

EULAR EVIDENCE BASED RECOMMENDATIONS FOR GOUT

- Part II Management

REPORT OF A TASK FORCE OF THE EULAR STANDING COMMITTEE FOR
INTERNATIONAL CLINICAL STUDIES INCLUDING THERAPEUTICS (ESCISIT)

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ABSTRACT

Objectives: To develop evidence based recommendations for the management of gout.

Methods: The multidisciplinary guideline development group comprised 19 rheumatologists and one evidence based medicine expert representing 13 European countries. Key propositions regarding management were generated using a Delphi consensus approach. Research evidence was searched systematically for each proposition. Where possible, effect size (ES), number needed to treat (NNT), relative risk (RR), odds ratio and incremental cost-effectiveness ratio (ICER) were calculated. The quality of evidence was categorised according to the level of evidence. The strength of recommendation (SOR) was assessed using the EULAR visual analogue and ordinal scales.

Results: Twelve key propositions were generated after 3 Delphi rounds. Propositions included both non-pharmacological and pharmacological treatments and addressed symptomatic control of acute gout, urate lowering therapy (ULT) and prophylaxis of acute attacks. The SOR for each proposition varied according to the research evidence and expert opinion. It was recognised that optimal management requires both non-pharmacological and pharmacological treatment and needs to be tailored to the individual. The importance of patient education, modification of adverse lifestyle (weight loss if obese; reduced alcohol consumption, especially beer; low animal purine diet) and treatment of associated comorbidity and risk factors (e.g., hypertension, hyperlipidaemia, hyperglycaemia) were emphasised. Recommended drugs for acute attacks were oral NSAID (a convenient option in the absence of contraindications), oral colchicine (ES=0.87, 95%CI 0.25, 1.50) or joint aspiration and injection of corticosteroid. Because of the toxicity of high dose colchicine, especially diarrhoea (RR=8.38, 95%CI 1.14, 61.38), lower doses (e.g., 0.5 mg three times daily) should be considered. ULT is indicated in patients with recurrent acute attacks, arthropathy, tophi or radiographic changes of gout. The aim of ULT is to promote crystal dissolution and prevent crystal formation – this is achieved by maintaining the serum uric acid below the saturation point for urate crystals (6 mg/dl or 360 μ mol/l). Allopurinol was confirmed as effective long-term ULT (ES=1.39, 95%CI 0.78, 2.01) with a dose-dependent effect; it should be started at a low dose (e.g., 100mg daily) and increased by 100 mg every 2-4 weeks if required. If allopurinol toxicity occurs, options include other xanthine oxidase inhibitors, allopurinol desensitisation (only for mild rash, not severe toxicity) or a uricosuric. The uricosurics probenecid and sulphinpyrazone are contra-indicated in patients with urolithiasis or reduced renal function and are less effective than allopurinol. The uricosuric benzbromarone on a head to head comparison is more effective than allopurinol (ES=1.50, 95%CI 0.76, 2.24) and can be used in patients with mild-moderate renal insufficiency but carries a risk of hepatotoxicity. When gout associates with use of diuretics stop the diuretic if possible; in patients with hypertension or hyperlipidaemia consider use of losartan and fenofibrate respectively because of their modest uricosuric effects (fenofibrate ES=1.13, 95%CI 0.18, 2.07). For prophylaxis against acute attacks either colchicine 0.5-1 mg daily (NNT=2, 95%CI 1, 6) and/or an NSAID (with gastroprotection if indicated) are recommended.

Conclusion: Twelve key recommendations for management of gout were developed using a combination of research-based evidence and expert consensus. The evidence was evaluated and the SOR provided for each proposition.

Key words: EULAR, gout, guidelines, treatment

INTRODUCTION

Despite reasonable understanding of its pathogenesis and the availability of effective treatment, gout is often misdiagnosed or diagnosed late in its clinical course and even when correctly diagnosed treatment is often suboptimal. For example, a recent cross-sectional study showed that the prevalence of pre-defined mismanagement of gout (no medicine, analgesic alone, or urate lowering therapy without prophylaxis) was over two times greater with physician management than with patient self-management (1). The risk was adjusted by age, gender, education, comorbidity and number of attacks and was especially high in the first year of disease (relative risk 3.8, $p < 0.005$) (1). Other medication errors associated with gout appear to be widespread, especially with respect to colchicine (2). Therefore, the European League Against Rheumatism (EULAR) Gout Task Force was formed to develop evidence based recommendations on aspects relating both to the diagnosis and to the management of gout. This paper reports the second part of the project – evidence based recommendations for the management of gout.

METHODS

Participants

The same multidisciplinary guideline development group as for Diagnosis (3) undertook the project. The objectives were [1] to agree key propositions related to the management of gout; [2] to identify and critically appraise research evidence for the effectiveness and cost-effectiveness of the relevant treatments; and [3] to generate recommendations based on a combination of the best available evidence and expert opinion.

Experts' consensus

Up to 10 propositions related to key clinical aspects in the management of gout were formulated employing the identical Delphi technique and process as that used to develop propositions for Diagnosis (3). However, because the first 10 selected propositions did not address all treatment modalities (specifically oral NSAIDs for acute gout) it was agreed that the final number of propositions should be extended to include the next 4 propositions with the highest votes in the final Delphi Round (Round 3) and, as with the first 10 propositions, to permit amalgamation or rephrasing, if required.

Systematic literature search

The same systematic search of the literature published between January 1945 and January 2005 was undertaken for both diagnosis and management of gout (for details see (3) and its Appendix 1). Following the Delphi exercise a proposition-specific search, using the same search strategy as for Diagnosis (3), was undertaken.

Inclusion/exclusion criteria

Studies retrieved from the literature search were included only if they were concerned with clinical aspects of gout. Studies of hyperuricaemia were included only if they measured uric acid as an outcome for management of gout. The main focus of interest was on systematic reviews/meta-analyses, randomised controlled trials (RCTs)/controlled trials, uncontrolled trials (e.g., one group intervention, quasi-experimental study, etc), cohort studies, case control studies, cross-sectional studies and economic evaluations. Case reports, review articles, editorials, commentaries were excluded. Studies on healthy subjects or animals were also excluded.

Level of evidence

Evidence for efficacy was categorised according to the design characteristics of available studies using an established hierarchy (4) (Table 1). Questions were answered using the best available evidence. For example, if a question on the effect of an intervention could be answered by level Ia evidence (i.e., systematic review of RCTs) then studies of a weaker design (RCT, level Ib) were not reviewed. Results of the latest systematic review were used if there was more than one systematic review for the same question. However, questions on adverse effects were answered using both RCTs and observational studies irrespective of gout since RCTs are not necessarily the best way to assess adverse effects and gout may not be the target condition for which the side effects of a particular intervention are assessed. Questions of cost effectiveness were answered according to the outcome measure of effectiveness. For example, if the effectiveness was measured as “number of attacks prevented” or “quality of life years (QALYs) gained” only studies for gout were eligible. If the effectiveness was measured as “adverse events averted” any study for the proposed intervention was included.

Table 1. Level of evidence

Ia – meta-analysis of randomised controlled trials
Ib – randomised controlled trial
IIa – controlled study without randomisation
IIb – quasi-experimental study
III – non-experimental descriptive studies, such as comparative, correlation, and case-control studies
IV – expert committee reports or opinion or clinical experience of respected authorities, or both

Studies with direct evidence were considered first. If no direct evidence was available, studies with indirect evidence were examined. For example, evidence for weight loss in the management of gout was sought first but if none was available evidence for overweight/obesity as a risk factor for gout was examined.

Outcome measures

1. Efficacy

For treatment efficacy, effect size (ES) compared with placebo or active control as specified within the propositions was calculated for continuous outcomes such as the reduction of serum uric acid (SUA). ES is the standard mean difference, i.e., the mean difference between a treatment and a control group divided by the standard deviation of the difference. It is therefore free of units and comparable across interventions. Clinically, an ES of 0.2 is considered small, 0.5 is moderate, and greater than 0.8 is large (5). For dichotomous data, such as the percentage of patients with acute attacks or more than 50% pain relief, the number needed to treat (NNT) was estimated (6). The NNT is the estimated number of patients that need to be treated to either

prevent an unwanted effect, such as an acute attack, or to obtain a wanted outcome such as pain relief; therefore the smaller the NNT the better the treatment effect. The 95% confidence interval (CI) of the NNT was calculated using Altman's method (7). The dose-response relationship between drug treatment and effects was analysed using a linearity test. Individual patient data were obtained from the original reports for this analysis and the results were pooled as appropriate. A multiple regression model was used to adjust co-variables such as concomitant treatment, age, gender, length of the disease and duration of the treatment.

