

Statement of Need

Gout is an ancient disease that has challenged clinicians for centuries. Despite long-term clinical experience with gout, the incidence and prevalence of this disease continues to rise, affecting approximately 5 million people in the United States. Pharmacists are often the initial point of contact for patients experiencing symptoms associated with gout and can make a quick referral to a physician for diagnosis. Approximately 3.9 million annual physician visits in the United States occur due to gout, with two-thirds at the primary care practitioner's office, where most prescriptions are written.

Once a diagnosis of gout is confirmed, pharmacists play an important role as counselor in the patient's treatment, providing pivotal information on efficacy and adverse events, the effect of polypharmacy, and comorbid conditions associated with gout.

This monograph will educate the pharmacist on lifestyle modifications, the importance of compliance, and how to appropriately use treatment to ensure optimal patient outcomes.

Target Audience

This activity is designed for pharmacists with a special interest in the topic of gout and hyperuricemia.

There is no fee to participate in this activity.

Learning Objectives

- Differentiate the clinical presentation of an acute attack of gout from that of the chronic disease
- Discuss the importance of counseling patients about lifestyle interventions for treating and preventing gout
- Educate patients on medication adherence and commitment to treatment in the successful management of gout
- Identify contraindications and drug interactions associated with the primary pharmacotherapy agents used in patients with gout

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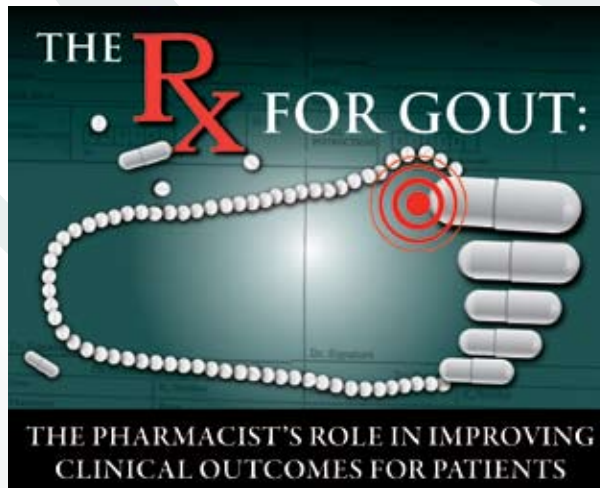
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Introduction

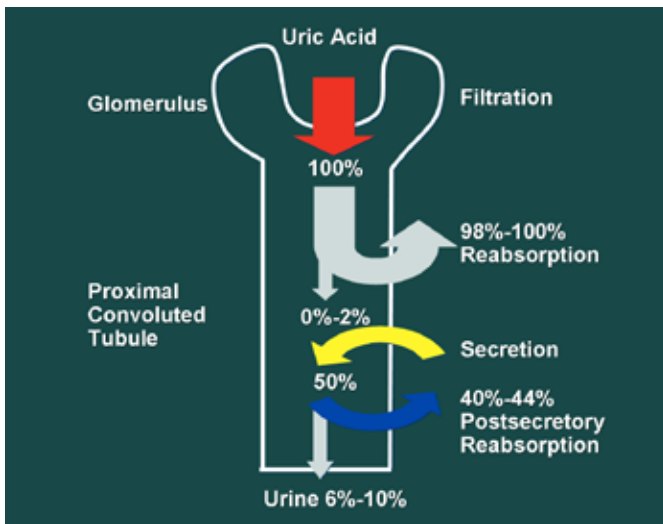
Gout is an ancient disease that has challenged clinicians for centuries. The prevalence of gout continues to rise: approximately 5 million people in the United States now suffer from gout,¹ which exceeds the numbers afflicted with rheumatoid arthritis, kidney disease, or even breast cancer.¹⁻³ Gout results in approximately 3.9 million annual physician visits in the United States, with two-thirds at the primary care practitioner's office.⁴ For patients diagnosed with gout, pharmacists can play the role of counselor, providing important information about the efficacy and safety of gout medications, monitoring drug interactions, and informing patients about comorbid conditions associated with gout. By educating patients about lifestyle modifications, the importance of compliance with medication regimens, and the appropriate use of various treatment options, the pharmacist can help gout patients achieve optimal outcomes.

Understanding Gout

Pathogenesis

Uric acid, or urate, is the end product of purine degradation in humans.⁵ In other mammals, the enzyme uricase breaks down uric acid into allantoin, a more water-soluble product.⁶ But in humans and the upper primates who lack uricase, uric acid cannot be further metabolized and accumulates in the serum.⁷ Serum uric acid (SUA) is excreted through the digestive tract (approximately 33%) and the kidneys (approximately 66%).⁸ As shown in Figure 1, renal excretion of uric acid involves 4 steps: first, almost all uric acid is filtered at the glomerulus; second, 98%-100% of filtered uric acid is reabsorbed from the proximal convoluted tubule; third, uric acid is secreted into the proximal tubule; and fourth, 40%-44% of uric acid is again reabsorbed in the last segment of the proximal tubule.⁷ The net effect is elimination of 6%-10% of SUA in the urine.

