Pharmacotherapy Handbook

Eleventh Edition
NOTICE

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The authors of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error or changes in medical sciences, neither the authors nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they disclaim all responsibility for any errors or omissions or the results obtained from use of the information contained in this work. Readers are encouraged to confirm the information contained herein with other sources. For example and in particular, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this work is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connection with new or infrequently used drugs.
Contents

Preface ................................................................. ix

INTRODUCTION

Edited by Cecily V. DiPiro and Terry L. Schwinghammer

The Patient Care Process ........................................... 1

SECTION 1: BONE AND JOINT DISORDERS

Edited by Terry L. Schwinghammer

1. Gout and Hyperuricemia ......................................... 7
2. Osteoarthritis ..................................................... 15
3. Osteoporosis ..................................................... 22
4. Rheumatoid Arthritis ............................................. 35

SECTION 2: CARDIOVASCULAR DISORDERS

Edited by Terry L. Schwinghammer

5. Acute Coronary Syndromes ..................................... 51
6. Arrhythmias ..................................................... 64
7. Cardiac Arrest ................................................... 76
8. Dyslipidemia ..................................................... 82
9. Heart Failure .................................................... 96
10. Hypertension ................................................... 112
11. Ischemic Heart Disease ......................................... 129
12. Shock Syndromes ............................................... 138
13. Stroke .......................................................... 149
14. Venous Thromboembolism .................................... 156

SECTION 3: DERMATOLOGIC DISORDERS

Edited by Terry L. Schwinghammer

15. Acne Vulgaris .................................................. 167
16. Dermatologic Drug Reactions and Common Skin Conditions .......... 174
17. Psoriasis ....................................................... 180

SECTION 4: ENDOCRINOLOGIC DISORDERS

Edited by Terry L. Schwinghammer

18. Adrenal Gland Disorders ....................................... 189
19. Diabetes Mellitus ............................................... 197
20. Thyroid Disorders ............................................. 218

SECTION 5: GASTROINTESTINAL DISORDERS

Edited by Joseph T. DiPiro and Terry L. Schwinghammer

21. Cirrhosis and Portal Hypertension ......................... 229
Contents

22. Constipation ................................................................. 239
23. Diarrhea .................................................................... 245
24. Gastroesophageal Reflux Disease ............................... 251
25. Hepatitis, Viral ............................................................ 260
26. Inflammatory Bowel Disease ...................................... 269
27. Nausea and Vomiting .................................................. 281
28. Pancreatitis ............................................................... 293
29. Peptic Ulcer Disease .................................................... 302

SECTION 6: GYNECOLOGIC AND OBSTETRIC DISORDERS
Edited by Vicki L. Ellingrod
30. Contraception ............................................................. 309
31. Hormone Therapy in Women ...................................... 329
32. Pregnancy and Lactation ............................................. 343

SECTION 7: HEMATOLOGIC DISORDERS
Edited by Cecily V. DiPiro
33. Anemias .................................................................. 357
34. Sickle Cell Disease ...................................................... 363

SECTION 8: INFECTIOUS DISEASES
Edited by Joseph T. DiPiro
35. Antimicrobial Regimen Selection ................................. 369
36. Central Nervous System Infections ............................... 379
37. Endocarditis ............................................................... 386
38. Fungal Infections, Invasive .......................................... 398
39. Fungal Infections, Superficial ...................................... 412
40. Gastrointestinal Infections .......................................... 422
41. Human Immunodeficiency Virus Infection .................... 429
42. Influenza .................................................................. 440
43. Intra-Abdominal Infections ......................................... 447
44. Respiratory Tract Infections, Lower .............................. 459
45. Respiratory Tract Infections, Upper .............................. 475
46. Sepsis and Septic Shock .............................................. 482
47. Sexually Transmitted Diseases ................................... 490
48. Skin and Soft-Tissue Infections .................................. 508
49. Surgical Prophylaxis .................................................... 531
50. Tuberculosis ............................................................... 541
51. Urinary Tract Infections and Prostatitis ....................... 558
52. Vaccines, Toxoids, and Other Immunobiologics ............ 568

SECTION 9: NEUROLOGIC DISORDERS
Edited by Vicki L. Ellingrod
53. Alzheimer Disease .......................................................... 575
54. Epilepsy and Status Epilepticus ....................................... 583
Contents

55. Headache: Migraine and Tension-Type ............................................. 617
56. Pain Management ................................................................. 630
57. Parkinson Disease ............................................................... 656

SECTION 10: NUTRITION SUPPORT
Edited by Cecily V. DiPiro
58. Obesity .............................................................................. 667
59. Nutrition Assessment and Support ..................................... 674

SECTION 11: ONCOLOGIC DISORDERS
Edited by Cecily V. DiPiro
60. Breast Cancer ................................................................. 687
61. Colorectal Cancer ............................................................ 699
62. Lung Cancer ................................................................. 712
63. Lymphomas ..................................................................... 721
64. Prostate Cancer ............................................................. 728

SECTION 12: OPHTHALMIC DISORDERS
Edited by Cecily V. DiPiro
65. Glaucoma ......................................................................... 741

SECTION 13: PSYCHIATRIC DISORDERS
Edited by Vicki L. Ellingrod
66. Anxiety Disorders ............................................................ 749
67. Bipolar Disorder .............................................................. 767
68. Depressive Disorder ........................................................ 783
69. Opioid Use Disorder ........................................................ 801
70. Schizophrenia .................................................................... 813
71. Sleep–Wake Disorders ...................................................... 830
72. Substance Use Disorders: Alcohol, CNS Depressants, Stimulants, Nicotine ... 839

SECTION 14: RENAL DISORDERS
Edited by Cecily V. DiPiro
73. Acid–Base Disorders .......................................................... 855
74. Acute Kidney Injury .......................................................... 864
75. Chronic Kidney Disease ..................................................... 872
76. Electrolyte Homeostasis ................................................... 889

SECTION 15: RESPIRATORY DISORDERS
Edited by Terry L. Schwinghammer
77. Allergic Rhinitis ............................................................... 905
78. Asthma .............................................................................. 915
79. Chronic Obstructive Pulmonary Disease ......................... 928
Contents

SECTION 16: UROLOGIC DISORDERS
Edited by Cecily V. DiPiro

80. Benign Prostatic Hyperplasia ........................................... 941
81. Erectile Dysfunction .................................................. 950
82. Urinary Incontinence .................................................. 966

APPENDICES
Edited by Terry L. Schwinghammer

Appendix 1. Pediatric Pharmacotherapy, Nutrition, and Neonatal Critical Care .......................... 975
Appendix 2. Geriatric Assessment and Pharmacotherapy ........................................ 984
Appendix 3. Critical Care: Patient Assessment and Pharmacotherapy ........................... 988
Appendix 4. Drug Allergy .................................................... 996
Appendix 5. Drug-Induced Hematologic Disorders ........................................ 1001
Appendix 6. Drug-Induced Liver Disease ...................................... 1007
Appendix 7. Drug-Induced Pulmonary Disease ...................................... 1009
Appendix 8. Drug-Induced Kidney Disease ....................................... 1017
Appendix 9. Drug-Induced Ophthalmic Disorders .................................. 1021
Index .................................................................................. 1023
Preface

The 11th edition of this companion to *Pharmacotherapy: A Pathophysiologic Approach* is designed to provide practitioners and students with critical information that can be used to guide medication decision-making in collaborative, interprofessional healthcare settings. To ensure brevity, clarity, and portability, the bulleted format provides essential textual information, key tables and figures, and treatment algorithms.

Corresponding to the major sections in the *Pharmacotherapy* textbook, medical conditions are alphabetized within the following sections: Bone and Joint Disorders; Cardiovascular Disorders; Dermatologic Disorders; Endocrinologic Disorders; Gastrointestinal Disorders; Gynecologic and Obstetric Disorders; Hematologic Disorders; Infectious Diseases; Neurologic Disorders; Nutrition Support; Oncologic Disorders; Ophthalmic Disorders; Psychiatric Disorders; Renal Disorders; Respiratory Disorders; and Urologic Disorders. The *Handbook* includes nine tabular appendices (four more than the 10th edition) involving pediatric pharmacotherapy, nutrition, and neonatal critical care; geriatric assessment and pharmacotherapy; critical care patient assessment and pharmacotherapy; drug allergy; drug-induced hematologic disorders; drug-induced liver disease; drug-induced pulmonary disease; drug-induced kidney disease; and drug-induced ophthalmic disorders. This edition also includes new chapters on the pharmacists' patient care process, opioid use disorder, and superficial fungal infections.

