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POSITION PAPER

Discordant American College of Physicians and international rheumatology guidelines for gout management: consensus statement of the Gout, Hyperuricemia and Crystal-Associated Disease Network (G-CAN)

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Abstract | In November 2016, the American College of Physicians (ACP) published a clinical practice guideline on the management of acute and recurrent gout. This guideline differs substantially from the latest guidelines generated by the American College of Rheumatology (ACR), European League Against Rheumatism (EULAR) and 3e (Evidence, Expertise, Exchange) Initiative, despite reviewing largely the same body of evidence. The Gout, Hyperuricemia and Crystal-Associated Disease Network (G-CAN) convened an expert panel to review the methodology and conclusions of these four sets of guidelines and examine possible reasons for discordance between them. The G-CAN position, presented here, is that the fundamental pathophysiological knowledge underlying gout care, and evidence from clinical experience and clinical trials, supports a treat-to-target approach for gout aimed at lowering serum urate levels to below the saturation threshold at which monosodium urate crystals form. This practice, which is truly evidence-based and promotes the steady reduction in tissue urate crystal deposits, is promoted by the ACR, EULAR and 3e Initiative recommendations. By contrast, the ACP does not provide a clear recommendation for urate-lowering therapy (ULT) for patients with frequent, recurrent flares or those with tophi, nor does it recommend monitoring serum urate levels of patients prescribed ULT. Results from emerging clinical trials that have gout symptoms as the primary end point are expected to resolve this debate for all clinicians in the near term future.

Hyperuricaemia
Elevation of circulating level of urate.

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Gout is a common form of inflammatory arthritis for which highly effective treatments are available, yet the management of this disease is frequently suboptimal. Gout often presents as an acute 'flare' of painful inflammation that typically resolves within a week or two, but can be difficult to control in some instances, can negatively affect quality of life, can be costly to experience and treat, and can warrant hospital admission. If gout-associated hyperuricaemia is inadequately treated, gout flares often progress in frequency and severity, and a state of chronic, inflammatory arthritis can supervene, leading to continuous pain, decreased joint function, and permanent joint damage.

Guidelines for the management of gout are intended to help physicians select the most effective course of treatment and to educate patients in order to ensure adherence. In November 2016, the American College of Physicians (ACP) published a clinical practice guideline for the management of acute and recurrent gout[1]. Despite evaluating similar evidence, the ACP clinical practice guideline differs substantially from all other gout management guidelines issued by major international rheumatology groups in the past 5 years, including the 2012 American College of Rheumatology (ACR) guidelines[2,3], 2014 3e (Evidence, Expertise, Exchange) Initiative recommendations[4] and 2016 European League

Uricase
An enzyme that degrades uric acid to allantoin and water.

Tophi
Foreign body granuloma-like structures that form in reaction to large accumulations of monosodium urate crystals.

Pegloticase
A recombinant PEGylated uricase used as a therapy option in severe cases of gout.

Against Rheumatism evidence-based recommendations[5] (TABLE 1). This Consensus Statement summarizes the view of the Gout, Hyperuricemia and Crystal-Associated Disease Network (G-CAN) regarding these discordant gout management guidelines.

The authors of this consensus document are an international expert panel of rheumatologists with clinical and research interests in gout and hyperuricaemia. This paper presents the rationale for the G-CAN position on guidelines for the management of gout; provides the G-CAN interpretion of, and specific responses to, the ACP recommendations; and examines the basis for the discordance between the ACP guidelines and those produced by the various rheumatology groups. This paper also discusses prospects for closing the gap between these recommendations by further clinical studies in the field.

Methods

The G-CAN panel, selected by the G-CAN Directorship (President (R.T.) and Vice President (H.K.C.)), consisted of a small cross-section of international gout experts from among active members of the organization (T.B., M.D., P.R., K.G.S. and L.K.S.) and G-CAN board members (H.K.C, N.D. F.L., R.T. and A.K.S.). Each panel member independently assessed the core aspects of the ACP gout guideline and were asked to vote on whether to accept or reject each ACP guideline recommendation. Collective assessments of the ACP guideline were tabulated and recorded by R.T. and H.K.C., and are presented in TABLE 1, which also compares the individual ACP gout recommendations to prior recommendations by rheumatology (ACR, EULAR and 3e Initiative) panels.

