Upon successful completion of this activity, the pharmacist should be able to:
1. Describe the pathophysiology of gout.
2. Recognize the clinical characteristics and various manifestations of gout.
3. Explain symptom management strategies for acute gout attacks.
4. Identify patients who are candidates for prophylactic therapy and select an appropriate agent and dose based on patient and drug characteristics.
5. Establish monitoring plans for gout treatments.
6. Provide appropriate patient education on non-pharmacologic strategies for gout, pharmacologic agents for acute gout and gout prophylaxis.

Upon successful completion of this activity, the pharmacy technician should be able to:
1. Describe the pathophysiology of gout.
2. List the clinical characteristics and various manifestations of gout.
3. Recognize patients who may be experiencing an acute gout attack and recommend pharmacist intervention.
4. Explain non-pharmacologic symptom management strategies for acute gout attacks and prophylaxis.

More than six million adults in the United States suffer from gout. Gout is an inflammatory joint disease associated with abnormal uric acid metabolism. Uric acid is formed when cells in the body and dietary protein break down. Patients with gout may produce more uric acid than can be solubilized (overproduction) or they may not be able to excrete enough uric acid (underexcretion).

Gout was first characterized thousands of years ago. It was incorrectly thought to be a “disease of kings” because of its predilection towards wealthier individuals who consume food and drink in excess. Interestingly, the treatment of gout preceded the actual understanding of the pathophysiologic mechanisms. Herbal therapies such as active colchicum are still a part of therapeutic plans today. Standard treatment of gout has not changed much in the past 50 years. However, recent drug approvals offer new approaches to therapy. The purpose of this article is to highlight the pathophysiology, risk factors, non-pharmacologic, and pharmacologic treatments for gout, and to summarize the pros and cons of each treatment.

**PATHOPHYSIOLOGY**

Gout is a type of arthritis associated with a disorder of purine metabolism characterized by the deposition of monosodium urate (MSU) crystals in joints, bones, and soft tissues. These crystals result in a local immune response leading to pain, erythema, and inflammation at the affected site. Prolonged presence of crystals can cause a sustained inflammatory response, often resulting in tissue damage.

MSU crystals are derived from uric acid, a water-soluble substance which has no physiological function and is an end product of purine metabolism. Purines ingested as dietary protein, as well as purines released from the DNA of degraded cells throughout the human body, are metabolized in a stepwise process. The final steps in the metabolic pathway involve the conversion of purine nucleotides to hypoxanthine, which is then converted...
to xanthine via the enzyme xanthine oxidase. Xanthine oxidase is also responsible for the conversion of xanthine to the uric acid end product. The majority of uric acid excretion occurs renally and a small amount of uric acid is broken down by bacteria in the colon and excreted via the gastrointestinal tract.

Elevated serum concentration of uric acid and decreased temperature of the local environment promote the precipitation of MSU crystals responsible for a gouty attack. Increased uric acid concentrations are caused by an imbalance between the metabolism and excretion of purines.

The vast majority of gout patients (85–90 percent) are underexcretors and do not eliminate uric acid efficiently. Primary causes of uric acid underexcretion include inherited disorders such as polycystic kidney disease, familial juvenile hyperuricemic nephropathy, and medullary kidney disease. Secondary causes of decreased renal excretion of uric acid include hypertension, chronic kidney disease, medications, and several metabolic disorders. The resultant buildup of uric acid leads to the precipitation of MSU crystals in tissues, consequently causing a gouty attack.

Overproducers, the minority of patients, synthesize excessive amounts of uric acid. Primary causes include inherited enzymatic defects such as glucose-6-phosphate dehydrogenase deficiency (G6PD), hypoxanthine-guanine phosphoribosyl transferase deficiency, and phosphoribosyl pyrophosphate synthetase deficiency. Secondary causes of uric acid overproduction include excessive dietary purine intake, ethanol consumption, medications (such as chemotherapy agents), and proliferative cancers. Increased uric acid production may be compensated via increased renal elimination. However, if renal elimination is not adequate to overcome overproduction, serum uric acid levels rise. As with underexcretors, hyperuricemia from overproduction results in MSU crystal precipitation and gout symptoms.

Deposition of MSU crystals results in the activation of the innate immune system. MSU crystals are believed to interact with receptors of local dendritic cells and macrophages, which activate the immune response. The resultant production of interleukin 1 (IL-1) initiates a cascade of pro-inflammatory mediators such as neutrophil chemotactic factors, tumor necrosis factor α (TNF α), interleukin 6 (IL-6), and interleukin 8 (IL-8). Inflammation follows the activation of these mediators and neutrophils invade the affected area, removing MSU crystals through the process of phagocytosis. The neutrophils are then lysed, releasing proteolytic enzymes into the joint or soft tissues that further increase inflammation and contribute to the manifestation of gout symptoms.

**Patient Case**

JG is a 45-year-old, obese, white male who comes to the pharmacy to purchase a bottle of aspirin for a swollen, painful toe. He appears to be very uncomfortable and is limping. He denies recent trauma to his foot and states he “never had pain this bad before and it’s been getting worse over the past hour.” His past medical history is significant for hypertension, which is treated with losartan 50 mg daily, and high cholesterol, which he manages with diet and over-the-counter niacin. He quit smoking a couple years ago but does drink “a couple 6-packs” on weekends.

**CLINICAL PRESENTATION OF GOUT**

The clinical presentation of gout is characterized by two clinical phases. The first phase is associated with acute intermittent arthritis attacks that resolve on their own after seven to ten days. If high uric acid levels (defined as uric acid 6.8 mg/dL or more) are allowed to persist, a second phase of chronic arthritis may occur. Tophi, or crystal deposition, may be observed at this stage. Presence of tophi is considered a pathognomonic feature of gout. Chronic tophaceous gout is seen more commonly in patients with gout for more than 20 years and is associated with multiple joint involvement and symptoms in between attacks.

