Pharmacists' assessment and management of acute and chronic gout

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GOUT IS AN INFLAMMATORY DISEASE CAUSED BY the accumulation of monosodium urate crystals in joints and soft tissues as a result of chronic hyperuricemia.¹ The prevalence of gout has been increasing and, as recently as 2012, affected 3.8% of Canadian adults.² Uncontrolled gout can lead to complications including tophi (large deposits of urate crystals in joints and bone), urolithiasis (formation of stones in the bladder or urinary tract) and progression of chronic kidney disease (CKD). The associated pain, discomfort and potential lost days of work can result in increased morbidity and decreased quality of life, and it can place higher costs on the health care system.^{1,3} Recent observational studies suggest that patients' lack of knowledge about the disease and treatment options, combined with health care practitioners' lack of familiarity with clinical practice guidelines, represent significant barriers to optimal gout treatment.⁴⁻⁶ In addition, most patients with gout are elderly and may have comorbidities, such as cardiovascular disease and/or renal impairment, which can further complicate treatment choices for both acute and chronic gout.^{7,8}

High serum uric acid (SUA) levels increase the chance of monosodium urate crystallization and raise a patient's risk of gout flare.^{1,9,10} The American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) guidelines provide recommendations for treating those with high serum uric acid (SUA) with urate-lowering therapy (ULT) to achieve a target SUA level of less than 360 $\mu\text{mol/L}$ and less than 300 $\mu\text{mol/L}$ for those with severe gout (ACR, based on consensus of experts; EULAR, based

on descriptive or case studies).^{1,9,11} Conversely, new guidelines from the American College of Physicians (ACP) encourage a treat-to-avoid-symptom strategy and avoid testing SUA levels altogether. They state that there are not enough data at this time to support the benefits of a treat-to-target strategy outweighing risks of increased monitoring and intensifying medication.¹² Additional clinical data are necessary to determine the most appropriate treatment strategy (i.e., treat to target vs treat to avoid symptoms), and currently, there is a discordance between guideline recommendations. In light of this uncertainty, patient and provider values, preferences and experience have more weight in the choice between treatment strategies.

Regardless of the treatment strategy, pharmacists are able to collaborate in the optimization of gout management. A randomized controlled trial by Goldfien et al.⁴ assessed the effect of a pharmacist intervention on achievement of a SUA level below 360 $\mu\text{mol/L}$. Adult patients (mean age 59 years) diagnosed with gout and with a recent SUA level above 416 $\mu\text{mol/L}$ or no SUA level within the past 12 months were included in the trial. The intervention consisted of a pharmacist who ordered laboratory tests, initiated and adjusted ULT medications based on SUA levels using a preauthorized protocol. Significantly more patients achieved the SUA target level after 26 weeks compared to control group, 35% vs 13% (95% confidence interval [CI], 20%-52% and 4%-27%, respectively) (relative risk [RR], 2.8; 95% CI, 1.1-7.1). The authors concluded that pharmacist involvement in an ongoing monitoring program in

the primary care setting for patients with gout may help maintain lower SUA levels long term and suggested a potential reduced cost of gout management. In addition to optimizing medications, pharmacists are available to educate and empower patients to assume self-management of the disease.

This practice tool is intended to provide guidance to pharmacists in assessing and managing both acute and chronic gout. The tool also provides a review of the management of drug-disease interactions associated with this population. The most recent guidelines from the ACR, ACP and EULAR for the management of gout were consulted. A literature search of Ovid MEDLINE, PubMed and International Pharmaceutical Abstracts was conducted from August to November 2016 to identify articles to review using various combinations of the following terms: *gout, hyperuricemia, management, pharmacist, pharmacy, urate lowering therapy, colchicine and allopurinol*. The authors also referred to the latest Canadian product monographs for colchicine, allopurinol and febuxostat for additional product information. Data were summarized in tables and organized alphabetically when no literature was available to support use of one class of medication over another.