Rationale for the G-CAN position

Unlike many other diseases, the particularly lucid understanding of the pathophysiology of gout provides a remarkably clear rationale for treatments that address the underlying cause of the disorder (FIG. 1). The cardinal pathophysiologic aspects of gout, which inform effective management (and thus underlie the G-CAN position), are outlined in this section.

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Gout, a chronic disease with acute exacerbations, is driven by monosodium urate (MSU) crystal deposition caused by hyperuricaemia; without serum levels of uric acid above the saturation point (and the resulting MSU crystals), gout does not exist — as is the case in non-primate mammals, which have uricase and thus serum urate levels ~10 times lower than that of humans.

MSU crystals form *in vitro* at saturation concentrations (>6.8 mg/dl (>405 µmol/l) at pH 7.0 and a temperature of 37 °C, and >6.0 mg/dl (>360 µmol/l) at pH 7.0 and a temperature of 35 °C)[6,7]. Pathology, imaging and intervention studies have demonstrated that the clinical manifestations of gout occur because of the host inflammatory response to deposited MSU crystals[8–13], exemplified by acute gout flares[10]. The acute flares characteristically present as an exquisitely painful inflammatory arthritis[14], which leads to severe limitation of activity, poor quality of life and work disability[15]. These events are highly consequential to the health-related quality of life of affected patients, and also have added socioeconomic effects[16].

Tophi are a cardinal feature of gout[12]. The tophus can discharge and ulcerate, restrict joint movement, cause joint damage (including bone erosion) and have a severe impact on quality of life[15,17,18]. In the majority of patients, tophi are the consequence of years of untreated or undertreated hyperuricaemia[19,20].

Urate-lowering drugs, including allopurinol, when successfully employed to reduce the serum urate level to below saturation concentrations, promote dissolution of MSU crystals in the joints (including on the surface of articular cartilage, in other joint tissues, and in synovial fluid)[21,22] (FIG. 1) and, therefore, removal of the root cause of disease. The velocity of crystal dissolution is dependent on the urate concentration[23,24]. Long-term studies have shown the clear clinical benefit of treating patients with urate-lowering therapy (ULT) to reach target serum urate levels, with complete suppression of flares, regression of tophi and improvement in quality of life over time[21,25–30]. Bone erosions due to tophaceous gout also have been shown to heal after expedited eradication of tissue MSU crystal deposits by use of pegloticase therapy[31]. The treat-to-target ULT approach involves gradually increasing the dose of ULT to achieve the target serum urate concentration, which needs to be monitored periodically. Anti-inflammatory prophylaxis of acute gout flares is commonly employed adjunctively in the early phase of treat-to-target ULT, as remodelling of tissue MSU crystal deposits by effective ULT can induce a temporary increase in the frequency of acute gout flares.

Assessment of the ACP recommendations

The G-CAN position on each of the four ACP recommendations for the management of gout is summarized in TABLE 2. Although the G-CAN panel agreed with some of the recommendations in whole or in part, there are some fundamental issues the panel concluded to be flaws in the ACP clinical practice guideline, specifically concerning the lack of clear advice about ULT for patients with recurrent flares, ULT for patients with tophi, and serum urate level monitoring for patients on ULT.

