Gout
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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

A 54-year-old man with crystal-proven gout has a history of four attacks during the previous year. Despite receiving 300 mg of allopurinol daily, his serum urate level is 7.2 mg per deciliter (428 μmol per liter). He is moderately obese and has hypertension, for which he receives hydrochlorothiazide, and his serum creatinine level is 1.0 mg per deciliter (88 μmol per liter). How should his case be managed?

THE CLINICAL PROBLEM

SYMPTOMS AND PREVALENCE

Gout is a type of inflammatory arthritis induced by the deposition of monosodium urate crystals in synovial fluid and other tissues. It is associated with hyperuricemia, which is defined as a serum urate level of 6.8 mg per deciliter (404 μmol per liter) or more, the limit of urate solubility at physiologic temperature and pH. Humans lack uricase and thus cannot convert urate to soluble allantoin as the end product of purine metabolism. Hyperuricemia that is caused by the overproduction of urate or, more commonly, by renal urate underexcretion is necessary but not sufficient to cause gout. In one cohort study, gout developed in only 22% of subjects with urate levels of more than 9.0 mg per deciliter (535 μmol per liter) during a 5-year period.¹

Gout has two clinical phases. The first phase is characterized by intermittent acute attacks that spontaneously resolve, typically over a period of 7 to 10 days, with asymptomatic periods between attacks. With inadequately treated hyperuricemia, transition to the second phase can occur, manifested as chronic tophaceous gout, which often involves polyarticular attacks, symptoms between attacks, and crystal deposition (tophi) in soft tissues or joints. Although the prevalence of tophaceous gout varies among populations, in one study, tophi were detected in three quarters of patients who had had untreated gout for 20 years or more.³ Recurrent attacks are common. In one study, approximately two thirds of patients with at least one gout attack in the previous year had recurrent attacks.⁴

An estimated 6.1 million adults in the United States have had gout.⁵ The prevalence increases with age and is higher among men than among women, with a ratio of 3 or 4 to 1 overall.⁵⁻⁷ However, this sex disparity decreases at older ages, at least in part because of declining levels of estrogen, which has uricosuric effects in women. The rising incidence and prevalence of gout are probably related to the aging of the population, increasing levels of obesity, and dietary changes.⁵⁻⁷

RISK FACTORS

The use of thiazide diuretics, cyclosporine, and low-dose aspirin (<1 g per day) can cause hyperuricemia, whereas high-dose aspirin (23 g per day) is uricosuric. Factors
that are associated with hyperuricemia and gout include insulin resistance, the metabolic syndrome, obesity, renal insufficiency, hypertension, congestive heart failure, and organ transplantation. The uricosuric effects of glycosuria in diabetes may reduce the risk of gout. Rare X-linked inborn errors of metabolism can cause gout. Genomewide association studies have identified common polymorphisms in several genes involved in renal urate transport that are associated with gout, including SLC2A9, ABCG2, SLC17A3, and SLC22A12. The risk of incident gout is increased in persons with an increased intake of dietary purines (particularly meat and seafood), ethanol (particularly beer and spirits), soft drinks, and fructose and is decreased in those with an increased intake of coffee, dairy products, and vitamin C (which lower urate levels).

Triggers for recurrent flares include recent diuretic use, alcohol intake, hospitalization, and surgery. Urate-lowering therapy, which reduces the risk of gout attacks in the long term, can trigger attacks in the early period after its initiation, presumably as a result of mobilization of bodily urate stores.

The diagnostic standard remains synovial fluid or tophus aspiration with identification of negatively birefringent monosodium urate crystals under polarizing microscopy. Crystals are detectable during attacks and also potentially between attacks, primarily in previously inflamed joints in patients with hyperuricemia. However, crystal evaluation is not performed routinely in clinical practice. Hyperuricemia may not be present during acute gout attacks and therefore may not be a helpful criterion for diagnosis. A typical presentation that is strongly suggestive of the diagnosis includes rapid development of severe pain (i.e., within 24 hours), erythema, and swelling in a characteristic joint distribution — for example, in the first metatarsophalangeal joint (podagra). In a population with a 0.5% prevalence of gout overall, a patient with hyperuricemia and this presentation has an 82% chance of having gout.