Management of acute and chronic gout therapy

Case—Part I

An obese 52-year-old man presents with an acute attack of a new diagnosis of gout. He has just come from the walk-in clinic with a prescription for indomethacin 50 mg orally as needed for pain. Medical history includes hypertension (average, 128/80 mmHg on treatment), type 2 diabetes and stage 3 chronic kidney disease (Cl_{Cr} = 48 mL/min).

Anti-inflammatory medication should be initiated within 24 hours of symptom onset for acute gout attacks. There is no direct comparative evidence differentiating colchicine, corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs) as the preferred first-line option. Choice of therapy should be individualized based on severity, chronic gout management, comorbid conditions and concomitant medications and tailored based on response to treatment (Table 1).^{9,11} Combination therapy with colchicine and NSAID or colchicine and

corticosteroids may be considered in patients with severe pain and/or multiarticular involvement.⁹ Chronic management of gout may include initiation of ULT with xanthine-oxidase inhibitors (i.e., allopurinol or febuxostat) in patients at high risk of complications or recurrent attacks (see Figure 1). Discordance exists between guidelines in regards to starting ULT during an acute attack, due to lack of clear evidence pertaining to efficacy and safety. The EULAR and ACP guidelines give no clear recommendation; however, based on expert opinion, the ACR guidelines indicate that ULT can be started during an acute attack as long as the appropriate medication for the acute attack is being used.¹ Prophylaxis with low-dose NSAID or colchicine should be continued for 3 to 6 months, as initiation of ULT may increase risk of gout attack.¹¹ Pharmacists should clarify the treatment strategy (i.e., treat to target vs empiric SUA lowering) with the patient and health care team.

Along with initiation of acute gout medications, general lifestyle measures should be encouraged to manage modifiable gout risk factors and comorbidities (Table 2).^{1,9,11} Education on the causes of gout, common risk factors for gout and role of acute therapy and ULT medications may help promote patient adherence and facilitate shared decision making.^{1,11,12}

Special populations

A large proportion of patients with gout have a contraindication or comorbidity that warrants caution with at least one of the medications available for gout treatment.⁷ Keenan et al.⁷ found that approximately 50% of patients (n = 575) in their observational study had at least one contraindication to colchicine use. Despite this, more than 30% of these patients were prescribed colchicine.⁷ Almost all drug-disease interactions with gout medications can be managed through dose adjustment or use of an alternate agent.^{1,9,11}

Populations most susceptible to adverse effects of gout medications include patients with CKD, heart failure (HF) and uncontrolled hypertension (Table 3), where NSAIDs should be avoided. Elderly patients are potentially the most complicated to treat due to the increased incidence of renal dysfunction, cardiovascular comorbidities and risk of drug interactions.^{8,18} When making treatment decisions, individual risks must be weighed against the benefit of the medication to the patient, considering