Figure 1. Renal Handling of Uric Acid⁷

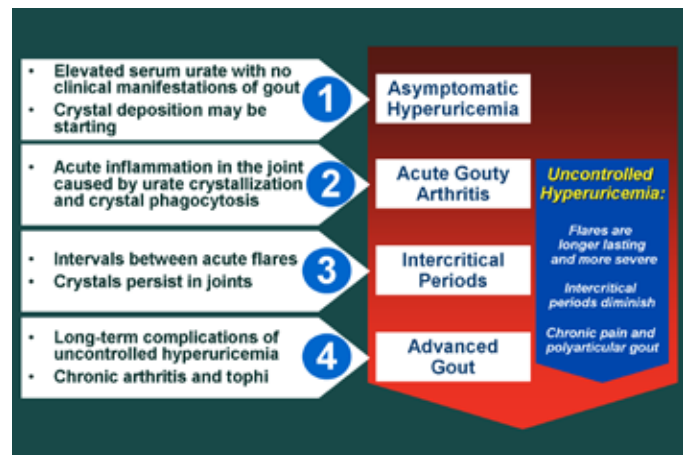


Hyperuricemia is defined as SUA at a concentration greater than 6.8 mg/dL, the saturation point at which urate crystallizes in biological fluids at normal body temperature (37°C).⁹ Hyperuricemia is believed to result from underexcretion (approximately 90% of the time) or overproduction (approximately 10% of the time) of uric acid.¹⁰ Although hyperuricemia necessarily precedes gout, some patients with hyperuricemia never experience a single attack of gouty arthritis. In general, the higher the patient's SUA level,

the greater the likelihood that the patient will develop gout.¹¹ In the Normative Aging Study, 22% of men with SUA levels ≥ 9.0 mg/dL developed gout in 5 years, compared with only 3% of men with an SUA level of 7.0-8.9 mg/dL.¹² Because it is difficult to predict which patients with asymptomatic hyperuricemia will develop articular gout, asymptomatic hyperuricemia is not treated.¹³

Gout develops when hyperuricemia leads to the deposition of monosodium urate (MSU) crystals in joints and soft tissues, as shown in Figure 2.^{11,14-16} After MSU crystals are deposited around joints, local factors such as trauma or irritation, previous disease, and lower temperatures may initiate the release of crystals into the joint space, triggering the inflammation of an acute gouty attack. While these attacks are usually self-limited (3-14 days), crystals often remain in the joint and cause low-grade inflammation between acute attacks.^{11,14}

Figure 2. The Clinical Stages of Gout



The classic presentation of gout is podagra, inflammation of the first metatarsophalangeal joint of the foot.¹⁷ This joint is eventually affected in approximately 90% of patients with gout. Joints in the lower extremities are the most common site of an initial acute gout attack, but gout may also affect bursae and tendons.¹¹ The shoulders, hips, spine, sacroiliac joints, and sternoclavicular joints are rarely affected in gout.¹⁷

Most (approximately 90%) initial gout attacks are monoarticular.¹¹ However, oligoarticular or polyarticular joint involvement has been observed in elderly patients (aged > 65 years) and organ transplantation recipients.^{11,18} Polyarticular disease has a different presentation than monoarticular disease: small joints and fingers are often affected, and tophi develop earlier in the disease process and in atypical locations.¹⁸

Figure 3. Polyarticular and Tophaceous Gout



This patient was originally treated for rheumatoid arthritis for 8 years. Image courtesy of N. Lawrence Edwards, MD.

As a result, polyarticular gout can be mistaken for rheumatoid arthritis (Figure 3) or psoriatic arthritis.¹¹ But acute gout attacks can be identified by their characteristic symptoms: warmth, swelling, redness, and severe pain in the affected joint, and often fever and a flulike malaise.^{11,14}



In the intervals between acute attacks, called intercritical periods, crystals persist in the joint fluid but do not provoke an inflammatory response.¹⁴ Some have proposed that this is due to the number of crystals present, their protein coating, or the nature of the resident synovial cells, but the mechanism is still unclear. Uric acid deposits continue during this time and low-grade inflammation may persist, although patients may not experience symptoms of gouty arthritis.^{11,14}

In advanced gout, aggregates of MSU crystals, called tophi, are deposited throughout the body, as shown in Figure 4.¹⁷ Tophi typically form at sites of trauma or friction, most commonly in the fingers, toes, and elbow.^{11,14,19} In advanced gout, tophi deposition and chronic MSU-induced inflammation can result in synovitis, cartilage loss, and bone erosion.⁸

Figure 4. Tophus on First Interphalangeal Joint



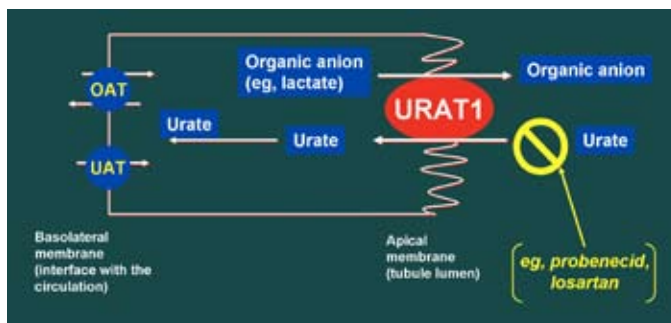
Factors Affecting SUA Levels

Preventing the inflammation and tophi deposition of advanced gout requires reduction of SUA levels. Pharmacists should be aware of the numerous factors and medications that affect SUA levels in

order to identify and dispense the most appropriate treatments to gout patients.

Uric acid is produced when purines are metabolized by xanthine oxidase.²⁰ Because uric acid is excreted primarily by the kidneys, the renal urate transporters, in particular urate transporter 1 (URAT1), are the most important regulators of SUA levels. URAT1 exchanges urate in the tubular lumen with organic anions including lactate in the proximal tubular epithelial cells, as shown in Figure 5.^{13,21} Many medications exert their effects on SUA levels by influencing URAT1 (Table 1).⁸

Figure 5. Urate Reabsorption in the Proximal Tubule^{13,21}



OAT: Organic anion transporter;
UAT: Voltage-sensitive urate transporter

Table 1. Agents Affecting SUA Levels⁸

Agent	Mechanism of Action
Urate-Increasing Agents	
Diuretics	Increase renal tubular reabsorption associated with volume depletion; may consequently stimulate URAT1
Cyclosporine	Increase renal tubular reabsorption
Pyrazinamide, nicotinate, lactate, acetoacetate	Trans-stimulation of URAT1
Salicylate* (low dose), ethambutol	Decrease renal urate excretion
Tacrolimus	Similar to cyclosporine
β-blockers	Unknown
Urate-Decreasing Agents	
Probenecid, losartan, salicylate (high dose)	Inhibit URAT1
Fenofibrate	May inhibit URAT1
Amlodipine	Increase renal urate excretion
Allopurinol, febuxostat	Inhibit xanthine oxidase

Adapted from Choi HK, et al. *Ann Intern Med.* 2005;143:499-516.