2. Adverse effects

For adverse effects, the relative risk (RR) was calculated from RCTs or cohort studies for the incident risk and from cross-sectional studies for prevalent risk, whereas the odds ratio (OR) was calculated from case control studies (8). Both present how many times more likely (or less likely) a subject who is exposed to the medication/intervention has adverse events than a subject who is not exposed. RR or OR = 1 indicates no increased risk, whereas RR or OR >1 or <1 indicates an increased or decreased risk respectively.

3. Economic evaluation

For economic evaluations, the incremental cost-effectiveness ratio (ICER) was calculated as the difference in cost between two treatments divided by their difference in effectiveness. When available, QALYs were used for the measurement of effectiveness, otherwise disease specific outcomes such as the reduction in SUA were used. In addition, study design, comparator, perspective, time horizon, discounting, total costs and effectiveness were critically appraised.

The outcomes are presented with the point estimate (e.g., mean) and 95% CI unless otherwise stated. Statistical pooling was undertaken as appropriate (9) when there was more than one estimate for the same outcome using the same study design and a systematic review was not available.

Ratification of propositions and strength of recommendation

Following the literature search on each proposition and the initial drafting of the manuscript, the Task Force met to discuss each proposition. At this stage the wording (but not the content) of propositions could be adjusted to better clarify specific statements and to reduce any ambiguity if the majority of the Task Force agreed. Two of the 14 propositions were amalgamated at this stage since they addressed the same intervention topic. The eventual 12 propositions were then ratified and a final adjusted manuscript was approved by all Task Force members. As for Diagnosis (3) the strength of each recommendation (SOR) was graded using the EULAR A-E ordinal scale (A=fully recommended, B=strongly recommended, C=moderately recommended, D=weakly recommended, and E=not recommended) and 0-100 mm visual analogue scale (VAS)(4) taking into account both the research evidence (efficacy, safety and cost-effectiveness) and their clinical expertise (logistics, patient perceived acceptance and tolerability). The mean VAS and 95% CI and the percentage of strongly to fully recommended (A-B) were calculated for each proposition.

Future research agenda

Up to 10 propositions for the future research agenda related to management of gout were formulated employing the identical Delphi technique and process as that used to develop the future research agenda for Diagnosis (3).

RESULTS

General literature search

The general literature search yielded 3316 hits (MEDLINE 1111, Old MEDLINE 6, EMBASE 820, CINAHL 17, Science Citation Index 1172, Cochrane 190). After deleting duplications 2352 remained. Of these, only 181 studies met inclusion criteria, including 83 for diagnosis(3), 86 for management and 12 for both. Figure 1 shows the treatment modalities addressed in the 98 studies related to management; 86% of publications related to pharmacological therapies (e.g., NSAIDs and coxibs, colchicine, steroid, allopurinol, febuxostat, uricosuric agents, losartan, fenofibrate); 3% to herbal remedies; and 11% to non-pharmacological therapies (e.g., ice, diet). Although a broad range of treatments have been used to manage gout only those agreed using the Delphi consensus approach were assessed. Figure 2 shows the categories of evidence according to study designs for the 98 management-related studies.

Expert's opinion approach

The experts were informed of the results of the general literature search and then the Delphi exercise was undertaken by email. The first round produced 146 propositions for management. After 3 anonymous Delphi rounds 14 propositions were voted in; 2 of these were amalgamated since they related to the same topic, leaving 12 final propositions (Table 2). The wording of 8 of these (propositions numbers 1, 2, 3, 5, 7, 9, 11, 12) were adjusted for clarification of key points at the final meeting.

Assessment of propositions

The proposition-specific search was then undertaken and the results were merged with the results from the general search to form the basis of evidence for the evaluation of each proposition or modalities within each proposition. The following propositions are grouped by topic (general, management of acute attacks, urate lowering therapies, prophylaxis of acute attacks) with no weighting according to order.

Table 2. Propositions and strength of recommendation (SOR) - order based on topic (general, acute management and chronic management)

Proposition	SOR (95% CI)	
	VAS 100 A+B%	
1. Optimal treatment of gout requires both non-pharmacological and pharmacological modalities and should be tailored according to: <ul style="list-style-type: none"> a) specific risk factors (levels of serum urate, previous attacks, radiographic signs) b) clinical phase (acute/recurrent gout, intercritical gout, and chronic tophaceous gout) c) general risk factors (age, gender, obesity, alcohol consumption, urate elevating drugs, drug interactions and comorbidity) 	96 (93, 98)	100
2. Patient education and appropriate lifestyle advice regarding weight loss if obese, diet, and reduced alcohol (especially beer) are core aspects of management.	95 (91, 99)	100
3. Associated comorbidity and risk factors such as hyperlipidaemia, hypertension, hyperglycaemia, obesity and smoking should be addressed as an important part of the management of gout.	91 (86, 97)	94
4. Oral colchicine and/or NSAID are first line agents for systemic treatment of acute attacks. In the absence of contraindications an NSAID is a convenient and well accepted option.	94 (91, 98)	100
5. High doses of colchicines lead to side effects and low doses (for example 0.5 mg three times daily) may be sufficient for some patients with acute gout.	83 (74, 92)	82
6. Intra-articular aspiration and injection of long-acting steroid is an effective and safe treatment for an acute attack.	80 (73, 87)	88
7. Urate lowering therapy is indicated in patients with recurrent acute attacks, arthropathy, tophi or radiographic changes of gout.	97 (95, 99)	100
8. The therapeutic goal of urate lowering therapy is to promote crystal dissolution and prevent crystal formation. This is achieved by maintaining the serum uric acid below the saturation point for monosodium urate ($\leq 360 \mu\text{mol/l}$)	91 (86, 96)	100
9. Allopurinol is an appropriate long-term urate lowering therapy. It should be started at a low dose (e.g., 100mg daily) and increased by 100 mg every 2-4 weeks if required. The dose must be adjusted in those with renal impairment. If allopurinol toxicity occurs, options include other xanthine oxidase inhibitors, a uricosuric agent or allopurinol desensitisation (the latter only in cases of mild rash).	91 (88, 95)	100
10. Uricosuric agents such as probenecid and sulphinpyrazone can be used as an alternative to allopurinol in patients with normal renal function but are relatively contra-indicated in patients with urolithiasis. Benzbromarone can be used in patients with mild to moderate renal insufficiency on a named patient basis but carries a small risk of hepatotoxicity.	87 (81, 92)	94
11. Prophylaxis against acute attacks during the first months of urate	90 (86, 95)	100

lowering therapy can be achieved by colchicine (0.5 – 1mg daily) and/or an NSAID (with gastro-protection if indicated).		
12. When gout associates with diuretic therapy, stop the diuretic if possible. For hypertension and hyperlipidemia consider use of losartan and fenofibrate respectively (both have modest uricosuric effects).	88 (82, 94)	100

VAS: visual analogue scale (0-100 mm, 0=not recommended at all, 100=fully recommended)

CI: confidence interval

A+B%: percentage of strongly to fully recommended, based on the EULAR ordinal scale

(A=fully recommended, B=strongly recommended, C=moderately recommended, D=weakly recommended, and E=not recommended).

1. Optimal treatment of gout requires both non-pharmacological and pharmacological modalities and should be tailored according to:

- a) specific risk factors (levels of serum urate, previous attacks, radiographic signs)***
- b) clinical phase (acute/recurrent gout, intercritical gout, and chronic tophaceous gout)***
- c) general risk factors (age, gender, obesity, alcohol consumption, urate elevating drugs, drug interactions and comorbidity)***

Strength of recommendation (95%CI): 96 (93, 98)

It is apparent that the management strategy will vary according to the clinical presentation. Asymptomatic hyperuricaemia does not equate to gout and currently there is no evidence to support treatment of isolated hyperuricaemia with urate lowering therapy (ULT), though advice regarding lifestyle and treatment of associated comorbidity may be warranted. Acute gout is extremely painful so a key management objective will be rapid relief of symptoms. By contrast, assessment of a patient during an intercritical period or when chronic tophaceous gout is already present should lead to the development of an individualised long-term management plan where the central objective is to reduce tissue levels of uric acid to dissolve existing crystals and to prevent further monosodium urate crystal formation (i.e., “cure”).