Each chapter is organized in a consistent format:

- Disease State Definition
- Pathophysiology
- Clinical Presentation
- Diagnosis
- Treatment
- Evaluation of Therapeutic Outcomes

The Treatment section may include goals of treatment, general approach to treatment, nonpharmacologic therapy, drug selection guidelines, dosing recommendations, adverse effects, pharmacokinetic considerations, and important drug-drug interactions. When more in-depth information is required, the reader is encouraged to refer to the corresponding chapter in the primary textbook, *Pharmacotherapy: A Pathophysiologic Approach*, 11th edition. These chapters now provide guidance on application of the pharmacists' patient care process for specific conditions.

The authors gratefully acknowledge Barbara G. Wells, PharmD, FASHP, FCCP, retired Dean Emeritus and Professor Emeritus, School of Pharmacy, The University of Mississippi, for her substantial contributions to the creation, design, and production of all previous editions of this work. Her vision, insight, and passion for the provision of patient-centered medication therapy are evident throughout the pages of the *Handbook*. In addition, this edition of the *Handbook* is dedicated to the memory of her late husband, Richard M. Wells: pharmacist, colleague, and friend.

It is our hope that students and practitioners find this book to be helpful on their daily journey to provide the highest quality individualized, patient-centered care. We invite your comments on how we may improve subsequent editions of this work.

Terry L. Schwinghammer
Joseph T. DiPiro
Vicki L. Ellingrod
Cecily V. DiPiro

Please provide your comments about this book, Schwinghammer et al., *Pharmacotherapy Handbook*, 11th edition, to its authors and publisher by writing to userservices@mheeducation.com. Please indicate the author and title of this handbook in the subject line of your e-mail.
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INTRODUCTION

Health professionals who provide direct patient care are often called practitioners. Health professionals practice when they use their unique knowledge and skills to serve patients. A healthcare practice is not a physical location or simply a list of activities. Rather, a professional practice requires three essential elements: (1) a philosophy of practice, (2) a process of care, and (3) a practice management system.

A practice philosophy is the moral purpose and commonly held set of values that guides the profession. It is the critical foundation on which the practices of pharmacy, medicine, nursing, and dentistry are built. Although the concept of pharmaceutical care is not formally included in the code of ethics for the pharmacy profession or the oath of a pharmacist, pharmacists understand that they have a unique responsibility for addressing the drug-related needs of patients and should be held accountable for preventing, identifying, and resolving drug therapy problems.

The patient care process is a fundamental series of actions that guide the activities of health professionals. In 2014, the Joint Commission for Pharmacy Practitioners (JCPP)—representing 11 national pharmacy organizations—endorsed a framework for providing clinically oriented patient care services called the Pharmacists’ Patient Care Process. This process includes five essential steps: (1) collecting subjective and objective information about the patient; (2) assessing the collected data to identify problems, determine the adequacy of current treatments, and set priorities; (3) creating an individualized care plan that is evidence-based and cost-effective; (4) implementing the care plan; and (5) monitoring the patient over time during follow-up encounters to evaluate the effectiveness of the plan and modify it as needed (Fig. 1). In addition to the five fundamental steps, a patient-centered approach to decision making is essential.

A practice management system is necessary to support the efficient and effective delivery of services, including physical, financial, and human resources with policies and procedures to carry out the work of patient care.

This chapter provides a brief summary of the patient care process applied to drug therapy management and the practice management issues influencing adoption and application of this process by pharmacists.

IMPORTANCE OF A STANDARD CARE PROCESS

The stimulus for developing the patient care process for pharmacy was the wide variation observed as pharmacists provided direct patient care, often using the same terminology to describe diverse services or, conversely, using different terminology to describe the same service. Without a consistent patient care process, it has been challenging for the pharmacy profession to communicate the pharmacist’s role to external groups and establish the distinct value pharmacists bring to an interprofessional care team. Moreover, the patient must know and understand what is to be delivered to determine how best to receive the care provided. Likewise, other members of the healthcare team must determine how best to integrate the pharmacist’s work into their efforts caring for the patient. A process of care must be built on a set of fundamental steps that can address the wide range of complexity that exists among patients. The process needs to be adaptable to varied settings, diverse populations, and different acuity levels.
INTRODUCTION

THE PATIENT CARE PROCESS TO OPTIMIZE PHARMACOTHERAPY

The application or focus of a profession-specific process of care depends upon the profession's knowledge and expertise. For pharmacy, the patient care process is focused on patient medication-related needs and experience with medication therapy. Each health profession then addresses patient needs by assessing patient-specific information in a unique manner. For pharmacists providing comprehensive medication management (CMM), the assessment step involves a systematic examination of the indication, effectiveness, safety, and adherence for each of the patient's medications. This is a unique way of approaching a patient's health needs; no other discipline applies a systematic assessment process to medications and the medication experience in this manner.

The pharmacists' patient care process is standardized and is not specific to a care setting—it can be applied wherever CMM is performed. However, the type of information collected, its sources, and the duration of time to complete the process may vary depending on the practice setting and acuity of care. The subsequent sections in this chapter briefly describe the steps in the patient care process for pharmacists.

COLLECT PATIENT-SPECIFIC INFORMATION

Collect relevant subjective and objective information about the patient and analyze the data to understand the medical/medication history and clinical status of the patient. Information from the health record may include patient demographics, active medical
The Patient Care Process

problem list, admission and discharge notes, office visit notes, laboratory values, diagnostic tests, and medication lists. Conduct a comprehensive medication review with the patient that also includes alcohol, tobacco and caffeine use; immunization status; allergies; and adverse drug effects. Ask whether the patient has questions or concerns for the visit. Document a complete medication list that includes all prescription and nonprescription medications as well as dietary supplements the patient is taking (ie, name, indication, strength and formulation, dose, frequency, duration, and response to medication). Gather past medication history, if pertinent. Collect information about the patient’s medication experience (eg, beliefs, expectations, and cultural considerations related to medications) and personal goals of therapy. Ask about the patient’s ability to access medications, manage medications at home, adhere to the therapy, and use medications appropriately. Gather additional important information (eg, physical assessment findings, review of systems, home-monitored blood glucose, blood pressure readings).

**ASSESS INFORMATION AND FORMULATE A MEDICATION THERAPY PROBLEM LIST**

Analyze the information collected to formulate a problem list consisting of the patient’s active medical problems and medication therapy problems in order to prioritize medication therapy recommendations that achieve the patient’s health goals. Assess the *indication* of each medication the patient is taking, including the presence of an appropriate indication; consider also whether the patient has an untreated medical condition that requires therapy. Assess the *effectiveness* of each medication, including progress toward achieving therapeutic goals; optimal selection of drug product, dose, and duration of therapy; and need for additional laboratory data to monitor medication response. Assess the *safety* of each medication by identifying adverse events; excessive doses; availability of safer alternatives; pertinent drug-disease, drug-drug, or drug-food interactions; and need for additional laboratory data to monitor medication safety. Assess *adherence* and the patient’s ability to take each medication (eg, administration, access, affordability). Ensure that medication administration times are appropriate and convenient for the patient. From all of this information, formulate and prioritize a medication therapy problem list, classifying the patient’s medication therapy problems based on indication, effectiveness, safety, and adherence (Table 1).

<table>
<thead>
<tr>
<th>TABLE 1 Medication Therapy Problem Categories Framework</th>
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<td><strong>Medication-Related Needs</strong></td>
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INTRODUCTION

DEVELOP THE CARE PLAN
Working in collaboration with other healthcare professionals and the patient or caregiver, develop an individualized, patient-centered care plan that is evidence based and affordable for the patient. Design the plan to manage the patient’s active medical conditions and resolve the identified medication therapy problems. Coordinate care with the primary care provider and other healthcare team members to reach consensus on the proposed care plan, when needed. Identify the monitoring parameters necessary to assess effectiveness, safety, and adherence, including frequency of follow-up monitoring. Design personalized education and interventions for the patient, and reconcile all medication lists (eg, from the medical record, patient, pharmacy) to arrive at an accurate and updated medication list. Determine who will implement components of the care plan (ie, patient, clinical pharmacist, other providers). Decide on the appropriate time frame and mode for patient follow-up (eg, phone, face-to-face).

IMPLEMENT THE CARE PLAN
Implement the care plan in collaboration with other healthcare professionals and the patient or caregiver. Discuss the care plan with the patient, educate the patient about the medications and goals of therapy, make sure the patient understands and agrees with the plan, and implement recommendations that are within your scope of practice. For recommendations that cannot be independently implemented, communicate the care plan to the rest of the team, indicating where input is required by other team members. Document the encounter in the health record (eg, assessment, medication therapy care plan, rationale, monitoring, and follow-up). Arrange patient follow-up based on the determined time frame and communicate follow-up instructions with the patient.