TABLE 1 Acute and chronic management of gout^{1,9,11,13,14}

Acute management		
Medication	Dose	Rationale/comment
Colchicine	Low-dose regimen: 1.2 mg orally now, then 0.6 mg 1 hour later, then in 12 hours start 0.6 mg orally daily or twice daily until gout attack is resolved (e.g., 3 to 10 days)	<ul style="list-style-type: none"> - Within 12 hours of symptom onset, low-dose regimen has similar efficacy to high-dose regimen (4.8 mg over 6 hours) and less diarrhea (76.9% vs 23.0%) - Contact prescribers regarding prescriptions for high-dose regimens (e.g., greater than 0.6 mg twice daily) to recommend lower dosing strategy - Consider other pharmacologic strategies if concomitant use of CYP3A4- and/or P-glycoprotein-inhibiting medications (e.g., clarithromycin, itraconazole, digoxin). Can increase colchicine concentrations and risk of toxicity - Toxic: Doses exceeding 0.5 mg/kg
Corticosteroids	Prednisone 0.5 mg/kg per day (effective dose: 20-50 mg/day) orally × 5-10 days	<ul style="list-style-type: none"> - Consider intra-articular injection if large joint involvement - Can cause hyperglycemia—avoid use in patients with diabetes - Monitor for adverse effects (e.g., insomnia, GI upset, agitation) - Tapers may be used in patients with complicated gout or those on corticosteroid therapy for longer than 2 weeks
NSAIDs	Naproxen 500 mg orally twice daily for 4-5 days or indomethacin 50 mg 3 times per day	<ul style="list-style-type: none"> - Scheduled use until pain subsides or benefits no longer outweigh risks - No single agent better than any other within the class - Consider COX2 inhibitor (e.g., celecoxib) or addition of a proton pump inhibitor if high risk of GI bleeds
Chronic management		
Allopurinol	Initiate at 100 mg orally daily Increase by 100 mg/day every 2-5 weeks until achieved target SUA level less than 360 µmol/L (less than 300 µmol/L if tophi present)*	<ul style="list-style-type: none"> - First-line ULT medication due to known safety, proven efficacy and low cost - Adverse effect: skin rash (1%-3%)
Febuxostat	80 mg orally daily	<ul style="list-style-type: none"> - Recommended if symptomatic gout and allergic to or unable to reach target SUA levels or desired symptom control with allopurinol - Third-party coverage may vary by insurer and by provincial drug plan

*If using a treat-to-target strategy

COX2, cyclooxygenase-2; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; SUA, serum uric acid; ULT, urate-lowering therapy.

comorbidities, medical history and concomitant medications.^{1,11,18}

Case—Part II

An NSAID is not the most appropriate drug therapy considering the patient's history of hypertension and CKD. Medical history of diabetes

suggests that corticosteroids would not be the first-line agent. You call the physician and suggest a low-dose colchicine regimen. You also provide your patient with education on gout and its management, as well as lifestyle measures to address his personal risk factors (e.g., obesity, hypertension and diabetes) (see Table 3).

FIGURE 1 Stepwise approach to management of gout **Case—Part III**

The patient returns twice in the next 6 months complaining of gout attacks. As your patient has frequent gout attacks and qualifies for ULT, you phone the physician and recommend initiation of allopurinol 100 mg daily.

Reassessing gout therapy

For patients on long-term ULT, there is insufficient evidence to recommend routine discontinuation for patients with infrequent or remote

history of gout attacks on long-term allopurinol.¹² Consider discontinuation in patients below SUA target if using a treat-to-target strategy, asymptomatic for 5 years or in whom benefits no longer outweigh the risks of therapy.¹² Suggestions for therapy reassessment are indicated in Table 4.

Gout is becoming the most common form of inflammatory arthritis in Canada.² Although a number of pharmacologic options exist for the acute and chronic management of the disease,

TABLE 2 Risk factors for gout and lifestyle modifications^{1,9,11,15-17}

Modifiable risk factors	Nonmodifiable risk factors
<ul style="list-style-type: none"> - Obesity - Diet <ul style="list-style-type: none"> o Rich in purines (e.g., organ meats) o Excessive alcohol intake (males: more than 2 drinks/day; females: more than 1 drink/day) o Large intake of high-fructose corn syrup - Comorbid conditions: diabetes, dyslipidemia, hypertension, smoking - Medications that can increase uric acid levels and risk of gout attack (e.g., loop diuretics, niacin, cyclosporine, tacrolimus) 	<ul style="list-style-type: none"> - Men older than 30 years - Women older than 50 years - History of urolithiasis - Renal dysfunction
Lifestyle modifications	
<ul style="list-style-type: none"> - Regular exercise to promote weight loss if applicable - Balanced diet <ul style="list-style-type: none"> o Avoid large, fatty meals and diets rich in meat and seafood o Avoid excessive alcohol intake - Control of comorbid conditions 	

TABLE 3 Management of acute and chronic gout in special populations^{1,3,9,11,19-25}

