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Gout

Search date June 2008
Martin Underwood

ABSTRACT

INTRODUCTION: Gout affects about 5% of men and 1% of women, with up to 80% of people experiencing a recurrent attack within 3 years. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of treatments for acute gout? What are the effects of treatments to prevent gout in people with prior acute episodes? We searched: Medline, Embase, The Cochrane Library, and other important databases up to June 2008 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 21 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: colchicine, corticosteroids, corticotrophin (ACTH), non-steroidal anti-inflammatory drugs (NSAIDs), sulfinpyrazone, xanthine oxidase inhibitors, advice to lose weight, advice to reduce alcohol intake, advice to reduce dietary intake of purines.

Key points

- Gout is characterised by deposition of urate crystals, causing acute monoarthritis and crystal deposits (tophi) in the skin.

  Gout affects about 5% of men and 1% of women, with up to 80% of people experiencing a recurrent attack within 3 years.

  Diagnosis is usually clinical, supported by signs of hyperuricaemia.

  Risk factors are those associated with increased serum urate concentrations, including: older age; non-white ethnicity; obesity; consumption of alcohol, meat, and fish; and use of diuretics.

  Hyperuricaemia may be associated with an increased risk of cardiovascular events; we don't know whether it is an independent risk factor.

- We don't know whether NSAIDs reduce pain and tenderness in an acute attack of gout, although they are commonly used in clinical practice. They are associated with increased risks of gastrointestinal, and possible cardiovascular, adverse effects.

  Indometacin is widely used to treat acute gout despite the absence of RCT evidence of benefit. Etoricoxib is as effective as indometacin with reduced risks of gastrointestinal adverse effects.

- Although it has been widely used for many years, we don't know whether oral colchicine improves symptoms in acute gout. Its use is limited by the high incidence of adverse effects.

- We don't know whether intra-articular, parenteral or oral corticosteroids, or corticotropin (ACTH), improve symptoms in acute gout.

- We don't know whether colchicine prevents attacks of gout in people with prior episodes, but it may reduce the risk of an attack in a person starting allopurinol treatment.

  We don't know whether advice to lose weight or reduce alcohol or dietary purine intake prevents further attacks of gout.

  We don't know whether allopurinol or febuxostat, or sulfinpyrazone reduce the risk of recurrent attacks compared with placebo or other treatments.

DEFINITION
Gout is a syndrome caused by deposition of urate crystals. [1] It typically presents as an acute monoarthritis of rapid onset. The first metatarsophalangeal joint is the most commonly affected joint (podagra). Gout also affects other joints; joints in the foot, ankle, knee, wrist, finger, and elbow are the most frequently affected. Crystal deposits (tophi) may develop around hands, feet, elbows, and ears. **Diagnosis:** This is usually made clinically. The American College of Rheumatology (ACR) criteria for diagnosing gout are as follows: (1) characteristic urate crystals in joint fluid; (2) a tophus proved to contain urate crystals; or (3) the presence of six or more defined clinical laboratory and x ray phenomena (see table 1, p 13). [2] We have included studies of people meeting the ACR criteria, studies in which the diagnosis was made clinically, and studies that used other criteria.

INCIDENCE/ PREVALENCE
Gout is more common in older people and men. [3] In people aged 65–74 years in the UK, the prevalence is about 50/1000 in men and about 9/1000 in women. [4] The annual incidence of gout in people aged over 50 years in the USA is 1.6/1000 in men and 0.3/1000 in women. [5] One 12-year longitudinal study of 47,150 male health professionals with no previous history of gout estimated that annual incidence of gout ranged from 1.0/1000 for those aged 40–44 years to 1.8/1000 for those aged 55–64 years. [6] Gout may become more common because of increasing longevity, obesity, meat and fish consumption, and use of diuretics. [7] Gout may be more common in some non-white ethnic groups. [3] A pooled analysis of two cohort studies of former medical students found the annual incidence of gout to be 3.1/1000 in black men and 1.8/1000 in white men. [8] After correcting for the higher prevalence of hypertension among black men, which is a risk factor for gout, the relative risk of gout in black men compared with white men was 1.30 (95% CI 0.77 to 2.19). A cross-sectional survey of 657 people aged 15 years and over in New Zealand found a higher prevalence of gout in Maoris than in people of a European background (6.4% in Maoris v 2.9% in people with European background; age-adjusted RR 3.2, 95% CI 1.6 to 6.6). [9]

