete symptom resolution.
    3. Patient information resources available online
        a. Arthritis Foundation offers a variety of resources, including a self-help course, books, and educational videos (www.arthritis.org/conditions-treatments/disease-center/fibromyalgia-fms/).
        b. Exercise videos are available for purchase ($30 per video) through the Fibromyalgia Information Foundation (www.myalgia.com).

Table 53. Drugs and Doses Reference Table

Medication Name	Brand Name	Dosing
Amitriptyline	Elavil	25–100 mg once daily at bedtime
Nortriptyline	Pamelor	25–100 mg once daily at bedtime
Cyclobenzaprine	Flexeril	5–10 mg by mouth three times daily
Fluoxetine	Prozac	20–80 mg by mouth once daily
Paroxetine	Paxil	20–60 mg by mouth once daily
Duloxetine	Cymbalta	60 mg by mouth once daily
Milnacipran	Savella	50 mg by mouth twice daily
Gabapentin	Neurontin	300–1200 mg by mouth three times daily
Pregabalin	Lyrica	75–150 mg twice daily

VI. SYSTEMIC LUPUS ERYTHEMATOSUS

A. Clinical Guidelines
    1. 2008 EULAR recommendations on management of SLE
    2. 2008 EULAR recommendation on monitoring patients with SLE in clinical practice and in observational studies

Table 54. Definitions/Stages of SLE

Active SLE	The patient has signs/symptoms and tests that are attributed to inflammation and are reversible (target organ damage) with therapy
Mild SLE	The patient's condition is clinically stable without progressing organ damage or toxicity
Uncontrolled SLE	The patient's signs/symptoms of SLE continue despite pharmacologic treatment
Remission	The patient does not have signs/symptoms of SLE and is not receiving treatment
Complete response	Clinical remission with pharmacologic treatment

SLE = systemic lupus erythematosus.

Table 55. Organ Systems Involved and Potential Complications

Organ System	Potential Complications
Cardiovascular	Hypertension, dyslipidemia, endocarditis, pericardial effusion, valvular disease
Central nervous system	Cognitive disorders, neuropsychiatric disorders, depression, seizures
Gastrointestinal tract	Mesenteric vasculitis, pancreatitis
Hematologic/oncologic	Hemolytic anemia, neutropenia, thrombosis, thrombocytopenia, thrombotic thrombocytopenic purpura, non-Hodgkin lymphoma
Joints	Arthritis
Kidneys	Renal disease (lupus nephropathy or lupus nephritis)
Lungs	Pulmonary hypertension, pneumonitis, pulmonary embolus, interstitial fibrosis

B. Risk Factors for Disease
   1. Family history of SLE or other autoimmune disorders
   2. Exposure to silica, mercury, and/or pesticides
   3. Drug-induced disease
      a. Captopril
      b. Chlorpromazine
      c. Hydralazine
      d. Isoniazid
      e. Methyldopa
      f. Procainamide
      g. Quinidine
      h. Sulfasalazine
      i. Estrogens and oral contraceptives (not causative, but may provoke and worsen flares in patients with lupus)

C. Clinical Presentation: There are several clinical findings during a patient's history and physical examination, but some are more common than others.

Table 56. Frequency of Presenting Symptoms

Symptoms	Frequency, %
Arthritis	48.1
Malar rash	31.1
Active nephropathy	27.9
Neurologic changes	19.4
Fever	16.6
Raynaud phenomenon	16.3
Serositis	16
Thrombocytopenia	13.4
Thrombosis	9.2

D. Diagnosis
   1. ACR criteria for classification require four positive (of possible 11) findings.
   2. Findings may be present sequentially or at the same time.

Table 57. Eleven Criteria to Evaluate for the Diagnosis of Systemic Lupus Erythematosus

Malar (butterfly) rash	Discoid lupus	Photosensitivity
Oral or nasopharyngeal ulcers	Serositis	Nonerosive arthritis
Persistent proteinuria or casts	Immunologic abnormalities	Hematologic changes
Nonorganic seizures or psychosis	Positive ANA test result without drug-induced causes	

ANA = antinuclear antibody.

Table 58. Diagnostic Testing for Systemic Lupus Erythematosus

Antinuclear antibody	Anti–double-stranded DNA antibody	Anti-Ro antibody
Anti-La antibody	Anti-RNP antibody	Anti-Sm antibody
Anti-phospholipid	C3, C4	

RNP = Ribonucleic protein.

Table 59. Other Pretreatment and "Routine" Testing for Systemic Lupus Erythematosus

Baseline		
Validated symptoms survey	Quality-of-life assessment	Ophthalmologic examination[a]
Routine every 6–12 months		
Complete blood cell count	Erythrocyte sedimentation rate	C-reactive protein
Albumin, serum	Creatinine, serum	Urinalysis
Creatinine/microalbumin ratio		

[a]See antimalarial drugs for more specific recommendations.

E. Drug Treatment Strategies (EULAR recommendations)
   1. Antimalarial drugs are first-line therapy for all patients with newly diagnosed SLE and/or without major organ involvement, unless otherwise contraindicated.
   2. Systemic corticosteroids may be used to prevent flares and clinical relapse.
   3. Steroids can be used in addition to antimalarial agents to control symptoms and prevent seromarker elevation.
   4. NSAIDs may be used for a brief period, but patients need to be aware of gastrointestinal, cardiovascular, and/or renal complications.
   5. Immunosuppressive agents (methotrexate, azathioprine, and/or mycophenolate) are reserved for patients who cannot achieve disease control with antimalarial drugs and corticosteroids.

Patient Case

14. D.B. is a 29-year-old woman with a medical history significant for SLE and lupus nephritis. Her current treatment is hydroxychloroquine 200 mg once daily, but she continues to have complications because of the disease, including persistent proteinuria and serositis. To control her symptoms, which intervention would be best?
    A. Increase the hydroxychloroquine dose to achieve a serum concentration greater than 1000 ng/mL.
    B. Add prednisone 40 mg daily for the next 6 months.
    C. Add omega-3 fatty acids (eicosapentaenoic acid [EPA] 1.8 g and docosahexaenoic acid [DHA] 1.2 g) per day.
    D. Add azathioprine 2 mg/kg/day.