The differential diagnosis of acute gout includes other crystal-induced arthritides (e.g., calcium pyrophosphate dihydrate) and a septic joint. Joint aspiration with Gram’s staining and culture must be performed if a septic joint is suspected, even if monosodium urate crystals are identified. Older adults, particularly women, may present with polyarticular involvement, which may be mistaken for rheumatoid arthritis; a tophus may be mistaken for a rheumatoid nodule. Tophaceous deposits that are not clinically apparent may be visualized by plain radiography or another imaging method. A diagnosis of gout should prompt evaluation for potentially modifiable risk factors (e.g., dietary habits) and associated coexisting illnesses (e.g., hypertension and hyperlipidemia) that may require intervention.

### Treatment Options

#### Acute Gout

The main aim of therapy for acute gout is rapid relief of pain and disability caused by intense inflammation. Options for managing acute attacks include the use of nonsteroidal antiinflammatory drugs (NSAIDs), colchicine, glucocorticoids, and possibly corticotropin. The choice of agent, dose, and duration of therapy is guided by consideration of coexisting illnesses that preclude the safe use of a particular regimen, as well as the severity of the gout. Adjunctive measures include applying ice to and resting the affected joint.

NSAIDs and colchicine are first-line agents for acute attacks (Table 1). Oral colchicine has long been used, although it has only recently (in 2009) been approved by the Food and Drug Administration (FDA) for use in patients with acute gout. In a randomized trial, colchicine (at a dose of 1.2 mg at the onset of a flare, followed by 0.6 mg 1 hour later) was significantly more likely than placebo to result in a reduction in pain of 50% or more 24 hours later (rates, 37.8% and 15.5%, respectively). This regimen had efficacy similar to that of a high-dose regimen (1.2 mg, then 0.6 mg per hour for 6 hours), with fewer gastrointestinal side effects. This study did not address treatment after the first 24 hours.

The relative efficacy of colchicine as compared with NSAIDs is unknown. In head-to-head studies, various NSAIDs have had similar benefits for acute gout, and a controlled trial showed the efficacy of tenoxicam over placebo.

When the use of NSAIDs or colchicine is poorly tolerated or contraindicated, glucocorticoids or corticotropin may be used, although evidence for the use of intraarticular and intramuscular glucocorticoids and corticotropin is limited by a lack
Table 1. Pharmacologic Management Options for Acute Gout Attacks.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Examples of Regimens from Randomized Clinical Trials</th>
<th>Alternative Regimens for Complete Attack Resolution*</th>
<th>Precautions</th>
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<tbody>
<tr>
<td>Nonsteroidal antiinflammatory drug†</td>
<td>500 mg orally twice daily for 5 days</td>
<td>375–500 mg orally twice daily for 3 days, then 250–375 mg orally twice daily for 4–7 days or until attack resolves</td>
<td>Avoid in patients with renal or hepatic insufficiency, bleeding disorder, congestive heart failure, or allergy; associated with an increased risk of adverse thrombotic and gastrointestinal events; may be administered with a proton-pump inhibitor in patients at risk for gastrointestinal events.</td>
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<tr>
<td>Naproxen</td>
<td>500 mg orally twice daily for 5 days</td>
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<tr>
<td>Indomethacin</td>
<td>50 mg orally three times daily for 2 days, then 25 mg orally three times daily for 3 days</td>
<td>50 mg orally three times daily for 3 days, then 25 mg orally three times daily for 4–7 days or until attack resolves</td>
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<tr>
<td>Colchicine</td>
<td>1.2 mg orally at first sign of gout flare, followed by 0.6 mg orally 1 hr later</td>
<td>Consider additional acute gout regimen to continue managing attack 12–24 hr after colchicine regimen (e.g., 0.6 mg of colchicine twice daily, a nonsteroidal antiinflammatory drug regimen, or an oral glucocorticoid regimen until attack resolves)</td>
<td>Avoid (or use lower dose) in older adults and those with renal insufficiency, hepatic dysfunction, or known gastrointestinal symptoms; adjust dose (and avoid in patients with renal or hepatic impairment) if used in conjunction with P-glycoprotein or CYP3A4 inhibitors (e.g., cyclosporine, clarithromycin, certain antiretroviral agents, certain antifungal agents, certain calcium-channel blockers, and grapefruit juice); avoid for gout-flare therapy in patients with renal or hepatic impairment who are already receiving colchicine prophylaxis; monitor for gastrointestinal symptoms, myotoxicity, and blood dyscrasias (details are available at <a href="http://www.fda.gov">www.fda.gov</a>).</td>
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<tr>
<td>Oral glucocorticoids</td>
<td>Prednisolone, 30–35 mg daily for 5 days</td>
<td>Prednisone, 30–60 mg daily for 2 days (depending on severity of attack), then reduce by 5–10 mg every 2 days (depending on starting dose) in 10-day taper</td>
<td>Use caution in patients with hyperglycemia or congestive heart failure; may be used in patients with moderate-to-severe renal impairment.</td>
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</table>