The advice given to a patient and the selection and dose of drug therapy will vary according to a number of factors. For example, the severity of hyperuricaemia and clinical gout, the presence of comorbidity (e.g., avoidance of uricosuric drugs in nephrolithiasis; dose adjustment of most drugs with renal impairment and old age), risk factors (e.g., weight reduction if obese, reduction in beer and alcohol if excessive) and patient age, gender and other demographic features. One cohort study compared long-term treatment effects (10 years) of urate lowering drugs between patients with chronic gout, grouped according to the presence or absence of tophi and/or radiographic damage of affected joints, but found no significant difference between groups since the treatment was effective for all types of patients (10). The dose requirement of allopurinol, used with prophylactic oral colchicine, has been shown to vary between patients in terms of achieving a target SUA level (uncontrolled trials) (11;12) and treatment response varies according to comorbidity such as hypertension and renal impairment (RCTs) (13;14).

For long-term treatment of chronic gout, it has been well documented that either non-pharmacological treatments such as weight loss (15) and low purine diet (16), or pharmacological treatments such as allopurinol (11-13) are effective. The combination of pharmacological and non-pharmacological therapies (including patient information) appears rational. For example, given that both are effective (Table 3), oral colchicine and topical ice packs may be combined to enhance the treatment effect for the relief of pain and other signs of inflammation (17;18), although the two treatments have not yet been investigated in the same RCT using a factorial design. As non-pharmacological treatments are usually less harmful and less costly, they should always be considered either alone or in combination with pharmacological treatments, especially for long-term management. With drug therapy, care must be taken to avoid increased toxicity through drug interaction, such as from colchicine with erythromycin (or cyclosporin) (19;20).

In conclusion, practitioners should always strive for optimal treatment. There is evidence that the combination of non-pharmacological and pharmacological treatments is more effective than individual monotherapy (level Ib). When managing gout it is important to take into account the clinical phase (level Ib), the serum uric acid level and the frequency of previous attacks (level Ib) and associated comorbidity and risk factors (level Ib).

Table 3. Evidence of efficacy - effect size (ES) and number needed to treat (NNT)

Comparison	Outcome	Level of evidence [¶]	ES (95% CI)	NNT (95% CI)	Reference
Acute management					
Colchicine vs. placebo	Pain VAS ↓ ≥50% pain relief	Ib, 48 hours	0.87 (0.25, 1.50)	- 3 (2, 11)	(17)
	Overall clinical improvement		- 1.21 (0.61, 1.92)	-	
Ice+colchicine + prednisone vs. colchicine + prednisone	Pain VAS ↓	Ib, 7 days	1.15 (0.15, 2.12)	-	(18)
NSAIDs	≥50% pain relief	Ib, 4 days	-	3 (1, 14)	(21)
Prophylaxis and chronic management					
Colchicine vs. placebo	≥ 1 attack prevented	Ib, 3 months	-	2 (1, 6)	(22)
Colchicine + probenecid vs. probenecid	Attacks/patient /month	Ib, 6 months	0.74 (0.08, 1.40)	-	(23)
Azapropazone vs. allopurinol	≥ 1 attack prevented	IIa, 6 months	-	7 (4, 17)	(24)
	SUA↓		0.00 (-0.26, 0.26)	-	
Allopurinol + colchicine vs. colchicines	≥ 1 attack prevented	Ib, 1 year	-	9 (-9, 3)	(25)
	SUA↓		1.39 (0.78, 2.01)	-	
Benzbromarone vs. allopurinol in patients with renal impairment	SUA↓	Ib, 2 years	1.50 (0.76, 2.24)	3 (2, 15)	(14)
Fenofibrate vs. placebo	SUA↓ Triglyceride↓	Ib, 6 weeks	1.13, (0.18, 2.07) 0.95 (0.02, 1.87)	-	(26)

[¶]See Table 1 for definitions

CI: confidence interval; VAS: visual analogue scale; -: not available; NSAIDs: non-steroidal anti-inflammatory drugs; SUA: serum uric acid

2. Patient education and appropriate lifestyle advice regarding weight loss if obese, diet, and reduced alcohol (especially beer) are core aspects of management.

Strength of recommendation (95%CI): 95 (91, 99)

There is a strong belief that patient education and information access is an important determinant of outcome, especially in relation to successful lifestyle alteration and adherence to long-term ULT. However, the benefits of education, either alone or as adjuvant therapy, have not been specifically studied in the management of gout.

Two cohort reports have shown that purine-rich food (meat and shellfish) and alcohol consumption (especially beer and spirits) both associate with gout (27;28). The RR was 1.51 (95% CI 1.17, 1.95) for seafood, 1.17 (95% CI 1.11, 1.22) for alcohol per 10 g increase, 1.49 (95% CI 1.32, 1.70) for beer per serving per day; and 1.15 (95% CI 1.04, 1.28) for spirit per serving per day; dairy products were inversely associated with SUA. The risks were independent of other major risk factors such as age, gender, body mass index (BMI), diuretic use, hypertension and renal failure. However, wine consumption did not increase SUA levels (27;28). A small uncontrolled weight loss trial in 13 patients with gout demonstrated that successful weight loss reduced SUA from 570 $\mu\text{mol/l}$ (95% CI 520, 620) at baseline to 470 $\mu\text{mol/l}$ (95% CI 420, 520) after 16 weeks of treatment (15). The reduction in SUA occurred earlier (in 4-weeks) with a specific low purine diet in a larger uncontrolled trial of 305 hyperuricaemic patients (16). Since weight loss was also observed in this trial further studies are required to determine whether diet and weight loss have independent effects.

In conclusion, both low animal purine foods and weight loss reduce SUA in patients with gout (level IIb). Alcohol, particularly beer, is an independent risk factor for gout (level III). Therefore life style advice that addresses obesity, dietary purine intake and the amount and type of alcohol consumption should be considered in the management of gout. There is general agreement, but no research data, that education on gout and its treatment improves outcome either directly (e.g., improved self-efficacy) or indirectly through effects on adherence and lifestyle alteration (level IV).

3. Associated comorbidity and risk factors such as hyperlipidaemia, hypertension, hyperglycaemia, obesity and smoking should be addressed as an important part of the management of gout.

Strength of recommendation (95% CI): 91 (86, 97)

It is well established that raised SUA associates with hyperlipidaemia (29-31), hypertension (32;33), diabetes and insulin resistance (34;35) and obesity (15;36) – conditions that are collectively termed the “metabolic syndrome”. Therefore it would seem obvious good practice to consider these associated conditions when a patient presents with gout. Although there is no direct evidence to support smoking as a risk factor for gout, smoking strongly associates with alcohol consumption (37) which may in turn associate with gout. Importantly, however, smoking is an important modifiable risk factor for cardiac and peripheral vascular disease, as well as many other diseases, and therefore needs to be addressed in a holistic approach to patient management.

Apart from the need to detect and treat these co-morbidities in their own right, there is RCT evidence that some of the treatments for these co-morbidities and risk factors may also benefit gout. For example, losartan and fenofibrate both reduce SUA as well as reducing blood pressure and serum lipids respectively (26;38-43).

In conclusion, recognition and treatment of co-morbidities and risk factors should be considered as a part of gout management and global patient care, and may benefit both the comorbidity and gout (level Ib).

