National Institute for Health and Care Excellence

Guideline version (Draft for Consultation)

# Gout: Diagnosis and Management

## [F] Evidence reviews for timing of urate-lowering therapy in relation to a flare, in people with gout

*NICE guideline <number>*

*Evidence reviews underpinning recommendation 1.5.4 and research recommendations in the NICE guideline*

*December 2021*

*Draft for Consultation*

*Developed by the National Guideline Centre, hosted by the Royal College of Physicians*

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ISBN:

# Contents

# Timing of urate-lowering therapy

## 1.1 Review question: When should urate-lowering therapy be started, in relation to a flare, in people with gout?

### 1.1.1 Introduction

Historically, it has been recommended that ULT is commenced at least 2 weeks, often later, following complete resolution of a gout flare. The reasons for this are two-fold: firstly, people are more likely to be able to discuss and absorb information and understand the need for long-term ULT when they are pain-free and not also dealing with an acute episode of gout. Secondly, as ULT can precipitate acute flares of gout when first introduced, there is potential to exacerbate a current flare if commenced during an acute episode of gout.

Some clinicians, however, adopt a differing viewpoint regarding timing of ULT initiation, believing that treatment should be initiated as soon as possible for the following reasons; firstly, people with intermittent episodes of gout that resolve rapidly with acute treatment may not return for review to discuss long-term, curative treatment with ULT and continue to have acute episodes of flare with associated morbidity. Secondly, people who have very frequent episodes of flare may have no opportunity to introduce ULT in a convalescent period between flares.

This review can address what evidence there is for waiting to commence ULT following resolution of flare as opposed to commencing treatment during a flare episode and the appropriate time to discuss the reason ULT is advised for long-term management of people with gout.

### 1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

**Table 1: PICO characteristics of review question**

| | |
|---|---|
| **Population** | Inclusion: Adults (18 years and older) with gout<br><br>Strata: None<br><br>Exclusion: People with calcium pyrophosphate crystal deposition, including pseudogout. (CPPD), also known as pseudogout. |
| **Intervention(s)** | Comparison 1:<br>Starting ULT at a specific time-point, for example:<br>• During a gout flare<br>• Immediately after a gout flare<br>• Another time-point<br><br>Comparison 2:<br>• Starting ULT during a flare |
| **Comparison(s)** | Comparison 1: |

| | |
|---|---|
| | • Starting ULT at a different time-point<br><br>Comparison 2:<br>• Starting placebo during flare<br>• Receiving usual care during flare.<br>• No ULT during a flare |
| **Outcomes** | All outcomes are considered equally important for decision making and therefore have all been rated as critical:<br>• health-related quality of life (e.g. as described by SF-36, Gout Assessment Questionnaire (GAQ) and the Gout Impact Scale (GIS) or other validated gout-specific HRQoL measures<br>• pain (measured on a visual analogue scale (VAS) or numerical rating scale such as the five-point Likert scale, or reported as pain relief of 50% or greater)<br>• joint swelling/joint inflammation<br>• joint tenderness<br>• frequency of flares<br>• flare duration<br>• patient global assessment of treatment success (response to treatment) (e.g. Likert scales, visual analogue scales (VAS), numerical ratings scales (NRS))<br>• serum urate levels<br>• admissions (hospital and A&E/urgent care)<br>• GP visits<br><br>Timepoints: short (up to two weeks), medium (two to six weeks) and long (> six weeks) term |
| **Study design** | RCT<br><br>Systematic reviews of RCTs<br><br>If insufficient RCT evidence is available (no or little evidence for interventions/comparisons), search for non-randomised studies (prospective and retrospective cohort studies will be considered if they adjust for key confounders:<br>• Age<br>• Gender<br><br>Published NMAs will be considered for inclusion. |

### 1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

## 1.1.4 Effectiveness evidence

### 1.1.4.1 Included studies

Two randomised controlled studies were included in the review[5, 13] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3 - Table 6).

Both studies examined the effect of allopurinol during a flare.

One randomised controlled trial evaluated allopurinol (mild severity dose 100-200 mg) versus placebo in mixed population of people with and without CKD. Patients were enrolled within 72 hours of starting flare treatment. One randomised controlled trial evaluated allopurinol (moderate severity dose 300-600 mg) in a non-CKD population. Patients were enrolled within 7 days of flare onset.

See also the study selection flow chart in Appendix C, study evidence tables in Appendix D, forest plots in Appendix E and GRADE tables in Appendix F.

### 1.1.4.2 Excluded studies

See the excluded studies list in Appendix J.

## 1.1.5 Summary of studies included in the effectiveness evidence

**Table 2: Summary of studies included in the evidence review**

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| Hill 20155 | Intervention (n=16)<br>Allopurinol for mild gout 100-200mg. Allopurinol initiated at 100mg daily for the first 14 days, and then increased to 200mg daily for the next 14 days. Duration 28 days. Concurrent medication/care: People were treated for acute gout as deemed appropriate by their referring physician. Each person was treated with prophylactic oral colchicine 0.6mg daily for the first 2 days, then 0.6mg twice daily from days 3-28. Dose reductions to 0.6mg daily were made for concomitant statin use or gastrointestinal intolerance. People unable to take colchicine because of prior adverse reactions received 15mg oral meloxicam daily for prophylaxis during allopurinol initiation.<br><br>Comparison (n=19)<br>Placebo. Duration 27 days. Concurrent medication/care: People were treated for acute gout as deemed appropriate by their referring physician. Each person was treated with | n=37<br>Study enrolled people within 72 hours of starting flare treatment.<br>People with an acute gout attack were considered if they met at least 1 of the following additional criteria for starting urate-lowering therapy: the presence of gouty tophi; more than 1 acute gout attack per year; a history of nephrolithiasis; urate overproduction (>1000mg in 24-hour urine collection)<br><br>Age – mean years (SD): 56.6 (31-84).<br><br>Gender (M:F): 56.6 (31-84)<br><br>Ethnicity: Not stated<br><br>Country: USA | Joint tenderness at 28 days<br><br>Joint inflammation at 28 days | CKD - mixed population (people with CKD and people without CKD). |

| Study | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|
| | prophylactic oral colchicine 0.6mg daily for the first 2 days, then 0.6mg twice daily from days 3-28. Dose reductions to 0.6mg daily were made for concomitant statin use or gastrointestinal intolerance. People unable to take colchicine because of prior adverse reactions received 15mg oral meloxicam daily for prophylaxis during allopurinol initiation. | | | |
| Taylor 201213 | Intervention (n=31)<br>Allopurinol 300mg. Duration 10 days. Concurrent medication/care: In addition to the 10-day course of allopurinol all patients received indomethacin 50 mg 3 times per day for 10 days and colchicine 0.6 mg 2 times per day for 90 days. All patients were started on open-label allopurinol 300 mg daily on day 11 and followed for 30 day<br><br>Comparison (n=26)<br>Placebo. Duration 10 days. Concurrent medication/care: In addition to the 10-day course of placebo, all patients received indomethacin 50 mg 3 times per day for 10 days and colchicine 0.6 mg 2 times per day for 90 days. | n=57<br>Patients presenting within 7 days of onset of an acute gout attack were evaluated, and American College of Rheumatology criteria for acute arthritis of gout were met, including the presence of monosodium urate crystals on arthrocentesis of the primary joint on the day of study entry<br><br>Age – mean years (SD): allopurinol group 57(14), placebo group 61(11)<br><br>Gender (M:F): all male – 51(100%)<br><br>Ethnicity: not stated<br><br>Country: USA | Frequency of flares at 30 days | CKD status was not mentioned in the study |

See Appendix D for full evidence tables.

