Concise Report

Effectiveness of interventions for the treatment of acute and prevention of recurrent gout—a systematic review

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Objective. To determine the evidence for the effectiveness of treatments for acute gout and the prevention of recurrent gout.

Method. Seven electronic databases were searched for randomized controlled trials of treatments for gout from their inception to the end of 2004. No language restrictions were applied. All randomized controlled trials of treatments routinely available for the treatment of gout were included. Trials of the prevention of recurrence were included only if patients who had had gout and had at least 6 months of follow-up were studied.

Results. We found 13 randomized controlled trials of treatment for acute gout, two of which were placebo controlled. Colchicine was found to be effective in one study; however, the entire colchicine group developed toxicity. The only robust conclusion from studies of non-steroidal anti-inflammatory drugs is that pain relief from indometacin and etoricoxib is equivalent. We found one randomized controlled trial, reported only as a conference abstract, of recurrent gout prevention.

Conclusion. The shortage of robust data to inform the management of a common problem such as gout is surprising. All of the drugs used to treat gout can have serious side effects. The incidence of gout is highest in the elderly population. It is in this group, who are at a high risk of serious adverse events, that we are using drugs of known toxicity. The balance of risks and benefits for the drug treatment of gout needs to be reassessed.

Key words: Gout, Treatment, Systematic review.

Introduction

Gout is a common problem affecting 1% of adult males in developed countries [1]. Recurrent attacks of gout are common. It is the commonest cause of inflammatory joint disease in men aged over 40 yrs; increasing obesity and an ageing population mean that it is becoming more frequent [2, 3]. Gout is essentially a disorder of urate metabolism [4]; however, diet and alcohol intake can affect its incidence [5, 6]. Deposition of urate crystals in hyperuricaemic individuals results in acute gout, characterized by agonizing pain and inflammation of rapid onset, most frequently affecting the first metatarsophalangeal joint, resulting in short-term disability [4]. Aims of the treatment are to relieve the pain and inflammation of the acute attack, and reduce the incidence of recurrent attacks. Internationally, there are considerable variations in management of acute and recurrent gout [7]. The commonest approaches to the treatment of acute gout are non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine. The side effects of these drugs, particularly in the frail, elderly population, who have the highest incidence of acute gout, can be serious. The commonest approach to the prevention of recurrent gout is to use allopurinol, a xanthine oxidase inhibitor. Allopurinol can have serious side effects such as allopurinol hypersensitivity syndrome [8, 9]. We present a systematic review of the randomized controlled trial evidence for the treatment and prevention of recurrent, acute gout.

Method

Identification of randomized controlled trials

We sought to identify all randomized controlled trials of currently available drug treatments, lifestyle and other interventions for the treatment of acute gout and the prevention of recurrent gout. Two of us (S.S. and R.K.), working independently, researched the following electronic databases: Medline, PubMed, Cochrane Controlled Trials Register, ISI Web of Science, Embase, and AMED, from inception to the end of 2004 for all randomized controlled trials of gout treatment using the following search strategy: ‘(gout* or uric* or urate* or hyperuric* or podagra) AND (random* or control* or clinical trial* or placebo* or intervention* or allocat* or blind*)’. No language or date restrictions were used. Citation tracking from identified trials and reviews identified additional randomized controlled trials. We combined the reference lists using Reference Manager (Version 10.1). Still working independently, the two researchers screened titles and abstracts to identify articles for retrieval; they also independently screened retrieved articles for inclusion. One of us (M.U.) mediated disagreements. We excluded non-randomized studies and studies in which one or more intervention is not routinely available for treating gout. These studies are briefly summarized.
Trials of acute gout treatments

We included all randomized controlled trials that included subjects with acute gout (however defined) and compared an active intervention with no treatment, placebo or another active intervention. Our primary outcomes of interest were pain at 24 and 48 h or the nearest equivalent. Our secondary outcomes were any other patient-centred outcomes reported by the authors. Additionally, we extracted any reported adverse event data.