FOLLOW-UP WITH THE PATIENT
Provide targeted follow-up and monitoring (whether in person, electronically, or via phone) to assess the effectiveness and safety of the care plan. Modify the plan when needed in collaboration with other team members and the patient or caregiver to achieve patient and clinical goals of therapy. Plan for a CMM follow-up visit at least once within a year of the initial visit, and repeat all steps of the patient care process at that time to ensure continuity of care and ongoing medication optimization. Refer the patient back to the provider (and document accordingly) if all medication therapy problems have been resolved, no new problems are identified, and it is determined that the patient no longer needs CMM services.

PRACTICE MANAGEMENT ISSUES
A practice management system is essential to the care process and includes the metrics to ensure patient health outcomes are being achieved; efficient workflow; communication and documentation using the power of information technology (IT); and data that accurately reflect the attribution and value the practitioner brings to patient care.

QUALITY METRICS
The patient care process sets a standard of achievable performance by defining the parameters of the process that can be measured. With the movement toward outcome-based healthcare models and value-based payment systems, it is critical to objectively measure the impact a patient care service has on a patient’s health and well-being. For the process to be measurable, each element must be clearly defined and performed in a similar manner during each patient encounter. The lack of clarity and consistency has hindered collection of robust evidence to support the value of pharmacists’ patient care services. The standard patient care process gives pharmacists an opportunity to show value on a large scale because the services are comparable and clearly understood across practice settings.
The Patient Care Process

WORKFLOW, DOCUMENTATION, AND INFORMATION SYSTEMS
Healthcare systems are rapidly embracing the power of technology to analyze information and gain important insights about the health outcomes being achieved. The uniform patient care process sets a standard for the practice workflow that allows IT systems to capture and extract data for analysis and sharing. The ability to capture clinical data is currently available through a number of coding systems, such as the International Classification of Diseases 10th edition (ICD-10) and the Systematized Nomenclature of Medicine—Clinical Terms (SNOMED-CT). Practitioners need to understand how coding systems operate behind the scenes when performing and documenting their clinical activities. This will enable practitioners to assist information technologists to effectively design systems to accurately document the elements of the process that can produce the data on medication-related outcomes.

DOCUMENTATION, ATTRIBUTION, AND PAYMENT
Payment to healthcare providers for patient care services in the United States has traditionally been based on the documentation and reporting of standard processes of care. Rules and guidance from Medicare and the Centers for Medicare and Medicaid Services (CMS) are considered the billing and payment standard for healthcare providers both for governmental and commercial payers. Reporting the complexity of care provided is built on top of the documentation requirements; complexity is determined by the number of required elements in each documentation domain. A billing code is then assigned to the patient encounter that equates to a payment commensurate with the level of care provided. This process is the basis for the current fee-for-service payment structure, and it is likely that this general format will remain in any future payment model. The traditional SOAP (Subjective, Objective, Assessment, Plan) note format is often used by pharmacists when documenting patient care and is particularly appropriate when providing services incident to an eligible Medicare Part B provider. However, some elements of the SOAP note that are required when using certain billing codes are not routinely performed by pharmacists (eg, comprehensive physical examination). The pharmacists' patient care process establishes a standard framework that reflects the pharmacist's work. Using a standard care process accompanied with a standard documentation framework will result in efficiencies of practice, enable appropriate and accurate billing, and facilitate the attribution of care to desired patient outcomes needed in value-based payment models.

See Chapter 1, The Patient Care Process, authored by Stuart T. Haines, Mary Ann Kliethermes, and Todd D. Sorensen for a more detailed discussion of this topic.
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Gout and Hyperuricemia

1. **Gout** involves hyperuricemia, recurrent attacks of acute arthritis with monosodium urate (MSU) crystals in synovial fluid leukocytes, deposits of MSU crystals in tissues in and around joints (tophi), interstitial kidney disease, and uric acid nephrolithiasis.

### Acute Gouty Arthritis

#### PATHOPHYSIOLOGY

- Uric acid is the end product of purine degradation. An increased urate pool in individuals with gout may result from overproduction or underexcretion.
- Purines originate from dietary purine, conversion of tissue nucleic acid to purine nucleotides, and de novo synthesis of purine bases.
- Overproduction of uric acid may result from abnormalities in enzyme systems that regulate purine metabolism (e.g., increased activity of phosphoribosyl pyrophosphate [PRPP] synthetase or deficiency of hypoxanthine-guanine phosphoribosyl transferase [HGPRT]).
- Uric acid may also be overproduced because of increased breakdown of tissue nucleic acids, as with myeloproliferative and lymphoproliferative disorders. Cytotoxic drugs can result in overproduction of uric acid due to lysis and the breakdown of cellular matter.
- Dietary purines are insignificant in generating hyperuricemia without some derangement in purine metabolism or elimination.
- Two-thirds of uric acid produced daily is excreted in urine. The remainder is eliminated through gastrointestinal (GI) tract after degradation by colonic bacteria. Decline in urinary excretion to a concentration below the rate of production leads to hyperuricemia and an increased pool of sodium urate.
- Drugs that decrease renal uric acid clearance include diuretics, nicotinic acid, salicylates (<2 g/day), ethanol, pyrazinamide, levodopa, ethambutol, cyclosporine, and cytotoxic drugs.
- Deposition of urate crystals in synovial fluid results in inflammation, vasodilation, increased vascular permeability, complement activation, and chemotactic activity for polymorphonuclear leukocytes. Phagocytosis of urate crystals by leukocytes results in rapid lysis of cells and discharge of proteolytic enzymes into cytoplasm. The ensuing inflammatory reaction causes intense joint pain, erythema, warmth, and swelling.
- Uric acid nephrolithiasis occurs in ~10% of patients with gout. Predisposing factors include excessive urinary excretion of uric acid, acidic urine (pH <6), and highly concentrated urine.
- In acute uric acid nephropathy, acute kidney injury occurs because of blockage of urine flow from massive precipitation of uric acid crystals in collecting ducts and ureters. Chronic urate nephropathy is caused by long-term deposition of urate crystals in the renal parenchyma.
- Tophi (urate deposits) are uncommon and are a late complication of hyperuricemia. The most common sites are the base of the fingers, olecranon bursae, ulnar aspect of forearm, Achilles tendon, knees, wrists, and hands.

#### CLINICAL PRESENTATION

- Acute gout attacks are characterized by rapid onset of excruciating pain, swelling, and inflammation. The attack is typically monoarticular, most often affecting the first
metatarsophalangeal joint (podagra), and then, in order of frequency, the insteps, ankles, heels, knees, wrists, fingers, and elbows. Attacks commonly begin at night, with the patient awakening with excruciating pain. Affected joints are erythematous, warm, and swollen. Fever and leukocytosis are common. Untreated attacks last from 3 to 14 days before spontaneous recovery.

- Acute attacks may occur without provocation or be precipitated by stress, trauma, alcohol ingestion, infection, surgery, rapid lowering of serum uric acid by uric acid-lowering agents, and ingestion of drugs known to elevate serum uric acid concentrations.

### DIAGNOSIS
- Definitive diagnosis requires aspiration of synovial fluid from the affected joint and identification of intracellular crystals of MSU monohydrate in synovial fluid leukocytes.
- When joint aspiration is not feasible, a presumptive diagnosis is based on presence of characteristic signs and symptoms as well as the response to treatment.

### TREATMENT
- **Goals of Treatment:** Terminate the acute attack, prevent recurrent attacks, and prevent complications associated with chronic deposition of urate crystals in tissues.

#### NONPHARMACOLOGIC THERAPY
- Local ice application is the most effective adjunctive treatment.
- Dietary supplements (eg, flaxseed, cherry, celery root) are not recommended.

#### PHARMACOLOGIC THERAPY (FIG. 1-1)
- Most patients are treated successfully with nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or colchicine. Treatment should begin as soon as possible after the onset of an attack.

### NSAIDS
- NSAIDs have excellent efficacy and minimal toxicity with short-term use. Indomethacin, naproxen, and sulindac have Food and Drug Administration (FDA) approval for gout, but others are likely to be effective (Table 1-1).
- Start therapy within 24 hours of attack onset and continue until complete resolution (usually 5–8 days). Tapering may be considered after resolution, especially if comorbidities such as impaired hepatic or kidney function make prolonged therapy undesirable.
- The most common adverse effects involve the GI tract (gastritis, bleeding, and perforation), kidneys (renal papillary necrosis, reduced glomerular filtration rate), cardiovascular system (increased blood pressure, sodium and fluid retention), and central nervous system (impaired cognitive function, headache, and dizziness).
- Selective cyclooxygenase-2 inhibitors (eg, celecoxib) may be an option for patients unable to take nonselective NSAIDs, but the risk-to-benefit ratio in acute gout is unclear, and cardiovascular risk must be considered.

