

# *Draft Systematic Review*

---

Number xx

## **Management of Gout**

**Prepared for:**

Agency for Healthcare Research and Quality  
U.S. Department of Health and Human Services  
540 Gaither Road  
Rockville, MD 20850  
www.ahrq.gov

**Contract No.**

**Prepared by:**

This information is distributed solely for the purposes of predissemination peer review. It has not been formally disseminated by the Agency for Healthcare Research and Quality. It does not represent and should not be construed to represent an Agency for Healthcare Research and Quality or Department of Health and Human Services (AHRQ) determination or policy.

**Investigators:**

**AHRQ Publication No. xx-EHCxxx**  
**<Month Year>**

This report is based on research conducted by an Evidence-based Practice Center (SCEPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. xxx-xxxx-xxxxx). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

This report may periodically be assessed for the urgency to update. If an assessment is done, the resulting surveillance report describing the methodology and findings will be found on the Effective Health Care Program Web site at [www.effectivehealthcare.ahrq.gov](http://www.effectivehealthcare.ahrq.gov). Search on the title of the report.

This document is in the public domain and may be used and reprinted without special permission. Citation of the source is appreciated.

Persons using assistive technology may not be able to fully access information in this report. For assistance contact [EffectiveHealthCare@ahrq.hhs.gov](mailto:EffectiveHealthCare@ahrq.hhs.gov).

None of the investigators has any affiliations or financial involvement related to the material presented in this report.
---

**Suggested citation:** To Be Added for Final Version

## Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see [www.effectivehealthcare.ahrq.gov/reference/purpose.cfm](http://www.effectivehealthcare.ahrq.gov/reference/purpose.cfm)

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site ([www.effectivehealthcare.ahrq.gov](http://www.effectivehealthcare.ahrq.gov)) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to [epc@ahrq.hhs.gov](mailto:epc@ahrq.hhs.gov).

Richard G. Kronick, Ph.D.  
Director  
Agency for Healthcare Research and Quality

David Meyers, M.D.  
Acting Director  
Center for Evidence and Practice Improvement  
Agency for Healthcare Research and Quality

Stephanie Chang M.D., M.P.H.  
Director, EPC Program  
Center for Evidence and Practice Improvement  
Agency for Healthcare Research and Quality

Aysegul Gozu, M.D., M.P.H.  
Task Order Officer  
Center for Evidence and Practice Improvement  
Agency for Healthcare Research and Quality

## **Acknowledgments**

The authors gratefully acknowledge the following individuals for their contributions to this project:

To Be Added For Final

## **Key Informants**

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

The list of Key Informants who participated in developing this report follows:

To Be Added For Final

## **Technical Expert Panel**

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

The list of Technical Experts who participated in developing this report follows:

To Be Added For Final Version

## **Peer Reviewers**

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential non-financial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential non-financial conflicts of interest identified.

The list of Peer Reviewers follows:

To Be Added For Final Version

# Management of Gout

## Structured Abstract

**Objectives.** To review the evidence base for treating patients with gout, both acute attacks and chronic disease. The review specifically focuses on the management of patients with gout in the primary care setting.

**Data Sources.** We searched Medline, EMBASE, the Cochrane Collection, and the Web of Science using the search terms “gout,” and “gouty,” and terms for tophi (from January 1, 2010 to April 28, 2014, or at least one year prior to the search dates for the most recent systematic reviews). We also obtained relevant references from 32 recent systematic reviews that cover nearly all of the Key Questions. We searched Clinicaltrials.gov and the Web of Science for recently completed studies and unpublished or non-peer-reviewed study findings. Searches were not limited by language of publication.

**Review Methods.** We used standard systematic review methods including duplicate screening and data extraction from relevant studies, and existing tools to assess the quality of previously published systematic reviews, the risk of bias of individual studies, and the strength of evidence across studies.

**Results.** A high strength of evidence supports the use of colchicine, nonsteroidal anti-inflammatory drugs (NSAIDs), systemic corticosteroids, and animal-derived ACTH formulation to reduce pain in patients with acute gout. A moderate strength of evidence supports the finding that low-dose colchicine is as effective as higher-dose colchicine for treating acute gout attacks, and has fewer side effects. Randomized controlled trials that assess symptomatic outcomes for specific dietary therapies show an insufficient strength of evidence. The strength of evidence is insufficient to support or refute the effectiveness of particular Traditional Chinese Medicine practices (e.g., herbal mixtures, acupuncture, and moxibustion) for symptomatic outcomes. A high strength of evidence supports that urate-lowering therapy (with allopurinol or febuxostat) reduces serum urate level. However the strength of evidence is low that treating to a specific target serum urate level reduces the risk of gout attacks. A high strength of evidence supports the failure of urate-lowering therapy (ULT) to reduce the risk of acute gout attacks within the first 6 months after initiation. A moderate strength of evidence suggests that ULT reduces the risk of acute gout attacks after about 1 year of treatment. The strength of evidence is high that prophylactic therapy with low-dose colchicine or low dose NSAIDs reduces the risk of acute gout attacks when beginning ULT. No criteria for when to discontinue ULT have been validated.

**Conclusions.** Effective treatments for acute gout include colchicine, NSAIDs, and corticosteroids/animal-derived ACTH formulation. Urate-lowering therapy achieves its goal of lowering serum urate levels. Urate lowering should lead to a reduction in gout attacks, but that has yet to be directly demonstrated, because initiation of urate-lowering therapy is itself a risk factor for gout flare (attack). Patient preferences and other clinical circumstances are likely to be important in decisions about treating patients with gout.

# Contents

<b>Executive Summary .....</b>	<b>ES-1</b>
Background and Objectives .....	ES-1
Scope and Key Questions .....	ES-3
Methods.....	ES-5
Peer Review and Public Commentary .....	ES-8
Results.....	ES-8
Findings.....	ES-10
Discussion.....	ES-14
<b>Introduction.....</b>	<b>1</b>
Background.....	1
Scope and Key Questions .....	4
Organization of this report.....	6
<b>Methods.....</b>	<b>6</b>
Criteria for Inclusion/Exclusion of Studies in the Review .....	6
Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions .....	9
Data Abstraction and Data Management .....	9
Assessment of Methodological Risk of Bias of Individual Studies.....	9
Data Synthesis/Analysis.....	10
Grading the Strength of the Body of Evidence for Each Key Question .....	11
Applicability .....	12
Peer Review and Public Commentary .....	12
<b>Results .....</b>	<b>13</b>
Introduction.....	13
Results of Literature Searches .....	13
Key Points.....	15
Description of included studies.....	15
Detailed Synthesis.....	19
Description of included studies.....	40
Detailed Synthesis.....	41
Key Points.....	52
Description of included studies.....	52
Detailed Synthesis.....	53
Key Points.....	83
Description of included studies.....	83
Detailed Synthesis.....	83
Key Points.....	86
Description of included studies.....	86
Detailed Synthesis.....	86
<b>Discussion.....</b>	<b>89</b>
<b>References .....</b>	<b>94</b>
<b>Abbreviations / Acronyms.....</b>	<b>103</b>

**Tables**

Table A. Pharmacologic agents used in the treatment of gout .....	ES-2
---	------

Table B. Summary of prior knowledge, findings from the systematic review, and strength of evidence, by key question .....	ES-16
Table 1. Pharmacologic agents used in the treatment of gout .....	3
Table 2. Randomized controlled trials included in systematic reviews .....	17
Table 3. Systematic reviews of pharmacologic therapy for acute gout treatment .....	24
Table 4. Randomized controlled trials of pharmacologic therapies for acute gout not included in existing systematic reviews.....	34
Table 5. Randomized controlled trials of NSAID vs. NSAID for treatment of acute gout .....	38
Table 6. Randomized controlled trials included in systematic reviews.....	41
Table 7. Dietary Risk Factors .....	45
Table 8. Systematic reviews of pharmacologic therapy for acute gout treatment .....	47
Table 9. Randomized controlled trials of pharmacologic therapies for acute gout not included in existing systematic reviews.....	50
Table 10. Randomized controlled trials included in systematic reviews (febuxostat vs. placebo) .....	55
Table 11. Systematic reviews of febuxostat or allopurinol vs. placebo for the management of chronic gout .....	57
Table 12. Randomized controlled trials of allopurinol vs. placebo in the management of chronic gout .....	59
Table 13. Randomized controlled trials of febuxostat vs. placebo in the management of chronic gout .....	61
Table 14. Randomized controlled trials of febuxostat vs. placebo for the management of chronic gout not included in existing systematic reviews .....	66
Table 15. Randomized controlled trials included in systematic reviews.....	68
Table 16. Systematic reviews of febuxostat vs. allopurinol for the management of chronic gout.....	73
Table 17. Randomized controlled trials of febuxostat vs. allopurinol or colchicine vs. allopurinol for the management of chronic gout not included in existing systematic reviews .....	75
Table 18. Systematic reviews of allopurinol vs. probenecid for the management of chronic gout .....	78
Table 19. Randomized controlled trials of pharmacologic therapies for chronic gout not included in existing systematic reviews .....	79
Table 20. Summary of prior knowledge, findings from the systematic review, and strength of evidence, by key question .....	91

## Figures

Figure A. Analytic Framework for Treatment of Acute Gout .....	ES-5
Figure B. Analytic Framework for Management of Chronic Gout .....	ES-5
Figure C. Framework for incorporating existing systematic reviews and studies not included in these reviews .....	7
Figure D. Literature flow diagram .....	8
Figure 1. Framework for incorporating existing systematic reviews and studies not included in these reviews .....	11
Figure 2. Literature flow diagram.....	14

## Appendices

Appendix A: Search Strategy
Appendix B: List of Excluded Studies

# Executive Summary

## Background and Objectives

Gout is the most common form of inflammatory arthritis and is characterized by acute intermittent episodes of synovitis presenting with joint swelling and pain (referred to as acute gouty arthritis). Gout is caused when excess urate in the body crystalizes (as monosodium urate [MSU]) in joint fluid, cartilage, bones, tendons, bursas or other sites. These crystals can directly stimulate an acute inflammatory attack. In some patients, over time acute gout attacks become more frequent, protracted, and severe and may eventually progress to a chronic inflammatory condition. Additionally, in some patients the deposits of urate crystals grow into larger collections, called tophi (singular tophus) when clinically apparent.

The aim of this report is to review the evidence for the treatment of patients with gout, focusing on the primary care setting.

## Etiology of Gout

Gout initially presents as an episode of acute inflammatory arthritis, most commonly involving the first meta-tarsal-phalanx joint, a condition commonly referred to as podagra. Typical attacks during the first few years last 7 to 14 days before resolving.

The primary risk factor for gout is hyperuricemia; however, not all patients with hyperuricemia go on to develop clinical gout, a state known as asymptomatic hyperuricemia. Patients with asymptomatic hyperuricemia may or may not have evidence of urate deposits in their joints (as documented by advanced imaging methods).<sup>1</sup>

The causes of gout are unclear but appear to be multifactorial, including a combination of genetic, hormonal, metabolic, and dietary factors. Family history, advancing age, male sex, or, in women, early menopause have been associated with a higher risk of gout and/or gout attacks (flares).<sup>2</sup> Dietary risk factors for gout have been postulated to include alcohol consumption, as well as consumption of meat, seafood, sugar-sweetened soft drinks, and foods high in fructose, whereas dairy foods and coffee have been associated with a lower risk of incident gout and in some cases a lower rate of gout attacks (flares).

## Diagnosis of Gout

A number of methods have been proposed to establish the diagnosis of gout. The evidence supporting the various methods for the diagnosis of gout is the subject of a separate systematic review.<sup>3</sup>

## Clinical Presentation and Management

Gout encompasses both acute and chronic phases.

### Acute Gouty Arthritis

The acute phase is self-limited and characterized by recurrent attacks of synovitis (articular inflammation) that present with pain, erythema, and swelling, most frequently in the large toe but also potentially involving other joints, tendons, bursae or other areas.

Primary treatments for acute gout attacks have included non-steroidal anti-inflammatory agents, corticosteroids (intraarticular), colchicine, and pituitary adrenocorticotrophic hormone

(ACTH, specifically animal-derived ACTH preparation) for the control of pain and inflammation.

## Chronic Gout

Although initial episodes may be brief and rare, acute episodes may increase in frequency and duration over time and lead to the development of chronic gout. In addition to more frequent attacks, chronic gout may be associated with deposits of uric acid crystals known as tophi. Tophi may develop in joints, cartilage, bone, and auricular or other cutaneous tissues.<sup>4</sup> The average interval between the onset of gout and appearance of tophi, in the absence of treatment, is approximately 10 years.<sup>4</sup>

Management of chronic gout may include both pharmacologic and non-pharmacologic strategies. Urate-lowering strategies are the primary pharmacologic intervention for management of long-term complications of gout. Non-pharmacologic methods advocated for management of chronic gout include a combination of lifestyle changes, including weight loss, exercise, smoking cessation, hydration, and dietary changes. The evidence for the efficacy of specific dietary changes in managing gout (preventing attacks) is a topic of this review. Several interleukin-1 $\beta$ -inhibitory anti-inflammatory agents currently approved for treatment of rheumatoid arthritis are in Phase II and III trials for treatment of gout, including anakinra, canakinumab, and riloncept,<sup>5-7</sup> and will not be included in this systematic review, because they are not prescribed in the primary care setting (see below).

Pharmacologic management of chronic gout consists primarily of agents that lower serum urate. These agents include xanthine oxidase inhibitors (XOIs- allopurinol and febuxostat) to reduce serum urate production; uricosurics (probenecid), which prevent renal reabsorption of uric acid (and increase urinary uric acid excretion); and uricases, which stimulate the breakdown of uric acid (pegloticase). These agents can be used alone or in specific combinations (e.g., XO plus probenecid). Pegloticase will not be included in this review because it would not be prescribed in a primary care setting (see below).

Table A lists the drugs used to treat gout and notes the ones covered in this systematic review.

**Table A. Pharmacologic agents used in the treatment of gout**

Drug Class	Agent (generic/brand)	Manufacturer
Anti-inflammatories*		
	NSAIDs (including Ibuprofen, naproxen, etodolac, diclofenac, indomethacin, COX-2 inhibitors)	Numerous
	Corticosteroids/ Animal-derived adrenocorticotrophic hormone (ACTH) formulation	Numerous
	Colchicine/Colcrys™	URL Pharma
	IL-1B Receptor Antagonists:**	
	Anakinra/kineret®	Sobi
	Canakinumab/Ilaris™	Novartis
	Riloncept/Arcalyst™	Regeneron
Uricosurics		
	Probenecid/Benemid® or Probalan	Multiple
Xanthine Oxidase Inhibitors		
	Allopurinol/Zyloprim®	Prometheus Labs
	Febuxostat/Uloric™	Teijin Pharma Ltd., Takeda
Uricase		
	Pegloticase/Krystexxa®***	Savient Pharmaceuticals

Drug Class	Agent (generic/brand)	Manufacturer
Combination agents		
	Colchicine-probenecid/Proben-C	Merck

Table notes: \*NSAIDs and corticosteroids will be considered only for their use in treating inflammation associated with gout; \*\*these agents will not be considered in this review, because they are not FDA-approved for use in treating gout and/or are not prescribed in the primary care setting.

Additional off-label agents that have been proposed as useful in the management of gout include the lipid lowering agent, fenofibrate; the angiotensin 2 receptor blocker, losartan; and calcium channel blockers (in patients being treated with these agents for other indications). These agents are not included in this review.

## Scope and Key Questions

### Scope of the Review

The purpose of this review is to assess the evidence on the management of patients with gout, both in the acute phase and chronic phase, including patients with tophaceous gout, and to assess management therapies that are FDA-approved and within the scope of practice of typical primary care providers. A protocol for the review was accepted and publicly posted on the AHRQ website on November 3, 2014 at:

<http://effectivehealthcare.ahrq.gov/ehc/products/564/1992/Gout-managment-protocol-141103.pdf>.

### Key Questions

The key questions that guided this review are based on questions posed by the American College of Physicians (ACP). These questions underwent revision based on input from a group of key informants, public comments, and input from a Technical Expert Panel (TEP).

#### Key Question 1: Acute Gout Treatment

- a. In patients with acute gout, what are the benefits and harms of different pharmacological therapies?
- b. Does effectiveness (benefits and harms) differ according to patient baseline demographic characteristics and co-morbid conditions (including renal function)?
- c. Does effectiveness (benefits and harms) differ according to disease severity, including initial clinical presentation (e.g., extent of joint involvement and time since start of flare) and laboratory values (serum and/or urine UA levels)?

#### Key Question 2: Dietary and Lifestyle Management of Gout

- a. In adults with gout, what are the benefits and harms of different dietary therapies and life style measures on intermediate (serum and/or urine UA levels) and final health outcomes (including recurrence of gout episodes and progression [e.g., development of tophi])?

b. Does effectiveness and comparative effectiveness of dietary modification differ according to disease severity (including presence of tophi and baseline serum UA), underlying mechanisms of hyperuricemia, or baseline demographic and co-morbid characteristics?

### Key Question 3: Pharmacologic Management of Hyperuricemia in Gout Patients

a. In adults with gout, what are the benefits and harms of different pharmacological therapies on intermediate (serum and/or urine UA levels) and long-term clinical health outcomes (including recurrence of gout episodes and progression)?

b. Does effectiveness and comparative effectiveness of urate lowering therapy differ according to disease severity (including presence of tophi and baseline serum UA), underlying mechanisms of hyperuricemia, or baseline demographic and co-morbid characteristics?

c. What is the effect of dietary modification in combination with pharmacologic therapy?

### Key Question 4: Treatment Monitoring of Patients with Gout

a. In adults with gout, does monitoring serum urate levels with pharmacologic treatment and/or dietary and/or lifestyle change measures (e.g., compliance) improve treatment outcomes?

b. Is achieving lower subsequent serum urate levels (less than 5 vs. 5–7mg/dL) associated with decreased risk for recurrent acute gout attack, progression to chronic arthritis or disability, resolution of tophi, or other clinical outcomes (including risk for comorbidities or progression of comorbidities) or patient-reported outcomes?

### Key Question 5: Discontinuation of Pharmaceutical Management for Patients on Acute or Chronic Gout Medications

In adults with gout, are there criteria that can identify patients who are good candidates for discontinuing

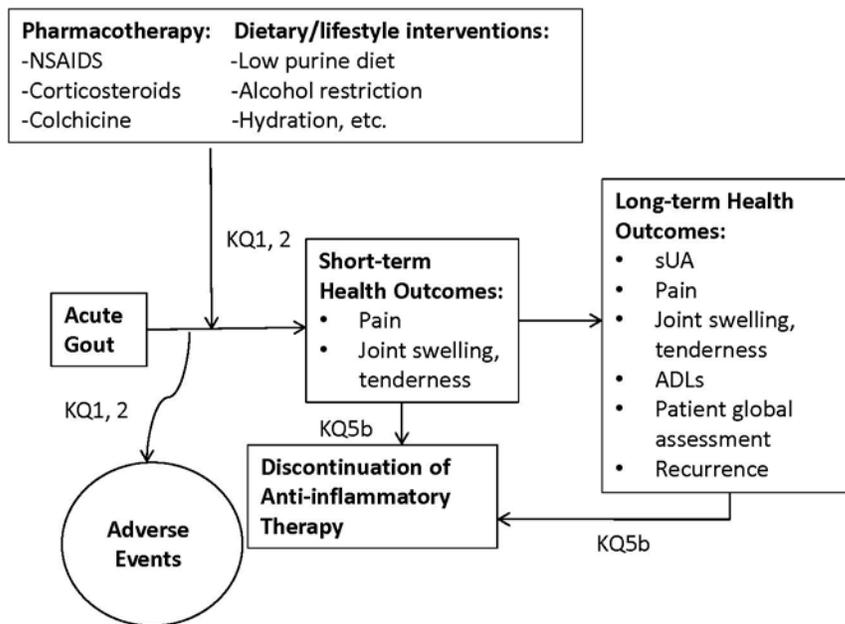
a. urate lowering therapy?

b. anti-inflammatory prophylaxis against acute gout attack for patients on urate lowering therapy after an acute gout attack?

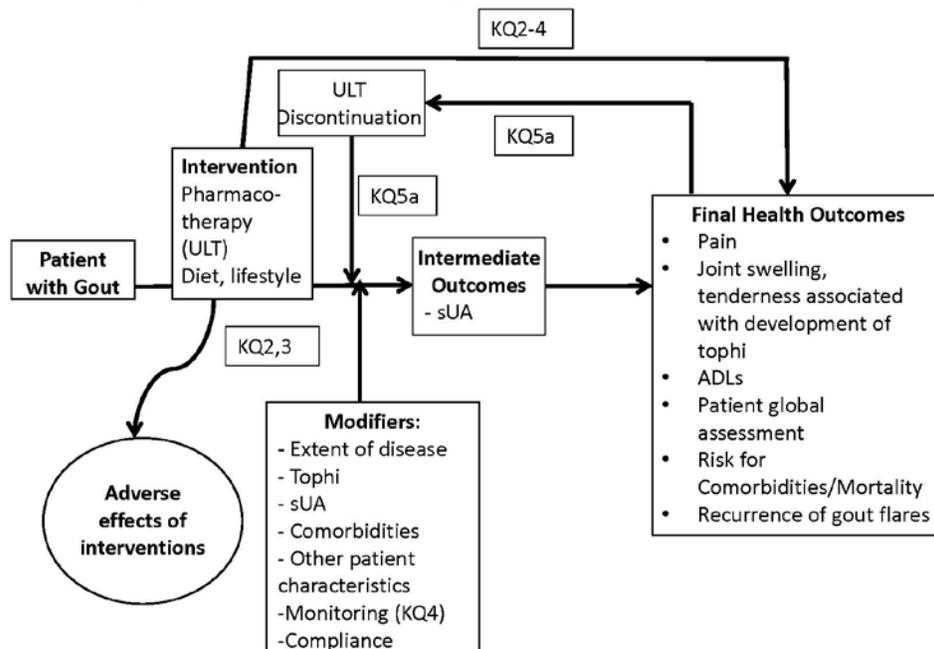
### **Analytic Frameworks**

We provide two analytic frameworks: one for acute gout and one for chronic gout.

**Figure A. Analytic Framework for Treatment of Acute Gout**



**Figure B. Analytic Framework for Management of Chronic Gout**



## Methods

In general, this systematic review follows the procedures of the January 2014 edition of the Methods Guide for Effectiveness and Comparative Effectiveness Reviews.<sup>8</sup>

## **Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions**

We searched PubMed, EMBASE, the Cochrane Collection, and the Web of Science using the search terms “gout”, “gouty”, and terms for tophi (January 1, 2010-April 28, 2014; at least one year to the search dates for the recent systematic reviews). We also obtained relevant references from at least 33 recent systematic reviews that cover nearly all of the Key Questions. We also searched Clinicaltrials.gov and the Web of Science for recently completed studies and unpublished or non-peer-reviewed study findings. Searches were not limited by language of publication. We contacted manufacturers of the prescription medications used to treat gout that are listed in Table A for unpublished data specific to the use of these medications for treatment of gout or symptoms related to gout. We also included any relevant studies identified in the searches we conducted for a simultaneous review on management of gout if not already identified in the searches for this review. Finally, we asked the TEP to assess our list of included studies and to provide references for any studies they believe should also be included.

## **Data Abstraction and Data Management**

Study level details from articles accepted for inclusion were abstracted by one reviewer and double checked by a second reviewer. Any disagreements were reconciled by the SCEPC Director, or the local subject matter expert if needed.

## **Assessment of Methodological Risk of Bias of Individual Studies**

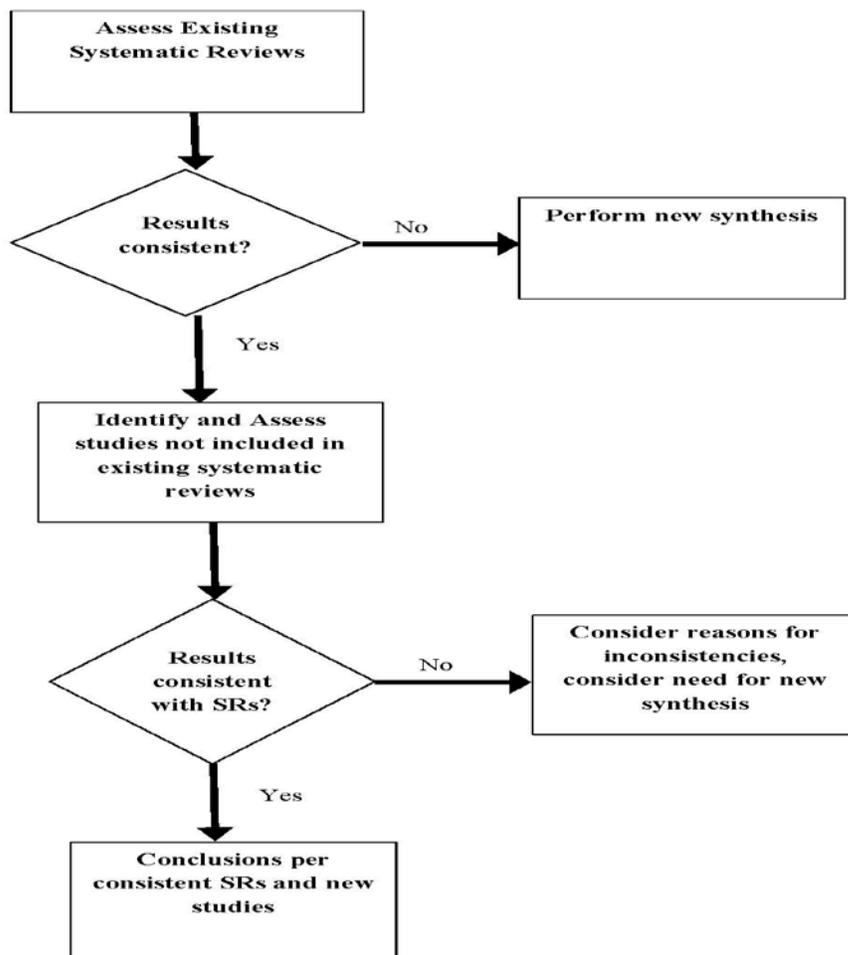
Risk of bias (study quality) of individual included studies was assessed independently by two reviewers using an adapted Cochrane Risk of Bias tool,<sup>9</sup> and assessments were reconciled, with any disagreements mediated by the project lead. We used a modified AMSTAR tool to assess the quality of existing systematic reviews that we included;<sup>10</sup> AMSTAR assessments were also conducted independently by two reviewers and reconciled.

## **Data Synthesis/Analysis**

Given the large number of existing systematic reviews on this topic, we used the following strategy for data synthesis/analysis:

1. Identify the existing systematic reviews and make a judgment about relevancy for the Key Questions, the end date of the search, and the methodologic quality as assessed by AMSTAR<sup>10</sup>, following the suggested process outlined by Whitlock and colleagues.<sup>11</sup>
2. Scan the references of these systematic reviews for included studies.
3. Search for new studies meeting the eligibility criteria for the Key Question.
4. Compare the conclusions of the existing systematic reviews.
5. Compare the results of new studies with the conclusions of existing systematic reviews.
6. Use the following guide for additional analyses/conclusions.

**Figure C. Framework for incorporating existing systematic reviews and studies not included in these reviews**



## **Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes**

We assessed the overall strength of evidence for each conclusion (e.g., the efficacy and safety of each pharmacologic agent or class of agents listed in the PICOTs, and differences by subgroup, if identified), using guidance suggested by the Effective Health Care Program.<sup>8</sup> This method is based on one developed by the GRADE Working Group and classifies the grade of evidence as High (also called Strong), Moderate, Low or Insufficient. The evidence grade is based on five required domains: study limitations, consistency, directness, precision, and publication bias. We also considered in our strength of evidence assessments the criteria proposed by AB Hill for causality.<sup>12</sup>

### **Assessing Applicability**

Because the charge for this review is clear on the setting, care providers, and patient population the review is intended to cover, applicability assessment was based primarily on the

similarity of the settings and populations to those for which this report is intended, namely primary and acute care settings that treat individuals, a high proportion of whom have comorbidities or are at risk for comorbidities such as hypertension and renal insufficiency.<sup>13</sup>

## **Peer Review and Public Commentary**

To be added for final report

## **Results**

This section first describes the results of the literature searches, followed by descriptions of the studies that met inclusion criteria for each of the key questions and the key points (conclusions).

### **Results of Literature Searches**

Our searches identified 4,967 titles/abstracts. Reference mining the previous systematic reviews (SRs) and guidelines identified in our searches resulted in an additional 217 titles, and hand searching resulted in an additional 15 titles. Our search of [clinicaltrials.gov](http://clinicaltrials.gov) identified 112 entries for gout. Of these 19 were potentially relevant, 10 were either included already in our report or identified in our searches and excluded as ineligible, one was withdrawn, and eight were recorded as being completed but no results were posted in [clinicaltrials.gov](http://clinicaltrials.gov) and we could find no published journal articles. Two manufacturers (Novartis and Regeneron of drugs) responded to requests by the AHRQ Scientific Resource Center for Scientific Information Packets on gout treatments. None of the trials described in these information packets was included in this report, as the drugs are currently non-FDA approved in the United States (US). Of a total of 5,311 titles/abstracts screened for inclusion, 4,666 titles/abstracts were excluded. At full text screening review, we rejected an additional 456 articles. Therefore, a total of 189 articles were included in our review.

For Key Question (KQ) 1, 10 SRs met our inclusion criteria; in addition, we identified 4 randomized controlled trials (RCTs) not included in prior SRs. For KQ2, we identified 11 SRs, three RCTs not included in prior SRs, and seven observational studies on dietary risk factors. For KQ3, we include 10 SRs and one meta-analysis, seven RCTs not included in prior SRs and one abstract that has not been published, five new analyses of studies included in existing SRs, and 15 studies on adverse events (AEs). For KQ4, we include one SR and 24 original studies. For KQ5, we include two original studies. See Figure D for the literature flow diagram.

Figure D. Literature flow diagram

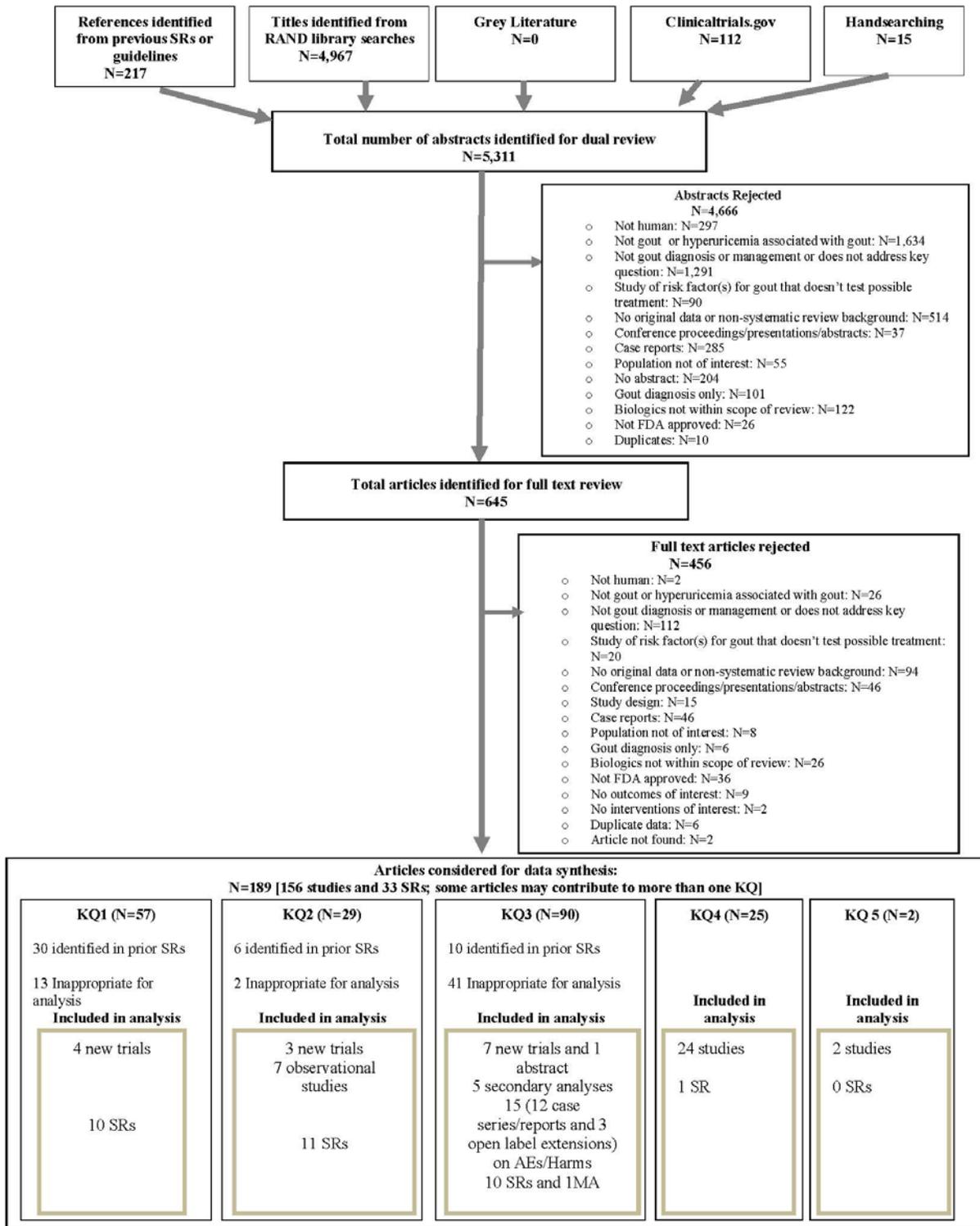


Figure notes: AE(s)=Adverse Event(s); KQ=Key Question; MA=Meta-analysis; RCT(s)=Randomized Controlled Trial(s); SR(s)=Systematic Review(s)

## Findings

The key findings and strength of evidence are in Table B.

### Key Question 1a-c. Acute Gout Treatment

- a. In patients with acute gout, what are the benefits and harms of different pharmacological therapies
- b. Does effectiveness (benefits and harms) differ according to patient baseline demographic characteristics and co-morbid conditions (including renal function)?
- c. Does effectiveness (benefits and harms) differ according to disease severity, including initial clinical presentation (e.g., extent of joint involvement and time since start of flare) and laboratory values (serum and/or urine UA levels)?

### Description of Included Studies

We identified 10 SRs on the following acute gout therapies: colchicine, NSAIDs, corticosteroids, and animal-derived ACTH formulation.<sup>14-23</sup> We further identified four new trials not included in previous SRs that met our inclusion criteria.<sup>24-27</sup>

### Key Findings and Strength of Evidence for Key Question 1a-c

- A high strength of evidence supports the efficacy of colchicine to reduce pain in acute gout.
- Moderate strength of evidence supports the finding that low-dose colchicine is as effective as higher dose for reducing pain, with fewer side effects.
- High strength of evidence supports the efficacy of NSAIDs to reduce pain in acute gout.
- Moderate strength of evidence supports a lack of difference among NSAIDs in effectiveness.
- High strength of evidence supports the efficacy of systemic corticosteroids to reduce pain in acute gout.
- High strength of evidence supports animal-derived ACTH formulation to reduce pain in acute gout.
- Strength of evidence is insufficient regarding the effect of therapies on other outcomes: joint swelling, tenderness, activities of daily living, patient global assessment.
- An insufficient strength of evidence was identified about differences in efficacy stratified by patient demographic, comorbid conditions, disease severity, clinical presentation, or lab values.
- The most common adverse effects associated with colchicine are gastrointestinal symptoms, reported in 23 to 77 percent of users. NSAIDs also have gastrointestinal side effects with dyspepsia or abdominal pain occurring in 10 percent or more of patients and more serious GI perforations, ulcers, and bleeds occurring in fewer than one percent of users, although the risk is greater in patients older than 65 years of age. Both colchicine and NSAIDs require dose reduction in renal impairment. The adverse effects of corticosteroids and animal-derived ACTH formulation are mostly related to long term use, although dysphoria, elevation in blood glucose, immune suppression and fluid retention may all occur even with short term use.

## Key Question 2a-b. Dietary and Lifestyle Management of Gout

- a. In adults with gout, what are the benefits and harms of different dietary therapies and life style measures on intermediate (serum and/or urine UA levels) and final health outcomes (including recurrence of gout episodes and progression [e.g., development of tophi])?
- b. Does effectiveness and comparative effectiveness of dietary modification differ according to disease severity (including presence of tophi and baseline serum UA), underlying mechanisms of hyperuricemia, or baseline demographic and co-morbid characteristics?

### Description of Included Studies

We identified 11 SRs that examined the efficacy of dietary and other lifestyle factors in the treatment of gout.<sup>2, 18, 28-36</sup> We further identified three original trials not included in previous SRs that met our inclusion criteria and examined dietary and lifestyle interventions in gout management.<sup>37-39</sup>

### Key Findings and Strength of Evidence for Key Question 2a-b

- The strength of evidence from RCTs that assess symptomatic outcomes is insufficient to support a role for specific dietary therapies (related to some of the risk factors, e.g., red meat, fructose, alcohol, etc.).
- Low strength of evidence supports that supplemental vitamin c in reducing serum urate levels (by less than 0.5mg/dl).
- There is low strength of evidence that gout-specific dietary advice (counseling about reducing red meat intake; avoiding offal, shellfish, and yeast-rich foods and beverages; and including low fat dairy products, vegetables, and cherries) is no more effective than nonspecific dietary advice (counseling about the importance of weight loss and reduced alcohol intake) at reducing serum urate levels.
- The strength of evidence is insufficient to support or refute the effectiveness of Traditional Chinese Medicine (TCM) (including herbs and acupuncture) on symptomatic outcomes.

## Key Question 3a-c. Pharmacologic Management of Hyperuricemia in Gout Patients

- a. In adults with gout, what are the benefits and harms of different pharmacological therapies on intermediate (serum and/or urine UA levels) and long-term clinical health outcomes (including recurrence of gout episodes and progression)?
- b. Does effectiveness and comparative effectiveness of urate lowering therapy differ according to disease severity (including presence of tophi and baseline serum UA), underlying mechanisms of hyperuricemia, or baseline demographic and co-morbid characteristics?

c. What is the effect of dietary modification in combination with pharmacologic therapy?

### **Description of Included Studies**

Our literature search identified nine SRs<sup>7, 40-47</sup> and one meta-analysis.<sup>48</sup> In addition, we identified one new abstract<sup>49</sup> and five secondary analyses<sup>50-54</sup> of trials already included in the SRs and seven new trials.<sup>27, 39, 55-59</sup> For AEs, we included 15 studies.<sup>60-74</sup>

### **Key Findings and Strength of Evidence for Key Question 3a-c**

- The strength of evidence is high that urate lowering therapy does not reduce the risk of acute gout attacks in the first six months.
- Moderate strength of evidence supports a reduction in the risk of acute gout attacks after about one year of urate lowering therapy.
- A high strength of evidence supports the efficacy of urate lowering therapy in reducing serum urate.
- A high strength of evidence supports the finding of no difference in serum urate lowering between 40mg febuxostat and 300mg allopurinol.
- Evidence is insufficient about the effectiveness and comparative effectiveness of allopurinol and febuxostat at reducing tophi.
- A high strength of evidence supports a lack of difference in overall adverse events between allopurinol 300mg and febuxostat 40mg.
- A high strength of evidence suggests that prophylactic therapy with low dose colchicine or low dose NSAIDs when beginning urate lowering therapy reduces the risk of acute gout attacks.
- Moderate strength of evidence supports that longer durations of prophylaxis with colchicine or NSAIDs (> 8 weeks) are more effective than shorter duration when initiating urate lowering therapy to prevent acute gout attacks.
- The strength of evidence is low that gout-specific dietary advice does not add to the effectiveness of urate lowering therapy in reducing serum urate.