AETIOLOGY/ RISK FACTORS
Urate crystals form when serum urate concentration exceeds 0.42 mmol/L. [10] Serum urate concentration is the principal risk factor for a first attack of gout, [11] although 40% of people have normal serum urate concentration during an attack of gout. [10] [12] [13] [14] A cohort study of 2046 men followed up for about 15 years found that the annual incidence was about 0.4% in men with a urate concentration of 0.42–0.47 mmol/L, rising to 4.3% when serum urate concentration was 0.45–0.59 mmol/L. [15] One 5-year longitudinal study of 223 asymptomatic men with hyperuricaemia estimated the 5-year cumulative incidence of gout to be 10.8% for those with baseline serum urate of 0.42–0.47 mmol/L, 27.7% for baseline urate of 0.48–0.53 mmol/L, and 61.1% for baseline urate levels of 0.54 mmol/L or more. [11] The study found that a 0.6 mmol/L difference in baseline serum urate increased the odds of an attack of gout by a factor of 1.8 (OR adjusted for other risk factors for gout: 1.84, 95% CI 1.24 to 2.72). One 12-year longitudinal study (47,150 male health professionals with no history of gout) estimated that the relative risks of gout associated with one additional daily serving of various foods (weekly for seafood) were as follows: meat 1.21 (95% CI 1.04 to 1.41), seafood (fish, lobster, and shellfish) 1.07 (95% CI 1.01 to 1.12), purine-rich vegetables 0.97 (95% CI 0.79 to 1.19), low-fat dairy products 0.79 (95% CI 0.71 to 0.87), and high-fat dairy products 0.99 (95% CI 0.89 to 1.10). [6] [16] Alcohol consumption of greater than 14.9 g daily significantly increased the risk of gout compared with no alcohol consumption (RR for 15.0–29.9 g/day: 1.49, 95% CI 1.14 to 1.94; RR for 30.0–49.9 g/day: 1.96, 95% CI 1.48 to 2.60; RR for at least 50 g/day: 2.53, 95% CI 1.73 to 3.70). [16] The longitudinal study also estimated the relative risk of gout associated with an additional serving of beer (355 mL, 12.8 g alcohol), wine (118 mL, 11.0 g alcohol), and spirits (44 mL, 14.0 g alcohol). It found that an extra daily serving of beer or spirits was significantly associated with gout, but an extra daily serving of wine was not (RR for 355 mL/day beer: 1.49, 95% CI 1.32 to 1.70; RR for 44 mL/day spirits: 1.15, 95% CI 1.04 to 1.28; RR for 118 mL/day wine: 1.04, 95% CI 0.88 to 1.22). Other suggested risk factors for gout include obesity, insulin resistance, dyslipidaemia, hypertension, dietary fructose intake and cardiovascular disorders. [17] [18] [19]

PROGNOSIS
We found few reliable data about prognosis or complications of gout. One study found that 3/11 (27%) people with untreated gout of the first metatarsophalangeal joint had spontaneous resolution after 7 days. [20] A case series of 614 people with gout who had not received treatment to reduce urate levels, and who could recall the interval between first and second attacks, reported recurrence rates of 62% after 1 year, 78% after 2 years, and 84% after 3 years. [21] An analysis of two prospective cohort studies of 371 black and 1181 white male former medical students followed up for about 30 years found no significant difference in risk of CHD in men who had developed gout compared with men who had not (RR 0.85, 95% CI 0.40 to 1.81). [22]

AIMS OF INTERVENTION
For treating gout: to reduce the severity and duration of pain and loss of function, with minimal adverse effects of treatment. **For preventing recurrence:** to reduce the frequency and severity of recurrent attacks, and minimise the adverse effects of interventions.

OUTCOMES	**For treating gout:** severity of symptoms (pain scores, proportion of people with improved symptoms), adverse effects of treatment. **For preventing recurrence (over 6 months):** number of recurrent episodes a year, severity of recurrent episodes a year, adverse effects of treatment.
METHODS	*Clinical Evidence* search and appraisal June 2008. The following databases were used to identify studies for this systematic review: Medline 1966 to May 2008, Embase 1980 to May 2008, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2008, Issue 2. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and NICE. We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the author for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in any language, at least single blinded and containing more than 20 people of whom more than 80% were followed up. For question 1 on treatment of acute gout there was no minimum length of follow-up required to include studies. For question 2 on prevention of recurrent gout the minimum length of follow-up is 6 months or longer, except for xanthine oxidase inhibitors plus prophylactic drugs where the minimum length of follow-up is 3 months. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as RRs and ORs. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 15).

QUESTION   **What are the effects of treatments for acute gout?**

OPTION   **COLCHICINE (ORAL) FOR TREATING ACUTE GOUT**

Symptom severity
Compared with placebo Colchicine may be more effective at reducing pain at 48 hours in people with gout (low-quality evidence).

Note
The high incidence of adverse effects in people taking colchicine precludes its use as a routine treatment. We found no clinically important results about the effects of colchicine compared with NSAIDs or corticosteroids in people with gout.

For GRADE evaluation of interventions for gout, see table, p 15 .