### Corticosteroids
- Corticosteroid efficacy is equivalent to NSAIDs; they can be used systemically or by intra-articular (IA) injection. If only one or two joints are involved, either IA or oral corticosteroids are recommended. Systemic therapy is necessary for polyarticular attacks.
- **Prednisone** or **prednisolone** oral dosing strategies include (1) 0.5 mg/kg daily for 5–10 days followed by abrupt discontinuation, or (2) 0.5 mg/kg daily for 2–5 days followed by tapering for 7–10 days. Tapering is often used to reduce the hypothetical risk of a rebound attack upon steroid withdrawal.
- **Methylprednisolone dose pack** is a 6-day regimen starting with 24 mg on day 1 and decreasing by 4 mg each day that may be considered.
- **Triamcinolone acetonide** 20–40 mg given by IA injection may be used if gout is limited to one or two joints; give 10–40 mg IA (large joints) or 5–20 mg IA (small joints). IA corticosteroids should be used with an oral NSAID, colchicine, or corticosteroid therapy.
Gout and Hyperuricemia  |  CHAPTER 1

Pain intensity

Mild/moderate

Initiate monotherapy: a
NSAID
Colchicine b
Systemic corticosteroid

Successful

Prevent recurrent attacks:
Recommend dietary modifications to prevent hyperuricemia c
Educate patient about the role of uric acid excess in gout attacks
Develop plan for patient to promptly self-treat any future attacks
Initiate urate-lowering therapy if indicated

Inadequate response

Switch to alternate monotherapy

Severe

Initiate combination therapy - examples include:
Colchicine + NSAID
Colchicine + Oral corticosteroid
NSAID + Intra-articular corticosteroid
Colchicine + Intra-articular corticosteroid
Oral corticosteroid + Intra-articular corticosteroid

Successful

Off-label Interleukin-1 inhibitor therapy

Inadequate response

Algorithm for management of an acute gout attack.

a) Recommendation for initial monotherapy with one of these medication groups supported unanimously by guidelines of the American College of Rheumatology (ACR), European League Against Rheumatism (EULAR), and American College of Physicians (ACP)
b) Colchicine should be started as soon as possible, ideally within 12-36 hours of pain onset
c) Noted as an area of inconclusive evidence by 2017 ACP guidelines

(Algorithm derived from 2017 ACP, 2016 EULAR, and 2012 ACR gout guidelines.)

FIGURE 1-1. Algorithm for management of an acute gout attack.
• Methylprednisolone (a long-acting corticosteroid) given by a single intramuscular (IM) injection followed by a short course of oral corticosteroid therapy is another reasonable approach. Alternatively, IM corticosteroid monotherapy may be considered in patients with multiple affected joints who cannot take oral therapy.

• Short-term corticosteroid use is generally well tolerated. Use with caution in patients with diabetes, GI problems, bleeding disorders, cardiovascular disease, and psychiatric disorders. Avoid long-term use because of risk for osteoporosis, hypothalamic–pituitary–adrenal axis suppression, cataracts, and muscle deconditioning.

• Adrenocorticotropic hormone (ACTH) gel: 40–80 USP units IM every 6–8 hours for 2 or 3 days and then discontinued. Limit use to patients with contraindications to first-line therapies (eg, heart failure, chronic kidney disease, and history of GI bleeding) or patients unable to take oral medications. However, the high drug price excludes ACTH as a viable treatment option.

Colchicine

• Colchicine is highly effective in relieving acute gout attacks; when it is started within the first 24 hours of onset, about two-thirds of patients respond within hours. Use only within 36 hours of attack onset because the likelihood of success decreases substantially if treatment is delayed.

• Colchicine causes dose-dependent GI adverse effects (nausea, vomiting, and diarrhea). Non-GI effects include neutropenia and axonal neuromyopathy, which may be worsened in patients taking other myopathic drugs (eg, statins) or with impaired kidney function. Use colchicine with caution in patients taking P-glycoprotein or strong CYP450 3A4 inhibitors (eg, clarithromycin) due to increased plasma colchicine levels and potential toxicity; colchicine dose reductions may be required. Also use colchicine with caution in patients with impaired kidney or hepatic function.

• Colcrys is an FDA-approved colchicine product available in 0.6 mg oral tablets. The recommended dose is 1.2 mg (two tablets) initially, followed by 0.6 mg (one tablet) 1 hour later. Although not an FDA-approved regimen, the American College of Rheumatology (ACR) gout treatment guidelines suggest that colchicine 0.6 mg once or
twice daily can be started 12 hours after the initial 1.2-mg dose and continued until the attack resolves. Colchicine is also available generically.

**Hyperuricemia In Gout**

- Recurrent gout attacks can be prevented by maintaining low uric acid levels, but adherence with nonpharmacologic and pharmacologic therapies is poor.

**NONPHARMACOLOGIC THERAPY**

- Patient education should address the recurrent nature of gout and the objective of each lifestyle/dietary modification and medication.
- Promote weight loss through caloric restriction and exercise in all patients to enhance renal urate excretion.
- Alcohol restriction is important because consumption correlates with gout attacks. ACR guidelines recommend limiting alcohol use in all gout patients and avoidance of any alcohol during periods of frequent gout attacks and in patients with advanced gout under poor control.
- Dietary recommendations include limiting consumption of high-fructose corn syrup and purine-rich foods (organ meats and some seafood) and encouraging consumption of vegetables and low-fat dairy products. The DASH diet (Dietary Approaches to Stop Hypertension) may lower serum uric acid by ~1.0 mg/dL in hyperuricemic patients who are adherent. However, no studies have demonstrated that dietary intervention improves clinical outcomes such as reduction in gout flares.
- Evaluate the medication list for potentially unnecessary drugs that may elevate uric acid levels. The ACR guidelines recommend elimination of nonessential uric acid-elevating medications in patients with hyperuricemia when feasible (eg, thiazide and loop diuretics, calcineurin inhibitors, niacin). Low-dose aspirin for cardiovascular prevention should be continued because aspirin has a negligible effect on elevating serum uric acid.

**PHARMACOLOGIC THERAPY (FIG. 1-2)**

- After the first attack of acute gout, prophylactic pharmacotherapy is recommended if patients have two or more attacks per year, even if serum uric acid is normal or only minimally elevated. Other indications include presence of tophi, kidney disease, or history of uric acid urolithiasis.
- Urate-lowering therapy can be started during an acute attack if anti-inflammatory prophylaxis has been initiated.
- Apply a stepwise approach to hyperuricemia (Fig. 1-2). Xanthine oxidase inhibitors are recommended first-line therapy, with uricosurics reserved for patients with a contraindication or intolerance to xanthine oxidase inhibitors. In refractory cases, combination therapy with a xanthine oxidase inhibitor plus a drug with uricosuric properties (probenecid, losartan, or fenofibrate) is suggested. Pegloticase may be used in severe cases in which the patient cannot tolerate or is not responding to other therapies.
- The ACR guideline goal of urate-lowering therapy is to achieve and maintain serum uric acid <6 mg/dL (357 μmol/L), and preferably <5 mg/dL (297 μmol/L) if gout is severe or signs and symptoms of gout persist. Urate lowering should be prescribed for long-term use.

**Xanthine Oxidase Inhibitors**

- Xanthine oxidase inhibitors reduce uric acid by impairing conversion of hypoxanthine to xanthine and xanthine to uric acid. Because they are effective in both overproducers and underexcretors of uric acid, they are the most widely prescribed agents for long-term prevention of recurrent gout attacks.
- **Allopurinol** lowers uric acid levels in a dose-dependent manner. ACR guidelines recommend a starting dose no greater than 100 mg daily in patients with normal kidney function and no more than 50 mg/day in patients with chronic kidney disease (stage 4 or worse) to avoid allopurinol hypersensitivity syndrome and prevent acute gout attacks common during initiation of urate-lowering therapy. The dose should be titrated gradually every 2–5 weeks up to a maximum of 800 mg/day until the serum urate target is achieved.
FIGURE 1-2. Algorithm for management of hyperuricemia in gout.