### **Key Question 4a-b. Treatment Monitoring of Patients with Gout**

a. In adults with gout, does monitoring serum urate levels with pharmacologic treatment and/or dietary and/or lifestyle change measures (e.g., compliance) improve treatment outcomes?

b. Is achieving lower subsequent serum urate levels (less than 5 vs. 5–7mg/dL) associated with decreased risk for recurrent acute gout attack, progression to chronic arthritis or disability, resolution of tophi, or other clinical outcomes (including risk for comorbidities or progression of comorbidities) or patient-reported outcomes?

### **Description of Included Studies**

For KQ4a, we identified two SRs<sup>75, 76</sup> from which 16 original studies were referenced mined.<sup>77-92</sup>

For KQ4b, we identified eight studies that addressed the question.<sup>93-100</sup>

## **Key Findings and Strength of Evidence for Key Question 4**

- Insufficient evidence supports or refutes that monitoring serum urate improves outcomes.
- A low strength of evidence supports the finding that treating to a specific target serum urate level reduces the risk of gout attacks.

## **Key Question 5. Discontinuation of Pharmaceutical Management for Patients on Acute or Chronic Gout Medications**

In adults with gout, are there criteria that can identify patients who are good candidates for discontinuing

a. urate lowering therapy?

b. anti-inflammatory prophylaxis against acute gout attack for patients on urate lowering therapy after an acute gout attack?

## **Description of Included Studies**

We identified two observational (prospective cohort) studies<sup>101, 102</sup> and also used data about three trials that addressed duration of anti-inflammatory prophylaxis urate lowering therapy trials.<sup>103-105</sup>

## **Key Findings and Strength of Evidence for Key Question 5**

- There is low strength of evidence that discontinuing urate lowering therapy in gout patients who completed five years of ULT therapy that kept serum urate levels < 7mg/dl, and in whom subsequent annual serum urate levels (off of ULT) stayed < 7mg/dl, did not result in an increased risk of acute gout attacks.
- Evidence is moderate that prophylaxis for acute gout when initiating urate lowering therapy with low dose colchicine or NSAIDs results in fewer gout attacks when treatment is given for longer than 8 weeks.

## Discussion

### Key Findings and Strength of Evidence

We found a large number of research studies about gout, yet only a relatively modest number of these provided evidence for some of our key questions, particularly for the treatment of acute gout: only a single placebo-controlled trial of NSAIDs for acute gout pain, two placebo controlled RCTs of colchicine, and none at all for corticosteroids or ACTH. Nevertheless, we reached strong conclusions about the usefulness of these drugs. This was due to some specific features of gout: symptoms are due to an inflammatory reaction to the deposition of uric acid crystals, which occurs when serum rate rises above its saturation point in the blood. Hence, medications aimed at blocking the inflammatory response were tried as treatments, in an era that pre-dated the widespread practice of placebo-controlled trial testing of therapies. Steroids are one of the most powerful and effective anti-inflammatory medications available. While there are no placebo-controlled RCTs of its use in acute gout, steroids have proven efficacy in other inflammatory conditions, and this gives us confidence that it is effective in treating the inflammatory reaction in acute gout. At this point, a placebo-controlled trial of steroids in acute gout may well be unethical, as it means withholding from the placebo-treated group therapies known to be effective (e.g., colchicine). Indeed, a recent, high profile study of the use of steroids in acute gout compared its use not to placebo, but to NSAIDs. Since NSAIDs also have no conclusive placebo-controlled trial evidence of their effectiveness in acute gout, could it be that this RCT, which found only minor differences in outcomes between the two treatments, actually was comparing two treatments that were equally ineffective? We think not. We believe that both drugs are effective in treating acute gout, and therefore judged the strength of evidence as high that their use relieves symptoms by a clinically important amount - despite the lack of placebo-controlled RCT evidence.

The key findings and strength of evidence are in Table B.

### Findings in Relationship to What is Already Known

In general, our findings support the results of existing systematic reviews. We did find a number of RCTs not included in prior reviews. Some of these studies were “first-of-their-kind,” such as those testing a specific dietary therapy and the duration of colchicine prophylaxis. However, most new studies either confirmed prior knowledge, or, in the case of studies of novel treatments, were not sufficiently high quality for us to draw conclusions.

### Applicability

Of the 156 studies assessed in detail (not counting SRs), 108 studies failed to state or did not clearly state the types of settings from which the patients were recruited. Only nine studies explicitly stated that patients came only from, or the study included patients from, primary care sites (including the ED and urgent care settings). In the major trials of pharmaceuticals, 10 percent to 25 percent of patients had tophi present at baseline; tophi are rarely seen in primary care settings. Patients enrolled in clinical trials usually have fewer comorbidities than those seen in practice since clinical trials have exclusion criteria. Thus, patients enrolled in most of the trials were probably more advanced on average with respect to their gout, and better on average with

respect to their other health conditions, than patients typically seen in primary care settings. We thus judged this evidence of moderate applicability to primary care.

## **Implications for Clinical and Policy Decisionmaking**

The implications of this review for clinical decision-making follow from the identification of which interventions for gout management have evidence of an effect on clinical outcomes, either directly or through a strong indirect evidence chain. Thus, the results in Table B will be useful in policy decision-making and in the development of practice guidelines.

## **Limitations of the Comparative Effectiveness Review Process**

For many of the key questions of interest, data were not reported on the subgroups or outcomes of interest, limiting the comparative effectiveness review. For the portion of the review on traditional Chinese medicine, the variability in tested interventions made comparisons across studies not justified.

## **Limitations of the Evidence Base**

The lack of studies of patients in primary care settings is a limitation, as is the lack of studies assessing clinical outcomes for urate lowering therapy (such as recurrent acute gout flare after one year) and intervention studies of dietary therapies for management of chronic gout. Longer term studies will be needed to assess to what degree ULT reduces acute gout attacks relative to the adverse events of long term use of the available medications.

## **Research Gaps**

The concept of “treat-to-target” (TTT) in gout, while supported by indirect evidence, has been untested. Guidelines and recommendations about TTT thresholds already vary, e.g., < 6mg/dL for all gout patients vs. < 5mg/dL for patients with significant gout morbidity. However, for many gout patients in primary care practice whose gout is well controlled on urate lowering therapy, no data support such targets. In fact, some data suggest that once gout has been quiescent for 5 years, urate lowering therapy might be discontinued (as long as serum urate levels remain acceptable, e.g., < 7mg/dL).<sup>101</sup> Therefore, the most important research gap is a randomized clinical trial comparing different TTT levels in patients with gout and elevated serum urate.

Treatment decisions are likely to be preference-sensitive, and studies are needed to assess patient preferences for different outcomes (to what degree do patient preferences differ for outcomes such as a decrease in risk from 2 percent to 0.5 percent for an acute gout attack in the coming year vs. a 5 percent chance of a skin rash and a <1 percent chance of a very serious skin rash).

Likewise, few studies have assessed the effect of specific dietary advice. Some dietary advice, such as generic advice to lose weight in overweight and obese patients, has evidence of benefit for other conditions and can be advocated in gout patients without additional data (e.g., it is always indicated to recommend dietary weight loss in patients who are obese). But primary care providers could more confidently recommend gout-specific dietary advice if compelling evidence supported an effect of such dietary changes on the risk for gout attacks or other gout-related outcomes. Therefore, another important research gap is evidence from randomized clinical trials for specific dietary changes (such as reducing or eliminating sugar-sweetened beverages or fructose) compared to standard healthy diet advice and weight loss in reducing the risk of gout attacks.

## Conclusions

Several drugs show moderate-to-high evidence of benefit in terms of reducing pain in patients with acute gout. It is clear that urate lowering therapy achieves its goal of lowering urate levels. Decreased serum urate should lead, over time, to a reduction in gout attacks, but that has yet to be demonstrated in a RCT, as outlined above. One of the main risks of initiating urate lowering therapy is that it is, itself, a risk factor for gout flare (attack). Patient preferences are likely to be important in decision-making (as specified above), and having better estimates of the size of the benefit of urate lowering therapy will make clinicians and patients more knowledgeable about the risk: benefit trade-off for the different decisions.

**Table B. Summary of prior knowledge, findings from the systematic review, and strength of evidence, by key question**

Key Question	Prior Knowledge Used in Determining Strength of Evidence	Sources of Evidence Included in This Systematic Review	Strength of Evidence
<b>KQ1 Acute Gout Treatment</b>			
Colchicine reduces pain	N/A	<ul style="list-style-type: none"> <li>2 placebo-controlled RCTs (N=45 and N=184) both with low risk of bias</li> </ul>	High
Low-dose colchicine is as effective as higher dose for reducing pain, with fewer side effects	N/A	<ul style="list-style-type: none"> <li>1 head-to-head RCT with low risk of bias (N=184)</li> </ul>	Moderate
NSAIDs reduce gout pain	<ul style="list-style-type: none"> <li>Biologic rationale (anti-inflammatory action)</li> <li>Placebo-controlled RCT evidence that NSAIDs provide temporary pain relief for numerous conditions</li> </ul>	<ul style="list-style-type: none"> <li>1 placebo-controlled RCT with high risk of bias (N=30)</li> <li>High strength observational data (NSAID use as prophylaxis against gout flare) (see below under KQ3)</li> </ul>	High
No difference between NSAIDs in effectiveness	<ul style="list-style-type: none"> <li>Equivalence in effectiveness among NSAIDs in numerous other conditions</li> </ul>	<ul style="list-style-type: none"> <li>16 head-to-head RCTs</li> </ul>	Moderate
Systemic corticosteroids reduce pain	<ul style="list-style-type: none"> <li>Biologic rationale (anti-inflammatory action)</li> </ul>	<ul style="list-style-type: none"> <li>No placebo-controlled RCTs</li> <li>Equivalence to NSAIDs in 4 RCTs (N=27, N=90, N=120, and N=60). Three of four RCTs had low risk of bias.</li> </ul>	High
Animal-derived ACTH formulation reduces pain	<ul style="list-style-type: none"> <li>Biologic rationale (anti-inflammatory action)</li> </ul>	<ul style="list-style-type: none"> <li>No placebo-controlled RCTs</li> <li>Equivalence to NSAIDs and intramuscular steroids in RCTs (one RCT of each, N=76 and N=31 both at high risk of bias)</li> </ul>	High
Differences stratified by patient demographic, comorbid conditions, disease severity, clinical presentation, or laboratory values	N/A	None of the included RCTs presented data stratified by these variables.	Insufficient
<b>KQ2 Diet and lifestyle management</b>			
Specific dietary therapies (related to certain risk factors, e.g., red	N/A	<ul style="list-style-type: none"> <li>1 RCT with high risk of bias (N=67)</li> </ul>	Insufficient

Key Question	Prior Knowledge Used in Determining Strength of Evidence	Sources of Evidence Included in This Systematic Review	Strength of Evidence
meat, fructose, alcohol) may affect symptomatic outcomes			
Supplemental vitamin C reduces serum urate levels by less than 0.5mg/dl	N/A	<ul style="list-style-type: none"> <li>1 systematic review (including 13 RCTs)</li> </ul>	Low
Gout-specific dietary advice (counseling about reducing red meat; avoiding offal, shellfish, and yeast-rich foods and beverages or increasing low-fat dairy products, vegetables, and cherries) is no more effective than nonspecific dietary advice (counseling about the importance of weight loss and reduced alcohol intake) at reducing serum urate levels	N/A	<ul style="list-style-type: none"> <li>1 RCT with high risk of bias (N=30)</li> </ul>	Low
Effectiveness of Traditional Chinese Medicine (TCM) (acupuncture, herbal mixtures, moxibustion) on symptomatic outcomes	N/A	<ul style="list-style-type: none"> <li>86 RCTs, all of idiosyncratic therapies, with conflicting results</li> </ul>	Insufficient
<b>KQ3 Management of hyperuricemia</b>			
Urate-lowering therapy does not reduce the risk of acute gout attacks within the first 6 months	N/A	<ul style="list-style-type: none"> <li>2 placebo-controlled RCTs, with low risk of bias (N=1,072 and N=57)</li> </ul>	High
Urate-lowering therapy reduces the risk of acute gout attacks after 1-year	<ul style="list-style-type: none"> <li>Acute gout attacks are caused by elevated serum urate concentrations</li> </ul>	<ul style="list-style-type: none"> <li>No placebo-controlled RCTs assess long-term risk of acute gout attacks</li> <li>RCTs with low risk of bias show that ULT reduces serum uric acid</li> <li>Open label extension study of ULT RCT shows reduced risk of acute gout attacks over time, plateauing at less than 5% at about 1 year</li> </ul>	Moderate
Urate-lowering therapy reduces serum urate	N/A	<ul style="list-style-type: none"> <li>4 placebo-controlled RCTs all with low risk of bias (N=1,072, N=96, N=153, and N=57)</li> </ul>	High
Forty mg febuxostat and 300mg allopurinol show no differences in serum urate lowering	N/A	<ul style="list-style-type: none"> <li>1 head-to-head RCT with low risk of bias (N=762)</li> </ul>	High
Effectiveness and comparative effectiveness of allopurinol and febuxostat at reducing tophi	N/A	<ul style="list-style-type: none"> <li>Subgroup analyses of included trials did not report consistent results when stratified on the presence of tophi.</li> </ul>	Insufficient
Age and race (Caucasian vs. African-American) do not affect the efficacy of febuxostat or allopurinol.	N/A	<ul style="list-style-type: none"> <li>Subgroup analyses of 1 head-to-head RCT with low risk of bias (N=2,269)</li> </ul>	Low
Prophylactic therapy with low-dose colchicine or low-dose NSAIDs when beginning urate-lowering therapy reduces the risk of acute gout attacks	N/A	<ul style="list-style-type: none"> <li>1 placebo-controlled RCT of colchicine with low risk of bias (N=43)</li> <li>Strong observational evidence across 3 RCTs with low risk of bias that included different durations of prophylaxis (N=762, N=2,269, and</li> </ul>	High

Key Question	Prior Knowledge Used in Determining Strength of Evidence	Sources of Evidence Included in This Systematic Review	Strength of Evidence
		N=1,072)	
Longer durations of prophylaxis with colchicine or NSAIDs (> 8 weeks) are more effective than shorter duration when initiating urate-lowering therapy	N/A	<ul style="list-style-type: none"> <li>Indirect evidence from comparisons across 3 RCTs of differing durations of prophylaxis</li> <li>1 RCT with high risk of bias (N=190)</li> </ul>	Moderate
Specific gout-dietary advice to reduce red meat, shellfish, etc. while increasing low-fat dairy products, vegetables, and cherries does not add to the effectiveness of urate-lowering therapy for reducing serum urate	N/A	<ul style="list-style-type: none"> <li>1 RCT with high risk of bias (N=30)</li> </ul>	Low
<b>KQ4 Treatment Monitoring</b>			
Serum urate monitoring improves outcomes	N/A	<ul style="list-style-type: none"> <li>No direct evidence</li> <li>An argument can be made indirectly, based on the evidence that elevated serum urate levels cause gout</li> </ul>	Insufficient
Treating to a specific target serum urate level reduces the risk of gout attacks	<ul style="list-style-type: none"> <li>Lower serum urate levels are associated with reduced risk of gout attacks</li> </ul>	<ul style="list-style-type: none"> <li>No RCT evidence</li> <li>Variable targets proposed or assessed in the literature</li> </ul>	Low
<b>KQ5 Criteria for discontinuation of pharmaceutical management</b>			
Hyperuricemia Urate-lowering therapy may be discontinued in gout patients with 5 years of urate-lowering therapy keeping serum urate levels <7mg/dl, with subsequent annual off-urate lowering therapy-serum urate levels <7mg/dl	N/A	<ul style="list-style-type: none"> <li>2 prospective cohort studies (N=211 and N=33)</li> </ul>	Low
Prophylaxis Prophylaxis for acute gout when initiating urate-lowering therapy with low-dose colchicine or NSAIDs should be longer than 8 weeks	N/A	<ul style="list-style-type: none"> <li>Indirect evidence from comparisons across 3 RCTs with low risk of bias of differing durations of prophylaxis (N=762, N=2,269, and N=1,072)</li> </ul>	Moderate

FDA = Food and Drug Administration; N/A = not applicable; NSAID = nonsteroidal anti-inflammatory drug; RCT = randomized controlled trial; ULT = urate-lowering therapy

# References

1. De Miguel E, Puig JG, Castillo C, et al. Diagnosis of gout in patients with asymptomatic hyperuricaemia: A pilot ultrasound study. *Annals of the Rheumatic Diseases*. 2012 January;71(1):157-8. PMID: 2011671627 MEDLINE PMID 21953340 (<http://www.ncbi.nlm.nih.gov/pubmed/21953340>) FULL TEXT LINK <http://dx.doi.org/10.1136/ard.2011.154997>.
2. Singh JA, Reddy SG, Kundukulam J. Risk factors for gout and prevention: a systematic review of the literature. *Curr Opin Rheumatol*. 2011 Mar;23(2):192-202. PMID: 21285714.
3. Diagnosis of Gout Protocol. Rockville, MD: Agency for Health Care Research and Quality, Effective Health Care Program,; July 17, 2014. <http://effectivehealthcare.ahrq.gov/ehc/products/564/1937/gout-protocol-140716.pdf>. Accessed on July 17 2014.
4. Doghramji PP, Wortmann RL. Hyperuricemia and gout: new concepts in diagnosis and management. *Postgrad Med*. 2012 Nov;124(6):98-109. PMID: 23322143.
5. Anderson A, Singh Jasvinder A. Pegloticase for chronic gout. *Cochrane Database of Systematic Reviews*: John Wiley & Sons, Ltd; 2010.
6. Crittenden DB, Pillinger MH. New therapies for gout. *Annu Rev Med*. 2013;64:325-37. PMID: 23327525.
7. Tayar Jean H, Lopez-Olivo Maria A, Suarez-Almazor Maria E. Febuxostat for treating chronic gout. *Cochrane Database of Systematic Reviews*: John Wiley & Sons, Ltd; 2012.
8. Agency for Healthcare Research and Quality. *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. January 2014. Chapters available at: [www.effectivehealthcare.ahrq.gov](http://www.effectivehealthcare.ahrq.gov).
9. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928. PMID: 22008217.
10. Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol*. 2007;7:10. PMID: 17302989.
11. Whitlock EP, Lin JS, Chou R, et al. Using existing systematic reviews in complex systematic reviews. *Ann Intern Med*. 2008 May 20;148(10):776-82. PMID: 18490690.
12. Hill AB. The Environment and Disease: Association or Causation? *Proc R Soc Med*. 1965 May;58:295-300. PMID: 14283879.
13. Atkins D, Chang S, Gartlehner G, et al. Assessing the Applicability of Studies When Comparing Medical Interventions. Agency for Healthcare Research and Quality; December 2010. *Methods Guide for Comparative Effectiveness Reviews*. AHRQ Publication No. 11-EHC019-EF.
14. Wechalekar Mihir D, Vinik O, Schlesinger N, et al. Intra-articular glucocorticoids for acute gout. *Cochrane Database of Systematic Reviews*: John Wiley & Sons, Ltd; 2013.
15. Moi John HY, Sriranganathan Melonie K, Edwards Christopher J, et al. Lifestyle interventions for acute gout. *Cochrane Database of Systematic Reviews*: John Wiley & Sons, Ltd; 2013.
16. Janssens Hein J, Lucassen Peter LBJ, Van de Laar Floris A, et al. Systemic corticosteroids for acute gout. *Cochrane Database of Systematic Reviews*: John Wiley & Sons, Ltd; 2008.
17. Daoussis D, Antonopoulos I, Andonopoulos AP. ACTH as a treatment for acute crystal-induced arthritis: Update on clinical evidence and mechanisms of action. *Semin Arthritis Rheum*. 2014 Apr;43(5):648-53. PMID: 24762710.
18. Khanna PP, Gladue HS, Singh MK, et al. Treatment of acute gout: A systematic review. *Semin Arthritis Rheum*. 2014 Feb 13 PMID: 24650777.
19. Richette P, Bardin T. Colchicine for the treatment of gout. *Expert Opin Pharmacother*. 2010 Dec;11(17):2933-8. PMID: 21050036.

20. Terkeltaub RA. Colchicine Update: 2008. *Seminars in Arthritis and Rheumatism*. 2009 Jun;38(6):411-9. PMID: WOS:000267026600001.
21. van Echteld I, Wechalekar Mihir D, Schlesinger N, et al. Colchicine for acute gout. *Cochrane Database of Systematic Reviews*: John Wiley & Sons, Ltd; 2014.
22. Wechalekar MD, Vinik O, Moi JHY, et al. The efficacy and safety of treatments for acute gout: Results from a series of systematic literature reviews including cochrane reviews on intraarticular glucocorticoids, colchicine, nonsteroidal antiinflammatory drugs, and interleukin-1 inhibitors. *Journal of Rheumatology*. 2014;41(SUPPL. 92):15-25.
23. van Durme CM, Wechalekar MD, Buchbinder R, et al. Non-steroidal anti-inflammatory drugs for acute gout. *Cochrane Database Syst Rev*. 2014;9:CD010120. PMID: 25225849.
24. Li T, Chen SL, Dai Q, et al. Etoricoxib versus indometacin in the treatment of Chinese patients with acute gouty arthritis: a randomized double-blind trial. *Chin Med J (Engl)*. 2013;126(10):1867-71. PMID: 23673101.
25. Taylor TH, Mecchella JN, Larson RJ, et al. Initiation of allopurinol at first medical contact for acute attacks of gout: a randomized clinical trial. *Am J Med*. 2012 Nov;125(11):1126-34 e7. PMID: 23098865.
26. Zhang YK, Yang H, Zhang JY, et al. Comparison of intramuscular compound betamethasone and oral diclofenac sodium in the treatment of acute attacks of gout. *Int J Clin Pract*. 2014 May;68(5):633-8. PMID: 24472084.
27. Karimzadeh H, Nazari J, Mottaghi P, et al. Different duration of colchicine for preventing recurrence of gouty arthritis. *J Res Med Sci*. 2006;11:104-7.
28. Moi John HY, Sriranganathan Melonie K, Edwards Christopher J, et al. Lifestyle interventions for chronic gout. *Cochrane Database of Systematic Reviews*: John Wiley & Sons, Ltd; 2013.
29. Juraschek SP, Miller ER, 3rd, Gelber AC. Effect of oral vitamin C supplementation on serum uric acid: a meta-analysis of randomized controlled trials. *Arthritis Care Res (Hoboken)*. 2011 Sep;63(9):1295-306. PMID: 21671418.
30. Choi TY, Kim TH, Kang JW, et al. Moxibustion for rheumatic conditions: A systematic review and meta-analysis. *Clinical Rheumatology*. 2011 July;30(7):937-45. PMID: 2011350115 MEDLINE PMID 21331532 (<http://www.ncbi.nlm.nih.gov/pubmed/21331532>) FULL TEXT LINK <http://dx.doi.org/10.1007/s10067-011-1706-5>.
31. Lee WB, Woo SH, Min BI, et al. Acupuncture for gouty arthritis: a concise report of a systematic and meta-analysis approach. *Rheumatology (Oxford)*. 2013 Jul;52(7):1225-32. PMID: 23424263.
32. Li XX, Han M, Wang YY, et al. Chinese herbal medicine for gout: a systematic review of randomized clinical trials. *Clin Rheumatol*. 2013 Jul;32(7):943-59. PMID: 23666318.
33. Wang DD, Sievenpiper JL, de Souza RJ, et al. The effects of fructose intake on serum uric acid vary among controlled dietary trials. *J Nutr*. 2012 May;142(5):916-23. PMID: 22457397.
34. Zhou L, Liu L, Liu X, et al. Systematic review and meta-analysis of the clinical efficacy and adverse effects of Chinese herbal decoction for the treatment of gout. *PLoS One*. 2014;9(1):e85008. PMID: 24465466.
35. Andres M, Sivera F, Falzon L, et al. Dietary supplements for chronic gout. *Cochrane Database Syst Rev*. 2014;10:CD010156. PMID: 25287939.
36. Wang MY, Jiang XB, Wu WL, et al. A meta-analysis of alcohol consumption and the risk of gout. *Clinical Rheumatology*. 2013 Nov;32(11):1641-8. PMID: WOS:000325809900011.
37. Zeng YC, Huang SF, Mu GP, et al. Effects of adjusted proportional macronutrient intake on serum uric acid, blood lipids, renal function, and outcome of patients with gout and overweight. *Chinese Journal of Clinical Nutrition*. 2012 August;20(4):210-4. PMID: 2012603533 FULL TEXT LINK <http://dx.doi.org/10.3760/cma.j.issn.1674-635X.2012.04.004>.
38. Zhang SJ, Liu JP, He KQ. Treatment of acute gouty arthritis by blood-letting cupping plus herbal medicine. *J Tradit Chin Med*. 2010 Mar;30(1):18-20. PMID: 20397456.
39. Holland R, McGill NW. Comprehensive dietary education in treated gout patients does not further

- improve serum urate. *Intern Med J.* 2015 Feb;45(2):189-94. PMID: 25495503.
40. Castrejon I, Toledano E, Rosario MP, et al. Safety of allopurinol compared with other urate-lowering drugs in patients with gout: a systematic review and meta-analysis. *Rheumatol Int.* 2014 Dec 18;34(12):2551-9. PMID: 25519877.
41. Seth R, Kydd AS, Buchbinder R, et al. Allopurinol for chronic gout. *Cochrane Database Syst Rev.* 2014;10:CD006077. PMID: 25314636.
42. Ye P, Yang S, Zhang W, et al. Efficacy and tolerability of febuxostat in hyperuricemic patients with or without gout: a systematic review and meta-analysis. *Clin Ther.* 2013 Feb;35(2):180-9. PMID: 23332451.
43. Faruque LI, Ehteshami-Afshar A, Wiebe N, et al. A systematic review and meta-analysis on the safety and efficacy of febuxostat versus allopurinol in chronic gout. *Semin Arthritis Rheum.* 2013 Dec;43(3):367-75. PMID: 24326033.
44. Manara M, Bortoluzzi A, Favero M, et al. Italian Society of Rheumatology recommendations for the management of gout. *Reumatismo.* 2013;65(1):4-21. PMID: 23550256.
45. Kydd AS, Seth R, Buchbinder R, et al. Uricosuric medications for chronic gout. *Cochrane Database Syst Rev.* 2014;11:CD010457. PMID: 25392987.
46. Latourte A, Bardin T, Richette P. Prophylaxis for acute gout flares after initiation of urate-lowering therapy. *Rheumatology (Oxford).* 2014 Apr 23;53(4):2475-88. PMID: 24758886.
47. Ramasamy SN, Korb-Wells CS, Kannangara DR, et al. Allopurinol hypersensitivity: a systematic review of all published cases, 1950-2012. *Drug Saf.* 2013 Oct;36(10):953-80. PMID: 23873481.
48. Chohan S, Becker MA, MacDonald PA, et al. Women with gout: efficacy and safety of urate-lowering with febuxostat and allopurinol. *Arthritis Care Res (Hoboken).* 2012 Feb;64(2):256-61. PMID: 22052584.
49. Saag KG, Becker MA, Whelton A, et al. Effect of febuxostat on serum urate levels in gout subjects with hyperuricemia and moderate-to-severe renal impairment: A randomized controlled trial. *Arthritis and Rheumatism.* 2013 October;65 SUPPL. 10:S498-S9.
50. Becker MA, MacDonald PA, Hunt B, et al. Treating hyperuricemia of gout: safety and efficacy of febuxostat and allopurinol in older versus younger subjects. *Nucleosides Nucleotides Nucleic Acids.* 2011 Dec;30(12):1011-7. PMID: 22132950.
51. Becker MA, MacDonald PA, Hunt BJ, et al. Diabetes and gout: efficacy and safety of febuxostat and allopurinol. *Diabetes Obes Metab.* 2013 Nov;15(11):1049-55. PMID: 23683134.
52. Goldfarb DS, MacDonald PA, Hunt B, et al. Febuxostat in gout: serum urate response in uric acid overproducers and underexcretors. *J Rheumatol.* 2011 Jul;38(7):1385-9. PMID: 21572152.
53. Jackson RL, Hunt B, MacDonald PA. The efficacy and safety of febuxostat for urate lowering in gout patients  $\geq 65$  years of age. *BMC Geriatr.* 2012;12:11. PMID: 22436129.
54. Wells AF, MacDonald PA, Chefo S, et al. African American patients with gout: efficacy and safety of febuxostat vs allopurinol. *BMC Musculoskelet Disord.* 2012;13:15. PMID: 22316106.
55. Huang X, Du H, Gu J, et al. An allopurinol-controlled, multicenter, randomized, double-blind, parallel between-group, comparative study of febuxostat in Chinese patients with gout and hyperuricemia. *Int J Rheum Dis.* 2014 Jan 28;17(1):244-67. PMID: 24467549.
56. Wortmann RL, Macdonald PA, Hunt B, et al. Effect of prophylaxis on gout flares after the initiation of urate-lowering therapy: analysis of data from three phase III trials. *Clin Ther.* 2010 Dec;32(14):2386-97. PMID: 21353107.
57. Borstad GC, Bryant LR, Abel MP, et al. Colchicine for prophylaxis of acute flares when initiating allopurinol for chronic gouty arthritis. *J Rheumatol.* 2004 Dec;31(12):2429-32. PMID: 15570646.
58. Gibson T, Rodgers V, Potter C, et al. Allopurinol treatment and its effect on renal function in gout: a controlled study. *Ann Rheum Dis.* 1982 Feb;41(1):59-65. PMID: 7039523.

59. Scott JT. Comparison of allopurinol and probenecid. *Ann Rheum Dis*. 1966 Nov;25(6 Suppl):623-6. PMID: 5335059.
60. Gilchrist MJ, Hebert B. Drug reaction with eosinophilia and systemic symptoms (DRESS). *Journal of General Internal Medicine*. 2011 May;26 SUPPL. 1:S423.
61. Tassaneeyakul W, Jantararoungtong T, Chen P, et al. Strong association between HLA-B\*5801 and allopurinol-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in a Thai population. *Pharmacogenet Genomics*. 2009 Sep;19(9):704-9. PMID: 19696695.
62. Becker MA, Fitz-Patrick D, Storgard C, et al. A large-scale, multicenter, prospective, open-label, 6-month study to evaluate the safety of allopurinol monotherapy in patients with gout. *Arthritis and Rheumatism*. 2013 October;65 SUPPL. 10:S502-S3.
63. Chaudrey K, Khan M, Madhoun M, et al. Allopurinol-induced dress syndrome: A reversible fatality. *American Journal of Gastroenterology*. 2013 October;108 SUPPL. 1:S153.
64. Ibie NC, Alper AB. She is all dressed up: A case of allopurinol deadly complication. *Journal of Investigative Medicine*. 2014 February;62(2):504-5.
65. Weiss KM, Jain R, Wells C, et al. A case of allopurinol-induced dress syndrome in a patient with asymptomatic gout. *Annals of Allergy, Asthma and Immunology*. 2011 November;107(5 SUPPL. 1):A26.
66. Kamatani N, Fujimori S, Hada T, et al. Multicenter, open-label study of long-term administration of febuxostat (TMX-67) in Japanese patients with hyperuricemia including gout. *J Clin Rheumatol*. 2011 Jun;17(4 Suppl 2):S50-6. PMID: 21654270.
67. Yaylaci S, Demir MV, Temiz T, et al. Allopurinol-induced DRESS syndrome. *Indian J Pharmacol*. 2012 May;44(3):412-4. PMID: 22701258.
68. Schumacher HR, Becker MA, Lloyd E, et al. Febuxostat in the treatment of gout: 5-yr findings of the FOCUS efficacy and safety study. *Rheumatology*. 2009 Feb;48(2):188-94. PMID: WOS:000262518500020.
69. Lee MH, Stocker SL, Anderson J, et al. Initiating allopurinol therapy: do we need to know the patient's human leucocyte antigen status? *Internal Medicine Journal*. 2012 Apr;42(4):411-6. PMID: WOS:000302796000017.
70. Hande KR, Noone RM, Stone WJ. Severe allopurinol toxicity. Description and guidelines for prevention in patients with renal insufficiency. *Am J Med*. 1984 Jan;76(1):47-56. PMID: 6691361.
71. Chen IH, Kuo MC, Hwang SJ, et al. Allopurinol-induced severe hypersensitivity with acute renal failure. *Kaohsiung J Med Sci*. 2005 May;21(5):228-32. PMID: 15960069.
72. Kumar A, Edward N, White MI, et al. Allopurinol, erythema multiforme, and renal insufficiency. *BMJ*. 1996 Jan 20;312(7024):173-4. PMID: 8563541.
73. Lupton GP, Odom RB. The allopurinol hypersensitivity syndrome. *J Am Acad Dermatol*. 1979 Oct;1(4):365-74. PMID: 159913.
74. Chung WH, Chang WC, Stocker SL, et al. Insights into the poor prognosis of allopurinol-induced severe cutaneous adverse reactions: the impact of renal insufficiency, high plasma levels of oxypurinol and granulysin. *Ann Rheum Dis*. 2014 Aug 12 PMID: 25115449.
75. De Vera M, Rai S, Bhole V. Medication adherence in patients with gout: A systematic review. *Arthritis and Rheumatism*. 2013 October;65 SUPPL. 10:S85.
76. Seth R, Kydd AS, Falzon L, et al. Preventing attacks of acute gout when introducing urate-lowering therapy: a systematic literature review. *J Rheumatol Suppl*. 2014 Sep;92:42-7. PMID: 25180127.
77. Zandman-Goddard G, Amital H, Shamrayevsky N, et al. Rates of adherence and persistence with allopurinol therapy among gout patients in Israel. *Rheumatology (Oxford)*. 2013 Jun;52(6):1126-31. PMID: 23392592.
78. Martini N, Bryant L, Karu LT, et al. Living With Gout in New Zealand An Exploratory Study Into People's Knowledge About the Disease and Its Treatment. *Jcr-Journal of Clinical Rheumatology*. 2012 Apr;18(3):125-9. PMID: WOS:000302141900003.

79. Silva L, Miguel ED, Peiteado D, et al. Compliance in gout patients. *Acta Reumatol Port*. 2010 Oct-Dec;35(5):466-74. PMID: 21245815.
80. Harrold LR, Andrade SE, Briesacher B, et al. The dynamics of chronic gout treatment: medication gaps and return to therapy. *Am J Med*. 2010 Jan;123(1):54-9. PMID: 20102992.
81. Harrold LR, Andrade SE, Briesacher BA, et al. Adherence with urate-lowering therapies for the treatment of gout. *Arthritis Res Ther*. 2009;11(2):R46. PMID: 19327147.
82. Halpern R, Mody RR, Fuldeore MJ, et al. Impact of noncompliance with urate-lowering drug on serum urate and gout-related healthcare costs: administrative claims analysis. *Curr Med Res Opin*. 2009 Jul;25(7):1711-9. PMID: 19485724.
83. Riedel AA, Nelson M, Joseph-Ridge N, et al. Compliance with allopurinol therapy among managed care enrollees with gout: a retrospective analysis of administrative claims. *J Rheumatol*. 2004 Aug;31(8):1575-81. PMID: 15290738.
84. Rascati K, Prasla K, Park H, et al. Evaluation of healthcare costs for patients with gout by serum uric acid. *Arthritis and Rheumatism*. 2011;63(10):2011-11.
85. Dalbeth N, House ME, Horne A, et al. Prescription and dosing of urate-lowering therapy, rather than patient behaviours, are the key modifiable factors associated with targeting serum urate in gout. *BMC Musculoskelet Disord*. 2012;13:174. PMID: 22978848.
86. Dalbeth N, Petrie KJ, House M, et al. Illness perceptions in patients with gout and the relationship with progression of musculoskeletal disability. *Arthritis Care Res (Hoboken)*. 2011 Nov;63(11):1605-12. PMID: 22034122.
87. Singh JA, Hodges JS, Asch SM. Opportunities for improving medication use and monitoring in gout. *Annals of the Rheumatic Diseases*. 2009 Aug;68(8):1265-70. PMID: WOS:000268010500006.
88. Sarawate CA, Brewer KK, Yang W, et al. Gout medication treatment patterns and adherence to standards of care from a managed care perspective. *Mayo Clin Proc*. 2006 Jul;81(7):925-34. PMID: 16835972.
89. Solomon DH, Avorn J, Levin R, et al. Uric acid lowering therapy: prescribing patterns in a large cohort of older adults. *Ann Rheum Dis*. 2008 May;67(5):609-13. PMID: 17728328.
90. Briesacher BA, Andrade SE, Fouayzi H, et al. Comparison of drug adherence rates among patients with seven different medical conditions. *Pharmacotherapy*. 2008 Apr;28(4):437-43. PMID: 18363527.
91. de Klerk E, van der Heijde D, Landewe R, et al. Patient compliance in rheumatoid arthritis, polymyalgia rheumatica, and gout. *J Rheumatol*. 2003 Jan;30(1):44-54. PMID: 12508389.
92. Deyo RA, Inui TS, Sullivan B. Noncompliance with arthritis drugs: magnitude, correlates, and clinical implications. *J Rheumatol*. 1981 Nov-Dec;8(6):931-6. PMID: 7328568.
93. Krishnan E, Akhras KS, Sharma H, et al. Serum urate and incidence of kidney disease among veterans with gout. *J Rheumatol*. 2013 Jul;40(7):1166-72. PMID: 23678154.
94. Wu EQ, Patel PA, Mody RR, et al. Frequency, risk, and cost of gout-related episodes among the elderly: does serum uric acid level matter? *J Rheumatol*. 2009 May;36(5):1032-40. PMID: 19369467.
95. Halpern R, Fuldeore MJ, Mody RR, et al. The effect of serum urate on gout flares and their associated costs: an administrative claims analysis. *J Clin Rheumatol*. 2009 Feb;15(1):3-7. PMID: 19125135.
96. Becker MA, MacDonald PA, Hunt BJ, et al. Determinants of the clinical outcomes of gout during the first year of urate-lowering therapy. *Nucleosides Nucleotides Nucleic Acids*. 2008 Jun;27(6):585-91. PMID: 18600509.
97. Sarawate CA, Patel PA, Schumacher HR, et al. Serum urate levels and gout flares: analysis from managed care data. *J Clin Rheumatol*. 2006 Apr;12(2):61-5. PMID: 16601538.
98. Bongartz T, Zleik N, Clement M, et al. The risk of future attacks in patients with incident gout: A population-based. *Annals of the Rheumatic Diseases*. 2013;72(3):2013-06.
99. Hamburger MI, Tesser JRP, Skosey JL, et al. Patterns of gout treatment and related outcomes in us

community rheumatology practices: The relation between gout flares, time in treatment, serum uric acid level and urate lowering therapy. *Arthritis and Rheumatism*. 2012 October;64 SUPPL. 10:S808-S9.

100. Khanna PP, Baumgartner S, Khanna D, et al. Assessing SUA, flare rates, and Tophi in patients with gout treated xanthine oxidase inhibitors in the United States. *Annals of the Rheumatic Diseases*. 2013;72(3):2013-06.

101. Perez-Ruiz F, Herrero-Beites AM, Carmona L. A two-stage approach to the treatment of hyperuricemia in gout: the "dirty dish" hypothesis. *Arthritis Rheum*. 2011 Dec;63(12):4002-6. PMID: 21898351.

102. Loebl WY, Scott JT. Withdrawal of allopurinol in patients with gout. *Ann Rheum Dis*. 1974 Jul;33(4):304-7. PMID: 4416909.