* Longer durations of therapy may be necessary for patients with long-standing disease and severe flares.
† There are no published trials establishing the efficacy of celecoxib, the only selective cyclooxygenase-2 inhibitor available in the United States, for use in acute gout.
‡ Although there are insufficient data to recommend the use of intraarticular glucocorticoid injection, it may be a useful alternative for attacks that are limited to one or two joints and amenable to aspiration and in the absence of joint sepsis.
of data from blinded, randomized, placebo-controlled trials24,27-29 (Table 1). Monoarticular attacks are often managed with the use of intraarticular glucocorticoids. In two randomized, placebo-controlled trials of a 5-day course of oral prednisolone (one evaluating a dose of 30 mg daily and the other a dose of 35 mg daily), the efficacy of prednisolone was equivalent to that of standard regimens of indomethacin (vs. the 30-mg dose of prednisolone) and naproxen (vs. the 35-mg dose).30,31

The dose and duration of therapy for acute gout should be sufficient to eradicate the profound inflammatory response. Although randomized trials have generally studied the effects of short courses of treatment on pain reduction, clinical experience suggests that 7 to 10 days of treatment may be necessary to ensure the resolution of symptoms. Increased doses of antiinflammatory drugs are typically prescribed for the first few days, with a reduction in the dose once symptoms begin to improve.32 Flares should be treated without interruption of urate-lowering therapy. A “medications in the pocket” strategy should be considered for patients with established gout so that therapy can be started promptly at the onset of symptoms that are consistent with typical attacks.

There is evidence that attacks of gout are caused by the activation of the NLRP3 inflammasome by urate crystals, leading to the release of interleukin-1β33 (Fig. 1). For this reason, interleukin-1 antagonists are being studied as potential options for patients in whom other treatments are not feasible.34 In a randomized trial, the fully human monoclonal antibody canakinumab significantly reduced pain from acute gout, as compared with 40 mg of intramuscular triamcinolone acetonide, 72 hours after administration of the study drug.35 Anakinra and rilonacept improved acute and chronic gout symptoms, respectively, in two small, uncontrolled pilot studies; however, rilonacept did not significantly reduce pain, as compared with indomethacin, in a randomized trial.34,36,37 More data are needed to assess the potential role of these agents.

HYPERURICEMIA
Pharmacologic Approaches
The purpose of lowering serum urate levels is to prevent acute flares and development of tophi. However, gout does not develop in all patients with hyperuricemia, and antihyperuricemic therapies are not without risk. Recommendations that are based on both consensus and evidence support the consideration of urate-lowering therapy in patients with hyperuricemia who have at least two gout attacks per year or tophi (as determined by either clinical or radiographic methods).38 However, the severity and frequency of flares, the presence of coexisting illnesses (including nephrolithiasis), and patient preference are additional considerations.24 Urate-lowering therapy should not be initiated during acute attacks but rather started 2 to 4 weeks after flare resolution, with a low initial dose that is increased as needed over a period of weeks to months, and with close monitoring of urate levels, renal function, and adverse effects. The dose should be adjusted as necessary to maintain a serum urate level below 6 mg per deciliter (357 μmol per liter), which is associated with a reduced risk of recurrent attacks and tophi.22,39,40 It is uncertain whether a more stringent target of less than 5 mg per deciliter (297 μmol per liter) results in greater disease control.41,42 Therapy is generally continued indefinitely.

