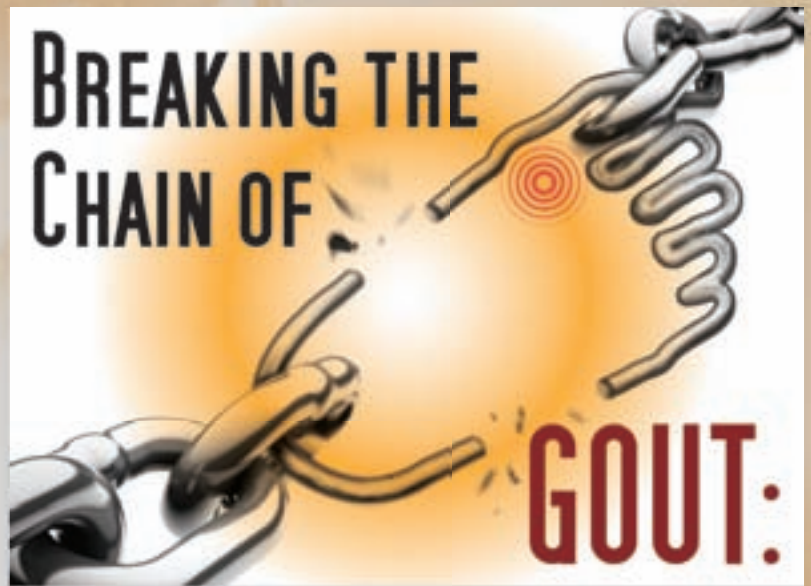


A Case-Based Monograph Focusing on Gout and Hyperuricemia for Pharmacists



**PHARMACIST STRATEGIES TO IMPROVE PATIENT
 OUTCOMES IN GOUT AND HYPERURICEMIA**

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STATEMENT OF NEED

Gout is a common rheumatic disease in humans that is characterized by elevated serum uric acid levels and deposition of monosodium urate crystals in the joints or soft tissue. The self-reported prevalence of gout in the United States has been steadily rising, where current estimates show approximately 6.1 million American adults being affected. This perceived rise is primarily associated with the increasing size of aging populations and lifestyle. Despite the increased awareness and clinical understanding of the condition, management of patients has been suboptimal. Pharmacists can play a valuable role in improving patient outcomes in gout by being able to recognize its early clinical presentation, and providing general counseling and patient education on the basic tenets for care, from lifestyle modifications to gout prevention and pharmacotherapies for treatment. Thus, it is essential that pharmacists be kept up-to-date on new insights into the pathophysiology of the gout disease states and on the safety and efficacy of appropriate or emerging therapies. A major impediment may be a lack of communication between pharmacist and patient. Therefore, to achieve successful management of gout, it is essential that pharmacists use case-specific strategies to advise patients on preventing gout – through lifestyle modifications and adherence to medication regimens.

This monograph will provide pharmacists with tools to assist them with communicating, educating, and counseling patients with both acute and chronic stages of gout and hyperuricemia in order to help improve overall 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

- Review and assess the increasing prevalence and pathophysiology of gout and its disease stages
- Apply practical communication strategies to better educate, counsel, and enhance adherence to prescribed therapies in patients being treated for chronic or recurring gout
- Identify the safety and efficacy profiles for currently available pharmacotherapies in the treatment of gout patients with acute and chronic disease stages

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Pharmacists



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Dixie-Ann Sawin, PhD, medical writer for TCL Institute, LLC, has nothing to disclose.

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INTRODUCTION

Gout is one of the oldest-recognized metabolic diseases, characterized by elevated serum uric acid (SUA) levels, inflammation, and deposition of monosodium urate (MSU) crystals in the joints or soft tissue.¹ Although knowledge about gout pathophysiology and available treatment options are increasing, management of patients with chronic gout is suboptimal and patient adherence to treatment is low. Pharmacists can help bridge this apparent gap by recognizing the early symptoms of gout, educating patients on the disease state, and stressing the importance of patient adherence to treatment regimens.

This monograph provides updated information on the pathophysiology, diagnosis, and treatment of gout and hyperuricemia. Additionally, strategies will be discussed that can help educate and improve communication with patients.

EPIDEMIOLOGY OF GOUT

Assessing the incidence and prevalence of gout is difficult because of its episodic nature. However, it is one of the most common conditions seen by primary care physicians (figure 1), and its prevalence is higher than rheumatoid arthritis (1.4% vs 0.5%-1.0%).³⁻⁶ The self-reported prevalence of gout in the United States has been steadily rising.⁷⁻⁹ The Third National Health and Nutrition Survey (NHANES III) data projected an increase in prevalence with age, reaching approximately 2 in 10 for males over 70 years of age and 1 in 100 for younger women.⁹ By recent estimates, gout affects more than 1% of adults in the United States.⁷ This increase has been attributed to increased longevity, rising use of diuretics for the treatment of hypertension, increasing numbers of associated comorbidities, and lifestyle changes.¹⁰⁻¹² Wallace and colleagues cross-sectionally examined the prevalence of gout and hyperuricemia in a US managed care population from 1990-1999; they found that people over 75 years of age showed an increased prevalence (20 per 1000) compared to younger ages.¹³ Mikuls and colleagues determined that the male to female ratio was 3.6:1 when younger women were considered, but the prevalence was similar in older men and postmenopausal women—since estrogen has a uricosuric effect and urate levels rise after menopause.^{12,14}

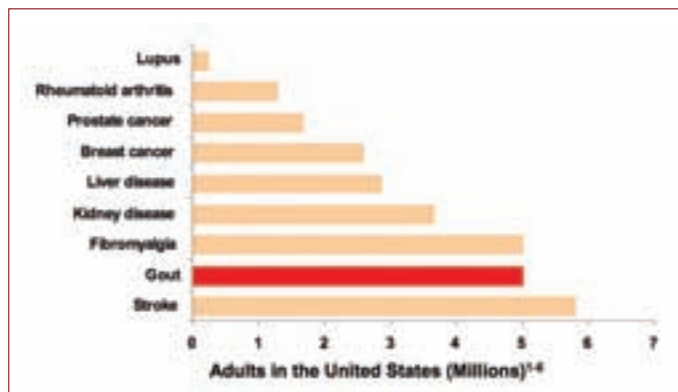


Figure 1. Annual Physician Visits in the United States by Disease Category (2/3 at the Primary Care Level), [Modified From^{5,6,9,16-19}]



Another factor that significantly contributes to increased prevalence and poor outcomes is low patient adherence with medication regimens. Riedel and colleagues examined adherence with allopurinol, the most commonly prescribed gout medication, in a US managed care population of 9482 patients.¹⁵ They found that 65.9% had filled at least 1 prescription during the 24-month follow-up period; 10.4% filled 1 prescription, then discontinued; 13.7% never achieved adherence with therapy; and 18.0% were adherent throughout the entire period.