Comorbidity	Preferred therapy	Comment
Renal impairment (Cl_{Cr} less than 90 mL/min)	Corticosteroids	<ul style="list-style-type: none"> - NSAIDs: Avoid. May result in acute kidney injury, hypertension and/or sodium and fluid retention - Colchicine: Consider monitoring for increases in SCr if using long term for prophylaxis
	Colchicine	
	<ul style="list-style-type: none"> - Consider dose reduction if Cl_{Cr} 30-89 mL/min (e.g., 0.6 mg daily or every other day for prophylaxis¹⁹) 	
	Allopurinol <ul style="list-style-type: none"> - Initiate at 50 mg/day in those with Cl_{Cr} less than 30 mL/min - Increase the dose by 50 mg/day every 2 to 5 weeks until target achieved if using treat to target 	<ul style="list-style-type: none"> - May increase doses past 300 mg/day with increased monitoring of SCr (e.g., monthly until stable SCr, then every 3 to 6 months) - Low initial dose may reduce risk of early gout flares and hypersensitivity
	Febuxostat <ul style="list-style-type: none"> - No dose adjustment in mild to moderate renal impairment (Cl_{Cr} 30-90 mL/min) 	<ul style="list-style-type: none"> - No data for Cl_{Cr} less than 30 mL/min; use is not recommended
Cardiovascular comorbidities	Colchicine	<ul style="list-style-type: none"> - NSAIDs: Avoid. Increased risk of HF exacerbations and worsening hypertension. Increased risk of CV events (MI, stroke, death) depending on the agent and individual CV risk - Corticosteroids: Avoid in HF. Increased risk of HF exacerbations and hypertensive episodes

Cl_{Cr}, creatinine clearance; CV, cardiovascular; HF, heart failure; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug; SCr, serum creatinine.

TABLE 4 Gout therapy reassessment^{1,9,11,15}

When to reassess?	<ul style="list-style-type: none"> - Frequent gout attacks despite ongoing ULT - Long-term acute analgesic/anti-inflammatory medications with no ULT - Significant change to health status and/or comorbidities (e.g., recent MI, new diagnosis of diabetes or CKD)
What to look at?	<ul style="list-style-type: none"> - SUA: Target less than 360 µmol/L (or less than 300 µmol/L if tophi present)* - SCr and Cl_{Cr}: Determine level of renal function and need to dose adjust medications - Medication list: Review for potential drug interactions (e.g., CYP3A4 inhibitors and colchicine)
What to do?	<ul style="list-style-type: none"> - If appropriate, initiate (or increase) ULT (see Table 1) - Measure SUA levels every 2-5 weeks during titration of ULT and every 6 months after target SUA is achieved or as often as practical

*If using a treat-to-target strategy.

CKD, chronic kidney disease; Cl_{Cr}, creatinine clearance; MI, myocardial infarction; SCr, serum creatinine; SUA, serum uric acid; ULT, urate-lowering therapy.

considerations in terms of age, renal function, comorbidities and drug interactions complicate therapy. There is evidence that pharmacists can play a significant role in optimizing the care of

this population. Through patient education and collaboration with prescribers, pharmacists may help to decrease the overall disease burden associated with gout. ■

