



Effective Health Care Program

Management of Gout

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, or acute gout attacks, or acute gout flares). It has been described as a disease of the foot since antiquity.¹ Approximately 8 million patients in the United States have gout. 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, acute gout attacks become progressively 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

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at www.effectivehealthcare.ahrq.gov/reports/final.cfm.

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.



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Although the primary risk factor for gout is hyperuricemia, not all patients with hyperuricemia go on to develop clinical gout; hyperuricemia that does not progress to gout is 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).²

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).³ Some prescription medications such as thiazides are also believed to be risk factors for gout.

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.⁴

Clinical Presentation and Management

Gout encompasses both acute and chronic phases.

Acute Gouty Arthritis

The acute phase of gout 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 other joints, tendons, bursae or other areas may be involved.

Primary treatments for acute gout attacks have included non-steroidal anti-inflammatory agents (NSAIDs), 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.⁵ The average interval between the onset of gout and appearance of tophi, in the absence of treatment, is approximately 10 years.⁵

Management of chronic gout may include both pharmacologic and non-pharmacologic strategies.

Historically, the treatment of chronic gout began with identification of patients as “overproducers” or “underexcretors” of uric acid, based on 24-hour urine collection. “Overproducers” were treated preferentially with allopurinol, whereas “underexcretors” were treated preferentially with the uricosuric probenecid. However, uricosuric agents may increase the risk of renal stones, requiring increased fluid intake and alkalinization for prevention. Probenecid use has fallen out of favor, because allopurinol was found to be effective in “underexcretors”.^{6,7} Urate lowering strategies are the primary pharmacologic intervention for management of long-term complications of gout.

Lifestyle Changes. Non-pharmacologic methods advocated for management of chronic gout include a combination of lifestyle changes, including weight loss, exercise, hydration, and dietary changes. Such changes include reduction of dietary purines and alcohol intake, based on observational studies assessing associations between dietary components and risk for gout or trials assessing the effect of specific foods or supplements on serum uric acid levels. 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). The evidence for the efficacy of specific dietary changes in managing gout (preventing attacks) is a topic of this review

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

Several interleukin-1 β -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,⁸⁻¹⁰ and will not be included in this systematic review, because they are not

Table A. Pharmacologic agents used in the treatment of gout

Drug Class	Agent (generic/brand)	Manufacturer
Anti-inflammatory Agents for Gout Attacks	NSAIDS (including Ibuprofen, naproxen, etodolac, diclofenac, indomethacin, COX-2 inhibitors)	Numerous
	Corticosteroids/ Animal-derived adrenocorticotrophic hormone (ACTH) formulation	Numerous
	Colchicine/Colcris™, Colchicine tablets, USP authorized generic	Takeda Pharmaceuticals, America, Inc.
	IL-1B Receptor Antagonists: ^a Anakinra/kineret®	Sobi
Urate Lowering Agents	Uricosurics: Probenecid/Benemid® or Probalan	Multiple
	Xanthine Oxidase Inhibitors: Allopurinol/ Zyloprim®	Prometheus Labs
	Febuxostat/Uloric™	Teijin Pharma Ltd., Takeda
	Uricase: Pegloticase/Krystexxa® ^a	Crealta
	Combination agents: Colchicine-probenecid/Proben-C	Merck

^aThese 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.

prescribed in the primary care setting (see below). These treatments do not act by lowering serum urate levels.

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; estrogen; 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, in both the acute and chronic phases, 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 Web site on November 3, 2014 at: <http://effectivehealthcare.ahrq.gov/ehc/products/564/1992/Gout-management-protocol-141103.pdf>.