IMPACT ON QUALITY OF LIFE

Patients with acute gout pain experience significant pain and swelling, which adversely impacts their quality of life (QOL). Long-term complications can also cause chronic, debilitating arthritis and disability. A survey of patients with gout reported that they experienced an overall decrease in QOL.²⁰

The burden of gout is also financial. The cost of treating chronic gout could represent up to 6% of yearly health care costs in elderly patients.²¹ Halpern et al. found important associations between allopurinol compliance, SUA, and gout-related costs; compliance was positively associated with favorable SUA levels.²² Furthermore, the diagnosis of gout was independently associated with higher comorbidity and health care utilization.²³ In 2003, Kim et al. showed that the annual direct health care costs for incident of acute gout among men in the United States was greater than \$27 million.²⁴ Thus, by likely being the first intervening health care provider, the pharmacist can significantly decrease patient health care costs and improve patient outcomes.

RISK FACTORS FOR GOUT DEVELOPMENT

Identifying the risk factors for gout can help pharmacists counsel patients and improve outcomes (table 1). Nonmodifiable risk factors include age, genetics, and sex. Due to their higher SUA levels (figure 2), men have a 4- to 9-fold greater risk of developing gout, compared to premenopausal women.^{11,25} In fact, gouty arthritis is the most common inflammatory joint disease in men aged > 40 years.²⁶

In 5%-25% of the human population, impaired renal excretion leads to hyperuricemia, and approximately 10% of people with hyperuricemia develop gout, suggesting a possible genetic link.²⁷

Modifiable risk factors include a body mass index (BMI) > 25 kg/m², elevated SUA levels, medication use, and consumption of high purine foods and alcohol. Additionally, data from the Health Professionals Follow-up Study showed that an increased relative risk of developing gout was associated with high-fructose corn syrup intake.²⁸ Interestingly, dairy product consumption was shown to decrease the risk of developing gout.²⁹

Hyperuricemia is the underlying metabolic risk factor for gout.^{7,10} Thus, gout development, or the influence on associated comorbidities, is dependent on the balance between the sources of purines—dietary intake, natural synthesis, and excretion (figure 3).³⁰

Male gender
Postmenopausal women
Longevity/Improved survival from comorbidities
High alcohol intake (beer > hard liquor > wine)
Red organ meats and seafood
High-fructose corn syrup
Drugs (diuretics, cyclosporine)
Major organ transplantation
Chronic kidney disease
Genetic influences

Table 1. Risk Factors for Gout Development (Adapted From^{7,30,31})

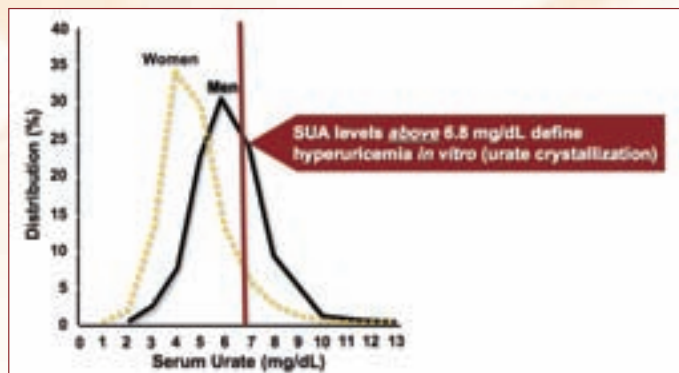


Figure 2. SUA Levels in Men and Women (Adapted From^{31,32})

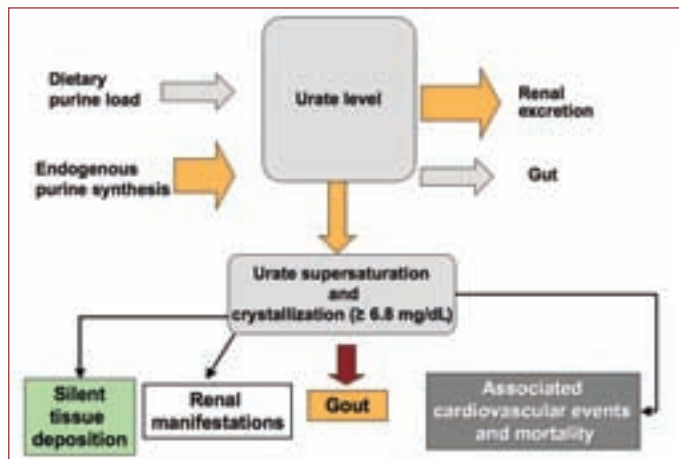


Figure 3. A Delicate Balance: the Hyperuricemia Cascade (Adapted From^{7,30,33})

COMORBIDITES ASSOCIATED WITH GOUT AND HYPERURICEMIA

Pharmacists should be aware of the potential comorbidities that are associated with gout and hyperuricemia. These include obesity, metabolic syndrome, type-2 diabetes mellitus, and renal disease.^{3,10,34-36} According to the NHANES III data, 62.8% of gout patients had metabolic syndrome, and the prevalence of metabolic syndrome by major associated complications (eg, BMI, hypertension, and diabetes) remained more significant among individuals with gout.³⁷ Whether the role of SUA is pathogenic or simply a surrogate marker for comorbid diseases is debatable and may depend on the associated disease. Clinical studies have also shown that hyperuricemia can adversely affect the kidneys and cardiovascular system.³⁸ A systematic review of evidence-based studies suggested that hyperuricemia might be causally related with cardiovascular

disease (CVD), heart failure, hypertension, and endothelial dysfunction.³⁶ In fact, almost 50% of untreated hypertensive persons have hyperuricemia, often preceding hypertension.⁷ Importantly, the Normative Aging Study found gout to be more common among hypertensive individuals on thiazide diuretics.¹⁰ A study of participants in a health screening program (n = 61,527) in Taiwan demonstrated a link between gout, not hyperuricemia, and a higher risk of mortality from all causes and cardiovascular diseases.³⁹ A positive association between hyperuricemia and CVD was found in a prospective cohort of 49,413 male Japanese railway workers.⁴⁰ SUA levels above 8.5 mg/dL were correlated with an increased risk of death, coronary heart disease, stroke, hepatic disease, and renal failure, compared to those with SUA levels between 5.0 and 6.4 mg/dL. Additionally, 2 studies maintained that hyperuricemia was an independent risk factor for cardiovascular mortality.^{41,42} Although this link may be real, Gaffo and colleagues suggest that caution be exercised, as the possibility that cardiovascular events can produce hyperuricemia is an epiphenomenon with an apparent link that still needs to be examined.³³