6. Antimalarial agents
    a. Chloroquine
    b. Hydroxychloroquine

Table 60. Antimalarial Agents STEPS

Safety	Cardiomyopathy with long-term hydroxychloroquine use (rare) May cause the following: Agranulocytosis, aplastic anemia, and/or thrombocytopenia Exfoliative dermatitis, Stevens-Johnson syndrome Myopathy and muscle weakness Exacerbation of porphyria and/or psoriasis Loss of visual acuity and macular pigment changes (risk is highest with hydroxychloroquine doses > 6.5 mg/kg of lean body weight) Use with caution in patients with hepatic disease or on concurrent hepatotoxic agents	
Tolerability	Abdominal cramping Alopecia Diarrhea Emotional changes	Nightmares Psychosis Tinnitus Urticaria
Efficacy	Reduces disease activity in most patients and reduces the average dose of corticosteroids needed to control symptoms Associated with a reduction in mortality, irreversible organ damage, and progression to active disease	
Preference (Pearls)	Recommended as first-line treatment by both EULAR (SLE without major organ involvement) and ACR (mild SLE) Dosing to achieve serum hydroxychloroquine concentration > 1000 ng/mL does not reduce the likelihood of disease flare American Academy of Ophthalmology recommends that patients have funduscopic and visual field examination within the first year of starting hydroxychloroquine; ophthalmologic screening recommendations are based on risk of drug-related disease (see Table 61)	
Simplicity	Initially dosed once or twice daily until sufficient patient response Once-daily maintenance dosing	

ACR = American College of Rheumatology; EULAR = European League Against Rheumatism; SLE = systemic lupus erythematosus; STEPS = Safety, Tolerability, Efficacy, Preference (Pearls), Simplicity.

Table 61. Ophthalmologic Screening Recommendations for Patients Treated with Antimalarial Agents

Risk Category	Recommendations	Criteria
Low	Screen as part of regular examination during the first 5 years Reevaluate if drug dose is increased or if there are changes in patient weight or renal/hepatic function	Dose < 6.5 mg/kg for hydroxychloroquine or 3 mg/kg for chloroquine Treatment for <5 years Lean or average fat level No renal or hepatic disease <60 years old
High	Annual screening May require additional testing for: Extended therapy duration Doses > 10 mg/day	Dose > 6.5 mg/kg for hydroxychloroquine or 3 mg/kg for chloroquine Treatment for >5 years High fat level (unless dose adjusted for obesity) Renal or hepatic disease Current retinal disease >60 years old

7. Corticosteroids (see Rheumatoid Arthritis section for full STEPS analysis)
   a. Corticosteroids will delay the onset and prevent relapse or flares of SLE.
   b. May be dosed daily or on opposite days for patients with stable disease
   c. Doses of 20 mg or higher (prednisone equivalent) may be necessary for patients with progressive end-organ damage caused by lupus.
8. Immunosuppressive therapy (azathioprine, cyclosporine, methotrexate, mycophenolate mofetil)
   a. Agent of choice for patients when unable to prevent disease progression or induce remission with antimalarial drugs
   b. Recommended for patients with organ involvement (neuropsychiatric lupus, lupus nephritis, cutaneous lupus)
   c. Consider for use in patients who are unable to reduce their corticosteroid dose (to less than 10 mg of prednisone equivalent) per day
   d. Appears that azathioprine and cyclosporine are equal with respect to efficacy and safety in patients with SLE
   e. Both methotrexate and mycophenolate mofetil will decrease steroid requirements for patients treated with higher-than-acceptable corticosteroid doses.
   f. Rituximab, belimumab, or epratuzumab (investigational), added to standard therapy, has demonstrated benefits in patients with treatment refractory disease.

F. Nonpharmacologic Interventions
1. Lifestyle modifications include smoking cessation, weight control, and exercise (where applicable)
   a. Omega-3 fatty acid intake (1.2 g of DHA and 1.8 g of EPA each day) reduced scores on validated SLE symptom surveys.
   b. Cardiovascular training programs may improve SLE symptom score surveys.
   c. Cognitive behavioral therapy and counseling may reduce fatigue and improve patient-reported mental health.
2. Recommend that patients regularly use sunscreen in all outdoor exposure
3. Do not use live vaccines in patients taking greater than 20 mg of corticosteroids (prednisone equivalents) each day.

G. Patient Information – Several online resources and professional groups provide patient information.
   1. American College of Rheumatology (www.rheumatology.org)
   2. Lupus Foundation of America (www.lupus.org)
   3. National Institute of Arthritis and Musculoskeletal and Skin Disease (www.naims.nih.gov)

Table 62. Drugs and Doses Reference Table

Medication Name	Brand Name	Dosing
Hydroxychloroquine	Plaquenil	400–600 mg by mouth each day

VII. GOUT AND HYPERURICEMIA

A. Professional Treatment Recommendations and Guidelines
   1. 2012 ACR guidelines for the management of gout
   2. 2006 EULAR evidence-based recommendations for the diagnosis and management of gout
   3. 2007 British Society for Rheumatology guideline for the management of gout

B. Gout and Hyperuricemia
   1. Peak onset is between 40 and 60 years of age.
   2. Men are 3–4 times more likely to develop gout and hyperuricemia, but the gender gap is less compared with postmenopausal women (estrogen stimulates renal elimination of uric acid).