Benefits:	**Colchicine versus placebo:** We found one systematic review (search date 2006) [23] which found one RCT. [24] The RCT was small (43 hospital inpatients with acute gout confirmed by synovial fluid examination, aged 55–91 years, 40/43 [93%] men), and compared colchicine (1 mg followed by 0.5 mg every 2 hours as tolerated or until complete response) versus placebo. [24] It found that colchicine significantly reduced pain compared with placebo after 48 hours (pain assessed on a 10 cm visual analogue scale; proportion with at least 50% improvement in pain: 16/22 [73%] with colchicine *v* 8/22 [36%] with placebo; RR 2.00, 95% CI 1.09 to 3.68; P less than 0.05). **Colchicine versus NSAIDs:** We found one systematic review (search date 2006), which found no RCTs. [23] We found no subsequent RCTs. **Colchicine versus corticosteroids:** We found one systematic review (search date 2006), which found no RCTs. [23] We found no subsequent RCTs.
Harms:	**Colchicine versus placebo:** The RCT found that all people taking colchicine experienced diarrhoea, vomiting, or both, within about 24 hours; 5/21 (24%) people taking placebo developed nausea (significance assessment not performed). [24] The 50% improvement in pain occurred before diarrhoea and vomiting in 9/22 (40%) people, after the onset of diarrhoea and vomiting in 12/22 (55%) people, and at the same time in 1/22 (5%) people.

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Colchicine versus NSAIDs:
We found no RCTs.

Colchicine versus corticosteroids:
We found no RCTs.

Comment: **Clinical guide:**
Colchicine has been used since antiquity to treat gout. A large number of observational studies support its use. Although it may be efficacious, narrow benefit-to-toxicity ratio limits its use in people with gout. [25] Colchicine may be useful in people for whom NSAIDs and corticosteroids are contraindicated. A dose of 0.5 mg three times daily may have fewer adverse events than the higher doses commonly used. [26]

OPTION	CORTICOSTEROIDS

Symptom severity
Compared with NSAIDS We don't know whether corticosteroids are more effective at reducing pain in people with acute arthritis suggestive of gout, but they are associated with fewer adverse effects (low-quality evidence).

Compared with corticotropin We don't know whether corticosteroids are more effective at reducing symptoms in people with acute gout (low-quality evidence).

Note
We found no clinically important results about the effects of intra-articular, parenteral, or oral corticosteroids compared with no active treatment, NSAIDs, or colchicine in people with gout.

For GRADE evaluation of interventions for gout, see table, p 15 .

Benefits: **Corticosteroids versus placebo:**
We found one systematic review (search date 2007), which identified no RCTs. [27] We found no subsequent RCTs.

Corticosteroids versus NSAIDs:
We found one systematic review (search date 2007), [27] which found one RCT. [28] We found no subsequent RCTs. The RCT (90 people with an acute arthritis suggestive of gout, 74 males, mean age 65 years) compared indometacin with prednisolone. People in the indometacin group were given intramuscular diclofenac initially, and people in both groups received paracetamol. The RCT found no significant difference in the mean rate of decrease in pain score over the first 2 hours between the two groups (pain assessed on a 100 mm visual analogue scale; 6.4 mm/hour in the indometacin group *v* 9.5 mm/hour in the prednisolone group, mean difference in pain, 3.2 mm/hour; 95% CI –0.78 mm/hour to +7.14 mm/hour; P = 0.12), but found that prednisolone significantly decreased mean pain scores during follow-up at days 1 to14 (mean rate of pain decrease; 0.3 mm/day in the indometacin group *v* 0.7 mm/day in the prednisolone group, mean difference in pain, 0.5 mm/day; 95% CI 0.03 mm/day to 0.89 mm/day; P = 0.04). After two weeks there was no significant difference in improvement between the two groups. [28]

Corticosteroids versus colchicine:
We found one systematic review (search date 2007), which found no RCTs. [27] We found no subsequent RCTs.

Corticosteroids versus corticotropin:
See benefits of corticotropin, p 5 .

Harms: Potential harms of oral corticosteroids are covered elsewhere in *Clinical Evidence* (see reviews on rheumatoid arthritis and asthma).

Corticosteroids versus placebo:
We found no RCTs.

Corticosteroids versus NSAIDs:
The RCT found indometacin significantly increased total adverse effects, epigastric pain, and gastrointestinal haemorrhage compared with prednisolone (total adverse effects: 12/44 [27%] with prednisolone *v* 29/46 [63%] with indometacin; P = 0.0007; epigastric pain: 0/44 [0%] with prednisolone *v* 14/30 [30%] with indometacin; P less than 0.0001; gastrointestinal haemorrhage: 0/44 [0%] with prednisolone *v* 5/46 [11%] with indometacin; P less than 0.05). The RCT found indometacin significantly increased hospital admission rates due to serious adverse effects (0/44 [0%] with prednisolone *v* 7/46 [15%] with indometacin; P less than 0.007). [28]

Corticosteroids versus colchicine:
We found no RCTs.

Corticosteroids versus corticotropin:
See harms of corticotropin, p 5 .

Comment: **Clinical guide:**
Both high-dose oral NSAIDs and colchicine have a high incidence of adverse events. Adverse events from occasional short courses of oral corticosteroids are uncommon. One RCT comparing indometacin and prednisolone found them to have similar effectiveness, but significantly more people in the indometacin group developed serious adverse effects. Oral corticosteroids may be preferable to either NSAIDs or colchicine for the occasional treatment of acute gout. [26]

OPTION	CORTICOTROPIN (ADRENOCORTICOTROPHIC HORMONE)

Symptom severity
Compared with corticosteroids Corticotropin and corticosteroids may be equally effective at reducing symptoms in people with acute gout (low-quality evidence).