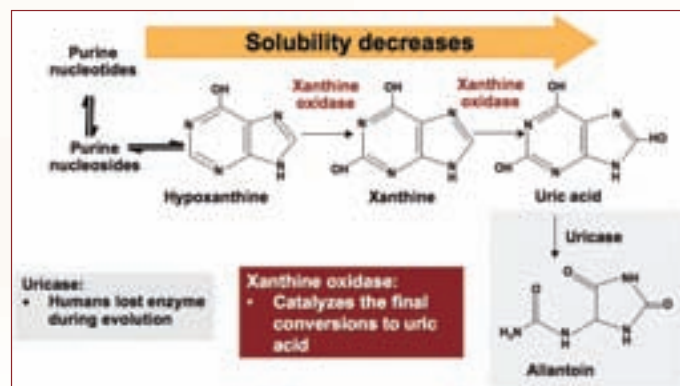


Figure 4. Uric Acid Formation (Adapted From⁴⁶)

PATHOPHYSIOLOGY

Gout is characterized by high SUA levels or hyperuricemia, usually due to overproduction (dietary or genetic causes, 10% of cases) or underexcretion (90% of cases) of uric acid.^{30,43} Uric acid is the metabolic end product of purine degradation in humans; important steps in this process include the degradation of xanthine and hypoxanthine by xanthine oxidase. In most mammals, with the exception of humans, uric acid is converted to allantoin via uricase (uric oxidase).⁴⁴ Humans have uniquely high SUA levels due to the inability to produce uricase because of 3 separate missense mutations that resulted in a nonfunctioning uricase gene (figure 4).⁴⁵

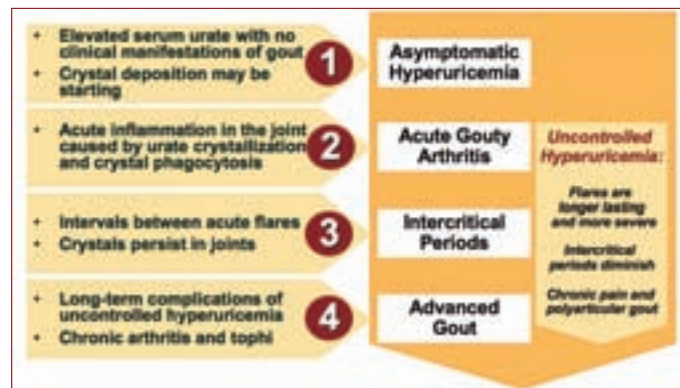


Figure 5. The Disease Stages of Gout (Adapted From^{10,43,47})

SUA levels above the concentrations at which urate precipitates out of solution (6.8 mg/dL at 37 °C, pH 7.4) determine hyperuricemia and gout.³⁰

THE 4 DISEASE STAGES OF GOUT: UNDERSTANDING THE DISEASE STATE

A necessary step toward successful management of gout as a disease is to understand its stages and symptomatology. Pharmacists should educate patients about this disease and its impact on their overall health and QOL. They should also stress that, once diagnosed with gout, patients would likely need to maintain life-long treatment that would involve lifestyle modifications and, most likely, pharmacotherapy. The following descriptions can help pharmacists understand each stage of gout, as shown in figure 5.

1. **Asymptomatic hyperuricemia:** This stage is characterized by SUA levels ≥ 6.8 mg/dL.⁴⁸ There is no diagnosis of gout associated with this finding, as the patient at this stage has no history of a gouty attack, nor physical or clinical manifestations associated with gout. This first stage does not warrant treatment. Some patients with asymptomatic hyperuricemia never experience gout attacks.^{7,10} For instance, in the Normative Aging Study (figure 6), 2046 initially healthy patients were followed for 14.9 years. Those with baseline SUA levels ≥ 9 mg/dL had a 22% annual incidence of gout, whereas those with ≤ 7 mg/dL and 7.0-8.9 mg/dL showed a 0.5% and 1% annual incidence, respectively. One very important issue for pharmacists to realize is that most clinical laboratories define hyperuricemia based on population norms around a mean level, which may be higher than biologically significant hyperuricemia (SUA serum concentration ≥ 6.8 mg/dL).
2. **Acute gouty attacks:** At high SUA levels, MSU precipitates out of the serum and is deposited as crystals in the joints or tendons, resulting in inflammation of the local area.⁴⁷ Changes to the local milieu, such as trauma (eg, in olecranon bursitis) or previous disease, could stimulate the release of crystals into the synovial fluid, leading to an acute gouty attack. Lower body temperature (eg, 35 °C), such as seen in the feet or ears (occurring commonly at night while sleeping), have also been shown to cause crystallization, even at SUA levels < 6.0 mg/dL.⁴⁹ Acute attacks usually affect the lower extremities. The first attack is usually monoarticular, but polyarticular episodes can occur with progression of disease, eg, in elderly patients.^{31,47} It typically starts with podagra, a condition that manifests as an acute onset of pain, erythema, inflammation, and swelling of the first metatarsophalangeal joint of the foot (in 90% of cases) (figure 7a), and possibly fever. These particularly painful flares are usually episodic and last 3-14 days, forcing the patient to visit a health care provider, which many times can be a pharmacist. Based on the presented descriptions, the pharmacist can recognize these signs of gout and direct the patient to appropriate over-the-counter pain medications and/or triage to the physician for further evaluation.
3. **Intercritical periods** (interval between acute attacks): During this stage, crystals may still be present at a low level in the synovial fluid, and possibly periarticular and synovial tissue, providing the nuclei for additional attacks if the condition goes untreated.^{1,31} In general, the presence of these crystals do not elicit an inflammatory response,

possibly due to the number of crystals present, their protein coating, or the nature of the synovial cell—the mechanism, however, remains unclear.³¹ In some cases, patients might manifest subjective sensations of heaviness due to mild gout neuropathy or low-grade inflammation during this stage.⁵⁰ It is important that pharmacists stress the importance of nonpharmacological measures and potential prophylactic or SUA-lowering medication during this stage in order to minimize the reoccurrence of future flares.