Table 63. Characteristics of Gout

Type	Characteristics
Acute gout (gouty arthritis)	Severe pain and swelling with erythema First event is usually monoarticular (first metatarsophalangeal joint) and presents to patient overnight or in the early morning Subsequent attacks may involve more joints such as the ankle, finger(s), foot, knee, and/or wrist May resemble cellulitis
Chronic tophaceous gout	Persistent pain and swelling, accompanied by joint stiffness Polyarticular involvement Soft tissue mass composed of monosodium urate crystals and forming in areas of lowest body temperature (fingers, hands, ears) Frequent recurrent attacks Persistently elevated serum uric acid concentrations

Table 64. Risk Factors for Developing Gout and Hyperuricemia (uric acid, serum concentration greater than 6.8 mg/dL)

Conditions	Lifestyle	Medications
Alcoholism Cardiovascular disease Diabetes mellitus Dyslipidemia Hypothyroidism Lead exposure Metabolic syndrome Organ transplant Renal disease Myeloproliferative disorders Genetic disorders	Obesity Increased animal purine intake Consuming high-fructose foods and drinks Alcohol (beers, liquors more than wines)	Thiazide diuretics Low- to moderate-dose aspirin Ethambutol Nicotinic acid Vitamin B_{12} Cyclosporine Levodopa Pyrazinamide Cytotoxic agents Ethanol

Table 65. Factors Associated with the Underexcretion or Overproduction of Uric Acid

Underexcretion of urate	Primary	Dehydration Hypertension Hyperparathyroidism Hypothyroidism Lactic acidosis Renal insufficiency Lead exposure (“saturnine gout”)
	Secondary	Ketosis Drug induced Aspirin (≤325 mg daily) Cyclosporine Diuretics Ethambutol Ethanol Levodopa Niacin Pyrazinamide
Overproduction of urate	Primary	Hypoxanthine-guanine phosphoribosyltransferase deficiency, phosphoribosyl pyrophosphate enzyme synthase activity, type I glycogen storage disease (von Gierke disease)
	Secondary	Excessive purine intake Exfoliative psoriasis Hypertriglyceridemia Rapidly dividing tumors Tumor lysis syndrome Myeloproliferative/lymphoproliferative disorders Cytotoxic agents Vitamin B_{12} Alcohol/ethanol

C. Gout Complications
   1. Uric acid nephrolithiasis
   2. Acute uric acid nephropathy
   3. Chronic kidney disease secondary to urate crystal deposition

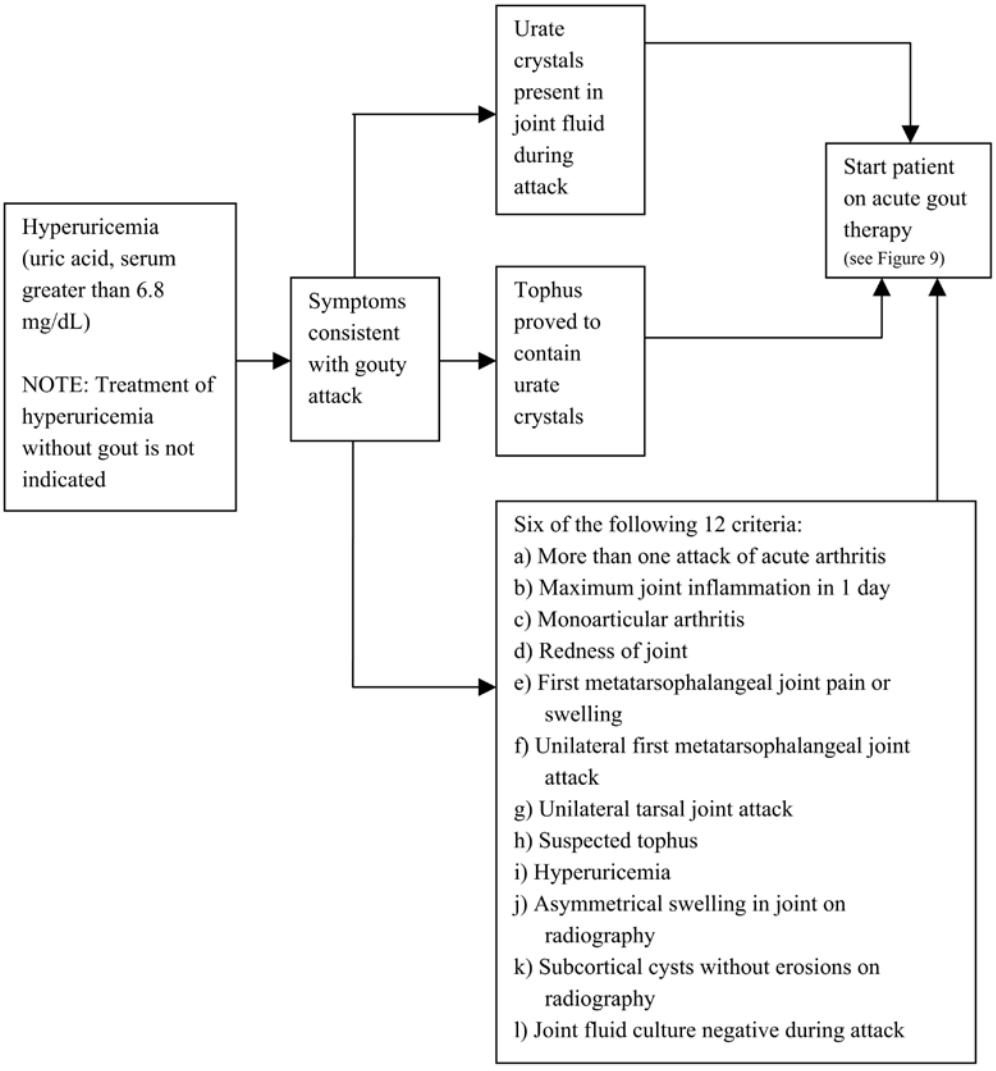

Figure 9. Decision to treat acute gout symptoms.

Based on the American College of Rheumatology preliminary criteria for the classification of the acute arthritis of primary gout (1977), as derived from: Wallace SL, Robinson H, Masi AT, et al. Preliminary criteria for the classification of the acute arthritis of primary gout. Arthritis Rheum 1977;20:895-900 .