Genetic Influences

In 40% of patients with primary gout, hyperuricemia is due to a genetic cause.²² In familial juvenile hyperuricemic nephropathy, the underlying defect is an autosomal dominant mutation in chromosome 16 causing renal urate hypoexcretion.²³ Hypoxanthine-guanine phosphoribosyl transferase deficiency and phosphoribosylpyrophosphate synthetase overactivity, the principal causes of gout in younger patients, are X-linked disorders that cause overproduction of uric acid.^{7,24} For most cases of gout, however, the exact genetic abnormality remains unclear.

Risk Factors for the Development of Gout

A number of risk factors contribute to the increased prevalence of gout. Men are 6 times more likely to have SUA ≥ 6.8 mg/dL than premenopausal women, but the prevalence of gout is equal in older men and women.^{10,25} Consumption of red meat, seafood, beer, liquor, and high-fructose corn syrup have also been shown to increase the risk of developing gout.²⁶ Longevity, which has increased as a result of improved survival from coronary artery disease and congestive heart failure, is also a risk factor for gout.¹³

Comorbidities Associated With Gout and Hyperuricemia

Pharmacists should be aware that hyperuricemia is associated with various comorbidities. Hypertension, cardiovascular disease, renal disease, and tumor lysis syndrome have all been associated with gout and/or hyperuricemia.²⁰ It is unclear, however, whether uric acid contributes to the development and progression of these diseases or is merely a marker of coexisting disease.⁷

Cardiovascular Disease in Patients With Hyperuricemia and Gout

Patients with gout are estimated to have a 30% elevated risk of cardiovascular disease.^{27,28} The Multiple Risk Factor Intervention Trial (MRFIT), which followed 12,866 men for an average of 6 years, demonstrated that hyperuricemia (SUA ≥ 7 mg/dL) is an independent risk factor for acute myocardial infarction.²⁹ In the Health Professionals Follow-up study (HPFS), gout was linked to an



increase in cardiovascular mortality in patients at high cardiovascular risk.³⁰ However, in patients at a relatively low risk for developing cardiovascular disease, SUA was a weak predictor of cardiovascular morbidity and mortality.

Hypertension and Hyperuricemia

Several studies have demonstrated that hyperuricemia is independently associated with an increased risk for developing hypertension within 5 years.³¹ The decrease in renal blood flow characteristic of the early stages of hypertension seems to raise SUA, although the exact mechanism remains unclear.²⁰ In MRFIT, which evaluated men without metabolic syndrome, hyperuricemia increased the risk of developing hypertension by approximately 80%, independent of blood pressure, body mass index, renal function, serum lipid levels, alcohol use, age, and proteinuria.³² In a study of 125 adolescents aged 6-18 years, elevated SUA (> 5.5 mg/dL) was observed in 56 (89%) of the 63 children with primary hypertension but only 12 (30%) of the 40 children with secondary hypertension.³³

This evidence of a link between hyperuricemia and hypertension causes some to speculate whether the onset of hypertension can be prevented or postponed by reducing SUA levels. Based on the currently available evidence, however, treatment of asymptomatic hyperuricemia is not recommended to prevent the development of hypertension.¹¹

Hyperuricemia and Renal Manifestations

End-stage renal disease (ESRD) is another important risk factor for hyperuricemia and gout.¹³ In a large study of Japanese men, those with SUA > 8.5 mg/dL had 8 times the risk for renal failure than those with SUA levels of 5.0-6.4 mg/dL.³⁴ In a similar study of male and female Japanese adults, the incidence of ESRD per 1000 patients was 1.22 for men with SUA < 7.0 mg/dL compared to 4.64 for those with SUA ≥ 7.0 mg/dL, and 0.87 for women with SUA < 6.0 mg/dL compared to 9.03 for those with SUA ≥ 6.0 mg/dL.³⁵ These results demonstrate that hyperuricemia is associated with a greater risk for developing ESRD.

ESRD frequently results in renal transplantation, which is also associated with hyperuricemia and gout.¹³ As many as 70%-80% of organ transplantation recipients treated with cyclosporine have hyperuricemia, with the SUA level in these patients reported to be as high as 12 mg/dL. The immunosuppressive agents cyclosporine and, to a lesser degree, tacrolimus, increase renal tubular reabsorption associated with decreased glomerular filtration, hypertension, and interstitial nephropathy.⁸

Case Study: Kevin



Kevin, a 66-year-old Caucasian male, comes in to refill his diuretic prescription. You notice that he is limping. He tells you that he is experiencing severe pain in his right big toe and asks if you can suggest an over-the-counter pain medication. He states that the pain started a few days ago, and his toe is red and so swollen that he has problems putting on his shoes. He

states that he has never experienced these symptoms before.

How would you counsel Kevin?

Diagnosing Gout

Before making a presumptive diagnosis of gout, pharmacists should be aware that the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) have established evidence-based guidelines for diagnosing gout (Tables 2 and 3).³⁶⁻³⁸ Identifying MSU crystals in synovial fluid is and remains the gold standard for diagnosing gout. But these guidelines can be helpful when making a preliminary diagnosis of gout without crystal confirmation.