Trials of prevention of recurrent gout

We included all randomized controlled trials of prevention of recurrent gout in subjects with at least one previous attack of acute gout (however defined) who had at least 6 months of treatment and follow-up. Our primary outcome of interest was incidence of recurrent gout and our secondary outcome was difference in serum urate between the intervention and control groups. Additionally, we extracted any reported adverse event data.

Quality assessment

Study quality was assessed using the Jadad criteria [10]. Each included study was rated on a 0–5 scale (0 = low quality, 5 = high quality).

Results

Initial searches identified 9854 references. We identified 13 studies of treatment for acute gout and one study of the prevention of recurrent gout that met our entry criteria (Table 1). Excluded studies are summarized in Table 2. A flow diagram of studies is provided in Fig. 1.

Treatment of acute gout

Methodological quality

Most of the research was of poor quality. Only 4/13 included studies were of high quality, a Jadad score of 4/5 or 5/5 [11–14]. The median number of participants per study was 34 (range 10–189). Only two studies had sample size calculations [12, 14]. Typically, the quality of reporting was poor with insufficient detail to understand the analyses. There was no consistent approach to reporting of results.

NSAIDs

We found one placebo-controlled trial of reasonable quality that compared tenoxicam 30 mg/day with placebo (n = 30). The knee was affected in 14 cases and the great toe in only two cases. After 24 h, 67% of tenoxicam group had >50% reduction in pain compared with 26% of placebo group (P < 0.05) [11]. However, at the end of the treatment (4 days), there was no significant difference between the groups.

We found nine studies comparing two NSAIDs [12–20]. Two, both of high quality, were equivalence studies comparing etoricoxib and indomethacin [12, 14]. Both studies pre-defined equivalence as the limits of the 95% confidence intervals for difference between the two groups for change in pain at days 2–5 to be no more than 0.5 Likert units, based on a four-point Likert scale. Both studies found indomethacin and etoricoxib to have an equivalent effect on pain over days 2–5. Both studies reported fewer drug-related adverse events in the etoricoxib group. There were no differences in overall adverse events.

The remaining seven studies were of generally poor quality. Only one [18] reported any differences in outcome; these were at one time point and unlikely to be of any clinical importance. Most of these studies were too small to detect any important differences.

Colchicine

We found one placebo-controlled trial of colchicine 1 mg initially, and then 0.5 mg every 2 h until resolution or toxicity occurred. After 24 h, 41% of the colchicine group and 9% of the placebo group had ≥50% reduction in pain since baseline (not significant). After 48 h, 73% of the colchicine group and 36% of the placebo group had ≥50% reduction in pain since baseline (P < 0.05). Everyone in the colchicine group developed toxicity (median time to onset 24 h). In only 41% did ≥50% improvement occur before toxicity. Five of the control group experienced nausea [21].

Steroids and adrenocorticotropic hormone

We found no placebo-controlled trials of steroids or related compounds. We found one poor quality study comparing intramuscular adrenocorticotropic hormone with intramuscular triamcinolone acetonide [22]. Effect on pain was not reported. There was no difference in time to complete resolution between the two groups. However, this study is probably too small to detect any important differences.

Ice

There is some evidence from one small study, with poor quality allocation concealment, that local ice provides additional relief when added to systemic treatment [23].

Prevention of recurrent gout

We found no randomized controlled trials of lifestyle interventions, such as a low purine diet, weight loss or advice to reduce alcohol intake, in patients with gout that had either the incidence of recurrent gout or changes in serum urate as an outcome. Nor did we find any randomized controlled trials of allopurinol for the prevention of recurrent gout or that reported its long-term effect on serum urate. One small (14 subjects) study, reported only as a conference abstract, suggested that although sulphinpyrazone reduces serum urate it does not affect incidence of recurrent gout [24]. However, this study is probably too small to detect any important differences.