Key Questions

The Key Questions (KQs) 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

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

- 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])?
- 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

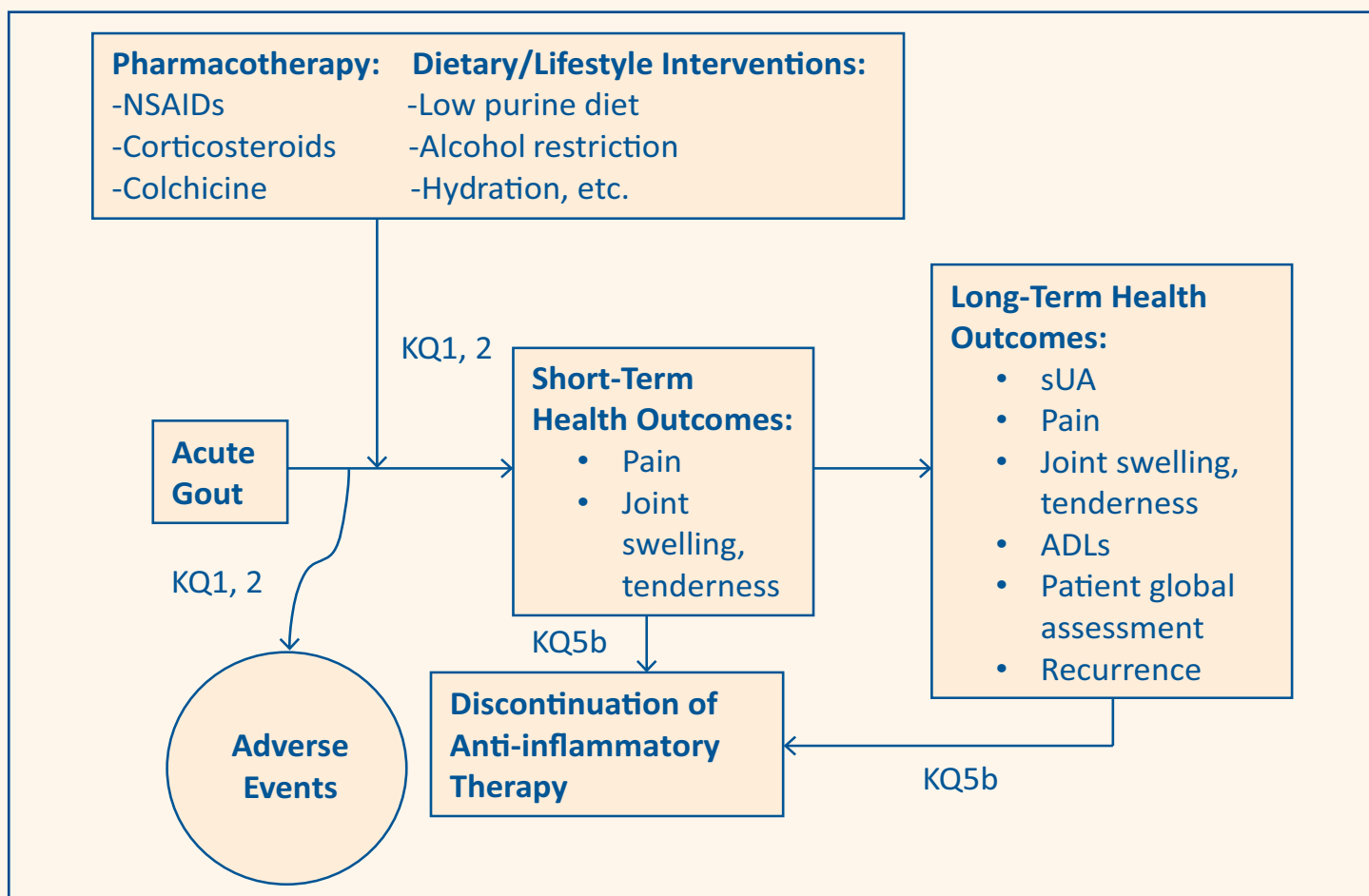
- In adults with gout, what are the benefits and harms of different pharmacological therapies on intermediate (serum and/or urine UA levels) and long-term clinical health outcomes (including recurrence of gout episodes and progression)?
- Does effectiveness and comparative effectiveness of urate lowering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