An acute gout attack is rapid, painful and severely worsens within the first 24 hours. Table 1 summarizes the typical subjective and objective findings associated with an acute gout attack. The most common site is the metatarsophalangeal joint of the big toe and knee joints. Gouty joint involvement is typically monoarticular (involves a single joint). Patients
65 years and older may present atypically with an insidious onset and involvement of multiple joints and/or the hand or wrist.

RISK FACTORS
Table 2 summarizes common risk factors associated with gout. Gout is strongly associated with hyperuricemia, variably defined as serum uric acid levels greater than 6.8–7mg/dL. One study suggests levels of uric acid greater than 10 mg/dL are associated with a 30 percent risk of developing gout over a five-year span. Men are more likely to develop gout than women initially, although once women reach menopause the difference is minimal. Declining amounts of estrogen may increase uric acid secretion. There also appears to be a link between family history of gout and risk of developing symptoms.

Drug-induced gout is an important therapeutic problem for pharmacists to recognize. Thiazide diuretics and low-dose aspirin are two common medications associated with hyperuricemia. Other medications associated with hyperuricemia are listed in Table 2. The majority of medications reduce renal elimination of uric acid, with the exception of chemotherapy which is associated with increased uric acid production due to cellular death. Substitution of therapeutic alternatives for these agents, when possible, may help to diminish attacks. Most clinicians opt to continue cardioprotective doses of aspirin as the benefits outweigh the risks. Initiation of urate-lowering
therapy is also associated with triggering acute attacks, possibly from increased mobilization of urate stores out of the joints and into the bloodstream.

Patient Case Continued

JG’s presentation is indicative of a gout attack. The attack appeared to be acute in onset, associated with severe pain, and it is located in his big toe. He presents with several risk factors including: obesity, hypertension, and alcohol use. It is important to take note of the OTC vitamin product he is using for cholesterol. Niacin should be discontinued if possible because it can precipitate a gout attack. Fenofibrate is a reasonable substitute that is also associated with reduced uric acid. Small studies suggest that fenofibrate counteracts the increased urate levels seen in patients on hydrochlorothiazide. Losartan is a logical substitute for hydrochlorothiazide based on its uricosuric properties. Other angiotensin receptor blockers and angiotensin converting enzyme inhibitors such as lisinopril do not appear to possess a urate lowering effect.

The patient should be warned that aspirin could potentially worsen his pain if he is experiencing an acute gout attack. The effect of aspirin on uric acid is dose-dependent. For example, doses greater than 3 grams daily enhance the renal excretion of uric acid, while aspirin dosed between 1–2 grams daily reduce uric acid excretion. Cardioprotective aspirin doses around 75 mg daily are associated with a 15 percent reduction in uric acid elimination. Low dose aspirin for myocardial infarction and stroke prevention may be considered if cardioprotective benefit outweighs the risk of gouty attacks. It is best to refer the patient to his primary care provider and discourage the aspirin purchase at this time.

CLINICAL DIAGNOSIS

Although microscopic evaluation of MSU crystals in synovial fluid (or tophi) is the gold standard, crystal inspection is not common in routine diagnostic practice due to invasiveness. Hyperuricemia is considered a risk factor for the development of gout. However, high uric acid levels are not always present during an acute attack. Therefore, uric acid level measurement is not the most useful tool for diagnosis. Radiographic changes may be present but are not specific to gout.

Another reason why aspiration is not always needed is because the clinical presentation associated with gout is a reliable method for diagnosis. Patients presenting with joint pain, swelling, and redness that develop within 24 hours (particularly in the metatarsophalangeal joint of the great toe) are extremely likely to have gout. When accompanied by hyperuricemia, 82 percent of patients presenting with these symptoms are likely to have gout. Differential diagnoses that should be ruled out include septic arthritis, lupus, and rheumatoid arthritis.

GOALS OF THERAPY

Treatment goals for gout include pain relief; identifying and remove exacerbating factors; preventing complications; and reducing recurrence.

Non-Pharmacologic Management

Affected joints should be immobilized for several days following an acute attack to avoid mechanical stimulation and further inflammation. Immobilization may decrease the need for acute pharmacological therapy. The use of ice packs should also be encouraged, but heating pads should be avoided.

Lifestyle modifications may help reduce the number of gout attacks. Overall, lifestyle modifications have been found to decrease uric acid levels and monthly attacks by 18 percent and 67 percent respectively, after four months. The 2012 American College of Rheumatology (ACR) Gout guidelines provide guidance on diet. Quantity limits for “limit” and “encourage” dietary are consciously not defined due to lack of consistent data on serving sizes and risk/benefit for gout. A general guideline for pharmacists is to recognize that patients with gout should avoid high-purine foods such as liver, sweetbreads and kidney. Newer findings suggest a correlation between high fructose corn syrup sweetened sodas and products; the ACR recommends patients with gout avoid these beverages and foods.

Patients should maintain an overall healthy diet and exercise regimen. Smoking cessation and weight loss for obese patients should be emphasized. Complete elimination
of dietary purine is not necessary, although Atkins type diets should be discouraged. Red meats such as beef, lamb, pork and shellfish may be consumed in moderation. Strict purine restriction typically results in a maximum of 1 mg/dL reduction in uric acid levels. Adherence concerns may arise when dietary modifications are too strict and patients feel deprived. Patients may benefit from consultation with a nutritionist.

Advise patients to maintain hydration by drinking at least eight glasses of water daily to prevent dehydration and promote renal excretion of uric acid.

Alcohol use should be limited in patients suffering from gout. Short-term alcohol use can decrease uric acid excretion, while long-term use increases purine levels. Patients should not consume any alcohol during an acute gout attack. Increased intake of coffee and vitamin C may reduce attack frequency, but more data is needed to recommend this universally. Increased consumption of low fat dairy products may reduce the frequency of attacks and is recommended by the ACR. Therapeutic lifestyle changes that benefit other comorbidities linked with gout such as hypertension and dyslipidemia should be encouraged and include low salt and high fiber food plans.

Patient Case Continued
JG agrees to see his doctor but will not be seen for two more hours. He is wondering if he should purchase a heating pad for relief. The pharmacist advises JG not to purchase a heating pad, explaining that it could exacerbate his pain. The pharmacist encourages him to apply ice to the area around his painful toe and to rest the joint if possible until he is seen by his physician.