Discussion

The shortage of robust data for a common problem such as gout is surprising. Current regimens for the treatment and prevention of recurrent gout were developed several decades ago. It is possible that we have overlooked some relevant randomized controlled trials. Firstly, some early studies that have not been indexed would not be identified by our searches. However, extensive citation checking of review articles and included studies did not identify any additional included studies. Secondly, it is possible that there are unpublished randomized controlled trial data that were produced for licensing purposes. We did not have the resources to systematically identify any such studies from multiple manufacturers and regulatory authorities. We are re-assured that this has not introduced substantial bias into our findings because for some drugs, for example allopurinol [25, 26], naproxen [27], diclofenac [28] and etidolac [29], we identified contemporary papers reviewing the early experience of these drugs for gout; none reported relevant randomized studies.
<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Intervention compareda</th>
<th>Diagnostic criteria</th>
<th>Joints affectedb</th>
<th>Results</th>
<th>Jadad score</th>
</tr>
</thead>
</table>
| **NSAID vs placebo for acute gout**
| de la Torre [11] | 30 | Tenoxicam 40 mg vs placebo | Clinical criteria + crystals or hyperuricaemia | Knee (14), ankle (7), wrists (4), elbow (3), big toe (2) | After one day: ≥50% reduction in spontaneous pain seen in 67% of tenoxicam and 26% of placebo group (P < 0.05). After four days: ≥50% reduction in spontaneous pain seen in 100% of both groups. After one day: ≥50% reduction in pain on mobilization of affected joint seen in 27% of tenoxicam and 7% of placebo group (P < 0.05). After 4 days: ≥50% reduction in pain on mobilization reported by 87% of tenoxicam and 93% of placebo group (NS). Adverse events: 2/15 in placebo group. None reported in tenoxicam group. | 4 |
| **NSAID vs NSAID for acute gout**
| Altman et al. [16] | 59 | Indometacin 225 mg for one day then 150 mg vs ketoprofen 450 mg for one day then 300 mg | Crystals or clinical criteria | Not stated | Measured on a 0–3 scale (0 = no pain, 3 = severe) mean pain after one day 0.91 for indometacin and 10.8 for ketoprofen. 70% of indometacin and 76% of ketoprofen reported good improvement after one day. No statistically significant difference in outcome measures. Adverse events: 16/30 in indometacin and 15/29 in ketoprofen group. Complete pain relief was seen at a mean of 3.75 days in acemethacin group and 1.06 days in indometacin group. No statistical test applied. Adverse events: None reported in acemethacin group, one reported in indometacin group. | 3 |
| Dorfler [19] | 10 | Indometacin 300 mg (days 1 and 2), 200 mg (day 3), 180 mg (days 4 and 5) vs acemethacin 360 mg (days 1 and 2), 240 mg (day 3), 180 mg (days 4 and 5) | Not stated | Not stated | Complete pain relief was seen at a mean of 3.75 days in acemethacin group and 1.06 days in indometacin group. No statistical test applied. Adverse events: None reported in acemethacin group, one reported in indometacin group. | 3 |
| Eberl and Dunky [15] | 20 | Indometacin 200 mg for one day then 150 mg vs meclofenamate 900 mg for one day then 300 mg daily | Previous history or hyperuricaemia | Knee (8), big toe (7), ankle (4), wrists (1), thumb (1) | After one day pain improved by 9% in indometacin group and by 16% in meclofenamate group. After two days the improvements were 22 and 33%, respectively. No statistical test applied. Adverse events: 50% of indometacin and 20% of meclofenamate group. | 2 |
| Klumb et al. [20] | 34 | Indometacin 200 mg (day 1), 150 mg (day 2–4), 100 mg (days 5–7) vs nimesulide 400 mg (day 1), 300 mg (days 2–4), 200 mg (day 5–7) | Crystals or hyperuricaemia + history | Knee (31%), ankle (27%), big toe (27%), wrist (12%), elbow (3%) | Rest pain measured on 0–5 visual scale. At day 3 rest pain 0.75 in nimesulide group and 0.71 in indometacin group. At day 7 rest pain 0 in nimesulide group and 0.13 in indometacin group. No statistically significant difference. Adverse events: 17/34 consultations in indometacin group, 14/39 consultations in nimesulide group. Two-day pain data presented graphically only. No statistically significant difference in any outcome measures. | 3 |
| Lederman [17] | 60 | Etodolac 600 mg vs naproxen 1500 mg | Previous history or hyperuricaemia | Not stated | Adverse events: 1/29 in etodolac group. None reported in naproxen group. | 2 |
Maccagno et al. [18] 61 Etodolac 600 mg vs naproxen 1000 mg