Table 2. Preliminary ACR Criteria for Gout Diagnosis³⁶

1	More than 1 attack of acute arthritis
2	Maximum inflammation develops within 1 day
3	Monoarthritis attack
4	Redness observed over joints
5	First metatarsophalangeal joint painful or swollen
6	Unilateral first metatarsophalangeal joint attack
7	Unilateral tarsal joint attack
8	Tophus (proven or suspected)
9	Hyperuricemia
10	Joint fluid culture negative for organisms during attack
11	Asymmetric swelling within a joint on x-ray
12	Subcortical cysts without erosions on x-ray

Table 3. EULAR Recommendations for Gout Diagnosis^{37,38}

1	In acute attacks, rapid development of severe pain, swelling, and tenderness, reaching peak at within 6-12 hours is highly suggestive of crystal inflammation, though not specific for gout
2	For typical gout presentations (eg, recurrent podagra), a clinical diagnosis of gout is reasonably accurate but not definitive unless crystal confirmed
3	Demonstration of MSU crystals in synovial fluid or tophus aspirates permits a definitive gout diagnosis
4	A routine search for MSU crystals is recommended in all synovial fluid aspirates from inflamed joints
5	Identification of MSU crystals from asymptomatic joints may allow gout diagnosis between attacks
6	Gout and sepsis may coexist; if sepsis is suspected, Gram stain and culture of synovial fluid should be carried out even if MSU crystals are identified
7	Although the most important risk factor for gout, serum urate levels do not confirm or exclude gout
8	Hyperuricemia as a marker in acute gout; renal uric acid excretion should be determined in selected gout patients, especially those with a family history of young onset gout, onset of gout under age 25, or with renal calculi
9	Radiographs may be useful for differential diagnosis and may show typical features in chronic gout; they are not useful in confirming a diagnosis of early or acute gout
10	Risk factors for gout and associated comorbidity should be assessed, including features of metabolic syndrome

Gout can be diagnosed if MSU crystals are found or if 6 of the 12 criteria are met.

Making a Presumptive Diagnosis and Communicating With a Gout Patient

Because a pharmacist may be the initial health care provider a gout patient encounters, as in the case study of Kevin, pharmacists play an important role in the care of gout patients. They can counsel patients and encourage them to seek treatment with their physician. They can also make a presumptive diagnosis of gout based on the patient's symptoms and complaints. By effectively listening to the patient, eliciting the appropriate information, and providing clear explanations, the pharmacist can help the patient



make informed decisions and seek appropriate treatment with his/her physician.³⁹

Questions the pharmacist can ask the patient to aid in forming a presumptive diagnosis include:

- When did the symptoms start? How rapidly did they progress?
- Is this the first time you experienced pain/swelling at this joint? If not, how often has this occurred?
- Have you experienced pain/swelling in other joints?
- Do you have a fever?
- Have any of your relatives had similar complaints?
- Are you taking any medications? If so, which ones?
- Describe your diet. Do you consume red meat, shellfish, or beer?

If the pharmacist suspects that the patient has gout, he/she should advise the patient to confirm the diagnosis with a physician. The pharmacist can counsel the patient that the physician will likely aspirate the joint and measure his/her SUA level.

Joint aspiration is important because it can differentiate gout from other conditions with similar symptoms and definitively diagnose gout.⁴⁰ Aspirating a joint involves removing a small amount (as little as 1-2 mL) of synovial fluid from the joint space.⁴¹ When this synovial fluid is examined under compensated polarized light, MSU crystals show strong, negative birefringence and are usually needle shaped.⁴⁰ Identifying MSU crystals in synovial fluid is the gold standard for diagnosing gout.

Pseudogout, which involves the deposition of calcium polyphosphate dehydrate (CPPD) crystals in joints, is often mistaken for gout.⁴⁰ But under compensated polarized light, the CPPD crystals characteristic of pseudogout show weak, positive birefringence and appear as a rhomboid, rods, or squares.^{40,42} Synovial fluid analysis from patients with septic arthritis, which can also be mistaken for gout, often reveals > 90% polymorphonuclear neutrophilic leukocytes (in most patients with septic arthritis, the white blood cell count is also elevated, > 2000 per mm³).⁴² Because gout and joint sepsis can occur concomitantly, synovial fluid from a patient with suspected gout should be analyzed for infection with Gram stain and culture.^{37,38,41}

Measuring SUA levels in patients with suspected gout is useful but not definitive, because during an acute attack, SUA levels may be normal.⁴³ In addition, many clinical laboratories use a "normal" range for SUA that includes levels clinicians consider hyperuricemic.¹¹ For example, at some laboratories, the "normal" range for SUA is 3.0 mg/dL to 8.0 mg/dL. Patients whose SUA falls between 6.8 mg/dL and 8.0 mg/dL would be classified by this laboratory as "normal", although they are actually hyperuricemic.

Managing Gout

The main objectives for gout therapy are to treat the acute attack, provide prophylaxis to prevent flares, and reduce uric acid levels to prevent tissue deposition of MSU crystals.¹⁹ The EULAR gout task force released 12 recommendations for the management of gout in 2006 (Table 4).^{37,44} These recommendations, which are based on the best available evidence and expert opinion, offer guidance on nonpharmacologic and pharmacologic treatments for acute gout, prophylaxis against acute attacks, and urate-lowering therapy. Pharmacists should keep these recommendations in mind when counseling patients, monitoring patient outcomes, and dispensing treatment.