PHARMACOLOGIC MANAGEMENT OF GOUT—ACUTE ATTACK MANAGEMENT
The 2012 ACR Gout guidelines outline the following treatment principles for acute gout attacks: first, pharmacologic therapy should be started within the first 24 hours; urate lowering treatment such as allopurinol should be continued during acute gout attacks; and first line options include non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and oral colchicine.

Patient-specific characteristics such as allergies, intolerances, and hepatic or renal impairment should be used to decide which treatment option is most appropriate for each patient. Severity of pain and number of joints involved also influence selection. Corticosteroids may be administered intramuscularly or intra-articularly, which may be helpful in patients with adherence barriers or who have only one joint affected. Polyarticular gout may benefit from combination therapy.

Various head to head clinical trials do not show an advantage of colchicine over NSAIDs for efficacy. In either case, the medication should be started in the first 12–24

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<tr>
<th>Drug</th>
<th>Dose/Route/Frequency</th>
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<tr>
<td>Indomethacin</td>
<td>50 mg PO TID</td>
<td>Decrease to 50 mg BID beginning on day 4</td>
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<td>Ibuprofen</td>
<td>600–800 mg PO TID or QID</td>
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<tr>
<td>Naproxen</td>
<td>500–1,000 mg PO in divided doses</td>
<td>Decrease to 500 mg or 750 mg daily in divided doses beginning on day 4</td>
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<tr>
<td>Colchicine</td>
<td>1.2 mg PO at symptom onset then 0.6 mg 1 hour later</td>
<td>May administer 0.6 mg PO once or twice daily during prophylactic administration. Dose adjustments warranted for concomitant CYP 3A4 inhibitors, P-glycoprotein inhibitors and renal dysfunction.</td>
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<tr>
<td>Prednisone</td>
<td>0.5 mg/kg/day x 5–10 days May give triamcinolone 60 mg IM x 1 followed by oral prednisone</td>
<td>Some experts suggest tapering over 7–10 days. Methylprednisolone dose pack may be an option.</td>
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# ACR guidelines recommend full dose treatment until gout attack resolves. Dose reduction can be considered in patients with multiple comorbidities.
TID: three times a day, QID: four times a day, BID: twice a day, PO: by mouth;
hours after onset of symptoms for maximal benefits. Dosing for acute regimens is summarized in Table 3.

**NSAIDs**
NSAIDs are a logical choice for the treatment of acute gout, given the inflammatory nature of an attack. FDA-approved NSAIDs include naproxen, indomethacin, and sulindac. Other NSAIDs may be equally effective. Indomethacin is not recommended in the elderly because of increased central nervous system adverse events.

NSAIDs are usually dosed higher for the first few days, then rapidly tapered and continued for at least one to two days after the patient is symptom-free. Complete relief is usually achieved within two weeks.

NSAIDs should be avoided in patients who suffer from peptic ulcer disease, congestive heart failure, hepatic or renal impairment (creatinine clearance <50ml/min), and those patients taking anticoagulants. NSAIDs should also be avoided in patients with hypersensitivity to aspirin or NSAIDs. Potential side effects of NSAIDs include but are not limited to: nausea, vomiting, peptic ulcers, increased bleeding risk (including GI bleeds), nephrotoxicity, and increased blood pressure. The use of proton pump inhibitors in patients taking NSAIDs has been shown to decrease the risk of peptic ulcers. Suggest taking the medication with food to reduce dyspepsia. Blood pressure may be monitored and a basic metabolic chemistry should be drawn to monitor for nephrotoxicity and/or electrolyte imbalances. Patients with elevated blood pressure at baseline may benefit from intra-articular administration of corticosteroids to limit systemic exposure and prevent further increases in blood pressure.

**Colchicine**
Colchicine is a narrow therapeutic index drug used for the treatment of gout attacks for decades. Historically, colchicine has been used at high doses such as 0.6 mg orally every one to two hours until the patient obtained sufficient pain relief or experienced severe diarrhea. The maximum dose was typically 5–7 mg. In 2010, a study was published comparing high-dose and low-dose colchicine vs. placebo in the treatment of acute gout. While both dosage regimens produced similar efficacy at 24 hours, the low dose colchicine regimen (defined as 1.8mg of colchicine administered within one hour of onset of symptoms) had a lower incidence of adverse effects. Adverse effects seen in low-dose colchicine were comparable to the placebo regimen. The FDA-approved dosage regimen of colchicine for the treatment of acute gout is 1.2 mg at the time of symptom onset, followed by 0.6 mg one hour later, limiting patients to 1.8 mg in one hour. Higher doses have not been approved by the FDA.

Colchicine dose should be adjusted in the elderly, in patients with hepatic or renal disease, and in patients taking interacting medications within the last two weeks (Tables 4 and 5). Cytochrome P450 (CYP) 3A4 inhibitors and p-glycoprotein (PGP) inhibitors are associated

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with increased toxicity and should be avoided if possible. Avoid use of colchicine in patients with arrhythmias and patients on dialysis.

The most common side effects of colchicine are nausea, vomiting, and diarrhea. In the study comparing high-dose colchicine to low-dose colchicine, 80 percent of patients on the higher dosage regimen complained of GI effects. Rare but serious side effects include myopathy, bone marrow suppression, alopecia, and neuropathy. Monitoring parameters for patients on long-term treatment include a CBC, CrCl, and liver function tests (LFTs). Patients should be educated to discontinue colchicine if severe side effects occur.

Colchicine was previously available intravenously; this formulation was removed from the market over concerns of toxicity.

CORTICOSTEROIDS
Corticosteroids play an important role in the treatment of acute gout for patients who have contraindications to or are intolerant of NSAIDs or colchicine. Some clinicians consider corticosteroids first line because they are useful in patients with renal disease and are available in numerous product formulations.

Oral steroids often produce relief in five to seven days, but they can be used up to 14 days. It was previously thought that five day, short course therapy would result in rebound attacks, but recent studies did not show a difference between short and long course strategies.