4. **Chronic gout:** A patient who reaches this stage of gout development has extended, persistent, uncontrolled hyperuricemia; active, untreated gout; or repeated episodes of painful acute attacks.¹ Chronic gout typically involves a polyarticular presentation (figure 7b) that differs from monoarticular disease; small joints and fingers are increasingly affected. Tissue stores of urate can persist in chronic hyperuricemia, allowing aggregates of MSU that appear as tophi (figure 7c) in atypical locations and earlier in the pathophysiology.⁵¹ Thus, there is a tendency to misdiagnose this condition as rheumatoid or psoriatic arthritis.¹ Pharmacists should be aware of this when counseling a chronic gout patient and should educate patients on the importance of diet and adhering to their treatment plan.

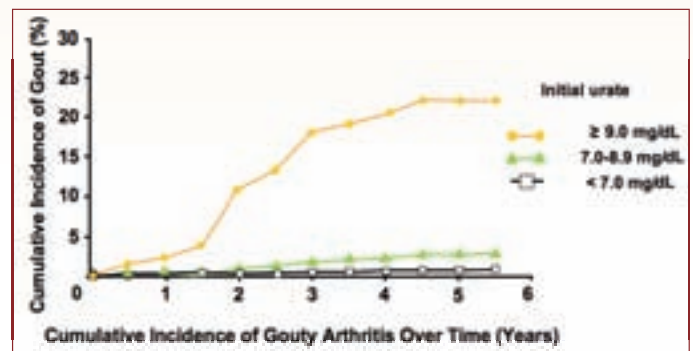


Figure 6. Cumulative Incidence of Gouty Arthritis Over Time (Adapted From¹⁰)

INFLAMMATION

MSU crystals can stimulate an inflammatory response via induction of a number of chemokines (eg, chemokine [C-X-C motif] ligand 1) and cytokines (eg, interleukin [IL]-1), occurring after phagocytosis by monocytes or macrophages to activate the NALP3 inflammasome.⁵² The identification of the NALP3 inflammasome and the pivotal role of IL-1 in gouty inflammation have given important insights into the pathophysiology of gout. This process promotes neutrophil influx into the synovial space, the primary pathological hallmark of gout. The inflammation is short-lived, due to resolution by proteolytic cleavage, cross-desensitization of chemokine receptors, and other anti-inflammatory mediators.^{30,53}

SECRETION AND REABSORPTION

It is important for pharmacists to recognize the different factors that affect SUA levels. The SUA level is dependent upon the balance between secretion and absorption.³⁰ Uric acid is typically secreted through the digestive (33%) and renal (66%) systems via 4 processes (figure 8).⁵⁴ The renal urate transporter 1 (URAT1) in the proximal tubule appears to be primarily responsible for the reabsorption of uric acid through the exchange of urate with organic anions. The pharmacologic importance of this finding is that many drugs seem to act on this transporter (table 2).



Figure 7. a. Acute Gout Attack in the First Metatarsophalangeal Joint (Podagra); b. Polyarticular Chronic Gout; c. Tophaceous

Gout Photos courtesy: a. 1972-2004 American College of Rheumatology Clinical Slide Collection. Used with permission. b. N. Lawrence Edwards, MD. c. Reproduced with permission from the Hand Center Website <http://www.handcenter.org>

Agent	Effect on SUA	Mechanism of Action
Diuretics	↑	Increase renal tubular reabsorption associated with volume depletion; might stimulate URAT1
Cyclosporine	↑	Increases renal tubular reabsorption
Pyrazinamide, nicotinate, lactate, acetosuccinate	↑	Trans-stimulation of URAT1
Salicylate (low-dose), ethambutol	↑	Decrease renal urate excretion
Tacrolimus	↑	Increases renal tubular reabsorption
β-blockers	↑	Unknown
Probenecid, losartan, salicylate	↓	Inhibit URAT1
Fenofibrate	↓	Might inhibit URAT1
Amlodipine	↓	Increases renal urate excretion
Allopurinol, febuxostat	↓	Inhibit xanthine oxidase

Table 2. Medications That Affect SUA Levels (Adapted From³⁰)

DIAGNOSIS

Patients with a suspected attack of gout should be advised to visit their physician for a definitive diagnosis. The pharmacist should educate the patient about his/her condition and the possible triggers and treatment options. The pharmacist may also inform the patient about the diagnostic process that would be based on:

- Initial presentation or recurrent attack
- Presence of risk factors
- Medical and family history
- Current medication use
- Physical examination
- SUA measurement, other diagnostic tests (eg, x-ray), and possible joint aspiration (arthrocentesis)

Patients suspected of acute gouty arthritis may be subjected to arthrocentesis and synovial fluid analysis on initial presentation. Although the gold standard for definitive diagnosis of gout is

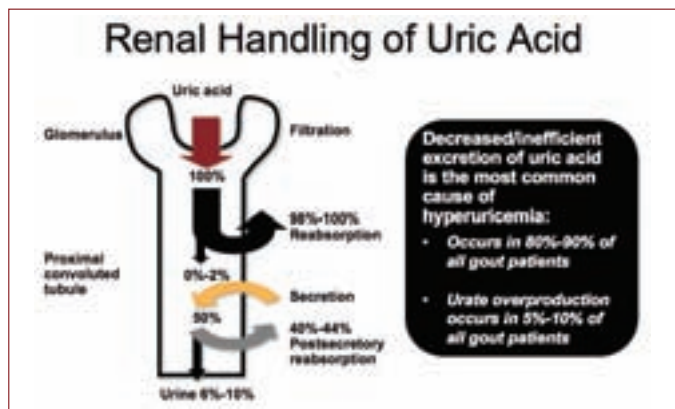


Figure 8. Renal Handling of Uric Acid (Adapted From^{46,55})

only achieved when MSU crystals are identified in the synovial fluid by joint aspiration or arthrocentesis, for practicality, physicians should be confident in their presumptive diagnoses, particularly with typical recurrence.⁴⁷ Arthrocentesis should be done if there is any question of the diagnosis or if the patient's risk factors or any clinical characteristics suggest infectious arthritis, such that occurs with septic joints, as this can represent a true medical emergency that can lead to loss of the joint if not treated immediately.