Note
We found no clinically important results about the effects of corticotropin compared with no active treatment or NSAIDs.

For GRADE evaluation of interventions for gout, see table, p 15 .

Benefits: **Corticotropin (adrenocorticotrophic hormone [ACTH]) versus placebo:**
We found one systematic review (search date 2007), which found no RCTs. [27] We found no subsequent RCTs.

Corticotropin versus NSAIDs:
We found one systematic review (search date 2007), which found no RCTs. [27] We found no subsequent RCTs.

Corticotropin versus corticosteroids:
We found one systematic review (search date 2007), which found one RCT. [27] The RCT (31 males mean age 64 years, mean number affected joints 2.6) found similar mean time to complete resolution of symptoms with both treatments (7.9 days with corticotropin *v* 7.6 days with triamcinolone; P = 0.89).

Harms: **Corticotropin versus placebo:**
We found no RCTs.

Corticotropin versus NSAIDs:
We found no RCTs.

Corticotropin versus corticosteroids:
We found one systematic review, which found one RCT that did not report on harms. [27]

Comment: **Clinical guide:**
Some observational data suggest that corticotropin may be worth considering for people who cannot tolerate other treatments. [29]

OPTION	NSAIDS

Symptom severity
Compared with placebo NSAIDs (tenoxicam) may be more effective at reducing pain at 1 day, but may be no more effective at reducing pain at 4 days, in people with acute gout (very low-quality evidence).

Compared with each other No one NSAID has been shown to be more effective than the others at reducing pain in people with acute gout (moderate-quality evidence).

Adverse effects
The adverse effects of different NSAIDs/COX-2 inhibitors include gastrointestinal ulceration and haemorrhage, and increased cardiovascular risk.

Note

We found no direct information about whether other NSAIDs are better than no active treatment, corticosteroids, or oral colchicine in people with gout.

For GRADE evaluation of interventions for gout, see table, p 15 .

Benefits: **NSAIDs versus placebo:**
We found one systematic review (search date 2005, [30] 1 RCT [31]). The RCT (30 people aged 21–70 years with gout of the knee, ankle, wrist, big toe, or elbow) compared tenoxicam (40 mg once daily) versus placebo. [31] Tenoxicam significantly increased the proportion of people showing at least a 50% reduction in pain and tenderness after 1 day compared with placebo (assessed on a 4-point scale: "disappeared", "improved by at least 50%", "unchanged or improved by less than 50%", or "increased"; AR for pain "improved by at least 50%": 10/15 [67%] with tenoxicam *v* 4/15 [26%] with placebo; P less than 0.05; AR for tenderness "improved by at least 50%": 6/15 [40%] with tenoxicam *v* 1/15 [7%] with placebo; P less than 0.05; AR for pain on mobilisation "improved at least 50%": 4/15 [27%] with tenoxicam *v* 1/15 [7%] with placebo; P less than 0.05). However, it found no significant difference between tenoxicam and placebo in physician-rated efficacy after 4 days ("good or excellent": 7/15 [47%] with tenoxicam *v* 4/15 [27%] with placebo; P value not reported).

NSAIDs versus each other:
We found one systematic review (search date 2005), which identified nine RCTs comparing different NSAIDs versus each other. [30] Two of the high-quality RCTs identified in the review were designed as equivalence studies comparing indometacin 50 mg three times daily versus etoricoxib 120 mg daily. These RCTs found indometacin and etoricoxib to be equally effective (see table 2, p 14). [32] [33] Four of the remaining seven RCTs identified in the systematic review satisfied our inclusion criteria. These RCTs failed to show a significant difference in the effect of different NSAIDs on pain (see table 2, p 14). [34] [35] [36] [37] However, they may have lacked power to show differences.

NSAIDs versus corticosteroids:
See corticosteroids, p 4 .

NSAIDs versus oral colchicine:
See colchicine (oral) for treating acute gout, p 3 .

Harms: The harms of NSAIDs/COX-2 inhibitors are considered in detail elsewhere in *Clinical Evidence* and include gastrointestinal ulceration and haemorrhage, and increased cardiovascular risk (see review on NSAIDs).

NSAIDs versus each other:
See table 2, p 14 for harms.

NSAIDs versus corticosteroids:
See harms of corticosteroids, p 4 .

NSAIDs versus oral colchicine:
See harms of colchicine (oral) for treating acute gout, p 3 .

Comment: **NSAIDs versus placebo:**
The RCT comparing tenoxicam versus placebo conducted multiple significance tests, and no adjustment was reported for this. [31]

NSAIDs versus each other:
Phenylbutazone and indometacin were established as treatments for gout based on uncontrolled studies. Only the comparisons between etoricoxib and indometacin were powered to show equivalence in efficacy between the two compounds tested. [32] [33] We found six RCTs that compared phenylbutazone versus other NSAIDs. These were not considered further because phenylbutazone for gout has been restricted in many countries because it can cause aplastic anaemia and other serious adverse effects. We found one RCT (93 people) comparing indometacin and azapropazone. [38] We have not considered this further because use of azapropazone has been restricted because of a high incidence of gastrointestinal, renal, and hepatic adverse events. [39] We found one RCT (62 people) comparing meloxicam versus diclofenac versus rofecoxib. [40] We have not considered this study further because rofecoxib has been withdrawn worldwide because of cardiovascular adverse effects. The RCT was not designed to compare meloxicam versus diclofenac directly. We found one RCT (235 people) comparing lumaricoxib with indometacin. [41] This non-inferiority study found lumaricoxib to be as effective as indometacin at relieving pain. We have not considered this study further as lumaricoxib has since been withdrawn worldwide because of hepatic adverse effects.