Steroids can be injected into the affected joint if the patient cannot be treated with systemic medications and only suffers from gout in one joint. Intra-articular administration appears to produce similar results to oral steroid regimens and oral NSAIDs indomethacin and naproxen. There is limited outcome data available comparing intra-articular and intramuscular routes. Corticosteroids should be avoided in patients with active peptic ulcer disease.

Corticosteroid use is associated with many side effects, though gout regimens are temporary. Potential side effects associated with short-term use include fluid retention, increased blood glucose, poor wound healing, GI bleeding, increased blood pressure, insomnia and mood disturbances. Patients taking steroids for longer periods of time should be monitored for symptoms of Cushing’s syndrome, osteoporosis, glaucoma, and liver dysfunction.

Patient Case Continued
JG calls the pharmacy to thank the pharmacist for encouraging a doctor visit. He was told his uric acid level was over 10 mg/dL and, although they did not aspirate the joint, he was diagnosed presumptively with gout and prescribed prednisone. He verbalized understanding that he should not use niacin anymore. What additional advice should the pharmacist offer the patient at this time?

First, the pharmacist should encourage the patient to take prednisone with food to counteract adverse GI events. All acute oral regimens used for gout may predispose the patient to stomach upset. JG should avoid alcohol and to reduce his weight through diet and exercise. Weight loss, in addition to lowering his risk for gout, will also help his blood pressure and cholesterol. The pharmacist should emphasize that if the patient cannot avoid alcohol altogether, beer intake should be limited to no more than two alcoholic servings per day (one serving for women). Beer is more likely than other alcoholic beverages to cause symptoms of gout. Other alcoholic beverages less likely to increase uric acid should still be consumed in moderation. If JG cannot refrain from drinking alcohol, a referral to his primary care provider or Alcoholics Anonymous should be considered.

JG should inform his physician that he was previously taking niacin to account for future changes to lipid panel results and initiate an alternative treatment. The pharmacist may wish to refer to reliable health information websites to download education handouts for JG which may encourage discussion (Table 6).

PHARMACOLOGIC MANAGEMENT OF GOUT—PROPHYLACTIC TREATMENT
The focus of preventative treatment is to lower the risk of recurrence by reducing the uric acid level below 6 mg/dL. Some patients may require levels as low as 5mg/dL to reduce attacks. Most patients will require pharmacologic treatment to sufficiently reduce uric acid levels.
Because prophylaxis is usually continued indefinitely, cost-effectiveness of therapy must be considered for each patient before prophylactic treatment is initiated. Patient indicators for chronic therapy include two or more gouty attacks per year or patients with gouty complications (tophi, joint damage, kidney stones). Severity of flares and patient preference should also be considered when initiating lifelong treatment. Recurrent flares should be treated without interruption of chronic suppressive therapy.

The main classes of chronic gout therapy are the uricostatics, uricosurics, and recombinant uricase. Uricostatic agents decrease the formation of uric acid, specifically by inhibiting the enzyme xanthine oxidase. Allopurinol (Zyloprim®) and febuxostat (Uloric®) are the two xanthine oxidase inhibitors used for the chronic management of gout. Uricosuric agents, namely probenecid, decrease serum uric acid levels by increasing the renal elimination of uric acid. The PEGylated recombinant uricase enzyme, pegloticase (Krystexxa®), decreases uric acid levels by facilitating the transformation of uric acid to allantoin. Dose recommendations for prophylactic regimens are listed in Table 7.

The 2012 ACR guidelines recommend xanthine oxidase inhibitors (XOI) as first line therapy. The guidelines do not prefer allopurinol over febuxostat. Febuxostat has less long-term safety data and significantly higher cost implications. Probenecid is considered an alternative if there is a contraindication or adverse event associated with XOI therapy. It should not be used if creatinine clearance is less than 50 ml/minute. Quantified, 24-hour urine collection to differentiate between overproducers and underexcretors is used rarely and restricted for patients with urate kidney stones or early gout onset.

The use of uricosuric agents such as probenecid is limited. Uricosurics are ineffective in patients with renal impairment and should be avoided in overproducers and underexcretors is used rarely and restricted for patients with urate kidney stones or early gout onset.

The main classes of chronic gout therapy are the uricostatics, uricosurics, and recombinant uricase. Uricostatic agents decrease the formation of uric acid, specifically by inhibiting the enzyme xanthine oxidase. Allopurinol (Zyloprim®) and febuxostat (Uloric®) are the two xanthine oxidase inhibitors used for the chronic management of gout. Uricosuric agents, namely probenecid, decrease serum uric acid levels by increasing the renal elimination of uric acid. The PEGylated recombinant uricase enzyme, pegloticase (Krystexxa®), decreases uric acid levels by facilitating the transformation of uric acid to allantoin. Dose recommendations for prophylactic regimens are listed in Table 7.

The 2012 ACR guidelines recommend xanthine oxidase inhibitors (XOI) as first line therapy. The guidelines do not prefer allopurinol over febuxostat. Febuxostat has less long-term safety data and significantly higher cost implications. Probenecid is considered an alternative if there is a contraindication or adverse event associated with XOI therapy. It should not be used if creatinine clearance is less than 50 ml/minute. Quantified, 24-hour urine collection to differentiate between overproducers and underexcretors is used rarely and restricted for patients with urate kidney stones or early gout onset.

The use of uricosuric agents such as probenecid is limited. Uricosurics are ineffective in patients with renal impairment and should be avoided in overproducers and patients with a history of, or who are at risk for, nephrolithiasis. Patients should be counseled to expect a potential flare during initiation of urate-lowering treatment. They should be advised to continue the urate-lowering therapy. Patients should receive anti-inflammatory prophylaxis if it is not contraindicated. Agents such as colchicine or NSAIDs may be used concomitantly in order to reduce the risk of precipitation or exacerbation of an acute gouty attack. Concurrent colchicine or NSAID therapy should be continued until goal serum uric acid levels are achieved or up to six months. A significant change in the 2012 ACR guidelines includes the recommendation that urate-lowering therapy should be initiated during an acute attack. Previously,
urate-lowering therapy was avoided from one to four weeks after resolution of an attack. Regardless of the chronic anti-hyperuricemia therapy chosen, goal serum uric acid levels should be set at less than, or equal to 6 mg/dL (357 μmol/L). Reduction of urate levels below 6 mg/dL results in significantly fewer acute gout flares, reduction in tophi size, and fewer MSU crystals in joints. Medication regimens should be adjusted every two to five weeks to achieve goal serum urate levels. During an acute attack, urate-lowering therapy should be continued and acute treatment initiated.