Table 1 | **Summary of recent major gout guidelines methods and conclusions**

Feature	ACR (2012)[2,3]	3e Initiative (2014)[4]	EULAR (2016)[5]	ACP (2016)[1]
Background of authors	• Rheumatologists (23) • Primary care physicians (3) • Nephrologist (1) • Patient advocate (1) • Medical trainees (5)	Rheumatologists (474)	• Rheumatologists (15) • Radiologist (1) • Primary care physicians (2) • Research trainee (1) • Patient advocates (2) • Non-physician methodologists (3)	• Primary care physicians (3) Other decision-making committee members: • primary care physicians (9), • rheumatologist (1), • pulmonologist (1)
Authors' location(s)	International (USA, Europe, New Zealand)	Multinational (14 countries)	Europe (12 European nations)	USA
Methodology	Followed the RAND/UCLA method, involving systematic literature review, the use of a core expert panel to develop case scenarios, preparation of a scientific evidence report (published in part) and a task force panel vote on the case scenarios, with subsequent ACR peer-review prior to publication	Ten clinically relevant questions were selected via a modified Delphi voting process, followed by systematic literature reviews, evaluation and grading of evidence, international scientific committee agreement, and Delphi process to produce the final recommendations	Standardized operating procedure endorsed by EULAR for the elaboration, evaluation, dissemination and implementation of recommendations. This process included systematic literature review, evaluation and grading of evidence, panel agreement and peer-review	Evidence-based approach as advocated by the Institute of Medicine, and using GRADE guideline methods, which assessed benefits, risks and burden. The process included systematic evidence review, grading of evidence, committee agreement and peer-review. RCT and clinical outcomes were emphasized, rather than the outcome of lower serum urate (which was viewed as a surrogate outcome)
Management guidance provided				
Acute gout (NSAIDs, corticosteroids, colchicine)	+	+	+	+
Use of low-dose colchicine for acute gout	+	+	+	+
Comorbidity screening	+	+	+	No clear advice
ULT indicated for patients with frequent flares	+	Not assessed	+	No clear advice
ULT indicated for patients with palpable tophi	+	+	+	No clear advice
Low starting dose of allopurinol, with dose escalation	+	+	+	No clear advice
Treat-to-target ULT	+	+	+	No clear advice
Monitoring of serum urate levels	+	+	+	No clear advice
Pegloticase	+	+	+	Not assessed

3e, Evidence, Expertise, Exchange; ACP, American College of Physicians; ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RAND/UCLA, Research and Development/University of California at Los Angeles; RCT, randomized controlled trial; ULT, urate-lowering therapy.

ACP indications for ULT

The G-CAN panel unanimously rejected the ACP recommendation against initiating long-term ULT in most patients after a first gout attack or in patients with fewer than two acute gout flares annually. In particular, the G-CAN panel expressed concern about the lack of clarity of this recommendation, as it applies specifically to patients with a first gout flare or infrequent acute gout flares without consideration of other indications for ULT besides acute gout flares (such as the presence of a palpable tophus (or tophi) or chronic synovitis due to gout). The ACP clinical practice guideline does not provide a clear recommendation about management of patients with gout and one or more palpable tophi, in stark contrast to rheumatology guidelines that recommend palpable gouty tophi as a definite indication for ULT. The G-CAN panel also expressed concern that this ACP recommendation ignores aspects of recurrent acute gout flares other than flare frequency (such as severity, responsiveness to therapy, number of joints affected, functional impairment or the need for emergency medical care and/or hospital admission), and also ignores the presence of comorbidities (which narrows the options for treatment of acute gout flares)