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Clinical guide:
Although there is little RCT evidence to support their use, traditional NSAIDs, specifically in-dometacin, are commonly used to treat gout. [42] The choice of NSAID probably depends on doctor or patient preference. Adverse effects of NSAIDs, including COX-2 inhibitors, often do not manifest early in treatment. However, it is usual to prescribe proton pump inhibitors to reduce the incidence of gastrointestinal bleeding as high doses of NSAIDS are used. [43]

QUESTION	What are the effects of treatments to prevent gout in people with prior acute episodes?

OPTION	ADVICE TO LOSE WEIGHT

We found no clinically important results about the effects of advice to lose weight on the prevention of attacks of gout in people with prior episodes.

For GRADE evaluation of interventions for gout, see table, p 15 .

Benefits: We found one systematic review (search date 2005), which identified no RCTs. [30] We found no subsequent RCTs.

Harms: We found no RCTs.

Comment: None.

OPTION	ADVICE TO REDUCE ALCOHOL INTAKE

We found no clinically important results about the effects of advice to reduce alcohol intake on preventing attacks of gout in people with prior episodes.

For GRADE evaluation of interventions for gout, see table, p 15 .

Benefits: We found one systematic review (search date 2005), which found no RCTs. [30] We found no subsequent RCTs.

Harms: We found no RCTs.

Comment: A large 12-year longitudinal study (47,150 male health professionals with no history of gout) found that increased intake of beer or spirits was associated with a significantly increased incidence of gout. [16] However it found no significant increase in incidence of gout with increased intake of wine (see aetiology).

OPTION	ADVICE TO REDUCE DIETARY INTAKE OF PURINES

We found no clinically important results about the effects of advice to reduce dietary intake of purines on preventing attacks of gout in people with prior episodes.

For GRADE evaluation of interventions for gout, see table, p 15 .

Benefits: We found one systematic review (search date 2005), which found no RCTs. [30] We found no subsequent RCTs.

Harms: We found no RCTs.

Comment: A large longitudinal study (47,150 male health professionals with no history of gout) found that increased intake of meat or seafood was associated with a significantly increased incidence of gout. [6] However, increased intake of purine-rich vegetables did not significantly affect the incidence of gout. It also found that an increased intake of low-fat dairy produce was associated with a significantly reduced incidence of gout (see aetiology).

OPTION	COLCHICINE FOR PREVENTING RECURRENCE

Recurrence of gout
Colchicine compared with placebo in people starting allopurinol Colchicine may be more effective at reducing the risk of recurrent attacks of gout at 6 months in people starting allopurinol for recurrent gout (low-quality evidence).

Note

We found no clinically important results about the effects of colchicine compared with no active treatment, xanthine oxidase inhibitors, sulfinpyrazone, or advice to lose weight, to reduce alcohol, or to reduce dietary purines.

For GRADE evaluation of interventions for gout, see table, p 15 .

Benefits: **Colchicine versus placebo:**
We found one systematic review (search date 2005), which found no RCTs. [30] We found no subsequent RCTs.

Colchicine versus advice to lose weight:
See advice to lose weight, p 7 .

Colchicine versus advice to reduce alcohol:
See advice to reduce alcohol intake, p 7 .

Colchicine versus advice to reduce dietary intake of purines:
See advice to reduce dietary intake of purines, p 7 .

Colchicine versus xanthine oxidase inhibitors:
We found one systematic review (search date 2005), which found no RCTs. [30] We found no subsequent RCTs.

Colchicine versus sulfinpyrazone:
We found one systematic review (search date 2005), which found no RCTs. [30] We found no subsequent RCTs.

Colchicine plus xanthine oxidase inhibitors versus xanthine oxidase inhibitors alone:
See benefits of xanthine oxidase inhibitors, p 9 .

Harms: **Colchicine versus placebo:**
We found no RCTs.

Colchicine versus advice to lose weight:
See advice to lose weight, p 7 .

Colchicine versus advice to reduce alcohol:
See advice to reduce alcohol intake, p 7 .

Colchicine versus advice to reduce dietary intake of purines:
See advice to reduce dietary intake of purines, p 7 .

Colchicine versus xanthine oxidase inhibitors:
We found no RCTs.

Colchicine versus sulfinpyrazone:
We found no RCTs.

Colchicine plus xanthine oxidase inhibitors versus xanthine oxidase inhibitors alone:
See harms of xanthine oxidase inhibitors, p 9 .