Three classes of drugs are approved for lowering urate levels: xanthine oxidase inhibitors, uricosuric agents, and uricase agents (Table 2 and Fig. 2). Xanthine oxidase inhibitors block the synthesis of uric acid and can be used regardless of whether there is overproduction of urate. In this class of drugs, the one most commonly prescribed to lower urate levels is allopurinol, which is effective in decreasing flares and tophi, particularly among patients in whom target urate levels are achieved.22,39 Although allopurinol has an acceptable side-effect profile in most patients, a mild rash develops in approximately 2%.22,39,43 Severe allopurinol hypersensitivity is much less common but can be life-threatening. Allopurinol desensitization can be attempted in patients with mild cutaneous reactions, but its safety in those with more serious reactions is unknown.44 The majority of patients receive 300 mg of allopurinol daily, but this dose is often inadequate to achieve target urate levels. Daily doses up to 800 mg may be used in patients with normal renal function. The dose is typically reduced in patients with renal impairment, owing to concerns about an increased risk of hypersensitivity in such patients. However, studies have not shown an association between dose and risk of hypersensitivity, and a reduced dose may contribute to suboptimal gout control.43
In 2009, another xanthine oxidase inhibitor, febuxostat, was approved by the FDA for the treatment of hyperuricemia in patients with gout. As compared with a daily dose of 300 mg of allopurinol, febuxostat at daily doses of 80 mg and 120 mg was 2.5 and 3 times as likely, respectively, to achieve serum urate levels of less than 6 mg per deciliter. During the initial 8 weeks of the study, the frequency of gout attacks was higher among patients receiving 120 mg of febuxostat than among those receiving either 80 mg of febuxostat or 300 mg of allopurinol, but there was no significant difference among the three groups for the remainder of the trial. In another study involving patients with renal impairment (defined as a creatinine clearance of 30 to 89 ml per minute), daily doses of 80 mg and 40 mg of febuxostat were superior to 300 mg of allopurinol (or 200 mg in patients with moderate renal impairment) for lowering serum urate to a level below 6 mg per deciliter. There was no increase in cardiovascular risk or hypersensitivity associated with the use of either dose of febuxostat, as compared with allopurinol, although the trial was not powered for such comparisons. Postmarketing surveillance is needed to better understand the risks and benefits of febuxostat.

Uricosuric drugs (including probenecid, sulfinpyrazone, and benzbromarone) block renal tubular urate reabsorption. Although these drugs can be used in patients with underexcretion of urate (accounting for up to 90% of patients with gout), they are used less frequently than xanthine oxidase inhibitors and are contraindicated in patients with a history of nephrolithiasis. Benzbromarone (not available in the United States) may be used in patients with mild-to-moderate renal insufficiency but is potentially hepatotoxic, whereas the other two drugs are generally ineffective in patients with renal impairment. In two open-label, randomized trials, benzbromarone was equivalent to allopurinol (the latter at a daily dose of as much as 600 mg) and superior to probenecid (among patients in whom target urate levels were not achieved with 300 mg of allopurinol) in lowering serum urate to 5 mg per deciliter or less.