Previous history + hyperuricaemia Not stated

Measured on a 1–5 scale (1 = none, 5 = very severe) after two days mean pain was 2.6 in etodolac group and 2.8 in naproxen group (NS). After two days 81% of etodolac group and 53% of naproxen group reported one or more point improvement in patients’ global assessment, measured on a 1–5 scale (1 = very good 5 = very poor) (no statistical test applied). After four days etodolac is reported to have a statistically significant greater benefit than indometacin on tenderness, range of motion and physician global assessment. Data are presented graphically only. These may be chance findings as a result of multiple comparisons.

Schumacher et al. [12] 150 Etoricoxib 120 mg vs indometacin 150 mg

ACR criteria Great toe (55%), other (36%), ankle (32%), knee (27%)

Difference in pain days 2–5, 0.11 (95% CI −0.14, 0.35). Within predefined bounds for equivalence (−0.5–0.5). Difference in patients’ global assessment of response on 0–4 scale (0 = excellent, 4 = poor) over days 2–8 was 0.10 (95% CI −0.22, 0.41).

Adverse events: 35/75 of etoricoxib and 45/75 of indometacin groups had adverse clinical experiences (P = 0.003).

Shrestha et al. [13] 20 Single dose intramuscular ketorolac 60 mg vs single dose oral indometacin. Followed by indometacin for both groups

ACR criteria7 Not stated

Difference in pain days 2–5, 0.08 (95% CI −0.29, 0.13). Within predefined bounds for equivalence (−0.5–0.5). Difference in patients’ global assessment of response on 0–4 scale (0 = excellent, 4 = poor) over days 2–8 was −0.11 (95% CI −0.39, 0.17).

Adverse events: none in either group.

Rubin et al. [14] 189 Etoricoxib 120 mg vs indometacin 150 mg

ACR criteria MTP (56%), ankle (48%), other (40%), Knee (25%), great toe proximal IP joint (20%)

At 24 h: ≥50% reduction in pain seen in 41% of colchicine group and 9% of placebo group (NS). At 48 h: ≥50% reduction in pain seen in 73% colchicine group and 36% of placebo group (P < 0.05).

Adverse events: All (22/22) colchicine group developed diarrhoea and/or vomiting (median time to onset 24 h) in 41% ≥50% improvement in pain occurred before toxicity. 5/21 of the placebo group experienced nausea.

Colchicine vs placebo for acute gout

Ahern et al. [21] 43 Colchicine 1 mg initially then 0.5 mg every 2 h vs placebo

Crystals Knee, ankle, wrist, MTP, MCP, IP

At 24 h: ≥50% reduction in pain seen in 41% of colchicine group and 9% of placebo group (NS). At 48 h: ≥50% reduction in pain seen in 73% colchicine group and 36% of placebo group (P < 0.05).

Adverse events: All (22/22) colchicine group developed diarrhoea and/or vomiting (median time to onset 24 h) in 41% ≥50% improvement in pain occurred before toxicity. 5/21 of the placebo group experienced nausea.