Comment: **Colchicine plus xanthine oxidase inhibitors versus xanthine oxidase inhibitors alone:**
See comment on xanthine oxidase inhibitors, p 9 .

Clinical guide:
Colchicine, which has been used since antiquity, may be worth considering for the prevention of gout for people who cannot tolerate allopurinol.

OPTION	SULFINPYRAZONE

Recurrence of gout
Sulfinpyrazone compared with placebo Sulfinpyrazone may be no more effective at preventing recurrence of gout in people taking colchicine (low-quality evidence).

For GRADE evaluation of interventions for gout, see table, p 15 .

Benefits: **Sulfinpyrazone versus placebo:**
We found one systematic review (search date 2005), which found one RCT, reported as a conference abstract only. [30] It found similar numbers of gout attacks between colchicine plus placebo and

colchicine plus sulfinpyrazone (29 attacks in 170 months of follow-up with colchicine plus placebo *v* 32 attacks in 173 months of follow-up with colchicine plus sulfinpyrazone; statistical assessment not peformed).

Sufinpyrazone versus xanthine oxidase inhibitors:
See xanthine oxidase inhibitors, p 9 .

Harms: The systematic review did not report on harms. [30]

Comment: The RCT identified in by the review was reported as a conference abstract only. [30]

| OPTION | XANTHINE OXIDASE INHIBITORS |

Recurrence of gout
Xanthine oxidase inhibitors compared with each other Allopurinol and febuxostat are equally effective at preventing recurrence of gout at 9–52 weeks, but higher-dose febuxostat may increase the risk of recurrence in the first 8 weeks of treatment in people also taking naproxen or colchicine (moderate-quality evidence).

Xanthine oxidase inhibitors alone compared with xanthine oxidase inhibitors plus prophylactic drugs Initiating treatment with allopurinol alone may be less effective than initiating treatment with allopurinol during colchicine prophylaxis at reducing the risk of recurrent attacks of gout at 6 months (low-quality evidence).

Note
We found no clinically important results about the effects of xanthine oxidase inhibitors compared with no active treatment, sulfinpyrazone, colchicine, or lifestyle interventions.

For GRADE evaluation of interventions for gout, see table, p 15 .

Benefits: **Xanthine oxidase inhibitors versus placebo:**
We found one systematic review (search date 2005), which found no RCTs. [30] We found no subsequent RCTs.

Xanthine oxidase inhibitors versus sulfinpyrazone:
We found one systematic review (search date 2005), which found no RCTs. [30] We found no subsequent RCTs.

Xanthine oxidase inhibitors versus colchicine:
We found one systematic review (search date 2005), which found no RCTs. [30] We found no subsequent RCTs.

Xanthine oxidase inhibitors versus lifestyle interventions:
We found one systematic review (search date 2005), which found no RCTs. [30] We found no subsequent RCTs.

Xanthine oxidase inhibitors versus each other:
We found one systematic review (search date 2005), which found no RCTs. [30] We found one subsequent RCT, which compared allopurinol 300 mg daily versus febuxostat 80 mg daily versus febuxostat 120 mg daily. [44] All participants also received naproxen 250 mg twice daily or colchicine 0.6 mg daily during the first 8 weeks of treatment, to reduce the increased incidence of gout flares that can occur when urate lowering medication is initiated. It found that allopurinol and febuxostat 80 mg significantly reduced the proportion of people with at least one recurrent attack of gout in the first 8 weeks compared with febuxostat 120 mg (760 people with a history of gout, mean age 52 years, 96% male; AR for recurrence of gout: 52/251 [21%] with allopurinol *v* 55/255 [22%] with febuxostat 80 mg *v* 90/250 [36%] with febuxostat 120 mg; P less than 0.001 for both allopurinol and febuxostat 80 mg *v* febuxostat 120 mg). However, there was no significant difference between either dose of febuxostat and allopurinol in recurrent attacks of gout between weeks 9 and 52 (150/234 [64%] with allopurinol *v* 147/228 [64%] with febuxostat 80 mg *v* 150/215 [70%] with febuxostat 120 mg; P = 0.99 for febuxostat 80 mg *v* allopurinol; P = 0.23 for febuxostat 120 mg *v* allopurinol).

Xanthine oxidase inhibitors alone versus xanthine oxidase inhibitors plus prophylactic drugs:
We found no systematic review. We found one RCT, which compared colchicine 0.6 mg twice daily versus placebo as prevention for recurrent gout in people starting treatment with allopurinol for chronic gouty arthritis. [45] Treatment was continued for 3 months after serum urate reached normal levels. The dose was reduced to once daily in people with renal insufficiency or gastrointestinal adverse effects. The RCT found that colchicine significantly reduced the proportion of

people with recurrent gout attacks at 6 months compared with placebo (proportion of people with at least 1 attack: 7/21 [33%] with colchicine [12 attacks in total] v 17/22 [77%] with placebo [65 attacks in total]; P = 0.008). The authors report that the finding was significant, but the basis of the statistical analysis was not clear. It found that colchicine significantly reduced the severity of attacks compared with placebo (median score on visual analogue scale [scale range not reported]: 3.64 with colchicine v 5.08 with placebo; P = 0.018). There was no significant difference in duration of attacks (6.00 days with colchicine v 5.56 days with placebo; P = 0.566). [45]

Harms:
Xanthine oxidase inhibitors versus placebo:
We found no RCTs.