103. Becker MA, Schumacher HR, Jr., Wortmann RL, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *N Engl J Med*. 2005 Dec 8;353(23):2450-61. PMID: 16339094.

104. Schumacher Jr HR, Becker MA, Wortmann RL, et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: A 28-week, phase III, randomized, double-blind, parallel-group trial. *Arthritis Care and Research*. 2008;59(11):1540-8.

105. Becker MA, Schumacher HR, Espinoza LR, et al. The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial. *Arthritis Res Ther*. 2010;12(2):R63. PMID: 20370912.

# Introduction

## Background

Gout is the most common form of inflammatory arthritis and is characterized by acute intermittent episodes of synovitis presenting with joint swelling and pain (referred to as acute gouty arthritis). Gout is caused when excess urate in the body crystalizes (as monosodium urate [MSU]) in joint fluid, cartilage, bones, tendons, bursas or other sites. These crystals can directly stimulate an acute inflammatory attack. In some patients, over time acute gout attacks become more frequent, protracted and severe and may eventually progress to a chronic inflammatory condition. Additionally, in some patients the deposits of urate crystals grow into larger collections, called tophi (singular tophus) when clinically apparent.

Based on data from the 2007-2008 National Health and Nutrition Examination Survey (NHANES), the prevalence of gout among adults in the United States was estimated to be 3.9 percent (8.3 million individuals), ranging from 2.0 percent in women to 5.9 percent in men.<sup>1</sup> Comparing the most recent figures for the prevalence of gout to those of previous cycles of NHANES shows that the prevalence of gout appears to be increasing. The rise in the prevalence of gout has paralleled the increase in prevalence of conditions associated with hyperuricemia, including obesity, hypertension, hypertriglyceridemia, hypercholesterolemia, type 2 diabetes and metabolic syndrome, and chronic kidney disease.<sup>2</sup> Certain medications also may increase the risk for developing gout (e.g., thiazide diuretics).

A 2013 study of ambulatory care costs associated with gout estimated the costs to be nearly \$1 billion (in 2008 figures). Of this figure, 32 percent of the costs were attributed to office visits for acute attacks (flares), and 61 percent were attributed to expenditures for prescription medications to treat the condition.<sup>3</sup>

The aim of this report is to review the evidence for the treatment of patients with gout, focusing on the primary care setting.

## Etiology of Gout

Gout initially presents as an episode of acute inflammatory arthritis, most commonly involving the first meta-tarsal-phalanx joint, a condition commonly referred to as podagra. Typical attacks during the first few years last 7 to 14 days before resolving. Over time, these attacks become prolonged and can become chronic. The acute gout attack is a result of urate crystals directly interacting with the immune system. Several factors affect deposition of urate crystals including temperature, local pH, but most critical, concentration of serum urate. The solubility factor of urate is 6.8mg/dl; urate concentration above this threshold leads to crystal deposition, levels below this threshold lead to crystal dissolution. Uric acid (UA) is a breakdown product of dietary or endogenous purines, (which are among the building blocks of nucleic acids) and is associated with the formation and deposition of the UA crystals. Hyperuricemia is most frequently the result of inadequate renal excretion of UA (90 percent of patients) or, less commonly, UA overproduction. Renal disease and medications can affect the excretion of serum urate. As serum urate concentration rises above 6.0mg/dl, the risk for developing an acute gout attack increases. From the Framingham Heart Study, among men, the 5-year incidence of acute gout attack increased from 10 percent where serum urate is between 6.0 and 6.9mg/dl to 48 percent for serum urate > 8mg/dl.<sup>4</sup> Once a patient has had an initial attack, hyperuricemia leads to higher risk of repeat attacks. The 1-year incidence of recurrent attack is 30 percent for patients

with serum urate between 6.0 and 6.9mg/dl and >70 percent for patients with serum urate > 8mg/dl.<sup>5</sup> The primary risk factor for gout is hyperuricemia; however, not all patients with hyperuricemia go on to develop clinical gout, a state known as asymptomatic hyperuricemia. Patients with asymptomatic hyperuricemia may or may not have evidence of urate deposits in their joints (as documented by advanced imaging methods).<sup>6</sup> The prevalence of hyperuricemia is about 21 percent, four-to ten-fold higher than the prevalence of gout.<sup>1</sup>

The causes of gout are unclear but appear to be multifactorial, including a combination of genetic, hormonal, metabolic, and dietary factors. Family history, advancing age, male sex, or, in women, early menopause have been associated with a higher risk of gout and/or gout attacks (flares).<sup>7</sup> Dietary risk factors for gout have been postulated to include alcohol consumption, as well as consumption of meat, seafood, sugar-sweetened soft drinks, and foods high in fructose, whereas dairy foods and coffee have been associated with a lower risk of incident gout and in some cases a lower rate of gout attacks (flares).

## **Diagnosis of Gout**

A number of methods have been proposed to establish the diagnosis of gout. The evidence supporting the various methods for the diagnosis of gout is the subject of a separate systematic review.<sup>8</sup>

## **Clinical Presentation and Management**

Gout is commonly divided into acute and chronic phases.

### **Acute Gouty Arthritis**

The acute phase is self-limited and characterized by recurrent attacks of synovitis (articular inflammation) that present with pain, erythema, and swelling, most frequently in the large toe but also potentially involving other joints, tendons, bursae or other areas.

A number of pharmacologic agents have been advocated for use in the management of acute gout. Commonly advocated agents to treat acute gout include non-steroidal anti-inflammatories (NSAIDs), colchicine (the microtubule disrupting agent), and/or corticosteroids (intra-articular or systemic) to manage pain and inflammation. The evidence for the efficacy of these agents in treating acute gout is a topic of this review.

### **Chronic Gout**

Although initial episodes may be brief and rare, acute episodes may increase in frequency and duration over time and lead to the development of chronic gout. In addition to more frequent attacks, chronic gout may be associated with deposits of uric acid crystals known as tophi. Tophi may develop in joints, cartilage, bone, and auricular or other cutaneous tissues.<sup>9</sup> The average interval between the onset of gout and appearance of tophi, in the absence of treatment, is approximately 10 years.<sup>9</sup> Increased frequency of attacks and tophi are highly correlated with the presence of hyperuricemia. In addition to the aforementioned manifestations of chronic gout, patients with long standing gout can develop uric acid nephrolithiasis, and chronic interstitial nephropathy. In addition, gout has also been associated with an higher risk for progression of kidney disease<sup>10</sup> and increased risk of atherosclerotic disease including myocardial infarction, heart failure, and stroke.<sup>11</sup>

Management of chronic gout may include both pharmacologic and non-pharmacologic strategies. Urate-lowering strategies are the primary pharmacologic intervention for management

of long-term complications of gout. Non-pharmacologic methods advocated for management of chronic gout include a combination of lifestyle changes, including weight loss, exercise, smoking cessation, hydration, and dietary changes. The evidence for the efficacy of specific dietary changes in managing gout (preventing attacks) is a topic of this review. Several interleukin-1 $\beta$ -inhibitory anti-inflammatory agents currently approved for treatment of rheumatoid arthritis are in Phase II and III trials for treatment of gout, including anakinra, canakinumab, and rilonacept,<sup>12-14</sup> and will not be included in this systematic review, because they are not prescribed in the primary care setting (see below).

Pharmacologic management of chronic gout consists primarily of agents that lower serum urate. These agents include xanthine oxidase inhibitors (XOIs- allopurinol and febuxostat) to reduce serum urate production; uricosurics (probenecid), which prevent renal reabsorption of uric acid (and increase urinary uric acid excretion); and uricases, which stimulate the breakdown of uric acid (pegloticase). These agents can be used alone or in specific combinations (eg. XOI plus probenecid). Pegloticase will not be included in this review because it would not be prescribed in a primary care setting (see below).

Table 1 lists the drugs used to treat gout and notes the ones covered in this systematic review.

**Table 1. Pharmacologic agents used in the treatment of gout**

Drug Class	Agent (generic/brand)	Manufacturer
Anti-inflammatories*		
	NSAIDS (including Ibuprofen, naproxen, etodolac, diclofenac, indomethacin, COX-2 inhibitors)	Numerous
	Corticosteroids/Animal-derived adrenocorticotrophic hormone (ACTH) formulation	Numerous
	Colchicine/Colcrys	URL Pharma
	IL-1B Receptor Antagonists:**	
	Anakinra/kineret <sup>®</sup>	Sobi
	Canakinumab/Ilaris <sup>™</sup>	Novartis
	Rilonacept/Arcalyst <sup>™</sup>	Regeneron
Uricosurics		
	Probenecid/Benemid or Probalan	Multiple
Xanthine Oxidase Inhibitors		
	Allopurinol/Zyloprim <sup>®</sup>	Prometheus Labs
	Febuxostat/Uloric	Teijin Pharma Ltd., Takeda
Uricase		
	Pegloticase/Krystexxa <sup>®***</sup>	Savient Pharmaceuticals
Combination agents		
	Colchicine-probenecid/Proben-C	Merck

Table notes: \*NSAIDS and corticosteroids will be considered only for their use in treating inflammation associated with gout; \*\*these agents will not be considered in this review, because they are not FDA-approved for use in treating gout and/or are not prescribed in the primary care setting.

Additional off-label agents that have been proposed as useful in the management of gout include the lipid lowering agent, fenofibrate; the angiotensin 2 receptor blocker, losartan; and calcium channel blockers (in patients being treated with these agents for other indications). These agents are not included in this review.

## **Issues of Concern for Management of Gout in Primary Care Settings**

The treatment of gout has spawned a proliferation of evidence-based guidelines,10-16 including a recently completed set of guidelines by the American College of Rheumatology (ACR) that considered both the treatment of acute gout and of hyperuricemia associated with chronic gout.<sup>15, 16</sup>

However, the majority of individuals with gout are initially seen, diagnosed, and treated in primary care or emergent care settings and may continue to receive their care in these settings. Therefore primary care physicians (PCPs) and emergency physicians need to be well-positioned to diagnose early-stage gout and implement management strategies. It is established that specialists and generalists systematically rate the benefits and harms of treatment differently,<sup>17</sup> and there have been some situations when guidelines on the same clinical topic developed by specialists or by generalists have had somewhat different recommendations.<sup>18</sup> Therefore, a new guideline, developed by primary care practitioners and focused on primary care practice, is warranted. This review is intended to provide the evidence for such a guideline.

## **Scope and Key Questions**

### **Scope of the Review**

The purpose of this review is to assess the evidence on the management of patients with gout, both in the acute phase and chronic phase, including patients with tophaceous gout, and to assess management therapies that are FDA-approved and within the scope of practice of typical primary care providers. AHRQ assigned this report to the Southern CA Evidence-based Practice Center (HHS A290201200006I). A protocol for the review was accepted and publicly posted on the AHRQ website on November 3, 2014 at: <http://effectivehealthcare.ahrq.gov/ehc/products/564/1992/Gout-management-protocol-141103.pdf>. The protocol was approved by the AHRQ Center for Evidence and Practice Improvement.

### **Key Questions**

#### **The Key Questions**

The key questions that guided this review are based on questions posed by the American College of Physicians (ACP). These questions underwent revision based on input from a group of key informants, public comments, and input from a Technical Expert Panel (TEP).

#### **Key Question 1: Acute Gout Treatment**

- a. In patients with acute gout, what are the benefits and harms of different pharmacological therapies?
- b. Does effectiveness (benefits and harms) differ according to patient baseline demographic characteristics and co-morbid conditions (including renal function)?

c. Does effectiveness (benefits and harms) differ according to disease severity, including initial clinical presentation (e.g., extent of joint involvement and time since start of flare) and laboratory values (serum and/or urine UA levels)?

## Key Question 2: Dietary and Lifestyle Management of Gout

a. In adults with gout, what are the benefits and harms of different dietary therapies and life style measures on intermediate (serum and/or urine UA levels) and final health outcomes (including recurrence of gout episodes and progression [e.g., development of tophi])?

b. Does effectiveness and comparative effectiveness of dietary modification differ according to disease severity (including presence of tophi and baseline serum UA), underlying mechanisms of hyperuricemia, or baseline demographic and co-morbid characteristics?

## Key Question 3: Pharmacologic Management of Hyperuricemia in Gout Patients

a. In adults with gout, what are the benefits and harms of different pharmacological therapies on intermediate (serum and/or urine UA levels) and long-term clinical health outcomes (including recurrence of gout episodes and progression)?

b. Does effectiveness and comparative effectiveness of urate lowering therapy differ according to disease severity (including presence of tophi and baseline serum UA), underlying mechanisms of hyperuricemia, or baseline demographic and co-morbid characteristics?

c. What is the effect of dietary modification in combination with pharmacologic therapy?

## Key Question 4: Treatment Monitoring of Patients with Gout

a. In adults with gout, does monitoring serum urate levels with pharmacologic treatment and/or dietary and/or lifestyle change measures (e.g., compliance) improve treatment outcomes?

b. Is achieving lower subsequent serum urate levels (less than 5 vs. 5–7mg/dL) associated with decreased risk for recurrent acute gout attack, progression to chronic arthritis or disability, resolution of tophi, or other clinical outcomes (including risk for comorbidities or progression of comorbidities) or patient-reported outcomes?

## Key Question 5: Discontinuation of Pharmaceutical Management for Patients on Acute or Chronic Gout Medications

In adults with gout, are there criteria that can identify patients who are good candidates for discontinuing

a. urate lowering therapy?

b. anti-inflammatory prophylaxis against acute gout attack for patients on urate lowering therapy after an acute gout attack?

## Organization of this report

The remainder of this report presents the methods used to conduct the literature searches, data abstraction, and analysis for this review; the results of the literature searches, organized by key question; the conclusions; and a discussion of the findings within the context of what is already known, the limitations of the review and the literature, as well as suggestions for future research.

## Methods

### Criteria for Inclusion/Exclusion of Studies in the Review

Included studies are limited to those that fit the PICOTs (below).

Studies in any clinical setting were included as long as they satisfy all other inclusion/exclusion criteria. The results of the report are intended for primary care and acute care settings, and therefore primary and acute settings are preferred. Case reports were excluded.

Studies were not limited by language. For studies of efficacy and effectiveness, we included only randomized controlled trials. Observational studies were included for the assessment of rare adverse events. Existing systematic reviews were included both as sources of original data (reference mining) and for their conclusions, following the methods proposed by Whitlock and colleagues.<sup>19</sup>

### PICOTs

- Population(s)
  - Adults ( $\geq 18$  years of age)
    - Subgroups
      - Male and female patients (KQ1-5)
      - Patients presenting with an acute episode (KQ1, 2, 5) and those with a history of gout (KQ1-5)
      - Patients with higher vs. lower serum UA (e.g.,  $<5$  vs.  $\geq 5$ )
      - Patients who are HLA-B5801-positive (KQ1)
      - Older ( $\geq 65$ ) vs. younger patients (KQ1-5)
      - Tophaceous and non-topaceous gout patients (KQ1-5)
      - Patients with comorbidities, including hypertension, Type 2 diabetes, chronic kidney disease (renal insufficiency: CKD 1-4) (KQ1-5)
- Interventions
  - Dietary interventions (KQ2, 4)
    - Low purine diet
    - Fructose restriction, other carbohydrate restriction
    - Ethanol restriction

- Sour cherry juice (proposed to be a XOI)
    - Dairy products and vegetables
    - Mediterranean diet
    - DASH diet
  - Other Lifestyle Measures (KQ2, 4)
    - Smoking cessation
    - Exercise
    - Hydration
  - Dietary supplements and other alternative treatments (KQ2, 4)
    - Vitamin C
    - Traditional Chinese Medicine (acupuncture or Chinese herbal remedies: Ermiao wan, Meadow saffron, Dandelion, Burdock root; Huzhang gout granule; Jinhuang ointment; Yinlian gout granule, Si Miao San, Gout chi)
  - Pharmacologic agents
    - Acute gout treatment (KQ1, 4, 5b)
      - Anti-inflammatories (NSAIDS, corticosteroids [intra-articular and/or oral])
      - Microtubule inhibitors (colchicine)
      - Combination therapy (colchicine and NSAIDS/ oral corticosteroids; intra-articular corticosteroids/anti-inflammatories)
    - Urate Lowering Therapies (KQ3, 5a)
      - Xanthine oxidase inhibitors (XOIs: allopurinol, febuxostat) (KQ3, 5)
      - Uricosuric agents (probenecid) (KQ3, 5a)
    - Combination medications
      - Probenecid/colchicine (KQ3)
      - XOIs/anti-inflammatories (KQ3)
    - Co-interventions (KQ3-5)
      - Included pharmacologic agents plus included diet and life style measures (KQ2, 3,4)
      - Included pharmacologic agents and included Traditional Chinese Medicine
- Comparators
  - Placebo or usual care (KQ 1, 3-5)
  - Active comparators (that are included interventions) (KQ1, 3-5)
  - Usual diet or level of activity or other dietary changes or dietary supplements that are included interventions (KQ2)
  - Early initiation of treatment (KQ 1, 2, 3)
- Outcomes:
  - For acute gout treatment (KQ1)
    - Efficacy
      - Short-term health outcomes (days following acute flare)
        - Pain

- Joint swelling, tenderness
  - Longer-term health outcomes:
    - sUA
    - Pain
    - Joint swelling, tenderness
    - Activities of daily living (ADLs)
    - Patient global assessment
    - Recurrence
  - Safety
    - Gastrointestinal and renal side effects (NSAIDS, colchicine)
    - Steroid induced osteoporosis, diabetes
- For diet and other lifestyle therapy (KQ2)
  - Efficacy
    - Intermediate outcomes: serum and/or urine uric acid
    - Health outcomes: recurrence
  - Harms
- For chronic gout treatment (uric acid lowering therapy), monitoring, and discontinuation (KQ3-5)
  - Efficacy:
    - intermediate outcomes: sUA
    - Final Health outcomes: pain, joint swelling, tenderness associated with the development of tophi, ADLs, patient global assessment, risk for comorbidities/mortality, recurrence of gout attacks (flares)
  - Safety
    - Inflammatory effects, including skin rash
    - Hematologic effects
    - Cardiovascular effects
    - Liver dysfunction
    - Renal dysfunction
- For anti-inflammatory prophylaxis with ULT therapy (same outcomes as for acute gout therapy)
- Timing
  - Acute treatment (KQ1): 24-72 hours follow-up
  - Chronic treatment (KQ2-4): any follow-up time
  - Delayed vs. immediate treatment (KQ1)
- Setting (all KQ)
  - Priority will be given to patients given being seen in primary care settings, which also includes urgent care clinics and emergency departments. If evidence from primary care settings is sparse, then studies of patients in outpatient specialist settings were included

## **Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions**

The search strategy was designed by our reference librarian in collaboration with our local content expert, who has participated in the two ACR systematic reviews on gout;<sup>15, 16</sup> the search strategy appears in Appendix A. We searched PubMed, EMBASE, the Cochrane Collection, and the Web of Science using the search terms “gout”, “gouty”, and terms for tophi (January 1, 2010-April 28, 2014; at least one year to the search dates for the recent systematic reviews). We also obtained relevant references from at least 33 recent systematic reviews that cover nearly all of the Key Questions. We also searched Clinicaltrials.gov and the Web of Science for recently completed studies and unpublished or non-peer-reviewed study findings. Searches were not limited by language of publication: Non-English language studies that met the inclusion/exclusion criteria based on a review of an English-language abstract were screened further in full text for the following languages: Chinese, French, German, Japanese, Spanish, Portuguese, and Russian. We contacted manufacturers of the prescription medications used to treat gout that are listed in Table 1 for unpublished data specific to the use of these medications for treatment of gout or symptoms related to gout.

We also included any relevant studies identified in the searches we conducted for a simultaneous review on management of gout if not already identified in the searches for this review. Finally, we asked the TEP to assess our list of included studies and to provide references for any studies they believe should also be included. An update search will be conducted after submission of the draft report and studies identified in the update search will also undergo the same process.

The output of the literature searches was transferred to DistillerSR™ for screening. Article titles and abstracts identified by the searches were independently screened by two literature reviewers using the predetermined inclusion and exclusion criteria, and those selected by either reviewer were accepted without reconciliation for further, full-text review. Full-text review was also conducted independently by two reviewers to exclude articles that did not meet the inclusion criteria of the review. Disagreements regarding inclusion at the full-text stage were reconciled, with the input of the project lead when necessary. We identified a huge number of systematic reviews on gout management for which we performed reference mining. We also searched the reference lists of included studies for additional titles that appeared to fit our inclusion criteria and screened these articles for inclusion.

## **Data Abstraction and Data Management**

Study level details from articles accepted for inclusion were abstracted by one reviewer and double checked by a second reviewer. Any disagreements were reconciled by the SCEPC Director, or the local subject matter expert if needed.

## **Assessment of Methodological Risk of Bias of Individual Studies**

Risk of bias (study quality) of individual included studies was assessed independently by two reviewers using an adapted Cochrane Risk of Bias tool,<sup>20</sup> and assessments were reconciled, with any disagreements mediated by the project lead. We used a modified AMSTAR tool to assess the

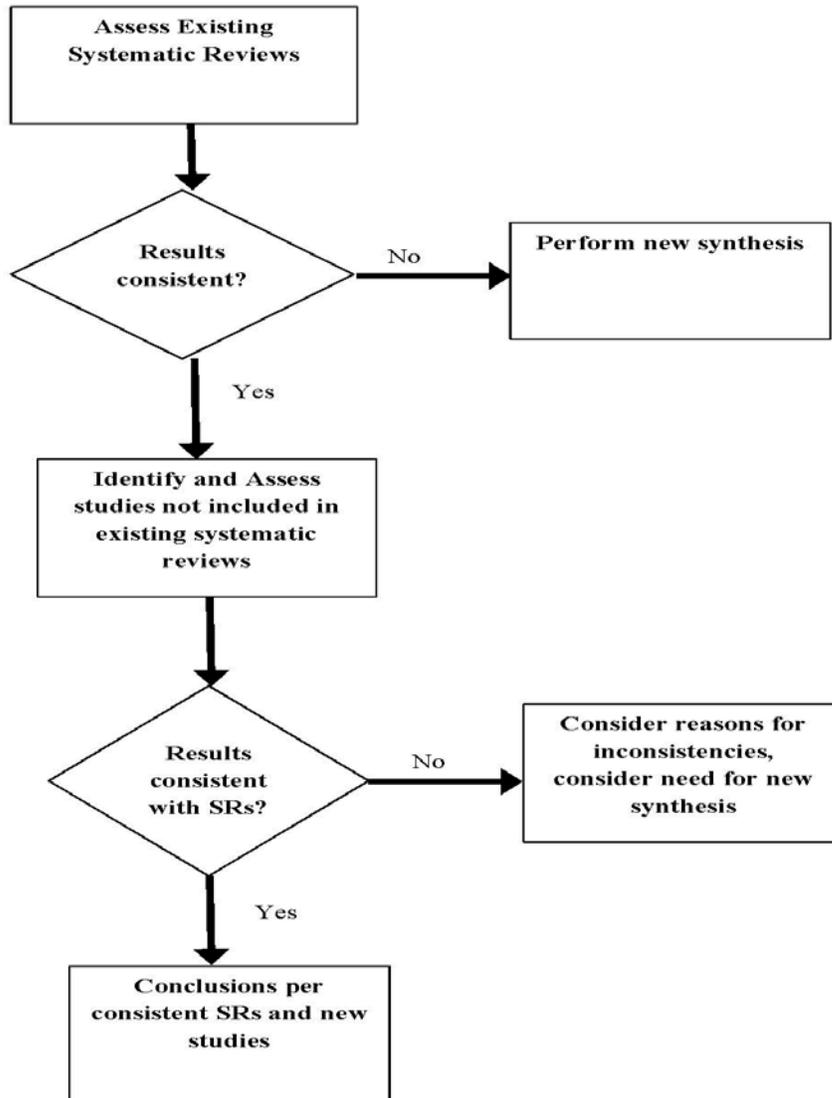
quality of existing systematic reviews that we included;<sup>21</sup> AMSTAR assessments were also conducted independently by two reviewers and reconciled.

## **Data Synthesis/Analysis**

Given the large number of existing systematic reviews on this topic, we used the following strategy for data synthesis/analysis:

1. Identify the existing systematic reviews and make a judgment about relevancy for the Key Questions, the end date of the search, and the methodologic quality as assessed by AMSTAR<sup>21</sup>, following the suggested process outlined by Whitlock and colleagues.<sup>19</sup>
2. Scan the references of these systematic reviews for included studies.
3. Search for new studies meeting the eligibility criteria for the Key Question.
4. Compare the conclusions of the existing systematic reviews.
5. Compare the results of new studies with the conclusions of existing systematic reviews.
6. Use the following guide for additional analyses/conclusions.

**Figure 1. Framework for incorporating existing systematic reviews and studies not included in these reviews**



## **Grading the Strength of the Body of Evidence for Each Key Question**

We assessed the overall strength of evidence for each conclusion (e.g., the efficacy and safety of each pharmacologic agent or class of agents listed in the PICOTs, and differences by subgroup, if identified), using guidance suggested by the Effective Health Care Program.<sup>22</sup> This method is based on one developed by the GRADE Working Group and classifies the grade of evidence as High (also called Strong), Moderate, Low or Insufficient. The evidence grade is based on five required domains: study limitations, consistency, directness, precision, and publication bias. We also considered in our strength of evidence assessments the criteria proposed by AB Hill for causality.<sup>23</sup> These criteria include the strength, consistency, and

specificity of the association, the temporal relationship, the “biologic gradient” or dose-response curve, the biologic plausibility, and coherence. For example, the biochemistry of urate is that it is soluble up to a concentration of about 6.0-7.0mg/dl. Numerous cohort studies show a gradient of gout attacks related to increasing serum urate levels. Pharmaceutical interventions (urate lowering therapy, ULT) have RCT evidence that they lower serum urate levels, but have only lasted 6-12 months and have not shown reductions in acute gout attack in part because the same pharmaceutical interventions increase the risk of acute gout attacks in the short term (months). Long term observational extension studies from the RCTs show that in patients who continued on pharmaceutical therapy had reduced serum urate levels and after about one year, a < 5 percent risk of acute gout attacks. This evidence chain includes biologic plausibility, consistency of association, the appropriate temporal relationship, experimental evidence, the biologic gradient, and coherence. We rated this chain of evidence as moderate for pharmaceutical therapies to reduce the risk of acute gout attack after about one year.

## **Applicability**

Because the charge for this review is clear on the setting, care providers, and patient population the review is intended to cover, applicability assessment will be based primarily on the similarity of the settings and populations to those for which this report is intended, namely primary and acute care settings that treat individuals, a high proportion of whom have comorbidities or are at risk for comorbidities such as hypertension and renal insufficiency.<sup>24</sup>

## **Peer Review and Public Commentary**

To be added for final report

# Results

## Introduction

This chapter first describes the results of the literature searches and then provides the results for each key question, including key points, an overview of the studies identified for that question, and a detailed synthesis of the studies.

## Results of Literature Searches

Our searches identified 4,967 titles/abstracts. Reference mining the previous systematic reviews (SRs) and guidelines identified in our searches resulted in an additional 217 titles and hand searching resulted in an additional 15 titles. Our search of clinicaltrials.gov identified 112 entries for gout. Of these 19 were potentially relevant, 10 were either included already in our report or identified in our searches and excluded as ineligible, one was withdrawn, and eight were recorded as being completed but no results were posted in clinicaltrials.gov and we could find no published journal articles. Two manufacturers (Novartis and Regeneron of drugs) responded to requests by the AHRQ Scientific Resource Center for Scientific Information Packets on gout treatments. None of the trials described in these information packets was included in this report, as the drugs are currently non-FDA approved in the United States (US). Of a total of 5,311 titles/abstracts screened for inclusion, 4,666 titles/abstracts were excluded for the following reasons: not human (297), not gout or hyperuricemia associated with gout (1,634), not gout diagnosis or management or did not address a key question (1,291), study of risk factor(s) for gout that doesn't test possible treatment (90), no original data or non-systematic reviews (514), conference proceedings/presentations/abstracts (37), case reports (285), population not of interest (55), titles with no abstracts (full-text articles or reports were obtained for a random sample of 10 percent of these titles and all were rejected as letters, commentaries, or non-systematic reviews with no original data, so on this basis, we decided not to consider the remainder) (204), gout diagnosis only (101), biologics not within scope of review (122), drug is not currently FDA approved (26) (see Figure 2). We reviewed 645 full text articles, of which 456 were further excluded for the following reasons: not human (2), not gout or hyperuricemia associated with gout (26), not gout diagnosis or management or did not address a key question (112), study of risk factor(s) for gout that doesn't test possible treatment (20), no original data or non-systematic reviews (94), conference proceedings/presentations/abstracts (46), study design (15), case reports (46), population not of interest (8), gout diagnosis only (6), biologics not within scope of review (26), drug is not currently FDA approved (36), no outcomes of interest (9), no interventions of interest (2), duplicate data (6), and article not found (2).

We considered 189 articles for data synthesis which includes 156 studies and 33 SRs. For Key Question (KQ) 1, we identified 57 studies. Thirteen studies were inappropriate for analysis and 31 were included in prior SRs. We included 10 systematic reviews (SRs) and four randomized controlled trials (RCTs) not included in prior SRs. For KQ2, we identified 29 studies. Two were inappropriate for analysis and six were included in prior SRs. We include 11 SRs, three RCTs not included in prior SRs, and seven observational studies on dietary risk factors. For KQ3, we identified 90 studies. Forty-one were inappropriate for analysis and 10 were identified in previous SRs. We include 10 SRs and one meta-analysis, seven RCTs not included in prior SRs and one abstract that has not been published, five new analyses of studies included in existing SRs, and 15 studies on adverse events (AEs). For KQ4, we include one SR

and 24 original studies. For KQ5, we include two original studies. See Figure 2 for the literature flow diagram. Appendix B includes the reasons for exclusion at data abstraction.

**Figure 2. Literature flow diagram**

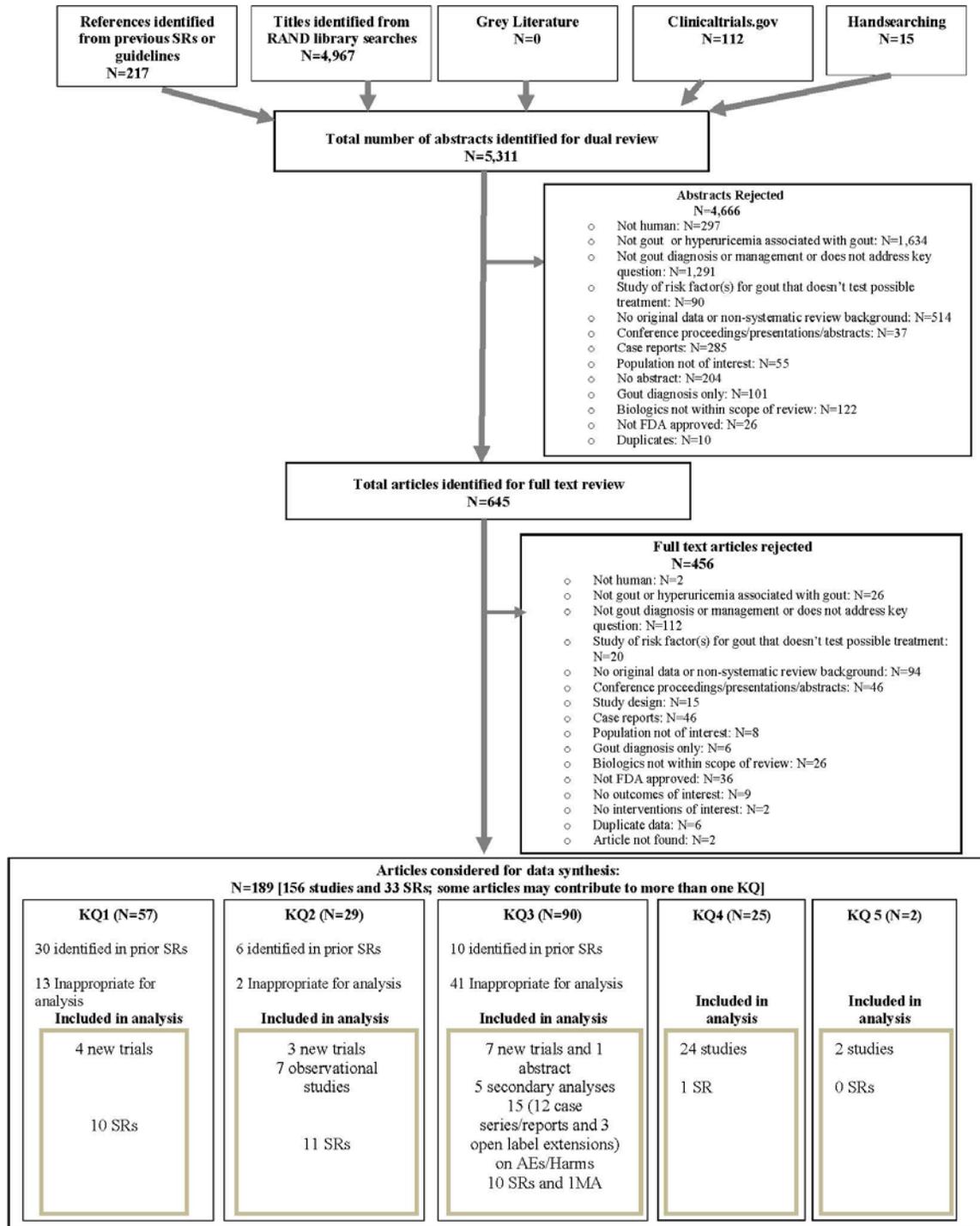


Figure notes: AE(s)=Adverse Event(s); KQ=Key Question; MA=Meta-analysis; RCT(s)=Randomized Controlled Trial(s); SR(s)=Systematic Review(s)

## Key Question 1a-c: Acute Gout Treatment

- a. In patients with acute gout, what are the benefits and harms of different pharmacological therapies?
- b. Does effectiveness (benefits and harms) differ according to patient baseline demographic characteristics and co-morbid conditions (including renal function)?
- c. Does effectiveness (benefits and harms) differ according to disease severity, including initial clinical presentation (e.g., extent of joint involvement and time since start of flare) and laboratory values (serum and/or urine UA levels)?

## Key Points

- A high strength of evidence supports the efficacy of colchicine to reduce pain in acute gout.
- Moderate strength of evidence supports the finding that low-dose colchicine is as effective as higher dose for reducing pain, with fewer side effects.
- High strength of evidence supports the efficacy of NSAIDs to reduce pain in acute gout.
- Moderate strength of evidence supports a lack of difference among NSAIDs in effectiveness.
- High strength of evidence supports the efficacy of systemic corticosteroids to reduce pain in acute gout.
- High strength of evidence supports animal-derived ACTH formulation to reduce pain in acute gout.
- Strength of evidence is insufficient regarding the effect of therapies on other outcomes: joint swelling, tenderness, activities of daily living, patient global assessment.
- An insufficient strength of evidence was identified about differences in efficacy stratified by patient demographic, comorbid conditions, disease severity, clinical presentation, or lab values.
- The most common adverse effects associated with colchicine are gastrointestinal symptoms, reported in 23 to 77 percent of users. NSAIDs also have gastrointestinal side effects with dyspepsia or abdominal pain occurring in 10 percent or more of patients and more serious GI perforations, ulcers, and bleeds occurring in fewer than one percent of users, although the risk is greater in patients older than 65 years of age. Both colchicine and NSAIDs require dose reduction in renal impairment. The adverse effects of corticosteroids and animal-derived ACTH formulation are mostly related to long term use, although dysphoria, elevation in blood glucose, immune suppression and fluid retention may all occur even with short term use.

## Description of included studies

We identified 10 prior SRs on the following acute gout therapies: colchicine, NSAIDs, corticosteroids, and animal-derived ACTH formulation (see Table 2).<sup>25-34</sup> Five systematic reviews received an AMSTAR rating of either 7/7, 9/9, 10/10 (see Table 3).<sup>25-27, 32, 34</sup> Two systematic reviews received an AMSTAR rating of 6/9<sup>29</sup> and 7/9.<sup>33</sup> Three reviews received an

AMSTAR rating of 1/9 or 2/9.<sup>28, 30, 31</sup> We also identified four new randomized-controlled trials which collectively involved 538 patients (range: 51 to 190 patients) with study time periods ranging from 5 days to 2 years. The primary outcomes of interest varied across studies as shown below (see Table 4).<sup>35-38</sup>

**NSAID vs. Intramuscular Glucocorticoid.** One trial involving 60 patients<sup>37</sup> monitored self-reported pain intensity in the affected joint, patient's global assessment of response to therapy, physician assessment of joint swelling, serum urate levels, and adverse events.

**NSAID vs. Selective COX-2 Inhibitors.** One trial involving 178 patients<sup>35</sup> monitored self-assessed pain, swelling and tenderness in affected joint, physician and patient assessment of global response to therapy, and number of withdrawals due to adverse events.

**Colchicine + Allopurinol, over time.** One trial involving 190 patients<sup>38</sup> monitored the probability of recurrence of gout attack, and the average time to recurrence. The patients were stratified by age, gender, and mean uric acid levels at baseline and follow-up.

**Allopurinol vs. Placebo (Colchicine as a prophylactic).** One trial involving 57 patients<sup>36</sup> assessed pain on a visual analog scale in the primary joint during days 1 – 10, the number of self-reported attacks (flares) in any joint through day 30, serum urate levels, sedimentation rates and c-reactive protein levels.

**Table 2. Randomized controlled trials included in systematic reviews**

RCTs	Systematic Reviews									
	Moi et al., 2013 <sup>26</sup>	Janssens et al., 2008 <sup>27</sup>	Richette and Bardin, 2010 <sup>30</sup>	van Echteld et al., 2014 <sup>32</sup>	Terkeltaub, 2008 <sup>31</sup>	Daoussis et al., 2014 <sup>28</sup>	van Durme et al., 2014 <sup>34</sup>	Khanna et al., 2014 <sup>29</sup>	Wechalekar et al., 2014 <sup>33</sup>	Wechalekar et al., 2013 <sup>25</sup> (Zero included studies)
Ahern 1987 <sup>39</sup>			X	X	X			X		
Alloway 1993 <sup>40</sup>		X						X	X	
Altman 1988 <sup>41</sup>							X	X		
Axelrod 1988 <sup>42</sup>						X	X	X		
Borstad 2004 <sup>43</sup>			X		X				X	
Butler 1985 <sup>44</sup>							X	X		
Cheng 2004 <sup>45</sup>							X	X	X	
Chou 1995 <sup>46</sup>								X	X	
Douglas 1970 <sup>47</sup>							X	X		
Eberl 1983 <sup>48</sup>							X	X	X	
Janssens 2008 <sup>49</sup>							X	X	X	
Lederman 1990 <sup>50</sup>							X	X		
Lomen 1986 <sup>51</sup>							X			
Maccagno 1991 <sup>52</sup>							X	X		
Man 2007 <sup>53</sup>		X					X	X		
Paulus 1974 <sup>54</sup>			X							
Rubin 2004 <sup>55</sup>							X	X	X	
Ruotsi 1978 <sup>56</sup>								X		
Schlesinger	X							X		

Systematic Reviews										
RCTs	Moi et al., 2013 <sup>26</sup>	Janssens et al., 2008 <sup>27</sup>	Richette and Bardin, 2010 <sup>30</sup>	van Echteld et al., 2014 <sup>32</sup>	Terkeltaub, 2008 <sup>31</sup>	Daoussis et al., 2014 <sup>28</sup>	van Durme et al., 2014 <sup>34</sup>	Khanna et al., 2014 <sup>29</sup>	Wechalekar et al., 2014 <sup>33</sup>	Wechalekar et al., 2013 <sup>25</sup> (Zero included studies)
2002 <sup>57</sup>										
Schumacher 2002 <sup>58</sup>							X		X	
Schumacher 2012 <sup>59</sup>							X	X		
Shi 2008 <sup>60</sup>								X	X	
Shrestha 1995 <sup>61</sup>							X	X	X	
Siegel 1994 <sup>62</sup>		X				X		X	X	
Siegmeth 1976 <sup>63</sup>							X			
Terkeltaub 2010 <sup>64</sup>				X				X		
Tumrasvin 1985 <sup>65</sup>										
Valdes 1987 <sup>66</sup>								X	X	
Weiner 1979 <sup>67</sup>								X		
Zhou 2012 <sup>68</sup>							X			

## **Detailed Synthesis**

### **Prior Systematic Reviews**

#### **Colchicine**

Six prior systematic reviews<sup>26, 29-33</sup> collectively identified 5 randomized controlled trials (RCTs) investigating the efficacy (pain reduction on VAS, number of acute gout attacks, and severity of attacks in terms of pain) and safety (total number of adverse events) of colchicine. Two of these studies were placebo-controlled trials of treatment in acute gout,<sup>39, 64</sup> two were placebo-controlled studies of prophylaxis against gout flare when initiating urate lowering therapy,<sup>43, 54</sup> and one study compared the addition to ice to colchicine and prednisone.<sup>57</sup> All reviews found that a greater fraction of colchicine-treated patients reported a greater than 50 percent pain reduction, as compared with placebo, especially if administered within the first 12 hours of an acute attack.<sup>26, 29-33</sup> Low-dose colchicine was found to be as effective as high-dose colchicine in terms of pain relief, but had a better tolerability profile in terms of gastrointestinal adverse events: 77 percent of participants in high-dose colchicine developed diarrhea versus 23 percent in the low-dose group vs. 14 percent in the placebo group.<sup>64</sup>

#### **Systemic Corticosteroids**

Identified systematic reviews did not find any placebo-controlled trials of systemic corticosteroids. These SRs did discuss active-controlled trials of corticosteroids discussed in the next section on comparative effectiveness.