Continued.
<table>
<thead>
<tr>
<th>Study</th>
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<th>Intervention compared</th>
<th>Diagnostic criteria</th>
<th>Joints affected</th>
<th>Results</th>
<th>Jadad score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids and adrenocorticotrophic hormone (ACTH) for acute gout</td>
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<td>Pain after one and two days not reported. Mean days to 100% resolution 7.92 in ACTH group and 7.60 in triamcinolone group ($P = 0.89$). 9/14 of ACTH group and 5/16 of triamcinolone group required one or more additional injection. Two of ACTH group also received triamcinolone because of failure to resolve after third injection. Adverse events: not reported.</td>
<td>2</td>
</tr>
<tr>
<td>Siegel et al. [22]</td>
<td>31</td>
<td>Intramuscular ACTH 40iu vs intramuscular triamcinolone acetonide 60mg</td>
<td>Crystals</td>
<td>Not stated</td>
<td></td>
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<tr>
<td>Schlesinger et al. [23]</td>
<td>19</td>
<td>Topical ice therapy for 30 min 4 times per day vs no topical ice.</td>
<td>Crystals</td>
<td>Knee (9), ankle (3), 1st MTP (5), MCP (2)</td>
<td>All participants received prednisolone 30mg for 2 days, 20mg for 2 days then 10mg for 2 days plus colchicine 0.6mg per day. Pain after one and two days not reported. After one week mean reduction in pain, measured on 10cm visual analogue score, 7.75cm in ice group and 4.42cm for controls $P = 0.021$ Wilcoxon rank sum test. Randomization was by ‘blindly drawing a folded paper’. Adverse events: not reported.</td>
<td>0</td>
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<tr>
<td>Other treatments for acute gout</td>
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<tr>
<td>Prevention of recurrent gout</td>
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<td></td>
<td>Conference abstract only. Cross over after 12–15 months. Serum urate 0.58mmol/l in colchicine group and 0.35mmol/l in colchicine + sulphinpyrazone group. 29 attacks of gout in 170 months of follow-up in colchicine group and 32 attacks of gout in 173 months of follow-up for Colchicine + sulphinpyrazone group. No statistical tests applied.</td>
<td>2</td>
</tr>
<tr>
<td>Gaines and Shulman [24]</td>
<td>14</td>
<td>Colchicine + placebo vs colchicine + sulphinpyrazone 400–800mg</td>
<td>Unclear</td>
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</tbody>
</table>

*aAll doses are total daily dose unless otherwise stated.
*bMultiple joints affected in some studies.
*cClinical features plus birefringent crystals on joint aspiration.
*dAmerican College of Rheumatology criteria [37].
Table 2. Excluded studies