Table 4. EULAR Recommendations for Gout Management^{37,44}

1	Optimal treatment of gout requires nonpharmacological and pharmacological modalities and should be tailored to specific risk factors (levels of serum urate, previous attacks, radiographic signs), clinical phase (acute/recurrent gout, interval gout, chronic tophaceous gout), general risk factors (age, obesity, alcohol consumption, urate-raising drugs, drug interaction, comorbidities)
2	Patient education and appropriate lifestyle advice regarding weight loss (if obese), diet, and reduced alcohol (especially beer) are core aspects of management
3	Associated comorbidity and risk factors such as hyperlipidemia, hypertension, hyperglycemia, and smoking should be addressed as an important part of the management of gout
4	Oral colchicine or nonsteroidal anti-inflammatory drugs (NSAIDs) are the first-line agents for systemic treatment of acute attacks; unless contraindicated, an NSAID is a convenient and well accepted option
5	High doses of colchicine lead to side effects, and low doses (for example 0.6 mg 3 times daily) may be sufficient for some patients with acute gout
6	Intra-articular aspiration and injection of a long-acting steroid is an effective and safe treatment for an acute attack
7	Urate-lowering therapy is indicated in patients with recurrent acute attacks, arthropathy, tophi, and radiographic changes of gout
8	The therapeutic goal of urate-lowering therapy is to promote crystal dissolution and prevent crystal formation; this is achieved by maintaining serum urate levels below the saturation point (~ 6.8 mg/dL) for monosodium urate; in practice, a serum urate level < 6.0 mg/dL should be sought
9	Allopurinol is an appropriate long-term urate-lowering drug; it should be started at a low dose (for example, 100 mg daily) and increased by 100 mg every 2-4 weeks as required to achieve a goal serum urate level; dose must be adjusted downward in patients with renal impairment; if allopurinol toxicity occurs, options include other xanthine oxidase inhibitors, a uricosuric agent, or allopurinol desensitization (the latter only in cases with mild rash)
10	Uricosuric agents such as probenecid (or sulfapyrazone – no longer available in the United States) can be used as an alternative to allopurinol in patients with normal renal function but are contraindicated in patients with urolithiasis; benzbromarone (not available in the United States) can be used in mild-to-moderate renal insufficiency but carries a risk of hepatotoxicity
11	Prophylaxis against acute attacks during the first months of urate-lowering therapy can be achieved by colchicine (0.6-1.2 mg daily) or an NSAID (with gastroprotection, if indicated)
12	When gout is associated with diuretic therapy, consider stopping the diuretic, if possible and as long as an effective antihypertensive regimen is available and affordable; for hypertension and hyperlipidemia, consider use of losartan and fenofibrate, respectively (both have modest uricosuric effects)

Nonpharmacologic Approaches: Changing the Gout Patient's Diet

Gout management should begin with patient education and lifestyle changes. Pharmacists should counsel patients to control their weight with daily exercise and dietary modification.^{26,45} In addition, as previously mentioned, patients should limit their consumption of red meat, including organ meats and wild game, and consider consuming plant-derived omega-3 fatty acids or supplements instead of fish.

Patients should also avoid consuming foods and drinks that contain fructose.^{46,47} High-fructose corn syrup, which was first introduced in 1967, now accounts for nearly half of the sweeteners consumed in the United States.⁴⁸ Consuming soft drinks, which are often sweetened with high-fructose corn syrup, has been shown to elevate the risk of developing gout in a reanalysis of data from the HPFS and Third National Health and Nutrition Examination Survey.^{46,47} Fructose may also play a role in the increased prevalence of diabetes, hypertension, and cardiovascular disease.⁴⁹

Patients should also consider increasing their intake of vitamin C. According to the HPFS, increased intake of vitamin C (1500 mg or more daily) is associated with decreased incidence of gout.⁵⁰ Other dietary recommendations for patients with gout encourage daily consumption of 1-2 servings of dairy or a calcium supplement and nuts and vegetables.^{26,45} There is also some evidence that coffee may have a beneficial effect on gout.²⁶



These dietary changes can improve the overall health of gout patients, especially those with metabolic syndrome, obesity, hypertension, or related disorders.⁴⁵ However, nonpharmacologic approaches are not sufficient as a sole treatment strategy because < 20% of patients maintain lifestyle changes.⁵¹ In addition, these dietary changes minimally reduce SUA levels.²²

Treating Acute Attacks

Pharmacists will likely dispense nonsteroidal anti-inflammatory drugs (NSAIDs) or colchicine to treat acute attacks.¹⁶ Corticosteroids are also an effective option.

NSAIDs

NSAIDs are a first-line, low-cost treatment option for acute gout that yield significant symptomatic relief.⁵² Anti-inflammatory doses of NSAIDs should be given immediately after the onset of symptoms, continued for 24 hours after the acute attack resolves, then tapered quickly over 2-3 days.¹⁹ All NSAIDs are effective, but they should be used with caution in older patients and in patients with heart failure, peptic ulcer disease, renal insufficiency, or liver disease.¹⁶ NSAIDs should be avoided by patients on anticoagulation therapy because they have been reported to interact with warfarin.⁵³

Colchicine

Oral colchicine is particularly effective if used within the first 12 to 36 hours of an acute attack.^{16,19} However, colchicine is associated with gastrointestinal adverse events, such as diarrhea, that can limit the standard dosing approach.^{16,19,54} EULAR recommends using colchicine at a dosage of 0.6 mg/day TID for acute attacks,³⁷ but there is currently no consensus on the most appropriate dosing regimen.⁵² A multicenter, randomized, double-blind, placebo-controlled trial compared the efficacy and safety of a high-dose colchicine regimen (1.2-mg loading dose followed by 0.6 mg/hour for 6 hours for a total of 4.8 mg) to a low-dose colchicine regimen (1.2-mg loading dose followed by 0.6 mg/hour for 1 hour for a total of 1.8 mg followed by 5 placebo doses hourly) in 184 patients.⁵⁵ Low-dose colchicine was shown to be as effective as high-dose colchicine, but was associated with a lower incidence of gastrointestinal adverse events.