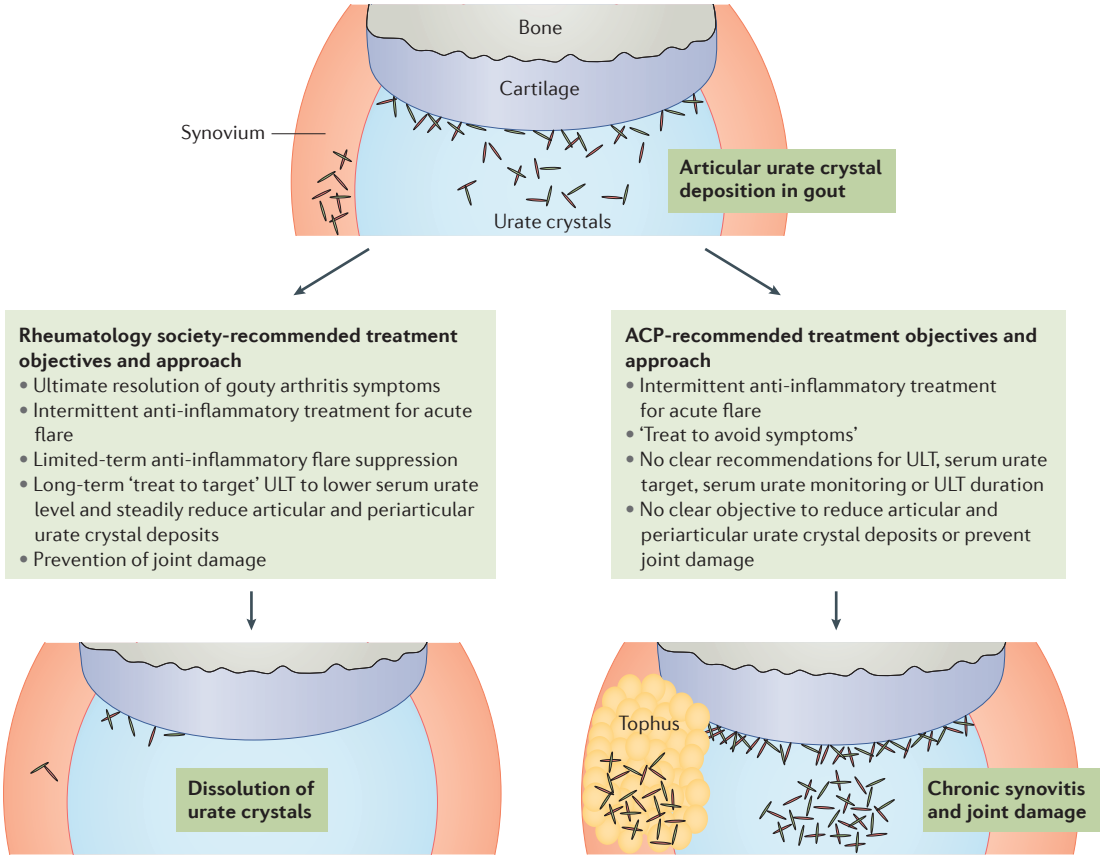

Figure 1 | **Schematic comparison of expected clinical-pathologic outcomes of gout from guidelines for the management of gout.** The schematic illustrates the main emphases of major guidelines for gout produced by rheumatology societies (left side of figure), compared with the American College of Physicians (ACP) guideline (right side), arising from differing perceptions of gout. Guidelines developed by expert rheumatology societies take into account gout pathophysiology and clinical course, generally seeing gout as a chronic condition with acute inflammatory flares and the frequent tendency, due largely to under-treatment of hyperuricaemia (rather than 'treat to target' urate-lowering therapy (ULT)), to progress to the development of palpable tophi, chronic synovitis and joint damage (including bone erosion). By contrast, the ACP guidance to 'treat to avoid symptoms' reflects a perception of gout as primarily an intermittent disorder of acute inflammation.

and presence of marked hyperuricaemia unlikely to resolve adequately with conservative treatment. This assessment by the G-CAN panel is in line with most rheumatology society guidelines, which advocate long-term ULT for specific patient scenarios[2], including in early gout[5].

ACP information for patients

The G-CAN expert panel unanimously agreed that patients should be given full information on their condition, available treatment options and the expected benefits and possible adverse effects of individual treatments, as laid out in ACP recommendation 4. However, this principle applies to every medical encounter and is as relevant to treatments for acute attacks as it is for long-term ULT. The G-CAN expert panel unanimously agreed that recommendation 4 lacks any clear advice concerning ULT and anti-inflammatory flare prophylaxis, and that this recommendation lacks sufficient specificity to provide practical guidance to clinicians.

Other issues

Several other important clinical practice points were not addressed by the ACP clinical practice guideline, including the time to commencement and duration of ULT. Notably, the ACP clinical practice guideline does not advocate either regular serum urate measurements or dose titration of ULT to reduce the serum urate level to a specific target; by contrast, the ACR, EULAR and 3e Initiative guidelines all recommend the treat-to-target approach for ULT. Moreover, the ACP guideline emphasized the risks of ULT, yet core elements of allopurinol risk management aimed at limiting allopurinol hypersensitivity syndrome (AHS) were omitted. Specifically, the ACP guideline did not adequately address either the strategy to avoid AHS by starting with a low initial dose of allopurinol before titrating upwards[32] or the valuable role of screening for *HLA-B*5801* to identify patients at markedly elevated risk of AHS within multiple well-defined ethnic and racial groups (such as Han Chinese, Korean, Thai, East Indian and African-American populations)[33,34]. G-CAN also supports screening for

Allopurinol hypersensitivity syndrome
A syndrome of severe hypersensitivity to allopurinol that is commonly associated with one or more of fever, rash, eosinophilia and multi-system organ damage and that has a high mortality rate.