4. **Oral colchicine and/or NSAID are first line agents for systemic treatment of acute gout. In the absence of contraindications an NSAID is a convenient and well accepted option.**

Strength of recommendation (95% CI): 94 (91, 98)

One small (43 patients) and short term (48 hours) open RCT showed that oral colchicine is effective for acute gout (17). This placebo controlled trial examined colchicine at the loading dose of 1 mg followed by 0.5 mg every 2 hours until development of toxicity (nausea, vomiting or diarrhoea). The ES was 0.87 (95%CI 0.25, 1.50) for pain relief and 1.21 (95%CI 0.61, 1.92) for overall clinical improvement. The NNT for at least 50% pain relief was 3 (95%CI 2, 11); that is, 1 out of 3 patients would experience that degree of pain relief, should colchicine be used. However, all 22 patients in the treatment group had nausea, vomiting or diarrhoea, whereas only 5 of 21 patients in the placebo group experienced these problems (RR=4.20, 95%CI 1.95, 9.03) (Table 4).

Table 4. Evidence of safety – relative risk (RR[†]) and 95% confidence interval (CI)

Comparison	Adverse events	RR (95%CI)	Evidence	Reference
Colchicine vs. placebo	Nausea, vomiting or diarrhoea	4.20 (1.95, 9.03)	RCT, 48 hours	(17)
	Diarrhoea	8.38 (1.14, 61.38)	RCT, 3 months	(22)
Colchicine+probenecid vs. probenecid	Any	1.69 (0.95, 3.00)	RCT, 6 months	(23)
	GI	1.69 (0.95, 3.00)	RCT, 6 months	(23)
	Diarrhoea	1.35 (0.60, 3.04)	RCT, 6 months	(23)
	Nausea/vomiting	1.98 (0.85, 4.60)	RCT, 6 months	(23)
Azapropazone vs. allopurinol	Acute duodenal ulcer	2.20 (0.09, 53.59)	CT, 6 months	(24)
	Nausea/dyspepsia	51.68 (3.21, 833.18)	CT, 6 months	(24)
	Diarrhoea/abdominal pain	2.20 (0.23, 20.85)	CT, 6 months	(24)
	Headache/dizziness	1.10 (0.19, 6.47)	CT, 6 months	(24)
Allopurinol allopurinol vs. placebo adjusted dose vs. unadjusted dose exposure vs. non-exposure	Creatinine clearance	Reduced, p>0.02	RCT, 2.5 years	(13)
	Rash, AHS, FPE, LCV	1.96 (0.34, 11.92)	Cohort study,	(44)
	Cataract	1.82 (1.18, 2.80)	Case control	(45)

[†] RR: relative risk between treatment group and control group. RR =1: no difference. RR>1: more risk with treatment. RR<1: more risk with control.
RCT: randomised controlled trial; CT: controlled trial

AHS: allopurinol hypersensitivity syndrome; FPE: fixed pigmented drug eruption; LCV: leucocytoclastic vasculitis

Intravenous (IV) colchicine has been used for treating acute gout. However, the potential for severe and even fatal toxicity from this route of administration causes great concern (46;47).

NSAIDs have a different mechanism of action but similar symptomatic effects to oral colchicine. One RCT has shown tenoxicam to be more effective than placebo for acute attacks (21). The NNT to obtain more than 50% pain relief was 3 (95%CI 1, 14); that is, 1 in every 3 patients would achieve more than 50% relief of pain if tenoxicam were used. The results suggest equal efficacy to colchicine although direct comparison between these two agents has yet to be undertaken.

A large number of head-to-head comparisons have shown that different NSAIDs give similar benefits in acute gout (24;48-64) with no evidence for individual superiority in terms of clinical efficacy. However, a major concern with NSAIDs is their toxicity on the gastrointestinal (GI) tract. Meta-analyses have been undertaken both for evidence of GI toxicity and strategies to minimise GI toxicity of NSAIDs, including co-administration of GI protectors and alternative use of COX-2 selective inhibitors(4). For acute gout, the COX-2 selective inhibitors rofecoxib and etoricoxib have been investigated (65-67). However, the potential cardiovascular risk from selective and non-selective COX-2 inhibitors has recently been highlighted (68;69). Whether they do more good than harm for gout - a condition which often co-exists with cardiovascular disorders - remains unknown.

In conclusion, oral colchicine or NSAID are both effective at relieving symptoms of acute gout (level Ib). However, colchicine can cause severe diarrhoea, especially in high and frequent dosing and NSAIDs associate with an increased risk of GI bleeding and may have cardiovascular toxicity. Although oral NSAIDs are most commonly used, this preference is largely based on tradition and personal experience since the two treatments have not been directly compared.

5. *High doses of colchicine lead to side effects and low doses (for example 0.5 mg three times daily) may be sufficient for some patients with acute gout.*

Strength of recommendation (95% CI): 83 (74, 92)

Clinical trials have demonstrated that colchicine at the standard recommended dose (e.g., 1g loading dose, followed by 0.5mg every 2-3 hours) is effective at relieving symptoms of acute gout (17). It is also effective, at the dose of 0.6mg three times per day, in preventing acute attacks in patients with chronic gout (22) (Table 3). However, both dosage regimens cause serious GI side effects, especially diarrhoea (Table 4). The possibility that a reduced dose and/or frequency may allow retention of efficacy with reduction in toxicity is widely debated. However, apart from case reports (70), there is no direct evidence to support a low dose regimen. Studies examining the benefits and risks from different doses of colchicine are still required.

In conclusion, oral colchicine at the high dose schedule is effective but also very toxic, even within a very short treatment period (level Ib). There is popular support for an alternative lower dose regimen, as stated in the proposition, though rigorous evidence to support this new schedule is lacking (level IV).

6. *Intra-articular aspiration and injection of long-acting steroid is an effective and safe treatment for an acute attack.*

Strength of recommendation (95% CI): 80 (73, 87)

Although commonly used in practice, intra-articular aspiration (for immediate reduction of painful intra-articular hypertension as well as for diagnosis) and intra-articular injection of long-acting steroid have not been investigated in controlled trials. In one uncontrolled trial a single intra-articular injection of triamcinolone acetonide 10 mg resulted in pain relief within 48 hours in all 19 patients with acute gout (71), the mean VAS pain score (0-100 mm) reducing from 88 (range 82-93) at baseline to 0 (range 0-12) at endpoint. The treatment was well tolerated, no patients had side effects or rebound attacks, and none required additional treatment for the attack. Systemic administration (prednisone, triamcinolone or ACTH) has also been used in patients in whom an NSAID or colchicine are contraindicated with reportedly good results (72-76). In practice, this systemic approach is most commonly recommended for patients with severe oligo- or polyarticular attacks and for attacks in sites (e.g., the midfoot) that are not readily amenable to aspiration. It is generally agreed that neither intra-articular nor systemic steroids should be used if co-existent septic arthritis is suspected.

In conclusion, intra-articular aspiration may be useful for an acute attack but there is no research evidence to support its use (level IV). Intra-articular injection of long-acting steroid is effective at relieving the pain of an acute attack (level IIb). This may be especially useful for patients with a severe mono-articular attack and in those in whom an NSAID and colchicine are contra-indicated.

7. *Urate lowering therapy is indicated in patients with recurrent acute attacks, arthropathy, tophi or radiographic changes of gout.*

Strength of recommendation (95% CI): 97 (95, 99)

Given the unfavourable natural history of untreated gout, non-pharmacological urate lowering therapy (e.g., advice on diet, lifestyle modification) should be initiated in every patient at presentation. However, there are sparse research data to guide the decision as to when to start urate lowering drug therapy. There is uniform agreement that urate lowering drugs should be recommended to patients with severe established gout, as indicated for example by tophi, gouty arthropathy, radiographic changes of gout, multiple joint involvement and associated uric acid nephrolithiasis. There is less agreement, however, concerning initiation of urate lowering drug therapy in less severe gout, for example following clinical presentation with the first acute attack. Opinion ranges from initiation of urate lowering drugs after even the first attack of gout (on the assumption that it is easier to treat and cure gout if there is a relatively small urate crystal load) through to waiting until further attacks occur and become sufficiently frequent to be troublesome (on the assumption that some patients will have relatively infrequent attacks that do not merit long-term medication with its associated inconvenience and risk of toxicity). As always, each clinical decision must be individualised according to specific patient characteristics (proposition 1), the balance of risk-benefit of long-term drug therapy and the wishes of the patient. It is agreed that informed patient opinion is central to such decision-making (level IV).