#### **NSAIDS**

Two prior systematic reviews<sup>33, 34</sup> found one low-quality trial comparing the NSAID tenoxicam 40mg once a day against placebo in 30 patients with gout and found larger between-group difference in the fraction of patients reporting greater than 50 percent pain relief at 24 hours, no between-group differences in joint swelling at 24 hours (11/15) in the tenoxicam group, 4/15 in the placebo group, and no overall between-group differences at day 4.<sup>69</sup> No difference in adverse events were reported among patients taking NSAIDs or placebo.

#### **Ice**

Two prior systematic reviews<sup>26, 29</sup> identified one controlled trial which concluded that topical ice application, in addition to colchicine and oral prednisolone, improved pain relief by 33 percent on the VAS (visual analog scale) but had no differential effect on joint swelling during gout episodes.

#### **Intra-articular Glucocorticoids**

One prior systematic review<sup>25</sup> on intra-articular glucocorticoids identified no randomized trials for inclusion.

## Comparative effectiveness

### Systemic Glucocorticoid vs. ACTH

Three prior systematic reviews<sup>27, 29, 33</sup> found one RCT comparing systemic corticosteroids against adrenocorticotrophic hormone (ACTH).<sup>62</sup> In this trial 31 male patients with acute gout were randomized to receive either 40 IU of ACTH or 60mg triamcinolone intramuscularly. The study is not described as double-blinded. The duration of the acute attack and the number of joints involved were not significantly different between the two groups, although the number of reinjections for continued symptoms were fewer in the triamcinolone group (14 vs. 6 p=0.075). No mention was made of side effects. We judged this trial as being at high risk of bias.

### Systemic Glucocorticoid vs. NSAIDs

Four prior systematic reviews<sup>27, 29, 33, 34</sup> identified three trials that compared the effectiveness of systemic corticosteroids against NSAIDs. All reviews found no differences in terms of time-to-resolution of symptoms, clinical joint status at follow-up, reduction of pain at rest per hour during the first two hours and at rest per day after two weeks, and reduction of pain with activity per day after two weeks. Gastrointestinal, non-gastrointestinal, and severe adverse events were more common in the NSAID than in the systemic glucocorticoid group.<sup>33</sup>

### NSAID vs. Selective COX-2 Inhibitors (COX-2)

Three prior systematic reviews<sup>29, 33, 34</sup> identified four controlled trials that compared NSAIDs against COX-2. COX-2 was effective as NSAIDs in terms of pain, joint swelling, global improvement, and health-related quality of life, but there were fewer withdrawals due to adverse events among those treated with selective COX-2 selective inhibitors (3 percent) versus NSAIDs (8 percent) and fewer total adverse events total among the recipients of selective COX-2 selective inhibitors (38 percent) versus recipients of NSAIDs (60 percent). Low doses of COX-2 were less effective in reducing pain than high doses, and NSAIDs were as effective as high-dose COX-2.<sup>29</sup>

### NSAID vs. ACTH

Three prior systematic reviews<sup>28, 29, 34</sup> all found the same trial comparing NSAIDs to ACTH.<sup>42</sup> In this randomized comparison of 40 IU intramuscular ACTH compared to 50 mg four times a day of indomethacin, among 76 (out of an initial sample of 100) men who completed 1 year of followup, the time to pain relief during an episode of acute gout was a mean of 3 hours in the ACTH-treated patients, whereas it was 24 hours in the NSAID-treated patients. There were no reported side effects in the ACTH group, whereas 55 percent of patients in the NSAID group reported abdominal discomfort or dyspepsia, and 38 percent reported headaches. We judged this trial as being at high risk of bias.

### NSAIDs vs. NSAIDs

We identified 16 studies that were RCTs of one NSAID versus another NSAID in patients with acute gout.<sup>35, 41, 44, 45, 47, 48, 50-52, 55, 56, 58, 59, 61, 63, 67</sup> Fifteen of these 16 studies were included in prior SRs. One trial is new and is described below.<sup>35</sup> Most of these studies were quite small, and therefore underpowered to detect differences. Half of the studies enrolled fewer than 30 subjects; only two studies enrolled more than 100 subjects. Many of the studied NSAIDs are either no longer on the market or not FDA-approved. No study included an assessment of ibuprofen,

which is one of the most-used NSAIDs in America. Nevertheless, in nearly every study there were no statistically or clinically important differences between NSAIDs in effectiveness outcomes. These data do not support a hypothesis that there are clinically important differences between equipotent doses of NSAIDs in terms of relief of symptoms from acute gout. A conclusion of no clinically important differences in effectiveness is compatible with how NSAIDs are viewed for most other conditions, e.g., their effectiveness is a class effect (see Table 5).

## **Evidence from new eligible studies**

We identified four RCTs that were not included in any of the reviews (see Table 4).<sup>35-38</sup>

Karimzadeh 2006<sup>38</sup> assessed the optimal duration of prophylactic use of colchicine when initiating urate lowering therapy. This study is discussed in detail in Key Question 3.

Zhang 2014<sup>37</sup> assessed the efficacy of glucocorticoids against NSAIDs in acute gout treatment, irrespective of gastrointestinal or cardiovascular risk factors. Sixty patients were randomized to receive either 7mg betamethasone intra-muscularly once during 7 days, or 75mg diclofenac sodium twice a day for 7 days. The end-points of treatment were pain intensity, tenderness, swelling and global assessment. Betamethasone had preferable efficacy (measured as change from baseline percentage of patients reporting severe or extreme pain) on Day 3 and equivalent efficacy on Day 7. There were fewer total adverse events in the betamethasone group (4/30) as compared to the NSAID group (8/30) but statistical testing for difference was not performed. We judged this trial as being at low risk of bias.

Taylor 2012<sup>36</sup> investigated how initiating allopurinol early could relieve acute gout attacks and pain associated with them. We rejected this study for this Key Question as allopurinol was not included in the scope as a treatment in acute gout.

Li 2013<sup>35</sup> randomized a sample of 178 patients to either etoricoxib (120mg/day for 5 days), or indomethacin (75mg twice daily) for 5 days. There was no difference in self-assessed pain in the affected joint nor in the total number of adverse events, between the two groups. We judged this study as being at low risk of bias.

From four new eligible studies the evidence is consistent with the conclusions of the systematic reviews.

## **Evidence about subgroups:**

With one exception there were no included studies that reported effectiveness stratified by any of the pre-specified subgroups of interest

- Gender: No studies presented data stratified by gender
- Acute Episode: No studies presented data stratified by acute episode
- History of gout: No studies presented data stratified by history of gout
- Serum Urate: Karimzadeh 2006<sup>38</sup> found no differences in serum urate level in the probability of recurrence of gout attack when using colchicine prophylactically during urate-lowering therapy.
- HLA-B5801 status: No studies presented data stratified by HLA-B5801 status
- Age: Karimzadeh 2006<sup>38</sup> found no differences by age in the probability of recurrence of gout attack when using colchicine prophylactically during urate-lowering therapy.
- Tophi: No studies presented data by tophi
- Comorbidities: No studies presented data by comorbidities.

## Harms

In the clinical trials included in this Key Question, the number of patients included in placebo-controlled studies is less than three hundred. Yet these drugs have been in widespread clinical use for more than 30 years, and used not just for gout, but for numerous other conditions as well. They have a large body of evidence on their harms that has been summarized in various different forms, including text books, systematic reviews, and online data sources. To ignore these data on harms when used in other conditions would give readers an incomplete view of the body of evidence about harms. We therefore provide here brief summaries of the important harms of the major drugs for acute gout. Unless otherwise referenced, the data are compiled from Lexicomp, Medline Plus ([www.nlm.nih.gov/medlineplus](http://www.nlm.nih.gov/medlineplus)) and/or the FDA ([www.fda.gov/downloads/drugs/drugsafety](http://www.fda.gov/downloads/drugs/drugsafety)).

## Colchicine

By far and away the most common adverse effects from colchicine use are gastrointestinal side effects, in particular diarrhea, with reported rates of 23 percent - 77 percent. In the one placebo-controlled study of acute gout included in this review, the authors note that all patients had gastrointestinal side effects before they had relief of gout pain. Gastrointestinal side effects are dose-dependent and this contributes to the popularity of “low dose” colchicine regimens, 0.5 mg twice a day.<sup>64</sup> Other gastrointestinal symptoms are also common, such as nausea, vomiting, cramps and pain.<sup>32</sup> Fatigue and headache are reported in a few percent (1 percent-4 percent) of patients taking colchicine. Dosage must be reduced in moderate renal impairment, and colchicine use is contraindicated in severe renal or hepatic impairment. Dosage reduction is also needed with concomitant CYP3A4 inhibitors such as erythromycin and fluconazole, and P-gp inhibitors like cyclosporine.

## NSAIDs

Nonsteroidal anti-inflammatory drugs are among the most commonly used drugs in the world, and have a safety profile sufficient for low dose NSAIDs to be over-the-counter. The main harms of NSAIDs are gastrointestinal side effects, both “minor” (dyspepsia) and more serious, the “perforations, ulcers, and bleeds” (PUBs), the former occurring in 10 percent or more of patients and the latter in up to 1 percent.<sup>70, 71</sup> PUBs are more common in older patients.<sup>72</sup> Another common adverse effect is on kidney function, occurring in 1 percent to 5 percent of patients, which can be acute kidney injury, worsening of hypertension, or electrolyte abnormalities. Mild-to-moderate renal impairment is a relative contraindication for NSAIDs use. NSAIDs are also reversible platelet inhibitors. Numerous other rare side effects have been reported, including bone marrow suppression, aseptic meningitis, and various dermatologic adverse events. NSAIDs have been associated with an increased risk of cardiac events, however in patients without known cardiovascular disease the increased risk is very small.

## Corticosteroids

Long term use of glucocorticoids are associated with a host of adverse reactions, effecting almost every organ system of the body. However, most of these harms are dose and duration-dependent. The effects of short courses of glucocorticoids are not as well understood, but do

include dysphoria and mood disorders, elevation of blood glucose levels, immune suppression, and fluid retention. These are all reversible on discontinuation of the glucocorticoids, but there is a cumulative effect of low doses over time.

## **ACTH**

Although less used and less well studied than corticosteroid use, since the mechanism of effectiveness of ACTH is in part via the stimulation of cortisol production by the body, the expected harms are probably very similar to those for glucocorticoids. In the one trial of ACTH included here, there were no reported side effects among 36 treated patients.

## **Strength of Evidence**

### **Colchicine**

We judged the strength of evidence that colchicine improves the symptom of pain in acute gout as high, since there are two placebo-controlled trials and both show large (~50 percent reduction) effects.

### **NSAIDs**

Although there is only one placebo-controlled trial of an NSAID in treating acute gout, we nevertheless judged the strength of evidence as high that NSAIDs improve the symptom of pain. We base this on the biology of gout (it is an inflammatory reaction to uric acid crystals) and NSAIDs mechanism of action as an anti-inflammatory. Furthermore, NSAIDs are FDA approved for marketing for the temporary relief of pain based on dozens of placebo-controlled trials for other painful conditions. Lastly, in patients starting on urate lowering therapy, which is a risk factor for acute gout attacks, there is high observational strength of evidence that prophylaxis with NSAIDs greatly reduces this risk of an acute attack. Therefore, the evidence from the one available placebo-controlled trial is strengthened by the biologic evidence and proven benefit in other painful conditions, and the large effect on prophylaxis against acute gout attacks with urate lowering therapy.

### **Systemic Corticosteroids**

While there are no placebo-controlled RCTs of systemic corticosteroids, we judged the strength of evidence as high that they reduce the symptom of pain in acute gout. This is based on the anti-inflammatory action of steroids and the equivalence in RCTs comparing systemic steroids to NSAIDs, which we judged as high strength of evidence in relieving pain.

## **ACTH**

While there are no placebo-controlled RCTs of ACTH in acute gout, we judged the strength of evidence as high that it reduces the symptoms of pain in acute gout. As a primary mechanism of action for ACTH is by increasing the body's release of corticosteroids, the reasons are the same as for corticosteroids.

**Table 3. Systematic reviews of pharmacologic therapy for acute gout treatment**

Author/Year/ Funding	End date of search	# of included studies	# of included patients/ Patient characteristics included	Setting(s)	Outcomes	Doses	Results	AMSTAR
Moi, et. al, 2013 <sup>26</sup> , Lifestyle intervention/ Funding: Royal Melbourne Hospital (in- kind), Monash University (in- kind), Cabrini Hospital (in- kind), Southampton General Hospital UK (in-kind)	4/5/2013	1 (RCT: oral prednisolone and colchicine with or w/out concomitant topical ice therapy)	19; "Adult patients (aged 18 years or older) diagnosed with acute gout, either via joint arthrocentesis with identification of uric acid crystals or according to the author's description. Populations that included a mix of people with acute gout and other musculoskeletal pain were excluded unless results for the acute gout population could be separated out from the analysis."	Hospital in- patient and outpatient clinic	Patient- reported pain in target joint; target joint inflammation and function; HRQoL; patient global assessment; study participant withdrawal due to AE; and serious AE	N/A	Significant difference in pain improvement at one week (3.33 points greater improvement on a 10 cm Visual Analog Scale) when topical ice was applied.  Joint swelling was not statistically significantly reduced through application of ice.	9/9

Author/Year/ Funding	End date of search	# of included studies	# of included patients/ Patient characteristics included	Setting(s)	Outcomes	Doses	Results	AMSTAR
Richette and Bardin, 2010 <sup>30</sup> ; Colchicine/ Funding: T Bardin received honorarium from sanofi-aventis and Mayoly-Spindler.	Aug-10	3 RCTs	Not reported	Not reported	Proportion of patients with at least 50% reduction in pain within 24 hrs; Number of acute gout attacks	AGREE Trial: Placebo vs 1.8mg colchicine vs. 4.8mg colchicine.  RCT2: 500mg probenecid tid + 1.5mg colchicine vs. 500mg probenecid tid + placebo.  RCT3: 0.6mg colchicine twice daily vs. placebo	Low-dose colchicine when given early as is effective as high-dose colchicine, in reducing pain and the number of acute gout attacks.	2/9
Janssens et. al., 2008 <sup>27</sup> ; Systemic corticosteroids/ Funding: Radboud University Nijmegen Medical Centre, Netherlands	Apr-07	3 head-to-head trials	148 patients; Patients of any age with acute gouty arthritis identified after MSU crystal identification or ACR criteria or clinical grounds	Hospital in-patient and out-patient	Patient assessment of pain and disability; investigator assessment of clinical symptoms; AE's	1. 60mg triamcinolone acetonide vs. 50mg indomethacin  2. 30mg oral prednisolone vs. 50mg indomethacin TID for 2 days, followed by 25mg TID for 3 days.  3. 60mg triamcinolone acetonide vs. 40 IU ACTH.	Inconclusive evidence for the efficacy and effectiveness of systemic corticosteroids compared to indomethacin in the treatment of acute gout. No AE's reported in the short-term.	9/9

Author/Year/ Funding	End date of search	# of included studies	# of included patients/ Patient characteristics included	Setting(s)	Outcomes	Doses	Results	AMSTAR
Van Durme et. al, 2014 <sup>34</sup> ; NSAIDs, COX-2, ACTH, Oral glucocorticoid s/ Funding: In- kind support by: Masstricht University Medical Center, Flinders University, UMNDJ, Cabrini Hopsital, Monash University, Leiding University Medical Center, Atrium Medical Centre, University of Amsterstam	10/7/2013	23 RCTs	N = 2200 / adults 18+ with a diagnosis of acute gout	Outpatients	Proportion of participants with >= 50% pain improvement; Proportion of participants with >=50% inflammation or joint swelling improvement; Functioning of target joing; HRQoL; Participant withdrawal due to AE's. Total number of AE's.	NSAID (40mg) vs. placebo (N=1) NSAID vs. NSAID (N=13) NSAID (50mg indomethacin x3) vs COX2 (etoricoxib 120mg x1 or celecoxib 50mg, 200mg or 400mg x2 or lumiracoxib 400mg x1) (N=4); NSAID (naproxen 500mg x1 or indomethacin 50mg x3) vs. oral glucocorticoids (prednisolone 30mg or 35mg x1) (N =2) NSAID (indomethacin 50mg x4) vs. ACTH (40 IU x1) (N = 1) NSAID (indomethacin 50mg x3 then 25mg x3) vs. rilonacept (320mg) (N=1) NSAID (indomethacin 25mg x3) vs. Acupuncture + IR	NSAID vs. placebo: More participants reported >50% pain relief after 24 hrs with NSAID; No difference in proportion with >50% improvement in joint swelling; No AE's with NSAIDs, but some with placebo.  NSAID vs. COXIB: similar pain, swelling and global improvement but fewer AE's with COXIB; fewer withdrawals due to AE's in COXIB. Lower total AE's with COXIB.  NSAID vs. glucocorticoid s: No difference in pain	10/10

Author/Year/ Funding	End date of search	# of included studies	# of included patients/ Patient characteristics included	Setting(s)	Outcomes	Doses	Results	AMSTAR
							reduction, function, or AE's.	

Author/Year/ Funding	End date of search	# of included studies	# of included patients/ Patient characteristics included	Setting(s)	Outcomes	Doses	Results	AMSTAR
Khanna, et. al, 2014 <sup>29</sup> ; NSAIDs, COX-2 inhibitors, ACTH, IL-1, Simiao Pill, topical ice. /Funding: ACR Gout Guidelines Grant	5/5/2013	30 RCTs (28 active comparator studies; 2 with a placebo- controlled group)	Number of patients not reported; pooled mean age 54.14 (SD = 11.94); 89.7% male	NR	Pain (multiple measures)	NR	Oral colchicine is effective for acute gout. Corticosteroid s and possibly ACTH potentially good alternative in subjects with contraindicati ons to NSAIDs or colchicine therapy. IL-1B promising for acute gout that is refractory or has contraindicati os to conventional therapy.	6/9

Author/Year/ Funding	End date of search	# of included studies	# of included patients/ Patient characteristics included	Setting(s)	Outcomes	Doses	Results	AMSTAR
Echteld et al., 2014 <sup>32</sup> /Colchi cine/Funding = Cochrane Musculoskelet al Group, Australia	4/30/2014	2 RCTs	N = 124/Age 18+ with diagnosis of acute gout (i.e. author defined or MSU crystals in joint aspirate or ACR criteria or Rome criteria or New York criteria)	Hospital and Outpatient	Proportion of participants with >50% decrease in pain; Withdrawal due to AE's; Reduction of inflammation; Function of target joint; Patient global assessment of treatment success; HRQoL; Total AE's, serious AE's, and type of AE's.	0.5mg colchicine every two hours; 4.8mg colchicine over 6 hours	Low-quality evidence that high dose colchicine relieves pain greater than 50%; Total AE's higher in high-dose colchicine vs. placebo; Low- quality evidence that high-dose colchicine provides 50% or greater decrease in joint inflammation score. Low-quality evidence that low-dose colchicine is more efficacious than placebo with respect to greater than 50% decrease in pain; there are no additional AE's for colchicine vs placebo. High-dose and low-dose colchicine	10/10

Author/Year/ Funding	End date of search	# of included studies	# of included patients/ Patient characteristics included	Setting(s)	Outcomes	Doses	Results	AMSTAR
							approximately equal in providing greater than 50% pain relief; More AE's with high-dose colchicine vs. low-dose colchicine.	

Author/Year/ Funding	End date of search	# of included studies	# of included patients/ Patient characteristics included	Setting(s)	Outcomes	Doses	Results	AMSTAR
Terkeltaub, 2008 <sup>31</sup> ; Colchicine/VA Research Service, NIH, AR Scientific, Regeneron, ARDEA, Novartis, Pfizer, TAP, Savient, BioCryst	Jul-08	2 RCTs	86/characteristics not reported	Not reported	Frequency and severity of gouty arthritis flares; Proportion of participants reporting >50% reduction in pain;	0.6mg twice daily vs. placebo (N=1)  1mg, then 0.5mg every 2 hours until a complete response or toxicity developed vs. placebo (N=1)	Addition of colchicine as a prophylactic in allopurinol treatment for urate- lowering therapy, reduced the frequency and severity of gouty arthritis flares.  Colchicine also effective in reducing the pain associated with gout flares.	1/9
Daoussis et. al., 2014 <sup>28</sup> /Fundin g: Not reported	Not reported	5 (2 RCTs, 3 retrospective chart reviews)	n=266/characteristics not reported	Not reported	Time to complete resolution; time to pain relief	40 IU ACTH single dose (N=2)  100 IU ACTH single dose (N=1)  40 or 80 IU ACTH tid, gradual tapering (N=2)	ACTH is effective in treating acute gout and can be used in patients with multiple comorbidities due to its excellent safety profile.	2/9

Author/Year/ Funding	End date of search	# of included studies	# of included patients/ Patient characteristics included	Setting(s)	Outcomes	Doses	Results	AMSTAR
Wechalekar,2014 <sup>33</sup> Intraarticular Glucocorticoids, Colchicine, NSAIDs, IL-1	9/30/2011	26 RCTs	N = NR/Adults 18+ with acute gout defined by study authors, presence of MSU crystals, or fulfilling the ACR, Rome, or New York criteria	NR	Pain; withdrawal due to AE's or SAE's; inflammation, patient global assessment, function of target joint, HRQoL, number of participants with AE's.	See Table 1 in study	Systemic GC as effective as NSAID but safer (moderate- quality, N=3); High and Low-dose colchicine more effective than placebo; Low-dose colchicine no safer than placebo but safer than high-dose colchicine (low-quality; N=1); No difference between NSAID and placebo in terms of pain (low-quality; N=1)	7/9

<b>Author/Year/ Funding</b>	<b>End date of search</b>	<b># of included studies</b>	<b># of included patients/ Patient characteristics included</b>	<b>Setting(s)</b>	<b>Outcomes</b>	<b>Doses</b>	<b>Results</b>	<b>AMSTAR</b>
Wechalekar 2013 <sup>25</sup> Intra- articular glucocorticoid s/ Funding: No sources supplied	10/16/2012	0	N/A	N/A	Pain; proportion of participant withdrawals due to AE's; inflammation; function; patient global assessment of treatment success; quality of life; proportion of participants with serious AE's	N/A	No trials were identified that evaluated the efficacy and safety of intra-articular glucocorticoid s for acute gout.	7/7

**Table 4. Randomized controlled trials of pharmacologic therapies for acute gout not included in existing systematic reviews**

Author/ Year	Objective	Population, Sample size	Diagnosis of gout	Intervention	Comparison	Outcomes	Timing	Results	Cochrane ROB
Karimzadeh 2006 <sup>38</sup>	Efficacy of colchicine prophylaxis in prevention of acute gout attacks for patients undergoing urate lowering therapy	N = 190, patients with gouty arthritis, at least one year after diagnosis, and on long-term ULT presenting to hospital rheumatology department	Unclear	Allopurinol + Colchicine for: 3-6 months (Group 1) vs. 7-9 months (Group 2) vs. 10-12 months (Group 3)	Allopurinol + Colchicine over time	Probability of recurrence of gout attacks; sUA levels	6 months, 12 months	<p>Probability of recurrence at 6 months: 46% (3-6mos), 11%(7-9 mos), 6% (10-12 mos).</p> <p>Probability of recurrence at 12 months: 54% (3-6 mos), 27.5% (7-9 mos), 23% (10-12 mos).</p> <p>No difference in sUA levels.</p>	<p>1. Sequence: Low</p> <p>2. Allocation concealment: High</p> <p>3a. Blinding participants: High</p> <p>3b. Blinding care providers: High</p> <p>3c. Blinding outcome assessors: High</p> <p>4a. Follow-up less than 20%: Low</p> <p>4b. Loss to follow-up missing data explained: High</p> <p>4c. Only those who completed the treatment program</p> <p>5. Outcome reporting: Low</p> <p>6. Findings reported as % who responded: High</p>

Author/Year	Objective	Population, Sample size	Diagnosis of gout	Intervention	Comparison	Outcomes	Timing	Results	Cochrane ROB
Zhang 2014 <sup>37</sup>	Comparing NSAIDs vs. IM GC in acute gout treatment	N = 60, patients with an acute gout attack within 24 hrs.	ACR guidelines	Betamethasone (glucocorticoid) 7mg IM once vs. Diclofenac Sodium 75mg b.i.d. for 7 days	Glucocorticoid vs. NSAID	Pain intensity, tenderness, swelling, and global assessment of response to therapy, sUA levels	7 days	<p>In terms of change in pain intensity from baseline, betamethasone preferred on Day 3 and comparable to diclofenac sodium on Day 7. (See Table 1)</p> <p>Fewer AE's for betamethasone (see Table 3)</p> <p>No significant differences in sUA levels.</p>	<p>1. Sequence: Low</p> <p>2. Allocation concealment: High</p> <p>3a. Blinding participants: Low</p> <p>3b. Blinding care providers: High</p> <p>3c. Blinding outcome assessors: High</p> <p>4a. Follow-up less than 20%: Low</p> <p>4b. Loss to follow-up missing data explained: Low</p> <p>4c. All participants randomized to particular groups</p> <p>5. Outcome reporting: Low</p> <p>6. Findings reported as % who responded: Low</p>

Author/Year	Objective	Population, Sample size	Diagnosis of gout	Intervention	Comparison	Outcomes	Timing	Results	Cochrane ROB
Taylor 2012 <sup>36</sup>	Assessing pain and subsequent attacks in early versus delayed initiation of allopurinol for acute gout attack	N=51, patients presenting within 7 days of acute gout attack	Crystal-proven	Allopurinol 300mg daily vs. Placebo  All subjects received: Indomethacin (50mg x 3) for 10 days and a prophylactic dose of colchicine (0.6mg x 2) for 90 days	Allopurinol vs. Placebo (Colchicine as a prophylactic)	Pain on the visual analog scale on days 1 to 10; self-reported flares in any joint on day 30. sUA and c-reactive protein levels	10 days	No statistical difference in mean VAS scores. (Initial VAS: 6.72 (allopurinol) vs. 6.28 (placebo) (p=0.37); day 10 VAS: 0.18 (allopurinol) vs. 0.27 (placebo) (p=0.54).  Subsequent gout flares: Allopurinol (2) vs. Placebo (3) (p=0.60).  sUA: reduced from 7.8mg/dL (baseline) to 5.9mg/dL (day 3) for allopurinol.  No difference in c-reactive protein and sedimentation rates between allopurinol and placebo.	1. Sequence: Low 2. Allocation concealment: Low 3a. Blinding participants: Low 3b. Blinding care providers: Low 3c. Blinding outcome assessors: Low 4a. Follow-up less than 20%: Low 4b. Loss to follow-up missing data explained: Low 4c. Only those who completed the treatment program 5. Outcome reporting: Low 6. Findings reported as % who responded: Unclear

Author/ Year	Objective	Population, Sample size	Diagnosis of gout	Intervention	Comparison	Outcomes	Timing	Results	Cochrane ROB
Li 2013 <sup>35</sup>	COX-2 vs. NSAIDs in treating acute gout	N=178, with an acute gouty attack (<48 hours)	ACR guidelines	Etoricoxib (120mg/day) vs. Indomethacin (75mg/day x 2)	COX-2 vs. NSAID	Self-assessed pain in affected joint, tenderness and swelling, global assessment of response to therapy, patients discontinuing treatment, AE	5 days	<p>No difference between etoricoxib and indomethacin in terms of pain in affected joint. Mean change difference from baseline to days 2- 5 was 0.03 (95% CI – 0.19 to 0.25; <math>P=0.6364</math>).</p> <p>No significant difference in adverse events. Absolute number of AE's: Etoricoxib (n=31) vs. Indomethacin (n=34).</p>	<p>1. Sequence: Low</p> <p>2. Allocation concealment: Unclear</p> <p>3a. Blinding participants: Low</p> <p>3b. Blinding care providers: Low</p> <p>3c. Blinding outcome assessors: Low</p> <p>4a. Follow-up less than 20%: Low</p> <p>4b. Loss to follow-up missing data explained: Low</p> <p>4c. All participants randomized to particular groups</p> <p>5. Outcome reporting: Low</p> <p>6. Findings reported as % who responded: High</p>

**Table 5. Randomized controlled trials of NSAID vs. NSAID for treatment of acute gout**

Author, Year	Sample Size	NSAID 1	Dose 1	NSAID 2	Dose 2	Statistically or clinically important differences in effectiveness
Douglas et al., 1970 <sup>47</sup>	25	Flufenamic acid	800mg/d x 4 d, then 400mg/d	Phenylbutazone	800mg/d x 4 d, then 400mg/d	No
Siegmeth et al., 1976 <sup>63</sup>	46	Ketoprofen	50mg/BID	Phenylbutazone	300mg/BID	No
Ruotsi et al., 1978 <sup>56</sup>	18	Proquazone	300mg/TID, then 300mg/QD	Indomethacin	50mg/TID, then 50mg/QD	No
Weiner et al., 1979 <sup>67</sup>	30	Fenoprofen	3.6g day1, then 3.0g day 2-4	Phenylbutazone	700mg day1, then 400mg day 2-4	No
Eberl et al., 1983 <sup>48</sup>	20	Meclofenamate	800mg/day, then 100mg/TID	Indomethacin	200mg/day, then 50mg/TID	No
Butler et al., 1985 <sup>44</sup>	33	Flurbiprofen	400mg/d x 2d, 200mg/d	Phenylbutazone	800mg/d x 2d, 400mg/day	No
Lomen et al., 1986 <sup>51</sup>	29	Flurbiprofen	400mg/d x 1 day, then 200mg/d	Indomethacin	200mg/day x 1 day, then 100mg/day	No
Altman et al., 1988 <sup>41</sup>	59	Ketoprofen	100mg/TID	Indomethacin	50mg/TID	No
Lederman et al., 1990 <sup>50</sup>	60	Etodolac	300mg/BID	Naproxen	500mg/TID	No
Maccagno et al., 1991 <sup>52</sup>	61	Etodolac	300mg/BID	Naproxen	500mg/BID	No
Shrestha et al., 1995 <sup>61</sup>	20	Ketorolac	60mg/once	Indomethacin	50mg/once	No
Schumacher et al., 2002 <sup>58</sup>	150	Etoricoxib	120mg/QD x 8d	Indomethacin	50mg/TID x 8d	No
Cheng et al., 2004 <sup>45</sup>	62	Rofecoxib	50mg	Diclofenac	150mg	Rofecoxib equivalent to diclofenac

Author, Year	Sample Size	NSAID 1	Dose 1	NSAID 2	Dose 2	Statistically or clinically important differences in effectiveness
				NSAID 3: Meloxicam	15mg	Rofecoxib superior to meloxicam Meloxicam equivalent to diclofenac
Rubin et al., 2004 <sup>55</sup>	189	Etoricoxib	120mg/QD	Indomethacin	50mg/TID	No
Schumacher et al., 2012 <sup>59</sup>	400	Celecoxib	50mg/BID, 200mg/ BID, 400mg/BID	Indomethacin	50mg/TID	High dose celecoxib equivalent to indomethacin Low dose celecoxib inferior to indomethacin
Li et al., 2013 <sup>35</sup>	78	Etoricoxib	120mg/d	Indomethacin	75mg/BID	No

## Key Question 2: Dietary and Lifestyle Management of Gout

- a. In adults with gout, what are the benefits and harms of different dietary therapies and life style measures on intermediate (serum and/or urine UA levels) and final health outcomes (including recurrence of gout episodes and progression [e.g., development of tophi])?
- b. Does effectiveness and comparative effectiveness of dietary modification differ according to disease severity (including presence of tophi and baseline serum UA), underlying mechanisms of hyperuricemia, or baseline demographic and co-morbid characteristics?

### Key points

- The strength of evidence from RCTs that assess symptomatic outcomes is insufficient to support a role for specific dietary therapies (related to some of the risk factors, e.g., red meat, fructose, alcohol, etc.).
- Low strength of evidence supports that supplemental vitamin c in reducing serum urate levels (by less than 0.5mg/dl).
- There is low strength of evidence that gout-specific dietary advice (counseling about reducing red meat intake; avoiding offal, shellfish, and yeast-rich foods and beverages; and including low fat dairy products, vegetables, and cherries) is no more effective than nonspecific dietary advice (counseling about the importance of weight loss and reduced alcohol intake) at reducing serum urate levels.
- The strength of evidence is insufficient to support or refute the effectiveness of Traditional Chinese Medicine (TCM) (including herbs and acupuncture) on symptomatic outcomes.

### Description of included studies

For KQ2, we include 11 systematic reviews.<sup>7, 29, 73-81</sup> Nine SRs are shown in Table 6 and Table 8. The remaining two SRs are described in Table 7.

Two systematic reviews<sup>7, 81</sup> (SR) and seven subsequent observational studies<sup>82-88</sup> examined the association between dietary factors and the risk for gout (see Table 7).

Six SRs of trials that examined the efficacy of dietary interventions in the treatment of gout or risk factors associated with gout.<sup>29, 73, 76-78, 80</sup> We further identified three original trials not included in previous SRs that met our inclusion criteria and that examined dietary and lifestyle interventions in gout management.<sup>89-91</sup>

Two SRs were Cochrane reviews and included studies that examined the effect of dietary factors such as skimmed milk powder and Vitamin C on management of gout.<sup>73, 78</sup> Both SRs were of good quality in terms of AMSTAR ratings. One SR of good quality examined the effects of Vitamin C on serum urate in patients with hyperuricemia. One SR of good quality examined trials of fructose-containing beverage administration on serum urate.

Two RCTs<sup>89, 91</sup> assessed the effects of dietary advice on gout management. These studies, published in 2010 and 2014, enrolled adult male patients with history of gouty arthritis. The 2010 study,<sup>89</sup> which was in Chinese, enrolled sixty-seven male patients with gout, average age of 61 years, history of overweight and at least one gouty attack during the six months before enrollment.

The 2014 study<sup>91</sup> enrolled 30 adult patients with a history of gout, receiving an appropriate and stable dose of urate lowering therapy (ULT).

Three SRs examined the efficacy of Traditional Chinese Medicine (TCM) in the management of gout while one examined the efficacy of acupuncture and one examined the efficacy of moxibustion for rheumatic conditions. The AMSTAR ratings of these 5 SRs ranged from moderate to good quality. A single RCT<sup>90</sup> evaluated the efficacy of TCM in gout management. The study was conducted in 2010 and enrolled male patients with acute gouty arthritis and an average age of 48.<sup>90</sup>

**Table 6. Randomized controlled trials included in systematic reviews**

RCTs	Systematic Reviews								
	Moi et al 2013 <sup>78</sup>	Andres et al., 2014 <sup>73</sup>	Li et al, 2013 <sup>77</sup>	Zhou et al 2013 <sup>80</sup>	Lee et al 2013 <sup>76</sup>	Khanna et al 2014 <sup>29</sup>	Choi et al. 2011 <sup>74</sup>	Juraschek et al 2011 <sup>75</sup>	Wang et al 2012 <sup>79</sup>
Zhou 2012 <sup>68</sup>					X				
Dalbeth 2012 <sup>92</sup>	X	X							
Chou 1995 <sup>46</sup>						X			
Shi 2008 <sup>60</sup>			X			X			
Schlesinger 2002 <sup>57</sup>						X			
Stamp et al., 2013 <sup>93</sup>		X							

## Detailed Synthesis

### Observational Studies on the Risk for Gout

Observational studies of dietary risk factors for gout are not part of the scope of this evidence report. Nevertheless, we provide a brief summary of such studies here, as they are an important contextual background for intervention studies of diet.

Based on observational evidence that dietary purines increase serum urate levels, avoidance of high-purine foods has been the mainstay of dietary management of gout for decades. Further evidence from recent observational studies suggests that a number of additional dietary factors may alter some gout-related outcomes.

A 2011 systematic review examined 53 observational studies that assessed the association of a variety of foods, other dietary factors, and other factors with the risk for incident gout.<sup>7</sup> Meat intake, seafood intake, consumption of alcohol, consumption of sugar-sweetened beverages and other high-fructose foods, and overweight were associated with an increased risk for gout. Consumption of dairy products and caffeine-containing beverages, as well as low BMI, were associated with a decreased risk for gout.

Assessing original studies, a 5-year prospective cohort study of hyperuricemic Chinese men that used a food frequency questionnaire found a significant association between consumption of shellfish, but not other foods, and risk for gout.<sup>82</sup>

Analysis of data from the Nurses' Health Study found an association between consumption of fructose-sweetened beverages and increased risk for gout among women.<sup>83</sup>

Analyzing data from the same study, Choi and colleagues found that increasing coffee consumption was associated with a dose-dependent decrease in the risk for gout among women.<sup>84</sup>

The association between alcohol consumption and risk for incident gout was examined in a 2013 SR and meta-analysis that included 17 observational studies, reported in 12 articles.<sup>81</sup> Light ( $\leq 1$  drink/day), moderate ( $>1$  to  $<3$  drinks/day), and heavy ( $\geq 3$  drinks/day) drinking were associated with significant increases in the risk for gout, compared with non- or occasional drinking (RR1.16 (95 % CI, 1.07–1.25), 1.58 (95 % CI, 1.50–1.66), and 2.64 (95 % CI, 2.26–3.09), respectively. We also identified two other studies not included in the 2013 SR that assessed the association between alcohol consumption and risk for gout.