Table 2 | **Summary of the G-CAN position on the ACP recommendations for gout management**[1]

ACP recommendation	Strength and basis of recommendation	G-CAN assessment
1. ACP recommends that clinicians choose corticosteroids, NSAIDs or colchicine to treat patients with acute gout	Strong recommendation, high-quality evidence	The G-CAN gout expert panel unanimously supported this recommendation
2. ACP recommends that clinicians use low-dose colchicine when using colchicine to treat acute gout	Strong recommendation, moderate-quality evidence	The G-CAN gout expert panel unanimously supported this recommendation
3. ACP recommends against initiating long-term ULT in most patients after a first gout attack or in patients with infrequent attacks (that is, <2 acute gout flares per year)	Strong recommendation, moderate-quality evidence	The G-CAN gout expert panel unanimously rejected this recommendation
4. ACP recommends that clinicians discuss benefits, harms, costs and individual preferences with patients before initiating ULT, including concomitant prophylaxis, in patients with recurrent gout attacks	Strong recommendation, moderate-quality evidence	The G-CAN expert panel unanimously agreed that patients should be given full information as laid out in this recommendation, but expressed concern that this recommendation lacks any clear advice concerning ULT and anti-inflammatory flare prophylaxis, and lacks sufficient specificity to provide practical guidance to clinicians

The ACP clinical practice guideline made four recommendations for the management of acute and recurrent gout, and were aimed at 'all clinicians' (REF. 1). ACP, American College of Physicians; G-CAN, Gout, Hyperuricemia and Crystal-Associated Disease Network; ULT, urate-lowering therapy.

comorbid conditions that are frequently associated with gout, such as chronic kidney disease and cardiovascular disease, as advocated by the 2012 ACR gout guidelines[2], but not mentioned in the ACP guidelines.

The G-CAN panel is very concerned that the ACP clinical practice guideline, using methodology that attempts to balance the benefits of therapy with risks and burden[35], does not provide a clear recommendation for ULT in patients with recurrent attacks. Most patients achieve effective urate-lowering with a single agent when individually dose-titrated[36]. Moreover, urate-lowering drugs are generally safer and better tolerated than frequently used anti-inflammatory drugs such as colchicine, NSAIDs or high-dose corticosteroids, particularly so in patients with comorbidities commonly associated with gout, including chronic kidney disease, hypertension, type 2 diabetes mellitus and ischemic heart disease[37–39].

Clearly, including guidance on these aspects of practice within the ACP clinical practice guideline would have had a major effect on the safety and effectiveness of management of gout in primary care.

Reasons for discordance

The discordance between the ACP guideline and the various rheumatology panel guidelines (including the G-CAN assessment) cannot simply be ascribed to differences in general methodologic approaches taken by these groups[40,41]. Many discordances extend from differences in the interpretation of the literature with respect to ULT.

Clinical benefits of successful ULT

The G-CAN position is that the medical literature overwhelmingly supports the concept that clinical benefits are observed in patients with gout who achieve long-term serum urate lowering to sub-saturation concentrations. Specifically, all open-label extension studies of randomized controlled trials (RCTs) of orally administered ULT have shown improvement in flares, tophus size and other clinically important outcomes over periods of >1 year of therapy[27–30]. Furthermore, RCTs of pegloticase, a parenteral agent which promotes profound serum urate lowering and rapid clearance of MSU crystals, clearly demonstrate that intensive lowering of serum urate levels leads to reductions in flares and tophus size and to improvements in health-related quality of life and activity limitation, even over a 6-month treatment period[42,43]. In addition, those patients with a durable response to pegloticase (with serum urate level <6 mg/dl) have an enduring improvement in all relevant clinical outcomes[29,30]. The ACP Clinical Guidelines Committee decided not to consider the pegloticase clinical trial data because pegloticase was considered an agent unlikely to be prescribed by primary care physicians[44]. Nevertheless, the high level of evidence showing a clear clinical benefit of this highly potent urate-lowering agent should help confirm the therapeutic principle of the treat-to-target ULT approach, already universally adopted by rheumatology guidelines.