Xanthine oxidase inhibitors versus sulfinpyrazone:
We found no RCTs.

Xanthine oxidase inhibitors versus colchicine:
We found no RCTs.

Xanthine oxidase inhibitors versus lifestyle interventions:
We found no RCTs.

Xanthine oxidase inhibitors versus each other:
The subsequent RCT found that allopurinol significantly increased adverse events compared with febuxostat 120 mg (215/253 [85%] with allopurinol v 205/256 [80%] with febuxostat 80 mg v 189/251 [75%] with febuxostat 120 mg; P = 0.01 for allopurinol v febuxostat 120 mg; other statistical assessments not reported). [44] There was no significant difference between treatments in adverse events considered by the investigators to be possibly, probably, or definitely associated with the study drug (57/253 [23%] with allopurinol v 63/256 [25%] febuxostat 80 mg v 60/251 [24%] with febuxostat 120 mg; differences reported as not significant; P value not reported). There was no significant difference between treatments in serious adverse events, all considered by the investigators to be unlikely to be related to study drugs (19/253 [8%] with allopurinol v 11/256 [4%] with febuxostat 80 mg v 21/251 [8%] with febuxostat 120 mg; differences reported as not significant; P value not reported). Four people died, two in each of the febuxostat groups (0.8% in both groups) and none in the allopurinol group (P = 0.31).

Xanthine oxidase inhibitors alone versus xanthine oxidase inhibitors plus prophylactic drugs:
The RCT found that colchicine significantly increased diarrhoea compared with placebo (38% with colchicine v 5% with placebo; P = 0.009). However, no one withdrew because of diarrhoea, and all cases resolved when the dose was reduced. [45]

Comment:
We found one open RCT comparing colchicine 0.5 mg twice daily versus colchicine 0.5 mg twice daily plus allopurinol 300 mg once daily. [46] Three people (10%) allocated to the colchicine plus allopurinol group who did not take allopurinol were included in the colchicine only group for analysis. In the first year there was no significant difference between treatments in recurrent attacks of gout (10/33 [30%] with colchicine alone v 5/26 [19%] with colchicine plus allopurinol; difference reported as not significant; P value not reported). [46] The primary outcome for the RCT comparing allopurinol versus febuxostat was a serum urate of less than 0.36 mmol/L at each of the last three monthly visits. [44] Both doses of febuxostat significantly increased the proportion of people achieving the primary end point compared with allopurinol (53/251 [21%] with allopurinol v 136/255 [53%] with febuxostat 80 mg v 154/250 [62%] with febuxostat 120 mg; P less than 0.001 for allopurinol v febuxostat 80 mg and febuxostat 120 mg).

Clinical guide:
Many experts believe that allopurinol should not normally be started during an attack of gout. There is some evidence to support the usual practice of co-prescribing prophylactic drugs, such as colchicine, when starting urate lowering medication. The focus of this review is the prevention of recurrent gout rather than reducing serum urate. It is not clear how effective xanthine oxidase inhibitors are at reducing the incidence of recurrent gout. If urate lowering drugs are used, then the dose should be titrated upwards to achieve a target urate level of less than 0.36 mmol/L which prevents crystal formation and promotes their dissolution. Febuxostat seems more effective than allopurinol at reducing serum urate, but does not result in a reduction in recurrent gout over the first year of treatment. Febuxostat might be an alternative for people who cannot tolerate allopurinol.

GLOSSARY

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Colchicine (oral) One updated systematic review added, which identified no new RCTs; [23] categorisation unchanged (Unknown effectiveness).
Corticosteroids One systematic review [27] added, which identified one RCT; [28] benefits data enhanced; categorisation unchanged (Unknown effectiveness).

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Martin Underwood
Professor of Primary Care Research
Warwick Medical School
Coventry
UK

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TABLE 1   **American College of Rheumatology criteria for acute gout (people must fulfill at least 6 criteria).** [2]

1	More than 1 attack of acute arthritis
2	Maximum inflammation developed within 1 day
3	Monoarthritis attack
4	Redness observed over joints
5	First metatarsophalangeal joint painful or swollen
6	Unilateral first metatarsophalangeal joint attack
7	Unilateral tarsal joint attack
8	Tophus (proved or suspected)
9	Hyperuricaemia
10	Asymmetric swelling within a joint on x ray film
11	Subcortical cysts without erosions on x ray film
12	Joint culture negative for organism during attack

Musculoskeletal disorders

TABLE 2	RCTs comparing NSAIDs versus each other in people with gout (see text, p 5).