Efficacy of urate-lowering therapy can be objectively monitored by evaluating serum uric acid levels at baseline and with allopurinol adjustment. Once stabilized, repeat uric acid levels should be rechecked every six to 12 months. Subjective monitoring of efficacy includes patient reported frequency of acute attacks, as well as development of tophi.

**XANTHINE OXIDASE INHIBITORS**

**Allopurinol (Zyloprim®)**

Allopurinol is first line therapy for a vast spectrum of patients, including overproducers, patients experiencing tophaceous gout, and patients with a history of nephrolithiasis or urate nephropathy. Patients with renal insufficiency require dose reductions.

Allopurinol is effective at lowering serum urate levels in both underexcretors and overproducers. Allopurinol is well-absorbed orally and has a relatively short half-life, ranging from two to three hours. Despite a short drug half-life, once-daily dosing of allopurinol is possible because the half-life of the active metabolite oxypurinol is approximately 24 hours. The elimination of oxypurinol is primarily renal excretion. Therefore, renal function has significant implications for patient-specific therapy.

Allopurinol initiation disrupts the balance between serum, tissue, and synovial fluid concentrations of uric acid. These rapid concentration changes may cause additional MSU crystals to precipitate, worsening gouty arthritic symptoms. Concurrent prophylactic colchicine or NSAID therapy during the initiation of allopurinol is beneficial.

Initiation of allopurinol at a low dose, such as 100 mg/day, followed by slow titration every two to five weeks to a dose sufficient to achieve goal serum urate levels may reduce the risk of symptom exacerbation and hypersensitivity reactions. Goal serum urate levels are achieved in 47–85 percent of patients treated at a dose of 300 mg/day. To reach therapeutic goals, the dose of allopurinol can be increased to a maximum of 800 mg/day. However, before increasing the dose, clinicians should determine patient adherence with the current dose. Pharmacists should talk to patients.

### Table 7. Prophylactic Gout Regimens

<table>
<thead>
<tr>
<th>Medication</th>
<th>Initial Dose and Titration</th>
<th>Renal Impairment Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allopurinol</td>
<td>50–100 mg/day (up to 800 mg/day with normal renal function)</td>
<td>CrCl 10–20 ml/min 200 mg/day</td>
</tr>
<tr>
<td></td>
<td>• 100 mg daily typical initial dose</td>
<td>CrCl less than 10 ml/min 100 mg/day or less</td>
</tr>
<tr>
<td></td>
<td>• 50 mg daily for CrCl &lt; 30 ml/min</td>
<td>CrCl less than 3 ml/min Increase dosage interval</td>
</tr>
<tr>
<td></td>
<td>• Titrate gradually every 2–5 weeks based on uric acid level</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Doses &gt; 300 mg daily should be divided</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Maximum dose may exceed 300 mg daily with CrCl &lt; 20 ml/min if needed. Monitor for rash. (Package insert states max dose is 200 mg daily)</td>
<td></td>
</tr>
<tr>
<td>Probenecid</td>
<td>250 mg twice daily (up to 500–2,000 mg/day in divided doses)</td>
<td>CrCl less than 50 ml/min Avoid Use</td>
</tr>
<tr>
<td>Febuxostat</td>
<td>Start with 40 mg po once a day; increase to 80 mg once a day if uric acid is greater than 6 mg/dL after 2 weeks</td>
<td>Minimal data available if CrCl is less than 30 ml/min</td>
</tr>
<tr>
<td>Pegloticase</td>
<td>8 mg intravenous infusion (over 2 hours) every 2 weeks</td>
<td>N/A</td>
</tr>
</tbody>
</table>

CrCl—creatinine clearance

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taking allopurinol about frequency of flares, and if the patient takes the prescribed dose every day. According to a 2004 retrospective study of allopurinol adherence, nearly half of patients undergoing treatment were not taking the prescribed daily dosage. Renal function should also be considered when titrating doses. There is limited long-term experience with doses beyond 300 mg daily.

Allopurinol is well-tolerated. The most commonly experienced adverse reactions related to allopurinol use include nausea, diarrhea, maculopapular rash, elevated LFTs, alkaline phosphatase elevations, and acute attacks of gout. The maculopapular rash, which occurs in approximately 2 percent of patients, is fairly mild. Concurrent treatment with ampicillin increases the maculopapular rash incidence to up to 20 percent of patients. Progression of the generalized rash to severe skin reactions, such as Stevens-Johnson syndrome, can occur.

The most significant adverse reaction of allopurinol therapy, known as allopurinol hypersensitivity syndrome (AHS), is a life-threatening condition with a 20 percent mortality rate. The syndrome is characterized by desquamating skin lesions, high fever (>102.2°F), leukocytosis, hepatic dysfunction, and renal failure. Clinicians should monitor patients carefully to quickly identify possible hypersensitivity reactions. Patients should be instructed to report skin rashes. Patients with a history of AHS should never be re-challenged with the medication. The ACR guidelines suggest that HLA-B*5801 gene testing be considered in patients at high risk for severe allopurinol hypersensitivity reactions. These include Koreans with stage 3 or higher kidney disease, and patients of Han Chinese or Thai heritage. Universal pharmacogenomics testing is not warranted for all patients started on allopurinol.

Several significant drug interactions are associated with allopurinol use. The effects of both theophylline and warfarin can be increased by allopurinol, although data regarding warfarin is conflicting. Allopurinol can significantly increase levels of purine analogues azathioprine and 6-mercaptopurine. Purine analogue dose reductions of 25–33 percent are necessary to avoid toxicity. Clinicians must be aware of such drug interactions for patients receiving allopurinol therapy, and monitor or modify therapy appropriately.