### 1.1.6 Summary of the effectiveness evidence

**Table 3: Clinical evidence summary: urate lowering therapy during gout flare: allopurinol versus placebo**

| Outcomes | № of participants (studies) Follow up | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with placebo | Risk difference with allopurinol |
| Flares (new or recurrent flares) | 51 (1 RCT) | LOW[a] | RR 0.64 (0.12 to 3.52) | 120 per 1,000 | 43 fewer per 1,000 (106 fewer to 302 more) |
| Joint inflammation (evidence of new joint inflammation, <3 months) | 34 (1 RCT) | LOW[a] | Peto OR 7.39 (0.15 to 372.38) | 0 per 1,000 | 60 more per 1,000 (90 fewer to 210 more) |
| Joint tenderness (pain in a new joint, <3 months) | 34 (1 RCT) | LOW[a] | RR 2.00 (0.20 to 20.04) | 59 per 1,000 | 59 more per 1,000 (47 fewer to 1,120 more) |

a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GRADE default MIDs were used; for dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25.

## 1.1.7 Economic evidence

### 1.1.7.1 Included studies

No health economic studies were included.

### 1.1.7.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix G.

## 1.1.8 Economic model

This area was not prioritised for new cost-effectiveness analysis.

## 1.1.9 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

| Resource | Cost per unit | Dosage |
|---|---|---|
| Allopurinol 100mg tablet | £0.04 | 100mg – 900mg per day |
| Allopurinol 300mg tablet | £0.06 | |
| Febuxostat 80mg tablet | £0.10 | 80mg – 120mg per day |
| Febuxostat 120mg tablet | £0.87 | |

*Source: British National Formulary, September 2021*[2]

## 1.1.10 Evidence statements

**Economic**

- No relevant economic evaluations were identified.

## 1.1.11 The committee's discussion and interpretation of the evidence

### 1.1.11.1. The outcomes that matter most

The committee considered the following outcomes as important for decision-making: health-related quality of life, pain, joint swelling/joint inflammation, joint tenderness, frequency of flares, flare duration, patient global assessment of treatment success, serum urate levels, admissions (hospital and A&E/urgent care) and GP visits. Evidence was found only for joint inflammation, joint tenderness and frequency of flares outcomes.

The committee decided to combine joint swelling and joint inflammation as they agreed that these outcomes are synonymous for people with gout. The committee also agreed to categorise time-points reported in the included studies by short-term (up to two weeks), medium-term (two to six weeks) and long-term (more six weeks).

### 1.1.11.2 The quality of the evidence

Two small randomised controlled trials (RCTs) evaluating long-term urate lowering therapies in patients during gout flares were identified. Neither looked at different timepoints for starting ULT but instead were the second comparison in the protocol of starting ULT during a flare. The studies were stratified by dose of allopurinol. One study initiated low dose allopurinol and the other moderate dose allopurinol.

One study compared low dose allopurinol (100-200mg) versus placebo in a mixed CKD population. The study enrolled people within 72 hours of starting flare treatment. The outcome data available was for inflammation and joint tenderness. All outcomes were reported as medium-term (two to six weeks). The quality of evidence was low for both outcomes due to imprecision.

The other study evaluated moderate dose allopurinol (300 mg) versus placebo in a non-CKD population. The study enrolled people within 7 days of flare onset. Outcome data was available for frequency of flares at medium-term (two to six weeks). The quality of evidence was low due to imprecision.

#### 1.1.11.3 Benefits and harms

The evidence showed a clinical harm for allopurinol when compared to placebo for joint inflammation and joint tenderness at medium-term (two to six weeks). The evidence showed no clinical difference for frequency of flares outcome at medium-term (two to six weeks). No evidence was found for Febuxostat. There was no evidence comparing starting urate lowering therapy at different time-points as both studies included patients during gout flare.

The committee agreed that the evidence was very limited as only two small (n=34 and n=51 patients), low-graded quality studies were included in the review. Although there was some evidence suggesting harm for inflammation of joints and joint tenderness, in a mixed CKD population, the committee noted the very low number of events and concluded the evidence was insufficient to base a recommendation on.

The committee discussed that historical, non-evidence based practice is to start urate-lowering therapy only after a flare has fully resolved. It is considered this reduces the risk of extending or further exacerbating the gout flare and this approach continues to be reflected in current practice. The reason for this might be because people were often started on allopurinol 300mg daily, which may be more likely to exacerbate an existing flare. It would be preferable to commence a lower starting dose of allopurinol and up-titrate slowly according to measured serum urate. The committee suggested that exacerbation of flares may be less common if people are prescribed ULT using a treat to target approach, starting at a low dose with slow up-titration.

For some people who experience frequent flares, it can be difficult to identify a flare-free window of sufficient duration to commence treatment. In these circumstances starting treatment during a flare may be unavoidable However, the committee also acknowledged initiating treatment during a flare may not be a good time if the person is in pain and unable to process the information about ULTs at that time point.

Colchicine was prescribed as prophylaxis against flares in both studies and the committee agreed a clinician would discuss with the person the option of taking either this, an NSAID or corticosteroid to help prevent flares when starting ULT. If prophylactic treatment is prescribed when starting ULT, the committee agreed there would be no reason to delay treatment until the flare subsided but agreed the decision on when to start should be based on patient preference.

Given the limited evidence, the committee decided to make a consensus recommendation based on their experience that if people with gout wish to start urate-lowering therapy this can be commenced either after a gout flare or during a flare if they are frequent.

The committee agreed because the evidence was very limited further research on the most effective time to initiate ULT was needed and decided to make a research recommendation.

#### 1.1.11.4 Cost effectiveness and resource use

No economic evidence was identified for this review question. Unit costs were presented to aid the committee's consideration of cost effectiveness.

The committee noted that delaying ULT initiation until after a gout flare has subsided may be a barrier to initiating treatment because a proportion of people may not return for another appointment as they are symptom free. In general, the committee discussed that not initiating ULT will result in downstream consequences for both a patient's quality of life and costs to the NHS due to more frequent flares and the need to access healthcare systems. In addition, starting ULT during a flare would reduce the cost of initial prophylaxis treatment by the duration of the person's gout flare (approximately one to two weeks). However, the committee noted these cost savings are minimal due to the low cost of NSAIDs, colchicine, and corticosteroids.

Conversely, the committee noted that when people are experiencing a gout flare, they may be in too much pain to process information about initiating ULT. The committee were also concerned that if people initiated ULT during a gout flare this may make the flare worse, and therefore people might discontinue their ULT. Subsequently the committee made a recommendation to start ULT two to four weeks after a gout flare has settled. The committee suggested GPs should provide a prescription for ULT when a person presents with a gout flare and provide education about commencing ULT. The information provided should include the dose to initiate ULT and instruction on when to initiate ULT (most likely two to four weeks following an acute flare). The committee discussed that this would remove the requirement for an additional GP appointment after a gout flare and also mitigate the risk of a person not re-presenting to their GP for a follow-up appointment to initiate ULT.

The committee agreed that delaying initiation of ULTs can be troublesome for people experiencing a high frequency of gout flares. For these groups of people, it may be impossible to initiate ULT when they are not experiencing a gout flare. Therefore, within the committee's recommendation it was stipulated ULT can be started during a flare for people experiencing more frequent flares.

The recommendations made are generally in line with current practice however these more optimised recommendations as to when to initiate ULTs could increase the number of people receiving ULTs and therefore there may be some resource impact. Although at the same time these recommendations will improve patient outcomes and reduce flare related costs to the NHS and ULTs have been found to be cost effective (Evidence Review E).

### 1.1.12 Recommendations supported by this evidence review

This evidence review supports recommendations 1.5.4 and the research recommendation on the effectiveness of starting ULT during a flare compared with starting ULT once a flare has settled.