The European League Against Rheumatism (EULAR) have established guidelines for gout diagnosis (table 3).⁵⁶ There are 5 essential outcome domains for acute gout: pain, joint swelling, joint tenderness, patient global assessment, and activity limitations.⁵⁷ Using these strategies, the pharmacist can provide the initial guidance for treatment, a step that is essential and can critically impact patient outcomes.

1	In acute attacks, rapid development of severe pain, swelling, and tenderness, reaching peak 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 crystals are 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, SUA levels do not confirm or exclude gout
8	Renal uric acid excretion should be determined in selected gout patients (family history of young onset gout, onset of gout at age < 25 years, or with renal calculi); hyperuricemia is a marker in acute gout
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

Table 3. EULAR Guidelines for Diagnosis of Gout (Adapted From^{56,58})

CASE STUDY: MARY



Mary, a postmenopausal 60-year-old Caucasian woman, comes to you to refill her prescription of allopurinol for treatment of chronic, polyarticular gout in the joints of her fingers on her left hand. She complains that her recurring symptoms have been troublesome, including debilitating pain in the affected joints, swelling, and redness.

What additional questions do you have for Mary?

GOUT TREATMENT

Gout treatment goals include:

- terminating the acute attack, alleviating pain and inflammation
- preventing future attacks
- preventing the deposition of MSU crystals
- reducing SUA to target level

It is necessary that the pharmacist stress the importance of proper timing of treatment and adherence to medication regimens, as it can reduce pain and inflammation. Early initiation of anti-inflammatory medication is critical and usually results in better outcomes.⁵⁹ It has also been suggested that gout is curable if existing deposits of MSU can be successfully removed and the formation of new precipitates prevented.⁶⁰ The most common reasons for patient nonadherence are failing to fill a prescription, forgetting to take medications, lack of

understanding of how to take the drug, and the drugs are too expensive.⁶¹ Each of these behaviors requires individual consideration in order to formulate strategies to enhance patient adherence.

STRATEGIES TO INCREASE PATIENT ADHERENCE⁶²

- Review the patient’s medication history at every visit
- Use of various strategies that tailor the treatment regimen to the patient’s daily routine and lifestyle, including the use of a pill box, setting up refill reminders, and suggesting appropriate diet and exercise regimens
- Optimize support from the provider, patient satisfaction with the visit, and the support of family members in the home environment
- Ensure patient is aware of most recent SUA level and if within goal range

NONPHARMACOLOGIC APPROACHES TO TREATING GOUT: THE ROLE OF THE PHARMACIST

The most important step towards successful gout management is patient education. Pharmacists should counsel patients on weight control and dietary modifications.⁵³ In particular, patients should be encouraged to limit red meat consumption, refrain from foods or drinks containing high-fructose corn syrup, consume 1-2 servings of dairy or calcium supplements daily, supplement with vitamin C (500 mg/day), consume nuts and vegetables daily, and limit alcohol intake—especially beer.^{29,63,64} There is also some evidence to suggest that resting and raising the affected limb and topical application of ice can alleviate symptoms and improve outcomes.^{11,65} Two caveats to this approach are that few patients (< 20%) actually adhere to management strategies, and dietary changes only minimally reduce SUA levels (\approx 1.0-2.0 mg/dL).^{64,66} Thus, to overcome these impediments, concomitant pharmacotherapy may be necessary.

PHARMACOLOGICAL APPROACHES FOR ACUTE GOUT TREATMENT

ANTI-INFLAMMATORY AGENTS

Nonsteroidal anti-inflammatory drugs (NSAIDs): Early, short-term treatment with an NSAID, typically naproxen or diclofenac (each at 500 mg BID), indomethacin (50 mg TID), or ibuprofen (up to 2400 mg/day) is the treatment of choice for the first acute gouty attack.¹¹ Therefore, the use of an equivalent dose with the correct timing regimen might be more important than the choice of NSAID itself.⁵⁹ For instance, in > 90% of patients, complete resolution of the symptoms occurs within 5-8 days following initiation of therapy.⁶⁷ When treating a full-blown attack, maximum doses should be started immediately.⁶⁸ Although some decrease in pain can occur within the first 4 hours, gradual improvement occurs over 6 days.⁴⁷ It is important to taper treatment gradually (starting 24 hours after the attack), and continuing NSAID pharmacotherapy for a few days after the symptoms have completely resolved.^{47,68} The main side effects associated with NSAIDs are nausea, vomiting, dyspepsia, diarrhea, and peptic ulcer disease.⁶⁹ For patients with a history of gastrointestinal ulcers or bleeding, concomitant gastroprotection, such as with a proton pump inhibitor, should be considered.⁵⁹

Colchicine: An alternative for patients with no renal insufficiency is oral administration of colchicine.⁷⁰ It is FDA-approved for

the treatment of gout flares and gout prophylaxis. Colchicine can inhibit the NALP3 inflammasome-mediated activation of caspase 1, decreasing MSU delivery to the joint.⁷¹ Colchicine treatment has the narrowest window of any gout therapy. Colchicine treatment is usually given during the first 12-36 hours of an acute attack.^{59,70} The most recent treatment guidelines suggest that colchicine be administered at an initial dose of 1.2 mg followed by 1 additional dose of 0.6 mg in 1 hour for a total dose of 1.8 mg.⁷² Adverse events of colchicine include diarrhea (dose-related); abdominal cramps; nausea; vomiting; and, rarely, bone marrow suppression neuropathy and myopathy.⁵³ Dosing in the elderly or those with renal or hepatic impairment should be reduced.