D. Treatment Options for Acute Attacks
   1. Nonpharmacologic
      a. Rest and elevate the affected joint(s).
      b. Ice packs

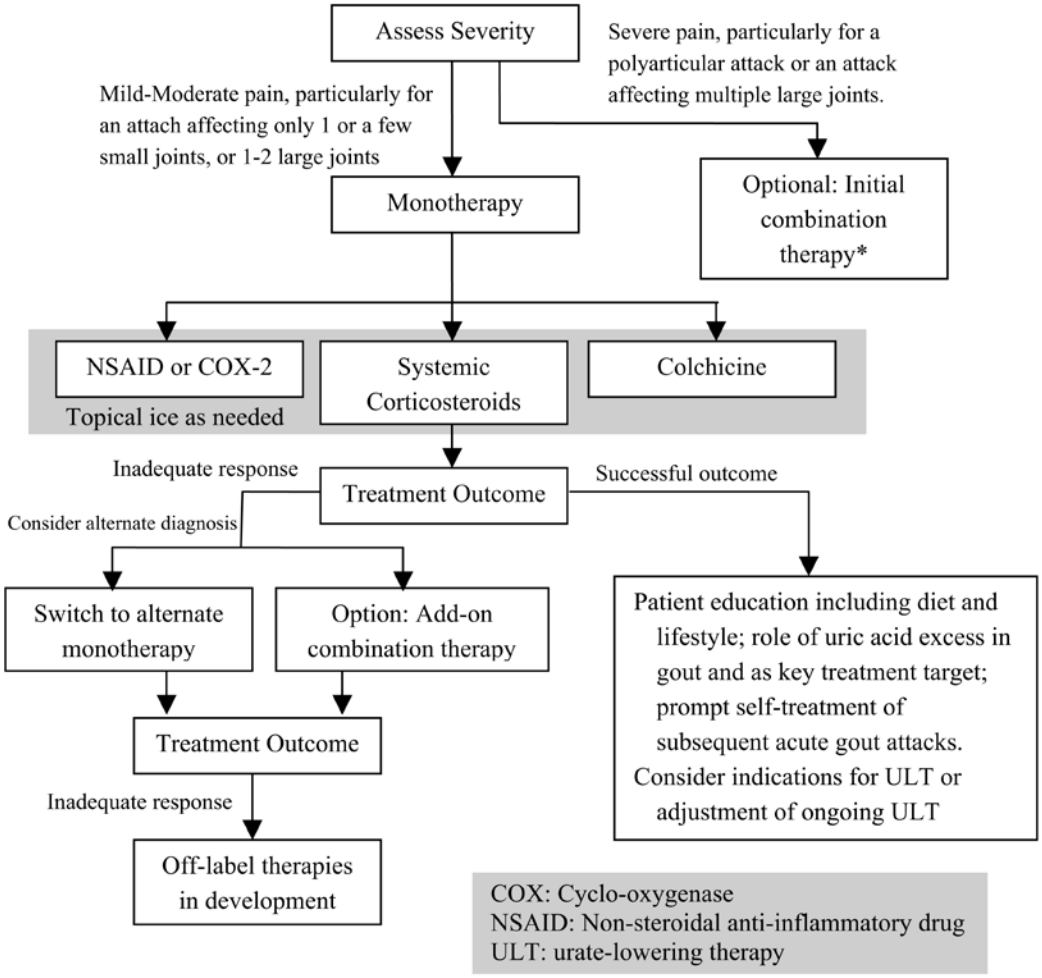

Figure 10. Management of acute gouty attack.

Reprinted with permission from: Khanna D, Khanna PP, Fitzgerald J, et al. 2012 American College of Rheumatology guidelines for the management of gout, part 2: therapy and anti-inflammatory prophylaxis of acute gouty arthritis. Arthritis Care Res 2012;64:1447-61.

2. Pharmacologic
    a. Nonsteroidal anti-inflammatory drugs
        i. Safety and tolerability discussed above in the Rheumatoid Arthritis section
        ii. All NSAIDs appear equally effective.
        iii. Treatment should continue until symptoms subside (1–2 weeks).

Patient Case

15. M.K. is a 46-year-old man with a medical history significant for chest pain with exertion, dyslipidemia, impaired fasting glucose, hypertension, obesity, and gout (one episode, 5 months ago). His current medications include simvastatin 40 mg daily, nicotinic acid (extended release) 1000 mg at bedtime, lisinopril 40 mg daily, amlodipine 5 mg daily, and aspirin 81 mg daily. He presents to his primary care practitioner's office with symptoms consistent with gout in his left first metatarsophalangeal joint and left ankle, starting this morning. The metatarsophalangeal joint is swollen, inflamed, erythematous, and sensitive to light touch. Which is the best approach to therapy for M.K.?

    A. Colchicine 1.2 mg for first dose and then 0.6 mg 1 hour after.
    B. Colchicine 1.2 mg for first dose and then 0.6 mg 1 hour after; also, start allopurinol 300 mg once daily.
    C. Colchicine 1.2 mg for first dose and then 0.6 mg every hour thereafter as tolerated.
    D. Colchicine 1.2 mg for first dose and then 0.6 mg every hour thereafter as tolerated; also, start allopurinol 300 mg once daily.

    b. Colchicine

Table 66. Colchicine STEPS

Safety	Doses > 4 mg may cause multiple organ failure and death Dose adjustment not necessary when CrCl > 30 mL/minute When CrCl < 30 mL/minute: Do not use more than one acute treatment course every 2 weeks Do not use >0.3 mg daily for prophylaxis initially Metabolized by the cytochrome P450 3A4 enzyme (elevated plasma colchicine concentrations can lead to fatal toxicity) Risk of adverse hematologic events includes myelosuppression, leukopenia, thrombocytopenia, and/or pancytopenia
Tolerability	GI discomfort Diarrhea
Efficacy	New(er) dosing strategy decreases the likelihood of adverse events without affecting efficacy
Preference (Pearls)	Slower to work than NSAIDs for pain relief, but still at least a 50% reduction in pain at 24 hours
Simplicity	Two tablets (0.6 mg each x 2 = 1.2 mg) within 12 hours of onset and one (0.6 mg) tablet 60 minutes later 2012 ACR recommendations suggest using 0.6 mg every 12 hours until acute symptoms resolve, starting immediately after the second 0.6-mg treatment dose

ACR = American College of Rheumatology; CrCl = creatinine clearance; GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug; STEPS = Safety, Tolerability, Efficacy, Preference (Pearls), Simplicity.

c. Corticosteroids
   i. Safety and tolerability discussed above in the Rheumatoid Arthritis section
   ii. Excellent option for patients with acute gout and renal insufficiency
   iii. Prednisone is equal in efficacy to NSAIDs for reducing pain and discomfort.
   iv. Intra-articular corticosteroids are especially effective with large joint involvement.
   v. Intra-articular formulations show benefits superior to oral NSAIDs at 72 hours, but equal at 1 week.