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

Key Question 4: Treatment Monitoring of Patients with Gout

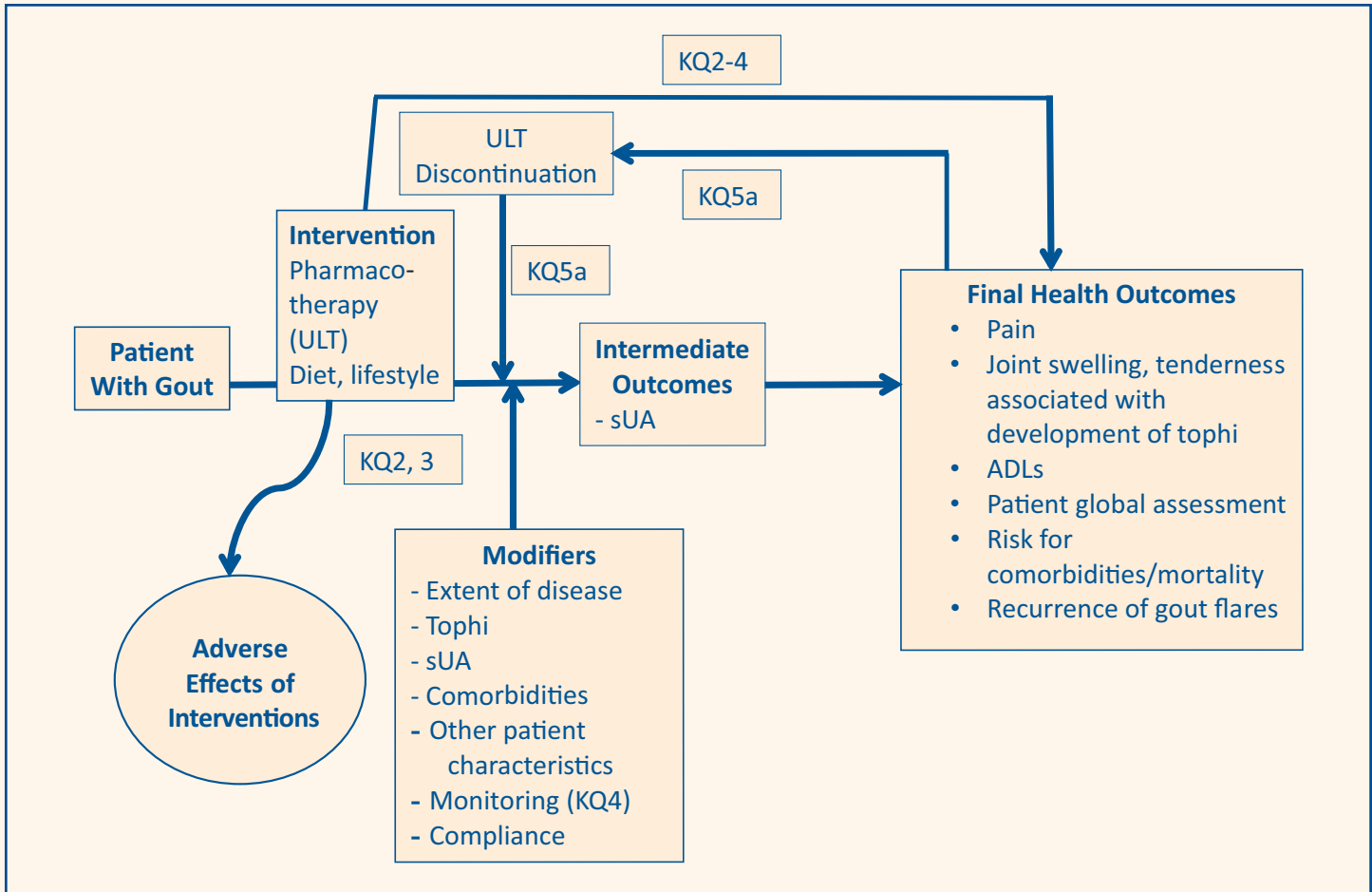
- In adults with gout, does monitoring serum urate levels with pharmacologic treatment and/or dietary and/or lifestyle change measures (e.g., compliance) improve treatment outcomes?
- Is achieving lower subsequent serum urate levels (less than 5 vs. 5–7mg/dL) associated with decreased risk for recurrent 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?

Figure A. Analytic framework



ADLs = activities of daily living; KQ = Key Question; sUA = serum uric acid; ULT = urate lowering therapy

Figure B. Analytic framework for management of chronic gout



ADLs = activities of daily living; KQ = Key Question; sUA = serum uric acid; ULT = urate lowering therapy

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—

- urate lowering therapy?
- 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 (Figure A) and one for chronic gout (Figure B).