### 1.1.13 References

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# Appendices

## Appendix A – Review protocols

Review protocol for when should urate-lowering therapy be started, in relation to a flare, in people with gout?

| ID | Field | Content |
|---|---|---|
| 0. | PROSPERO registration number | CRD42021246610 |
| 1. | Review title | When should urate-lowering therapy be started, in relation to a flare, in people with gout? |
| 2. | Review question | When should urate-lowering therapy be started, in relation to a flare, in people with gout? |
| 3. | Objective | To determine when people with gout who are identified as requiring urate-lowering therapy should have their treatment initiated? |
| 4. | Searches | The following databases (from inception) will be searched:<br>Cochrane Central Register of Controlled Trials (CENTRAL)<br>Cochrane Database of Systematic Reviews (CDSR)<br>Embase<br>MEDLINE<br><br>Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details)<br><br>Searches will be restricted by:<br>English language studies<br>Human studies<br><br>The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant.<br><br>The full search strategies will be published in the final review. |
| 5. | Condition or domain being studied | Gout (including people with gout and chronic kidney disease) |

| | | |
|---|---|---|
| 6. | Population | Inclusion: Adults (18 years and older) with gout<br><br>Strata: None<br><br>Exclusion: People with calcium pyrophosphate crystal deposition, including pseudogout. |
| 7. | Intervention | Comparison 1:<br>• Starting ULT at a specific time-point, for example:<br>• During a gout flare<br>• Immediately after a gout flare<br>• Another time-point<br><br>Comparison 2:<br>• Starting ULT during a flare |
| 8. | Comparator | Comparison 1:<br>• Starting ULT at a different time-point<br><br>Comparison 2:<br>• Starting placebo during flare<br>• Receiving usual care during flare.<br>• No ULT during a flare. |
| 9. | Types of study to be included | RCT<br>Systematic reviews of RCTs<br>If insufficient RCT evidence is available (no or little evidence for interventions/comparisons), search for non-randomised studies (prospective and retrospective cohort studies will be considered if they adjust for key confounders:<br>• Age<br>• Gender<br>Published NMAs will be considered for inclusion. |

| | | |
|---|---|---|
| 10. | Other exclusion criteria | • Non-English language studies.<br>• Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available. |
| 11. | Context | As part of who should get ULT, it was thought important to answer when should ULT be given. There is uncertainty as to whether ULT should be given during a gout flare or after for the best outcomes. |
| 12. | Primary outcomes (critical outcomes) | All outcomes are considered equally important for decision making and therefore have all been rated as critical:<br>• health-related quality of life (e.g. as described by SF-36, Gout Assessment Questionnaire (GAQ) and the Gout Impact Scale (GIS) or other validated gout-specific HRQoL measures<br>• pain (measured on a visual analogue scale (VAS) or numerical rating scale such as the five-point Likert scale, or reported as pain relief of 50% or greater)<br>• joint swelling/joint inflammation<br>• joint tenderness<br>• frequency of flares<br>• flare duration<br>• patient global assessment of treatment success (response to treatment) (e.g. Likert scales, visual analogue scales (VAS), numerical ratings scales (NRS))<br>• serum urate levels<br>• admissions (hospital and A&E/urgent care)<br>• GP visits<br>• Time-points: short (up to two weeks), medium (two to six weeks) and long (> six weeks) term |
| 13. | Secondary outcomes (important outcomes) | None |
| 14. | Data extraction (selection and coding) | EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be |

| | | |
|---|---|---|
| | | screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above.<br><br>A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4).<br><br>10% of all evidence reviews are quality assured by a senior research fellow. This includes checking:<br><br>papers were included /excluded appropriately<br><br>a sample of the data extractions<br><br>correct methods are used to synthesise data<br><br>a sample of the risk of bias assessments<br><br>Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.<br><br>Study investigators may be contacted for missing data where time and resources allow. |
| 15. | Risk of bias (quality) assessment | Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual<br><br>For Intervention reviews<br><br>Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS)<br><br>Randomised Controlled Trial: Cochrane RoB (2.0)<br><br>Non-randomised study, including cohort studies: Cochrane ROBINS-I |
| 16. | Strategy for data synthesis | Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences.<br><br>Heterogeneity between the studies in effect measures will be assessed using the $I^2$ statistic and visually inspected. An $I^2$ value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups |

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| | | using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects.<br><br>If sufficient data is available and it is methodologically appropriate, network meta-analysis (NMA) will conducted.<br><br>NMA will be prioritised for the following outcomes, based on the importance of the outcomes for decision-making and the committee's knowledge about the availability of evidence:<br>Serum urate levels<br>Frequency of flares<br><br>GRADEpro will be used to assess the quality of evidence for each risk factors, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome.<br><br>The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/<br><br>Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. | |
| 17. | Analysis of sub-groups | Subgroups that will be investigated if heterogeneity is present:<br>• Setting (primary and secondary care)<br>CKD (with or without CKD) | |
| 18. | Type and method of review | ☒ | Intervention |
| | | ☐ | Diagnostic |
| | | ☐ | Prognostic |
| | | ☐ | Qualitative |
| | | ☐ | Epidemiologic |
| | | ☐ | Service Delivery |
| | | ☐ | Other (please specify) |
| 19. | Language | English | |

| | | | | |
|---|---|---|---|---|
| 20. | Country | England | | |
| 21. | Anticipated or actual start date | 4th December 2020 | | |
| 22. | Anticipated completion date | 13th June 2022 | | |
| 23. | Stage of review at time of this submission | Review stage | Started | Completed |
| | | Preliminary searches | ☑ | ☑ |
| | | Piloting of the study selection process | ☑ | ☑ |
| | | Formal screening of search results against eligibility criteria | ☑ | ☑ |
| | | Data extraction | ☐ | ☐ |
| | | Risk of bias (quality) assessment | ☐ | ☐ |
| | | Data analysis | ☐ | ☐ |
| 24. | Named contact | 5a. Named contact<br>National Guideline Centre<br><br>5b Named contact e-mail<br>managementofgout@nice.org.uk<br>5e Organisational affiliation of the review<br>National Institute for Health and Care Excellence (NICE) and National Guideline Alliance / National Guideline Centre / NICE Guideline Updates Team / NICE Public Health Guideline Development Team | | |
| 25. | Review team members | From the National Guideline Centre:<br>Gill Ritchie [Guideline lead]<br>Sedina Lewis [Senior systematic reviewer]<br>Audrius Stonkus [Systematic reviewer]<br>Alexandra Bonnon [Health economist]<br>Amber Hernaman [Project manager]<br>Joseph Runicles [Information specialist] | | |
| 26. | Funding sources/sponsor | This systematic review is being completed by the National Guideline Centre which receives funding from NICE. | | |
| 27. | Conflicts of interest | All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert | | |

| | | |
|---|---|---|
| | | witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline. |
| 28. | Collaborators | Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage]. |
| 29. | Other registration details | [Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.] |
| 30. | Reference/URL for published protocol | [Give the citation and link for the published protocol, if there is one.] |
| 31. | Dissemination plans | NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as:<br>notifying registered stakeholders of publication<br>publicising the guideline through NICE's newsletter and alerts<br>issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE. |
| 32. | Keywords | [Give words or phrases that best describe the review.] |
| 33. | Details of existing review of same topic by same authors | [Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible. NOTE: most NICE reviews will not constitute an update in PROSPERO language. To be an update it needs to be the same review |

| | | | |
|---|---|---|---|
| | | question/search/methodology. If anything has changed it is a new review] | |
| 34. | Current review status | ☒ | Ongoing |
| | | ☐ | Completed but not published |
| | | ☐ | Completed and published |
| | | ☐ | Completed, published and being updated |
| | | ☐ | Discontinued |
| 35.. | Additional information | [Provide any other information the review team feel is relevant to the registration of the review.] | |
| 36. | Details of final publication | www.nice.org.uk | |

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## 1 Health economic review protocol

| Review question | All questions – health economic evidence |
|---|---|
| **Objectives** | To identify health economic studies relevant to any of the review questions. |
| **Search criteria** | • Populations, interventions and comparators must be as specified in the clinical review protocol above.<br>• Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis).<br>• Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.)<br>• Unpublished reports will not be considered unless submitted as part of a call for evidence.<br>• Studies must be in English. |
| **Search strategy** | A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below. |
| **Review strategy** | Studies not meeting any of the search criteria above will be excluded. Studies published before 2005 abstract-only studies and studies from non-OECD countries or the USA will also be excluded.<br>Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[10]<br><br>**Inclusion and exclusion criteria**<br>• If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile.<br>• If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile.<br>• If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included.<br><br>**Where there is discretion**<br>The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.<br><br>The health economist will be guided by the following hierarchies.<br>*Setting:*<br>• UK NHS (most applicable).<br>• OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). |

| | |
|---|---|
| | • OECD countries with predominantly private health insurance systems (for example, Switzerland).<br>• Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.<br>*Health economic study type:*<br>• Cost–utility analysis (most applicable).<br>• Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).<br>• Comparative cost analysis.<br>• Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.<br>*Year of analysis:*<br>• The more recent the study, the more applicable it will be.<br>• Studies published in 2005 or later but that depend on unit costs and resource data entirely or predominantly from before 2005 will be rated as 'Not applicable'.<br>• Studies published before 2005 will be excluded before being assessed for applicability and methodological limitations.<br>*Quality and relevance of effectiveness data used in the health economic analysis:*<br>• The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline. |