E. Prevention Options for Recurrent Attacks
   1. Nonpharmacologic
      a. Adequate hydration (2 L or more of water daily)
      b. Discontinue diuretic therapy whenever possible.
      c. Moderate, low-impact exercise
      d. Restrict dietary animal and yeast purine intake and alcohol (especially beer).
      e. Avoid highly refined carbohydrates and sugars.
      f. Weight reduction
   2 Consideration and expectations of prevention
      a. Consider preventive therapy in individuals experiencing more than one acute gouty arthritis attack per year.
      b. Therapy goal is serum uric acid concentrations less than 5 mg/dL (with tophi) or 6 mg/dL (without tophi).
      c. 2012 guidelines suggest that prophylactic therapy can be initiated during an acute gouty attack, provided anti-inflammatory management has been started.
      d. Evaluate serum uric acid concentrations every 3 months for the first year after an attack and then annually thereafter.
      e. May try to discontinue agents at any time, but most will have at least one gouty attack (90%) during the next 10 years

   3. Xanthine oxidase inhibitors
      a. Allopurinol (Zyloprim)
      b. Febuxostat (Uloric)

Table 67. Allopurinol STEPS

Safety	Exfoliative dermatitis Stevens-Johnson syndrome Hepatotoxicity	Mucositis Renal insufficiency Thiazides decrease excretion of allopurinol
Tolerability	Elevated transaminases or alkaline phosphatase values Transient rash	
Efficacy	Shown to prevent recurrent gouty arthritis attacks and reduce uric acid concentrations Useful to reduce tophi in patients with tophaceous gout	

Table 67. Allopurinol STEPS *(continued)*

Preference (Pearls)	First-line agent for prevention of recurrent gout and hyperuricemia Evaluate renal function for possible dose adjustments NOT for use in patients with asymptomatic hyperuricemia Do not stop therapy during an acute attack if the patient's condition is already managed with allopurinol Start at 100 mg daily and titrate by 100 mg daily every 2–4 weeks (maximum 800 mg daily) to achieve a uric acid concentration < 5–6 mg/dL Maximal dose should be 200 mg/day with CrCl < 20 mL/minute and <100 mg/day with CrCl < 10 mL/minute 2012 ACR guidelines suggest HALB*5801 testing for at-risk populations (patients of Korean descent with CKD stage 3 or worse, Han Chinese descent, or Thai descent)
Simplicity	Daily dosing Relatively inexpensive (<$20 a month)

ACR = American College of Rheumatology; CKD = chronic kidney disease; CrCl = creatinine clearance; STEPS = Safety, Tolerability, Efficacy, Preference (Pearls), Simplicity.

Table 68. Febuxostat STEPS

Safety	Contraindicated in patients using azathioprine, mercaptopurine, or theophylline (Canada only) Higher incidence of cardiovascular events observed compared with incidence in patients using allopurinol, though no causal relationship has been proved Hepatotoxicity
Tolerability	Arthralgias Nausea Rash
Efficacy	Approved to treat hyperuricemia in patients with gout
Preference (Pearls)	Greater efficacy for reducing uric acid concentration, but no more efficacious for preventing gout flares than allopurinol Used to reduce tophi in patients with tophaceous gout NOT for use in patients with asymptomatic hyperuricemia
Simplicity	Daily dosing Considerably more expensive than allopurinol (about $150–$200 per month)

STEPS = Safety, Tolerability, Efficacy, Preference (Pearls), Simplicity.

4. Uricosuric agent – Probenecid

Table 69. Probenecid STEPS

Safety	Avoid use in patients with uric acid kidney stones May worsen existing blood dyscrasias Many drug interactions and may increase the serum concentration of target agents
Tolerability	Dyspepsia Reflux esophagitis
Efficacy	Increases urate excretion and decreases serum uric acid concentrations Efficacy may be diminished when coadministered with salicylates

Table 69. Probenecid STEPS *(continued)*

Preference (Pearls)	Ineffective in patients with even mild renal insufficiency Start with low doses to reduce the likelihood of precipitating another gouty attack
Simplicity	Coformulated with colchicine May cost $35–$100 per month (depending on daily dose and frequency)

STEPS = Safety, Tolerability, Efficacy, Preference (Pearls), Simplicity.

5. Other medications
   a. Colchicine
      i. For prophylaxis of gout induced by urate-lowering therapy
      ii. Not for use as monotherapy to prevent gouty attacks
      iii. Give during the first 6 months of urate-lowering therapy.

Patient Case

16. Y.W. is a 58-year-old man with a medical history significant for hypertension, type 2 diabetes mellitus, dyslipidemia, and obesity. His medications include glimepiride 2 mg daily, hydrochlorothiazide 12.5 mg daily, bisoprolol 5 mg daily, and simvastatin/ezetimibe 20/10 mg at night. During routine laboratory evaluation, his primary care provider finds his serum uric acid concentration to be 7.3 mg/dL. Which is the most appropriate strategy to decrease the patient's serum uric acid concentration?