Comparison	Population	Outcomes	Results	Adverse events
Indometacin (50 mg 3 times daily) v etoricoxib (120 mg/day). Equivalence study [24]	189 people, gout for less than 48 hours, who had previously responded to NSAIDS, 93% male, mean age 52 years	Pain measured on Likert scale over days 2–5: 0 = no pain to 4 = extreme pain; Equivalence pre-specified as a difference of no more than ± 0.5	Difference: –0.08, 95% CI –0.29 to +0.13	People reporting at least 1 adverse events: 45/103 (44%) with etoricoxib v 49/86 (57%) with indometacin; P = 0.08 Drug-related adverse events: 17/103 (17%) with etoricoxib v 32/86 (37%) with indometacin; P = 0.002*
Indometacin (50 mg 3 times daily) v etoricoxib (120 mg/day). Equivalence study [30]	150 men, gout for less than 24 hours, mean age 49 years	Pain measured on Likert scale over days 2–5: 0 = no pain to 4 = extreme pain; Equivalence pre-specified as a difference of no more than ± 0.5	Difference: +0.11, 95% CI –0.14 to +0.35	Proportion with adverse events: 17/75 (23%) with etoricoxib v 35/75 (47%) with indometacin; P = 0.003
Etodolac (300 mg twice daily) v naproxen (500 mg twice daily) [26]	61 people, 18–75 years	Mean pain scores assessed on a scale 0–5 (higher scores indicating worse pain) after 2, 4, and 7 days	Day 2: 2.6 with etodolac v 2.8 with naproxen; reported as not significant; Day 4: 1.8 with etodolac v 2.0 with naproxen; reported as not significant; Day 7: 1.4 with etodolac v 1.4 with naproxen; reported as not significant	The study reported no important adverse events
Etodolac (300 mg twice daily) v naproxen (500 mg twice daily) [29]	60 people, 18–75 years	Pain assessed on a 5-point rating scale: 1 = no pain to 5 = very severe pain after 1, 2, 4, and 7 days	The study reported there was no significant difference in pain between etodolac and naproxen after 1, 2, 4, and 7 days; results presented graphically, no AR or P values reported	The study reported no important adverse events
Indometacin (up to 225 mg for 1 day in divided doses followed by 50 mg 3 times daily) v ketoprofen (450 mg in divided doses for 1 day followed by 100 mg 3 times daily) [31]	59 people, gout for less than 48 hours, 35–88 years	Mean pain scores assessed on a 4-point scale: 0 = no pain to 3 = severe pain after 2, 5, or 8 days	Day 2: 0.9 with indometacin v 1.1 with ketoprofen; P value reported as not significant; Day 5: 0.8 with indometacin v 1.3 with ketoprofen; P value reported as not significant; Day 8: 0.3 with indometacin v 0.4 with ketoprofen; P value reported as not significant	No differences in important adverse event rates were found
Indometacin (50 mg 4 times daily for 4 days followed by 25 mg 4 times daily for 5 days) v flurbiprofen (100 mg 4 times daily for 1 day followed by 50 mg 4 times daily for 5 days) [32]	29 people	Proportion of people with improved pain at rest after 2 days	11/12 (92%) with indometacin v 11/12 (92%) with flurbiprofen; P value not reported	No differences in important adverse event rates were found

*The RCT did not define serious and drug-related adverse events.

TABLE	GRADE evaluation of interventions for gout

Important outcomes	Symptom severity, recurrence of gout, adverse effects								
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of treatments for acute gout?									
1 (43) [24]	Symptom severity	Colchicine v placebo	4	−1	0	−1	0	Low	Quality point deducted for sparse data. Directness point deducted for narrow inclusion criteria
1 (90) [27]	Symptom severity	Corticosteroids v NSAIDS	4	−1	−1	0	0	Low	Quality point deducted for sparse data. Consistency point deducted for different results at different end points
1 (31) [30]	Symptom severity	Corticosteroids v corticotropin	4	−1	0	−1	0	Low	Quality point deducted for sparse data. Directness point deducted for only assessing one corticosteroid
1 (30) [31]	Symptom severity	NSAIDs v placebo	4	−2	−1	−1	+1	Very low	Quality points deducted for sparse data and statistical flaws. Consistency point deducted for conflicting results at different end points. Directness point deducted for assessing only one drug. Effect-size point added for RR greater than 2
6 (548) [24] [30] [26] [29] [31] [32]	Symptom severity	NSAIDs v each other	4	0	0	−1	0	Moderate	Directness point deducted for assessment of only some NSAIDs
What are the effects of treatments to prevent gout in people with prior acute episodes?									
1 RCT [30]	Recurrence of gout	Sulfinpyrazone plus colchicine v colchicine plus placebo	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (760) [44]	Recurrence of gout	Xanthine oxidase inhibitors v each other	4	0	−1	0	0	Moderate	Consistency point deducted for conflicting results at different end points and with different doses
1 (43) [45]	Recurrence of gout	Xanthine oxidase inhibitors alone v xanthine oxidase inhibitors plus prophylactic drugs	4	−2	0	0	0	Low	Quality points deducted for sparse data and for uncertainty about basis of statistical analysis

Type of evidence: 4 = RCT; 2 = Observational;
Consistency: similarity of results across studies.
Directness: generalisability of population or outcomes.
Effect size: based on relative risk or odds ratio.