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Intervention compared</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute gout</strong></td>
<td></td>
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<tr>
<td>Unavailable treatments for acute gout</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bach [38]</td>
<td>28</td>
<td>Intramuscular phenylbutazone vs intramuscular diclofenac</td>
<td>In German. Translated abstract indicates no difference in outcome.</td>
</tr>
<tr>
<td>Butler et al. [39]</td>
<td>33</td>
<td>Phenylbutazone vs flurbiprofen</td>
<td>Pain at one or two days not reported. Median duration of attack 3 days for phenylbutazone and 4 for flurbiprofen $P &gt; 0.10$. Not an intention-to-treat analysis.</td>
</tr>
<tr>
<td>Cheng et al. [40]</td>
<td>62</td>
<td>(a) Diclofenac vs rofecoxib</td>
<td>Single blind study, participants aware of allocation. Modified intention-to-treat analysis. Pain after one or two days not reported. Measured on 0-4 scale (0 = none, 4 = extreme) mean improvements in pain after 12 h were 1.6, 1.8 and 1.5 in rofecoxib, diclofenac and meloxicam groups, respectively. No statistical test applied. 84, 57 and 40% of rofecoxib, diclofenac and meloxicam groups, respectively, reported good or excellent response to treatment after 3 days (diclofenac vs rofecoxib not significant, meloxicam vs rofecoxib $P = 0.005$).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(b) Meloxicam vs rofecoxib</td>
<td></td>
</tr>
<tr>
<td>Chou and Kuo [41]</td>
<td>20</td>
<td>Indomethacin vs danggui-nian-tong-tang</td>
<td>Pain at one or two days not reported. Report of 31 attacks of gout in 28 subjects. Mean days to pain relief 3.6 for phenylbutazone and 4.5 for flufenamic acid.  No statistical test applied.</td>
</tr>
<tr>
<td>Ma et al. [43]</td>
<td>40</td>
<td>Tongfengkang vs indomethacin + allopurinol</td>
<td>Inadequate randomization. After 10 days 14/20 of Tongfengkang and 15/20 allopurinol + indomethacin groups reported the treatment to be highly effective.</td>
</tr>
<tr>
<td>Reardon et al. [44]</td>
<td>24</td>
<td>Phenylbutazone vs feprazone</td>
<td>Pain at one or two days not reported. Mean time to response 2.3 days for phenylbutazone and 2 days for flufenamic acid. No statistical test applied.</td>
</tr>
<tr>
<td>Ruotsi and Vainio [45]</td>
<td>18</td>
<td>Indomethacin vs proquazone</td>
<td>No pain data reported. 8/9 of indomethacin and 7/9 proquazone groups reported substantial improvement or complete remission. Follow-up time not stated. No statistical test applied.</td>
</tr>
<tr>
<td>Siegmeth and Placheta [46]</td>
<td>46</td>
<td>Intramuscular phenylbutazone vs intramuscular ketoprofen</td>
<td>In German. English abstract indicates no statistically significant differences between groups.</td>
</tr>
<tr>
<td>Smyth and Percy [47]</td>
<td>28</td>
<td>Phenylbutazone vs indomethacin</td>
<td>Reports 31 attacks of gout in 28 subjects. Pain at one or two days not reported. Mean time to complete recovery 5 days in both groups. No statistical test applied.</td>
</tr>
<tr>
<td>Sturge et al. [48]</td>
<td>41</td>
<td>Phenylbutazone vs naproxen</td>
<td>Mean time to end of attack 3.4 days in phenylbutazone group and 2.9 days in naproxen group (NS). In Spanish. English abstract indicates that both groups improved. Outcome similar in both groups. No statistical tests applied.</td>
</tr>
<tr>
<td>Valdes et al. [49]</td>
<td>20</td>
<td>Indomethacin vs carprofen</td>
<td>Pain at one or two days not reported. Mean reduction in overall severity after one and two days were 31 and 53%, respectively for phenylbutazone and 35 and 59% for carprofen. Differences were not statistically significant.</td>
</tr>
<tr>
<td>Weiner et al. [50]</td>
<td>30</td>
<td>Phenylbutazone vs fenoprofen</td>
<td></td>
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<tr>
<td><strong>Inadequate randomization</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Alloway et al. [51]</td>
<td>27</td>
<td>Intramuscular triamcinolone acetonide vs oral indomethacin</td>
<td>Those with contra-indications to indomethacin received triamcinolone acetonide. Mean time to resolution for indomethacin was 8 days and for triamcinolone it was 7 days. Alternate allocation used, prior to onset of gout attack. Mean time to pain relief for ACTH was 3 h and to indomethacin it was 24 h.</td>
</tr>
<tr>
<td>Axelrod and Preston [52]</td>
<td>76</td>
<td>Intramuscular adrenocorticotropic hormone vs indomethacin</td>
<td></td>
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</tbody>
</table>