8. *The therapeutic goal of urate lowering therapy is to promote crystal dissolution and prevent crystal formation. This is achieved by maintaining the serum uric acid below the saturation point for monosodium urate ($\leq 360 \mu\text{mol/l}$ or $\leq 6 \text{mg/dl}$).*

Strength of recommendation (95% CI): 91 (86, 96)

Gout is a true crystal deposition disease that only occurs if urate crystals are present. If further urate crystal formation is halted in a patient and existing crystals are dissolved away then that

patient is essentially “cured”. There are a number of strategies to reduce tissue urate levels below the saturation point where urate crystal formation can occur and to a low level that encourages crystal dissolution. Apart from urate saturation, the balance of inhibitory and promoting factors in joint tissues also influences urate crystal formation and dissolution; these factors may explain why a minority of people who are supersaturated for monosodium urate ever form crystals. The level of SUA is presumed to be an indirect indication of joint tissue urate levels. The normal range of SUA is determined by sampling of the local population and therefore varies from country to country and with time depending on the prevalence of factors (e.g., obesity) that influence SUA; furthermore the normal range is lower in women, though less so after the menopause. In many populations a SUA that is in the “normal range” may still reflect levels in joint tissues that are above the saturation point for monosodium urate. Therefore the target of urate lowering therapy is best centred on a SUA level that is linked to the saturation point of monosodium urate rather than to a normal laboratory range.

A level of SUA $\leq 360 \mu\text{mol/l}$ reflects a tissue level that is likely to be well below this saturation point. One cohort study has shown that maintaining the SUA below 6.2 mg/dl (370 $\mu\text{mol/l}$) would significantly reduce tophi, whereas a SUA above 8.2 mg/dl (490 $\mu\text{mol/l}$) did not reduce tophi (10). This was supported by other two cohort studies in which a linear relationship was found between the level of SUA and reduction in tophi (77), and where depletion of urate crystals from knee synovial fluids could be achieved if the SUA was maintained below 6 mg/dl (360 $\mu\text{mol/l}$) for at least 12 months (78). In some patients, for example those with extensive tophi and a presumed very high crystal load, the therapeutic target may be to achieve SUA levels that are well below this minimum level to permit a faster “velocity” of tophi reduction (78). The specific SUA level that is made the therapeutic target may thus vary according to individual patient characteristics (proposition 1).

In summary, the aim of urate lowering therapy is “cure” through prevention of urate crystal formation and enhancement of crystal dissolution. To achieve this aim there are clinical data to support the requirement to maintain the SUA at or below a level of 360 $\mu\text{mol/l}$ (6mg/dl) (Level III). This SUA level reflects a tissue level that is below the saturation point for monosodium urate.

9. *Allopurinol is an appropriate long-term urate lowering therapy. It should be started at a low dose (100mg daily) and increased by 100 mg every 2-4 weeks if required. The dose must be adjusted in those with renal impairment. If allopurinol toxicity occurs, options include other xanthine oxidase inhibitors, a uricosuric agent or allopurinol desensitisation (the latter only in cases of mild rash).*

Strength of recommendation (95% CI): 91 (88, 95)

Although allopurinol has been used as an effective treatment for gout for decades, its clinical efficacy has not been examined in placebo controlled RCTs. One open RCT in 59 patients with chronic gout compared the combination of allopurinol 200 mg daily plus colchicine 0.5mg bid (n = 26) against colchicine 0.5 mg bid alone (n = 33). After two years a significantly greater reduction in SUA level was observed in those taking allopurinol plus colchicine (ES=1.39, 95%CI 0.78, 2.01). However, the number of patients experiencing acute attacks was similar in both groups during the first year (NNT=9, 95%CI -9, 3); serum creatinine levels were also similar in the two groups (25).

One could question the requirement of a placebo control when a biochemical measure (SUA) is the primary outcome studied. Certainly a large number of uncontrolled trials

demonstrate the urate lowering capability of allopurinol. A re-analysis based on individual patient data from 2 studies (11;12) showed a significant dose-response relationship between allopurinol and SUA (Figure 3) in which every 100 mg increment of allopurinol reduced SUA by approximately 1 mg/dl (60 μ mol/L) (Table 5). There is general support for the “go low, go slow” strategy of starting allopurinol at 100 mg daily and increasing by 100 mg increments every few weeks until the therapeutic SUA target is achieved. Compared to giving only a fixed dose of 300 mg (very common practice throughout Europe) the possible benefits of slowly titrating up the dose include: less likely provocation of acute attacks; reduced incidence of toxicity; tailoring of the dose to suit individual requirements; and emphasis on the importance of a sufficiently low target SUA. Nevertheless, although this strategy has some face validity and some potential advantages, formal comparison with a fixed dose strategy has not been undertaken.

Table 5. Reduction of serum uric acid (SUA) upon treatment variables in patients with primary gout

Variable	β	95% CI		p
Allopurinol (100 mg increments)	-1.09	-0.94	-1.24	0.000
Sulphinpyrazone (100 mg increments)	-0.09	-0.01	-0.18	0.034
Duration of treatment (weeks)	-0.08	-0.04	-0.11	0.000
Age (10 year increments)	-0.36	-0.18	-0.53	0.000

Dependent Variable: SUA. Individual patient data was obtained from Yu’s study (1964)(12). Negative values mean reduction of SUA in mg/dl.

Allopurinol may cause adverse events including the rare but potentially life-threatening allopurinol hypersensitivity syndrome (AHS). This consists of an erythematous, desquamating rash, fever, hepatitis, eosinophilia, and worsening renal function (79). One single blind, placebo-controlled trial compared renal function (serum creatinine and creatinine clearance) in subjects with hyperuricaemia who received either allopurinol or placebo (13). After 2.5 years of treatment the trial overall found no significant increase of serum creatinine or decrease of creatinine clearance compared to placebo, but there was a significant reduction of creatinine clearance with allopurinol in hypertensive patients with glomerular filtration rates above 80 ml/min ($p < 0.02$). Unfortunately the trial did not report details of allopurinol dosage and the optimal doses of allopurinol in patients with varying renal function remains unknown, though the principle of using lower (especially starting) doses of allopurinol in patients with impaired renal function is generally accepted. One retrospective cohort study ($n=120$) compared the risk of adverse drug reactions between patients whose allopurinol maintenance dose matched the recommended dose according to their creatinine clearance rate ($n=52$) and patients whose maintenance dose exceeded the recommended dose ($n=68$) (44). The risk of rash, AHS, fixed pigmented drug eruption or leucocytoclastic vasculitis was similar between the two groups (RR=1.96, 95%CI 0.34, 11.92). Interestingly, one case control study showed a higher risk of cataract extraction in elderly patients taking allopurinol (OR=1.82, 95%CI 1.18, 2.80)(45).

In an economic analysis allopurinol, selected as the prototype and most widely used urate lowering drug, was shown to be more effective (72% vs. 5% acute attacks averted per year) and more costly than non-urate lowering drug therapy (\$ 426.27 versus 267.27 per patient per year) (80). ICER (i.e., cost per acute attack averted) was \$247.40 at base case scenario, and varied from \$99.59 to \$489.26 depending on patient characteristics and probability estimates. This

suggested that for each patient taking allopurinol, it would cost society an additional \$99.59 to \$489.26 to prevent an additional acute attack of gouty arthritis compared with the strategy of not prescribing urate lowering drugs. Interestingly, the urate lowering drugs become cost saving (i.e., more effective and less costly than non-urate lowering drug therapy) once a patient suffers 3 or more attacks per year.

If allopurinol toxicity does occur, alternative urate lowering treatments may be employed. As discussed in proposition 2, non-pharmacological approaches such as education, weight loss, reducing alcohol consumption and dietary modification should always be considered. However, if urate lowering drugs are required, the current alternatives are other xanthine oxidase inhibitors or uricosuric agents. A number of RCTs have demonstrated that xanthine oxidase inhibitors other than allopurinol (e.g., the metabolite of allopurinol – oxipurinol, tisopurine and febuxostat) are effective in reducing SUA (81-88). However, their safety in patients who previously have developed AHP has not been established. Clinically up to 40% of patients show cross reactivity between allopurinol and oxipurinol (89;90); the non-purine xanthine oxidase febuxostat is not reported to cause severe skin reactions and might be expected to have less cross-reactivity than oxipurinol (though this has not been studied directly). Alternatively, as discussed in proposition 10, uricosuric agents may be considered. Allopurinol desensitisation may be successful but is only recommended if the above alternatives fail. It should not be attempted in patients with severe reactions or AHS (91-94).