Methods

In general, this systematic review follows the procedures of the January 2014 edition of the “Methods Guide for Effectiveness and Comparative Effectiveness Reviews.”¹¹

Searching for the Evidence

We searched multiple databases for systematic reviews on gout and studies not included in those systematic reviews. In general, we include studies of effectiveness only if they were randomized controlled trials. If no trials could be identified of interest, observational studies were included for assessing the role of nutrition. Observational studies were also included for rare adverse events. Evidence obtained through the systematic review process was considered in light of what is already known about the physiology of gout and about the treatment of painful and inflammatory conditions.

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” and “gouty,” and terms for tophi (January 1, 2010–April 23, 2015; at least one year prior to the search dates for the recent systematic reviews). We also obtained relevant

references from at least 28 recent systematic reviews that cover nearly all of the KQs. 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 diagnosis 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 additional studies they believed 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,¹² 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;¹³ 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 KQs, the end date of the search, and the methodologic quality as assessed by AMSTAR,¹³ following the process outlined by Whitlock and colleagues.¹⁴
2. Scan the references of these systematic reviews for included studies.
3. Search for new studies meeting the eligibility criteria for the KQ.
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 guide shown in Figure C for additional analyses/conclusions.

Grading the Strength of Evidence (SoE) for Major Comparisons and Outcomes

We assessed the overall SoE for each conclusion (e.g., the efficacy and safety of each pharmacologic agent or class of agents listed in the PICOTs (Participants, Interventions, Control, Outcome, and Timeframe and Setting), and differences by subgroup, if identified), using guidance suggested by the Effective Health Care Program.¹¹ 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. The grades and their definitions are presented below.¹¹

High: We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions

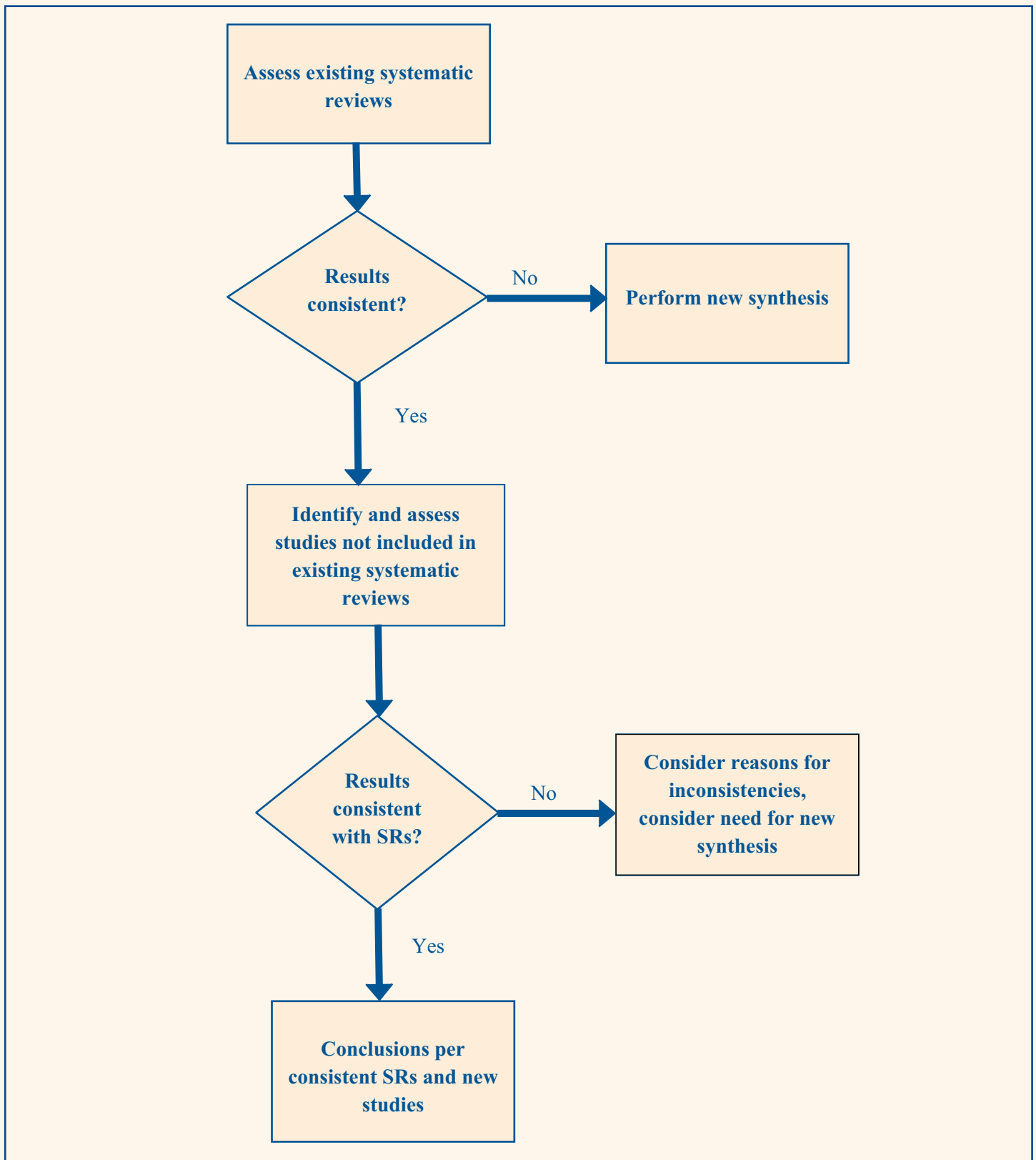
Moderate: We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.