Interpreting limits of past ULT trials

A guiding doctrine of the ACP guideline was that retrospective studies and even RCTs that used the decline in serum urate level to a pre-stipulated target as an indirect, surrogate outcome, rather than demonstrating the improvement in a clinical outcome such as reduction in frequency of acute gout flares during the randomized phase of an RCT, were insufficient data for the standard of evidence-based guidelines defined by the Institute of Medicine (since renamed the National Academy of Medicine)[40]. G-CAN, like the ACP and rheumatology society panels, recognized that no long-term (that is, more than 12 months' duration) RCTs have specifically examined the treat-to-target approach to gout management. Moreover, the G-CAN expert panel, and a largely separate panel of rheumatologists[45], agree with the ACP panel that evidence is still lacking for reduction in frequency of acute gout flares by oral ULT measures during the randomized, controlled phase of clinical trials. However, G-CAN strongly supports the treat-to-target

ULT strategy, as the various rheumatology groups have consistently done, on the basis of the breadth of available evidence, including long-term, open-label extensions of oral ULT RCTs, prospective observational studies, and the trials of intensive ULT with pegloticase[45]. By comparison, the hierarchical approach to evidence used by the ACP panel placed unbending emphasis on the randomized controlled phases of clinical trials. The G-CAN panel's assessment is that the ACP approach was probably too rigid for the evidence in gout, where the collective data provide very high confidence for disease-modifying effects of effective serum urate-lowering, consistent with the remarkably well-understood pathophysiology of gout (FIG. 1).

Different approaches, different conclusions

The ACP reached evidence-based health care decisions using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach, which assessed benefits, risks and burden and which places a much higher emphasis on clinical outcomes that patients are directly aware of (for example, symptom severity or quality of life) than on surrogate outcomes (such as serum uric acid level in gout). By contrast, the rheumatology panels perceived the uric acid burden — reflected not only by hyperuricaemia, but also by chronic, progressive tissue inflammation and joint damage — as a crucial aspect of the disease burden in gout. As such, differences between the final conclusions of the ACP and the rheumatology panels (TABLE 1) reflect major differences in the perceived importance of periodic symptoms and of the chronic disease burden in gout.

Merits of evidence-based practice approach

The G-CAN position is that the multiple scenarios and clinical phenotypes of gout, an understanding of rational treatment directed to gout pathophysiology, and the current state of evidence in gout, make a three-pillared evidence-based practice (EBP) approach more appropriate[41]. The principles of this approach are that treatment is based on the best available research evidence, the expertise of the clinician as applied to the diagnosis and overall health status of each patient coupled with assessment of the risk–benefit balance of potential therapies, and the preferences and values of the patient. This EBP approach was taken by the ACR, EULAR and 3e Initiative in construction of their respective gout management recommendations, but not by the ACP (TABLE 1). As a consequence, several fundamental aspects of EBP gout management covered in the major rheumatology guidelines are not clearly addressed in the ACP recommendations, namely the use of ULT in patients with recurrent gout attacks, ULT in patients with gout and one or more palpable tophi, and monitoring patients taking ULT.

The decision-making in the ACP clinical practice guideline is difficult to comprehend in part because their systematic review acknowledges that moderate-to-high quality evidence shows that ULT reduces the risk of acute gout attacks after 1 year of follow-up[1]. This finding is based on data from studies that employed a fixed dose of ULT (as opposed to the recommended upwards titration of ULT dose), which would have underestimated clinical benefit[46–48]. Furthermore, when using oral ULT at the low doses frequently prescribed in clinical practice, MSU crystal dissolution can be slow, particularly in patients with prolonged disease duration or if the serum urate level is not intensively lowered[22]. For this reason, the clinical benefits of oral ULT for flares, chronic synovitis or tophi often take many months or several years after treatment is initiated. Substantial benefits with respect to clinical end points for gout have been reported in publications of the longer-duration open-label studies of oral ULT, beyond the randomized phase of clinical trials[27,28,49–51]. In the end, these data did not sway the ACP when considering the value of long-term oral ULT.