In conclusion, allopurinol is a cost-effective treatment for the long-term management of chronic gout (level Ib) and an effective urate-lowering drug with a demonstrated dose-response effect on SUA (level IIb). Although not formally studied, the strategy of giving a starting dose of 100mg daily (especially in those with renal impairment) with further 100 mg increments until the target level of SUA is achieved is favoured over a fixed dose strategy (level IV). For patients hypersensitive to allopurinol, other urate lowering therapies may be considered. Allopurinol desensitisation is a further option, but only in those with mild hypersensitivity to allopurinol (level IV).

10. Uricosuric agents such as probenecid and sulphinyprazole can be used as an alternative to allopurinol in patients with normal renal function but are relatively contra-indicated in patients with urolithiasis. Benzbromarone can be used in patients with mild to moderate renal insufficiency on a named patient basis but carries a small risk of hepatotoxicity.

Strength of recommendation (95% CI): 87 (81,92)

One controlled trial compared the efficacy of probenecid 1-2 g/day or sulphinyprazole 400 mg/day to allopurinol 300-600 mg/day for up to 2 years of treatment (95). Forty patients with uncomplicated chronic gout were allocated to either treatment according to the hospital record number (even or odd). The results showed that a similar number of patients experienced acute attacks (11/20 vs 9/17, P=0.90) but the mean reduction in SUA was greater with allopurinol (4.6 mg/dl or 270 μ mol/l) than with probenecid or sulphinyprazole (3.3 mg/dl or 200 μ mol/l). However, detailed statistical data for SUA were not presented. Uncontrolled trials have investigated both agents, one of them demonstrating smaller but statistically significant urate lowering effects of sulphinyprazole (0.09 mg/dl, 95%CI 0.01, 0.18) compared to allopurinol (1 mg/dl, 95%CI 0.94, 1.24) per 100 mg incremental dose (Table 5). Another uncontrolled trial examined probenecid in patients with and without renal impairment; reduction in SUA was greater in those without renal impairment (96).

Benzbromarone was compared with allopurinol in an open RCT of chronic gout patients with renal impairment (14). After 2-years treatment the benzbromarone regimen (100-200 mg /day using 50mg increments until the desired SUA level was achieved) demonstrated a significantly greater reduction of SUA compared to the allopurinol regimen (100-200 mg/day using 50-150 mg increments until the desired SUA level was achieved). The ES was 1.50 (95%CI 0.76, 2.24) and more patients achieved the optimal SUA (<6 mg/dl or 360 μ mol/l) with benzbromarone (NNT=3, 95%CI 2, 15). However, because of several case reports of hepatic failure or toxicity (97-101) the use of benzbromarone has become restricted in some European countries.

In conclusion, probenecid and sulphinpyrazone are both effective but probably inferior to allopurinol in lowering SUA (level IIa). They should not be used in patients with renal impairment (level IIb). In contrast, benzbromarone is a powerful uricosuric that is effective, even more than allopurinol, in patients with renal impairment (level Ib). Its use, however, has been restricted due to rare cases of serious hepatic toxicity.

11. Prophylaxis against acute attacks during the first months of urate lowering therapy can be achieved by colchicine (0.5 – 1mg daily) and/or an NSAID (with gastro-protection if indicated).

Strength of recommendation (95% CI): 90 (86, 95)

Because acute gouty attacks may be induced by the rapid reduction in SUA that follows initiation or an increase in dose of urate lowering drugs (102), strategies have been devised to reduce or prevent such provocation of attacks during the first months of therapy. Two double blind RCTs have examined colchicine in this respect (22;23). In one placebo controlled trial 43 patients commencing allopurinol for gout were randomly allocated to either colchicine 0.6 mg bid (n=21) or placebo (n=22). After 3 months the percentage of patients with acute attacks was significantly less in the treatment (7/21) than in the placebo group (17/22). The NNT was 2 (95%CI 1, 6), suggesting that colchicine would prevent 1 in every 2 patients from experiencing an attack. However, colchicine also caused more diarrhoea than placebo (RR=8.38, 95%CI 1.14, 61.38). In a head to head comparison trial, 52 patients with intercritical gout were randomly allocated to probenecid 500 mg tid plus colchicine 0.5 mg daily or to probenecid 500 mg tid plus placebo daily for 6 months (23). Both groups showed similar reduction in SUA (ES=-0.44, 95%CI -1.09, 0.20) but the group co-prescribed colchicine had less attacks per patient per month than the probenecid only group (ES=0.74, 95%CI 0.08, 1.40). Although both groups in this study had similar safety profiles (Table 4) the possibility of toxicity, especially neurotoxicity, from long-term colchicine therapy requires consideration.

Oral NSAIDs are also used for prophylaxis. Two published controlled trials compared azapropazone 600 mg bid (an NSAID with uricosuric effects) with allopurinol (24;49), although one trial (49) was part of the other multi-centre study (24). Overall, 156 patients were treated for 24 weeks (24). While both treatments showed similar reductions in SUA (ES=0.00, 95%CI -0.26, 0.26) azapropazone demonstrated an additional prophylactic benefit against acute attacks. The NNT was 7 (4, 17); that is, treating every 7 patients with azapropazone would prevent 1 more patient from suffering an acute attack than if allopurinol were used. However, this was offset by a higher incidence of GI upset in the azapropazone group (Table 4). There are sparse data to guide duration of prophylaxis though, in general, longer prophylaxis is given for patients with higher crystal loads. The benefits of long-term prevention must be balanced against toxicity.

In conclusion, evidence to support the use of low dose colchicine for prophylaxis against acute attacks when commencing urate lowering therapy is reasonable (level Ib), whereas evidence for NSAIDs for the same purpose is less convincing (level IIa). Both agents associate with potentially serious side effects and their benefits and harms need to be carefully weighed.

12. When gout associates with diuretic therapy, stop the diuretic if possible. For hypertension and hyperlipidaemia consider use of losartan and fenofibrate respectively (both have modest uricosuric effects).

Strength of recommendation (95% CI): 88 (82, 94)

Diuretics, widely prescribed in the community, are a common risk factor for gout (OR=1.72, 95%CI 1.67, 1.76)(103). Depending on its indication, it may be possible to stop chronic diuretic therapy in a patient who develops gout, or switch to an alternative drug regimen that does not contain a diuretic. For patients with gout and hypertension an antihypertensive regimen that does not contain a thiazide should be considered. The angiotensin II receptor antagonist losartan is not only effective for hypertension but also has a uricosuric action (40;41;43); it therefore may lower both blood pressure and SUA.

Apart from hypertension, hyperlipidaemia and other features of the metabolic syndrome also associate with gout. A double-blind, placebo controlled, cross-over RCT of the lipid lowering agent fenofibrate has demonstrated uricosuric and serum urate lowering effects (26). Ten patients with hyperlipidemia were randomly assigned to one of three sequential treatments comprising fenofibrate 100 mg tid, bezafibrate 200 mg tid or placebo tid. Each treatment was 6 weeks, with 3 weeks washout in between. Fenofibrate showed significant reduction of SUA by 20% (95%CI 14%, 26%) with an effect size of 1.13 (95%CI 0.18, 2.07). This reduction was accompanied by a 30% increase in renal uric acid clearance. However, there are no long-term randomised controlled studies of losartan or fenofibrate as urate lowering agents for treating gout, either as monotherapy or in combination with other urate lowering drugs, so their clinical usefulness in gout remains unclear.

In conclusion, diuretics should be stopped if possible in patients with gout (level IV) and, if appropriate, alternative anti-hypertensive therapy without diuretics should be considered (level IV). Uricosuric and urate-lowering effects have been demonstrated for the antihypertensive agent losartan (level IIb) and lipid lowering agent fenofibrate (level Ib), making them attractive therapies for gout patients requiring antihypertensive or lipid lowering treatment, respectively. However, the clinical role and cost-effectiveness of these drugs is still unknown.