ARIC, a 12-year prospective cohort study, identified an association between high levels of alcohol consumption and increased risk for incident gout,<sup>85</sup> and a case-crossover study has shown an association between intake of all types of alcohol and an increase in recurrence of acute attacks in those already diagnosed with gout.<sup>86</sup>

A decrease in gout related outcomes has also been associated with consumption of cherries as well as with weight loss. An online case-crossover study of gout patients found that intake of cherries and cherry extract is associated with a decrease in the risk for gout attacks.<sup>87</sup>

Finally, the MRFIT trial, a prospective cohort study of US men at increased risk for CVD found that weight loss was associated with decreased serum urate although less effective than ULT.<sup>88</sup>

## Interventions Involving Dietary Factors

### Systematic Reviews

We identified four systematic reviews that examined the evidence from randomized controlled trials on the efficacy of dietary factors for gout management or management of risk factors for gout (see Table 7).<sup>73, 75, 78, 79</sup>

A 2011 SR by Juraschek and colleagues reviewed 13 trials on the administration of vitamin C supplements on serum urate.<sup>75</sup> These trials enrolled a total of 556 participants, the median dosage of vitamin C was 500mg/day, trial size ranged from 8–184 participants, and the median study duration was 30 days. Pretreatment serum urate ranged from 2.9 to 7mg/dL. The pooled decrease in serum urate compared with placebo was significant  $-0.35$ mg/dl (95% confidence interval  $-0.66$ ,  $-0.03$  [ $P=0.032$ ]). Trials showed significant heterogeneity.

Two Cochrane reviews<sup>73, 78</sup> identified a trial<sup>92</sup> that assessed whether skim milk powder (SMP) enriched with glycomacropeptide (GMP) and G600 milk fat extract, non-enriched SMP, or lactose powder significantly reduced the frequency of gout attacks (flares) over a three-month study period. The frequency of gout attacks (flares) decreased from baseline in all three groups, however there was no significant difference among the three arms in terms of the change in the number of gout attacks (flares) or in adverse events. The systematic reviews were of good quality according to AMSTAR ratings, although the quality of evidence of the included RCT was judged to be low.

One of the two Cochrane reviews<sup>73</sup> also identified an RCT of 40 adult gout patients by Stamp and colleagues<sup>93</sup> that compared the effects of vitamin C supplementation to that of allopurinol.<sup>93</sup> The study found that the reduction in serum urate level over 8 weeks was significantly less in those patients receiving vitamin C compared to those who started or increased their dose of allopurinol (mean reduction 0.014 mmoles/liter [0.23mg/dl] versus 0.118 mmoles /liter [1.9mg/dl];  $P < 0.001$ ). They concluded that when administered as monotherapy or in combination

with allopurinol, the uric acid lowering effect of a modest dose of vitamin C seems to be small in patients with gout.<sup>93</sup>

A 2012 systematic review that included 18 studies examined the effects of fructose intake on serum urate levels in both normo-glycemic and diabetic patients. The review included both studies in which fructose isocalorically replaced other dietary components and those that added fructose to increase the caloric load. The review found no increase in serum urate with isocaloric fructose consumption but high levels of fructose that increased overall calorie intake increased serum urate.<sup>79</sup>

## Original Randomized Controlled Trials of Dietary Interventions

We identified two new RCTs<sup>89,91</sup> that assessed the effects of dietary advice on gout and one new RCT that evaluated the efficacy of TCM in gout management (see Table 9).

Holland & McGill 2014<sup>91</sup> in an RCT with high risk of bias compared the effects of comprehensive dietary advice with basic advice on serum urate in gout patients. The study divided 30 gout patients into an intervention group (n=14) that received comprehensive dietary advice based on the British Society of Rheumatology Guidelines and a control group (N=15), which received basic advice regarding the importance of compliance with therapy and the benefit of weight loss. The study found no differences in serum urate between the two groups at the end of 6 months  $P>0.05$ .<sup>91</sup> Another RCT with high risk of bias conducted by Zeng 2012<sup>89</sup> investigated the effects of adjusted proportional macronutrient intake on serum urate and gout attacks in overweight patients with gout. The study found that frequency of gouty attacks (17 vs 28,  $P=0.000$ ) and serum urate levels [(420.25±36.78) vs (466.81±41.97) (μmol/L,  $P=0.000$ )] were significantly reduced in high protein group compared to low purine group.<sup>89</sup>

## Traditional Chinese Medicine (TCM)

TCM encompasses herbal medicine, acupuncture, massage, exercise, and dietary therapies. For this review, we limited it to acupuncture (moxibustion) and herbal therapies. We identified five SRs that evaluated the efficacy of TCM practices in gout management: three compared TCM to conventional medicine (Table 8), one SR evaluated the efficacy of acupuncture compared to conventional medicine in gout management, and one evaluated moxibustion for the treatment of rheumatic conditions.<sup>77, 29, 74, 76, 80</sup> The TCM evaluated included a wide range of delivery methods (including decoction, granule, capsule, and pill) and multiple mixtures of herbs (up to 23 in one SR), whose extracts have been found in some cases to contain active ingredients such as colchicine.<sup>77</sup> In aggregate, the SRs of TCM included evidence from 86 RCTs.<sup>29, 76, 77, 80</sup> Of these, 58 assessed uric acid reduction efficacy of TCM compared to conventional therapies, 2 assessed recurrences of attacks (flares), 13 assessed pain reductions, 12 assessed inflammation/joint swelling reduction and 44 assessed adverse reactions due to TCM.

Two SRs<sup>77, 80</sup> that reported pooled estimates found conflicting evidence on the efficacy of TCM in reducing serum urate level in gout management. Li et al 2013<sup>77</sup> concluded from their pooled estimate that the mean serum urate level after treatment in the intervention groups that had TCM was 50.1 micromol/L lower than the mean serum urate level after treatment in the control groups which had conventional medicine. (MD -50.10 [-54.37, -45.83]). The SR was of good quality while the quality of evidence of pooled estimate was judged to be moderate.<sup>77</sup> On the other hand, results from a meta-analysis by Zhou et al 2013<sup>80</sup> found that once gout had progressed to the acute arthritis stage there was no significant difference in clinical efficacy between Chinese herbal decoctions and traditional Western medicine as measured by serum urate (standardized mean

difference (SMD):0.35, 95% CI: 0.03 -0.67) and overall clinical response (relative risk (RR): 1.05, 95% CI: 1.01-1.10). The SR was moderate in quality. In addition, Khanna et al 2014<sup>29</sup> in their SR describe an RCT<sup>46</sup> of 40 adult gout patients that found no significant reduction in serum urate level in a group given a Chinese herbal formulation compared to indomethacin and allopurinol.

Two SRs addressed the efficacy of TCM in pain relief for gout management.<sup>29, 77</sup> A trial<sup>46</sup> described by Khanna et al 2014<sup>29</sup> found no significant improvement in pain score for treatment with DDNT compared to indomethacin. Li et al 2013<sup>77</sup> also concluded from the results of their meta-analysis of 12 studies that there is not enough evidence showing that TCM was statistically more effective than conventional medications in pain relief [mean difference (MD), -0.03; 95 % confidence interval (CI), -0.06, 0.00], but TCM combined with conventional medicines may have better effectiveness (MD, -0.33; 95 %CI, -0.59, -0.07).

There is also conflicting evidence on the efficacy of TCM in reducing inflammation and joint swelling. Li et al 2013<sup>77</sup> conclude from their pooled analysis of 10 RCTs that the mean inflammation of joint swelling after treatment in the intervention groups (TCM) was 0.14 lower (0.25 to 0.03 lower) compared to the mean inflammation of joint swelling after treatment in the control groups (conventional medicine) (MD -0.07 [-0.11, -0.02]). The quality of evidence (GRADE) from the pooled analysis was judged to be moderate. In addition Khanna et al 2014<sup>29</sup> describe a study by Shi et al 2008<sup>60</sup> that finds Simiao pill more efficacious than Indomethacin at Day 7 in reducing joint swelling and tenderness. However another study<sup>46</sup> described by them found no significant improvement in reducing the number of painful and swollen joint by treatment with a herbal formulation (DGNT) compared to indomethacin.

Li et al 2013<sup>77</sup> found evidence suggesting that TCM leads to fewer side reactions compared to conventional therapies [risk ratio (RR), 0.11; 95% CI, 0.08 to 0.15]. Zhou et al 2013<sup>80</sup> also described evidence suggesting that a Chinese herbal decoction was significantly better than traditional Western medicine in controlling adverse drug reactions (RR: 0.06, 95% CI: 0.03 to 0.13). Li et al 2013<sup>77</sup> found no evidence showing that TCM prevents recurrence of gout attacks (flares).

We identified one systematic review that evaluated the efficacy of acupuncture in comparison with conventional therapy for gout management.<sup>76</sup> Results from pooled analysis suggest that acupuncture therapy is more effective in reducing serum urate level (MD = 30.37; 95% CI 4.28, 56.47; P<0.00001) and pain (MD=2.23; 95% CI 1.39 - 3.08; P<0.0001) compared to conventional therapy. However, two out of the 8 trials (120 patients) reported a worse effect than the control group on uric acid.<sup>76</sup> The quality of the systematic review was moderate.

We identified one SR that evaluated the efficacy of moxibustion in comparison with conventional therapies for the treatment of pain and inflammation associated with rheumatic conditions.<sup>74</sup> Two of the included studies enrolled gout patients, however only one compared moxibustion with a medication approved for use in the U.S., allopurinol. Patients treated with ginger moxibustion showed an increased response rate compared to patients treated with allopurinol (100 percent response rate vs. 75 percent response rate, respectively)..

Zhang 2010<sup>90</sup> in a study that we judged had high risk of bias investigated the cure rate in a group that received blood-letting cupping plus TCM compared to a control group that received Diclofenac Sodium Enteric-coated Tablets. They found that the cure rate (measured by resolved joint swelling, reduced pain, and normal or decreased blood uric acid) was higher in the treatment group (61 percent) than in the control group (58 percent), however the difference was not significant at the 5 percent level.

**Table 7. Dietary Risk Factors**

Author, year, Design	Participants	Interventions/exposures	Outcomes
SRs of RCTs			
Moi, 2013 <sup>78</sup> Cochrane SR	1 study included: Dalbeth	Milk powder	Recurrence of gout attacks
Andres, 2013 <sup>73</sup> Cochrane SR of RCTs (Sivera is senior author so probably 3e	2 studies included: Dalbeth and Stamp	Milk powder Vitamin C	Recurrence for milk powder serum urate for vitamin C
Wang, 2012 <sup>79</sup> SR RCTs	16 reports of 18 studies	Fructose	hyperuricemia
Juraschek, '11 <sup>75</sup> SR of RCTs	Healthy, not gout patients	Vitamin C	
RCTs			
Stamp, 2013 <sup>93</sup> RCT	Patients with ACR-dx gout	Vitamin C compared with allopurinol, open label	serum urate
Dalbeth, 2012 <sup>92</sup> RCT		Skim Milk powder enriched with glycomacropeptide and milk fat	Recurrence of gout attacks
SR of observational Studies			
Wang, 2013 <sup>81</sup>		Alcohol	Gout risk
Singh, 2011 <sup>7</sup>		Meat, dairy, fruit, seafood, fiber... Sugar-sweetened beverages Alcohol Coffee Weight loss	
Individual observational studies			
Wang, 2013 <sup>82</sup> 5-year prospective cohort	Hyperuricemic patients in China	Multiple exposures	Gout risk
Zhang, 2013 <sup>87</sup> Case-crossover	Hyperuricemia?	Cherry juice	Risk of recurrent gout attacks
Choi, 2010 <sup>83</sup> Prospective cohort	NHS	Fructose-rich beverages	Gout risk
Choi 2010b <sup>84</sup> Prospective cohort	NHS	Caffeine	Gout risk
Demarco, 2011 <sup>85</sup> 12-year prospective cohort (ARIC)	US multisite cohort	alcohol	Gout risk
Neogi, 2014 <sup>86</sup> Case-crossover	US	alcohol	Risk for recurrent gout attacks
Zhu, 2010 <sup>88</sup> Observational	US men with increased CVD risk	Weight loss	Serum urate

### Evidence about subgroups:

There were no identified studies that presented data stratified by gender, baseline or achieved serum urate, HLA-B5801 status, age, tophi or comorbidities on the effectiveness of dietary advice for gout, specific dietary therapies, or TCM in management of gout.

## **Strength of Evidence**

### **Gout-specific diets and dietary advice**

We judged the strength of evidence that gout specific diets and dietary advice is insufficient to reach conclusions, as we identified only two small RCTs with a high risk of bias.

### **Supplemental vitamin C**

We judged the strength of evidence that supplemental vitamin C reduces serum uric acid as low, while there is a meta-analysis of 13 studies, heterogeneity in results is high, and none of the studies assessed the effect in patients with gout.

### **TCM including herbs and acupuncture**

Although there are numerous RCTs of various herbal therapies or acupuncture, the results of these studies are inconsistent, and the interventions all differ from study-to-study, making it impossible for us to draw any conclusions.

**Table 8. Systematic reviews of pharmacologic therapy for acute gout treatment**

Author/Year/Funding	Search End date	# of included studies	# of included patients/Patient characteristics	Setting(s)	Outcomes	Doses	Results	AMSTAR
Moi et al, 2013 <sup>78</sup> ; Special Diet; Funding: Royal Melbourne Hospital, Monash University, Cabrini Hospital, and Southampton General Hospital	March 2013	1 RCT	120 participants with chronic gout: predominantly middle-aged Caucasian men (mean age in the fifth decade); duration of gout ranged from 13 to 17 years, and 20% to 43% of participants had tophaceous disease.	Outpatient, Community	Acute gout attack frequency	(lactose powder 15 grams per day and skim milk powder [SMP] 15 grams per day); SMP enriched with dairy fractions glycomacropeptide (GMP) 1.5 grams per day and 0.525 grams per day of G600 milk fat extract [SMP/GMP/G600]	SMP/GMP/G600, standard SMP and lactose powder all significantly reduced the frequency of gout flares over a three-month study period. After combining the two control groups (standard SMP, lactose powder), there was no statistical difference between SMP/GMP/G600 compared to the two control groups in terms of the change in the number of gout flares from baseline: mean difference (MD) -0.21 (95% confidence interval (CI) -0.76 to 0.34).	9/9
					Adverse events		There were no significant between-group differences in terms of withdrawals due to adverse effects (risk ratio (RR) 1.27, 95% CI 0.53 to 3.03), and serious adverse events resulting in hospitalization (2/40 SMP/GMP/G600 group versus 3/80 controls; RR 1.33, 95%CI 0.23 to 7.66).	
Andres et al., 2014 <sup>73</sup> ; Special diet/Funding: NR	No date restrictions	1 RCT	120 adults (aged 18 years or older) with a diagnosis of chronic gout.)	primary and secondary care clinics, public advertisement	Acute gout attack frequency, Adverse events	As shown in Moi et al., 2013 above	As shown in Moi et al., 2013 above	9/9
		1 RCT	40 adults (90% male)-middle-aged with gout		Serum urate	Twenty patients already taking allopurinol were randomized to receive an increase in the dose of allopurinol (n=10) 50 to 100mg daily or to commence taking vitamin C (500mg/day)(n=10). 20 patients who had not been taking allopurinol were randomized to start receiving either allopurinol (up to 100 g/day) [n=10] or vitamin	Vitamin C did not lower sUA as much as allopurinol (-0.014 mmol/L in vitamin C group versus -0.118 mmol/L in allopurinol group; MD 0.10, 95% CI 0.06 to 0.15; low-quality evidence).	

Author/Year r/Funding	Search End date	# of inclu- ded studies	# of included patients/ Patient characteristics	Settin g(s)	Outcomes	Doses	Results	AMSTAR
						C (500mg/day)[n=10].		
Li et al, 2013 <sup>77</sup> ; Traditional Chinese Medicine/ Funding: Program for Innovative Research Team of Beijing University of Chinese Medicine (2011- CXTD-09) and the Project for Standard Operation Procedure of Clinical Appraisal in the Program for Significant New Drugs Developmen t	Dec. 2012	12 RCTs	885 male and female adult patients (18 years and older) with a diagnosis of gout	Inpatie nt and/or Outpati ent or NR	Pain relief	Traditional Chinese Medicine compared to colchicine (8 trials), allopurinol (4 trials), colchicine and allopurinol (3 trials), NSAID (12 trials), colchicine and NSAID (6 trials), allopurinol and NSAID (4 trials), uricosuric agents (1 trial), uricosuric and colchicines (1 trial), uricosuric and NSAID (2 trials).	There is not enough evidence showing that TCM was statistically more effective than conventional medications in pain relief [mean difference (MD), -0.03; 95 % confidence interval (CI), -0.06, 0.00],but TCM combined with conventional medicines may have better effectiveness (MD, -0.33; 95 %CI, -0.59, -0.07).	10/11
		2 RCTs	159 patients		Recurrence (calculated as the number of patients with at least one flare during the follow-up).		There was no evidence showing that TCM prevents gout recurrence better.	
		40 RCTs	2975 gout patients		Serum urate level reduction		The mean serum urate level after treatment in the intervention groups was 50.1 lower (54.37 to 45.83 lower) than the mean serum urate level after treatment in the control groups (MD -50.10 [-54.37, -45.83]).	
		10 RCTs	685 gout patients		Inflammati on of joint swellings after treatment		The mean inflammation of joint swelling after treatment in the intervention groups was 0.14 lower (0.25 to 0.03 lower) compared to the mean inflammation of joint swelling after treatment in the control groups. MD -0.07 [-0.11, -0.02]	
		37 RCTs	NR		Adverse reactions		The current data show that TCM leads to fewer side reactions compared to conventional therapies [risk ratio (RR), 0.11; 95 % CI, 0.08 to 0.15].	

Author/Year r/Funding	Search End date	# of includ- ed studies	# of included patients/ Patient characteristics	Setting (s)	Outcomes	Doses	Results	AMSTAR
Zhou et al, 2013 <sup>80</sup> ; Traditional Chinese Medicine/ Funding: Natural Science Foundation of China	June 2012	17 RCTs	1042 patients diagnosed with primary gout in the phase of acute arthritis.	NR	clinical efficacy: Serum urate level reduction etc.	Chinese herbal decoctions (6-45g) vs traditional Western medicine[colchicine(0.5g /4-8g);Allopurinol (0.1 g*3); Ibuprofen (0.1 g*3);Diclofenac Sodium (25mg*3); Meloxicam (7.5mg); Indomethacin (25mg) etc]	The results of the meta-analysis showed that when gout had progressed to the stage of acute arthritis, there was no significant difference in clinical efficacy between Chinese herbal decoctions and traditional Western medicine, as indicated based on the following parameters: serum urate (standardized mean difference (SMD):0.35, 95% confidence interval (CI): 0.03 to 0.67), C reactive protein (SMD: 0.25, 95% CI: 20.18 to 0.69), erythrocyte sedimentation rate (SMD: 0.21, 95% CI: -0.02 to 0.45) and overall clinical response (relative risk (RR): 1.05, 95% CI: 1.01 to 1.10).	8/11
		7 RCTs	507 patients diagnosed with primary gout in the phase of acute arthritis		adverse reactions		The Chinese herbal decoction was significantly better than traditional Western medicine in controlling adverse drug reactions (RR: 0.06, 95% CI: 0.03 to 0.13).	
Lee et al, 2013 <sup>76</sup> ; Acupuncture /Funding: National Research Foundation of Korea	August 2012	8 RCTs	632 patients with gouty arthritis	NR	Uric acid level reduction	Acupuncture [electro- acupuncture treatment (EAT) & acupuncture treatment (AT) 5-15days] in treatment group vs Western therapy [Allopurinol 350mg/day; Indomethacin 25mg; Probenecid 0.5 g/day; benzbromarone qd X6 days] in control group	The pooled analysis showed that acupuncture therapy alone decreased uric acid more than western therapy (MD = 30.37; 95% CI 4.28, 56.47; P<0.00001). Two out of the 8 trials (120 patients) reported a worse effect than the control group on uric acid.	9/11
		4 RCTs	380 patients with gouty arthritis		Visual Analogue Scale		The pooled analysis showed that acupuncture therapy alone improved the VAS more than western therapy (MD=2.23; 95% CI 1.39 - 3.08; P<0.0001).	
Khanna, et. al. 2014 <sup>29</sup> ; Traditional Chinese Medicine/Fu nding: ACR Gout Guidelines Grant	May 2013	30 RCTs (Only 2 relevant to Traditio nal Chinese Medicin e)	Number of patients not reported; pooled mean age 54.14 (SD = 11.94); 89.7% male	NR	Joint swelling, Pain, serum urate	Danggui-Nian- Tong_Tang (DNNT) (6 tablets/day) vs Indomethacin (125mg/day) and Allopurinol (200mg/day); Simiao Pill vs Indomethacin (50mg per time, 3 times a day)	No significant improvement in reducing the number of painful and swollen joint (p<0.05) and pain score (p<0.01) by treatment with DGNTT compared to indomethacin. Also no significant reduction in serum urate level in DGNTT group (p>0.05) compared to allopurinol group (p<0.001); Simiao pill more efficacious than Indomethacin at Day 7 in reducing joint swelling and tenderness (p<0.05).	6/9

**Table 9. Randomized controlled trials of pharmacologic therapies for acute gout not included in existing systematic reviews**

Author/Year	Population , Sample size	Intervention	Outcomes	Timing	Results	Cochrane ROB
Zeng, 2012 <sup>89</sup>	Sixty-seven male patients with gout and overweight with history of at least one gouty attacks during the six months before enrollment; age(34-83 yrs) Average age 61.4yrs; BMI>25kg/m <sup>2</sup>	Randomized into high protein group and low purine group. Dietary recommendations consisted of calorie restriction to 6276 kJ per day with 40% derived from carbohydrate, 30% from protein, and 30% from fat, and the refined carbohydrates were replaced with complex ones and saturated fats with mono- and polyunsaturated ones. High protein group didn't limit purine intake. Dietary of low purine group consisted of 60% derived from carbohydrate, 10% from protein, and 30% from fat, and limited of purine <150mg/d.	Serum urate (UA); number of gout attacks	6 months	Dietary measures resulted in weight loss [(65.75±3.26) vs (69.31±7.78) kg, P=0.043) and a decrease in the frequency of six-month gout attacks (17 vs 28, P=0.000). After the trial, compared to low-purine group, UA [(420.25±36.78) vs (466.81±41.97) (μ)mol/L, P=0.000] decreased significantly in the high protein group. Gouty attacks were reduced and decreased by 48.48% and 22.22% in high protein group and low purine group, respectively. The differences between the two group was statistically significant (P=0.000) Change in proportional macronutrient intake is beneficial for lowering UA, and decreasing the frequency of gout attacks.	1. Sequence: Low 2. Allocation concealment: High 3a. Blinding participants: Unclear 3b. Blinding care providers: Unclear 3c. Blinding outcome assessors: Unclear 4a. Follow-up less than 20%: Low 4b. Loss to follow-up missing data explained: Low 4c. Only those who completed the treatment regimen 5. Outcome reporting: Low 6. Findings reported as % who responded: High
Zhang, 2010 <sup>90</sup>	67 cases of acute gouty arthritis; male; aged 32-71 with an average of 48.	blood-letting cupping plus TCM (treatment group) vs. Diclofenac Sodium Enteric-coated Tablets(control group) (3 times daily for 3–7 days)	Cure rate (resolved joint swelling, reduced pain, and normal or decreased blood uric acid)	1 week	Cure rate (resolved joint swelling, reduced pain, and normal or decreased blood uric acid) was 61% in treatment group compared to 58% in the control group. However the difference was not significant at the 5% level.	1. Sequence: Low 2. Allocation concealment: High 3a. Blinding participants: High 3b. Blinding care providers: High 3c. Blinding outcome assessors: High 4a. Follow-up less than 20%: Low 4b. Loss to follow-up missing data

Author/Year	Population , Sample size	Intervention	Outcomes	Timing	Results	Cochrane ROB
						explained: Low 4c. All participants randomized to particular groups 5. Outcome reporting: Low 6. Findings reported as % who responded: Low
Holland & McGill 2014 <sup>91</sup>	30 patients (aged >18 years; 27 males) with a history of gout, receiving an appropriate and stable dose of ULT.	At baseline and 3 months, the control group (n=15) received basic advice regarding the importance of compliance with therapy and the benefit of weight loss. While the intervention group (n=14) received comprehensive dietary advice based on the British Society of Rheumatology Guidelines.	Serum urate levels	6 months	At 6 months, there was no significant difference in mean serum urate between groups, with the mean in the control group 0.27 mmol/L ( $\pm 0.07$ , 0.18–0.44) and in the intervention group 0.30 mmol/L ( $\pm 0.08$ , 0.17–0.51), $P > 0.05$ .	1. Sequence: Low 2. Allocation concealment: High 3a. Blinding participants: Low 3b. Blinding care providers: High 3c. Blinding outcome assessors: Unclear 4a. Follow-up less than 20%: Low 4b. Loss to follow-up missing data explained: Low 4c. Unclear if all participants randomized to particular groups 5. Outcome reporting: Low 6. Findings reported as % who responded: High

## Key Question 3: Pharmacologic Management of Hyperuricemia in Gout Patients

- a. In adults with gout, what are the benefits and harms of different pharmacological therapies on intermediate (serum and/or urine UA levels) and long-term clinical health outcomes (including recurrence of gout episodes and progression)?
- b. Does effectiveness and comparative effectiveness of urate lowering therapy differ according to disease severity (including presence of tophi and baseline serum UA), underlying mechanisms of hyperuricemia, or baseline demographic and co-morbid characteristics?
- c. What is the effect of dietary modification in combination with pharmacologic therapy?

### Key Points

- The strength of evidence is high that urate lowering therapy does not reduce the risk of acute gout attacks in the first six months.
- Moderate strength of evidence supports a reduction in the risk of acute gout attacks after about one year of urate lowering therapy.
- A high strength of evidence supports the efficacy of urate lowering therapy in reducing serum urate.
- A high strength of evidence supports the finding of no difference in serum urate lowering between 40mg febuxostat and 300mg allopurinol.
- Evidence is insufficient about the effectiveness and comparative effectiveness of allopurinol and febuxostat at reducing tophi.
- A high strength of evidence supports a lack of difference in overall adverse events between allopurinol 300mg and febuxostat 40mg.
- A high strength of evidence suggests that prophylactic therapy with low dose colchicine or low dose NSAIDs when beginning urate lowering therapy reduces the risk of acute gout attacks.
- Moderate strength of evidence supports that longer durations of prophylaxis with colchicine or NSAIDs (> 8 weeks) are more effective than shorter duration when initiating urate lowering therapy.
- A strength of evidence is low that gout-specific dietary advice does not add to the effectiveness of urate lowering therapy in reducing serum urate.

### Description of included studies

**Placebo-controlled trials.** Our literature search identified one SR<sup>94</sup> that included data from two placebo-controlled trials of allopurinol, and two systematic reviews<sup>14, 95</sup> that included data from two placebo-controlled trials of febuxostat. In addition, we identified one abstract of a febuxostat placebo-controlled trial<sup>96</sup>, and one secondary analysis of a febuxostat placebo-controlled trial<sup>97</sup>

already included in the systematic reviews. In addition, we identified one meta-analysis that compared the efficacy of febuxostat or allopurinol versus placebo for female patients.<sup>98</sup>

**Febuxostat vs. Allopurinol.** Our literature search identified six SRs and one meta-analysis.<sup>14, 94, 95, 98-101</sup> Four of which were high quality (AMSTAR > 8).<sup>14, 94, 95, 99</sup> and one was low quality.<sup>100, 102, 103</sup> The four high quality reviews included eight trials. The results of these studies were dominated by the FACT<sup>104</sup>, APEX<sup>105</sup>, CONFIRMS<sup>106</sup>, and EXCEL<sup>107</sup> trials. Our review identified one new randomized controlled trial that was not included in any of the prior systematic reviews.<sup>108</sup> We also identified a meta-analysis of the FACT, APEX, and CONFIRMS studies looking at comparative effectiveness of allopurinol and febuxostat in women with gout.<sup>98</sup>

**Adverse events.** We identified one SR<sup>109</sup> and 15 studies reporting on adverse events.<sup>110-124</sup>

**Colchicine vs. Allopurinol.** Our literature search identified one new trial on colchicine vs. allopurinol.<sup>43</sup>

**Allopurinol vs. Probenecid.** We identified one systematic review<sup>125</sup> which included one trial on probenecid vs. allopurinol.<sup>126</sup> We did not identify any new trials not covered in any of the existing systematic reviews.

**Prophylaxis against acute gout attacks when starting urate lowering therapy.** We include two SRs<sup>127, 128</sup> and three studies.<sup>38, 43, 129</sup>

**Dietary modification in addition to pharmacologic therapy.** We included one trial that was included for KQ2.<sup>91</sup>

## Detailed Synthesis

### Placebo-Controlled trials

#### Allopurinol vs. Placebo

Our literature search identified one systematic review<sup>94</sup> that included data from two placebo-controlled trials of allopurinol<sup>36, 105</sup> (see Table 11 for the systematic reviews and Table 12 for the two trials included).

The first study by Schumacher 2008<sup>105</sup> was a 28-week double-blind RCT (the APEX trial) that compared allopurinol, febuxostat and placebo. Patients enrolled were adults with hyperuricemia and gout with normal or impaired renal function. One hundred and thirty-four patients were assigned to the placebo group and 268 patients were in the allopurinol 300mg group (allopurinol 100mg was given to patients with renal impairment in the allopurinol group). The study found a significantly higher proportion of patients treated with allopurinol achieving serum urate < 6.0mg/dl than placebo and allopurinol produced greater reduction in serum urate level from baseline than placebo. There was no significant difference in gout attacks (flares), number of tophi, reduction in median tophus size and incidence of adverse events between the two groups. Based on a very small sample, no patients with renal impairment receiving allopurinol 100mg or

placebo achieved last 3 monthly serum urate levels < 6.0mg/dl, or attained serum urate < 6.0mg/dl at either the week 28 or final visits.

The second study by Taylor et al. 2012<sup>36</sup> was a 10-day double-blind RCT followed by open label study from day 11 to day 30. Patients included were adult males with crystal-proven gout experiencing an acute gout attack. Thirty-one patients were assigned to the allopurinol 300mg group and 26 were assigned to the placebo group. No difference in Visual Analog Scale pain scores or the incidence of recurrent gout attacks (flares) were found between the treatment and the placebo groups during the 10-day RCT period. Subgroup analysis comparing subjects having a first gout attack versus those having had prior attacks also revealed insignificant differences in pain scores. During the placebo-controlled period of the study, serum urate levels were decreased significantly by day 10 in the allopurinol group, while serum urate levels remained elevated in the placebo group during this period. Open-label allopurinol was initiated in all groups on day 11 and average serum urate decreased to similar levels in both groups to less than 6.0mg/dl by day 30.

## **Harms of Allopurinol**

Allopurinol has a 40+ year history of use and high level evidence of its harms in treatment of patients with gout and other conditions. The most common adverse event with allopurinol is a skin rash occurring in up to 5 percent of patients. While most of these are mild and reversible, serious skin reactions including Toxic Epidermal Necrolysis and Stevens Johnson Syndrome have been reported. Allopurinol has been proposed as a cause of the DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms).<sup>110, 113-115, 117</sup> These serious side effects are sufficiently rare that clinical trials do not have sufficient power to detect them. In two placebo-controlled trials that included 268<sup>105</sup> and 26<sup>36</sup> patients treated with allopurinol, there were no statistically significant increases in skin reactions in the allopurinol groups compared to placebo. There was only one death across both studies, an 80 year old male who had multiple medical problems.<sup>36</sup> The most commonly reported adverse events in these two trials were upper respiratory tract infections (19 percent), and musculoskeletal and connective tissue signs and symptoms (10 percent), but these were not statistically different from the placebo group (16 percent and 10 percent, respectively).<sup>105</sup> Therefore, our knowledge of serious AEs comes from case reports and case series.<sup>109, 120-123</sup> In one large series of patients (N=1,732) being treated with allopurinol for gout (93 percent male, 75 percent white, mean age=51 years and mean BMI=34 kg/m<sup>2</sup>) the proportion of patients with serious treatment-emergent gout adverse events occurred in 3.0 percent, and death in 0.2 percent; adverse events leading to allopurinol withdrawal or study discontinuation were 4.3 percent.<sup>112</sup> HLA-B5801 is associated with an increased risk of these serious side effects.<sup>109, 111, 119, 124</sup> Allopurinol requires a dose reduction in chronic kidney disease.

## **Febuxostat vs. Placebo**

Our literature search identified two systematic reviews<sup>14, 95</sup> that included data from two placebo-controlled trials of febuxostat (see Tables 10 and 11). In addition, we identified one new abstract of a febuxostat placebo-controlled trial<sup>96</sup>, and one new secondary analysis of a febuxostat placebo-controlled trial already included in the systematic reviews (see Tables 13 and 14).

A total of two trials evaluating the effect of febuxostat versus placebo for gout patients were included in the four systematic reviews. The results of one trial are supplemented by a secondary subgroup analysis. The first study by Becker et al. 2005b<sup>130</sup> was a 28-day double-blind RCT with

38, 37, 40 and 38 patients assigned to placebo, febuxostat 40mg, febuxostat 80mg and febuxostat 120mg, respectively (note that febuxostat doses above 80mg are not approved for use in the USA). Adult patients with gout and hyperuricemia were enrolled. There was no difference between the 40mg febuxostat and placebo in terms of overall incidence of gout attacks (flares), but the incidence increased with dosage of febuxostat (43 percent with 80mg and 55 percent with 120mg). The incidence of gout attacks (flares) was lower (8-13 percent) for all groups when colchicine was administered with febuxostat or placebo. No difference in adverse events was found between febuxostat and placebo groups. All doses of febuxostat were associated with a significantly higher proportion of patients reaching target serum urate < 6.0mg/dl and a greater reduction in serum urate from baseline, with the 120mg febuxostat being the most effective. A five year open label extension study of this trial found that the percentage of patients that required treatment for acute gout attacks decreased to less than 5 percent after about 12 months of ULT.<sup>118</sup> As to treatment effect heterogeneity, significant pairwise difference in percentage reductions in serum urate between each of the febuxostat groups and the placebo group were observed regardless of baseline urinary uric acid production. Compared to either 80 or 120mg, patients with the highest baseline serum urate levels were less likely to reach a serum urate level < 6.0mg/dl when treated with 40mg/day of febuxostat on day 28. A secondary analysis by Goldfarb 2011<sup>97</sup> concluded that the percentage change in serum urate at day 28 from baseline was similar between overproducers and underexcretors among all febuxostat groups and were significantly greater than the placebo group.

The second study by Schumacher et al. 2008<sup>105</sup> conducted a 28-week double-blind RCT (the APEX trial) with 134 patients in the placebo group and 267, 269 and 134 patients in the febuxostat 80, 120 and 240mg group, respectively (note that febuxostat doses above 80mg are not approved for use in the USA). Patients included were adults with hyperuricemia and gout with normal or impaired renal function. Patients receiving higher dose of febuxostat were more likely to require treatment for gout attacks (flares) during the first 8 weeks when gout flare prophylaxis was provided, but no differences were observed in gout flares across treatment groups after prophylaxis ended, between weeks 8 and 28. There was no substantial difference in the number of tophi, the reduction in median tophus size or adverse event rate across groups, with the exception that febuxostat 120mg achieved a higher mean percent decrease in the number of tophi compared to placebo at week 28. All doses of febuxostat were associated with significantly higher proportion of patients reaching serum urate < 6.0mg/dl, with the 240mg febuxostat being the most effective.

**Table 10. Randomized controlled trials included in systematic reviews (febuxostat vs. placebo)**

RCTs	Systematic reviews	
	Tayar et al., 2012 <sup>14</sup>	Ye et al., 2013 <sup>*95</sup>
Becker et al., 2005 <sup>130</sup>	X	X
Goldfarb et al., 2011 <sup>97</sup>		
Schumacher et al., 2008 <sup>105</sup>	X	X

\*Two trials were excluded from our review that were included in Ye, et al., 2013 as the two trials excluded patient with gouty arthritis

## Harms of Febuxostat

There is much less clinical experience with febuxostat than with allopurinol. In the three placebo-controlled trials cited above, a total of 779 patients were treated with febuxostat, of which 210 received 120mg per day (higher than the FDA-approved maximum).<sup>97, 105, 130</sup> The most commonly reported adverse events in these trials were abdominal pain, diarrhea, and musculoskeletal pain (5 percent-20 percent for each), but these were not statistically significantly different than placebo-treated patients. There were no deaths. Across all three studies, only one

serious adverse event was reported that study investigators judged related to febuxostat: an increase in serum creatinine from 1.1mg/dl to 1.5mg/dl while receiving 240mg/day, which decreased to 1.3mg/dl when the patients was changed to 120mg/day.<sup>105</sup> In a one-year open label study of 171 Japanese men all treated with febuxostat, there were four serious AEs (gastric ulcer hemorrhage, spinal stenosis, sinusitis, and aggravated spinal osteoarthritis) but these were all judged to be unrelated to treatment. No deaths were reported.<sup>116</sup>

## **Evidence from new eligible studies**

The only new eligible study we identified reports was published as an abstract only. This study reports results from a placebo-controlled trial of febuxostat. We did not identify any new studies comparing allopurinol versus placebo.

The study by Saag et al. 2013<sup>96</sup> conducted a RCT with 12-month follow up targeting gout subjects with hyperuricemia and moderate-to-severe renal impairment. Thirty two patients each were randomly allocated to receive either febuxostat 30mg BID, febuxostat 40/mg QDm or placebo. Compared with placebo, febuxostat was associated with a higher proportion of patients achieving a serum urate < 6.0mg/dl and greater reduction in serum urate, with febuxostat 30mg BID being more effective than febuxostat 40/80mg once a day. The conclusions of the new RCT is consistent with SRs comparing febuxostat with placebo.

## **Evidence about subgroups:**

There were only limited data about differences in effectiveness stratified by the pre-specified subgroups:

- Chohan 2012<sup>98</sup> conducted a meta-analysis that compared the efficacy of febuxostat or allopurinol versus placebo for female patients, pooling data from three major RCTs (the FACT trial, APEX trial and CONFIRM trial). Female patients treated with either febuxostat or allopurinol were more likely to achieve serum urate < 6.0mg/dl than placebo. No female patients receiving placebo achieved target serum urate level. The proportion of patients with AEs was similar across placebo, febuxostat and allopurinol groups. Becker 2005<sup>130</sup> stratified the sample by baseline serum urate levels and found febuxostat 40mg was less effective in reducing serum urate levels than 80 or 120mg among patients with highest baseline serum urate.
- Schumacher 2008<sup>105</sup> looked at the effectiveness of febuxostat or allopurinol versus placebo in reducing serum urate for patients with mild to moderate renal impairment. The proportion of patients achieving target serum urate levels was numerically lower among patients with impaired renal function than those with normal renal function across all treatment groups. The evidence is of low quality due to the very small sample size of patients with impaired renal function (ranging from 5 to 11).