    A. Therapy is not indicated because the patient has not yet experienced a gouty attack.
    B. Start allopurinol 100 mg daily and titrate to achieve a serum uric acid concentration less than 6 mg/dL.
    C. Start febuxostat 40 mg daily and titrate to achieve a serum uric acid concentration less than 6 mg/dL.
    D. Start probenecid 500 mg twice daily and titrate to achieve a serum uric acid concentration less than 6 mg/dL.

   b. Pegloticase

Table 70. Pegloticase STEPS

Safety	Contraindicated in patients with G6PD deficiency FDA black box warning regarding anaphylaxis and infusion reactions; patients should be closely monitored for at least 2 hours after infusion, though delayed reactions have been reported Risk of infusion reaction is increased when the patient's uric acid concentration is >6 mg/dL; consider discontinuing therapy if uric acid concentration is >6 mg/dL, especially if it is above this limit on two consecutive occasions Acute gout flare within the first 3 months of therapy Heart failure exacerbations have been reported in clinical trials Increased risk of anaphylaxis in patients who are restarting therapy after discontinuing it for >4 weeks	
Tolerability	Bruising Chest pain Constipation Dyspnea	Erythema Nausea Pruritus Urticaria

Table 70. Pegloticase STEPS *(continued)*

Efficacy	Showed decreased uric acid concentrations and number of gout flares in clinical trials
Preference (Pearls)	Administer by intravenous infusion during120 minutes Vials must be refrigerated and stored in a carton to protect them from light Elimination half-life is about 14 days Recommended to begin gout flare prophylaxis (NSAIDs or colchicine) 1 week before infusion and continue for at least 6 months
Simplicity	120-minute infusion (8 mg) every 2 weeks

FDA = U.S. Food and Drug Administration; G6PD = glucose-6-phosphate dehydrogenase; NSAID = nonsteroidal anti-inflammatory drug; STEPS = Safety, Tolerability, Efficacy, Preference (Pearls), Simplicity.

c. Rasburicase
   i. Uricolytic agent, FDA approved only for tuhmor lysis syndrome
   ii. Seldom used for this indication
   iii. Some research shows rasburicase decreases tophi and uric acid concentrations in patients with gout.
d. Rilonacept
   i. Interleukin-1 inhibitor labeled for use in cryopyrin-associated periodic syndromes
   ii. When added to allopurinol therapy, it decreased the number of acute gout attacks.
   iii. Administered as a subcutaneous injection

6. Patient information
   a. Information from National Institute of Arthritis and Musculoskeletal and Skin Diseases (www.niams.nih.gov/Health_Info/Gout/default.asp)
   b. Gout and Uric Acid Education Society
      i. Web site for information and social networking
      ii. http://gouteducation.org/

Table 71. Drugs and Doses Reference Table

Medication Name	Brand Name	Dosing
Colchicine	Colcrys	0.6 mg twice daily (for prophylaxis)
Allopurinol	Zyloprim	200–300 mg by mouth each day
Febuxostat	Uloric	40–80 mg by mouth each day
Probenecid		250–500 mg by mouth twice daily
Pegloticase	Krystexxa	8 mg intravenously every 2 weeks

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: C

Many medications contribute to BMD loss by either accelerating bone resorption or inhibiting osteogenesis. For this patient, levothyroxine most significantly affected her BMD by speeding up the bone resorption process. Excessive thyroid hormone supplementation or drug-induced hyperthyroidism puts patients at risk of osteoporosis and fracture. Practitioners should be cognizant of TSH and free thyroid hormone concentrations, treating patients to a euthyroid state and a TSH concentration of around 2.0–3.0 mIU/L. This suggestion does not apply for patients who require maximal thyroid hormone suppression (i.e., history of thyroid cancer).

2. Answer: B

The patient in question has not yet undergone a DEXA scan and received a T-score for her lumbar spine or femoral neck. Therefore, antiresorptive therapy is not warranted until the results are available. However, according to the USPSTF, the patient is a candidate for undergoing DEXA scan before age 65 years, given that her FRAX score for major osteoporotic fracture is greater than 9.3%. She should also begin treatment with calcium and vitamin D to preserve BMD. If the DEXA findings show osteopenia (T-score between −1.0 and −2.5), bisphosphonate therapy will be initiated because the patient's risk of hip fracture in the next 10 years is greater than 3%.

3. Answer: D

Because the patient has an extensive history of GI disease and receives chronic therapy with a proton pump inhibitor, she will most likely benefit from treatment with a calcium citrate supplement. Calcium carbonate salts, when administered with an acid-suppressing agent, yield less calcium availability than a calcium citrate formulation. However, when converting from a calcium carbonate tablet to a calcium citrate tablet, the "serving size" is usually doubled, and the patient requires two tablets of calcium citrate to equal the elemental calcium in one calcium carbonate tablet.

4. Answer: A

This patient's inability to be mobile (and possibly upright) drastically limits the medication choices for the primary prevention of an osteoporotic fracture. Zoledronic acid seems to be the most appropriate agent because there are data to support its ability to maintain vertebral bone density, and patients do not have to adhere to strict postdosing restrictions when using it. Risedronate is appropriate if the patient can remain upright for 30–60 minutes, but this may be too physically demanding for the patient. The calcitonin nasal spray is less effective than the bisphosphonate options and would be a poor choice for the patient. Raloxifene has a high incidence of venous thromboembolism and, in conjunction with the patient's limited mobility, might increase her risk of a venous thromboembolism.

5. Answer: C

Rheumatoid factor is one of four clinically relevant markers when predicting disease prognosis. The other indicators include functional limitations, positive anti–citrullinated protein antibody (or positive RF finding) finding, radiographic evidence of bony erosions, and extra-articular disease. These prognostic factors are then used when determining initial therapy using the ACR algorithms. Joint involvement, ESR, and CRP are important when classifying RA, but they are not good indicators of prognosis.

6. Answer: C

To assess the most appropriate therapy for the patient, the provider must identify that she has high disease activity, poor prognostic factors, and disease duration of less than 6 months. Monotherapy with a nonbiologic DMARD would be inappropriate, given her level of disease activity and poor prognosis. The use of anakinra is not supported by the ACR 2012 recommendations because of the lack of sufficient efficacy data since the 2008 publication. For this patient, the use of a TNF inhibitor plus methotrexate is appropriate and meets the recommendations from the ACR for a person with high disease activity for less than 6 months and poor prognostic factors.