Future research agenda

Sixty one research topics were recommended initially. The 9 that were agreed, after 3 Delphi rounds, as the most important topics for future research according to currently available research evidence and clinical practice are shown in Table 6.

Table 6. Future research agenda – propositions developed through three Delphi rounds

No.	Proposition
1.	The optimal drug (colchicine or NSAID), dose and duration for prophylaxis of acute attacks when commencing urate-lowering therapy, and whether this should vary in different clinical settings (e.g., presence of tophi) needs to be determined.
2.	Studies are required to determine the optimal dose and frequency of oral colchicine for treatment of an acute attack.
3.	Further studies are required to determine the target SUA for urate-lowering therapy that ensures crystal dissolution and eventual cure.
4.	Direct comparison (efficacy, side-effects, cost utility) between allopurinol and alternative urate lowering treatments are needed.
5.	The efficacy and safety of combined urate lowering therapies (e.g., allopurinol plus a uricosuric drug) should be determined and compared to monotherapy in patients with severe gout.
6.	The efficacy of educational programs for life-style modification (e.g., weight loss, reduced alcohol intake and restriction of dietary purines) in patients with gout need to be assessed.
7.	The indications for initiating urate-lowering therapy (e.g., recurrent acute attacks, tophi, polyarticular acute attacks, radiographic joint damage) need further evaluation.
8.	Whether initiation of urate lowering therapy during an acute attack is disadvantageous and should be avoided, and if so for how long, requires investigation.
9.	The possible benefits on cardiovascular disease of lowering SUA merits investigation.

Discussion

These are the first recommendations for the management of gout to be developed by EULAR. As with previous EULAR Task Forces for management of specific musculoskeletal disease (4;104-106) we used an evidence-based format that permits inclusion of both research evidence and expert opinion whilst maintaining clear distinction between the two.

A number of other practice guidelines for the management of gout have been published in recent years(107-110). However, the current EULAR recommendations have several differences and possible advantages over these guidelines, including: (1) an international panel of gout experts permitting broad representation of clinical practice within Europe; (2) the inclusion of more recent research data, and (3) the use of a rigorous evidence-based format. The format that we used involved an anonymous Delphi consensus approach to derive key management propositions; a systematic search for research evidence to support each proposition; the pooling of data across populations where possible; and separate presentation of (1) the category of evidence of supporting research data and (2) the strength of recommendation for each proposition. Possible benefits of such an international evidence-based approach include reduction in personal bias, good external validity and generalisability, and ready identification of areas of clinical practice where more research data are required (111).

Several methodological issues merit emphasis. Firstly, we used the EULAR visual analogue and ordinal scale to grade strength of recommendations (4). Unlike the traditional scale which only reflects the level of efficacy evidence (111;112), the EULAR scales allow a trade off between benefits versus harm and research evidence versus clinical expertise, and the 95% CI reflects the confidence of the group decision making (the wider the CI the greater the variance within the group in supporting a proposition). This system has been used successfully in other evidence based recommendations (4;104;105;113) and is discussed further in the accompanying report on EULAR recommendations for diagnosis of gout(3).

Secondly, again as discussed in the accompanying report on Diagnosis of gout(3), the Task Force discussed at length the details relating to the Delphi exercise and the way in which propositions are developed. Particularly pertinent to the management propositions was the decision by the Task Force to opt for (1) a free range of submitted propositions without specifying specific headings that each needed to be addressed by at least one proposition, and (2) acceptance of just 10 final propositions, as for previous EULAR projects (4;104-106). The Task Force realised that this approach would not necessarily result in exhaustive coverage of the topic and indeed, when the preliminary results were presented for feedback at the EULAR congress (Vienna, 2005) there was concern that the first 10 selected propositions did not address all treatment modalities (specifically there was omission of the use of oral NSAIDs for acute gout). Therefore it was agreed that the number of propositions should be extended to include the 4 next propositions with the highest votes in the final Delphi Round (Round 3) which then resulted in inclusion of this topic. Nevertheless, these recommendations still only highlight certain aspects of management – they are not designed to be fully comprehensive or to cover every clinical situation related to gout. The Task Force recommend that for future projects, depending on the disease and the objectives, the possibility of inviting propositions under pre-specified headings be considered if comprehensive coverage is desired. Also the more formal inclusion of feedback from EULAR members prior to finalisation of the recommendations should be considered since this clearly expanded and improved the current recommendations and resulted in a guideline set that more genuinely reflects the views of the EULAR membership. This feedback could be by oral and written communication following presentations at the EULAR Congress or

electronically following display of preliminary recommendations on the EULAR website. Finally, as with the recommendations for diagnosis, the Task Force agreed to minor modifications, for the sake of clarity, to the wording of some propositions for management after they had been voted in, researched and fully discussed, but no change was made to the key content of the propositions at this late stage.

There are a number of limitations to these recommendations. Firstly, there are caveats relating to the research data. For example, as with any search strategy it is possible that some relevant research data were overlooked; most studies and clinical trials involve specialist-referred gout patients who may be unrepresentative of the majority of the population with gout; and the quality of individual studies was not systematically assessed using established check lists such as the CONSORT statement for RCTs or the QUOROM statement for systematic reviews(114;115). Secondly, although we examined the research evidence and combined this with expert opinion, the third important element of evidence-based medicine, patient opinion (116), was omitted. For future Task Forces ESCISIT is currently considering appropriate ways in which patient opinion can be included. Thirdly, the Task Force was comprised solely of rheumatologists. The omission of general practitioners, who manage a substantial proportion of gout patients in Europe, may have reduced the generalisability of the recommendations. It was interesting that even within the group of rheumatologists interested in gout there was considerable diversity of practice with respect to certain management issues, most notable: when to initiate urate lowering drug therapy in a patient with confirmed gout; whether to use colchicine or NSAID prophylaxis when initiating urate lowering therapy and what doses to use and for how long; the starting dose of allopurinol, the rate of dose escalation and the maximum dose that may be used, and; willingness to use intra-articular corticosteroid for an acute attack. Therefore for relevant application of the recommendations we urge the user to study the commentary as well as the statements, to examine the CI for each strength of recommendation (this reflects the diversity of opinion), and to examine the future research agenda which highlights where the group agreed it would be most helpful to have further research data to help guide clinical decisions.

In conclusion, we have developed the first EULAR recommendations for the management of gout based on both clinical practice and the best available evidence. Twelve key recommendations that include non-pharmacological and pharmacological modalities, management of the acute attack of gout, the use of long-term urate lowering drug therapy, prophylaxis against acute attacks and attention to comorbidity have been evaluated. Full review of this topic has also prompted 10 key recommendations for the future research agenda. We trust that together with the accompanying propositions for diagnosis (3) these recommendations for management will lift the profile of this eminently treatable arthropathy and act as a catalyst for discussion between all health professionals involved in the diagnosis and management of patients with gout.

Acknowledgements

The authors would like to thank the European League Against Rheumatism, for financial support, Helen Richardson for logistical support, Jane Robertson for literature search and database development and Maggie Wheeler for language translations.

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Figure 1. Treatment modalities in the management of gout for which there is published research data

Figure 2. Types of evidence in the studies relating to management of gout

Figure 3. Dose dependent relationship between allopurinol and serum uric acid (SUA)

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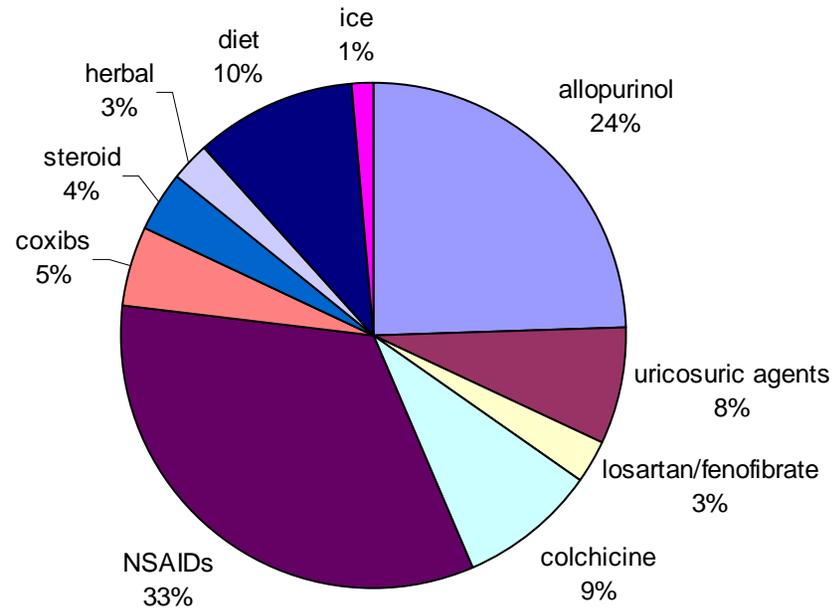