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# Appendix B – Literature search strategies

- When should urate-lowering therapy be started, in relation to a flare, in people with gout?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[10]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

## B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

**Table 4: Database date parameters and filters used**

| Database | Dates searched | Search filter used |
|---|---|---|
| Medline (OVID) | 1946 – 06 July 2021 | Randomised controlled trials<br>Systematic review studies<br>Observational studies<br><br>Exclusions (animal studies, letters, comments) |
| Embase (OVID) | 1974 – 06 July 2021 | Randomised controlled trials<br>Systematic review studies<br>Observational studies<br><br>Exclusions (animal studies, letters, comments) |
| The Cochrane Library (Wiley) | Cochrane Reviews to 2021 Issue 7 of 12<br>CENTRAL to 2021 Issue 7 of 12 | None |

**Medline (Ovid) search terms**

| | |
|---|---|
| 1. | exp Gout/ |
| 2. | gout*.ti,ab. |
| 3. | toph*.ti,ab. |
| 4. | podagra.ti,ab. |
| 5. | pseudogout.ti,ab. |
| 6. | or/1-5 |
| 7. | letter/ |
| 8. | editorial/ |
| 9. | news/ |
| 10. | exp historical article/ |

| | |
|---|---|
| 11. | Anecdotes as Topic/ |
| 12. | comment/ |
| 13. | case report/ |
| 14. | (letter or comment*).ti. |
| 15. | or/7-14 |
| 16. | randomized controlled trial/ or random*.ti,ab. |
| 17. | 15 not 16 |
| 18. | animals/ not humans/ |
| 19. | exp Animals, Laboratory/ |
| 20. | exp Animal Experimentation/ |
| 21. | exp Models, Animal/ |
| 22. | exp Rodentia/ |
| 23. | (rat or rats or mouse or mice).ti. |
| 24. | or/17-23 |
| 25. | 6 not 24 |
| 26. | Limit 25 to English language |
| 27. | randomized controlled trial.pt. |
| 28. | controlled clinical trial.pt. |
| 29. | randomi#ed.ti,ab. |
| 30. | placebo.ab. |
| 31. | randomly.ti,ab. |
| 32. | Clinical Trials as topic.sh. |
| 33. | trial.ti. |
| 34. | or/27-33 |
| 35. | Meta-Analysis/ |
| 36. | exp Meta-Analysis as Topic/ |
| 37. | (meta analy* or metanaly* or metaanaly* or meta regression).ti,ab. |
| 38. | ((systematic* or evidence*) adj3 (review* or overview*)).ti,ab. |
| 39. | (reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab. |
| 40. | (search strategy or search criteria or systematic search or study selection or data extraction).ab. |
| 41. | (search* adj4 literature).ab. |
| 42. | (medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab. |
| 43. | cochrane.jw. |
| 44. | ((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab. |
| 45. | or/35-44 |
| 46. | Epidemiologic studies/ |
| 47. | Observational study/ |
| 48. | exp Cohort studies/ |
| 49. | (cohort adj (study or studies or analys* or data)).ti,ab. |
| 50. | ((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab. |

| | |
|---|---|
| 51. | ((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab. |
| 52. | Controlled Before-After Studies/ |
| 53. | Historically Controlled Study/ |
| 54. | Interrupted Time Series Analysis/ |
| 55. | (before adj2 after adj2 (study or studies or data)).ti,ab. |
| 56. | exp case control studies/ |
| 57. | case control*.ti,ab. |
| 58. | Cross-sectional studies/ |
| 59. | (cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab. |
| 60. | or/46-59 |
| 61. | 26 and (34 or 45 or 60) |

1 **Embase (Ovid) search terms**

| | |
|---|---|
| 1. | exp Gout/ |
| 2. | gout*.ti,ab. |
| 3. | toph*.ti,ab. |
| 4. | podagra.ti,ab. |
| 5. | pseudogout.ti,ab. |
| 6. | or/1-5 |
| 7. | letter.pt. or letter/ |
| 8. | note.pt. |
| 9. | editorial.pt. |
| 10. | case report/ or case study/ |
| 11. | (letter or comment*).ti. |
| 12. | or/7-11 |
| 13. | randomized controlled trial/ or random*.ti,ab. |
| 14. | 12 not 13 |
| 15. | animal/ not human/ |
| 16. | nonhuman/ |
| 17. | exp Animal Experiment/ |
| 18. | exp Experimental Animal/ |
| 19. | animal model/ |
| 20. | exp Rodent/ |
| 21. | (rat or rats or mouse or mice).ti. |
| 22. | or/14-21 |
| 23. | 6 not 22 |
| 24. | Limit 23 to English language |
| 25. | random*.ti,ab. |
| 26. | factorial*.ti,ab. |
| 27. | (crossover* or cross over*).ti,ab. |
| 28. | ((doubl* or singl*) adj blind*).ti,ab. |
| 29. | (assign* or allocat* or volunteer* or placebo*).ti,ab. |
| 30. | crossover procedure/ |
| 31. | single blind procedure/ |

| | |
|---|---|
| 32. | randomized controlled trial/ |
| 33. | double blind procedure/ |
| 34. | or/25-33 |
| 35. | systematic review/ |
| 36. | meta-analysis/ |
| 37. | (meta analy* or metanaly* or metaanaly* or meta regression).ti,ab. |
| 38. | ((systematic* or evidence*) adj3 (review* or overview*)).ti,ab. |
| 39. | (reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab. |
| 40. | (search strategy or search criteria or systematic search or study selection or data extraction).ab. |
| 41. | (search* adj4 literature).ab. |
| 42. | (medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab. |
| 43. | cochrane.jw. |
| 44. | ((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab. |
| 45. | or/35-44 |
| 46. | Clinical study/ |
| 47. | Observational study/ |
| 48. | family study/ |
| 49. | longitudinal study/ |
| 50. | retrospective study/ |
| 51. | prospective study/ |
| 52. | cohort analysis/ |
| 53. | follow-up/ |
| 54. | cohort*.ti,ab. |
| 55. | 53 and 54 |
| 56. | (cohort adj (study or studies or analys* or data)).ti,ab. |
| 57. | ((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab. |
| 58. | ((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab. |
| 59. | (before adj2 after adj2 (study or studies or data)).ti,ab. |
| 60. | exp case control study/ |
| 61. | case control*.ti,ab. |
| 62. | cross-sectional study/ |
| 63. | (cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab. |
| 64. | or/46-52,55-63 |
| 65. | 24 and (34 or 45 or 64) |

1 **Cochrane Library (Wiley) search terms**

| | |
|---|---|
| #1. | MeSH descriptor: [Gout] explode all trees |
| #2. | gout*:ti,ab |
| #3. | toph*:ti,ab |
| #4. | podagra:ti,ab |
| #5. | pseudogout:ti,ab |

| | |
|---|---|
| #6. | (or #1-#5) |

## B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to a Gout population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA – this ceased to be updated after March 2018). NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics studies and quality of life studies.