Uricase converts uric acid into soluble allantoin. Pegloticase, a polyethylene glycolylated (pegylated) modified porcine recombinant uricase, was approved by the FDA in 2010 for chronic gout that is refractory to conventional treatments. The approval was based on data from two double-blind, randomized, placebo-controlled, 6-month trials showing the drug's urate-lowering and tophus-reducing effects. However, pegloticase must be administered intravenously, and infusion reactions were common. Rasburicase, which is approved for use in preventing the tumor lysis syn-
Table 2. Pharmacologic Options for Hyperuricemia Therapy in Gout.*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Example of Regimen</th>
<th>Considerations or Precautions</th>
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</thead>
<tbody>
<tr>
<td>Urate-lowering therapy</td>
<td>Aim to maintain serum urate levels below 6 mg per deciliter, which requires regular monitoring and may require dose adjustments. Accompany the initiation of therapy with flare prophylaxis.</td>
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</tr>
<tr>
<td>Xanthine oxidase inhibitor</td>
<td>Use in patients with urate overproduction or underexcretion. Avoid use (or monitor closely) in patients receiving azathioprine or 6-mercaptopurine because these drugs are metabolized by xanthine oxidase.</td>
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</tr>
<tr>
<td>Allopurinol</td>
<td>Starting dose: 50–100 mg orally daily; increase dose every 2–4 wk to achieve serum urate target, with dose based on creatinine clearance; average daily dose, 300 mg, although many patients require higher doses</td>
<td>Use with caution in patients with renal insufficiency (based on creatinine clearance). The maximal dose may be as high as 800 mg daily, but there are limited data for doses above 300 mg daily. A mild rash occurs in approximately 2% of patients, and the risk is potentially increased by coadministration of ampicillin, amoxicillin, thiazide diuretics, or ACE inhibitors. Allopurinol hypersensitivity is rare, occurring in approximately 0.1% of patients, but can be fatal (rate of death, 20%). If the target serum urate level is not achieved, consider dose escalation beyond the level suggested by guidelines in patients with renal impairment (with close monitoring) or consider the use of an alternative therapy (e.g., febuxostat). Allopurinol can increase the anticoagulant effect of warfarin.</td>
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<tr>
<td>Febuxostat</td>
<td>Starting dose: 40 mg orally daily; increase to 80 mg orally daily after 2–4 wk to achieve serum urate target, if necessary†</td>
<td>Use as a second-line agent for patients who have contraindications or an inadequate response to allopurinol or uricosuric therapy. Although no dose adjustment is required for patients with mild-to-moderate renal or hepatic insufficiency, there are insufficient data for use in patients with a creatinine clearance of &lt;30 ml per minute or severe hepatic impairment. Currently contraindicated for use with theophylline. Febuxostat has a higher cost than allopurinol.</td>
</tr>
<tr>
<td>Uricosuric agent (probenecid)</td>
<td>Starting dose: 250 mg orally daily; increase by 500 mg per mo to a maximal dose of 2–3 g per day (2 divided doses) in patients with normal renal function to achieve serum urate target</td>
<td>Avoid in patients with a history of nephrolithiasis and a creatinine clearance of &lt;30 ml per minute. Adequate hydration is required to reduce risk of nephrolithiasis. The use of this drug can increase serum penicillin levels. Evaluate for renal uric acid excretion in patients with a family history of early onset of gout, onset of gout at &lt;25 yr, or a history of nephrolithiasis, since this may identify patients with an overproduction of urate in whom uricosuric therapy should be avoided because of the risk of nephrolithiasis.</td>
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</table>
Flare prophylaxis during initiation of urate-lowering therapy

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Details</th>
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<tbody>
<tr>
<td>Colchicine</td>
<td>0.6 mg orally once or twice daily as tolerated</td>
</tr>
<tr>
<td>NSAID</td>
<td>Naproxen, 250 mg twice daily</td>
</tr>
</tbody>
</table>

Use for chronic gout in adults whose disease is refractory to conventional therapy (e.g., lack of normalization of serum urate, inadequate control of signs and symptoms with the use of a xanthine oxidase inhibitor at maximum medically appropriate dose, or other contraindication). There is a risk of infusion reactions (26%, vs. 5% in placebo group) even with premedication, particularly in patients without a therapeutic response (in whom serum urate levels increase to above 6 mg per deciliter, particularly on two consecutive occasions) or with antibodies against pegloticase. Anaphylaxis occurs in 5% of patients (vs. 0% in placebo group). No data are available regarding retreatment after stopping treatment for longer than 4 weeks. Do not use in patients with G6PD deficiency, and use caution in patients with congestive heart failure (insufficient safety data; some exacerbations in clinical trials). Cost is higher than for other therapies.