Consequences of guideline discordance

The ACP clinical practice guideline[1], which is stated to be intended for 'all clinicians', instead reflects an apparent chasm within the medical community (FIG. 1) regarding the perception of patients with gout — a chasm that is multifactorial and longstanding. Clinicians in primary care and acute care settings might treat patients for acute 'attack' symptoms, which could reinforce a view of gout as an intermittent and, in many cases, self-inflicted disease. In many cases, clinicians can deem gout a lesser priority than comorbid issues. Gout-specific patient education and gout outcomes correspondingly suffer. By contrast, rheumatologists generally see gout as a chronic, very often progressive, condition that has acute flares but a tendency to progress. With gout increasing in prevalence, and with so many patients being older and affected by multiple comorbidities, gout is becoming more challenging to manage, as indicated (in part) by a marked increase in severe acute gout flares requiring hospitalization[52,53].

The G-CAN position is that the ACP's stance on ULT, essentially that ULT can be prescribed without urate monitoring or optimization of ULT dose to achieve urate concentrations below the saturation threshold of soluble urate[1], is particularly troubling as it could help perpetuate the common practice pattern of underdosing of ULT[54]. Prescribing a drug without consideration of an individual patient's response to the specific intent of the medication (in this case, ULT without monitoring urate levels) lacks logic or clinical sense. This practice would be analogous to prescribing anti-hypertensive medication without measuring blood pressure or hypoglycaemic therapy without measuring HbA1c (glycated haemoglobin) levels. Moreover, adherence is a major issue for patients who have commenced ULT[55], and serum urate testing enables direct, objective assessment of adherence to ULT. The results of such testing often prompt the clinician to initiate further discussions with the patient about gout management, including ULT, as advocated in the ACP clinical practice guideline[36].

The ACP clinical practice guideline focus on high-value care is laudable. The authors noted that "an estimated $1 billion is spent annually on ambulatory care for gout, largely on treatments and prescription medications"[1]. At present, however, most of the costs of treating gout relate to management of acute flares and

poorly controlled disease[56–58] and most patients with gout do not receive ULT or regular serum urate testing[54,59]. Rheumatology opinion, shared by the G-CAN panel, is that the benefits of this test in guiding individualized patient care far outweigh its small costs (and indeed far outweigh the direct and indirect costs of poorly controlled gout)[2]. Similarly, allopurinol, the most widely used ULT drug, has been available for more than 60 years, and the cost of generic allopurinol is low. A 2014 cost-effectiveness analysis incorporating all available evidence found that allopurinol therapy is cost-saving, particularly when using an up-titration approach to dosing[60].

The G-CAN position is that widespread adoption of the ACP clinical practice guideline, with its focus on episodic acute gout therapy and lack of clear recommendations regarding indications for ULT or serum urate monitoring, has the potential to perpetuate clinical (therapeutic) inertia[61], leading to a greater burden of poorly managed gout and rising costs to affected patients and society.

G-CAN also is highly concerned that failure to provide clear indications for ULT or advocate serum urate monitoring ignores available data for the allure of so-called 'absence of evidence', which we know not to be 'evidence of absence' to support long-term ULT in gout.

Another apprehension of the G-CAN panel is that the ACP clinical practice guideline could promote excessive use of NSAIDs, colchicine and prednisone for long-term 'symptom suppression' in gout, due to lack of attention to core disease pathophysiology.

Addressing the evidence gaps

The results of completed and new RCTs of urate-lowering agents and strategies that will be published over the next few years are eagerly awaited. One example is a 2-year double-blind, placebo-controlled trial of titrated treat-to-target ULT in patients with early gout that includes radiographic analyses of bone erosion, MRI imaging of bone erosion, bone marrow oedema and synovitis, and flares[62]. Another example is a controlled trial, conducted in Nottingham, UK, comparing primary care management of gout with nurse-led titration of ULT according to the treat-to-target ULT strategy recommended by rheumatology society guidelines[63].