**Table 11. Systematic reviews of febuxostat or allopurinol vs. placebo for the management of chronic gout**

Author/Year/ Funding	End date of search	# of included studies [indicate study design]	# of included patients/ Patient characteristics included	Setting(s)	Outcomes	Doses	Results	AMSTAR
Seth et al., 2014 <sup>94</sup> ; No external funding	January 2014	2 placebo- controlled trials of allopurinol	1072 (Schumacher 2008) + 57 (Taylor 2012); patients with chronic gout per ARA criteria	NR	Acute gout attacks, serum urate level, AEs	Allopurinol : 100/300m g Febuxosta t: 80/120/24 0mg	Compared with placebo, allopurinol (100 to 300mg daily) is not associated with a significant reduction in acute gout attacks, but increases the proportion of participants achieving sUA < 6.0mg/dl, without increasing withdrawals due to AEs or serious adverse event rates	11/11
Tayar et al., 2012 <sup>14</sup> ; No external funding	July 2011	4 placebo- controlled trials of febuxostat , 2 open- label extension trials of febuxostat	3978 chronic gout patients (Becker 2005a, 2005b, 2009, 2010; Schumacher 2008, 2009) - 2619 randomized to febuxostat, 172 to placebo and 1187 to allopurinol	NR	Frequency of gout flares, serum urate level, AEs	Febuxosta t: 40/80/120/ 240mg	Compared with placebo, patients treated with all doses of febuxostat were more likely to achieve sUA < 6.0mg/dl; gout flares were more frequent among patients treated with febuxostat 120/240mg than those with	11/11

Author/Year/ Funding	End date of search	# of included studies [indicate study design]	# of included patients/ Patient characteristics included	Setting(s)	Outcomes	Doses	Results	AMSTAR
							placebo but there were no differences observed for 40/80mg; no statistically significant difference in AEs between any doses of febuxostat and placebo.	
Ye et al., 2013 <sup>95</sup> ; National Natural Science Foundation of China	February 2012	4 placebo-controlled RCTs of febuxostat	1225 (Becker 2005, Schumacher 2008, Kamatani 2011-phase II, 2011-phase III); hyperuricemic (sUA $\geq$ 7mg/dl) adults with/without gout, mean age 47.5-52; 989 in febuxostat group and 236 in Placebo group	NR	Serum urate	Febuxostat: 20-240mg	All of the Febuxostat doses were associated with a significantly higher percent of patients achieving target serum urate levels.	10/11

**Table 12. Randomized controlled trials of allopurinol vs. placebo in the management of chronic gout**

Author/Year	Population, Sample size	Intervention	Outcomes	Timing	Results	Cochrane ROB
Schumacher et al., 2008 <sup>105</sup>	<p>Adults with hyperuricemia (serum urate level &gt;8.0mg/dl) and gout (defined by the ACR criteria) with normal or impaired (serum creatinine level &gt;1.5 to &lt;2.0mg/dl) renal function.</p> <p>N = 1,072 (134 placebo, 268 allopurinol 300mg, ) (For febuxostat vs. placebo results, see Table 13)</p> <p>167 participating sites in the US; the majority of investigators were primary care physicians.</p>	<p>Allopurinol: 300mg</p> <p>Naproxen or colchicine was provided during the first 8 weeks</p>	<p>Proportion of subjects with last 3 monthly serum urate levels &lt; 6.0mg/dl;</p> <p>Proportion of subjects with serum urate level &lt; 6.0mg/dl at week 28 or final visit;</p> <p>Percent reduction in serum urate level;</p> <p>Proportion of subjects requiring treatment for gout flare;</p> <p>Total number and size of tophi;</p> <p>Adverse events</p>	28 weeks	<p>22% of individuals receiving allopurinol and 0% of those receiving placebo achieved last 3 monthly serum urate level &lt; 6.0mg/dl (P &lt; 0.001).</p> <p>41% of those treated with allopurinol and 1% of those treated with placebo achieved serum urate level &lt; 6.0mg/dl at the week 28 (P &lt; 0.05).</p> <p>Allopurinol produced 34% reduction in serum urate level from baseline, compared to 4% reduction for those treated with placebo.</p> <p>During the first 8 weeks of the study, when gout flare prophylaxis was provided, 23% of those treated with allopurinol and 20% of those with placebo required treatment for gout flares. Between weeks 8 and 28, there were no statistically significant differences in the proportion of subjects requiring treatment for gout flares observed between the treatment groups.</p> <p>No significant difference between allopurinol and placebo in the number of tophi observed or the reduction in median tophus size.</p> <p>AEs occurred with similar frequency across treatment groups and were mild or moderate in severity.</p>	<p>1. Sequence: Low</p> <p>2. Allocation concealment: High</p> <p>3a. Blinding participants: Low</p> <p>3b. Blinding care providers: Low</p> <p>3c. Blinding outcome assessors: Low</p> <p>4a. Follow-up less than 20%: High</p> <p>4b. Loss to follow-up missing data explained: Low</p> <p>4c. All participants randomized</p> <p>5. Outcome reporting: Low</p> <p>6. Findings reported as % who responded: Low</p>

Author/Year	Population, Sample size	Intervention	Outcomes	Timing	Results	Cochrane ROB
Taylor et al., 2012 <sup>36</sup>	<p>Adult male with crystal-proven gout based on ACR criteria and the presence of MSU crystals on arthrocentesis of the primary joint.</p> <p>N = 57 (31 allopurinol, 26 placebo)</p> <p>Veteran's Affairs Medical Center in White River Junction, Vermont.</p>	Allopurinol: 300mg	<p>Pain score measured by visual analogue scale for the primary affected joint on day 1 to 10;</p> <p>Self-reported gout flares in any joint during day 1 to 30;</p> <p>Adverse events</p>	<p>10 days (double blind, placebo-controlled);</p> <p>Day 11 - 30 (open label allopurinol 300mg)</p>	<p>Initial mean VAS pain scores for the allopurinol and placebo groups were 6.72 versus 6.28 (P = 0.37) decreasing to 0.18 versus 0.27 (P = 0.54) at day 10. Mean VAS pain scores did not statistically significantly differ between study groups at any point between days 1 and 10. Subgroup analysis comparing subjects having a first gout attack versus those having had prior attacks revealed insignificant differences.</p> <p>No differences in the rate of new or recurrent gout flares between days 1 and 30 was observed - rates were 2 of 26 (7.7%) in the allopurinol group and 3 of 25 (12.0%) in the placebo group (P = 0.61).</p> <p>Elevation of serum creatinine &gt; 1.5mg/dL occurred in 1 subject from each study arm. Colchicine reductions due to gastrointestinal symptoms occurred in 8 subjects (31%) in the allopurinol group and 12 subjects (48%) in the placebo group. There was one death in the allopurinol group.</p>	<p>1. Sequence: Low</p> <p>2. Allocation concealment: Low</p> <p>3a. Blinding participants: Low</p> <p>3b. Blinding care providers: Low</p> <p>3c. Blinding outcome assessors: Low</p> <p>4a. Follow-up less than 20%: Low</p> <p>4b. Loss to follow-up missing data explained: Low</p> <p>4c. Only those who completed the treatment program</p> <p>5. Outcome reporting: Low</p> <p>6. Findings reported as % who responded: Unclear</p>

**Table 13. Randomized controlled trials of febuxostat vs. placebo in the management of chronic gout**

Author/Year	Population, Sample size	Intervention	Outcomes	Timing	Results	Cochrane ROB
Becker et al., 2005 <sup>130</sup>	<p>Adult patients with gout and hyperuricemia (sUA &gt; 8.0mg/dl). All patients met the ACR criteria for the classification of the acute arthritis of primary gout.</p> <p>N = 153 (38 placebo, 37 febuxostat 40mg, 40 febuxostat 80mg, 38 febuxostat 120mg)</p> <p>Setting unclear.</p>	<p>Febuxostat: 40/80/120mg</p> <p>Colchicine prophylaxis, 0.6mg twice daily, was provided during the 2-week washout period and the first 2 weeks of double-blind treatment</p>	<p>Proportion of subjects with serum urate levels &lt; 6.0mg/dl;</p> <p>Percent reduction in serum urate level;</p> <p>Incidence of gout flares</p>	28 days	<p>56%, 76% and 94% of individuals treated with febuxostat 40, 80 and 120mg, respectively, achieved serum urate acid &lt; 6.0mg/dl on day 28, compared to none in the placebo group (p &lt; 0.001). Compared to either 80 or 120mg, patients with the highest baseline sUA levels were less likely to reach a sUA level &lt; 6.0mg/dl when treated with 40mg/day of febuxostat on day 28.</p> <p>The mean percentage reductions in sUA from baseline levels were significantly greater in each febuxostat group than in the placebo group, regardless of baseline urinary uric acid production. The greatest reductions in the febuxostat group receiving 120mg/day (range of mean change 53–59% at each visit).</p> <p>The overall incidence of gout flares were similar in the placebo group (37%) and 40mg febuxostat group (35%) but higher in the 80mg febuxostat (43%) and the 120mg febuxostat group (55%). The incidence of gout flares was lower (i.e., 8-13%) when treatment was administered with colchicine and higher when administered alone. When administered alone, higher doses of febuxostat were associated with higher incidence of gout flares (34%, 30%, 40%, 42% for placebo, febuxostat 40, 80 and 120mg, respectively).</p>	<p>1. Sequence: Low</p> <p>2. Allocation concealment: High</p> <p>3a. Blinding participants: Low</p> <p>3b. Blinding care providers: Unclear</p> <p>3c. Blinding outcome assessors: Low</p> <p>4a. Follow-up less than 20%: Low</p> <p>4b. Loss to follow-up missing data explained: Low</p> <p>4c. All participants randomized to particular groups</p> <p>5. Outcome reporting: Low</p> <p>6. Findings reported as % who responded: Low</p>

Author/Year	Population, Sample size	Intervention	Outcomes	Timing	Results	Cochrane ROB
					<p>No significant differences between the febuxostat and placebo groups in the overall incidence of treatment-related adverse events, with the majority of events being mild or moderate in severity.</p>	

Author/Year	Population, Sample size	Intervention	Outcomes	Timing	Results	Cochrane ROB
Goldfarb et al., 2011 <sup>97</sup>  Subgroup analysis of Becker, 2005b.	Adult patients with gout and hyperuricemia (sUA 8.0mg/dl). All patients met the ACR preliminary criteria for the classification of the acute arthritis of primary gout.  N = 153 (38 placebo, 37 febuxostat 40mg, 40 febuxostat 80mg, 38 febuxostat 120mg)  Setting unclear.	Febuxostat: 40/80/120mg  Colchicine prophylaxis, 0.6mg twice daily, was provided during the washout period and the first 2 weeks of double-blind treatment	Proportion of subjects with serum urate levels < 6.0mg/dl at day 28;  Percentage change in serum urate from baseline to day 28	28 days	Treatment with any dose of febuxostat led to the majority of subjects achieving sUA < 6.0mg/dl on day 28 in both overproducers and underexcretors; febuxostat 40mg appeared to be more efficacious in overproducers (sample size too small to perform statistical test).  The percentage change in serum urate from baseline to day 28 was similar between overproducers and underexcretors among all treatment groups.	1. Sequence: Low 2. Allocation concealment: High 3a. Blinding participants: Low 3b. Blinding care providers: Low 3c. Blinding outcome assessors: Low 4a. Follow-up less than 20%: Low 4b. Loss to follow-up missing data explained: Low 4c. Only those who had baseline sUA 5. Outcome reporting: Low 6. Findings reported as % who responded: Low

Author/Year	Population, Sample size	Intervention	Outcomes	Timing	Results	Cochrane ROB
Schumacher et al., 2008 <sup>105</sup>	<p>Adults with hyperuricemia (serum urate level &gt;8.0mg/dl) and gout (defined by the ACR criteria) with normal or impaired (serum creatinine level &gt;1.5 to &lt;2.0mg/dl) renal function.</p> <p>N = 1,072 (134 placebo, 267 febuxostat 80mg, 269 febuxostat 120mg, 134 febuxostat 240mg) (For allopurinol vs. placebo results, see Table 12)</p> <p>167 participating sites in the US; the majority of investigators were primary care physicians.</p>	<p>Febuxostat: 80/120/240mg Placebo</p> <p>Naproxen or colchicine was provided during the first 8 weeks.</p>	<p>Proportion of subjects with last 3 monthly serum urate levels &lt; 6.0mg/dl;</p> <p>Proportion of subjects with serum urate level &lt; 6.0mg/dl at week 28 or final visit;</p> <p>Percent reduction in serum urate level;</p> <p>Proportion of subjects requiring treatment for gout flare;</p> <p>Total number and size of tophi;</p> <p>Adverse events</p>	28 weeks	<p>48%, 65% and 69% of individuals treated with febuxostat 80, 120 and 240mg, respectively, achieved last 3 monthly serum urate levels &lt; 6.0mg/dl; none of those with placebo did (p &lt; 0.001). The proportions of subjects with impaired renal function attaining last 3 monthly serum urate levels &lt; 6.0mg/dl were 44% (4 out of 9 patients with impaired renal function) in the febuxostat 80mg group, 46% (5 out of 11) in the 120mg group, and 60% (3 out of 5) in the 240mg group.</p> <p>At week 28, 76%, 87% and 94% of subjects treated with febuxostat 80, 120 and 240mg, respectively, achieved serum urate levels &lt; 6.0mg/dl, whereas 1% of those treated with placebo achieved the same goal (p &lt; 0.05).</p> <p>No statistically significant differences in the proportion of subjects requiring treatment for gout flares observed between treatment groups between weeks 8 and 28. During the first 8 weeks, when gout flare prophylaxis was provided, greater proportions (p &lt; 0.05) of subjects receiving febuxostat 120mg (36%) and 240mg (46%) required treatment for gout flares, compared with those receiving febuxostat 80mg (28%) or placebo (20%).</p> <p>No significant difference between febuxostat and placebo in the number of tophi observed or the reduction in median tophus size,</p>	<p>1. Sequence: Low 2. Allocation concealment: High 3a. Blinding participants: Low 3b. Blinding care providers: Unclear 3c. Blinding outcome assessors: Low 4a. Follow-up less than 20%: High 4b. Loss to follow-up missing data explained: Low 4c. All participants randomized 5. Outcome reporting: Low 6. Findings reported as % who responded: Low</p>

Author/Year	Population, Sample size	Intervention	Outcomes	Timing	Results	Cochrane ROB
					<p>except for a significant mean percent decrease in the number of tophi observed with febuxostat 120mg (-1.2) versus placebo (-0.3) at week 28 (P &lt; 0.05).</p> <p>AEs occurred with similar frequency across treatment groups and were mild or moderate in severity.</p>	

**Table 14. Randomized controlled trials of febuxostat vs. placebo for the management of chronic gout not included in existing systematic reviews**

Author/Year	Population, Sample size	Intervention	Outcomes	Timing	Results	Cochrane ROB
Saag et al., 2013 <sup>96</sup> Abstract only	Gout subjects with hyperuricemia and moderate-to-severe renal impairment fulfilling ARA criteria, patients with tophi were excluded  N = 96 (32 placebo, 32 febuxostat 30mg BID, 32 febuxostat 40/80mg QD)  Setting unclear.	Febuxostat: 30mg BID Febuxostat: 40/80mg QD (titrated from FEB 40mg to 80mg QD based on day 14 sUA)	Proportion of subjects with serum urate <6.0mg/dL;  Change from baseline in serum urate and estimated glomerular filtration rate (eGFR);  Adverse events	12 months	The proportion of subjects with sUA < 6.0mg/dL at month 12 was 69%, 45%, and 0% for febuxostat 30mg BID, febuxostat 40/80mg QD, and PLB, respectively (P < 0.001 vs. placebo).  Change in serum urate from baseline was -5.1, -4.3 and 0.07 at month 6, and -5.0, -4.2 and -0.15 at month 12 for febuxostat 30mg BID, febuxostat 40/80mg QD, and PLB, respectively (P < 0.001 vs placebo).  Mean eGFR change from baseline at month 12 was not significant different across groups.  The majority of AEs were mild to moderate in intensity and not considered to be related to study treatment.	1. Sequence: Low 2. Allocation concealment: High 3a. Blinding participants: Low 3b. Blinding care providers: Low 3c. Blinding outcome assessors: Low 4a. Follow-up less than 20%: Unclear 4b. Loss to follow-up missing data explained: Unclear 4c. Unclear if all participants were randomized 5. Outcome reporting: Low 6. Findings reported as % who responded: Low

# Comparative Effectiveness

## Febuxostat vs. Allopurinol

### Systematic reviews comparing effectiveness of febuxostat and allopurinol

Four high quality systematic reviews (AMSTAR > 8) reviewed comparative efficacy of febuxostat and allopurinol.<sup>14, 94, 95, 99</sup> The results of these reviews were broadly consistent and the results of these studies were dominated by the FACT<sup>104</sup>, APEX<sup>105</sup>, CONFIRMS<sup>106</sup>, and EXCEL<sup>107</sup> trials (see Tables 15 and 16).

In terms of clinical outcomes, gout flare incidence was higher at high doses of febuxostat (120mg or 240mg) than with allopurinol 100-300mg. Gout flare incidence was not statistically different between febuxostat 40mg, febuxostat 80mg, and allopurinol (100-300mg). There were more mixed conclusions regarding changes in tophi. One review concluded that tophus area reduction was greater in patients taking febuxostat than allopurinol, but the median reduction in the number of tophi did not differ between these groups.<sup>14</sup> Other reviews reported non-significant differences in tophi changes and resolution.<sup>94, 99</sup> Conclusions about adverse events varied. In one review, the high-dose febuxostat (240mg) groups experienced more adverse events than patients taking allopurinol, but the allopurinol groups had more adverse events when compared to febuxostat 80mg (note that febuxostat doses above 80mg are not approved for use in the USA). When all doses were analyzed together, adverse event rates did not differ between febuxostat and allopurinol. The non-clinical biomarker outcome results of serum urate level were consistent across these reviews. Patients taking febuxostat at doses of 80mg or higher were more likely than patients taking allopurinol 100-300mg to reach target serum urate levels of less than 6.0mg/dl.

One systematic review<sup>95</sup> looked at the comparative effectiveness of febuxostat and allopurinol in patients with and without gout. Pooled data demonstrate that both febuxostat and allopurinol groups had similar rates of AEs, which were mostly mild or moderate in severity. In the febuxostat groups, the most common AE that led to study withdrawal was elevated liver enzymes and the most frequent serious AE were cardiovascular in nature. Patients taking febuxostat were more likely than patients taking allopurinol to achieve target sUA level  $\leq 6.0\text{mg/dL}$  at the final visit (all doses analyzed together). The proportion achieving target serum urate increased with the febuxostat dose (40mg: OR 1.2, 95% CI [1.05, 1.49], 80mg: OR 3.27, 95% CI [2.14-5.00], 120mg: OR 6.67 95% CI [5.23, 8.51]). There were no significant differences in AEs between the two groups.

One low-quality systematic review was also identified and had results that were broadly consistent with the high-quality systematic reviews.<sup>100</sup>

We also identified an SR specifically comparing the safety of urate lowering drugs. This 2014 review included seven RCTs and four SRs. Two of the included studies assessed allopurinol compared to benzbromarone, a drug not included in our scope. The other five included RCTs are all already included in one section below on major RCTs.<sup>104-106, 116, 131</sup> This review concluded there was no statistically significant difference in total AEs between allopurinol and febuxostat (pooled relative risk =1.04, 95% CI, 0.98, 1.11) (AMSTAR of 8/11).<sup>101</sup>

**Table 15. Randomized controlled trials included in systematic reviews**

RCTs	Systematic reviews				
	Tayar et al., 2012 <sup>14</sup>	Faruque et al., 2013 <sup>99</sup>	Ye, et al., <sup>95</sup> Hyperuricemia with and without gout	Seth et al., 2014 <sup>94</sup>	Manara et al., 2013 <sup>100</sup>
Singal et al., 2011 <sup>132</sup> Bangladesh				X	X
Becker et al., 2010 <sup>106</sup> CONFIRMS	X	X	X	X	X
Kamatani et al., 2011 <sup>131</sup> Japan		X	X		X
Schumacher et al., 2008 <sup>105</sup> APEX	X	X	X	X	X
Becker et al., 2009 <sup>107</sup> EXCEL	X		X		
Becker et al., 2005 <sup>104</sup> FACT	X	X	X	X	X
Whelton et al., 2010 <sup>133</sup> Renal impairment	X				
Naoyuki et al., 2011 <sup>134</sup>		X	X		

### Major RCTs comparing effectiveness of febuxostat and allopurinol

All systematic reviews we identified that compared the efficacy of febuxostat with allopurinol included data from the FACT<sup>104</sup> and APEX<sup>105</sup> clinical trials, with later studies including CONFIRMS<sup>106</sup> and EXCEL.<sup>107</sup> The results of the systematic reviews are dominated by these studies, due to the small sample sizes of other included trials. Trials included in at least one systematic review were Singal, 2011<sup>132</sup>, Kamatani, 2011<sup>131</sup>, and Naoyuki, 2011.<sup>134</sup> One abstract that was identified was also included.<sup>133</sup> The most important trials, FACT, APEX, CONFIRMS, and EXCEL are summarized here. All of these trials used gout flare prophylaxis during the study period. FACT, APEX, and EXCEL withdrew prophylaxis after week eight. CONFIRMS prescribed prophylaxis for the entire study duration.

The FACT trial<sup>104</sup> compared 760 patients who received either febuxostat (80 or 120mg) or allopurinol (300mg) per day for 52 weeks (note that febuxostat doses above 80mg are not approved for use in the USA). No statistically significant differences in clinical outcomes were found. The overall incidence of gout attacks (flares) was similar in all groups (64 percent, 70 percent, and 64 percent, respectively) from weeks 9 to 52 (p=0.23 for febuxostat 120mg vs. allopurinol). The median reduction in tophus area was 83 percent, 66 percent, and 50 percent, respectively (p=0.08 for febuxostat 80mg vs. allopurinol, p=0.16 for febuxostat 120mg vs. allopurinol). More patients in the febuxostat 120mg group than the allopurinol group (p=0.003) or

the febuxostat 80mg group discontinued the study. Four of the 507 patients in the febuxostat groups (0.8 percent) died, compared to none in the allopurinol group ( $p=0.31$ ). The outcome of achieving a target serum urate level of  $<6.0\text{mg/dl}$  was greater for the febuxostat groups (53 percent, 62 percent, and 21 percent, respectively,  $p<0.001$  for comparing each febuxostat group to allopurinol).

The APEX trial<sup>105</sup> compared 1,072 patients over 28 weeks who received either febuxostat (80, 120, or 240mg/day), allopurinol (100mg or 300mg per day, based on renal function), or placebo. There were no differences in the proportion of subjects with gout attacks (flares) requiring treatment observed between weeks 8 and 28 between the groups. During the first 8 weeks of the study (when gout flare prophylaxis was provided), more patients in the high-dose (120 and 240mg) febuxostat groups required treatment for gout attacks (flares) (36 percent and 46 percent) compared to febuxostat 80mg (28 percent) and allopurinol (23 percent) ( $p<0.05$ ). No significant differences in number of tophi were observed between the allopurinol and febuxostat groups. Reductions in median tophus size were reported in all treatment groups, but there were no significant differences between the allopurinol, febuxostat, or placebo groups. The only difference between groups in terms of decrease in number of tophi was between the febuxostat 120mg (-1.2) and placebo (-0.3) at the end of the study ( $P<0.05$ ). Proportions of adverse events were similar across groups, except for dizziness and diarrhea, which were more frequent in the group taking febuxostat 240mg. The outcome of achieving serum urate levels  $<6.0\text{mg/dl}$  for the last three months of the study were observed in 48 percent of the febuxostat 80mg group, 65 percent of febuxostat 120mg, and 69 percent of febuxostat 240mg, which was significantly higher than the number who achieved that outcome in the allopurinol group (22 percent). In patients with impaired renal function, more patients treated with febuxostat (all doses) achieved a serum urate of  $<6.0\text{mg/dl}$  compared to allopurinol 100mg.

The CONFIRMS trial<sup>106</sup> compared 2,268 patients receiving febuxostat 40mg per day, febuxostat 80mg per day, and allopurinol 200 or 300mg per day (depending on renal function). The only clinical outcomes reported were gout flare and safety outcomes. Rates of flare requiring treatment occurred in 10 percent-15 percent of patients in all groups during the first two months and declined during the trial. There were no statistically significant differences between groups. Prior use of urate-lowering therapy was associated with lower rates of flare compared to those without prior use ( $p<0.001$ ) for each comparison. Adverse events were reported by 56 percent of subjects, but the rates of occurrence did not differ among the treatment groups, and most were mild or moderate. The outcome of serum urate level  $<6.0\text{mg/dl}$  at six months was reached in 45 percent of the febuxostat 40mg group, 67 percent of the febuxostat 80mg group, and 42 percent of the allopurinol group ( $p<0.001$  for febuxostat 80mg compared to both groups). Febuxostat 80mg was similarly superior in patients with mild to moderate renal impairment, although febuxostat 40mg was superior to allopurinol in these patients as well.

The EXCEL trial<sup>107</sup> is an open-label extension study of 1,086 patients receiving febuxostat 80 or 120mg or allopurinol 300mg for up to 40 months. Gout attacks (flares) increased after prophylaxis withdrawal in week 8, but flare rates decreased over time in all treatment groups. Gout flare was reported in  $<4$  percent of subjects after 18 months of treatment. Subjects with tophi who maintained the target serum urate level over time experienced greater reductions in the areas of index tophi, the number of tophi, and index tophi resolution. Baseline tophus resolution was achieved by 46 percent, 36 percent, and 29 percent of subjects maintained on febuxostat 80mg, febuxostat 120mg, and allopurinol, respectively. Overall adverse event rates were similar among the treatment groups. After one month of initial treatment, 81 percent and 87 percent of patients

receiving 80mg and 120mg achieved serum urate < 6.0mg/dl, as compared to 46 percent for patients receiving allopurinol. To achieve a serum urate <6.0mg/dl, more subjects originally assigned to allopurinol switched to febuxostat than the other way around.

## **RCTs not included in any systematic review**

One new RCT<sup>108</sup> comparing febuxostat and allopurinol in chronic gout was identified (see Table 17). This study randomized 512 Chinese gout patients to febuxostat 40mg, febuxostat 80mg, or allopurinol 300mg for 28 weeks, with flare prophylaxis provided through week 8. No significant changes in the number of tophi were observed at the final visit from baseline in all treatment groups. The rates of gout flares requiring treatment from weeks 9 through 28 and incidence of adverse events were similar among all groups. The endpoint of serum urate <6.0mg/dl for the last 3 months was reached in 45 percent of patients receiving 80mg of febuxostat, 27 percent of those receiving febuxostat 40mg, and 24 percent of those receiving allopurinol. Efficacy of febuxostat 80mg at reducing serum urate was higher than the other groups (p<0.001). Allopurinol and febuxostat 40mg were equally effective.

## **Evidence about subgroups:**

No studies stratified results by HLA-B5801 status. One study stratified results by presence of tophi at baseline.<sup>106</sup> Two studies<sup>104, 106</sup> stratified results by baseline serum urate. Two studies<sup>105, 106</sup> stratified results by renal function. Four studies<sup>135-138</sup> were identified that compared the effectiveness of febuxostat and allopurinol in various subpopulations of the CONFIRMS trial, including diabetics, older vs. younger patients, the elderly, and African Americans. One study performed a meta-analysis of the FACT, APEX, and CONFIRMS studies looking at comparative efficacy of allopurinol and febuxostat in women with gout.<sup>98</sup>

## **Presence of tophi at baseline**

Becker et al., 2010<sup>106</sup> stratified results for achievement of target serum urate by presence of tophus at baseline. Overall, the presence of tophi was associated with lower rates of achieving target serum urate level. Across treatment groups, patients taking febuxostat 80mg with baseline tophus were more likely to achieve target serum urate (57 percent) than patients taking febuxostat 40mg or allopurinol 200-300mg (35 percent and 32 percent). Patients without tophus at baseline achieved target serum urate levels at rates of 70 percent, 48 percent, and 45 percent, respectively.

## **Baseline serum urate**

Becker et al., 2005<sup>104</sup> stratified results for achievement of target serum urate by serum urate level at baseline. Febuxostat 80mg was more effective than allopurinol 300mg at all levels of baseline serum urate levels for achieving target serum urate (47 percent of those with baseline serum urate  $\geq 10.0$ mg/dl to 57 percent of those with baseline serum urate <9.0mg/dl versus 8 percent of those with serum urate  $\geq 10.0$ mg/dl to 40 percent with serum urate <9.0mg/dl). Becker et al., 2010<sup>106</sup> also stratified results for achievement of target serum urate by serum urate level at baseline. Patients with high baseline serum urate achieved target serum urate levels at lower rates than those with lower baseline serum urate. Febuxostat 80mg was more effective for reaching target serum urate among people with high baseline serum urate (>9.0mg/dl) (49 percent-70

percent) compared to febuxostat 40mg (26 percent-47 percent) or allopurinol 200-300mg (31 percent -40 percent).

## Renal function

Becker et al., 2010<sup>106</sup> stratified results for achievement of target serum urate by renal function at baseline. Across treatment groups, about 71 percent of patients with mild or moderate renal impairment achieved target serum urate levels while taking febuxostat 80mg, compared to 43-52 percent of patients taking febuxostat 40mg or 31-46 percent of patients taking allopurinol 200-300mg. Compared to patients with normal renal function, patients taking either febuxostat or allopurinol with mild renal impairment achieved higher rates of target serum urate. Schumacher et al., 2008<sup>105</sup> observed similar better comparative efficacy with febuxostat 80mg compared to allopurinol but this was based on a small number of observations.

Gibson 1981<sup>139</sup> randomized 59 patients to receive either 0.5mg colchicine (twice daily) or allopurinol (200mg) and colchicine. Patients were followed for up to two years. The mean glomerular filtration rate was statistically significantly lower in the colchicine group and declined over the study period as compared to the allopurinol group in which it slightly increased. Urate clearance fell both groups but the decline trend was significant only in the allopurinol group. The study monitored renal function, including: blood urea concentration, blood creatinine, glomerular filtration rate, urine concentrating ability, and number of patients with proteinuria and quantity of proteinuria. For a subgroup of patients receiving colchicine who had achieved glomerular filtration rate reduction of more than 10ml/min/(1x73 m<sup>2</sup>), the results were stratified by age and presence or absence of hypertension.

## Age

Becker et al., 2011<sup>135</sup> performed a secondary analysis of the CONFIRMS trial that compared efficacy of febuxostat and allopurinol in the elderly (>65 years) with younger patients (<65 years). Among 374 older subjects, both drugs were comparably efficacious to younger patients and were well tolerated in spite of high comorbidity rates and renal impairment in this group. Among patients with mild renal impairment and within each treatment, urate-lowering efficacy was higher in patients aged 65 and older than in younger patients. Among patients with moderate renal impairment, older patients were more likely to achieve target serum urate than younger patients within 40 and 80mg febuxostat groups but not within allopurinol treatment group.

Jackson et al., 2012<sup>137</sup> was another secondary analysis of the CONFIRMS data looking at efficacy in the elderly subgroup only. Rates of AEs were low and comparable across treatments. Febuxostat 80mg was significantly more efficacious (82 percent) than febuxostat 40mg (62 percent; p < 0.001) or allopurinol (47 percent; p < 0.001) for achieving the primary efficacy endpoint of serum urate <6.0mg/dl.

## Race

Wells et al., 2012<sup>138</sup> was a secondary analysis of 228 African Americans in the CONFIRMS trial. African American patients were mostly male and obese, and were more likely to have diabetes, renal impairment, and cardiovascular disease. Rates of adverse events, gout flare, and efficacy in all treatment groups, regardless of renal function, were comparable between African American and Caucasian patients. Febuxostat 80mg was more effective than febuxostat 40mg or allopurinol 200/300mg in African American patients with mild or moderate renal impairment.

## **Gender**

Chohan et al., 2012<sup>98</sup> was a retrospective analysis of the FACT, APEX, and CONFIRMS trials comparing the efficacy of allopurinol and febuxostat in 226 women with gout. Women enrolled in these studies were older, more likely to be obese, have higher rates of renal impairment, hypertension, hyperlipidemia, and diabetes. Tophus resolution and incidence of gout flare were not reported. Adverse events rates were similar across groups. The most common adverse events were upper respiratory tract infections, musculoskeletal/connective tissue disorders, and diarrhea. The proportions of women achieving serum urate levels <6.0mg/dl was greater in all febuxostat dosage groups compared to the allopurinol group, with efficacy significantly greater in the 80mg ( $p<0.001$ ) and 120mg ( $p=0.006$ ). Efficacy results appear to hold in the case of mild renal impairment, though low-dose febuxostat (40mg) was less efficacious in female patients with moderate/severe renal impairment. However the number of patients in most of the renal function subgroups was small and the evidence should be interpreted with caution.

## **Diabetes**

Becker et al., 2013<sup>136</sup> performed a secondary analysis of the CONFIRMS trial that compared efficacy of gout drugs in 312 diabetic and 1957 non-diabetic patients. Diabetic gout patients were older, more likely to be female, and had longer gout duration. Comorbidities were more common among diabetics, including cardiovascular disease, impaired renal function, hyperlipidemia, and obesity. Febuxostat 80mg efficacy exceeded that of febuxostat 40mg or allopurinol ( $p <0.050$ ) at all levels of renal function, achieving serum urate levels in most diabetic and non-diabetic patients. Diabetics and non-diabetics reported similar adverse events.

**Table 16. Systematic reviews of febuxostat vs. allopurinol for the management of chronic gout**

Author/Year Funding	End date of search	# of included studies	# of included patients/ participant characteristics	Setting	Doses	Outcomes	Results	AMSTAR
Manara, 2013 <sup>100</sup> No external funding	March 2012	NR (~8?)	NR	NR	FEB: 40, 80, 120, 240mg/d ay, ALL: 100, 200, 300mg/d ay	Achievement of sUA <6.0, gout attacks, AEs	Febuxostat is an effective urate lowering agent in patients with gout and has shown greater efficacy at a dosage of 80mg or more when compared to allopurinol at the maximum dose of 300mg in the short-term control of hyperuricaemia. Treatment with febuxostat has been shown to be safer in patients with mild or moderate renal insufficiency when compared to treatment with allopurinol.	2/11
Tayar, 2012 <sup>14</sup> No external funding	July 2011	4	3,978 patients at least 16 years old meeting ACR for acute arthritis of primary gout, or diagnosis as described by the authors	Multiple primary care centers, US and Canada	FEB: 40, 60, 80, 120, 240mg/d ay ALL: 100, 200, 300mg/d ay	Gout flare, proportion of patients with sUA <6.0mg/dl AEs, tophus burden,	FEB 40mg vs ALL: groups did not differ by gout flare incidence, achievement of sUA <6mg/dl, or AEs. FEB 80mg vs ALL: groups did not differ by gout flare incidence, but febuxostat patients more likely to achieve sUA <6mg/dl, but reduction of sUA from baseline was not statistically significant. Allopurinol group had more AEs. FEB 120/240mg vs ALL: febuxostat group had more gout flares, but also more likely to achieve sUA <6mg/dl, and there was a statistically significant reduction of sUA from baseline. AEs higher in allopurinol compared with febuxostat 120mg, but AEs were higher than allopurinol at 240mg. All doses: Tophus area reduction was greater in the febuxostat groups, but the proportion of patients with a reduction and the median reduction on the number of tophi were similar. There was no statistically significant difference in harms at 3 years.	11/11

Author/Year Funding	End date of search	# of included studies	# of included patients/ participant characteristics	Setting	Doses	Outcomes	Results	AMSTAR
Faruque, 2013 <sup>99</sup> Alberta Heritage Foundation for Medical Research and University Hospital Foundation	Feb 2012	5	4,250 patients of all ages with chronic gout (MSU crystals or 6/12 ACR)	Multiple	FEB: 40, 60, 80, 120, 240mg/day ALL: 100, 200, 300mg/day	Proportion of gout flares, proportion achieving target serum urate (<6mg/dl), patient and physician global assessment, tophus resolution, AEs	Patients were more likely to have a gout flare on febuxostat compared to allopurinol, but this difference depends on the dose (high-dose febuxostat produced a high risk of flare while low dose <=80mg/day was similar to allopurinol in flare frequency). Febuxostat recipients had a lower risk of adverse events compared to those on allopurinol. Patients on febuxostat were more likely to reach target serum urate levels. Tophus changes were not significantly different.	10/11
Ye, 2013 <sup>95</sup> National Natural Science Foundation of China	Feb 2012	7 RCTs (10 total studies, 7 for ALL vs. FEB)	5,690 Adults >=18 years with hyperuricemia (SUA >=7mg/dl) with and without gout	NR	ALL: 100-300mg/day FEB: 40-240mg/day	Achievement of target serum urate (<6mg/dl), AEs	SUA target reached in more people in febuxostat group. No difference in AE outcomes Compared with the allopurinol group, the proportion of patients who achieved a target sUA level <=6.0mg/dL at the final visit was higher in the febuxostat-treated group. There were no significant differences in AEs between the two groups.	10/11
Seth, 2014 <sup>94</sup> No external funding	Jan 2014	4 comparing allopurinol with febuxostat	4203 adults with chronic gout	NR	FEB: 40, 80, 120, 240mg/day, ALL: 100, 200, 300mg/day	AEs, SAEs, gout attacks, achievement of target sUA <6mg/dl, tophus resolution	Similar rates of AEs, SEAs, and gout attacks were found when allopurinol was compared to febuxostat (80mg/day). Gout attacks were higher in febuxostat at higher doses (>80 mg/day) than allopurinol. Allopurinol was less successful than febuxostat at achieving sUA < 6mg/dl. Tophus resolution was also similar for allopurinol (200-300mg/day) and febuxostat (80 mg/day).	10/10

**Table 17. Randomized controlled trials of febuxostat vs. allopurinol or colchicine vs. allopurinol for the management of chronic gout not included in existing systematic reviews**

Author/Year	Population, Sample size	Intervention	Outcomes	Timing	Results	Cochrane ROB
Huang 2014 <sup>108</sup> Febuxostat vs. allopurinol	516 patients (18-70 years) with gout (ACR criteria) and sUA $\geq 8.0$ mg/dl Chronic 14 sites in China (care setting NR)	Febuxostat 40mg/day Febuxostat 80mg/day Allopurinol 300mg/day	sUA <6.0mg/dl at 20, 24, and 28 weeks Reduction of sUA from baseline Tophi resolution Gout flares requiring treatment AEs	2, 6, 10, 14, 16, 20, 24, and 28 weeks	27.33%, 44.77%, and 23.84% of patients in the febuxostat 40mg, 80mg, and allopurinol groups reached target sUA, respectively. Febuxostat 80mg also achieved higher reductions in sUA from baseline. Groups did not differ on tophus resolution, gout flare, or AEs.	1. Sequence: Low 2. Allocation concealment: Low 3a. Blinding participants: Low 3b. Blinding care providers: Low 3c. Blinding outcome assessors: Low 4a. Follow-up less than 20%: Low 4b. Loss to follow-up missing data explained: Low 4c. All participants randomized 5. Outcome reporting: Unclear 6. Findings reported as % who responded: Yes
Gibson 1982 <sup>139</sup> Colchicine vs. allopurinol	N=59, with at least one acute gouty arthritis attack.	Colchicine (0.5mg/day x 2) vs. Colchicine + Allopurinol (200mg/day)	glomerular filtration rate, blood urea, blood creatinine, renal calculi, urine concentrating ability, urine pH, plasma uric acid	1 year, 2 year	Greater decline of mean GFR in colchicine group; Greater decline of plasma uric acid in allopurinol group; Greater decline and sharper trend decline for urate clearance in allopurinol group	1. Sequence: Low 2. Allocation concealment: High 3a. Blinding participants: High 3b. Blinding care providers: High 3c. Blinding outcome assessors: High 4a. Follow-up less than 20%: Low 4b. Loss to follow-up missing data explained: Low 4c. Only those who completed the treatment program 5. Outcome

						reporting: Low 6. Findings reported as % who responded: Unclear
--	--	--	--	--	--	--

## **Allopurinol vs. Probenecid**

We identified one systematic review covering the comparative efficacy of probenecid and allopurinol was identified.<sup>125</sup> Only one study<sup>126</sup> comparing probenecid and allopurinol was included in that review. In terms of clinical outcomes, the study groups did not differ in terms of reduction of frequency of gout attacks or tophus resolution (though only a small number of patients presented with tophi), though both groups improved on these measures from baseline. The allopurinol group experienced a mean reduction in serum urate from 9.3mg/dl to 4.7mg/dl by the last measurement, while the probenecid group was reduced from 8.5mg/dl to 5.2mg/dl at the final measurement, though whether this effect is statistically significant was not stated. The groups did not appear to differ significantly in terms of adverse event frequency, though the nature of these events were different among the groups. All adverse events were deemed to be minor. No data on subgroups were presented (see Tables 18 and 19).