Low: We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.

Insufficient: We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

We also considered in our strength of evidence assessments the criteria proposed by Bradford Hill for causality.¹⁵ 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. These principles allow us to construct and evaluate evidence

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



SR(s) = systematic review(s)

chains. For example, in assessing the evidence regarding pharmacological urate lowering therapy (ULT) agents, we considered the biochemical properties of urate in serum: urate is soluble in serum 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. RCTs of ULT have demonstrated evidence that they lower serum urate levels, but the longest trials have lasted only 6 to 12 months and have not shown reductions in acute gout attacks 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 these RCTs show that patients who continued on pharmaceutical therapy had reduced serum urate levels and after about 1 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 attacks after about 1 year.

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.¹⁶

Peer Review and Public Commentary

A draft version of the report was posted for peer review on June 25 2015, and revised in response to reviewer comments.

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 KQs and the key points (conclusions).

Results of Literature Searches

Our searches identified 6,269 titles/abstracts. Reference mining the previous systematic reviews (SRs) and guidelines identified in our searches resulted in an additional 233 titles. Our search of clinicaltrials.gov

identified 270 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, 1 was withdrawn, and 8 were recorded as being completed but no results were posted in clinicaltrials.gov, and we could find no published journal articles. Two manufacturers of drugs (Novartis and Regeneron) 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 not-FDA approved. Of a total of 6,772 titles/abstracts screened for inclusion, 6,087 titles/abstracts were excluded. At full text screening review, we rejected an additional 542 articles. Therefore, a total of 143 articles were included in our review.

For KQ 1, we included a total of 45 studies of which 15 were included in our analysis (3 RCTs, 2 studies that reported only on adverse events [AEs], and 10 systematic reviews [SRs]). The remaining 30 studies were identified in prior SRs. For KQ2, we included 22 studies of which 17 were included in our analysis (6 RCTs that examined dietary, lifestyle, Traditional Chinese Medicine [TCM] treatment, 3 observational studies [reported in 6 publications] on dietary factors, and 5 SRs). The remaining 10 studies were identified in prior SRs. For KQ3, we include a total of 55 studies of which 45 were included in our analysis (7 RCTs, 1 abstract that has not been published, 5 secondary analyses, 20 studies that reported on AEs, 11 SRs and 1 meta-analysis). The remaining 10 studies were identified in prior SRs. For KQ4, we include a total of 26 studies (24 original studies and 2 SRs). For KQ5, we include three original studies. See Figure D for the literature flow diagram.