Corticosteroids: Corticosteroids act on the cytosolic glucocorticoid receptor to alter gene expression.⁵³ In the treatment of gout, corticosteroids can be given orally, intramuscularly, intravenously, or intrarticularly if 1 or 2 joints are affected. A randomized clinical trial of prednisolone 35 mg/day or naproxen 500 mg BID for 5 days was conducted in 120 patients with confirmed gout.⁷⁴ After 90 hours, the reduction in pain score suggested equivalence of these drugs in the treatment of acute gout. In a prospective study of acute gout treatment with corticosteroids, Groff and colleagues observed symptom improvement within 12-48 hours in patients for whom NSAIDs were contraindicated.⁷⁵ The use of glucocorticosteroids is a valuable option in the elderly and in cases of intolerance to first-line NSAID options, renal or gastrointestinal impairment, limited joint involvement, or when other therapies are contraindicated.^{53,67} At this time, there is not enough evidence to support the use of glucocorticosteroids systemically or as treatment of the first acute attack of gout.⁷⁶ Pharmacists should be aware that if steroid therapy is initiated, adverse events may occur at low doses and may be dose- or duration-dependent.⁷⁷ Although useful in patients with renal and gastrointestinal impairment, corticosteroid use is contraindicated in patients with septic arthritis, and caution should be exercised when administering to patients with diabetes.^{78,79} Table 4 shows examples of doses of the above-mentioned drug classes.

Combination therapy: Separately, colchicine and NSAIDs are the most commonly prescribed monotherapies for treating acute gout (37% and 77%, respectively).⁶⁷ The use of combination anti-inflammatory therapies was shown to be common practice for gout management. In the largest survey of rheumatologists evaluating the treatment of gout in the United States, most rheumatologists (64%) were found to use combination therapies of NSAIDs and corticosteroids or colchicine.⁸⁰ Importantly, the pharmacist can assess the patient’s situation and advise him/her accordingly.

Drug Class	Dosing Examples	Contraindications	Long-Term Complications
NSAIDs	Indomethacin 50 mg TID; Naproxen 500 mg BID	Renal insufficiency, peptic ulcer, GI- bleeding, severe heart failure	Gastrointestinal and renal side effects
Colchicine	Initial dose of 1.2 mg followed by 1 more dose of 0.6 mg in 1 hr	Dialysis, renal insufficiency, ongoing diarrhea	Potential for serious side effects
Corticosteroids	Prednisone 20-60 mg/day	Diabetes, active infection	High blood pressure, raises blood sugar, osteoporosis, gastrointestinal side effects

Table 4. Drugs for the Treatment of Acute Gout (Modified From^{11,81})

PROPHYLAXIS TREATMENT

Prophylaxis in gout management refers to the use of anti-inflammatory agents to prevent flares in patients with intercurrent or chronic gout, and should be sustained for at least 6 months (and possibly up to 12 months).⁵⁹ Prophylaxis is an important step that should be considered whenever newly initiating urate-lowering therapy (ULT), as this period is frequently associated with an increased number of flares due to mobilization of uric acid. Trials with febuxostat showed that 43%-53% of patients required additional treatment of a gouty flare 8-16 weeks after the attack when prophylaxis with NSAID or colchicine was withdrawn early.^{59,82} Due to the persistence of MSU crystals during the intercritical period, a significant proportion of patients (90%) will experience repeated flares or disease progression within the following 5 years.¹¹ In these cases, the pharmacist should evaluate the benefits of a patient receiving concomitant low-dose NSAIDs or colchicine in addition to SUA-lowering therapy.⁸³ Low-dose colchicine is the most frequently used prophylactic treatment for gout.⁵⁹ Results from randomized, controlled trials suggest that effective prophylaxis can be achieved with low-dose colchicine (0.6 mg/day or BID) added to pharmacotherapy with probenecid or allopurinol for at least 3 months and up to 6 months.^{84,85} Adverse events, mostly diarrhea, reported for both studies were higher in the colchicine group, limiting prophylaxis with colchicine in patients with renal dysfunction. Although it has been suggested that such treatment should begin before ULT and continue for 6 months, rapidly reducing the levels of uric acid could exacerbate the condition; thus, there is no definitive proof for this.¹¹ Other studies suggest that prophylaxis should commence with ULT to minimize flares, as repeated episodes can contribute to patient nonadherence.⁵³ The pharmacist should consult with the physician on the appropriate regimen and should also stress to the patient the importance of adhering to the prophylactic treatment, as it is necessary for successful management of the disease.

TREATMENT FOR CHRONIC GOUT

ULT: An underlying concept in gout management is that MSU crystal deposition induces acute and chronic inflammation and that dissolution of these crystals is associated with improved clinical outcomes.⁸⁷ Thus, treatment with agents that lower the SUA is recommended for patients with recurrent, polyarticular, or tophaceous gout attacks; radiographical joint damage; or severe hyperuricemia.⁵⁹ Available treatment options include uricosuric agents and xanthine oxidase inhibitors. Patients usually visit their physician after 1 or 2 attacks; therefore, pharmacists should counsel patients to receive a diagnosis earlier. This can lead to faster and better clinical outcomes. The current guidelines recommend the goal of treatment is reaching SUA levels < 6.0 mg/dL.⁸³ The pharmacist should stress that the patient will see a reduction in clinical flares over time, once the urate concentration are kept below this threshold.⁵⁹ It should also be noted that achieving this level often requires adjustments in the dose of the urate-lowering drug. Notably, acute flares can and do occur during ULT and may interfere with patient adherence.⁵³ Thus, the pharmacist should make the patient fully aware that resolution is slow and may take several years—especially in patients with tophi—even after SUA levels reach the desired level. In rare cases, tophi are complicated by infection and may require surgical treatment.

Uricosuric agents: Probenecid inhibits the URAT1 transporter, preventing reabsorption of SUA in the distal segment of the proximal tubule and correcting defective underexcretion.^{53,88} Probenecid is usually used for treatment of patients with normal renal function who are uric acid underexcretors and

likely to comply with the increased need for oral fluid intake to decrease the risk of uric acid stone formation within the kidney. It is indicated for the long-term management of hyperuricemia associated with chronic gout.