- **Does patient have an indication for Urate Lowering Therapy (ULT)?**
  - Yes
    - **Evidence of gout activity while taking ULT?**
      - Yes
        - **Discontinue prophylactic therapy after the greater of:**
          - 1) Six months
          - 2) Three months after achieving urate target
      - No
      - **Discontinue prophylactic therapy six months after achieving urate target**
  - No
    - **Does patient have an indication for Urate Lowering Therapy (ULT)?**
      - Yes
        - **Evidence of gout activity while taking ULT?**
          - Yes
            - **Discontinue prophylactic therapy after the greater of:**
              - 1) Six months
              - 2) Three months after achieving urate target
          - No
          - **Discontinue prophylactic therapy six months after achieving urate target**
      - No
        - **Does patient have an indication for Urate Lowering Therapy (ULT)?**
          - Yes
            - **Evidence of gout activity while taking ULT?**
              - Yes
                - **Discontinue prophylactic therapy after the greater of:**
                  - 1) Six months
                  - 2) Three months after achieving urate target
              - No
              - **Discontinue prophylactic therapy six months after achieving urate target**
          - No
            - **Does patient have an indication for Urate Lowering Therapy (ULT)?**
              - Yes
                - **Evidence of gout activity while taking ULT?**
                  - Yes
                    - **Discontinue prophylactic therapy after the greater of:**
                      - 1) Six months
                      - 2) Three months after achieving urate target
                  - No
                  - **Discontinue prophylactic therapy six months after achieving urate target**
              - No
                - **Does patient have an indication for Urate Lowering Therapy (ULT)?**
                  - Yes
                    - **Evidence of gout activity while taking ULT?**
                      - Yes
                        - **Discontinue prophylactic therapy after the greater of:**
                          - 1) Six months
                          - 2) Three months after achieving urate target
                      - No
                      - **Discontinue prophylactic therapy six months after achieving urate target**
                  - No
                    - **Does patient have an indication for Urate Lowering Therapy (ULT)?**
                      - Yes
                        - **Evidence of gout activity while taking ULT?**
                          - Yes
                            - **Discontinue prophylactic therapy after the greater of:**
                              - 1) Six months
                              - 2) Three months after achieving urate target
                          - No
                          - **Discontinue prophylactic therapy six months after achieving urate target**
                      - No
                        - **Does patient have an indication for Urate Lowering Therapy (ULT)?**
                          - Yes
                            - **Evidence of gout activity while taking ULT?**
                              - Yes
                                - **Discontinue prophylactic therapy after the greater of:**
                                  - 1) Six months
                                  - 2) Three months after achieving urate target
                              - No
                              - **Discontinue prophylactic therapy six months after achieving urate target**
                          - No
                            - **Does patient have an indication for Urate Lowering Therapy (ULT)?**
                              - Yes
                                - **Evidence of gout activity while taking ULT?**
                                  - Yes
                                    - **Discontinue prophylactic therapy after the greater of:**
                                      - 1) Six months
                                      - 2) Three months after achieving urate target
                                  - No
                                  - **Discontinue prophylactic therapy six months after achieving urate target**
                              - No
                                - **Does patient have an indication for Urate Lowering Therapy (ULT)?**
                                  - Yes
                                    - **Evidence of gout activity while taking ULT?**
                                      - Yes
                                        - **Discontinue prophylactic therapy after the greater of:**
                                          - 1) Six months
                                          - 2) Three months after achieving urate target
                                      - No
                                      - **Discontinue prophylactic therapy six months after achieving urate target**
                                  - No
                                - No
                                  - **Discontinue prophylactic therapy six months after achieving urate target**
                          - No
                          - **Discontinue prophylactic therapy six months after achieving urate target**
                        - No
                          - **Discontinue prophylactic therapy six months after achieving urate target**
                      - No
                    - No
                      - **Discontinue prophylactic therapy six months after achieving urate target**
                - No
                  - **Discontinue prophylactic therapy six months after achieving urate target**
              - No
                - **Discontinue prophylactic therapy six months after achieving urate target**
          - No
            - **Discontinue prophylactic therapy six months after achieving urate target**
        - No
          - **Discontinue prophylactic therapy six months after achieving urate target**
      - No
        - **Discontinue prophylactic therapy six months after achieving urate target**
    - No
      - **Discontinue prophylactic therapy six months after achieving urate target**
  - No
    - **Does patient have an indication for Urate Lowering Therapy (ULT)?**
      - Yes
        - **Evidence of gout activity while taking ULT?**
          - Yes
            - **Discontinue prophylactic therapy after the greater of:**
              - 1) Six months
              - 2) Three months after achieving urate target
          - No
          - **Discontinue prophylactic therapy six months after achieving urate target**
        - No
          - **Discontinue prophylactic therapy six months after achieving urate target**
  - No
    - **Discontinue prophylactic therapy six months after achieving urate target**

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**Nonpharmacologic Urate Lowering Strategies**
- Dietary Modifications
  - Reduce/avoid alcohol and organ meats
  - Increase vegetable and dairy consumption
- Eliminate Urate Elevating Medications if Unnecessary
  - Diuretics
  - Niacin
  - Calcineurin inhibitors

**ULT Initiation**
- First-Line
  - Allopurinol
- Alternative
  - Febuxostat
  - Probenecid

**Anti-inflammatory Gout Prophylaxis During ULT Initiation**
- First-Line
  - Low dose colchicine
  - Low dose NSAID
- Second Line
  - Low dose prednisone or prednisolone

a) Indications for urate-lowering therapy include: 1) presence of tophus 2) ≥ 2 gout attacks per year 3) kidney disease 4) past urolithiasis. EULAR, but not ACR or ACP Guidelines, also recognize the following indications for ULT: 1) first diagnosis of gout at age < 40 years 2) uric acid > 8.0 mg/dL 3) high-risk comorbidities (hypertension, ischemic heart disease, hear failure)
b) Recognized as first line by ACR Guidelines but cardiovascular safety concerns have been reported since guideline publication
c) EULAR Guidelines also recognize calcium channel blockers and statins as add-on therapy for uric acid lowering when indicated for treatment of comorbidities
d) The effectiveness of dietary intervention in improving clinical outcomes is noted as an area of inconclusive evidence by 2017 ACP guidelines
e) Targeting and maintaining a specific urate level is noted as an area of inconclusive evidence by 2017 ACP guidelines

NSAID, nonsteroidal anti-inflammatory drug; ULT, urate-lowering therapy; XOI, xanthine oxidase inhibitor.

(Algorithm derived from 2017 ACP, 2016 EULAR, and 2012 ACR gout guidelines.)
• Mild adverse effects of allopurinol include skin rash, leukopenia, GI problems, headache, and urticaria. A more severe adverse reaction known as allopurinol hypersensitivity syndrome, which includes severe rash (toxic epidermal necrolysis, erythema multiforme, or exfoliative dermatitis), hepatitis, interstitial nephritis, and eosinophilia, occurs rarely but is associated with a 20%–25% mortality rate.

• Febuxostat (Uloric) also lowers serum uric acid in a dose-dependent manner. The recommended starting dose is 40 mg once daily. Increase the dose to 80 mg once daily for patients who do not achieve target serum uric acid concentrations after 2 weeks of therapy. Adverse events include nausea, arthralgias, and minor hepatic transaminase elevations. Febuxostat does not require dose adjustment in hepatic or kidney dysfunction. Recent clinical trial evidence demonstrated an increase in all-cause and cardiovascular mortality compared to allopurinol, resulting in addition of a warning in the FDA-approved labeling. Because of these safety concerns, lack of evidence of superior efficacy compared to equivalent-dosed allopurinol, and increased cost, febuxostat is considered a second-line option. Due to rapid mobilization of urate deposits during initiation, give concomitant therapy with colchicine or an NSAID for at least the first 8 weeks of therapy to prevent acute gout flares.

Uricosurics

• Uricosuric drugs increase renal clearance of uric acid by inhibiting the postsecretory renal proximal tubular reabsorption of uric acid. Patients with a history of urolithiasis should not receive uricosurics. Start uricosuric therapy at a low dose to avoid marked uricosuria and possible stone formation. Maintaining adequate urine flow and urine alkalization during the first several days of therapy may also decrease likelihood of uric acid stone formation. Uricosuric treatment is limited to patients with creatinine clearance (CrCl) >45–50 mL/min.

• Probenecid: The initial dose is 250 mg twice daily for 1–2 weeks, then 500 mg twice daily for 2 weeks. Increase the daily dose thereafter by 500-mg increments every 1–2 weeks until satisfactory control is achieved or a maximum dose of 2 g/day is reached. Major side effects include GI irritation, rash and hypersensitivity, precipitation of acute gouty arthritis, and urolithiasis.