Patients taking allopurinol should be counseled to drink plenty of water to avoid kidney stones, and should report painful urination or hematuria immediately. Allopurinol may be taken after meals to reduce stomach upset and remind patients that they may be more prone to gouty attacks for the first two to six weeks of allopurinol therapy. Skin rash and fever should be reported to the prescriber.

Patient Case Continued
JG accompanies his father to the pharmacy where his father is picking up a refill for 100 mg of allopurinol. They are both a bit anxious about their gout diagnoses and hope that the pharmacist can help.

His father is complaining because he doesn’t think the allopurinol is helping and wonders if he should stop it since he had two attacks in the past couple months. JG also questions why his father is taking allopurinol for his gout and he is not. Should his twin brother have his uric acid checked just in case he is at risk too? What should the pharmacist advise?

Usually, more than one gout attack is warranted before prophylactic treatment should be considered. Recall that JG was taking niacin that could have triggered the event, it was discontinued when he presented with acute gout. The pharmacist should encourage non-pharmacological strategies to reduce risk. No prophylactic therapy is warranted at this time.

The pharmacist should recognize that adherence rates with allopurinol are usually low. JG’s father’s adherence to allopurinol should be assessed using objective refill history data and patient interview to address barriers (adverse events, knowledge, etc). If he is adherent to therapy, and because he is on the lowest dose, a uric acid level should be checked to determine if it is below 6 mg/dL for best outcomes. Before suggesting any dose modification, the pharmacist should refer JG’s father to his primary care provider; preexisting renal impairment may have played a role in setting the dose. The patient interview should also include
an evaluation of gout history that includes the number of past attacks, severity of attacks, and presence of risk factors that can be modified to improve patient understanding of the medication purpose.

JG’s father admits his “diet is not the best” and upon observation appears obese. He has been cutting back on his daily bottle of beer intake to two drinks per day. His blood pressure is 160/90 mmHg and heart rate is 72 beats per minute. He states he rarely takes the HCTZ because it makes him run to the bathroom; he only takes it on weekends when he is not at work. He also takes fish oil 1,000 mg twice a day and was prescribed pravastatin 10 mg daily last month but did not start it because he was already on the fish oil for cholesterol. He only takes the allopurinol a couple times a week since it doesn’t seem to work. He was not aware he was to take it continuously.

The pharmacist should target some of the adherence barriers noted with allopurinol, HCTZ and pravastatin. He should be educated that acute attacks may occur during allopurinol initiation; colchicine and NSAIDs are often used concomitantly for six months. Because of his blood pressure, colchicine is preferred. He should report attacks to his provider.

Interestingly, his poor adherence to HCTZ might have reduced gout attacks as it is a known risk for hyperuricemia. The provider should be contacted for an alternative antihypertensive, once other co-morbidities are addressed; losartan may be considered for its beneficial effects in lowering uric acid levels. The patient should be educated that simvastatin targets the low density lipoprotein concentration, unlike fish oil which benefits triglycerides. He should be encouraged to start simvastatin. Simple diet tips can be accessed online (Table 6) and written material may be used to supplement recommendations reviewed earlier. The patient should be applauded for his attempt to reduce beer intake. He should be advised that no beer should be consumed during an attack. Alcohol should also be limited during concomitant treatment with simvastatin. Fenofibrate may be an alternative in the future for triglyceride reduction if goals are not met; it also benefits in lowering uric acid levels.

JG’s brother does not need to have a uric acid level checked just because his brother and father have a history of gout attacks. Isolated high uric acid levels in the absence of symptoms are not typically treated. His brother may wish to be proactive by adopting non-pharmacologic strategies to prevent gout, such as alcohol in moderation, weight loss if he is overweight, and avoidance of high-protein fad diets.

**FEBUXOSTAT (ULORIC)®**

Febuxostat, a non-purine-selective xanthine oxidase inhibitor, was approved by the FDA in 2009 for the treatment of chronic hyperuricemia associated with gout. Structurally, febuxostat and allopurinol differ significantly. Febuxostat may be significantly more potent with respect to decreasing serum urate levels, as well as decreasing acute attack frequency and tophi formation. However, fixed dose allopurinol was used in clinical trials instead of patient-specific dose titration to achieve goal serum urate levels. Therefore, the clinical superiority of febuxostat over allopurinol remains to be sufficiently demonstrated.

The starting dose of febuxostat is 40 mg orally, once daily. After two weeks, if serum uric acid levels have not decreased to goal, the dose can be increased to 80 mg once daily. In contrast to allopurinol, dose adjustments of febuxostat are not necessary for mild to moderate renal impairment since it is metabolized in the liver.

Febuxostat is relatively well-tolerated by patients. Common adverse reactions include rash, LFT abnormalities, and non-gouty arthralgias. As with allopurinol, febuxostat decreases the metabolism of azathioprine and 6-mercaptopurine. Febuxostat is contraindicated in combination with these agents.

Currently, the exact role of febuxostat in the anti-hyperuricemic treatment of gout is not well established. While structural differences between allopurinol and febuxostat seem to offer an alternative for patients intolerant to allopurinol, more data is needed. The possible superiority of febuxostat may make it an option for patients who do not experience adequate serum uric acid lowering on allopurinol.
Patient Case Continued
JG asks about a medication he read about in a magazine, febuxostat. Should he or his father be on it also? Febuxostat is usually used if allopurinol does not achieve uric acid goals or if the patient has adverse effects from allopurinol. It is a more expensive agent with less long term experience. JG has not had enough attacks to justify prophylactic therapy, though he should be referred to his provider if he has additional questions. Since his father was nonadherent, the allopurinol is worth a try first. Allopurinol and febuxostat are not used together.

URICOSURICS
Probenecid
Probenecid is a member of the urate-lowering medications known as the uricosurics. Uricosuric medications reduce hyperuricemia by correcting the most common physiologic abnormality associated with gout, the underexcretion of uric acid. Probenecid increases the renal elimination of uric acid by inhibiting the organic URAT1 transporter. Inhibition of URAT1, which is located on the apical membrane of the proximal convoluted tubule, results in decreased reabsorption of uric acid.