7. Answer: C

Although the maximal studied dose of methotrexate for patients with RA can be up to 30 mg weekly, the maximal recommended dose is 20 mg weekly. If a patient reaches the 20-mg dose by mouth without sufficient clinical effect, a prescriber should begin to reconsider the effectiveness of the current therapeutic approach. Although it is possible to switch to injectable methotrexate, this approach is not preferred and should be reserved for patients who cannot afford a TNF inhibitor. Both adalimumab and infliximab are TNF inhibitors, but only adalimumab may be used as monotherapy

(between the two agents). Infliximab should always be given in combination with methotrexate.

8. Answer: C
The patient should discontinue etanercept and begin therapy with abatacept. The ACR recommends using abatacept for patients without an adequate rheumatologic response to methotrexate and an anti-TNF agent. Increasing and continuing prednisone may help alleviate some pain, but long-term treatment with corticosteroids is not warranted for everyone, and efforts should focus on the best way to maximally suppress bone deformation. Adding another anti-TNF agent or combining abatacept with an anti-TNF agent is also not recommended.

9. Answer: B
The CASPAR criteria are used to assist in the diagnosis of psoriatic arthritis. These criteria are based on five questions that have a total cumulative score of up to 6 points. Patients are given 2 points if they have active psoriasis (1 point for a history of psoriasis) and 1 point for each of the following: dactylitis ("sausage digits"), negative RF findings, juxta-articular new bone formation, and/or nail dystrophy. If the score is greater than 3 points, the patient is considered to have psoriatic arthritis. In this particular case, the patient scored 5 of 6 points: active psoriasis, dactylitis, negative RF findings, and nail dystrophy.

10. Answer: D
The patient presents with severe psoriatic arthritis and requires treatment with a combination biologic and nonbiologic DMARD, in this case golimumab and methotrexate. Although using either agent alone may help alleviate the symptoms, the extreme severity of the patient's symptoms requires an aggressive treatment approach that could eventually be decreased, once his symptoms are lessened with combination therapy. The use of systemic corticosteroids is not recommended in patients with psoriatic arthritis. This is an insufficient dose of burst therapy, and systemic corticosteroids should not be used as chronic maintenance therapy for controlling the symptoms of psoriatic arthritis.

11. Answer: D
The man in this case has moderate to severe osteoarthritis of the knee that causes considerable limitations in the activities of daily living. Given his history of a myocardial infarction, ibuprofen is discouraged by the ACR for pain control because of its potential interaction to decrease the cardioprotective efficacy of aspirin. Although naproxen is recommended over ibuprofen, the patient's heart failure may be made worse with scheduled use. The acetaminophen dose exceeds 4 g daily. The topical NSAID is appropriate for this person because of its low likelihood of adverse events and interactions with other medications and disease states.

12. Answer: A
Although the patient's physical symptoms meet the criteria for diagnosing fibromyalgia (WPI score 8 and SSS estimated to be greater than 5), she has experienced these symptoms for only the past 4 weeks. According to the ACR, the patient must have symptoms for at least 3 months and elevated WPI and SSS scores. If these symptoms continue, the patient will qualify for a diagnosis of fibromyalgia, and she should be treated with a tricyclic antidepressant such as amitriptyline to start. If she is unable to achieve sufficient pain relief or if she has adverse events, she may try one of the alternative agents such as duloxetine, fluoxetine, or gabapentin.

13. Answer: C
This patient may benefit most from a trial of duloxetine 60 mg once daily. She has minor depressive disorder and states that some of her symptoms (sad feelings and sleep issues) improved with the tricyclic antidepressant, but the main reason for the medication (her pain) was unaffected. When patients do not respond to the first-line treatment, alternative agents should be used. The α2δ ligands (gabapentin and pregabalin) are acceptable agents, but her beneficial response for non-pain symptoms with the antidepressant would warrant a trial of another agent with antidepressant properties. In addition, tramadol is recommended only for patients with fibromyalgia when all other alternative agents have been tried and have failed.

14. Answer: D
In this patient's situation, adding azathioprine will offer more benefit to the patient than the other listed options. In patients with SLE and evidence of lupus-related organ damage, adding an immunologic agent is warranted when the patient lacks a sufficient response to an antima-

larial agent such as hydroxychloroquine. The practice of treating patients to a serum hydroxychloroquine concentration of greater than 1000 mg/mL has not proved beneficial. In addition, using systemic corticosteroid doses greater than 10 mg daily for extended periods is not recommended. The purpose of introducing an immunologic agent is to control symptoms and limit the amount of systemic corticosteroid use in the patient.

15. Answer: A

Because this patient is suffering from an acute gouty attack, the use of allopurinol is inappropriate. Allopurinol should be initiated at a starting dose (100 mg), but the time separating acute attack and prophylaxis remains unanswered (immediate vs. 1 to 2 weeks later). With respect to the colchicine dose, recent information indicates that both of the doses listed are equally effective, but the lower cumulative dose causes considerably fewer GI adverse events. The "as-tolerated" instructions for Answer C and Answer D put the patient at risk of overdosing and could cause the patient to experience GI adverse effects and even life-threatening hematologic effects.

16. Answer: A

The patient should not receive treatment for his hyperuricemia. Patients should not receive therapy until they have experienced their first gouty attack. One to 2 weeks after the first attack, patients may begin uric acid–lowering therapy, and they should be treated until a serum uric acid concentration of less than 6 mg/dL is attained. Until their first attack, treatment with a xanthine oxidase inhibitor or uricosuric agent is not indicated.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: D

According to her DEXA scan results, the patient would traditionally be classified as having osteopenia in her lumbar spine. In many cases, this would require her to be treated only with calcium and vitamin D supplementation. However, because her 10-year risk of a hip fracture is greater than 3% with the FRAX tool, the NOF would consider this patient as having osteoporosis and recommend she receive antiresorptive therapy. Of the choices, alendronate is the only agent to have antiresorptive properties, and of the two doses, 70 mg once weekly is the recommended treatment dose. Alendronate 35 mg once weekly is considered a prevention dose for bisphosphonates.