Colchicine should not be taken by patients with renal or hepatic impairment, and it carries a risk for bone marrow suppression and hepatic toxicity.^{16,52,54} Pharmacists should also keep in mind that colchicine interacts with cyclosporine, macrolides, and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors.^{53,56}

Corticosteroids

Corticosteroids are also used to treat acute attacks and can be administered orally or via intra-articular or intramuscular injection.¹⁹ They are a useful alternative when patients have renal and/or gastrointestinal contraindications to other treatments,¹⁹ but should be avoided in patients with joint sepsis and used with caution in diabetic patients.^{16,52} Oral corticosteroids should of course be tapered gradually.¹⁶

Anti-inflammatory Prophylaxis

Most patients (62%) will experience a second flare within 1 year of their first acute gout attack.⁵⁷ Because MSU crystals persist during intercritical periods and are often associated with low-grade inflammation, gout patients are at risk for additional flares and disease progression.^{8,53} Prophylaxis against acute attacks should be initiated prior to urate-lowering therapy and continue for 6-12 months.^{19,53}

Pharmacists can dispense either NSAIDs or colchicine as prophylaxis against flares.^{19,53,58} When used for gout prophylaxis, colchicine is usually given at doses lower than for acute attacks, with dosage graded according to creatinine clearance.¹⁶

Urate-lowering Therapy

Pharmacists will ultimately need to dispense urate-lowering therapy to patients with continued flares or tophi formation. The pharmacist should counsel patients that treatment may be associated with a higher incidence of flares initially, but will lower flare incidence by 1 year.⁵⁹ Patients should also be reassured that although urate-lowering therapy will be lifelong,⁸ it can reduce tophi and decrease the risk for acute attacks.¹⁹ Urate-lowering therapy is not started during an acute attack because lowering SUA rapidly can increase the risk for additional gout attacks.^{19,52} If an attack does occur after urate-lowering therapy has been initiated, treatment should not be discontinued because discontinuation may cause further fluctuations in urate levels.

Uricosuric Agents

Uricosuric agents correct renal urate underexcretion by inhibiting postsecretory SUA reabsorption.⁵² Probenecid, the only uricosuric available in the United States, has been shown to be effective at reducing SUA levels in patients without renal impairment.^{44,60} Probenecid is rapidly metabolized to its major metabolite, acylmonoglucuronide, and renally excreted.¹⁹ Therefore, it should only be taken by patients with normal renal function without urolithiasis or uric acid overexcretion. Patients taking probenecid should be counseled to increase fluid consumption and comply with therapy to alkalinize urine.⁶¹ Because probenecid has a short half-life (6-12 hours), multiple medication doses are required, which may impact patient compliance.¹⁹

Other agents with uricosuric properties include atorvastatin, amlodipine, and vitamin C (500 to \geq 1500 mg/day).^{8,50,62} Losartan and fenofibrate are mild uricosurics, so they can be substituted for other hypertension or lipid reduction therapies, respectively.^{63,64} The pharmacist should note, however, that the effectiveness of these uricosuric agents decreases as renal function deteriorates.²⁴

Xanthine Oxidase Inhibitors: Allopurinol

In contrast to uricosurics, xanthine oxidase inhibitors are effective in patients who overproduce or underexcrete uric acid.⁵ The xanthine oxidase inhibitor allopurinol has been the mainstay of urate-lowering therapy for more than 40 years. Allopurinol is a structural analogue of hypoxanthine that competitively inhibits the conversion of hypoxanthine to xanthine and the conversion of xanthine to uric acid. It therefore decreases uric acid levels in the serum and urine and increases serum and urinary hypoxanthine and xanthine levels.^{19,65} The half-life of allopurinol is approximately 40 minutes, and its major metabolite oxipurinol, which



has a significantly longer half-life, is excreted by the kidneys. It maximally lowers SUA within 14 days of initiating treatment.

In a prospective trial evaluating allopurinol, 53% of 49 male patients taking 300 mg of allopurinol daily achieved an SUA level of < 6.0 mg/dL.⁶⁶ Those who did not achieve the target SUA level at the 300-mg dose were titrated up to a dose of 450-600 mg daily. Although the maximum dose of allopurinol is 800 mg/day,⁵ most patients do not receive doses higher than 300 mg/day.⁶⁷ In an observational study of a managed care organization, 97% of gout patients on allopurinol received ≤ 300 mg/day. Of these, less than 25% achieved the target SUA level of < 6.0 mg/dL. Those who did not achieve the target level were 59% more likely to have an acute gout flare than those who did. Despite the less-than-optimal dosing of allopurinol in this study, allopurinol did significantly reduce median SUA levels from 8.7 mg/dL to 7.1 mg/dL ($P < 0.001$).