The use of probenecid should be limited to patients with demonstrated underexcretion of uric acid. It is ineffective in overproducers. It is also ineffective in patients with impaired renal function (CrCl<50ml/min). Occasionally, it may be used in combination with allopurinol in patients not achieving uric acid goals.

Patients should be advised to maintain adequate hydration during therapy to minimize the risk of nephrolithiasis. It is recommended they consume 1.5–2 liters (six to eight, 8-ounce glasses) of fluid per day. This is because upon initiation of probenecid therapy, as the concentration of uric acid in the urine will increase temporarily as a result of increased renal elimination. Elevated concentrations of uric acid in the lumen of the kidney increase the risk for deposition of uric acid crystals there, and subsequent nephrolithiasis. Consideration may be given to the use of potassium citrate or sodium bicarbonate to alkalinize the urine, providing additional protection against nephrolithiasis. Patients with a history of nephrolithiasis should not receive probenecid.

The most common side effects experienced during probenecid therapy include gastrointestinal upset, dizziness, nausea, vomiting, sore gums, and flushing. Blood dyscrasias may occur in patients with G6PD deficiency.

Probenecid drug interactions that alter the metabolism and elimination of several frequently used medications limit its use. The plasma concentration of various penicillins can increase by approximately 200–400 percent as a result of decreased elimination. Patients undergoing methotrexate therapy should not receive probenecid, as plasma concentration of methotrexate may become toxic. Higher aspirin doses (600–1,200 mg daily) may blunt the uricosuric response to probenecid and should be avoided in combination. Clinicians should exercise caution when prescribing probenecid to patients with type II diabetes as sulfonlyurea concentrations may rise to levels sufficient to develop hypoglycemia. The serum levels of non-steroidal anti-inflammatory drugs (NSAIDs) may be elevated by probenecid, increasing the risk of toxicity.

Initiation of probenecid at a low dose, such as 250 mg twice daily, is recommended to reduce the risk of precipitating an acute gouty flare, exacerbating existing symptoms, or developing renal uric acid crystals. Specific recommendations vary with respect to dose titration.

RECOMBINANT URICASE
Pegloticase (Krystexxa®)
Pegloticase is an intravenously administered, pegylated, recombinant form of the enzyme uricase. It is FDA-approved for the treatment of gout. The enzyme uricase is responsible for the oxidation of uric acid to allantoin. Allantoin is a water soluble substance readily eliminated by the kidneys. Uricase is not found in humans, thus the need for a recombinant product. The addition of polyethylene glycol to the recombinant uricase increases the half-life and decreases immunogenicity of the protein. Upon administration, pegloticase catalyzes the oxidation reaction of uric acid to allantoin, subsequently reducing the levels of uric acid in the body.
 Pegloticase should be reserved for patients with refractory gout due to the inconvenience of intravenous administration, expense, and the risk of anaphylaxis and other immunogenic reactions. It is contraindicated in patients with G6PD deficiency. Clinicians should perform screening in patients at higher risk for G6PD deficiency (such as patients of African or Mediterranean descent).

A black box warning is established regarding the elevated risk of anaphylaxis and infusion-related reactions. Pretreatment with an antihistamine and intravenous corticosteroid is recommended prior to each infusion. Patients with elevated serum uric acid levels (greater than or equal to 6 mg/dL) appear to be at greater risk of anaphylaxis. Serum uric acid concentrations should be monitored prior to infusions; clinicians should consider discontinuing therapy in patients with persistently elevated uric acid levels (such as two consecutive labs show uric acid greater than 6 mg/dL).

The most common serious adverse events associated with pegloticase include anaphylaxis, infusion-reactions, and gout flares. Other side effects commonly experienced include nausea and nasopharyngitis. As with other urate-lowering therapies, the risk of gout flares is increased during treatment initiation. Therefore, prophylaxis with colchicine or NSAIDs should begin one week prior to pegloticase treatment.

The usual dose of pegloticase is 8 mg via intravenous infusion (over two hours) every two weeks. Renally impaired patients do not require a dose adjustment. Long-term treatment durations have not yet been clearly established.

Pegloticase administration is typically reserved to specialty care. Pharmacists can advise patients to expect gout flares during the initial months of treatment and report attack frequency to the provider. NSAIDs or colchicine should be started a week before therapy begins. Patients should be advised on the expense associated with pegloticase.

**CONCLUSION**

Gout is a common but straightforward disease to treat. Pharmacists can assist patients with gout by providing education on non-pharmacologic treatments, identifying drug interactions, and preventing adverse events. Pharmacists can help physicians navigate gout treatment options by discussing the pros and cons of each treatment and recognizing and promoting management of risk factors. 

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Treatment Options for Gout
March 1, 2013 (expires March 1, 2016) • Activity Type: Knowledge-based

CONTINUING EDUCATION QUIZ
Select the correct answer.

1. The pathophysiology of gout is characterized by elevated concentrations of which substance?
   a. Sodium chloride
   b. Ammonium
   c. Uric acid
   d. Sodium bicarbonate

2. The inflammation associated with gout symptoms is caused by the lysis of which of the following components of the immune system?
   a. Helper T-cells
   b. Neutrophils
   c. Cytotoxic T-cells
   d. B-cells

3. JM is a 49-year-old male who states he recently recovered from his first acute gout attack a little over a week ago. He heard that patients who suffer from gout may experience joint damage. He asks if he should be afraid of this since he just experienced an attack. What is the best response for JM?
   a. JM should be concerned because joint destruction generally follows the first acute attack.
   b. JM should be reassured joint damage and chronic symptoms are normally only present in individuals who have lived with gout for many years.
   c. JM should schedule an appointment with an orthopedic surgeon for evaluation.
   d. JM should be reassured his gout most likely will never return so he should not worry.