**Table 18. Systematic reviews of allopurinol vs. probenecid for the management of chronic gout**

Author/Year Funding	End date of search	# of included studies	# of included patients/ participant characteristics	Setting	Doses	Outcomes	Results	AMSTAR
Kydd, 2014 <sup>125</sup>	May 2013	1 study compared probenecid with allopurinol	37 patients with chronic gout	"clinic"	Allopurinol 300mg daily, raised to 400mg or 600mg where necessary Probenecid 1 g daily, increased to 2 g after 2 weeks	Frequency of acute gout Tophi Serum urate Adverse events	Groups did not differ with respect to reductions in gout attacks, although both groups experienced a reduction. The few patients in the study that had tophi both experienced resolution. Decreases in serum urate were observed in both groups, but the decreases were greater for the patients taking allopurinol. Adverse events occurred in both groups.	9/9

**Table 19. Randomized controlled trials of pharmacologic therapies for chronic gout not included in existing systematic reviews**

<b>Author/Year</b>	<b>Population, Sample size</b>	<b>Intervention</b>	<b>Outcomes</b>	<b>Timing</b>	<b>Results</b>	<b>Cochrane ROB</b>
Scott, 1966 <sup>126</sup>	37 patients with chronic gout referred to "clinic"	Allopurinol 300mg daily, raised to 400mg or 600mg where necessary Probenecid 1 g daily, increased to 2 g after 2 weeks	Frequency of acute gout Tophi Serum urate Adverse events	2 weeks, 1 month, 2 months, 3 months, and 3 month intervals up to 24 months	Groups did not differ with respect to reductions in gout attacks, although both groups experienced a reduction. The few patients in the study that had tophi both experienced resolution. Decreased in serum urate were observed in both groups, but the decreases were greater for the patients taking allopurinol. Adverse events occurred in both groups.	1. Sequence: Low 2. Allocation concealment: High 3a. Blinding participants: High 3b. Blinding care providers: High 3c. Blinding outcome assessors: High 4a. Follow-up less than 20%: Low 4b. Loss to follow-up missing data explained: Low 4c. Only those who completed the treatment program 5. Outcome reporting: Low 6. Findings reported as % who responded: High

## Prophylaxis against acute gout attacks (flares) when starting urate lowering therapy

For nearly 50 years it has been known that the initiation of urate lowering therapy is associated with an increase in the frequency of acute gout attacks (flares).<sup>140</sup> More than 30 years ago investigators performed trials using colchicine as prophylaxis against acute attacks when starting uricosuric therapy.<sup>54, 141</sup> However, it was not until 2004 that the first randomized, placebo controlled trial of colchicine prophylaxis when initiating allopurinol therapy was published.<sup>43</sup> In this study, investigators randomized 51 patients to colchicine, 0.6mg BID or placebo when starting allopurinol at 100mg once a day and titrating upwards with a target serum urate of 6.5mg/dl. Eight patients dropped out before they received any study drug. The 43 patients who started the study drug and completed the trial were about 63 years of age, overwhelmingly male, 70 percent were white, more than 60 percent had tophi and about 10 percent had chronic renal insufficiency. Patients were followed for 6 months. Seven patients withdrew during treatment, 3 in the colchicine group and 4 in the placebo group, two in the latter group due to a high frequency of attacks (flares). The occurrence of gout attacks (flares) was recorded by patient recall at 3-month and 6-month visits. The reduction in attacks (flares) between treatment groups was dramatic: attacks (flares) occurred in 77 percent of placebo-treated patients and 33 percent of colchicine-treated patients ( $p=0.008$ ). During the first 3 months of treatment, there was on average about 2 attacks (flares) per patient in placebo-treated patients and about 0.5 flares per patient in the placebo group. From months 3 to 6, this advantage diminished somewhat, with about 1 flare per patient in the placebo group and almost zero in the colchicine group. Diarrhea was much more common in colchicine-treated patients, occurring in 43 percent of subjects, compared to about 4 percent in placebo-treated patients.

Since then, and even pre-dating publication of this trial, the use of prophylactic therapy concomitant with the initiation of urate-lowering therapy has been the standard of care according to both EULAR and ACR guidelines.<sup>15, 16, 142</sup> All 3 of the recent large urate-lowering therapy trials, FACT, APEX, and CONFIRMS, used prophylaxis with colchicine or NSAIDs.<sup>104-106</sup> Note that there have been no randomized trials assessing NSAIDs as a prophylactic therapy in this situation. In the FACT and APEX trials, prophylaxis was given for 8 weeks, and both trials showed spikes in the number of acute attacks (flares) concomitant with the discontinuation of prophylaxis (an approximate doubling of the proportion of patients reporting a flare, from 20 percent to 40 percent). CONFIRMS continued prophylaxis for the entire 6 months of the trial, and there was no spike in attacks (flares). Wortmann and colleagues collected the adverse event data from all 3 trials, and pooled data for FACT and APEX.<sup>129</sup> Note that in all 3 trials, patients were not randomized to different prophylaxis regimens, rather this was at the discretion of the treating physician. Hence, selection bias is potentially present. Overall adverse events were higher with colchicine prophylaxis than with naproxen prophylaxis (55 percent vs. 44 percent). Diarrhea was about 3 times more common with colchicine rather than naproxen prophylaxis (8.4 percent vs. 2.7 percent). In CONFIRMS, there was no statistically significant difference in overall AEs reported (about 55 percent in both colchicine and naproxen-treated patients), but gastrointestinal and abdominal pains were about 3 times more common in naproxen-treated patients (3.2 percent vs. 1.2 percent). Headache was more commonly reported in colchicine-treated patients. In all studies, upper respiratory infection was the most commonly reported AE (8 percent-9 percent in each group, no statistically significant difference). In a 2014 systematic review that included the one RCT mentioned above, plus 4 others involving prophylaxis when initiating therapies not included in the scope of this review (rilonacept and canakinumab), Latourte and colleagues concluded that

low-dose colchicine and low dose NSAIDs are the two first-line options for prophylaxis, and that choice between them depends on comorbidities and tolerance and potential interaction with other prescribed medications (AMSTAR of 3/9).<sup>127</sup> In another 2014 SR, on preventing acute gout attacks when initiating urate lowering therapy, done as part of the 3e initiative on the Diagnosis and Management of gout, Seth and colleagues identified four placebo-controlled RCTs: the one study described above,<sup>43</sup> one described below,<sup>38</sup> an one study included in an included SR,<sup>54</sup> and one study that used concomitant canakinumab, a drug not included in our scope. This review (AMSTAR of 7/9) concluded, like the other review and our assessment of the original trials, that colchicine prophylaxis for at least six months, when starting urate lowering therapy, reduces the risk of acute attacks.<sup>128</sup>

The optimal duration of prophylaxis is unknown. Discontinuation of prophylaxis at 8 weeks is associated with a spike in attacks (flares) that does not occur when prophylaxis is continued for 6 months, but it was not reported in CONFIRMS what happened when prophylaxis is discontinued at 6 months (in terms of any spike in flares).

We identified one RCT that compared different durations of colchicine prophylaxis when initiating allopurinol therapy in patients with gout.<sup>38</sup> In this study, 229 patients with gout who were beginning allopurinol therapy were randomized to receive colchicine therapy (1mg/day) for either 3-6 months, 7-9 months, or 9-12 months duration. The only clinical data presented about the patients is that they were about 47 years of age, overwhelmingly male, and had a pre-treatment mean serum urate level of 8.5 and a on-treatment serum urate level of 6.1mg/dl. The outcome measure was "any evidence of recurrence of gouty arthritis", but the criteria for this clinical event were not specified. Of the enrolled patients, 190 (82 percent) contributed data to the outcome. Loss to followup by group was not specified, but almost equal numbers of patients were included in each group at followup, so there was probably not differential loss to followup. At both 6 months and 1 year, the proportion of patients having recurrence was much higher in those randomized to 3-6 months of therapy rather than those randomized to longer durations of therapy (at 6 months, 46 percent vs. 11 percent vs 6 percent; at 1 year 54 percent vs. 27.5 percent vs 23 percent). We judged this study as being at high risk of bias, and therefore we could draw no conclusions from it.

## **Effect of dietary modification in addition to pharmacologic therapy**

The only randomized trial of dietary modification in addition to pharmacologic therapy tested specific dietary advice compared to general dietary advice.<sup>91</sup> No difference was seen in serum urate between groups. The trial is discussed in more detail in Key Question 2.

## **Strength of Evidence**

### **Urate lowering therapy and short term changes in acute gout attacks**

We judged the strength of evidence as high that urate lowering therapy does not reduce the risk of acute gout attacks, up to about six months, based on two placebo-controlled trials that each reported no difference in that outcome between groups.

### **Urate lowering therapy and longer term changes in acute gout attacks**

There are no RCTs that examine acute gout outcomes longer than six months from initiation of therapy. Nevertheless, we judged the strength of evidence as moderate that urate lowering therapy reduces the risk of acute gout attacks, based on the RCT evidence that urate lowering therapy

reduces serum urate, the primary role elevated serum urate has as a risk factor for acute gout attacks, and by the results of open-label extensions of the urate lowering therapy trials that show that there is a steadily decreasing risk for acute gout attacks and that after about 1 year of therapy it remains at a very low level (< 5 percent/year).

### **Prophylactic therapy**

While there is only a single placebo-controlled trial of prophylactic therapy when starting urate lowering therapy, we judged the strength of evidence as high that such therapy reduces the risk of acute gout attacks. We base this on the large size of the effect in the one trial that does exist (of colchicine), and the evidence from three large RCTs of urate lowering therapy.

In two of these trials, prophylaxis was given for eight weeks and discontinuation of prophylaxis was accompanied by a sudden two fold increase in the risk of acute gout attacks. In the third trial, prophylaxis was continuous throughout the six month trial, and no “spike” of increased risk occurred.

### **Duration of prophylaxis**

We judge the strength of evidence as moderate that a duration of prophylaxis longer than eight weeks is more effective than eight weeks based primarily on a comparison of acute gout attacks in the three ULT trials, above. This is also supported by one RCT at high risk of bias.

### **Addition of dietary advice**

We judged the strength of evidence as low that the addition of gout-specific dietary advice adds to the effectiveness of urate lowering therapy, based on the lack of effectiveness seen in one small RCT at high risk of bias.

## Key Question 4: Treatment Monitoring of Patients with Gout

a. In adults with gout, does monitoring serum urate levels with pharmacologic treatment and/or dietary and/or lifestyle change measures (e.g., compliance) improve treatment outcomes?

b. Is achieving lower subsequent serum urate levels (less than 5 vs. 5–7mg/dL) associated with decreased risk for recurrent acute gout attack, progression to chronic arthritis or disability, resolution of tophi, or other clinical outcomes (including risk for comorbidities or progression of comorbidities) or patient-reported outcomes?

### Key Points

- Insufficient evidence supports or refutes that monitoring serum urate improves outcomes.
- A low strength of evidence supports the finding that treating to a specific target serum urate level reduces the risk of gout attacks.

### Description of included studies

For KQ4a, we include one SR<sup>143</sup> from which 16 original studies were referenced mined.<sup>144-159</sup>  
For KQ4b, we identified eight studies that addressed the question.<sup>10, 160-166</sup>

### Detailed Synthesis

a. In adults with gout, does monitoring serum urate levels with pharmacologic treatment and/or dietary and/or lifestyle change measures (e.g., compliance) improve treatment outcomes?

Our literature search identified one systematic review of studies assessing factors associated with medication adherence in gout (AMSTAR rating of 5 out of 9).<sup>143</sup> This study searched multiple databases through July 2013 and supplemented this with hand searches and Google scholar. Inclusion criteria were a patient population with gout, measurement and/or reporting of medication adherence, and publication in one of 3 languages. Data from randomized controlled trials were excluded as not being representative of real-world patient settings. From 1,398 titles, the authors identified 16 studies. We retrieved these and reviewed them to see if monitoring serum urate levels was tested for associations with compliance. Eleven studies did not test for the effect of serum urate on compliance.<sup>146-148, 150, 152, 153, 155, 157-159, 167</sup> Four studies did assess serum acid, but analyzed whether measures of compliance were associated with subsequent serum urate levels.<sup>144, 149, 154, 168</sup> One study tested the effect of serum “uric acid measurements” on compliance.<sup>156</sup> This analysis included 9,823 Medicare patients who had a pharmacy benefit via the Pennsylvania Pharmacy Assistance Contract for the Elderly. The measure of compliance was the Percentage of Days Covered, which the authors claimed is nearly identical to the more commonly used Medication Possession Ratio. A value of 80 percent was used as the threshold between compliance and non-compliance. A number of factors were considered as possible predictors of noncompliance, including socio-demographic variables, and “gout specific factors”. The latter included uric acid measurements. This factor was not a statistically significant predictor of

compliance. Contact with the first author of this paper confirmed this: “We found no evidence that performing tests was associated with adherence” (DH Solomon, personal communication, Jan 30th, 2015).

We performed an update search, using the authors search strategy, from May 2013 to January 2015. We identified an additional 115 titles. Applying the same inclusion/exclusion criteria yielded no new studies assessing the effect of serum urate measurement on compliance or outcomes.

We identified no studies that assessed whether monitoring serum urate levels for gout patients on treatment influences outcomes.

## Summary

We found no evidence to support or refute the hypothesis that monitoring gout patients on treatment with serum urate measurements leads to improved compliance or improved outcomes.

b. Is achieving lower subsequent serum urate levels (less than 5 vs. 5-7mg/dl) associated with decreased risk for recurrent gout attack, progression to chronic arthritis or disability, resolution of tophi, or other clinical outcomes (including risk for comorbidities or progression of comorbidities) or patient reported outcomes?

There is a large body of evidence supporting the hypothesis that lower serum urate levels are causally associated with a lower rate of acute gout attacks (flares). Underlying this hypothesis is the basic chemistry of uric acid, which is that it is soluble up to a concentration of about 6.8mg/dl, and above which it may start to precipitate. However, this threshold is not absolute, as patients with serum urate levels above this threshold may still be asymptomatic while gout patients with serum urate levels below this threshold still may have acute attacks (flares).

Probably the best data about the relationship between serum urate levels and risk of acute attack come from analyses of the large trials of urate-lowering therapy, FACT and APEX. In a post-hoc analysis combining data from both of these trials, that included between them more than 1800 subjects with gout and a baseline serum urate level of 8.0mg/dl or greater, the serum urate level achieved was one of three variables (along with the baseline presence of tophi and the percent change in serum urate level from baseline) that in multivariate logistic regression was associated with acute gout attacks (flares) requiring treatment (adjusted odd ratio of 1.42 (95% CI 1.16, 1.73) and adjusted odds ratio of 2.70 (95% CI 1.72, 4.22), at either 6 months or 12 months after initiation of therapy).<sup>162</sup> When the serum urate level achieved was dichotomized at 6.0mg/dl, at the end of one year those patients, regardless of treatment group, that had achieved a value below 6.0mg/dl had acute gout attacks (flares) at about a 5 percent rate, whereas this was between 10 percent-15 percent for patients with serum urate levels at or above 6.0mg/dl (p value reported as less than 0.05).

Supporting this result are many retrospective cohort studies. Not all of these studies restricted the eligible patients to those with gout on urate-lowering therapy, but we nevertheless deemed their results relevant for this study question. For example, among 2237 patients aged 65 and older in the Integrated Healthcare Information Services claims database between 1999 and 2005, there were 633 patients with gout and a serum urate level than 6mg/dl, 1,173 persons with a serum urate level of between 6.0 and 8.99mg/dl, and 431 patients with a serum urate level of 9.0mg/dl or greater. The proportion of patients with at least one gout flare over a 12 month period, as defined

by a visit for gout and receiving a prescription for typical acute gout pharmacologic therapy, was 27 percent, 43 percent, and 46 percent, respectively.<sup>160</sup> In another study, patient-level data were collected from 125 rheumatologists and 124 primary care providers in the US. Data on 1,245 patients with gout were analyzed. Serum urate level was positively correlated with the occurrence of a gout flare over 12 months ( $r=0.29$ ,  $p$  value reported as less than 0.01)<sup>166</sup> In another study of similar design, patient-level data were collected from 50 US practices on recent patients with gout seen in 2010-2011. Of 479 patients assessed, in bivariate analyses serum urate level was associated with a flare-related visit ( $p=0.004$ ).<sup>165</sup> Two other administrative claims analysis studies, one including 18,243 patients and the other including 5,942 patients, both of which used algorithms involving claims and pharmacologic prescriptions to identify gout patients, reported that patients with a serum urate level of greater than 6.0 had 1.3 times the odds of an acute gout flare<sup>161</sup> or a 1.59 relative risk.<sup>163</sup>

Fewer studies have related serum urate levels to comorbidities. One study of US Veterans with gout used the VA data warehouse follow 2116 patients with gout for a mean followup of 6.5 years. Comparing patients with high versus low serum urate levels, the investigators reported about a 2 fold difference in new diagnoses of kidney disease (2 percent vs 4 percent at year 1, 5 percent vs 9 percent at year 3).<sup>10</sup> This study had a limited ability to control for confounding, however.

Lastly, an abstract presented by investigators at Mayo concerning gout in Rochester, Minnesota, followed 46 patients with incident gout for a mean of 12.9 years. The mean serum urate level was 8.1mg/dl. A higher serum urate was predictive of a subsequent acute gout flare (odds ratio = 1.69, 95% CI 1.26, 2.27). Interestingly, though, only 61 percent of these patients had a flare during this extended followup, meaning 39 percent of patients had only the 1 incident episode (72 percent of which were podagra).<sup>164</sup>

Limiting the evidence base for using a serum urate value as a target value for treatment, as for example blood pressure and hemoglobin A1c are used in the management of hypertension and diabetes, is the lack of any experimental study basing treatment decisions on a target. Treating to a target necessarily means using increased doses of medication, which increases the risk of side effects, and therefore changes the benefit: risk assessment.

## **Strength of Evidence**

### **Monitoring serum urate levels**

There were no studies assessing the effect of monitoring serum urate levels, and hence we judged this as insufficient. An argument can be made that without monitoring, treatment cannot be adjusted.

### **Treating to Target**

We judged the strength of evidence as low that treating to a specific serum urate level reduces the risk of acute gout attacks. While elevated serum urate is the primary risk factor for acute gout attacks, and lowering serum urate levels can be expected to reduce the risk of acute gout attacks, it is the concept of a specific target value, such as 6.0mg/dl, that has not been tested. Different targets have been proposed (7.0mg/dl, 6.0mg/dl, 5.0mg/dl, etc) and trying to lower serum urate levels to a target in patients who may be asymptomatic (in that they have not had a recent acute gout attack) at higher-than-target levels will necessitate increasing use of medication. The value of that strategy has yet to be proven, and there are examples from other asymptomatic conditions

where treating to target resulted in more side effects than benefit. Thus, despite the strong biologic appeal of such a strategy, we judged the strength of evidence as low.

## Key Question 5: Discontinuation of Pharmaceutical Management for Patients on Acute or Chronic Gout Medications

In adults with gout, are there criteria that can identify patients who are good candidates for discontinuing

- a. urate lowering therapy?
- b. anti-inflammatory prophylaxis against acute gout attack for patients on urate lowering therapy after an acute gout attack?

### Key Points

- There is low strength of evidence that discontinuing urate lowering therapy in gout patients who completed five years of ULT therapy that kept serum urate levels < 7mg/dl, and in whom subsequent annual serum urate levels (off of ULT) stayed < 7mg/dl, did not result in an increased risk of acute gout attacks.
- Evidence is moderate that prophylaxis for acute gout when initiating urate lowering therapy with low dose colchicine or NSAIDs results in fewer gout attacks when treatment is given for longer than 8 weeks.

### Description of included studies

We identified two observational (prospective cohorts) studies that assessed two clinical course of patients in whom urate lowering therapy was discontinued.<sup>169, 170</sup>

The data about duration of anti-inflammatory prophylaxis when initiating urate lowering therapy comes from the results of the FACT, APEX, and CONFIRMS trials, previously discussed in detail.

### Detailed Synthesis

#### Discontinuation of urate lowering therapy

We identified two prospective observational cohorts of patients in whom urate lowering therapy was discontinued and patients were followed for an extended period of time.<sup>169, 170</sup>

More than 30 years ago, Loebl and Scott followed 33 patients with gout on allopurinol. All but one patient was male, the mean age was 58, and none of the patients were overproducers of uric acid as assessed by 24 hour urinary uric acid analysis. The mean serum urate level before treatment was 8.4mg/dl and this decreased to 5.5mg/dl while on therapy. Patients were on therapy for a mean of 93 weeks before discontinuation. They were followed for a mean of 86 weeks off therapy. In all patients, serum urate levels rose quickly following discontinuation of therapy. However, only 12 patients (36 percent) experienced a recurrence, the other 21 patients remained asymptomatic. Twenty of these continued off allopurinol at mean of 107 weeks. Five additional

patients had a “mild” recurrence, and 15 remained asymptomatic. The main difference between symptomatic and asymptomatic patients was the serum urate level on therapy: which was 6.2mg/dl in the former and 5.1mg/dl in the latter (statistical testing was not performed).<sup>170</sup>

In the second study, Perez-Ruiz and colleagues<sup>169</sup> assembled a cohort of 211 patients with gout who met the following criteria:

- An average serum urate level of <7mg/dl for “the entire duration of therapy” in urate lowering therapy.
- Compliance with urate lowering therapy for 5-years, or 5 years after resolution of any tophi. Compliance was defined as  $\geq 80$  percent of all serum urate levels while in therapy being <6mg/dl.

Patients were overwhelming male, and about 65 years of age. About 25 percent had subcutaneous tophi at baseline. Mean pre-treatment serum urate levels were 8.0mg/dl, the mean duration of urate lowering therapy was 66 months, the mean serum urate level on therapy was 4.9mg/dl, and the mean serum urate level following discontinuation of therapy was 8.5mg/dl. The mean followup time was 33 months. Among the 27 patients who maintained a serum urate level less than 7mg/dl off therapy, none had a clinical recurrence. Of the remainder, clinical recurrences were highly correlated with off-treatment serum urate level: 13 percent of 61 patients with a value of 7.0-8.2mg/dl, 51 percent of 61 patients with a value of 8.2-9.3mg/dl, and 61 percent of 62 patients with a serum urate level about 9.3mg/dl. The authors speculate that a period of “crystal depletion” with a target serum urate level “far below” 6mg/dl, of 5 years durations, could be followed by more relaxed, or even no therapy, designed to keep serum urate levels less than 7mg/dl.

## **Discontinuation of prophylaxis**

In FACT and APEX, anti-inflammatory prophylaxis was discontinued after 8 weeks and in both studies there was a spike of increased acute gout flare immediately thereafter (about double the rate). In CONFIRMS, anti-inflammatory prophylaxis was continued for 6 months, to the conclusion of the trial, and no spike occurred at 8 weeks.

One older 1989 trial of intermittent urate lowering therapy concluded it was less effective than continuous therapy. This study did not use true random assignment and therefore did not meet our eligibility criteria; nevertheless we include discussion as it is the only trial of its type. This study assigned 50 patients by the even/odd hospital number to either continuous allopurinol (titrated to a dose of about 300mg/day) or 8 weeks cycles on and off allopurinol. In the first two years of therapy, there was no statistically significant difference between groups in the number of acute gout attack, but in subsequent years (up to 4) attacks were more common. In the intermittent treatment group (10 attacks) than the continuous treatment group (0 attacks).<sup>171</sup>

## **Strength of Evidence**

### **When to discontinue ULT**

We judged the strength of evidence as low that patients who were asymptomatic for five years with a serum uric acid of <7mg/dl could have their ULT discontinued. Although this was the finding in a cohort of 200+ patients with gout, it has been demonstrated in just the one cohort. This strategy will need testing in an RCT. Selection bias is always a concern in observational studies of treatment strategies.

## **Prophylactic discontinuation**

We judged the strength of evidence as moderate that duration of prophylaxis longer than eight weeks have better outcomes than eight week durations, based on the cross-study comparison of risk of acute gout in three urate lowering therapy trials, described above.

# Discussion

## Key Findings and Strength of Evidence

We found a large number of research studies about gout, yet only a relatively modest number of these provided evidence for some of our key questions, particularly for the treatment of acute gout: only a single placebo-controlled trial of NSAIDs for acute gout pain, two placebo controlled RCTs of colchicine, and none at all for corticosteroids or ACTH. Nevertheless, we reached strong conclusions about the usefulness of these drugs. This was due to some specific features of gout: symptoms are due to an inflammatory reaction to the deposition of uric acid crystals, which occurs when serum rate rises above its saturation point in the blood. Hence, medications aimed at blocking the inflammatory response were tried as treatments, in an era that pre-dated the widespread practice of placebo-controlled trial testing of therapies. Steroids are one of the most powerful and effective anti-inflammatory medications available. While there are no placebo-controlled RCTs of its use in acute gout, steroids have proven efficacy in other inflammatory conditions, and this gives us confidence that it is effective in treating the inflammatory reaction in acute gout. At this point, a placebo-controlled trial of steroids in acute gout may well be unethical, as it means withholding from the placebo-treated group therapies known to be effective (e.g., colchicine). Indeed, a recent, high profile study of the use of steroids in acute gout compared its use not to placebo, but to NSAIDs. Since NSAIDs also have no conclusive placebo-controlled trial evidence of their effectiveness in acute gout, could it be that this RCT, which found only minor differences in outcomes between the two treatments, actually was comparing two treatments that were equally ineffective? We think not. We believe that both drugs are effective in treating acute gout, and therefore judged the strength of evidence as high that their use relieves symptoms by a clinically important amount - despite the lack of placebo-controlled RCT evidence.

The key findings and strength of evidence are in Table 20.

## Findings in Relationship to What is Already Known

In general, our findings support the results of existing systematic reviews. We did find a number of RCTs not included in prior reviews. Some of these studies were “first-of-their-kind,” such as those testing a specific dietary therapy and the duration of colchicine prophylaxis. However, most new studies either confirmed prior knowledge, or, in the case of studies of novel treatments, were not sufficiently high quality for us to draw conclusions.

## Applicability

Of the 156 studies assessed in detail (not counting SRs), 108 studies failed to state or did not clearly state the types of settings from which the patients were recruited. Only nine studies explicitly stated that patients came only from, or the study included patients from, primary care sites (including the ED and urgent care settings). In the major trials of pharmaceuticals, 10 percent to 25 percent of patients had tophi present at baseline; tophi are rarely seen in primary care settings. Patients enrolled in clinical trials usually have fewer comorbidities than those seen in practice since clinical trials have exclusion criteria. Thus, patients enrolled in most of the trials were probably more advanced on average with respect to their gout, and better on average with respect to their other health conditions, than patients typically seen in primary care settings. We thus judged this evidence of moderate applicability to primary care.

## **Implications for Clinical and Policy Decisionmaking**

The implications of this review for clinical decision-making follow from the identification of which interventions for gout management have evidence of an effect on clinical outcomes, either directly or through a strong indirect evidence chain. Thus, the results in Table 20 will be useful in policy decision-making and in the development of practice guidelines.

## **Limitations of the Comparative Effectiveness Review Process**

For many of the key questions of interest, data were not reported on the subgroups or outcomes of interest, limiting the comparative effectiveness review. For the portion of the review on traditional Chinese medicine, the variability in tested interventions made comparisons across studies not justified.

## **Limitations of the Evidence Base**

The lack of studies of patients in primary care settings is a limitation, as is the lack of studies assessing clinical outcomes for urate lowering therapy (such as recurrent acute gout flare after one year) and intervention studies of dietary therapies for management of chronic gout. Longer term studies will be needed to assess to what degree ULT reduces acute gout attacks relative to the adverse events of long term use of the available medications.

## **Research Gaps**

The concept of “treat-to-target” (TTT) in gout, while supported by indirect evidence, has been untested. Guidelines and recommendations about TTT thresholds already vary, e.g., < 6mg/dL for all gout patients vs. < 5mg/dL for patients with significant gout morbidity. However, for many gout patients in primary care practice whose gout is well controlled on urate lowering therapy, no data support such targets. In fact, some data suggest that once gout has been quiescent for 5 years, urate lowering therapy might be discontinued (as long as serum urate levels remain acceptable, e.g., < 7mg/dL).<sup>169</sup> Therefore, the most important research gap is a randomized clinical trial comparing different TTT levels in patients with gout and elevated serum urate.

Treatment decisions are likely to be preference-sensitive, and studies are needed to assess patient preferences for different outcomes (to what degree do patient preferences differ for outcomes such as a decrease in risk from 2 percent to 0.5 percent for an acute gout attack in the coming year vs. a 5 percent chance of a skin rash and a <1 percent chance of a very serious skin rash).

Likewise, few studies have assessed the effect of specific dietary advice. Some dietary advice, such as generic advice to lose weight in overweight and obese patients, has evidence of benefit for other conditions and can be advocated in gout patients without additional data (e.g., it is always indicated to recommend dietary weight loss in patients who are obese). But primary care providers could more confidently recommend gout-specific dietary advice if compelling evidence supported an effect of such dietary changes on the risk for gout attacks or other gout-related outcomes. Therefore, another important research gap is evidence from randomized clinical trials for specific dietary changes (such as reducing or eliminating sugar-sweetened beverages or fructose) compared to standard healthy diet advice and weight loss in reducing the risk of gout attacks.

## Conclusions

Several drugs show moderate-to-high evidence of benefit in terms of reducing pain in patients with acute gout. It is clear that urate lowering therapy achieves its goal of lowering urate levels. Decreased serum urate should lead, over time, to a reduction in gout attacks, but that has yet to be demonstrated in a RCT, as outlined above. One of the main risks of initiating urate lowering therapy is that it is, itself, a risk factor for gout flare (attack). Patient preferences are likely to be important in decision-making (as specified above), and having better estimates of the size of the benefit of urate lowering therapy will make clinicians and patients more knowledgeable about the risk: benefit trade-off for the different decisions.

**Table 20. Summary of prior knowledge, findings from the systematic review, and strength of evidence, by key question**

Key Question	Prior Knowledge Used in Determining Strength of Evidence	Sources of Evidence Included in This Systematic Review	Strength of Evidence
<b>KQ1 Acute Gout Treatment</b>			
Colchicine reduces pain	N/A	<ul style="list-style-type: none"> <li>2 placebo-controlled RCTs (N=45 and N=184) both with low risk of bias</li> </ul>	High
Low-dose colchicine is as effective as higher dose for reducing pain, with fewer side effects	N/A	<ul style="list-style-type: none"> <li>1 head-to-head RCT with low risk of bias (N=184)</li> </ul>	Moderate
NSAIDs reduce gout pain	<ul style="list-style-type: none"> <li>Biologic rationale (anti-inflammatory action)</li> <li>Placebo-controlled RCT evidence that NSAIDs provide temporary pain relief for numerous conditions</li> </ul>	<ul style="list-style-type: none"> <li>1 placebo-controlled RCT with high risk of bias (N=30)</li> <li>High strength observational data (NSAID use as prophylaxis against gout flare) (see below under KQ3)</li> </ul>	High
No difference between NSAIDs in effectiveness	<ul style="list-style-type: none"> <li>Equivalence in effectiveness among NSAIDs in numerous other conditions</li> </ul>	<ul style="list-style-type: none"> <li>16 head-to-head RCTs</li> </ul>	Moderate
Systemic corticosteroids reduce pain	<ul style="list-style-type: none"> <li>Biologic rationale (anti-inflammatory action)</li> </ul>	<ul style="list-style-type: none"> <li>No placebo-controlled RCTs</li> <li>Equivalence to NSAIDs in 4 RCTs (N=27, N=90, N=120, and N=60). Three of four RCTs had low risk of bias.</li> </ul>	High
Animal-derived ACTH formulation reduces pain	<ul style="list-style-type: none"> <li>Biologic rationale (anti-inflammatory action)</li> </ul>	<ul style="list-style-type: none"> <li>No placebo-controlled RCTs</li> <li>Equivalence to NSAIDs and intramuscular steroids in RCTs (one RCT of each, N=76 and N=31 both at high risk of bias)</li> </ul>	High
Differences stratified by patient demographic, comorbid conditions, disease severity, clinical presentation, or laboratory values	N/A	None of the included RCTs presented data stratified by these variables.	Insufficient
<b>KQ2 Diet and lifestyle management</b>			

Key Question	Prior Knowledge Used in Determining Strength of Evidence	Sources of Evidence Included in This Systematic Review	Strength of Evidence
Specific dietary therapies (related to certain risk factors, e.g., red meat, fructose, alcohol) may affect symptomatic outcomes	N/A	<ul style="list-style-type: none"> <li>1 RCT with high risk of bias (N=67)</li> </ul>	Insufficient
Supplemental vitamin C reduces serum urate levels by less than 0.5mg/dl	N/A	<ul style="list-style-type: none"> <li>1 systematic review (including 13 RCTs)</li> </ul>	Low
Gout-specific dietary advice (counseling about reducing red meat; avoiding offal, shellfish, and yeast-rich foods and beverages or increasing low-fat dairy products, vegetables, and cherries) is no more effective than nonspecific dietary advice (counseling about the importance of weight loss and reduced alcohol intake) at reducing serum urate levels	N/A	<ul style="list-style-type: none"> <li>1 RCT with high risk of bias (N=30)</li> </ul>	Low
Effectiveness of Traditional Chinese Medicine (TCM) (acupuncture, herbal mixtures, moxibustion) on symptomatic outcomes	N/A	<ul style="list-style-type: none"> <li>86 RCTs, all of idiosyncratic therapies, with conflicting results</li> </ul>	Insufficient
<b>KQ3 Management of hyperuricemia</b>			
Urate-lowering therapy does not reduce the risk of acute gout attacks within the first 6 months	N/A	<ul style="list-style-type: none"> <li>2 placebo-controlled RCTs, with low risk of bias (N=1,072 and N=57)</li> </ul>	High
Urate-lowering therapy reduces the risk of acute gout attacks after 1-year	<ul style="list-style-type: none"> <li>Acute gout attacks are caused by elevated serum urate concentrations</li> </ul>	<ul style="list-style-type: none"> <li>No placebo-controlled RCTs assess long-term risk of acute gout attacks</li> <li>RCTs with low risk of bias show that ULT reduces serum uric acid</li> <li>Open label extension study of ULT RCT shows reduced risk of acute gout attacks over time, plateauing at less than 5% at about 1 year</li> </ul>	Moderate
Urate-lowering therapy reduces serum urate	N/A	<ul style="list-style-type: none"> <li>4 placebo-controlled RCTs all with low risk of bias (N=1,072, N=96, N=153, and N=57)</li> </ul>	High
Forty mg febuxostat and 300mg allopurinol show no differences in serum urate lowering	N/A	<ul style="list-style-type: none"> <li>1 head-to-head RCT with low risk of bias (N=762)</li> </ul>	High
Effectiveness and comparative effectiveness of allopurinol and febuxostat at reducing tophi	N/A	<ul style="list-style-type: none"> <li>Subgroup analyses of included trials did not report consistent results when stratified on the presence of tophi.</li> </ul>	Insufficient
Age and race (Caucasian vs. African-American) do not affect the efficacy of febuxostat or allopurinol.	N/A	<ul style="list-style-type: none"> <li>Subgroup analyses of 1 head-to-head RCT with low risk of bias (N=2,269)</li> </ul>	Low
Prophylactic therapy with low-dose colchicine or low-dose NSAIDs when beginning urate-lowering therapy reduces the risk of acute gout attacks	N/A	<ul style="list-style-type: none"> <li>1 placebo-controlled RCT of colchicine with low risk of bias (N=43)</li> <li>Strong observational evidence across 3 RCTs with low risk of bias that included different</li> </ul>	High

Key Question	Prior Knowledge Used in Determining Strength of Evidence	Sources of Evidence Included in This Systematic Review	Strength of Evidence
		durations of prophylaxis (N=762, N=2,269, and N=1,072)	
Longer durations of prophylaxis with colchicine or NSAIDs (> 8 weeks) are more effective than shorter duration when initiating urate-lowering therapy	N/A	<ul style="list-style-type: none"> <li>Indirect evidence from comparisons across 3 RCTs of differing durations of prophylaxis</li> <li>1 RCT with high risk of bias (N=190)</li> </ul>	Moderate
Specific gout-dietary advice to reduce red meat, shellfish, etc. while increasing low-fat dairy products, vegetables, and cherries does not add to the effectiveness of urate-lowering therapy for reducing serum urate	N/A	<ul style="list-style-type: none"> <li>1 RCT with high risk of bias (N=30)</li> </ul>	Low
<b>KQ4 Treatment Monitoring</b>			
Serum urate monitoring improves outcomes	N/A	<ul style="list-style-type: none"> <li>No direct evidence</li> <li>An argument can be made indirectly, based on the evidence that elevated serum urate levels cause gout</li> </ul>	Insufficient
Treating to a specific target serum urate level reduces the risk of gout attacks	<ul style="list-style-type: none"> <li>Lower serum urate levels are associated with reduced risk of gout attacks</li> </ul>	<ul style="list-style-type: none"> <li>No RCT evidence</li> <li>Variable targets proposed or assessed in the literature</li> </ul>	Low
<b>KQ5 Criteria for discontinuation of pharmaceutical management</b>			
Hyperuricemia Urate-lowering therapy may be discontinued in gout patients with 5 years of urate-lowering therapy keeping serum urate levels <7mg/dl, with subsequent annual off-urate lowering therapy-serum urate levels <7mg/dl	N/A	<ul style="list-style-type: none"> <li>2 prospective cohort studies (N=211 and N=33)</li> </ul>	Low
Prophylaxis Prophylaxis for acute gout when initiating urate-lowering therapy with low-dose colchicine or NSAIDs should be longer than 8 weeks	N/A	<ul style="list-style-type: none"> <li>Indirect evidence from comparisons across 3 RCTs with low risk of bias of differing durations of prophylaxis (N=762, N=2,269, and N=1,072)</li> </ul>	Moderate

FDA = Food and Drug Administration; N/A = not applicable; NSAID = nonsteroidal anti-inflammatory drug; RCT = randomized controlled trial; ULT = urate-lowering therapy

## References

1. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. *Arthritis Rheum.* 2011 Oct;63(10):3136-41. PMID: 21800283.
2. Annemans L, Spaepen E, Gaskin M, et al. Gout in the UK and Germany: prevalence, comorbidities and management in general practice 2000-2005. *Ann Rheum Dis.* 2008 Jul;67(7):960-6. PMID: 17981913.
3. Li C, Martin BC, Cummins DF, et al. Ambulatory resource utilization and cost for gout in United States. *American Journal of Pharmacy Benefits.* 2013 March/April;5(2):e46-e54. PMID: 2013264278.
4. Bhole V, de Vera M, Rahman MM, et al. Epidemiology of gout in women: Fifty-two-year followup of a prospective cohort. *Arthritis Rheum.* 2010 Apr;62(4):1069-76. PMID: 20131266.
5. Shoji A, Yamanaka H, Kamatani N. A retrospective study of the relationship between serum urate level and recurrent attacks of gouty arthritis: evidence for reduction of recurrent gouty arthritis with antihyperuricemic therapy. *Arthritis Rheum.* 2004 Jun 15;51(3):321-5. PMID: 15188314.
6. De Miguel E, Puig JG, Castillo C, et al. Diagnosis of gout in patients with asymptomatic hyperuricaemia: A pilot ultrasound study. *Annals of the Rheumatic Diseases.* 2012 January;71(1):157-8. PMID: 2011671627 MEDLINE PMID 21953340 (<http://www.ncbi.nlm.nih.gov/pubmed/21953340>) FULL TEXT LINK <http://dx.doi.org/10.1136/ard.2011.154997>.
7. Singh JA, Reddy SG, Kundukulam J. Risk factors for gout and prevention: a systematic review of the literature. *Curr Opin Rheumatol.* 2011 Mar;23(2):192-202. PMID: 21285714.
8. Diagnosis of Gout Protocol. Rockville, MD: Agency for Health Care Research and Quality, Effective Health Care Program,; July 17, 2014. <http://effectivehealthcare.ahrq.gov/ehc/products/564/1937/gout-protocol-140716.pdf>. Accessed on July 17 2014.
9. Doghramji PP, Wortmann RL. Hyperuricemia and gout: new concepts in diagnosis and management. *Postgrad Med.* 2012 Nov;124(6):98-109. PMID: 23322143.
10. Krishnan E, Akhras KS, Sharma H, et al. Serum urate and incidence of kidney disease among veterans with gout. *J Rheumatol.* 2013 Jul;40(7):1166-72. PMID: 23678154.
11. Zhu Y, Pandya BJ, Choi HK. Comorbidities of gout and hyperuricemia in the US general population: NHANES 2007-2008. *Am J Med.* 2012 Jul;125(7):679-87 e1. PMID: 22626509.
12. Anderson A, Singh Jasvinder A. Pegloticase for chronic gout. *Cochrane Database of Systematic Reviews: John Wiley & Sons, Ltd; 2010.*
13. Crittenden DB, Pillinger MH. New therapies for gout. *Annu Rev Med.* 2013;64:325-37. PMID: 23327525.
14. Tayar Jean H, Lopez-Olivo Maria A, Suarez-Almazor Maria E. Febuxostat for treating chronic gout. *Cochrane Database of Systematic Reviews: John Wiley & Sons, Ltd; 2012.*
15. Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American college of rheumatology guidelines for management of gout. part 1: Systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care and Research.* 2012;64(10):1431-46.
16. Khanna D, Khanna PP, Fitzgerald JD, et al. 2012 American college of rheumatology guidelines for management of gout. part 2: Therapy and antiinflammatory prophylaxis of acute gouty arthritis. *Arthritis Care and Research.* 2012;64(10):1447-61.
17. Kahan JP, Park RE, Leape LL, et al. Variations by specialty in physician ratings of the appropriateness and necessity of indications for procedures. *Med Care.* 1996 Jun;34(6):512-23. PMID: 8656718.
18. Garber AM, Browner WS. Cholesterol screening guidelines. Consensus, evidence, and common sense. *Circulation.* 1997 Mar 18;95(6):1642-5. PMID: 9118535.
19. Whitlock EP, Lin JS, Chou R, et al. Using existing systematic reviews in complex systematic reviews. *Ann Intern Med.* 2008 May 20;148(10):776-82. PMID: 18490690.
20. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of

bias in randomised trials. *BMJ*. 2011;343:d5928. PMID: 22008217.

21. Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol*. 2007;7:10. PMID: 17302989.

22. Agency for Healthcare Research and Quality. *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. January 2014. Chapters available at: [www.effectivehealthcare.ahrq.gov](http://www.effectivehealthcare.ahrq.gov).

23. Hill AB. The Environment and Disease: Association or Causation? *Proc R Soc Med*. 1965 May;58:295-300. PMID: 14283879.

24. Atkins D, Chang S, Gartlehner G, et al. Assessing the Applicability of Studies When Comparing Medical Interventions. Agency for Healthcare Research and Quality; December 2010. *Methods Guide for Comparative Effectiveness Reviews*. AHRQ Publication No. 11-EHC019-EF.

25. Wechalekar Mihir D, Vinik O, Schlesinger N, et al. Intra-articular glucocorticoids for acute gout. *Cochrane Database of Systematic Reviews*: John Wiley & Sons, Ltd; 2013.

26. Moi John HY, Sriranganathan Melonie K, Edwards Christopher J, et al. Lifestyle interventions for acute gout. *Cochrane Database of Systematic Reviews*: John Wiley & Sons, Ltd; 2013.

27. Janssens Hein J, Lucassen Peter LBJ, Van de Laar Floris A, et al. Systemic corticosteroids for acute gout. *Cochrane Database of Systematic Reviews*: John Wiley & Sons, Ltd; 2008.

28. Daoussis D, Antonopoulos I, Andonopoulos AP. ACTH as a treatment for acute crystal-induced arthritis: Update on clinical evidence and mechanisms of action. *Semin Arthritis Rheum*. 2014 Apr;43(5):648-53. PMID: 24762710.

29. Khanna PP, Gladue HS, Singh MK, et al. Treatment of acute gout: A systematic review. *Semin Arthritis Rheum*. 2014 Feb 13 PMID: 24650777.

30. Richette P, Bardin T. Colchicine for the treatment of gout. *Expert Opin Pharmacother*. 2010 Dec;11(17):2933-8. PMID: 21050036.

31. Terkeltaub RA. Colchicine Update: 2008. *Seminars in Arthritis and Rheumatism*. 2009 Jun;38(6):411-9. PMID: WOS:000267026600001.

32. van Echteld I, Wechalekar Mihir D, Schlesinger N, et al. Colchicine for acute gout. *Cochrane Database of Systematic Reviews*: John Wiley & Sons, Ltd; 2014.

33. Wechalekar MD, Vinik O, Moi JHY, et al. The efficacy and safety of treatments for acute gout: Results from a series of systematic literature reviews including cochrane reviews on intraarticular glucocorticoids, colchicine, nonsteroidal antiinflammatory drugs, and interleukin-1 inhibitors. *Journal of Rheumatology*. 2014;41(SUPPL. 92):15-25.

34. van Durme CM, Wechalekar MD, Buchbinder R, et al. Non-steroidal anti-inflammatory drugs for acute gout. *Cochrane Database Syst Rev*. 2014;9:CD010120. PMID: 25225849.

35. Li T, Chen SL, Dai Q, et al. Etoricoxib versus indometacin in the treatment of Chinese patients with acute gouty arthritis: a randomized double-blind trial. *Chin Med J (Engl)*. 2013;126(10):1867-71. PMID: 23673101.

36. Taylor TH, Mecchella JN, Larson RJ, et al. Initiation of allopurinol at first medical contact for acute attacks of gout: a randomized clinical trial. *Am J Med*. 2012 Nov;125(11):1126-34 e7. PMID: 23098865.

37. Zhang YK, Yang H, Zhang JY, et al. Comparison of intramuscular compound betamethasone and oral diclofenac sodium in the treatment of acute attacks of gout. *Int J Clin Pract*. 2014 May;68(5):633-8. PMID: 24472084.

38. Karimzadeh H, Nazari J, Mottaghi P, et al. Different duration of colchicine for preventing recurrence of gouty arthritis. *J Res Med Sci*. 2006;11:104-7.

39. Ahern MJ, Reid C, Gordon TP, et al. Does colchicine work? The results of the first controlled study in acute gout. *Aust N Z J Med*. 1987 Jun;17(3):301-4. PMID: 3314832.

40. Alloway JA, Moriarty MJ, Hoogland YT, et al. Comparison of triamcinolone acetone with indomethacin in the treatment of acute gouty arthritis. *J Rheumatol*. 1993 Jan;20(1):111-3. PMID: 8441139.

41. Altman RD, Honig S, Levin JM, et al. Ketoprofen versus indomethacin in patients with acute gouty arthritis: a multicenter, double blind comparative study. *J Rheumatol*. 1988 Sep;15(9):1422-6. PMID: 3058974.
42. Axelrod D, Preston S. Comparison of parenteral adrenocorticotrophic hormone with oral indomethacin in the treatment of acute gout. *Arthritis Rheum*. 1988 Jun;31(6):803-5. PMID: 2454635.
43. Borstad GC, Bryant LR, Abel MP, et al. Colchicine for prophylaxis of acute flares when initiating allopurinol for chronic gouty arthritis. *J Rheumatol*. 2004 Dec;31(12):2429-32. PMID: 15570646.
44. Butler RC, Goddard DH, Higgins CS, et al. Double-blind trial of flurbiprofen and phenylbutazone in acute gouty arthritis. *Br J Clin Pharmacol*. 1985 Nov;20(5):511-3. PMID: 3907678.
45. Cheng TT, Lai HM, Chiu CK, et al. A single-blind, randomized, controlled trial to assess the efficacy and tolerability of rofecoxib, diclofenac sodium, and meloxicam in patients with acute gouty arthritis. *Clin Ther*. 2004 Mar;26(3):399-406. PMID: 15110132.
46. Chou CT, Kuo SC. The anti-inflammatory and anti-hyperuricemic effects of Chinese herbal formula danggui-nian-tong-tang on acute gouty arthritis: a comparative study with indomethacin and allopurinol. *Am J Chin Med*. 1995;23(3-4):261-71. PMID: 8571922.
47. Douglas G, Thompson M. A comparison of phenylbutazone and flufenamic acid in the treatment of acute gout. *Ann Phys Med*. 1970 May;10(6):275-80. PMID: 4913482.
48. Eberl R, Dunky A. Meclofenamate sodium in the treatment of acute gout. Results of a double-blind study. *Arzneimittelforschung*. 1983;33(4A):641-3. PMID: 6349648.
49. Bakris GL, Doghramji PP, Keenan RT, et al. CaseBook Challenges: Managing Gout, Hyperuricemia and Comorbidities-Dialogue with the Experts. *American Journal of Medicine*. 2013.
50. Lederman R. A double-blind comparison of etodolac and high doses of naproxen in the treatment of acute gout. *Adv Ther*. 1990;7:344-54.
51. Lomen PL, Turner LF, Lamborn KR, et al. Flurbiprofen in the treatment of acute gout. A comparison with indomethacin. *Am J Med*. 1986 Mar 24;80(3A):134-9. PMID: 3963020.
52. Maccagno A, Di Giorgio E, Romanowicz A. Effectiveness of etodolac ('Lodine') compared with naproxen in patients with acute gout. *Current Medical Research and Opinion*. 1991 1991;12(7):423-9. PMID: 1991250613 MEDLINE PMID 1838075 (<http://www.ncbi.nlm.nih.gov/pubmed/1838075>).
53. Man CY, Cheung IT, Cameron PA, et al. Comparison of oral prednisolone/paracetamol and oral indomethacin/paracetamol combination therapy in the treatment of acute goutlike arthritis: a double-blind, randomized, controlled trial. *Ann Emerg Med*. 2007 May;49(5):670-7. PMID: 17276548.
54. Paulus HE, Schlosstein LH, Godfrey RG, et al. Prophylactic colchicine therapy of intercritical gout. A placebo-controlled study of probenecid-treated patients. *Arthritis Rheum*. 1974 Sep-Oct;17(5):609-14. PMID: 4606955.
55. Rubin BR, Burton R, Navarra S, et al. Efficacy and safety profile of treatment with etoricoxib 120 mg once daily compared with indomethacin 50 mg three times daily in acute gout: a randomized controlled trial. *Arthritis Rheum*. 2004 Feb;50(2):598-606. PMID: 14872504.
56. Ruotsi A, Vainio U. Treatment of acute gouty arthritis with proquazone and indomethacin. A comparative, double-blind trial. *Scand J Rheumatol Suppl*. 1978(21):15-7. PMID: 356235.
57. Schlesinger N, Detry MA, Holland BK, et al. Local ice therapy during bouts of acute gouty arthritis. *J Rheumatol*. 2002 Feb;29(2):331-4. PMID: 11838852.
58. Schumacher HR, Jr., Boice JA, Daikh DI, et al. Randomised double blind trial of etoricoxib and indometacin in treatment of acute gouty arthritis. *BMJ*. 2002 Jun 22;324(7352):1488-92. PMID: 12077033.
59. Schumacher HR, Berger MF, Li-Yu J, et al. Efficacy and Tolerability of Celecoxib in the Treatment of Acute Gouty Arthritis: A Randomized Controlled Trial. *Journal of Rheumatology*. 2012 Sep;39(9):1859-66. PMID: WOS:000308774000018.
60. Shi XD, Li GC, Qian ZX, et al. Randomized and controlled clinical study of modified prescriptions of

- Simiao Pill in the treatment of acute gouty arthritis. *Chin J Integr Med.* 2008 Mar;14(1):17-22. PMID: 18219456.
61. Shrestha M, Morgan DL, Moreden JM, et al. Randomized double-blind comparison of the analgesic efficacy of intramuscular ketorolac and oral indomethacin in the treatment of acute gouty arthritis. *Ann Emerg Med.* 1995 Dec;26(6):682-6. PMID: 7492036.
62. Siegel LB, Alloway JA, Nashel DJ. Comparison of adrenocorticotrophic hormone and triamcinolone acetonide in the treatment of acute gouty arthritis. *J Rheumatol.* 1994 Jul;21(7):1325-7. PMID: 7966077.
63. Siegmeth W, Placheta P. [Double-blind trial: ketoprofen versus phenylbutazone in acute gouty arthritis (author's transl)]. *Wien Klin Wochenschr.* 1976 Sep 3;88(16):535-7. PMID: 793186.
64. Terkeltaub RA, Furst DE, Bennett K, et al. High versus low dosing of oral colchicine for early acute gout flare: Twenty-four-hour outcome of the first multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison colchicine study. *Arthritis Rheum.* 2010 Apr;62(4):1060-8. PMID: 20131255.
65. Tumrasvin T, Deesomchok U. Piroxicam in treatment of acute gout high dose versus low dose. *J Med Assoc Thai.* 1985 Mar;68(3):111-6. PMID: 3894554.
66. Valdes EF. Use of tenoxicam in patients with acute gouty arthritis. *Eur J Rheumatol Inflamm.* 1987;9(2):133-6. PMID: 3329106.
67. Weiner GI, White SR, Weitzner RI, et al. Double-blind study of fenoprofen versus phenylbutazone in acute gouty arthritis. *Arthritis Rheum.* 1979 Apr;22(4):425-6. PMID: 371630.
68. Zhou L, Xu QF, Zhang WS. Comparative observation of therapeutic effects of acupuncture combined with infrared irradiation and western medicine on acute gouty arthritis. *World Journal of Acupuncture - Moxibustion;* 2012. p. 30-4.
69. Torre Gdl. A comparative, double-blind, parallel study with tenoxicam vs placebo in acute in acute gouty arthritis. *Invest Med Int.* 1987;14:92-7.
70. Ofman JJ, MacLean CH, Straus WL, et al. A metaanalysis of severe upper gastrointestinal complications of nonsteroidal antiinflammatory drugs. *J Rheumatol.* 2002 Apr;29(4):804-12. PMID: 11950025.
71. Ofman JJ, Maclean CH, Straus WL, et al. Meta-analysis of dyspepsia and nonsteroidal antiinflammatory drugs. *Arthritis Rheum.* 2003 Aug 15;49(4):508-18. PMID: 12910557.
72. Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs. A meta-analysis. *Ann Intern Med.* 1991 Nov 15;115(10):787-96. PMID: 1834002.
73. Andres M, Sivera F, Falzon L, et al. Dietary supplements for chronic gout. *Cochrane Database Syst Rev.* 2014;10:Cd010156. PMID: 25287939.
74. Choi TY, Kim TH, Kang JW, et al. Moxibustion for rheumatic conditions: A systematic review and meta-analysis. *Clinical Rheumatology.* 2011 July;30(7):937-45. PMID: 2011350115 MEDLINE PMID 21331532 (<http://www.ncbi.nlm.nih.gov/pubmed/21331532>) FULL TEXT LINK <http://dx.doi.org/10.1007/s10067-011-1706-5>.
75. Juraschek SP, Miller ER, 3rd, Gelber AC. Effect of oral vitamin C supplementation on serum uric acid: a meta-analysis of randomized controlled trials. *Arthritis Care Res (Hoboken).* 2011 Sep;63(9):1295-306. PMID: 21671418.
76. Lee WB, Woo SH, Min BI, et al. Acupuncture for gouty arthritis: a concise report of a systematic and meta-analysis approach. *Rheumatology (Oxford).* 2013 Jul;52(7):1225-32. PMID: 23424263.
77. Li XX, Han M, Wang YY, et al. Chinese herbal medicine for gout: a systematic review of randomized clinical trials. *Clin Rheumatol.* 2013 Jul;32(7):943-59. PMID: 23666318.
78. Moi John HY, Sriranganathan Melonie K, Edwards Christopher J, et al. Lifestyle interventions for chronic gout. *Cochrane Database of Systematic Reviews: John Wiley & Sons, Ltd;* 2013.
79. Wang DD, Sievenpiper JL, de Souza RJ, et al. The effects of fructose intake on serum uric acid vary among controlled dietary trials. *J Nutr.* 2012 May;142(5):916-23. PMID: 22457397.
80. Zhou L, Liu L, Liu X, et al. Systematic review and meta-analysis of the clinical efficacy and adverse effects of Chinese herbal decoction for the treatment

of gout. *PLoS One*. 2014;9(1):e85008. PMID: 24465466.

81. Wang MY, Jiang XB, Wu WL, et al. A meta-analysis of alcohol consumption and the risk of gout. *Clinical Rheumatology*. 2013 Nov;32(11):1641-8. PMID: WOS:000325809900011.

82. Wang Y, Yan S, Li C, et al. Risk factors for gout developed from hyperuricemia in China: a five-year prospective cohort study. *Rheumatol Int*. 2013 Mar;33(3):705-10. PMID: 22544037.

83. Choi HK, Willett W, Curhan G. Fructose-rich beverages and risk of gout in women. *JAMA*. 2010 Nov 24;304(20):2270-8. PMID: 21068145.

84. Choi HK, Curhan G. Coffee consumption and risk of incident gout in women: the Nurses' Health Study. *American Journal of Clinical Nutrition*. 2010 Oct;92(4):922-7. PMID: WOS:000282234100032.

85. DeMarco M, Maynard J, Coresh J. Alcohol intake is associated with incident gout in ARIC. *American Journal of Epidemiology*. 2011 1;173 SUPPL. 11:S57.

86. Neogi T, Chen C, Niu J, et al. Alcohol Quantity and Type on Risk of Recurrent Gout Attacks: An Internet-based Case-crossover Study. *Am J Med*. 2014 Apr;127(4):311-8. PMID: 24440541.

87. Zhang Y, Neogi T, Chen C, et al. Cherry consumption and decreased risk of recurrent gout attacks. *Arthritis Rheum*. 2012 Dec;64(12):4004-11. PMID: 23023818.

88. Zhu Y, Zhang Y, Choi HK. The serum urate-lowering impact of weight loss among men with a high cardiovascular risk profile: the Multiple Risk Factor Intervention Trial. *Rheumatology (Oxford)*. 2010 Dec;49(12):2391-9. PMID: 20805117.

89. Zeng YC, Huang SF, Mu GP, et al. Effects of adjusted proportional macronutrient intake on serum uric acid, blood lipids, renal function, and outcome of patients with gout and overweight. *Chinese Journal of Clinical Nutrition*. 2012 August;20(4):210-4. PMID: 2012603533 FULL TEXT LINK <http://dx.doi.org/10.3760/cma.j.issn.1674-635X.2012.04.004>.

90. Zhang SJ, Liu JP, He KQ. Treatment of acute gouty arthritis by blood-letting cupping plus herbal medicine. *J Tradit Chin Med*. 2010 Mar;30(1):18-20. PMID: 20397456.

91. Holland R, McGill NW. Comprehensive dietary education in treated gout patients does not further improve serum urate. *Intern Med J*. 2015 Feb;45(2):189-94. PMID: 25495503.

92. Dalbeth N, Ames R, Gamble GD, et al. Effects of skim milk powder enriched with glycomacropeptide and G600 milk fat extract on frequency of gout flares: a proof-of-concept randomised controlled trial. *Ann Rheum Dis*. 2012 Jun;71(6):929-34. PMID: 22275296.

93. Stamp LK, O'Donnell JL, Frampton C, et al. Clinically insignificant effect of supplemental vitamin C on serum urate in patients with gout: a pilot randomized controlled trial. *Arthritis Rheum*. 2013 Jun;65(6):1636-42. PMID: 23681955.

94. Seth R, Kydd AS, Buchbinder R, et al. Allopurinol for chronic gout. *Cochrane Database Syst Rev*. 2014;10:CD006077. PMID: 25314636.

95. Ye P, Yang S, Zhang W, et al. Efficacy and tolerability of febuxostat in hyperuricemic patients with or without gout: a systematic review and meta-analysis. *Clin Ther*. 2013 Feb;35(2):180-9. PMID: 23332451.

96. Saag KG, Becker MA, Whelton A, et al. Effect of febuxostat on serum urate levels in gout subjects with hyperuricemia and moderate-to-severe renal impairment: A randomized controlled trial. *Arthritis and Rheumatism*. 2013 October;65 SUPPL. 10:S498-S9.

97. Goldfarb DS, MacDonald PA, Hunt B, et al. Febuxostat in gout: serum urate response in uric acid overproducers and underexcretors. *J Rheumatol*. 2011 Jul;38(7):1385-9. PMID: 21572152.

98. Chohan S, Becker MA, MacDonald PA, et al. Women with gout: efficacy and safety of urate-lowering with febuxostat and allopurinol. *Arthritis Care Res (Hoboken)*. 2012 Feb;64(2):256-61. PMID: 22052584.

99. Faruque LI, Ehteshami-Afshar A, Wiebe N, et al. A systematic review and meta-analysis on the safety and efficacy of febuxostat versus allopurinol in chronic gout. *Semin Arthritis Rheum*. 2013 Dec;43(3):367-75. PMID: 24326033.

100. Manara M, Bortoluzzi A, Favero M, et al. Italian Society of Rheumatology recommendations for the management of gout. *Reumatismo*. 2013;65(1):4-21. PMID: 23550256.

101. Castrejon I, Toledano E, Rosario MP, et al. Safety of allopurinol compared with other urate-lowering drugs in patients with gout: a systematic review and meta-analysis. *Rheumatol Int.* 2014 Dec 18;PMID: 25519877.
102. Stevenson M, Pandor A. Febuxostat for the treatment of hyperuricaemia in people with gout: a single technology appraisal. *Health Technol Assess.* 2009 Oct;13 Suppl 3:37-42. PMID: 19846027.
103. Gaffo AL, Saag KG. Febuxostat: The evidence for its use in the treatment of hyperuricemia and gout. *Core Evidence.* 2009;4:25-36.
104. Becker MA, Schumacher HR, Jr., Wortmann RL, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *N Engl J Med.* 2005 Dec 8;353(23):2450-61. PMID: 16339094.
105. Schumacher Jr HR, Becker MA, Wortmann RL, et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: A 28-week, phase III, randomized, double-blind, parallel-group trial. *Arthritis Care and Research.* 2008;59(11):1540-8.
106. Becker MA, Schumacher HR, Espinoza LR, et al. The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial. *Arthritis Res Ther.* 2010;12(2):R63. PMID: 20370912.
107. Becker MA, Schumacher HR, MacDonald PA, et al. Clinical Efficacy and Safety of Successful Longterm Urate Lowering with Febuxostat or Allopurinol in Subjects with Gout. *Journal of Rheumatology.* 2009 Jun;36(6):1273-82. PMID: WOS:000266891500030.
108. Huang X, Du H, Gu J, et al. An allopurinol-controlled, multicenter, randomized, double-blind, parallel between-group, comparative study of febuxostat in Chinese patients with gout and hyperuricemia. *Int J Rheum Dis.* 2014 Jan 28;PMID: 24467549.
109. Ramasamy SN, Korb-Wells CS, Kannangara DR, et al. Allopurinol hypersensitivity: a systematic review of all published cases, 1950-2012. *Drug Saf.* 2013 Oct;36(10):953-80. PMID: 23873481.
110. Gilchrist MJ, Hebert B. Drug reaction with eosinophilia and systemic symptoms (DRESS). *Journal of General Internal Medicine.* 2011 May;26 SUPPL. 1:S423.
111. Tassaneeyakul W, Jantararungtong T, Chen P, et al. Strong association between HLA-B\*5801 and allopurinol-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in a Thai population. *Pharmacogenet Genomics.* 2009 Sep;19(9):704-9. PMID: 19696695.
112. Becker MA, Fitz-Patrick D, Storgard C, et al. A large-scale, multicenter, prospective, open-label, 6-month study to evaluate the safety of allopurinol monotherapy in patients with gout. *Arthritis and Rheumatism.* 2013 October;65 SUPPL. 10:S502-S3.
113. Chaudrey K, Khan M, Madhoun M, et al. Allopurinol-induced dress syndrome: A reversible fatality. *American Journal of Gastroenterology.* 2013 October;108 SUPPL. 1:S153.
114. Ibie NC, Alper AB. She is all dressed up: A case of allopurinol deadly complication. *Journal of Investigative Medicine.* 2014 February;62(2):504-5.
115. Weiss KM, Jain R, Wells C, et al. A case of allopurinol-induced dress syndrome in a patient with asymptomatic gout. *Annals of Allergy, Asthma and Immunology.* 2011 November;107(5 SUPPL. 1):A26.
116. Kamatani N, Fujimori S, Hada T, et al. Multicenter, open-label study of long-term administration of febuxostat (TMX-67) in Japanese patients with hyperuricemia including gout. *J Clin Rheumatol.* 2011 Jun;17(4 Suppl 2):S50-6. PMID: 21654270.
117. Yaylaci S, Demir MV, Temiz T, et al. Allopurinol-induced DRESS syndrome. *Indian J Pharmacol.* 2012 May;44(3):412-4. PMID: 22701258.
118. Schumacher HR, Becker MA, Lloyd E, et al. Febuxostat in the treatment of gout: 5-yr findings of the FOCUS efficacy and safety study. *Rheumatology.* 2009 Feb;48(2):188-94. PMID: WOS:000262518500020.
119. Lee MH, Stocker SL, Anderson J, et al. Initiating allopurinol therapy: do we need to know the patient's human leucocyte antigen status? *Internal Medicine Journal.* 2012 Apr;42(4):411-6. PMID: WOS:000302796000017.
120. Hande KR, Noone RM, Stone WJ. Severe allopurinol toxicity. Description and guidelines for

- prevention in patients with renal insufficiency. *Am J Med.* 1984 Jan;76(1):47-56. PMID: 6691361.
121. Chen IH, Kuo MC, Hwang SJ, et al. Allopurinol-induced severe hypersensitivity with acute renal failure. *Kaohsiung J Med Sci.* 2005 May;21(5):228-32. PMID: 15960069.
122. Kumar A, Edward N, White MI, et al. Allopurinol, erythema multiforme, and renal insufficiency. *BMJ.* 1996 Jan 20;312(7024):173-4. PMID: 8563541.
123. Lupton GP, Odom RB. The allopurinol hypersensitivity syndrome. *J Am Acad Dermatol.* 1979 Oct;1(4):365-74. PMID: 159913.
124. Chung WH, Chang WC, Stocker SL, et al. Insights into the poor prognosis of allopurinol-induced severe cutaneous adverse reactions: the impact of renal insufficiency, high plasma levels of oxypurinol and granulysin. *Ann Rheum Dis.* 2014 Aug 12; PMID: 25115449.
125. Kydd AS, Seth R, Buchbinder R, et al. Uricosuric medications for chronic gout. *Cochrane Database Syst Rev.* 2014;11:CD010457. PMID: 25392987.
126. Scott JT. Comparison of allopurinol and probenecid. *Ann Rheum Dis.* 1966 Nov;25(6 Suppl):623-6. PMID: 5335059.
127. Latourte A, Bardin T, Richette P. Prophylaxis for acute gout flares after initiation of urate-lowering therapy. *Rheumatology (Oxford).* 2014 Apr 23; PMID: 24758886.
128. Seth R, Kydd AS, Falzon L, et al. Preventing attacks of acute gout when introducing urate-lowering therapy: a systematic literature review. *J Rheumatol Suppl.* 2014 Sep;92:42-7. PMID: 25180127.
129. Wortmann RL, Macdonald PA, Hunt B, et al. Effect of prophylaxis on gout flares after the initiation of urate-lowering therapy: analysis of data from three phase III trials. *Clin Ther.* 2010 Dec;32(14):2386-97. PMID: 21353107.
130. Becker MA, Schumacher HR, Jr., Wortmann RL, et al. Febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase: a twenty-eight-day, multicenter, phase II, randomized, double-blind, placebo-controlled, dose-response clinical trial examining safety and efficacy in patients with gout. *Arthritis Rheum.* 2005 Mar;52(3):916-23. PMID: 15751090.
131. Kamatani N, Fujimori S, Hada T, et al. An allopurinol-controlled, randomized, double-dummy, double-blind, parallel between-group, comparative study of febuxostat (TMX-67), a non-purine-selective inhibitor of xanthine oxidase, in patients with hyperuricemia including those with gout in Japan: phase 3 clinical study. *J Clin Rheumatol.* 2011 Jun;17(4 Suppl 2):S13-8. PMID: 21654265.
132. Singal KK, Goyal S, Gupta P, et al. Comparison between Allopurinol and Febuxostat in management of gout patients - A prospective study. *Bangladesh Journal of Medical Science.* 2011 2011;10(4):257-9. PMID: 2012068233.
133. Whelton A, Becker MA, MacDonald P, et al. [Gout subjects with hyperuricemia and renal impairment treated with febuxostat or allopurinol for 6 months]. *International Journal of Rheumatic Diseases.* 2010;13:172-7.
134. Naoyuki K, Shin F, Toshikazu H, et al. An allopurinol-controlled, multicenter, randomized, open-label, parallel between-group, comparative study of febuxostat (TMX-67), a non-purine-selective inhibitor of xanthine oxidase, in patients with hyperuricemia including those with gout in Japan: phase 2 exploratory clinical study. *J Clin Rheumatol.* 2011 Jun;17(4 Suppl 2):S44-9. PMID: 21654269.
135. Becker MA, MacDonald PA, Hunt B, et al. Treating hyperuricemia of gout: safety and efficacy of febuxostat and allopurinol in older versus younger subjects. *Nucleosides Nucleotides Nucleic Acids.* 2011 Dec;30(12):1011-7. PMID: 22132950.
136. Becker MA, MacDonald PA, Hunt BJ, et al. Diabetes and gout: efficacy and safety of febuxostat and allopurinol. *Diabetes Obes Metab.* 2013 Nov;15(11):1049-55. PMID: 23683134.
137. Jackson RL, Hunt B, MacDonald PA. The efficacy and safety of febuxostat for urate lowering in gout patients  $\geq 65$  years of age. *BMC Geriatr.* 2012;12:11. PMID: 22436129.
138. Wells AF, MacDonald PA, Chefo S, et al. African American patients with gout: efficacy and safety of febuxostat vs allopurinol. *BMC Musculoskelet Disord.* 2012;13:15. PMID: 22316106.
139. Gibson T, Rodgers V, Potter C, et al. Allopurinol treatment and its effect on renal function

in gout: a controlled study. *Ann Rheum Dis.* 1982 Feb;41(1):59-65. PMID: 7039523.

140. Rundles RW, Metz EN, Silberman HR. Allopurinol in the treatment of gout. *Ann Intern Med.* 1966 Feb;64(2):229-58. PMID: 5322938.

141. Hollingworth P, Reardon JA, Scott JT. Acute gout during hypouricaemic therapy: prophylaxis with colchicine. *Ann Rheum Dis.* 1980 Oct;39(5):529. PMID: 7436588.

142. Zhang W, Doherty M, Bardin T, et al. EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR standing committee for international clinical studies including therapeutics (ESCSIT). *Annals of the Rheumatic Diseases.* 2006 Oct;65(10):1312-24. PMID: WOS:000240508600009.

143. De Vera M, Rai S, Bhole V. Medication adherence in patients with gout: A systematic review. *Arthritis and Rheumatism.* 2013 October;65 SUPPL. 10:S85.

144. Zandman-Goddard G, Amital H, Shamrayevsky N, et al. Rates of adherence and persistence with allopurinol therapy among gout patients in Israel. *Rheumatology (Oxford).* 2013 Jun;52(6):1126-31. PMID: 23392592.

145. Martini N, Bryant L, Karu LT, et al. Living With Gout in New Zealand An Exploratory Study Into People's Knowledge About the Disease and Its Treatment. *Jcr-Journal of Clinical Rheumatology.* 2012 Apr;18(3):125-9. PMID: WOS:000302141900003.

146. Silva L, Miguel ED, Peiteado D, et al. Compliance in gout patients. *Acta Reumatol Port.* 2010 Oct-Dec;35(5):466-74. PMID: 21245815.

147. Harrold LR, Andrade SE, Briesacher B, et al. The dynamics of chronic gout treatment: medication gaps and return to therapy. *Am J Med.* 2010 Jan;123(1):54-9. PMID: 20102992.

148. Harrold LR, Andrade SE, Briesacher BA, et al. Adherence with urate-lowering therapies for the treatment of gout. *Arthritis Res Ther.* 2009;11(2):R46. PMID: 19327147.

149. Halpern R, Mody RR, Fuldeore MJ, et al. Impact of noncompliance with urate-lowering drug on serum urate and gout-related healthcare costs: administrative

claims analysis. *Curr Med Res Opin.* 2009 Jul;25(7):1711-9. PMID: 19485724.

150. Riedel AA, Nelson M, Joseph-Ridge N, et al. Compliance with allopurinol therapy among managed care enrollees with gout: a retrospective analysis of administrative claims. *J Rheumatol.* 2004 Aug;31(8):1575-81. PMID: 15290738.

151. Rascati K, Prasla K, Park H, et al. Evaluation of healthcare costs for patients with gout by serum uric acid. *Arthritis and Rheumatism.* 2011;63(10):2011-11.

152. Dalbeth N, House ME, Horne A, et al. Prescription and dosing of urate-lowering therapy, rather than patient behaviours, are the key modifiable factors associated with targeting serum urate in gout. *BMC Musculoskelet Disord.* 2012;13:174. PMID: 22978848.

153. Dalbeth N, Petrie KJ, House M, et al. Illness perceptions in patients with gout and the relationship with progression of musculoskeletal disability. *Arthritis Care Res (Hoboken).* 2011 Nov;63(11):1605-12. PMID: 22034122.

154. Singh JA, Hodges JS, Asch SM. Opportunities for improving medication use and monitoring in gout. *Annals of the Rheumatic Diseases.* 2009 Aug;68(8):1265-70. PMID: WOS:000268010500006.

155. Sarawate CA, Brewer KK, Yang W, et al. Gout medication treatment patterns and adherence to standards of care from a managed care perspective. *Mayo Clin Proc.* 2006 Jul;81(7):925-34. PMID: 16835972.

156. Solomon DH, Avorn J, Levin R, et al. Uric acid lowering therapy: prescribing patterns in a large cohort of older adults. *Ann Rheum Dis.* 2008 May;67(5):609-13. PMID: 17728328.

157. Briesacher BA, Andrade SE, Fouayzi H, et al. Comparison of drug adherence rates among patients with seven different medical conditions. *Pharmacotherapy.* 2008 Apr;28(4):437-43. PMID: 18363527.

158. de Klerk E, van der Heijde D, Landewe R, et al. Patient compliance in rheumatoid arthritis, polymyalgia rheumatica, and gout. *J Rheumatol.* 2003 Jan;30(1):44-54. PMID: 12508389.

159. Deyo RA, Inui TS, Sullivan B. Noncompliance with arthritis drugs: magnitude, correlates, and clinical

implications. *J Rheumatol*. 1981 Nov-Dec;8(6):931-6. PMID: 7328568.

160. Wu EQ, Patel PA, Mody RR, et al. Frequency, risk, and cost of gout-related episodes among the elderly: does serum uric acid level matter? *J Rheumatol*. 2009 May;36(5):1032-40. PMID: 19369467.

161. Halpern R, Fuldeore MJ, Mody RR, et al. The effect of serum urate on gout flares and their associated costs: an administrative claims analysis. *J Clin Rheumatol*. 2009 Feb;15(1):3-7. PMID: 19125135.

162. Becker MA, MacDonald PA, Hunt BJ, et al. Determinants of the clinical outcomes of gout during the first year of urate-lowering therapy. *Nucleosides Nucleotides Nucleic Acids*. 2008 Jun;27(6):585-91. PMID: 18600509.

163. Sarawate CA, Patel PA, Schumacher HR, et al. Serum urate levels and gout flares: analysis from managed care data. *J Clin Rheumatol*. 2006 Apr;12(2):61-5. PMID: 16601538.

164. Bongartz T, Zleik N, Clement M, et al. The risk of future attacks in patients with incident gout: A population-based. *Annals of the Rheumatic Diseases*. 2013;72(3):2013-06.

165. Hamburger MI, Tesser JRP, Skosey JL, et al. Patterns of gout treatment and related outcomes in us community rheumatology practices: The relation between gout flares, time in treatment, serum uric acid level and urate lowering therapy. *Arthritis and Rheumatism*. 2012 October;64 SUPPL. 10:S808-S9.

166. Khanna PP, Baumgartner S, Khanna D, et al. Assessing SUA, flare rates, and Tophi in patients with gout treated xanthine oxidase inhibitors in the United States. *Annals of the Rheumatic Diseases*. 2013;72(3):2013-06.

167. Martini N, Bryant L, Te Karu L, et al. Living with gout in New Zealand: an exploratory study into people's knowledge about the disease and its treatment. *J Clin Rheumatol*. 2012 Apr;18(3):125-9. PMID: 22426580.

168. Park H, Rascati KL, Prasla K, et al. Evaluation of health care costs and utilization patterns for patients with gout. *Clin Ther*. 2012 Mar;34(3):640-52. PMID: 22381710.

169. Perez-Ruiz F, Herrero-Beites AM, Carmona L. A two-stage approach to the treatment of hyperuricemia in gout: the "dirty dish" hypothesis. *Arthritis Rheum*. 2011 Dec;63(12):4002-6. PMID: 21898351.

170. Loebel WY, Scott JT. Withdrawal of allopurinol in patients with gout. *Ann Rheum Dis*. 1974 Jul;33(4):304-7. PMID: 4416909.

171. Bull PW, Scott JT. Intermittent control of hyperuricemia in the treatment of gout. *J Rheumatol*. 1989 Sep;16(9):1246-8. PMID: 2681764.

## Abbreviations / Acronyms

3e	Evidence, Expertise, Exchange
ACR	American College of Rheumatology
ACP	American College of Physicians
ACTH	Adrenocorticotrophic Hormone
AE	Adverse event
AHRQ	Agency for Healthcare Research and Quality
ALL	Allopurinol
BMI	Body Mass Index
CI	Confidence interval
CT (Scan)	Computerized tomography
CVD	Cardiovascular disease
DNTT	Danggui-Nian-Tong Tang
eGFR	Estimated glomerular filtration rate
EPC	Evidence-based Practice Center
FEB	Febuxostat
GC	Glucocorticoid
GI	Gastrointestinal
GMP	glycomacropeptide
HRQoL	Health Related Quality of Life
KQ	Key Question
MD	Mean difference
MSU	Monosodium urate
NHANES	National Health and Nutrition Examination Survey
Non-GI	Non-gastrointestinal
NSAIDS	Nonsteroidal anti-inflammatory drugs
OR	Odds Ratio
PCPs	Primary care physicians
PICOTS	Populations, Interventions, Comparators, Outcomes, and Timing
PLB	Placebo
RR	Relative risk
SCEPC	Southern California Evidence-based Practice Center
SMD	Standardized mean difference
SMP	Skim milk powder
SRs	Systematic Reviews
sUA	Serum urate
TCM	Traditional Chinese Medicine
TEP	Technical Expert Panel
UA	Uric acid
ULT	Urate Lowering Therapy

US

VA

XOI

United States

Veterans Administration

Xanthine oxidase inhibitor