• Lesinurad (Zurampic) inhibits urate transporter 1 in proximal renal tubules, thereby increasing uric acid excretion. It is approved as combination therapy with a xanthine oxidase inhibitor for treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid concentrations with xanthine oxidase inhibitor monotherapy. The approved lesinurad dose is 200 mg once daily in the morning with food and water in combination with a xanthine oxidase inhibitor. Lesinurad should not be used in patients with CrCl <45 mL/min. Adverse effects include urticaria and elevated levels of serum creatinine, lipase, and creatine kinase. It carries a black box warning about increased risk of acute renal failure when used in the absence of xanthine oxidase inhibitor therapy. A combination product (Duzallo) is available that contains two different allopurinol strengths: lesinurad 200 mg/ allopurinol 200 mg (for patients with CrCl 45–59 mL/min) and lesinurad 200 mg/ allopurinol 300 mg (for patients with CrCl >59 mL/min).

Pegloticase

• Pegloticase (Krystexxa) is a pegylated recombinant uricase that reduces serum uric acid by converting uric acid to allantoin, which is water soluble. Pegloticase is indicated for antihyperuricemic therapy in adults refractory to conventional therapy.

• The dose is 8 mg by IV infusion over at least 2 hours every 2 weeks. Because of potential infusion-related allergic reactions, patients must be pretreated with antihistamines and corticosteroids. Pegloticase is substantially more expensive than first-line urate-lowering therapies.

• The ideal duration of pegloticase therapy is unknown. Development of pegloticase antibodies resulting in loss of efficacy may limit the duration of effective therapy.

• Because of its limitations, reserve pegloticase for patients with refractory gout who are unable to take or have failed all other urate-lowering therapies.
**Miscellaneous Urate-Lowering Agents**

- **Fenofibrate** is thought to increase clearance of hypoxanthine and xanthine, leading to a sustained reduction in serum urate concentrations of 20%–30%.

- **Atorvastatin** and **rosuvastatin** have also been associated with serum uric acid lowering, although the effect is less than with fenofibrate. The mechanism is unclear but is thought to be due to decreased renal reabsorption of uric acid.

- **Losartan** inhibits renal tubular reabsorption of uric acid and increases urinary excretion, properties that are not shared with other angiotensin II receptor blockers. It also alkalinizes the urine, which helps reduce the risk for stone formation.

- **Amlodipine**, **nifedipine**, and **diltiazem** (calcium channel blockers) have been associated with a lower risk of gout, which has been attributed to increased renal elimination of uric acid.

**ANTI-INFLAMMATORY PROPHYLAXIS DURING INITIATION OF URATE-LOWERING THERAPY**

- Initiation of urate-lowering therapy can precipitate an acute gout attack due to remodeling of urate crystal deposits in joints after rapid lowering of urate concentrations. Prophylactic anti-inflammatory therapy is often used to prevent such gout attacks.

- The ACR guidelines recommend low-dose oral colchicine (0.6 mg twice daily) or low-dose NSAIDs (eg, naproxen 250 mg twice daily) as first-line prophylactic therapies, with stronger evidence supporting use of colchicine. For patients on long-term NSAID prophylaxis, a proton pump inhibitor or other acid-suppressing therapy is indicated to protect from NSAID-induced gastric problems.

- Low-dose corticosteroid therapy (eg, prednisone ≤10 mg/day) is an alternative for patients with intolerance, contraindication, or lack of response to first-line therapy. The potential severe adverse effects of prolonged corticosteroid therapy preclude their use as first-line therapy.

- Continue prophylaxis for at least 6 months or 3 months after achieving target serum uric acid, whichever is longer. For patients with one or more tophi, continue prophylactic therapy for 6 months after achieving the serum urate target (Fig. 1-2).

**EVALUATION OF THERAPEUTIC OUTCOMES**

- Check the serum uric acid level in patients suspected of having an acute gout attack, particularly if it is not the first attack, and a decision is to be made about starting prophylaxis. However, acute gout can occur with normal serum uric acid concentrations.

- Monitor patients with acute gout for symptomatic relief of joint pain as well as potential adverse effects and drug interactions related to drug therapy. Acute pain of an initial gout attack should begin to ease within about 8 hours of treatment initiation. Complete resolution of pain, erythema, and inflammation usually occurs within 48–72 hours.

- For patients receiving urate-lowering therapy, obtain baseline assessment of kidney function, hepatic enzymes, complete blood count, and electrolytes. Recheck the tests every 6–12 months in patients receiving long-term treatment.

- During titration of urate-lowering therapy, monitor serum uric acid every 2–5 weeks; after the urate target is achieved, monitor uric acid every 6 months.

- Because of the high rates of comorbidities associated with gout (diabetes, chronic kidney disease, hypertension, obesity, myocardial infarction, heart failure, and stroke), elevated serum uric acid concentrations or gout should prompt evaluation for cardiovascular disease and the need for appropriate risk reduction measures. Clinicians should also look for possible correctable causes of hyperuricemia (eg, medications, obesity, malignancy, and alcohol abuse).

See Chapter 109, Gout and Hyperuricemia, authored by Michelle A. Fravel and Michael E. Ernst, for a more detailed discussion of this topic.
• Osteoarthritis (OA) is a common, progressive disorder affecting primarily weight-bearing diarthrodial joints, characterized by progressive destruction of articular cartilage, osteophyte formation, pain, limitation of motion, deformity, and disability.

**PATHOPHYSIOLOGY**

• **Primary (idiopathic) OA**, the more common type, has no known cause.
• **Secondary OA** is associated with a known cause such as inflammation, trauma, metabolic or endocrine disorders, and congenital factors.
• OA usually begins with damage to articular cartilage through injury, excessive joint loading from obesity or other reasons, or joint instability. Damage to cartilage increases activity of chondrocytes in attempt to repair damage, leading to increased synthesis of matrix constituents with cartilage swelling. Normal balance between cartilage breakdown and resynthesis is lost, with increasing destruction and cartilage loss.
• Subchondral bone adjacent to articular cartilage undergoes pathologic changes and releases vasoactive peptides and matrix metalloproteinases. Neovascularization and increased permeability of adjacent cartilage occur, which contribute to cartilage loss and chondrocyte apoptosis.
• Cartilage loss causes joint space narrowing and painful, deformed joints. Remaining cartilage softens and develops fibrillations, followed by further cartilage loss and exposure of underlying bone. New bone formations (osteophytes) at joint margins distant from cartilage destruction are thought to help stabilize affected joints.
• Inflammatory changes can occur in the joint capsule and synovium. Crystals or cartilage shards in synovial fluid may contribute to inflammation. Interleukin-1, prostaglandin E₂, tumor necrosis factor-α, and nitric oxide in synovial fluid may also play a role. Inflammatory changes result in synovial effusions and thickening.
• Pain may result from distention of the synovial capsule by increased joint fluid; microfracture; periosteal irritation; or damage to ligaments, synovium, or the meniscus.

**CLINICAL PRESENTATION**

• Risk factors include increasing age, obesity, sex, certain occupations and sports activities, history of joint injury or surgery, and genetic predisposition.
• The predominant symptom is deep, aching pain in affected joints. Pain accompanies joint activity and decreases with rest.
• Joints most commonly affected are the distal interphalangeal (DIP) and proximal interphalangeal (PIP) joints of the hand, first carpometacarpal joint, knees, hips, cervical and lumbar spine, and first metatarsophalangeal (MTP) joint of the toe.
• Limitation of motion, stiffness, crepitus, and deformities may occur. Patients with lower extremity involvement may report weakness or instability.
• Upon arising, joint stiffness typically lasts less than 30 minutes and resolves with motion.
• Presence of warm, red, and tender joints suggests inflammatory synovitis.
• Physical examination of affected joints reveals tenderness, crepitus, and possibly enlargement. Heberden and Bouchard nodes are bony enlargements (osteophytes) of the DIP and PIP joints, respectively.
DIAGNOSIS

- Diagnosis is made through patient history, physician examination, radiologic findings, and laboratory testing.
- American College of Rheumatology criteria for classification of OA of the hips, knees, and hands include presence of pain, bony changes on examination, normal erythrocyte sedimentation rate (ESR), and radiographs showing osteophytes or joint space narrowing.
- For hip OA, patients must have hip pain and two of the following: (1) ESR < 20 mm/hr (5.6 μm/sec), (2) radiographic femoral or acetabular osteophytes, and/or (3) radiographic joint space narrowing.
- For knee OA, patients must have knee pain and radiographic osteophytes in addition to one or more of the following: (1) age > 50 years, (2) morning stiffness lasting ≤ 30 minutes, (3) crepitus on motion, (4) bony enlargement, (5) bony tenderness, and/or (6) palpable joint warmth.
- ESR may be slightly elevated if inflammation is present. Rheumatoid factor is negative. Analysis of synovial fluid reveals high viscosity and mild leukocytosis (< 2000 white blood cells/mm³ [2 × 10⁹/L]) with predominantly mononuclear cells.