Dosing is usually 250-500 mg BID (maximum 2 g/day) and is ineffective if creatinine clearance is < 50 ml/minute.^{86,88} The use of probenecid with medications that may increase SUA, such as thiazides, is not recommended.⁸⁹ Adverse effects include kidney stones and renal dysfunction.⁶⁸

Losartan and fenofibrate also have demonstrated uricosuric effects.⁴⁷ Thus, the potential use of these therapies to treat gout in patients with indicated comorbidities is advantageous. When used with other ULTs, these agents can decrease SUA by 40%.⁵³ Several studies have also suggested that high doses of vitamin C have uricosuric effects. In 1 study, vitamin C 4.0 g/day led to a 2-fold increase in functional clearance of uric acid within 6 hours; vitamin C 8.0 g/day for 3-7 days reduced SUA up to 3.1 mg/dL.⁹² Due to its favorable safety profile and uricosuric effects, vitamin C may be useful as adjunctive therapy. The pharmacist should inform appropriate patients of this cost-effective means to assist with gout management.

Xanthine oxidase inhibitors: Xanthine oxidase catalyzes the oxidation of hypoxanthine to xanthine and xanthine to uric acid, producing reactive oxygen species as a byproduct.⁹⁴ Xanthine oxidase inhibitors can block uric acid production, causing an increase in hypoxanthine and xanthine. These products are converted to the closely related purine ribotides adenosine and guanosine monophosphate.⁹⁵ Increased levels of these ribotides cause feedback inhibition of amidophosphoribosyl transferase, the first and rate-limiting enzyme of purine biosynthesis.

Allopurinol: Allopurinol, a structural isomer of hypoxanthine, inhibits uric acid formation and purine synthesis.⁹⁶ Used for the past 50 years, it is the first-line therapy for most chronic gout patients.⁵⁹ Allopurinol does not alleviate symptoms of acute attacks, but is useful for treating chronic gout and preventing future attacks in uric acid overproducers and underexcretors. It is also commonly used as prophylaxis to prevent tumor-lysis syndrome, which can rapidly produce severe hyperuricemia. There is a significant inverse relationship between the dose of allopurinol and SUA levels.⁸³ Allopurinol dosing is usually started low (100 mg/day) and increased every 2-4 weeks to a maximum of 800 mg/day to achieve an SUA < 6.0 mg/dL. The aim is therefore to 'treat to target', not to achieve a specific allopurinol dose.⁹⁸

The average dose is 200-300 mg/day for patients with mild gout and 400-600 mg/day for those with tophaceous gout of moderate severity. It is important to note that the majority of patients are never titrated up to an appropriate and effective dose to reduce SUA below 6.0 mg/dL.

Side effects are usually limited to rash and fever.⁸¹ In some patients (0.004%), though rare, allopurinol hypersensitivity syndrome (AHS) can be life-threatening. AHS is an immune reaction that starts with a rash and a fever and can progress to kidney failure, liver failure, Steven-Johnsons type syndrome, and death.⁹⁹ Chronic kidney disease (CKD) may be a risk factor for the development of AHS.⁶⁸ Allopurinol can be used in patients with renal impairment, but is initiated at lower doses and guidelines exist for dosing in patients with renal insufficiency.¹⁰⁰ These guidelines were based on a report by Hande and colleagues who found a correlation between patients with pre-existing renal impairment on long-term use of 300 mg/day of allopurinol who showed increased steady-state levels of oxipurinol. They suggested the use of low-dose

allopurinol treatment to increase the number of patients who achieve optimal SUA levels. More recent data from 2 large, case-controlled studies challenged this still-used regimen, suggesting that there were no significant effects due to allopurinol doses between patients who had developed AHS and those who were tolerant to allopurinol.^{101,102} The optimal allopurinol starting dose should be based on the glomerular filtration rate.¹⁰³ In cases of CKD, the allopurinol dose should be carefully titrated to attain SUA levels < 6.0 mg/dL, yet adjusted initially for the patient's renal function.^{96,103}

Interacting Drug	Potential Effect
Azathioprine/ 6-mercaptopurine	Increased 6-mercaptopurine serum concentration with increased risk of bone marrow suppression; reduce azathioprine dose by 75%
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 AUC, $t_{1/2}$, and reduction in clearance

Table 5. Allopurinol Drug Interactions (Adapted From¹⁰⁵)

Theoretically, allopurinol should be effective in almost any patient with hyperuricemia if a sufficient dose is taken, but achieving target SUA levels can be difficult in patients with renal impairment or transplant recipients.⁶⁸ As a result, many patients are on suboptimal doses of allopurinol that can lead to frequent treatment failure to reach target SUA levels.¹⁰⁴ This, in addition to allopurinol intolerance, facilitated the ongoing development of alternative pharmacotherapies. Possible drug interactions with allopurinol that can impact treatment and outcomes are shown in table 5.

Febuxostat: Approval by the FDA of the nonpurine selective xanthine oxidase inhibitor, febuxostat (40-80 mg), allowed an alternative treatment of chronic gout and hyperuricemia, including those patients with mild-to-moderate renal insufficiency.^{98,106,107} In the Febuxostat versus Allopurinol Controlled Trial, treatment with 80 mg and 120 mg febuxostat was superior to allopurinol 300 mg, with respect to the number of patients that attained the target SUA level of < 6.0 mg/dL. In a randomized, double-blind, parallel-group, phase III trial, febuxostat 80 or 120 mg treatment achieved optimal SUA levels and resolved tophi with greater efficiency than treatment with a standard dose of allopurinol (300 mg). Similar rates of adverse events in patients were seen for both drugs.¹⁰⁸

In a phase III, randomized, controlled, multicenter, double-blind trial assessing the efficacy of febuxostat in patients, the effects of febuxostat 40 and 80 mg were superior to allopurinol 300 mg.¹⁰⁹ Results from the Confirmation of Febuxostat in Reducing and Maintaining Serum Urate trials showed that patient treatment with febuxostat 80 mg was superior to febuxostat 40 mg or allopurinol 300 mg (200 mg if creatinine clearance < 60 ml/min) for 6 months to 1 year in achieving the target SUA levels, after adjusting for baseline characteristics (SUA, age, gender, renal function, BMI, tobacco use, and presence of tophi) or treatment.¹¹⁰ Patients with mild-to-moderate renal impairment had a significantly higher response rate with febuxostat 40 mg than allopurinol 300 mg/day. Furthermore, no adjustment of dose should be required with mild-to-moderate renal insufficiency (creatinine clearance \geq 30 ml/minute).¹¹¹