**Table 5: Database date parameters and filters used**

| Database | Dates searched | Search filter used |
|---|---|---|
| Medline | Health Economics<br>1 January 2014 – 14 June 2021<br>Quality of Life<br>1946 – 14 June 2021 | Health economics studies<br>Quality of life studies<br><br>Exclusions (animal studies, letters, comments) |
| Embase | Health Economics<br>1 January 2014 – 14 June 2021<br>Quality of Life<br>1974 – 14 June 2021 | Health economics studies<br>Quality of life studies<br><br>Exclusions (animal studies, letters, comments) |
| Centre for Research and Dissemination (CRD) | HTA - Inception – 31 March 2018<br>NHSEED - Inception to March 2015 | None |

**Medline (Ovid) search terms**

| | |
|---|---|
| 1. | exp Gout/ |
| 2. | gout*.ti,ab. |
| 3. | toph*.ti,ab. |
| 4. | Uric Acid/ |
| 5. | uric acids*.ti,ab. |
| 6. | (urate adj (crystal* or sodium or mono sodium)).ti,ab. |
| 7. | hyperuricemia/ |
| 8. | (hyperuric* or hyper uric*).ti,ab. |
| 9. | podagra.ti,ab. |
| 10. | or/1-9 |
| 11. | letter/ |
| 12. | editorial/ |
| 13. | news/ |

| | |
|---|---|
| 14. | exp historical article/ |
| 15. | Anecdotes as Topic/ |
| 16. | comment/ |
| 17. | case report/ |
| 18. | (letter or comment*).ti. |
| 19. | or/11-18 |
| 20. | randomized controlled trial/ or random*.ti,ab. |
| 21. | 19 not 20 |
| 22. | animals/ not humans/ |
| 23. | exp Animals, Laboratory/ |
| 24. | exp Animal Experimentation/ |
| 25. | exp Models, Animal/ |
| 26. | exp Rodentia/ |
| 27. | (rat or rats or mouse or mice).ti. |
| 28. | or/21-27 |
| 29. | 10 not 28 |
| 30. | limit 29 to English language |
| 31. | Economics/ |
| 32. | Value of life/ |
| 33. | exp "Costs and Cost Analysis"/ |
| 34. | exp Economics, Hospital/ |
| 35. | exp Economics, Medical/ |
| 36. | Economics, Nursing/ |
| 37. | Economics, Pharmaceutical/ |
| 38. | exp "Fees and Charges"/ |
| 39. | exp Budgets/ |
| 40. | budget*.ti,ab. |
| 41. | cost*.ti. |
| 42. | (economic* or pharmaco?economic*).ti. |
| 43. | (price* or pricing*).ti,ab. |
| 44. | (cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab. |
| 45. | (financ* or fee or fees).ti,ab. |
| 46. | (value adj2 (money or monetary)).ti,ab. |
| 47. | or/31-46 |
| 48. | quality-adjusted life years/ |
| 49. | sickness impact profile/ |
| 50. | (quality adj2 (wellbeing or well being)).ti,ab. |
| 51. | sickness impact profile.ti,ab. |
| 52. | disability adjusted life.ti,ab. |
| 53. | (qal* or qtime* or qwb* or daly*).ti,ab. |
| 54. | (euroqol* or eq5d* or eq 5*).ti,ab. |

| | |
|---|---|
| 55. | (qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab. |
| 56. | (health utility* or utility score* or disutilit* or utility value*).ti,ab. |
| 57. | (hui or hui1 or hui2 or hui3).ti,ab. |
| 58. | (health* year* equivalent* or hye or hyes).ti,ab. |
| 59. | discrete choice*.ti,ab. |
| 60. | rosser.ti,ab. |
| 61. | (willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab. |
| 62. | (sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab. |
| 63. | (sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab. |
| 64. | (sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab. |
| 65. | (sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab. |
| 66. | (sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab. |
| 67. | or/48-66 |
| 68. | 30 and (47 or 67) |

1 **Embase (Ovid) search terms**

| | |
|---|---|
| 1. | exp gout/ |
| 2. | gout*.ti,ab. |
| 3. | toph*.ti,ab. |
| 4. | exp uric acid/ |
| 5. | uric acid*.ti,ab. |
| 6. | (urate adj (crystal* or sodium or mono sodium)).ti,ab. |
| 7. | exp hyperuricemia/ |
| 8. | (hyperuric* or hyper uric*).ti,ab. |
| 9. | podagra.ti,ab. |
| 10. | or/1-9 |
| 11. | letter.pt. or letter/ |
| 12. | note.pt. |
| 13. | editorial.pt. |
| 14. | Case report/ or Case study/ |
| 15. | (letter or comment*).ti. |
| 16. | or/11-15 |
| 17. | randomized controlled trial/ or random*.ti,ab. |
| 18. | 16 not 17 |
| 19. | animal/ not human/ |
| 20. | Nonhuman/ |
| 21. | exp Animal Experiment/ |
| 22. | exp Experimental animal/ |
| 23. | Animal model/ |
| 24. | exp Rodent/ |
| 25. | (rat or rats or mouse or mice).ti. |
| 26. | or/18-25 |
| 27. | 10 not 26 |

| | |
|---|---|
| 28. | limit 27 to English language |
| 29. | health economics/ |
| 30. | exp economic evaluation/ |
| 31. | exp health care cost/ |
| 32. | exp fee/ |
| 33. | budget/ |
| 34. | funding/ |
| 35. | budget*.ti,ab. |
| 36. | cost*.ti. |
| 37. | (economic* or pharmaco?economic*).ti. |
| 38. | (price* or pricing*).ti,ab. |
| 39. | (cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab. |
| 40. | (financ* or fee or fees).ti,ab. |
| 41. | (value adj2 (money or monetary)).ti,ab. |
| 42. | or/29-41 |
| 43. | quality adjusted life year/ |
| 44. | "quality of life index"/ |
| 45. | short form 12/ or short form 20/ or short form 36/ or short form 8/ |
| 46. | sickness impact profile/ |
| 47. | (quality adj2 (wellbeing or well being)).ti,ab. |
| 48. | sickness impact profile.ti,ab. |
| 49. | disability adjusted life.ti,ab. |
| 50. | (qal* or qtime* or qwb* or daly*).ti,ab. |
| 51. | (euroqol* or eq5d* or eq 5*).ti,ab. |
| 52. | (qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab. |
| 53. | (health utility* or utility score* or disutilit* or utility value*).ti,ab. |
| 54. | (hui or hui1 or hui2 or hui3).ti,ab. |
| 55. | (health* year* equivalent* or hye or hyes).ti,ab. |
| 56. | discrete choice*.ti,ab. |
| 57. | rosser.ti,ab. |
| 58. | (willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab. |
| 59. | (sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab. |
| 60. | (sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab. |
| 61. | (sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab. |
| 62. | (sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab. |
| 63. | (sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab. |
| 64. | or/43-63 |
| 65. | 28 and (42 or 64) |

1 **NHS EED and HTA (CRD) search terms**

| | |
|---|---|
| #1. | MeSH DESCRIPTOR Gout EXPLODE ALL TREES |
| #2. | (gout*) |
| #3. | (toph*) |
| #4. | MeSH DESCRIPTOR Uric Acid EXPLODE ALL TREES |

| | |
|---|---|
| #5. | (uric acid*) |
| #6. | ((urate near (crystal* or sodium or mono sodium))) |
| #7. | MeSH DESCRIPTOR Hyperuricemia EXPLODE ALL TREES |
| #8. | ((hyperuric* or hyper uric*)) |
| #9. | (podagra) |
| #10. | #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 |