TREATMENT

- Goals of Treatment: (1) Educate the patient, family members, and caregivers; (2) relieve pain and stiffness; (3) maintain or improve joint mobility; (4) limit functional impairment; and (5) maintain or improve quality of life.

NONPHARMACOLOGIC THERAPY

- Educate the patient about the disease process and extent, prognosis, and treatment options. Promote dietary counseling, exercise, and a weight loss program for overweight patients.
- Physical therapy—with heat or cold treatments and an exercise program—helps maintain range of motion and reduce pain and need for analgesics.
- Assistive and orthotic devices (canes, walkers, braces, heel cups, and insoles) can be used during exercise or daily activities.
- Surgical procedures (eg, osteotomy, arthroplasty, joint fusion) are indicated for functional disability and/or severe pain unresponsive to conservative therapy.

PHARMACOLOGIC THERAPY (TABLE 2-1)

- Drug therapy is targeted at relief of pain. A conservative approach is warranted because OA often occurs in older individuals with other medical conditions.
- Apply an individualized approach (Figs. 2-1 and 2-2). Continue appropriate nondrug therapies when initiating drug therapy.

Knee and Hip OA

- Acetaminophen is a preferred first-line treatment; it may be less effective than oral nonsteroidal anti-inflammatory drugs (NSAIDs) but has a lower risk of serious gastrointestinal (GI) and cardiovascular (CV) events. Acetaminophen is usually well tolerated, but potentially fatal hepatotoxicity with overdose is well documented. It should be avoided in chronic alcohol users or patients with liver disease.
- Nonselective NSAIDs or cyclooxygenase-2 (COX-2) selective inhibitors (eg, celecoxib) are recommended if a patient fails acetaminophen. Nonselective NSAIDs may cause minor GI complaints such as nausea, dyspepsia, anorexia, abdominal pain, and diarrhea. They may cause gastric and duodenal ulcers and bleeding through direct (topical) or indirect (systemic) mechanisms. Risk factors for NSAID-associated ulcers and ulcer complications (perforation, gastric outlet obstruction, and GI bleeding) include longer duration of NSAID use, higher dosage, age older than 16
<table>
<thead>
<tr>
<th><strong>Drug</strong></th>
<th><strong>Starting Dose</strong></th>
<th><strong>Usual Range</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral analgesics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>325–500 mg three times a day</td>
<td>325–650 mg every 4–6 hours or 1 g three to four times/day</td>
</tr>
<tr>
<td>Tramadol</td>
<td>25 mg in the morning</td>
<td>Titrate dose in 25-mg increments to reach a maintenance dose of 50–100 mg three times a day</td>
</tr>
<tr>
<td>Tramadol ER</td>
<td>100 mg daily</td>
<td>Titrate to 200–300 mg daily</td>
</tr>
<tr>
<td>Hydrocodone/acetaminophen</td>
<td>5 mg/325 mg three times daily</td>
<td>2.5–10 mg/325–650 mg three to five times daily</td>
</tr>
<tr>
<td>Oxycodone/acetaminophen</td>
<td>5 mg/325 mg three times daily</td>
<td>2.5–10 mg/325–650 mg three to five times daily</td>
</tr>
<tr>
<td><strong>Topical analgesics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capsaicin 0.025%–0.15%</td>
<td>Apply to affected joint three to four times per day</td>
<td></td>
</tr>
<tr>
<td>Diclofenac 1% gel</td>
<td>Apply 2 or 4 g per site as prescribed, four times daily</td>
<td></td>
</tr>
<tr>
<td>Diclofenac 1.3% patch</td>
<td>Apply one patch twice daily to the site to be treated, as directed</td>
<td></td>
</tr>
<tr>
<td>Diclofenac 1.5% solution</td>
<td>Apply 40 drops to the affected knee, applying and rubbing in 10 drops at a time. Repeat for a total of four times daily.</td>
<td></td>
</tr>
<tr>
<td><strong>Intra-articular corticosteroids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>5–15 mg per joint</td>
<td>10–40 mg per large joint (knee, hip, shoulder)</td>
</tr>
<tr>
<td>Methylprednisolone acetate</td>
<td>10–20 mg per joint</td>
<td>20–80 mg per large joint (knee, hip, shoulder)</td>
</tr>
<tr>
<td><strong>NSAIDs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin (plain, buffered, or enteric-coated)</td>
<td>325 mg three times a day</td>
<td>325–650 mg four times a day</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>100 mg daily</td>
<td>100 mg twice daily or 200 mg daily</td>
</tr>
<tr>
<td>Diclofenac IR</td>
<td>50 mg twice a day</td>
<td>50–75 mg twice a day</td>
</tr>
<tr>
<td>Diclofenac XR</td>
<td>100 mg daily</td>
<td>100–200 mg daily</td>
</tr>
<tr>
<td>Diflunisal</td>
<td>250 mg twice a day</td>
<td>500–750 mg twice a day</td>
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<tr>
<td>Etodolac</td>
<td>300 mg twice a day</td>
<td>400–500 mg twice a day</td>
</tr>
<tr>
<td>Fenoprofen</td>
<td>400 mg three times a day</td>
<td>400–600 mg three to four times a day</td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>100 mg twice a day</td>
<td>200–300 mg/day in two to four divided doses</td>
</tr>
</tbody>
</table>

(Continued)
SECTION 1  |  Bone and Joint Disorders

60 years, past history of peptic ulcer disease of any cause, history of alcohol use, and concomitant use of glucocorticoids or anticoagulants. Options for reducing the GI risk of nonselective NSAIDs include using (1) the lowest dose possible and only when needed, (2) misoprostol four times daily with the NSAID, and (3) a PPI or full-dose H₂-receptor antagonist daily with the NSAID. • COX-2 inhibitors pose less risk for adverse GI events than nonselective NSAIDs, but this advantage is substantially reduced for patients taking aspirin. Both nonselective and selective NSAIDs are associated with an increased risk for CV events (hypertension, stroke, myocardial infarction, and death). • NSAIDs may also cause kidney diseases, hepatitis, hypersensitivity reactions, rash, and CNS complaints of drowsiness, dizziness, headaches, depression, confusion, and tinnitus. NSAIDs inhibit COX-1–dependent thromboxane production in platelets, thereby increasing bleeding risk. Unlike aspirin, celecoxib and nonspecific NSAIDs inhibit thromboxane formation reversibly, with normalization of platelet function 1–3 days after drug discontinuation. Avoid NSAIDs in late pregnancy because of risk of premature closure of the ductus arteriosus. The most potentially serious drug interactions include use of NSAIDs with lithium, warfarin, oral hypoglycemics, methotrexate, antihypertensives, angiotensin-converting enzyme inhibitors, β-blockers, and diuretics.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting Dose</th>
<th>Usual Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>200 mg three times a day</td>
<td>1200–3200 mg/day in three to four divided doses</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>25 mg twice a day</td>
<td>Titrate dose by 25–50 mg/day until pain controlled or maximum dose of 50 mg three times a day</td>
</tr>
<tr>
<td>Indomethacin SR</td>
<td>75 mg SR once daily</td>
<td>Can titrate to 75 mg SR twice daily if needed</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>50 mg three times a day</td>
<td>50–75 mg three to four times a day</td>
</tr>
<tr>
<td>Meclofenamate</td>
<td>50 mg three times a day</td>
<td>50–100 mg three to four times a day</td>
</tr>
<tr>
<td>Mefenamic acid</td>
<td>250 mg three times a day</td>
<td>250 mg four times a day</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>7.5 mg daily</td>
<td>15 mg daily</td>
</tr>
<tr>
<td>Nabumetone</td>
<td>500 mg daily</td>
<td>500–1000 mg one to two times a day</td>
</tr>
<tr>
<td>Naproxen</td>
<td>250 mg twice a day</td>
<td>500 mg twice a day</td>
</tr>
<tr>
<td>Naproxen sodium</td>
<td>220 mg twice a day</td>
<td>220–550 mg twice a day</td>
</tr>
<tr>
<td>Naproxen sodium CR</td>
<td>750–1000 mg once daily</td>
<td>500–1500 mg once daily</td>
</tr>
<tr>
<td>Oxaprozin</td>
<td>600 mg daily</td>
<td>600–1200 mg daily</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>10 mg daily</td>
<td>20 mg daily</td>
</tr>
<tr>
<td>Salsalate</td>
<td>500 mg twice a day</td>
<td>500–1000 mg two to three times a day</td>
</tr>
</tbody>
</table>

Patient requires pharmacologic treatment

Is acetaminophen contraindicated?