Continued.
<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Intervention compared</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lomen et al. [53]</td>
<td>29</td>
<td>Flurbiprofen vs indometacin</td>
<td>First two participants at each centre received the same treatment. More than 50% of patients in both groups showed improvement after 24 h.</td>
</tr>
<tr>
<td>Fraser et al. [18]</td>
<td>93</td>
<td>Indometacin vs azapropazone</td>
<td>No pain data reported. 40/46 azapropazone and 35/47 indometacin groups reported treatment suited them.</td>
</tr>
<tr>
<td><strong>Recurrence gout</strong></td>
<td></td>
<td></td>
<td>(NS) 10/47 and 8/46 left indometacin and azapropazone groups, respectively because of reported side effects.</td>
</tr>
<tr>
<td><strong>Unavailable treatments for the prevention of recurrent gout</strong></td>
<td></td>
<td></td>
<td>Subjects did not have gout.</td>
</tr>
<tr>
<td>Berg [54]</td>
<td>60</td>
<td>Allopurinol vs allopurinol + benz bromarone</td>
<td>Conference abstract only. In Chinese. Follow-up for 12 weeks. English abstract reports incidence of acute gout 5% in benz bromarone group and 17% in probenecid group (P &lt; 0.001).</td>
</tr>
<tr>
<td>Bluhm and Riddle [55]</td>
<td>35</td>
<td>Probenecid vs halofate</td>
<td>25 attacks of gout in 47 subjects in allopurinol group and 18 attacks in 46 subjects in azapropazone group. Urate results presented graphically only. No significant differences.</td>
</tr>
<tr>
<td>Liang [56]</td>
<td>74</td>
<td>Benzbromarone vs probenecid</td>
<td>In German. Translation indicates not all subjects had gout.</td>
</tr>
<tr>
<td>Fraser et al. [57]</td>
<td>93</td>
<td>Allopurinol vs azapropazone</td>
<td>Only data from 38 subjects, deemed to be compliant because of a fall in serum urate, were included in the analysis. Mean number of attacks per month was 0.48 in the probenecid group and 0.19 in the probenecid + colchicine group (P &lt; 0.05). Not truly randomized, participants allocated by last digit of hospital number. Follow-up for up to 2 yrs, 9/20 in allopurinol group and 8/17 of probenecid group had no further attacks of gout.</td>
</tr>
<tr>
<td>Frerick et al. [58]</td>
<td>80</td>
<td>Allopurinol vs allopurinol + benz bromarone</td>
<td>Three subjects in colchicine + allopurinol group deemed non-compliant because serum urate did not fall re-allocated to colchicine group for analysis. Over 1 yr, 30% of colchicine group and 19% of colchicine + allopurinol group had recurrent attacks of gout (NS).</td>
</tr>
<tr>
<td>Paulus et al. [59]</td>
<td>51</td>
<td>Probenecid vs probenecid + colchicine</td>
<td>Trial of colchicine for first 3 months of allopurinol treatment. Mean number of flares in 3 months: 0.52 in colchicine group, 2.92 in placebo group (P = 0.008), in months 3-6 mean number of flares 0 in the colchicine group and 1.05 in placebo group (P = 0.033). Follow-up for 1 month only.</td>
</tr>
<tr>
<td>Scott et al. [60, 61]</td>
<td></td>
<td>Allopurinol vs probenecid</td>
<td>Follow-up for 3 months only. 26% of azapropazone group and 52% of allopurinol + colchicine group had repeat acute attack.</td>
</tr>
<tr>
<td><strong>Study not truly randomized</strong></td>
<td></td>
<td></td>
<td>Previous attacks of gout were not an entry requirement for patients to be entered into study.</td>
</tr>
<tr>
<td><strong>Follow-up/treatment period less than 6 months</strong></td>
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<td>Borstad et al. [63]</td>
<td>43</td>
<td>Colchicine + allopurinol vs placebo + allopurinol</td>
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<td>Chou and Kuo [41]</td>
<td>20</td>
<td>Allopurinol vs danggui-niantong-tang</td>
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<td>Gibson et al. [64]</td>
<td>40</td>
<td>Azapropazone vs Allopurinol + colchicine</td>
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<td><strong>Study entrants did not all have gout</strong></td>
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<tr>
<td>Ettinger et al. [65]</td>
<td>60</td>
<td>Allopurinol vs placebo</td>
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Acute gout