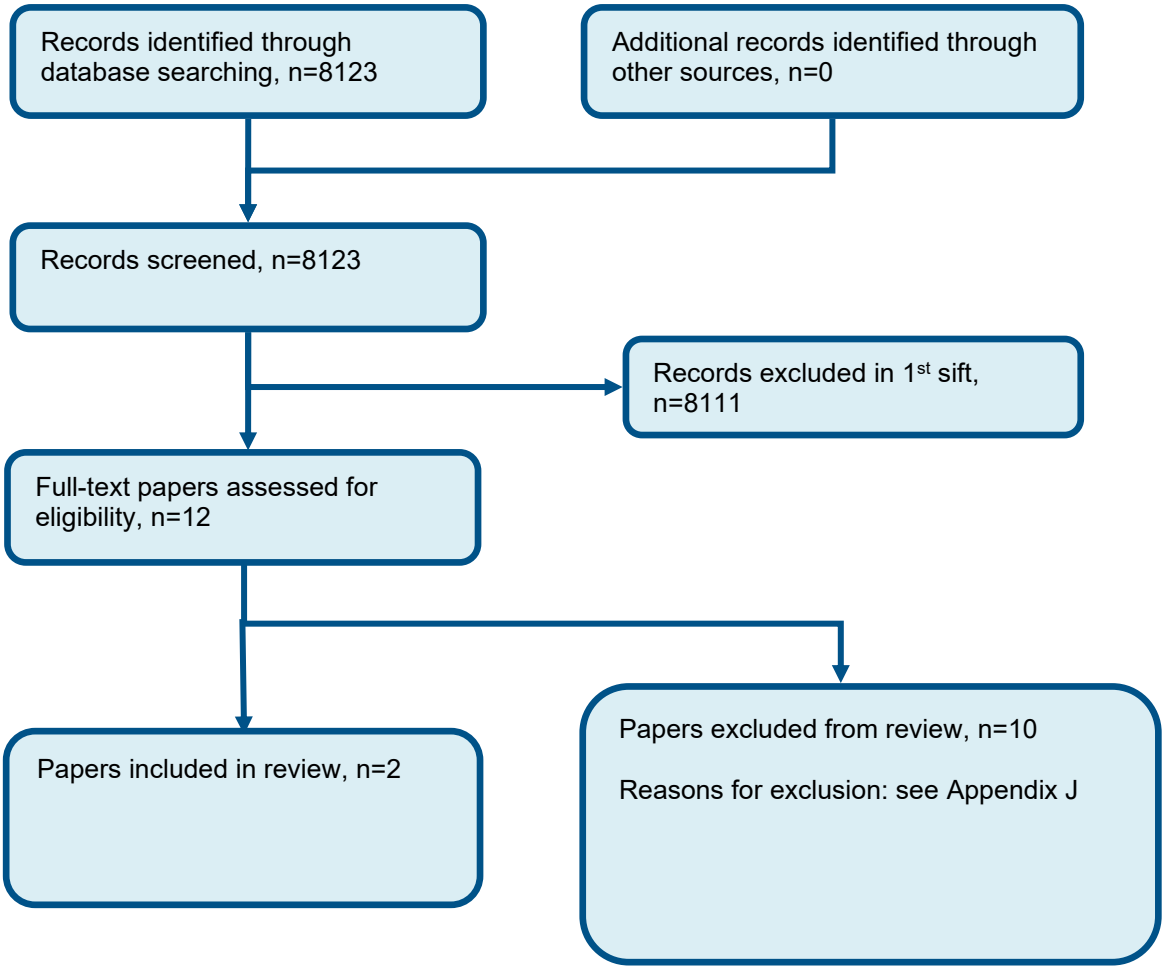
1

2

3

# Appendix C – Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of when should urate-lowering therapy be started, in relation to a flare, in people with gout?



# Appendix D – Effectiveness evidence

| Study | Hill 2015[5] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=37) |
| Countries and setting | Conducted in USA; Setting: Outpatient follow up |
| Line of therapy | 1st line |
| Duration of study | Intervention + follow up: 28 days |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis: People with crystal-proven gout by arthrocentesis presenting with an acute gout attack within 72 hours after initial therapy |
| Stratum | Mixed population (people with chronic kidney disease and people without chronic kidney disease) |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | People with an acute gout attack were considered if they met at least 1 of the following additional criteria for starting urate-lowering therapy: the presence of gouty tophi; more than 1 acute gout attack per year; a history of nephrolithiasis; urate overproduction (>1000mg in 24-hour urine collection) |
| Exclusion criteria | Glomerular filtration rate of less than 50mL/min; aspartate and alanine aminotransferases or alkaline phosphatase greater than 1.25 times the upper limit of normal; prior use of allopurinol in the past 6 months; history of an adverse reaction to allopurinol; ongoing cancer treatment; myelodysplastic syndrome; leukaemia; women of childbearing potential; concomitant use of azathioprine or cyclophosphamide; inability to return for repeated examinations; premorbid pain in the involved joint of more than 3 on a 10-point numerical rating scale; neurologic deficit causing decreased pain sensation around the involved joint |
| Recruitment/selection of patients | No additional information |
| Age, gender and ethnicity | Age - Mean (range): 56.6 (31-84). Gender (M:F): 33:2. Ethnicity: Not stated |
| Further population details | 1. Age: < 65 years 2. Setting: Secondary care |
| Extra comments | Baseline serum urate: Not stated |
| Indirectness of population | No indirectness |

| | |
|---|---|
| Interventions | (n=16) Intervention 1: Xanthine oxidase inhibitor - Allopurinol for mild gout 100-200mg. Allopurinol initiated at 100mg daily for the first 14 days, and then increased to 200mg daily for the next 14 days. Duration 28 days. Concurrent medication/care: People were treated for acute gout as deemed appropriate by their referring physician. Each person was treated with prophylactic oral colchicine 0.6mg daily for the first 2 days, then 0.6mg twice daily from days 3-28. Dose reductions to 0.6mg daily were made for concomitant statin use or gastrointestinal intolerance. People unable to take colchicine because of prior adverse reactions received 15mg oral meloxicam daily for prophylaxis during allopurinol initiation. Indirectness: No indirectness<br>Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only):<br><br>(n=19) Intervention 2: Uricase - Rasburicase. Placebo. Duration 27 days. Concurrent medication/care: People were treated for acute gout as deemed appropriate by their referring physician. Each person was treated with prophylactic oral colchicine 0.6mg daily for the first 2 days, then 0.6mg twice daily from days 3-28. Dose reductions to 0.6mg daily were made for concomitant statin use or gastrointestinal intolerance. People unable to take colchicine because of prior adverse reactions received 15mg oral meloxicam daily for prophylaxis during allopurinol initiation. Indirectness: No indirectness<br>Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): |
| Funding | Funding not stated |

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ALLOPURINOL FOR MILD GOUT 100-200MG versus PLACEBO

Protocol outcome 1: Joint swelling/joint inflammation at short (< 3 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Joint inflammation at 28 days; Group 1: 1/17, Group 2: 0/17
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: Serious indirectness, Comments: Dichotomous outcome rather than continuous; Baseline details: Reported age, gender, disease duration, previous attacks, nephrolithiasis, tophi, erosions and initial treatment; Group 1 Number missing: 2, Reason: 1 unable to make visits, 1 epistaxis; Group 2 Number missing: 2, Reason: 1 nausea and vomiting, 1 elevated liver enzymes

Protocol outcome 2: Joint tenderness at short (< 3 months)
- Actual outcome for Mixed population (people with chronic kidney disease and people without chronic kidney disease): Joint tenderness at 28 days; Group 1: 2/17, Group 2: 1/17
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: Serious indirectness, Comments: Dichotomous outcome rather than continuous; Baseline details: Reported age, gender, disease duration, previous attacks, nephrolithiasis, tophi, erosions and initial treatment; Group 1 Number missing: 2, Reason: 1 unable to make visits, 1 epistaxis; Group 2 Number missing: 2, Reason: 1 nausea and vomiting, 1 elevated liver enzymes

| | |
|---|---|
| Protocol outcomes not reported by the study | Health-related quality of life at short (< 3 months); Health-related quality of life at medium (3 to 12 months); Health-related quality of life at long (>12 months); Pain at short (< 3 months); Pain at medium (3 to 12 months); Pain at long (>12 months); Joint swelling/joint inflammation at medium (3 to 12 months); Joint swelling/joint inflammation at long (> 12 months); Joint tenderness at medium (3 to 12 months); Joint tenderness at long (> 12 months); Patient global assessment of treatment success (response to treatment) at short (< 3 months); Patient global assessment of treatment success (response to treatment) at medium (3 to 12 months); Patient global assessment of treatment success (response to treatment) at long (> 12 months); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at medium (3 to 12 months); Admissions (hospital & A&E) at medium 3 to 12 months); Admissions (hospital & A&E) at long (> 12 months); Discontinuation of ULT at short (< 3 months); Discontinuation of ULT at medium (3 to 12 months); Discontinuation of ULT at long (> 12 months); Frequency of flares at short (< 3 months); Frequency of flares at medium (3 to 12 months); Frequency of flares at long (> 12 months); Serum urate levels at short (< 3 months); Serum urate levels at medium (3 to 12 months); Serum urate levels at long (> 12 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at short (< 3 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at medium (3 to 12 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at long (> 12 months) |