Furthermore, the ACP and the G-CAN panel are in agreement that well-designed, prospective, controlled clinical trials are needed to clarify several issues around ULT. Questions to be resolved concern determining the effect of ULT on adverse health outcomes beyond acute gout, the duration of ULT, and the optimum serum urate target for reduction of symptoms, comorbidities and minimal harms (in addition to confirming the clinical efficacy and safety of the treat-to-target approach). Studies are also needed to establish the risk of recurrent acute gout attacks, symptomatic chronic gout, comorbidities and disability following a first attack of gout, in order to inform clinicians and patients considering the potential costs, benefits and harms of commencing ULT or delaying treatment until further attacks have occurred.

Conclusions

Guidelines for the management of gout developed by the ACP primary care in comparison to the rheumatology society gout guidelines groups (namely ACR, EULAR and 3e Initiative) are discordant, despite assessment of largely the same evidence, with the exception of trials of pegloticase. Other published assessments of the ACP guideline for gout[64,65] and of the value of treat-to-target ULT[56,66] buttress the opinions of the G-CAN panel presented in this paper. However, controversy persists, since support has also been voiced for the ACP guidelines[67]. The G-CAN panel believes that emerging and future studies will enable alignment and consensus in guidelines for primary care physicians, rheumatologists and other specialists involved in management of patients with gout.

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Author contributions
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N.D., F.L., H.K.C. and R.T. were co-authors of the 2012 ACR guidelines for management of gout; M.D., F.L., A.K.S., P.R. and T.B. were co-authors of the 2016 updated EULAR evidence-based recommendations for the management of gout; and N.D., L.K.S. and M.D. were rheumatologist participants in the development of the 2014 international 3e Initiative recommendations for gout management. N.D. declares that she has received research grant support from AstraZeneca, has serverd as a speaker for Menarini, Ardea/AstraZeneca, and Takeda, and acted as a consultant to AstraZeneca, Crealta, Cymabay, Fonterra, Pfizer, and Takeda. T.B. declares that he has received research support from AstraZeneca, Ipsen and Menarini and has served as a consultant and/or speaker for Astellas, AstraZeneca, Cymabay, Grunenthal, Ipsen, Menarini, Novartis, Savient, Sobi and Takeda. M.D. declares that he has received research grant support from AstraZeneca and has served as a consultant to AstraZeneca, Grunenthal, Nordic Biosciences and Roche. F.L. has served as an adviser to Ardea, AstraZeneca, Grunenthal, Ipsen Pharma, Menarini and Novartis, received educational grants from Ardea, AstraZeneca, Grunenthal, Ipsen Pharma, Mayoly-Spindler, Menarini, Novartis, Société Française de Rhumatologie and SOBI, and acted as speaker for AstraZeneca, Ipsen Pharma, Mayoly-Spindler, Menarini and Novartis. P.R. declares that he has acted as a consultant for AstraZeneca, Grunenthal, Ipsen Pharma/Menarini and Savient. K.G.S. declares that he has served as a consultant and paid investigator for Ardea/AstraZeneca, Horizon, SOBI and Takeda. L.K.S. declares that she has received research support from Ardea/AstraZeneca and is a member of the Rheumatology Subcommittee of the Pharmaceutical Management Agency of New Zealand. A.K.S. declares that he has received honoraria and acted as a consultant for AstraZeneca, Menarini and SOBI in relation to gout studies. H.K.C. declares that he has served as a consultant for Ardea/AstraZeneca and Takeda. R.T. declares that he has received research support from Ardea/Astra-Zeneca and has served as a consultant for Aequus, Ardea/AstraZeneca, CymaBay, Horizon, ProteoThera, Relburn, Revive, Selecta and SOBI. The G-CAN organization is supported, in an arms-length manner, by unrestricted grants from a number of pharmaceutical companies: AstraZeneca, CymaBay, Horizon, Selecta, SOBI, Takeda and Teijin. G-CAN members have demonstrated research expertise in gout, hyperuricaemia and/or crystal arthropathy. A.K.S., F.L., H.K.C. and R.T. are G-CAN Board members.

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