Treatment with febuxostat could improve or maintain the estimated glomerular filtration rate in hyperuricemic gout patients, but confirmation of this requires more clinical studies.¹¹² Febuxostat was generally well-tolerated in clinical trials. The most commonly reported adverse events were mild to moderate, including abnormal liver function tests, headache, hypertension, and arthralgia.¹¹³ A numerically greater, but not significant number of adverse events were seen in patients with underlying etiologies.⁸² The significance of these findings remains unknown and a causal relationship has not been established. Febuxostat might serve as a useful adjunct, particularly in patients with both mild-to-moderate renal impairment and allopurinol intolerance.^{53,114}

MANAGEMENT OF REFRACTORY OR TREATMENT-FAILURE GOUT

Despite the availability of effective ULTs, there remains a subset of patients with gout in whom treatment has been unsuccessful or suboptimal, leading to recurrent flares, chronic arthritis, persistent tophi, and failure to reduce SUA levels below 6.0 mg/dL in some patients, commonly termed refractory gout.^{104,115} Contributing factors include delayed therapeutic intervention, inadequate dosing with ULT, failure to titrate ULT doses effectively, patient nonadherence, medication intolerance, and incomplete response in spite of appropriate therapies.¹⁰⁴ Patients with refractory gout have persistently swollen and tender joints, chronic pain, reduced functional status, and impaired QOL.¹¹⁶ Additionally, a major problem in treating refractory gout is the presence of comorbidities in these patients, especially CKD. Emerging therapies attempt to address the complicated issue of treating refractory gout.¹¹⁷ The pharmacist should, therefore, be aware of the availability, indications, and efficacies of these emerging therapies.

Recombinant enzyme technologies: Since nascent uricase is highly antigenic and can elicit severe anaphylactic reactions leading to death, the development of recombinant uricase is being considered as a potential therapy for patients with chronic gout who have not had successful management with conventional ULT due to lack of response, intolerability, or contraindications.¹¹⁸⁻¹²⁰ Pegloticase is a PEGylated form of mammalian uricase that effectively lowered SUA and reduced the frequency of gout flares when administered in doses of 4-24 mg in small phase I and II trials. In 1 study, pegloticase administration (8 mg every 2 weeks for 12-14 weeks) reduced plasma uric acid levels to \leq 6.0 mg/dL within 6 hours in 50%-80% of patients, and was maintained throughout the treatment period.¹¹⁸ Many patients (88%) had gout flares that were probably due to rapid lowering of SUA. In a pivotal, placebo-controlled, randomized, 6-month, phase III trial with open-label extension of 212 patients with severe gout, who were given prophylaxis with fexofenadine, acetaminophen, and hydrocortisone to limit infusion reactions, 40% reached optimal SUA levels at 6 months with pegloticase 8 mg every 2 weeks.¹²¹ There was also rapid debulking of the tophi at this dosage and resolution in patients after treatment.¹¹⁹ Adverse events were mild to moderate and determined to be unrelated to pegloticase treatment.¹²⁰ However, those results were contradicted by unpublished pooled data from phase II and III trials, which suggested that high titers of anti-polyethylene glycol (PEG)-uricase antibodies and any titer of antiPEG antibodies were associated with poor treatment responses to infusion reactions.¹²² Currently, it is not known whether uricase treatment causes significant subclinical oxidative stress at the tissue level beyond 6-12 month periods.^{117,123,124} FDA approval of this is pending.

Novel anti-inflammatory approaches: With the discovery of inflammasome as a major regulator of IL-1 β production from

macrophages and dendritic cells, IL-1 has recently become a new focal point for targeted gout therapies.^{125,126} A pilot, uncontrolled, open-label study of treatment with anakinra (IL-1 inhibitor) for refractory gout showed that IL-1 blockade could theoretically be an effective therapy for acute gouty arthritis.¹²⁷ In a placebo-controlled, monosequence, crossover, nonrandomized, single-blind pilot study, another IL-1 β inhibitor, rilonacept, produced at least 75% improvement in symptoms of chronic gouty arthritis in 5 of 10 patients over a 14-week period.¹²⁸ High-sensitivity C-reactive protein levels were also significantly reduced. Tumor necrosis factor- α , another inflammatory cytokine, may also be involved in gout pathogenesis, as its inhibition could potentially improve gout symptoms.^{129,130}

As a pharmacist, you can provide a point-of-service consultation. You encourage her to be re-evaluated by her physician. You stress that she should adhere to her medication plan, incorporating lifestyle changes, such as daily exercise and decreasing red meat consumption. You inform her that her dosage might have to be changed and prophylactic therapy against gouty flares added. You address that she could be on life-long ULT, but that such therapy will eventually reduce the symptoms and frequency of future attacks. You can provide her with electronic or paper reminders for prescription refills and consult with her physician on repeat prescriptions or issues that might cause concern.¹³¹⁻¹³³

CASE STUDY SUMMARY: MARY



It is important to listen effectively to Mary's symptoms and history and involve her in the decision-making process. You counsel Mary about her symptoms and complaints, asking key questions such as:

- How long have you been on your current medication?
- Have your symptoms been getting worse?
- How many gouty flares have you experienced in the past year?
- Have you had any adverse reactions with your current medications?
- Have you been taking your medication as prescribed by your physician?
- When was your last visit to your physician?
- Do you exercise?
- Can you describe your diet?
 - Do you consume large amounts of red meat, shellfish, or beer?

CONCLUSIONS

Hyperuricemia predisposes the affected individual to the development of gout and has been associated with multiple other disease states. It is important for pharmacists to understand the progression and symptoms of gout in order to effectively help patients manage their symptoms. Undertreating or inappropriate treatment of gout can have devastating effects on patients; the number and frequency of flares can significantly increase, and the overall QOL and productivity can severely decrease. The pharmacist plays a very important role in the overall success of the patient's outcomes by appropriately identifying the shortfalls in physician treatment or patient adherence. It is important that the pharmacist carefully review patient signs and symptoms individually and in relation to the 4 clinical stages of gout. When counseling the patient, the pharmacist should consider the comorbidities present and tailor the recommendations to the individual patient to improve outcomes. Finally, the pharmacist can also help the individual gout patient by providing practical patient education on the types of available pharmacotherapies, and the importance of adhering to prescribed regimens.

THANK YOU FOR PARTICIPATING IN THIS CPE ACTIVITY.

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