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| **Study** | **Taylor 2012[13]** |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | (n=57) |
| Countries and setting | Conducted in USA |
| Line of therapy | 1st line |
| Duration of study | Intervention + follow up: 30 days |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis |
| Stratum | People without chronic kidney disease or people with CKD stages 1-2 |
| Subgroup analysis within study | Not applicable |

| | |
|---|---|
| Inclusion criteria | Patients presenting within 7 days of onset of an acute gout attack were evaluated, and American College of Rheumatology criteria for acute arthritis of gout were met, including the presence of monosodium urate crystals on arthrocentesis of the primary joint on the day of study entry |
| Exclusion criteria | Exclusion criteria included secondary gout (because it is dependent on the treatment of the underlying disease); the presence of tophaceous gout (because of concern that tophi could make evaluation of resolution and exacerbations difficult); a history of congestive heart failure; anticoagulant use; a recent serum creatinine greater than 1.3 mg/dL (because these patients should not receive indomethacin); or the use of steroids, colchicine, allopurinol, uricosuric drugs, chemotherapy, or immunosuppressive therapy in the past 6 months. Although all subjects brought to the attention of the principal investigator were screened consecutively, primary providers also made decisions regarding eligibility and subjects were highly selected by study criteria; thus, information regarding the number and characteristics of those excluded could not be reliably tracked. |
| Age, gender and ethnicity | Age - Mean (SD): Allopurinol 57(14); Placebo 61(11). Gender (M:F): male 51 (100%). Ethnicity: not reported |
| Further population details | 1. Age: < 65 years 2. Setting: Primary care |
| Indirectness of population | No indirectness |
| Interventions | (n=31) Intervention 1: Xanthine oxidase inhibitor - Allopurinol for moderate gout 300-600mg. Allopurinol 300mg. Duration 10 days. Concurrent medication/care: In addition to the 10-day course of allopurinol or placebo, all patients received indomethacin 50 mg 3 times per day for 10 days and colchicine 0.6 mg 2 times per day for 90 days. All patients were started on open-label allopurinol 300 mg daily on day 11 and followed for 30 days. Indirectness: No indirectness<br>Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): (Allopurinol 300mg).<br><br>(n=26) Intervention 2: Uricase - Rasburicase. Placebo. Duration 10 days. Concurrent medication/care: In addition to the 10-day course of allopurinol or placebo, all patients received indomethacin 50 mg 3 times per day for 10 days and colchicine 0.6 mg 2 times per day for 90 days. All patients were started on open-label allopurinol 300 mg daily on day 11 and followed for 30 days. Indirectness: No indirectness<br>Further details: 1. Choice of drug (drugs within the class, based on the intervention arm only): |
| Funding | No funding |

| | |
|---|---|
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ALLOPURINOL FOR MODERATE GOUT 300-600MG versus RASBURICASE<br><br>Protocol outcome 1: Frequency of flares at short (< 3 months)<br>- Actual outcome for People without chronic kidney disease or people with CKD stages 1-2: New or recurrent flares at 30 days; Group 1: 2/26, Group 2: 3/25<br>Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5; Group 2 Number missing: 1 | |
| Protocol outcomes not reported by the study | Health-related quality of life at short (< 3 months); Health-related quality of life at medium (3 to 12 months); Health-related quality of life at long (>12 months); Pain at short (< 3 months); Pain at medium (3 to 12 months); Pain at long (>12 months); Joint swelling/joint inflammation at short (< 3 months); Joint swelling/joint inflammation at medium (3 to 12 months); Joint swelling/joint inflammation at long (> 12 months); Joint tenderness at short (< 3 months); Joint tenderness at medium (3 to 12 months); Joint tenderness at long (> 12 months); Patient global assessment of treatment success (response to treatment) at short (< 3 months); Patient global assessment of treatment success (response to treatment) at medium (3 to 12 months); Patient global assessment of treatment success (response to treatment) at long (> 12 months); Adverse events – cardiovascular, renal and gastrointestinal (e.g. diarrhoea) at medium (3 to 12 months); Admissions (hospital & A&E) at short (< 3 months); Admissions (hospital & A&E) at medium 3 to 12 months); Admissions (hospital & A&E) at long (> 12 months); Discontinuation of ULT at short (< 3 months); Discontinuation of ULT at medium (3 to 12 months); Discontinuation of ULT at long (> 12 months); Frequency of flares at medium (3 to 12 months); Frequency of flares at long (> 12 months); Serum urate levels at short (< 3 months); Serum urate levels at medium (3 to 12 months); Serum urate levels at long (> 12 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at short (< 3 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at medium (3 to 12 months); Adverse events and complications of gout (radiographic joint damage, renal stones, tophi) at long (> 12 months) |

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# Appendix E – Forest plots

**Figure 2: CKD status not reported – allopurinol (moderate severity dose 300 - 600mg) vs placebo – Flares (new or recurrent) at <3 months**


**Figure 3: mixed CKD population – allopurinol (mild severity dose 100 - 200mg) vs placebo - Joint inflammation at <3 months**

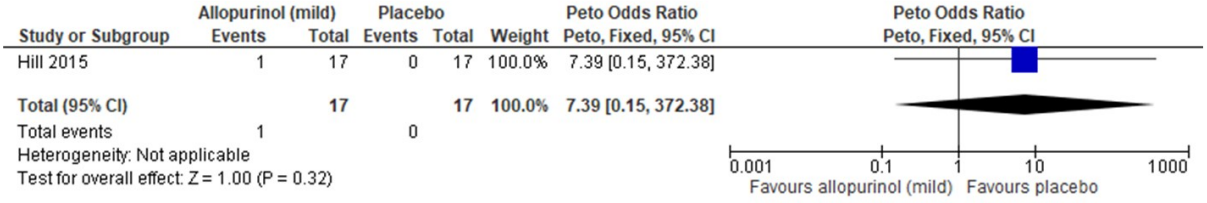
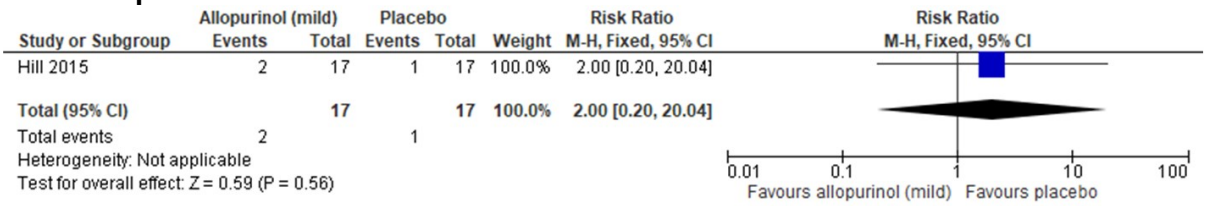



**Figure 4: mixed CKD population – allopurinol (mild severity dose 100 - 200mg) vs placebo – Joint tenderness at <3 months**