Flare Prophylaxis during Initiation of Urate-Lowering Therapy

* ACE denotes angiotensin-converting enzyme, and NSAID nonsteroidal antiinflammatory drug.
† Febuxostat at a dose of 120 mg is available in Europe.
‡ Benzbromarone and sulfinpyrazone are available in a limited number of countries but not in the United States.
Data are limited regarding the safety and efficacy of combination therapies for the treatment of gout (e.g., the use of a xanthine oxidase inhibitor and a uricosuric agent for hyperuricemia or the use of multiple drugs for acute gout attacks). The safety and cost-effectiveness of new agents for gout, including inhibitors of urate transporter 1 and purine nucleoside phosphorylase, which are under development, and interleukin-1 antagonists, require further study. Preliminary data have suggested the potential efficacy of the interleukin-1 antagonists canakinumab and rilonacept for flare prophylaxis.54

Risk factors for recurrent gout flares may differ from those that predispose patients to the initial attack. Whether factors that lower serum urate levels over the long term in persons without gout would have similar effects with short-term or episodic exposure in persons with gout requires clarification.

It is not known to what level urate can be safely lowered. Observational data have suggested associations between low urate levels and an increased risk of Parkinson’s disease,50 but it is unclear whether the low levels are a cause or consequence of disease. The optimal duration of urate-lowering therapy is also uncertain, and such therapy is recommended indefinitely at this time. In one study, the withdrawal of urate-lowering therapy was associated with prolonged symptom-free intervals (3 to 4 years) in a cohort of 89 patients after long-term control of urate levels (<7 mg per deciliter), flares, and tophi resolution,51 but further study is needed.

Finally, the concept of asymptomatic hyperuricemia as a benign condition is being challenged. Experimental data suggest that urate may contribute to vascular remodeling and hypertension, although it remains uncertain whether urate plays a causal role in cardiovascular disease.9

GUIDELINES

The American College of Rheumatology is currently developing guidelines for the management of gout. The European League against Rheumatism and the British Society for Rheumatology have published guidelines for the evaluation and management of gout on the basis of trial data (when available) and expert consensus.23,24,42 The present recommendations are largely consistent with these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

In patients presenting with suspected gout, the diagnosis should be confirmed by examination of synovial fluid or tophus aspirate for monosodium urate crystals. Management should be tailored to the stage of disease and coexisting illnesses. The patient who is described in the vignette has crystal-proven gout, with multiple attacks and a serum urate level of more than 6 mg per deciliter despite receipt of allopurinol at a dose of 300 mg per day.
Since his renal function is normal, the allopurinol dose should be increased (e.g., 100-mg increments every 2 to 4 weeks until the target urate level is reached), with monitoring of renal function and serum urate levels and assessment for potential adverse reactions. Colchicine prophylaxis (0.6 mg once or twice daily) is reasonable while the dose of allopurinol is escalated. If target serum urate levels cannot be achieved or if the patient has serious side effects at higher allopurinol doses, the use of either febuxostat or a uricosuric agent is another option, given his normal renal function.

The patient should understand that the intake of alcohol and an excessive amount of meat or seafood and sugar-sweetened drinks may contribute to elevated urate levels and should be minimized. He should be advised to keep well hydrated and to lose weight. Associated cardiovascular risk factors should be identified and treated. Although the use of hydrochlorothiazide may contribute to the increased urate level, I would not necessarily change that medication if it is effectively controlling his blood pressure, and I would advise him to take the diuretic consistently, since intermittent use may precipitate flares. The addition of losartan for the hypertension might be considered. He should be advised to maintain his urate-lowering regimen during flares, which can be managed with colchicine. Follow-up is necessary to ensure that appropriate serum urate levels are achieved and maintained and to monitor the patient for adverse effects.

Dr. Neogi reports serving as a core expert panel leader for the American College of Rheumatology Gout Treatment Guidelines. I declare no other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

I thank Drs. Saralynn Allaire, Hyon Choi, and Yuqing Zhang for their review of the first draft of the manuscript and Dr. Robert Terkeltaub for his review of an earlier version of Figure 1.

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