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References

1. Khanna D, Fitzgerald J, Khanna P. 2012 American College of rheumatology guidelines for management of gout. Part 1: Systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res* 2012;64(10):1431-46.
2. Rai SK. Population-based epidemiologic studies of gout in British Columbia, Canada. Unpublished thesis/dissertation. Vancouver: University of British Columbia; 2016. Available: <https://oc-web.library.ubc.ca/cIRcle/collections/ubctheses/24/items/1.0314140> (accessed Jan. 28, 2017).
3. Kim Y, Shin S, Kim K. Effect of urate lowering therapy on renal disease progression in hyperuricemic patients with chronic kidney disease. *J Rheumatol* 2015;42(11):2143-48.
4. Goldfien R, Pressman A, Jacobson A, et al. A pharmacist-staffed, virtual gout management clinic for achieving target serum uric acid levels: a randomized clinical trial. *Perm J* 2016;20(3):18-23.
5. Nasser-Ghods N, Harrold LR. Overcoming adherence issues and other barriers to optimal care in gout. *Curr Opin Rheumatol* 2015;27(2):134-8.
6. Kuo C, Grainge M, Mallen C, et al. Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study. *Ann Rheum Dis* 2015;74(4):661-7.
7. Keenan R, O'Brien W, Lee K, et al. Prevalence of contraindications and prescription of pharmacologic therapies for gout. *Am J Med* 2011;124(2):155-63.

8. Stamp L, Jordan S. The challenges of gout management in the elderly. *Drugs Aging* 2011;28(8):591-608.
9. Richette P, Doherty M, Pascual E, et al. 2016 updated EULAR evidence-based recommendation for the management of gout. *Ann Rheum Dis* 2017;76:29-42.
10. Perez-Ruiz F. Treating to target: a strategy to cure gout. *Rheumatology* 2009;48:ii9-ii14.
11. Khanna D, Khanna P, Fitzgerald J. 2012 American College of Rheumatology guidelines for management of gout. Part 2: Therapy and anti-inflammatory prophylaxis of acute gouty arthritis. *Arthritis Care Res* 2012;64(10):1447-61.
12. Qaseem A, Harris R, Forciea M, et al. Management of acute and recurrent gout: a clinical practice guideline from the American College of Physicians. *Ann Intern Med* 2017;166:58-68.
13. Terkeltaub R, Furst D, Bennett K, et al. High versus low dosing of oral colchicine for early acute gout flare: twenty-four hour outcome of the first multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison colchicine study. *Arthritis Rheum* 2010;62(4): 1060-8.
14. Rostom A, Moayeddi P, Hunt R; Canadian Association of Gastroenterology Consensus Group. Canadian consensus guidelines on long-term nonsteroidal anti-inflammatory drug therapy and the need for gastroprotection: benefits versus risks. *Aliment Pharmacol Ther* 2009;29(5):481-96.
15. Kiltz U, Smolen J, Bardin T. Treat-to-target (T2T) recommendations for gout. *Ann Rheum Dis* 2017;76:632-8.
16. Krishnan E, Svendsen K, Neaton J; MRFIT Research Group. Long-term cardiovascular mortality among middle-aged men with gout. *Arch Intern Med* 2008;168(10): 1104-10.
17. Underwood M. Sugary drinks, fruit, and increased risk of gout. *BMJ* 2008;336(7639):285-6.
18. Fravel M, Ernst M. Management of gout in the older adult. *Am J Geriatr Pharmacother* 2011;9(5):271-85.
19. Kapur S, Kraag G. Gout and hyperuricemia: compendium of therapeutic choices. 2015. Available: <https://www.e-therapeutics.ca/search> (accessed Aug. 13, 2016).
20. Euro-Pharm International Canada. Colchicine tablets USP [product monograph]. 2013 November. Montréal, QC.
21. Apotex. Allopurinol tablets, USP [product monograph]. 2010. Toronto, ON.
22. Takeda Canada. Uloric: febuxostat tablets [product monograph]. 2016. Oakville, ON.
23. Clinical Resource. Managing NSAID Risks. Pharmacist's Letter/Prescriber's Letter. 2016 December.
24. Givertz M, Anstrom K, Redfield M, et al. Effect of xanthine oxidase inhibition in hyperuricemic heart failure patients. *Circulation* 2015;131(20):1763-71.
25. National Kidney Foundation. A clinical update on gout: optimizing care for patients with chronic kidney disease. National Kidney Foundation, Inc. 2014. Available: <https://www.kidney.org/content/gout-clinical-bulletin> (accessed Jan. 15, 2017).