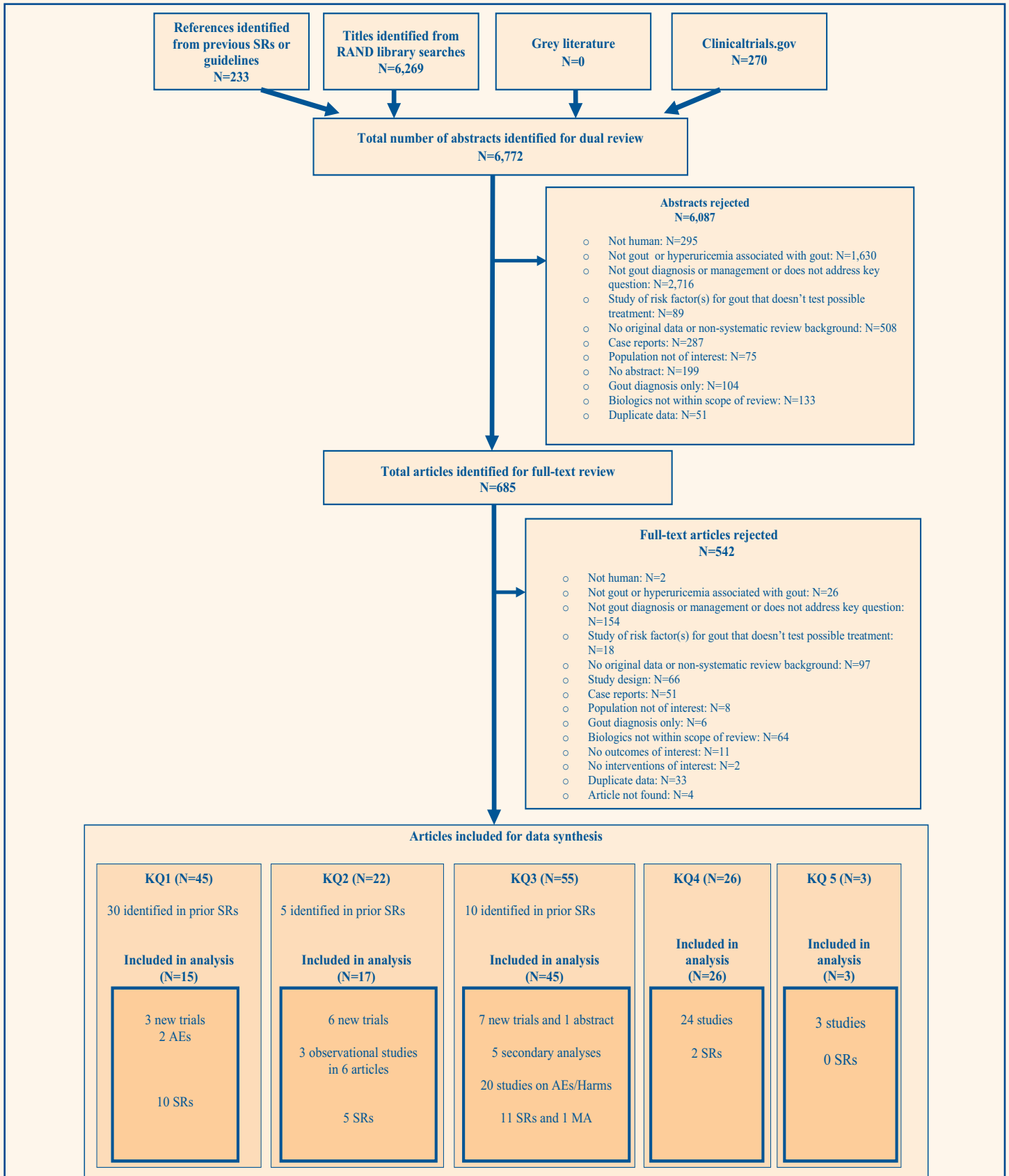
Findings

The key findings and SoE are in Table B.

Key Questions 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)?