4. Common features that best describe an acute gout attack include:
   a. Intense pain that progresses quickly, usually in the toe joint
   b. Bilateral joint involvement, intense pain that progresses over a few weeks
   c. Blurry vision, stomach upset, shoulder pain
   d. Sore lower back, elevated red blood cells, renal failure
5. NH is a 62-year-old female questioning whether her dietary habits or medications could be causing her increased gout attacks over the past couple months. She has been treated for hypertension and high triglycerides with amlodipine, lisinopril, and fenofibrate for years and started taking hydrochlorothiazide a couple months ago. She consumes red meat, yogurt and potatoes daily, and consumes 1–2 beers a day, “sometimes more.” The best strategy to prevent future gout attacks in NH is:
   a. Increase yogurt intake, consult her doctor to switch from lisinopril to losartan
   b. Consult her doctor to stop amlodipine and fenofibrate immediately
   c. Limit beer and moderate intake of red meat; consult her doctor to evaluate hydrochlorothiazide use
   d. None of the above are appropriate strategies.

6. BG is a 65-year-old male presenting with severe joint pain in his left big toe beginning suddenly the night before. The joint appears swollen and is red. He has a history of osteoarthritis in his right shoulder, hypertension, and dyslipidemia. The only medications he takes are acetaminophen and simvastatin. He is overweight but tries to exercise regularly and watch his diet. He was told at a routine physical a month ago that his uric acid level was high and wonders why they didn’t do anything about it then. He has no history of gout. The best advice regarding uric acid levels for BG is:
   a. Uric acid levels are risk factors for gout but the risk of drug side effects outweighs the benefit of treatment before symptoms start.
   b. Uric acid levels over 10 mg/dL should be treated even if the patient has no history of gout.
   c. Uric acid levels over 6 mg/dL should be treated even if the patient has no history of gout.
   d. None of the above are appropriate strategies.

7. BG is diagnosed with gout. Appropriate non-pharmacologic approaches to treatment include:
   a. Immobilize the affected joint and apply ice.
   b. Massage the affected joint and use a heating pad.
   c. Normal use of affected joint and use of an ice pack.
   d. Elevate affected joint and use of a heating pad.

8. Which of the following choices would be most appropriate to treat BG’s acute gout?
   a. Ibuprofen
   b. Colchicine
   c. Indomethacin
   d. Sulindac

9. A patient fills a new prescription for clarithromycin for a chest infection. He is taking colchicine once a day for a few months while he is started on allopurinol. He is not taking any other medications at this time. He would like to know if he can take all the meds at once. What do you advise?
   a. Colchicine has very few interactions with other drugs and can be taken along with his other meds.
   b. Allopurinol decreases absorption of clarithromycin; separate administration by two hours.
   c. Clarithromycin inhibits metabolism of colchicine increasing side effect risk; contact his doctor for a substitute antibiotic.
   d. Colchicine should be taken twice a day while on clarithromycin due to metabolism induction.

10. Colchicine should not be used in a patient with which of the following scenarios?
    a. Hypertension
    b. Type 2 diabetes mellitus
    c. Dermatitis
    d. Cardiac arrhythmias

11. You are working in an ambulatory care clinic when a nurse practitioner asks for a recommendation for the treatment of acute gout in a 65-year-old with a history of chronic kidney disease and depression which is being treated with nefazodone. His most recent creatinine clearance was 25ml/min. Which of the following would you recommend?
    a. Prednisone
    b. Naproxen
    c. Colchicine
    d. Indomethacin
12. A patient calls your pharmacy complaining of another gout attack. He was recently hospitalized with a gastric bleed caused by a peptic ulcer and was just discharged last week. He previously took naproxen to treat his gout and wants to know if he can still use naproxen. What is your best reply?
   a. “Naproxen is not a good choice because it is known to potentially cause ulcers and bleeding. I’ll ask your doctor about starting you on prednisone.”
   b. “Naproxen is not a good choice because it is known to potentially cause ulcers and bleeding. I’ll ask your doctor about starting you on colchicine.”
   c. “Naproxen is not a good choice because it is known to potentially cause ulcers and bleeding. I’ll ask your doctor about starting you on ibuprofen.”
   d. “Naproxen is safe to take as long as you eat something when you take it.”

13. A physician asks for your recommendation for the treatment of acute gout in a 62-year-old male who is HIV-positive. He takes lopinavir/ritonavir and reports trouble breathing with ibuprofen. Which of the following do you recommend?
   a. Indomethacin
   b. Prednisone
   c. Colchicine
   d. Naproxen

14. What scenario would justify prophylactic treatment?
   a. Two or more gout attacks per year
   b. Tophaceous gout
   c. Uric acid kidney stones
   d. All of the above

15. The physician decides to initiate prophylactic therapy for a patient with normal renal function. He prescribes allopurinol, but is unsure of the appropriate starting dose. Which of the following starting doses should be recommended for the patient?
   a. 40–80 mg orally once a day
   b. 8 mg IV every two weeks
   c. 100 mg orally once a day
   d. 250 mg orally twice daily

16. As you are filling the allopurinol prescription at the pharmacy, you notice several other medications in the patient’s profile. The dose of which of the patient’s current medications must be adjusted to avoid significant drug-drug interactions?
   a. Theophylline
   b. Pravastatin
   c. Losartan
   d. Clonazepam

17. Which of the following medications used for the prophylactic treatment of gout is associated with a hypersensitivity syndrome characterized by desquamating skin lesions, high fever (>102.2°F), leukocytosis, hepatic dysfunction, and renal failure?
   a. Allopurinol
   b. Febuxostat
   c. Probenecid
   d. Recombinant Uricase

18. A physician is developing a prophylactic treatment regimen for a patient with mild renal impairment. Which of the following medication options would not require a dose adjustment in such a patient?
   a. Probenecid
   b. Febuxostat
   c. Allopurinol
   d. Colchicine

19. The prophylactic therapy best reserved for patients with refractory, tophaceous gout is:
   a. Probenecid
   b. Febuxostat
   c. Allopurinol
   d. Pegloticase

20. Prophylactic gout therapy should be titrated to a uric acid level less than:
   a. 10 mg/dL
   b. 5 mg/dL
   c. 6 mg/dL
   d. 1 mg/dL