Data from the United Kingdom General Practice research database demonstrated a variety of dosing errors with allopurinol: allopurinol was prescribed at a dose greater than 300 mg daily to 48 (25.9%) of 185 patients with significant renal impairment; allopurinol dosage was not adjusted down in patients concomitantly taking azathioprine or 6-mercaptopurine in 13 (25%) of 52 patients; and urate-lowering therapy was begun in 267 (56.7%) of 471 patients with asymptomatic hyperuricemia.⁶⁸ These prescribing errors occurred more commonly in older patients, male patients, and those on several medications. Errors in prescribing allopurinol and low rates of achieving target SUA levels were also observed in a cohort of veterans diagnosed with gout: of 643 patients initiating allopurinol, 297 (46%) were given a long-term prescription; only 66 (10%) received colchicine or an NSAID as prophylaxis against acute attacks; and only 126 (20%) achieved a target SUA level of ≤ 6 mg/dL.⁶⁹

A number of medications may interact with allopurinol (Table 5).⁷⁰

Table 5. Potential Drug Interactions With Allopurinol⁷⁰

Interacting Drug	Potential Effect
Azathioprine/ 6-mercaptopurine	Increased 6-mercaptopurine serum concentration with increased risk of bone marrow suppression; reduce azathioprine dose to one-quarter
Warfarin	Anecdotal reports of increased potential for bleeding
Angiotensin-converting enzyme inhibitors	Increased risk of allopurinol hypersensitivity
Cyclophosphamide	Increased risk of bone marrow suppression
Ampicillin/amoxicillin	Increased risk of rash
Antacids/aluminum salts	Decreased absorption of allopurinol
Chlorpropamide	Increased hypoglycemic effect
Cyclosporine	Increased cyclosporine concentrations with potential for toxicity
Probenecid	Increased renal elimination of oxypurinol; inhibition of probenecid metabolism
Phenytoin	Inhibited metabolism of phenytoin resulting in increased serum concentrations
Theophylline	Increase in theophylline area under the curve, $t_{1/2}$, and reduction in clearance

For optimal outcomes with allopurinol, dosage should be adjusted based on creatinine clearance or glomerular filtration rate, which are often not measured.^{71,72} In patients with chronic kidney disease (CKD), allopurinol dosage should be carefully titrated to attain an SUA level of ≤ 6 mg/dL. It is widely recommended that allopurinol doses be gradually increased to prevent gout flares, although there are little evidence-based data to support this practice.⁷³ Pharmacists should inform patients about the importance

of cautiously increasing their dose of allopurinol, especially those patients with CKD.^{73,74}

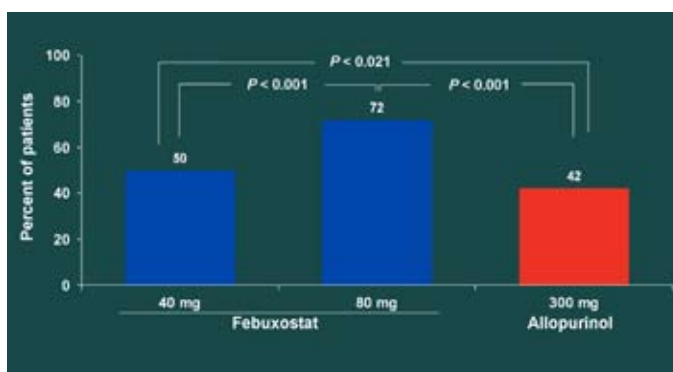
In less than 1% of patients, allopurinol treatment is associated with a hypersensitivity reaction whose mechanism remains unknown.^{74,75} This reaction usually appears within the first 5 weeks of treatment, but it has also occurred in patients on allopurinol for 2 years or more. This hypersensitivity may present as mild erythema, which can progress to Stevens-Johnson syndrome or toxic epidermal necrolysis if allopurinol therapy is continued.^{75,76} Milder reactions usually subside when allopurinol is discontinued, but severe reactions can lead to hepatomegaly, jaundice, and renal and hepatic dysfunction. Risk factors for allopurinol hypersensitivity include renal dysfunction, hepatic disease, chronic alcohol abuse, and thiazide diuretic use. Rechallenge with allopurinol should not be performed.

Xanthine Oxidase Inhibitors: Febuxostat

Febuxostat is a nonpurine, selective xanthine oxidase inhibitor recently approved by the US Food and Drug Administration for the chronic management of hyperuricemia in patients with gout.^{77,78} Because febuxostat is mostly metabolized by the liver,¹⁹ no dose adjustment is needed for patients with mild-to-moderate renal impairment.⁷⁸ Common adverse events associated with febuxostat include abdominal pain, diarrhea, and urinary frequency.

In a phase III, multicenter, double-blind 6-month randomized controlled trial of 2269 gout patients, febuxostat (40 mg or 80 mg daily) was compared to allopurinol (300 mg daily or 200 mg daily for patients with CKD) for its efficacy in reducing SUA levels to < 6.0 mg/dL.⁷⁹ Febuxostat at a dose of 40 mg had efficacy comparable to allopurinol, with significantly greater efficacy than allopurinol at a dose of 80 mg ($P < 0.001$). In patients with CKD, febuxostat at both doses demonstrated significantly greater efficacy than allopurinol 300 mg/200 mg, as shown in Figure 6. Adverse events, including cardiovascular events, were comparable across all 3 groups and when compared by renal function. Equal numbers of predefined Anti-Platelet Trialists' Collaboration (APTC) events (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) occurred among patients receiving febuxostat 80 mg and allopurinol, but no APTC events occurred in patients receiving febuxostat 40 mg.

Figure 6. Patients With CKD Achieving SUA Levels < 6 mg/dL at 6 Months⁷⁹



In a 5-year extension study of this trial, 95 (83%) of 114 patients had an SUA level < 6 mg/dL, and mean SUA levels were reduced



45% to 59% from baseline.⁸⁰ While on a maintenance dose of febuxostat, 55 (47%) of the 116 enrolled patients reported gout flares requiring treatment. By the end of the extension study, the number of patients experiencing gout flares declined to 0. Of the 26 patients with a palpable tophus at baseline, the index tophus had resolved in 18 (69%) by the end of the study. Half the patients in this study terminated prematurely, many for unspecified personal reasons, with 13 (11.2%) withdrawing due to adverse events and 8 because of gout flares.