There is only one small randomized controlled trial to support the use of NSAIDs for the treatment of acute gout. The size, quality and comparisons made in most of the studies comparing different NSAIDs are such that they cannot inform our management. The only robust conclusion that can be drawn from the available randomized data is that the pain-relieving properties of indometacin and etoricoxib are equivalent. However, in the absence of a placebo-controlled trial of either of these drugs for the treatment of gout, we can only speculate on the magnitude of their clinical effect. The high incidence of gastrointestinal and other side effects of the high dose of indometacin used to treat acute gout is well-documented [30]. Etoricoxib has fewer gastrointestinal adverse events, but concerns about cardiovascular adverse events from COX-2 inhibitors mean that this cannot be assumed to be a safer option than indometacin (http://medicines.mhra.gov.uk/ourwork/monitorsafequalmed/safetymessages/ddlcox2170205.pdf). Likewise, although colchicine appears to be effective in one randomized controlled trial, it has too high an incidence of adverse reactions for routine use [21, 31].

The incidence of gout is highest in the elderly population [32], who may be frail, and it is particularly common in those with cardiovascular disease [33]. It is in this group, who are at high risk of serious adverse events, that we are using drugs of known toxicity in the absence of randomized controlled trials of their effectiveness.

There is a need to re-appraise how we treat acute gout. This re-appraisal needs to consider the risks and benefits of the drugs we use to treat a condition that usually improves spontaneously even without treatment [34]. For example, does a treatment with analgesics or oral steroids and ice packs [23] provide an improved balance between risks and benefits compared with routine treatment with non-selective NSAIDs, COX-2 inhibitors or colchicine for most patients with acute gout?

Prevention of recurrent gout

Allopurinol is the mainstay of recurrent gout prevention. In 2002–03, 2,423,000 allopurinol prescriptions, at a cost of £6,848,000, were dispensed in England (http://www.publications.doh.gov.uk/stats/pca2003.htm). Making a very crude assumption that each person on prophylactic allopurinol has 12 prescriptions per year, then at least 200,000 people in England are on regular allopurinol.

The absence of long-term data on the effect of allopurinol on either incidence of recurrent gout or serum urate is surprising, particularly as it has well-recognized, rare but serious side effects [9, 35]. A number of studies show that it does reduce serum urate, at least in the short term [36] and there is a well-documented relationship between serum urate and the incidence of acute gout [32]. These data, and extensive clinical experience, suggest that allopurinol is effective in preventing recurrent gout.

There is a need to re-appraise how we use allopurinol and sulphinpyrazone. For example, what are the risks and benefits of allopurinol/sulphinpyrazone? At what levels of urate and frequency of attacks is it worth considering allopurinol/sulphinpyrazone?

Although there are no randomized controlled trials of dietary changes for the prevention of recurrent gout, there are now good-quality observational data showing the relationship between...
diet and alcohol intake, and a first attack of gout [5, 6]. These data suggest that practical lifestyle changes may be an alternative to drug treatment. The role of lifestyle advice for the prevention of recurrent gout also needs to be re-assessed.

What is already known on this topic:

- Gout is a common disorder.
- Non-steroidal anti-inflammatory drugs or colchicine are common treatments for acute gout. Allopurinol or sulphinpyrazone are commonly used to prevent recurrence.
- All of the drugs used in the management of gout can have potentially serious side effects.

What this study adds:

- The efficiency of drugs commonly used to treat gout has not been established.
- The balance of risks and benefits from these drugs is unknown.
- Current approaches to the treatment of gout need to be re-assessed.

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References