Acetaminophen* maximum 4 g/day

Is treatment effective?

Alternative second-line agents
- Opioid analgesics
- Surgery
- Duloxetine (knee only)
- Intra-articular hyaluronates (knee only)

Alternative first-line agents
- Topical NSAIDs (knee only) and/or intra-articular corticosteroids and/or tramadol and/or oral NSAIDs (if <75 yo or low CV and GI risk)*

When used for chronic management of OA, consider addition of a proton-pump inhibitor.
(See insert for color.)

FIGURE 2-1. Treatment recommendations for hip and knee osteoarthritis.

- **Topical NSAIDs** are recommended for knee OA if acetaminophen fails, and they are preferred over oral NSAIDs in patients older than 75 years. Topical NSAIDs provide similar pain relief with fewer adverse GI events than oral NSAIDs but may be associated with adverse events at the application site (eg, dry skin, pruritus, and rash). Patients using topical products should avoid oral NSAIDs to minimize the potential for additive side effects. Use of topical NSAIDs has not been linked with increased risk of CV events.

- **Intra-articular (IA) corticosteroid injections** are recommended for both hip and knee OA when analgesia with acetaminophen or NSAIDs is suboptimal. They can provide excellent pain relief, particularly when joint effusion is present. Local anesthetics such as lidocaine or bupivacaine are commonly combined with corticosteroids to provide rapid pain relief. Injections may also be given with concomitant oral analgesics for additional pain control. After aseptic aspiration of the effusion and corticosteroid injection, initial pain relief may occur within 24–72 hours, with peak relief occurring after 7–10 days and lasting for 4–8 weeks. Local adverse effects can include infection, osteonecrosis, tendon rupture, and skin atrophy at the injection site. Do not administer injections more frequently than once every 3 months to minimize systemic adverse effects. Systemic corticosteroid therapy is not recommended in OA, given lack of proven benefit and well-known adverse effects with long-term use.

- **Tramadol** is recommended for hip and knee OA in patients who have failed scheduled full-dose acetaminophen and topical NSAIDs, who are not appropriate candidates for oral NSAIDs, and who are not able to receive IA corticosteroids. Tramadol can be added to partially effective acetaminophen or oral NSAID therapy. Tramadol is associated with opioid-like adverse effects such as nausea, vomiting, dizziness, constipation, headache, and somnolence. However, tramadol is not associated with life-threatening GI bleeding, CV events, or renal failure. The most serious adverse event is seizures. Tramadol is classified as a Schedule IV controlled substance due to its potential for dependence, addiction, and diversion. There is increased risk of serotonin syndrome when tramadol is used with other serotonergic medications, including duloxetine.

- **Opioids** should be considered in patients not responding adequately to nonpharmacologic and first-line pharmacologic therapies. Patients who are at high surgical risk and cannot undergo joint arthroplasty are also candidates for opioid therapy. Use opioid analgesics in the lowest effective dose and the smallest quantity needed. Avoid combinations of opioids and sedating medications whenever possible.
Inform patients on how to use, store, and dispose of opioid medications. Sustained-release compounds usually offer better pain control throughout the day. Common adverse effects include nausea, somnolence, constipation, dry mouth, and dizziness. Opioid dependence, addiction, tolerance, hyperalgesia, and issues surrounding drug diversion may be associated with long-term treatment. Assess opioid use at least every 3 months, evaluating patient progression toward functional treatment goals, risks of harm, and adverse effects.

- **Duloxetine** can be used as adjunctive treatment of knee (not hip) OA in patients with partial response to first-line analgesics (acetaminophen, oral NSAIDs). It may be a preferred second-line medication in patients with both neuropathic and musculoskeletal OA pain. Pain reduction occurs after about 4 weeks of therapy. Duloxetine may cause nausea, dry mouth, constipation, anorexia, fatigue, somnolence, and dizziness. Serious rare events include Stevens-Johnson syndrome and liver failure. Concomitant use with other medications that increase serotonin concentration (including tramadol) increases risk of serotonin syndrome.

- **IA hyaluronic acid** (sodium hyaluronate) is not routinely recommended because injections have shown limited benefit for knee OA and have not been shown to benefit hip OA. Injections are usually well tolerated, but acute joint swelling, effusion, stiffness, and local skin reactions (eg, rash, ecchymoses, or pruritus) have been reported. IA preparations and regimens for OA knee pain include:
  - **Cross-linked hyaluronate 30 mg/3 mL** (Gel-One) single injection
  - **Hyaluronan 30 mg/2 mL** (Orthovisc) once weekly for three injections
  - **Hyaluronan 88 mg/4 mL** (Monovisc) single injection

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*Selection of a medication should consider patient-specific characteristics.*

*When used for chronic management of OA, consider addition of a proton-pump inhibitor.*

*Should not combine topical NSAIDs and oral NSAIDs.*

(CV, cardiovascular; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug.)

**FIGURE 2-2.** Treatment recommendations for hand osteoarthritis.
✓ Hylan polymers 16 mg/2 mL (Synvisc) once weekly for three injections
✓ Hylan polymers 48 mg/6 mL (Synvisc-One) single injection
✓ Sodium hyaluronate 20 mg/2 mL (Hyalgan) once weekly for five injections
✓ Sodium hyaluronate 20 mg/2 mL (Euflexxa) once weekly for three injections
✓ Sodium hyaluronate 25 mg/2.5 mL (Supartz FX) once weekly for five injections
✓ Sodium hyaluronate 25 mg/2.5 mL (GenVisc 850) once weekly for five injections

• Glucosamine and/or chondroitin and topical rubefacients (eg, methyl salicylate, trolamine salicylate) lack uniform improvement in pain control or functional status for hip and knee pain and are not preferred treatment options. Glucosamine adverse effects are mild and include flatulence, bloating, and abdominal cramps. The most common adverse effect of chondroitin is nausea.

Hand OA

• Topical NSAIDs are a first-line option for hand OA. Topical diclofenac has efficacy similar to oral NSAIDs with fewer adverse GI events, albeit with some local application site events. Efficacy with topical NSAIDs typically occurs with 1–2 weeks.
• Oral NSAIDs are an alternative first-line treatment for patients who cannot tolerate the local skin reactions or who received inadequate relief from topical NSAIDs.
• Capsaicin cream is an alternative first-line treatment; small clinical trials have demonstrated about 50% reduction in pain scores. It is a reasonable option for patients unable to take oral NSAIDs. Capsaicin must be used regularly to be effective, and it may require up to 2 weeks to take effect. Adverse effects are primarily local and include burning, stinging, and/or erythema that usually subsides with repeated application. Warn patients not to get cream in their eyes or mouth and to wash hands after application. Application of the cream, gel, solution, or lotion is recommended four times daily.
• Tramadol is an alternative first-line treatment and is a reasonable option for patients who do not respond to topical therapy and are not candidates for oral NSAIDs because of high GI, CV, or renal risks. Tramadol may also be used in combination with partially effective acetaminophen, topical therapy, or oral NSAIDs.

EVALUATION OF THERAPEUTIC OUTCOMES

• To monitor efficacy, assess baseline pain with a visual analog scale, and assess range of motion for affected joints with flexion, extension, abduction, or adduction.
• Depending on the joint(s) affected, measurement of grip strength and 50-ft walking time can help assess hand and hip/knee OA, respectively.
• Baseline radiographs can document extent of joint involvement and follow disease progression with therapy.
• Other measures include the clinician’s global assessment based on patient’s history of activities and limitations caused by OA, the Western Ontario and McMaster Universities Arthrosis Index, Stanford Health Assessment Questionnaire, and documentation of analgesic or NSAID use.
• Ask patients about adverse effects from medications. Monitor for signs of drug-related effects, such as skin rash, headaches, drowsiness, weight gain, or hypertension from NSAIDs.
• Obtain baseline serum creatinine, hematologic profile, and serum transaminases with repeat levels at 6- to 12-month intervals to identify specific toxicities to the kidney, liver, GI tract, or bone marrow.

See Chapter 106, Osteoarthritis, authored by Lucinda M. Bays and Sara A. Wiedenfeld, for a more detailed discussion of this topic.