Figure 1. Treatment modalities in the management of gout for which there is published research data

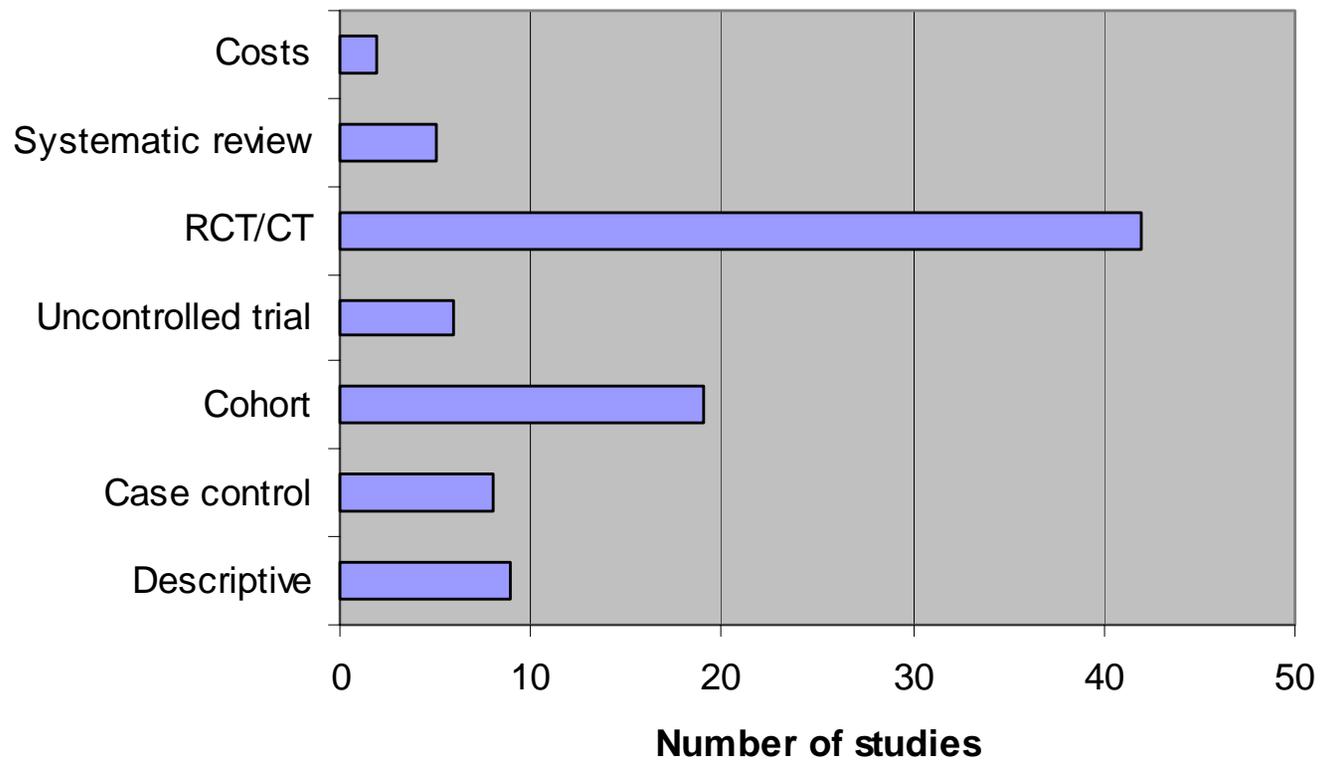


Figure 2. Types of evidence in the studies relating to management of gout (RCT: randomised controlled trial, CT: controlled trial)

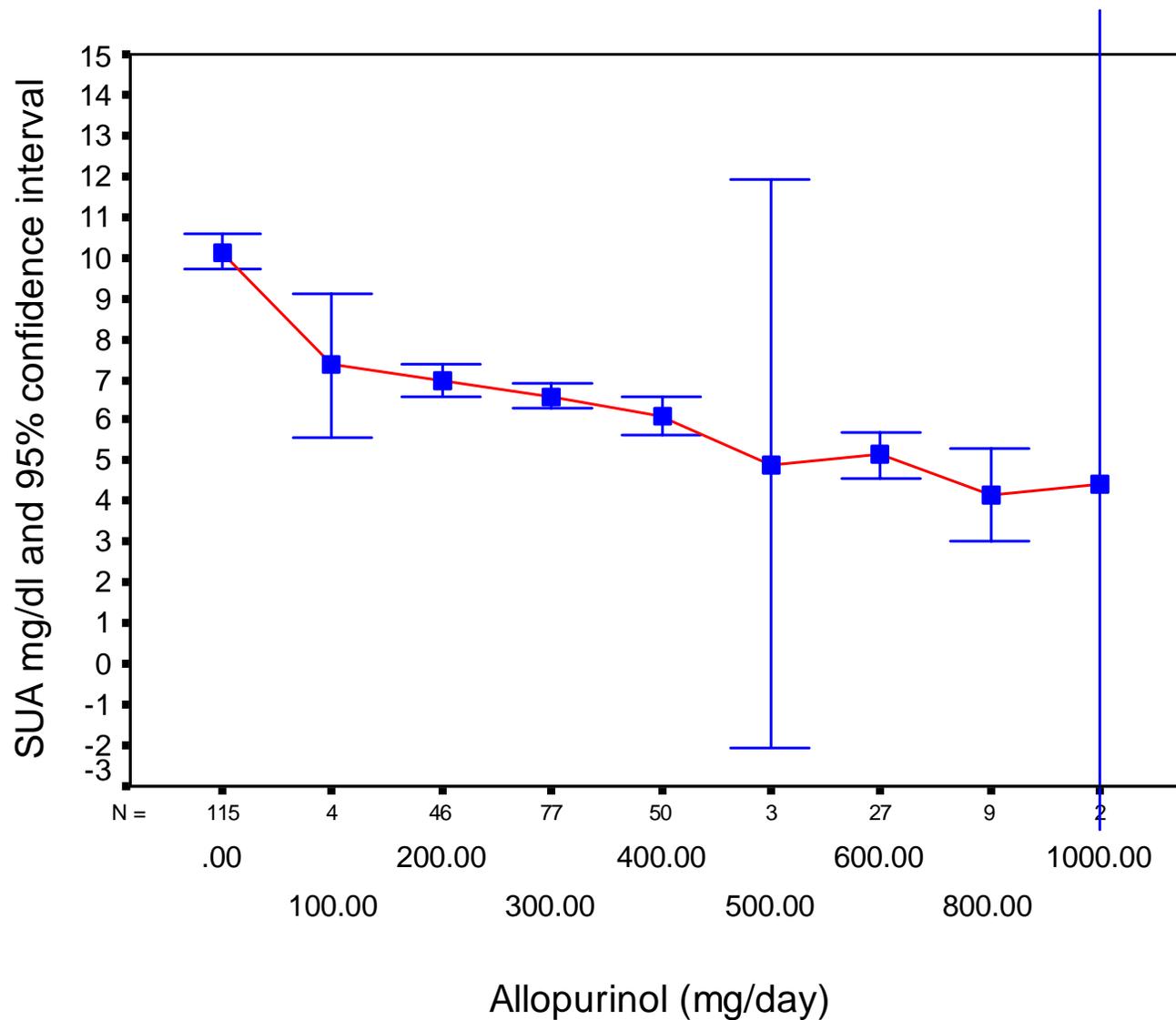


Figure 3. Dose dependent relationship between allopurinol and serum uric acid (SUA) – pooled results from Rundles (1966)(11) and Yu (1964)(12) studies ($r = 0.70$, $p < 0.01$)