# Appendix F – GRADE

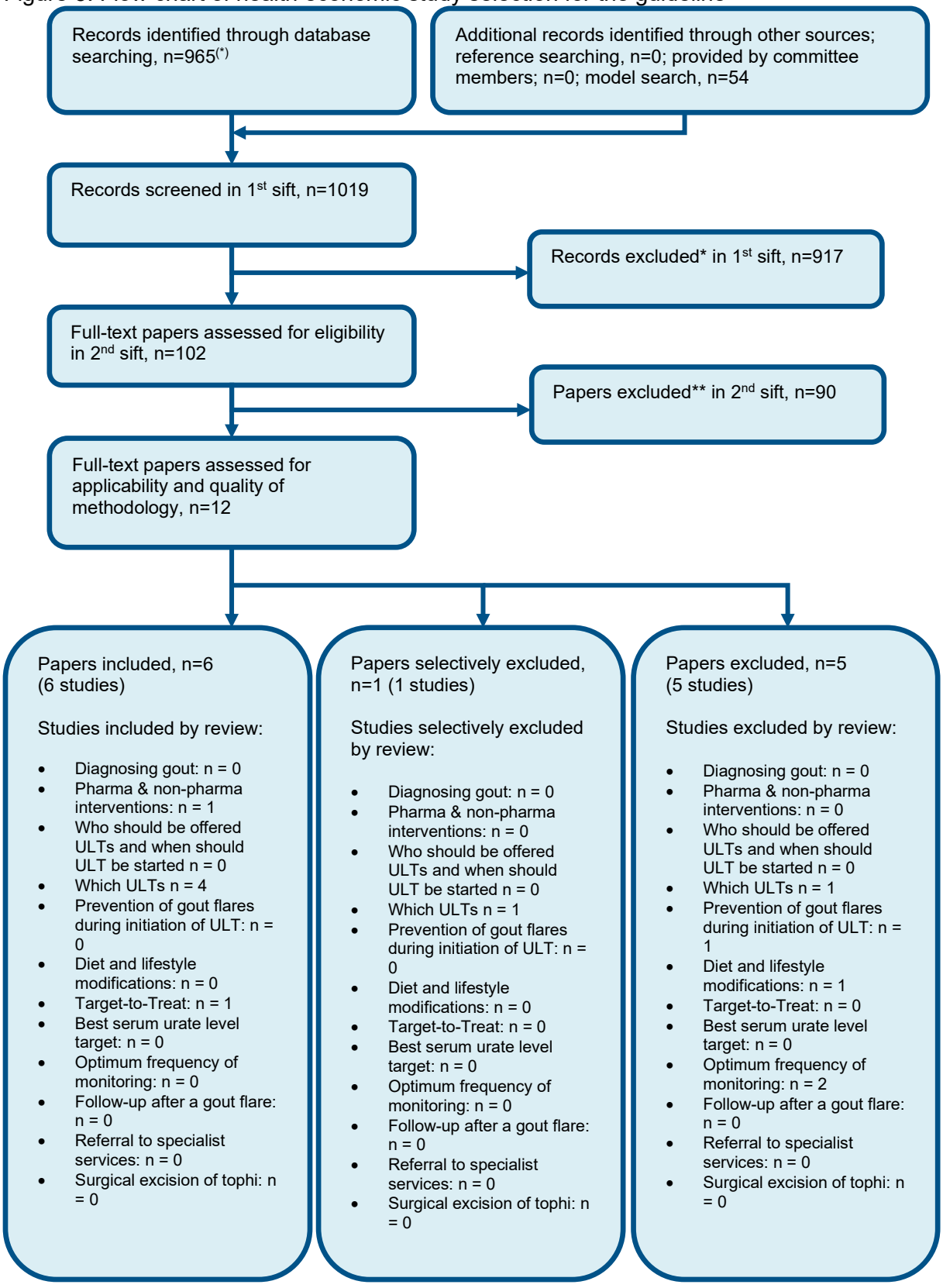
## Table 6: Clinical evidence summary: urate lowering therapy during gout flare: allopurinol versus placebo

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | during flare allopurinol | placebo | Relative (95% CI) | Absolute (95% CI) | | |
| **Flares (new or recurrent flares)** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | not serious | very serious [a] | none | 2/26 (7.7%) | 3/25 (12.0%) | **RR 0.64** (0.12 to 3.52) | **43 fewer per 1,000** (from 106 fewer to 302 more) | ⨁⨁◯◯ LOW | CRITICAL |
| **Joint inflammation (evidence of new joint inflammation, <3 months)** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | not serious | very serious [a] | none | 1/17 (5.9%) | 0/17 (0.0%) | **Peto OR 7.39** (0.15 to 372.38) | **60 more per 1,000** (from 90 fewer to 210 more) | ⨁⨁◯◯ LOW | CRITICAL |
| **Joint tenderness (pain in a new joint, <3 months)** | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | not serious | very serious [a] | none | 2/17 (11.8%) | 1/17 (5.9%) | **RR 2.00** (0.20 to 20.04) | **59 more per 1,000** (from 47 fewer to 1,000 more) | ⨁⨁◯◯ LOW | CRITICAL |

**a. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. GRADE default MIDs were; for dichotomous outcomes MIDs were taken to be RRs of 0.8 and 1.25.**

# 1 Appendix G – Economic evidence study selection

Figure 5: Flow chart of health economic study selection for the guideline




* excludes conference abstracts (n=280)

**Non-relevant population, intervention, comparison, design or setting; non-English language

# Appendix H – Economic evidence tables

None.

# Appendix I – Health economic model

No original economic modelling was undertaken for this review question.

# Appendix J – Excluded studies

## Clinical studies

**Table 7: Studies excluded from the clinical review**

| Study | Exclusion reason |
|---|---|
| Becker 2009[1] | Incorrect comparison - RCT comparing febuxostat 80mg versus febuxostat 120mg vs allopurinol 300mg, all starting at the same time point |
| Eminaga 2016[3] | Systematic review - of the studies had an incorrect intervention and comparison (azapropazone versus indomethacin) |
| Frazer 1987[4] | Incorrect comparison - azapropazone versus indomethacin (1-28 days) followed by allopurinol (29-225 days) |
| Huizinga 2011[6] | Incorrect comparison - Canakinumab (various doses) compared to Colchicine, both are not ULT |
| Jia 2021[7] | Incorrect dosage – febuxostat 40mg. |
| Latourte 2014[8] | Systematic review - incorrect interventions – prophylaxis for flares |
| Moon 2011[9] | Incorrect comparison - colchicine versus placebo (Colchicine is not ULT) |
| Schlesinger 2012[11] | Incorrect comparison - paper reported 2 RCTs, both comparing canakinumab 150mg vs triamcinolone 40mg, treatments starting at the same time |
| Taylor 2013[12] | Abstract only |
| Wortmann 2010[14] | Incorrect comparison – the paper reports 3 RCTs, all comparing Febuxostat 80mg vs febuxostat 120mg vs Allopurinol 300 mg, all at the same time point. |

## Health Economic studies

**None.**

# Appendix K- Research recommendations – full details

## Research recommendation

What is the clinical and cost effectiveness of starting ULT during a flare compared with starting ULT once a flare has settled?

## Why this is important

Long-term management of gout involves taking urate-lowering therapy (ULT) to reduce serum urate levels, prevent gout flares and shrink tophi. ULT is usually initiated a few weeks after a gout flare has settled because starting during a flare is thought to worsen the existing flare. If ULT is started and worsens the flare, the person may stop taking ULT because it is perceived as having made the gout worse. People with gout may also not consult with a clinician again after the flare has settled, losing the opportunity to start ULT. Furthermore, some people with gout have very frequent flares meaning there is not a long enough time-period between flares in which to start ULT.

## Rationale for research recommendation

| | |
|---|---|
| Importance to 'patients' or the population | Better understanding of whether initiating ULT during a gout flare exacerbates the existing flare would provide evidence to inform the timing of ULT initiation and hence improve uptake of and adherence to ULT. |
| Relevance to NICE guidance | Limited evidence was found comparing the effect on pain and inflammation of starting ULT during a flare with starting placebo. No studies were identified which compared starting ULT during a flare with starting it after the flare has settled. Further research in this area would support future updates of the guideline. |
| Relevance to the NHS | The outcome would determine the effect of starting ULT during a gout flare and inform the optimum time to start ULT. Better understanding of the extent to which starting ULT during a flare exacerbates the flare will provide information to improve uptake of and adherence to ULT and reduce frequent suboptimal management of gout. |
| National priorities | None |
| Current evidence base | We identified 2 small RCTs that compared starting ULT during a flare with starting placebo, but none which compared starting ULT during a flare with starting it once the flare has settled. |
| Equality considerations | None known |

# Modified PICO table

| | |
|---|---|
| Population | People with gout experiencing a gout flare |
| Intervention | ULT initiated during the flare |
| Comparator | ULT initiated 4 weeks after the flare has settled |
| Outcome | Pain severity, inflammation, quality of life, healthcare utilisation including hospitalisation for gout, adherence to ULT, serum urate level |
| Study design | Randomised controlled trial |
| Timeframe | Medium term (e.g. 6-12 months) |
| Additional information | None |