In another randomized, double-blind, parallel-group phase III trial comparing febuxostat (80 mg or 120 mg) to allopurinol (300 mg or 100 mg for those with renal impairment), the incidence of adverse events was similar across treatment groups.⁸¹ No deaths were reported and most adverse events were mild or moderate in severity. The most commonly reported serious adverse events were cardiovascular disorders, experienced only by patients with a history of underlying cardiovascular disease and/or risk factors.

Novel and Investigational Treatments for Gout

Current treatment options for gout may not sufficiently alleviate symptoms for all gout patients. Pharmacists should be aware of novel and investigational treatments that may soon be available for patients who are not fully responsive to the previously mentioned options.

Recombinant Uricase Enzymes

Uricase, which converts uric acid to allantoin, is being investigated as a potential therapy for gout.⁸² However, native uricase is highly antigenic, and multiple administrations of uricase have been reported to cause anaphylaxis, allergic reactions, and death. A recombinant uricase has been developed, which lowers SUA levels and promotes accelerated tophus dissolution.¹³ In addition, a pegylated uricase named pegloticase, which should have reduced antigenicity than uricase and a longer half-life, is also being investigated.⁸² In early trials, pegloticase has yielded efficacy in reducing tophus burden and SUA levels.⁸³⁻⁸⁵ In a phase II randomized trial, 41 patients received pegloticase in a dosing schedule of 4 mg every 2 weeks, 8 mg every 2 weeks, 8 mg every 4 weeks, or 12 mg every 4 weeks.⁸⁶ With pegloticase, mean plasma urate levels were rapidly reduced to ≤ 6 mg/dL in all treatment groups except the group receiving 4 mg every 2 weeks. Patients receiving 8 mg pegloticase every 2 weeks were normouricemic for the highest percentage of time. Most adverse events reported were mild to moderate (93%) and judged by the investigator to be unrelated to pegloticase (60%).

The GOUT1 and GOUT2 phase III randomized, double-blind trials evaluated reduction in tophus size in treatment-failure gout (TFG) patients receiving pegloticase 8 mg every 2 or 4 weeks.⁸³ TFG was defined as ≥ 3 flares in the previous 18 months, ≥ 1 tophus, or gouty arthropathy; prior failure of or contraindication to allopurinol; and an SUA level > 8.0 mg/dL.⁸⁴ A complete response was defined as complete resolution of ≥ 1 tophus, without an increase in size in any other tophus or the appearance of new tophi.⁸³ In patients receiving pegloticase every 2 weeks, tophus burden was reduced by 40%, and within the first 13 weeks of treatment, 10 (20%) of the 49 patients achieved a complete

resolution. Of the 104 patients in GOUT1, the target SUA level of < 6 mg/dL was achieved by 47% of the patients receiving pegloticase 8 mg every 2 weeks ($P < 0.001$) and 20% of the patients receiving pegloticase 8 mg every 4 weeks ($P = 0.044$).^{83,84} Of the 108 patients in GOUT2, the target SUA level was achieved by 38% of the patients receiving pegloticase every 2 weeks ($P = 0.001$) and 49% of the patients receiving pegloticase every 4 weeks ($P = 0.001$).

The most commonly reported adverse events in the GOUT1 and GOUT2 trials were gout flares and infusion reactions.⁸⁴ Serious adverse events (undefined) were experienced by 24% of the patients receiving pegloticase every 2 weeks and 23% of those receiving pegloticase every 4 weeks, compared to 12% of the patients receiving placebo. Infusion reactions were associated with high antipegloticase titers and any level of anti-polyethylene glycol antibodies.⁸⁵

Managing Inflammatory Manifestations of Gout

Patients with contraindications to treatment options for acute gout may someday benefit from investigational treatments that inhibit interleukin-1 (anakinra, rilonacept) and TNF- α (etanercept, infliximab, adalimumab).⁷⁴ Small uncontrolled trials that evaluated these agents have reported promising results. In a trial evaluating anakinra in 10 patients for 3 days, clinical improvement was seen within 48 hours, with pain reduction ranging from 50% to 100%. TNF- α inhibition has likewise proven successful. A trial of etanercept normalized levels of inflammatory markers and reduced the number of painful joints and frequency of gout flares in a patient with polyarticular gout.

Case Summary: Kevin



You make a preliminary diagnosis of gout for Kevin and recommend that he seek a definitive diagnosis from his physician.

Kevin was diagnosed with gout by his physician and returns with a prescription for anti-inflammatory medication. You review with him the proper timing and dosing of his medication and

emphasize the importance of adhering to treatment to avoid future gouty attacks. You also advise Kevin to make dietary changes and suggest that he exercise daily, perhaps by walking or swimming. You mention to Kevin that he may be on urate-lowering therapy lifelong, which could be started as early as 2 weeks from today, with concomitant prophylactic therapy against further gouty attacks for at least 6 months.

Conclusion

Pharmacists are often the initial point of contact with the health care system for patients with gout. Pharmacists can carefully review the patient's signs and symptoms, suggest a potential diagnosis of gout, and refer the patient to his/her physician for definitive diagnosis. By applying their knowledge of the 4 stages of gout, pharmacists can counsel these patients and assist the physician in helping patients achieve the target SUA level of



< 6.0 mg/dL. Pharmacists should also encourage their patients to adopt lifestyle modifications in addition to pharmacologic treatment. When dispensing pharmacotherapy, pharmacists should emphasize the importance of correct dosing, including timing and adherence. Pharmacists can also offer advice on treatments for the acute gout attack, for long-term prophylaxis, and for urate-lowering therapy, and information about adverse events and comorbidities. Finally, pharmacists should keep in mind that new and investigational therapies currently being evaluated may provide the patient with a wider array of treatments to successfully manage gout.

Thank you for participating in this CPE activity.

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