2. Answer: C

The patient should restart therapy but change to a different bisphosphonate. The use of a bisphosphonate for this patient is important because of her history of a fragility fracture. Reinitiating alendronate at 70 mg may be appropriate, but the likelihood of the same adverse event is high. Reducing the dose would not be appropriate for secondary fracture prevention. Although raloxifene is efficacious for secondary fracture prevention, its usefulness is limited to vertebral fractures, not hip fractures. Changing bisphosphonates may decrease the chances of the adverse drug event recurring, and the dose and dosing interval for risedronate are appropriate for this patient and her medical condition. The patient should be counseled on the proper way to take bisphosphonate.

3. Answer: C

According to the latest edition of the ACR's guidelines for managing glucocorticoid-induced osteoporosis, bisphosphonates should be used for postmenopausal women with moderate fracture risk (based on age and T-score) if they are using 7.5 mg or more of prednisone daily for more than 1 month. Because the patient meets these criteria, risedronate 150 mg monthly plus calcium and vitamin D supplementation are warranted.

4. Answer: D

The use of raloxifene may increase a woman's risk of a venous thromboembolism. Because the patient had an idiopathic (unprovoked) deep venous thromboembolism 18 months earlier, SERM use is not warranted. The use of raloxifene, which has been beneficial for patients with invasive breast cancer, has not been linked to lower extremity edema. In addition, despite the possible recurrence of hot flashes and spotting, raloxifene has not been associated with significant uterine abnormalities.

5. Answer: D

Patients with RA receiving biologic DMARDs should not be administered live vaccines such as varicella zoster. Nor should live vaccines be administered for 3 months after discontinuing biologic DMARDs. The trivalent seasonal influenza vaccine and 23-valent pneumococcal vaccine are acceptable to give to all patients, according to the schedule recommended by the Centers for Disease Control and Prevention (CDC) and Advisory Committee on Immunization Practices (ACIP). The Tdap vaccine may also be safely administered to patients who are considered (non-HIV) immune compromised or receiving immune system–compromising agents.

6. Answer: D

According to the ACR recommendations, patients with newly diagnosed RA should begin DMARDs within the first 3 months of diagnosis to achieve the best prognosis. The EULAR does not recommend a timeframe for treatment initiation but states that patients should begin therapy with a DMARD immediately.

7. Answer: C

For a patient who wants to have a baby in the next 24 months, it is appropriate to rule out the use of all agents with a high potential of being teratogenic. Methotrexate, leflunomide, and minocycline all may cause abnormal or fatal fetal outcomes and should be avoided in pregnancy. Although sulfasalazine is not considered a first-line agent for treating RA, it is effective and likely the safest (though not without risk) in pregnancy. For patients receiving sulfasalazine during pregnancy, there have been reports of an increased risk of kernicterus, jaundice, and hemolytic anemia when used near term. Although the benefits appear to outweigh the risks in this situation, patient education and understanding of risk are essential.

8. Answer: B

This patient has risk factors for a poor prognosis with RA and has not achieved a sufficient response with methotrexate alone. The best choice for this patient is to change to an injectable form of methotrexate to possibly increase drug delivery and efficacy. Ideally, the patient's medication would be transitioned to TNF-inhibitor, but the significant cost of these agents is prohibitive for patients without adequate prescription insurance coverage. Rituximab should not be recommended until the patient has an adequate trial with and subsequent failure with TNF-inhibitor therapy.

9. Answer: A

According to the ACR and GRAPPA, patients with minimal to no functional limitations from the psoriatic arthritis need be treated only with NSAIDs or other analgesics. When the symptoms progress to moderate severity and affect the patient's activities of daily living, or when the symptoms do not respond to simple analgesics, providers should consider adding either a DMARD (e.g., sulfasalazine) or a biologic agent (e.g., etanercept). Combination DMARD and biologic agent should be reserved for patients with severe disease or for those whose condition does not respond to either agent alone.

10. Answer: B

For this patient, the next best choice for pain relief is topical diclofenac 1% gel. The ACR 2012 guidelines do not recommend the routine use of glucosamine and chondroitin or opiate analgesia for osteoarthritis pain. In addition, treatment recommendations prefer topical NSAID therapy to systemic NSAIDs for patients older than 75 years.

11. Answer: C

Patients who are treated with hydroxychloroquine require ophthalmologic evaluations regularly, but the initial evaluation and follow-up depends on the weight-based dose, duration of therapy, and several other factors. Patients who are younger than 60 years, nonobese, without renal or hepatic disease, treated for less than 5 years, and with treatment of less than 6.5 mg/kg will need an initial screening within the first 5 years of therapy and then annually after 5 years. Annual evaluations are not required before year 5 unless one of the above criteria is not met.

12. Answer: C

It would be best for the patient to begin treatment with pregabalin 75 mg twice daily. Although all the medications listed are appropriate for treating fibromyalgia syndrome, several issues need to be considered. Nortriptyline and duloxetine would create a significant drug-drug interaction with selegiline, most likely resulting in hypertensive crisis and/or serotonin syndrome. The gabapentin dose is too low for the patient and would most likely not produce a clinically significant change in her symptoms. The target dose for gabapentin for fibromyalgia is 1800–2400 mg daily (divided three times).

13. Answer: B

The patient has chronic kidney disease, thereby limiting the choice of medications and doses that may be used to prevent recurrent gouty attacks. The patient is a candidate for gout prevention and treatment of hyperuricemia. The number of attacks per year does not factor into initiating therapy. Probenecid should be avoided in patients with a CrCl of less than 50 mL/minute. Colchicine has no effect on tophi formation. Xanthine oxidase inhibitors are the drug of choice for patients with tophi. Because the patient has a CrCl between 21 and 40 mL/minute, the suggested maximal dose of allopurinol is 150 mg daily. Some recommendations do not start limiting allopurinol's dose until the CrCl is less than 20 mL/minute, but the general therapeutic rule for allopurinol is to start at 100 mg daily and titrate to a serum uric acid concentration of less than 6 mg/dL.