Figure D. Literature flow diagram



AE(s) = adverse event(s); KQ = Key Question; MA = meta-analysis; RCT(s) = randomized controlled trial(s); SR(s) = systematic review(s)

Description of Included Studies

We identified 10 SRs on the following acute gout therapies: colchicine, NSAIDs, corticosteroids, and animal-derived ACTH formulation.¹⁷⁻²⁶ We further identified three new trials not included in previous SRs that met our inclusion criteria,²⁷⁻³⁰ and two studies on adverse events (AEs).^{31,32}

Key Findings and SoE for Key Questions 1a–c

- High-strength evidence supports the efficacy of colchicine to reduce pain in acute gout.
- Moderate-strength evidence supports the finding that low-dose colchicine is as effective as higher dose for reducing pain, with fewer side effects.
- High-strength evidence supports the efficacy of NSAIDs to reduce pain in acute gout.
- Moderate-strength evidence supports a lack of difference among NSAIDs in effectiveness.
- High-strength evidence supports the efficacy of systemic corticosteroids to reduce pain in acute gout.
- Moderate-strength evidence supports animal-derived ACTH formulation to reduce pain in acute gout.
- SoE is insufficient regarding the effect of therapies on other outcomes: joint swelling, tenderness, activities of daily living, patient global assessment.
- SoE is insufficient regarding 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, and cumulative doses from repeated short term courses may also cause harms similar to long term use.

Key Questions 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 comorbid characteristics?**

Description of Included Studies

We identified five SRs that examined the efficacy of dietary and other lifestyle factors in the treatment of gout.^{21,33-36} In addition, we identified six original RCTs and three prospective observational studies (the latter described in six publications) not included in previous SRs that met our inclusion criteria and examined dietary and lifestyle interventions in gout management.³⁷⁻⁴⁸

Key Findings and SoE for Key Questions 2a–b

- The SoE from RCTs that assess symptomatic outcomes is insufficient to support a role for specific dietary changes (including reducing intakes of dietary purines, protein, or alcohol; increasing intakes of cherries, modified milk products, or supplemental vitamin C; or achieving weight loss) in gout management.
- The SoE is insufficient to support a role for 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) compared with nonspecific dietary advice (counseling about the importance of weight loss and reduced alcohol intake) for reducing serum urate levels in patients with gout.
- The SoE is insufficient to support or refute the effectiveness of Traditional Chinese Medicine (TCM; including herbs and acupuncture) on symptomatic outcomes.

Key Questions 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 comorbid characteristics?
- c. What is the effect of dietary modification in combination with pharmacologic therapy?

Description of Included Studies

Our literature search identified 11 SRs^{10,49-58} and one meta-analysis.⁵⁹ In addition, we identified one new abstract⁶⁰ and five secondary analyses⁶¹⁻⁶⁵ of trials already included in the SRs and seven new trials.^{30,47,66-70} For AEs, we included 20 studies.⁷¹⁻⁹⁰

Key Findings and SoE for Key Questions 3a–c

- High-strength evidence supports the finding that urate lowering therapy does not reduce the risk of acute gout attacks in the first 6 months.
- Moderate-strength evidence supports a reduction in the risk of acute gout attacks after about 1 year of urate lowering therapy.
- High-strength evidence supports the efficacy of urate lowering therapy in reducing serum urate.
- High-strength evidence supports the finding of no difference between 40mg febuxostat and 300mg allopurinol in serum urate lowering.
- Evidence is insufficient about the potential effect of the presence of tophi on the effectiveness and comparative effectiveness of allopurinol and febuxostat.
- High-strength 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 evidence supports the finding that longer courses of prophylaxis with colchicine or NSAIDs (> 8 weeks) are more effective than courses of shorter duration to prevent acute gout attacks when initiating urate lowering therapy.

- The SoE is insufficient that gout-specific dietary advice adds to the effectiveness of urate lowering therapy in reducing serum urate.
- The most common adverse event associated 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). These serious side effects are sufficiently rare that clinical trials lack power to detect them. The risk of DRESS is greatly increased in patients with the HLA-B*5801 allele. Some evidence indicates that allopurinol reactions are more likely to occur in the first six months of treatment.
- Clinical expertise with febuxostat is less than with allopurinol. The most commonly reported adverse events in trials of febuxostat were abdominal pain, diarrhea, and musculoskeletal pain (5 percent-20 percent for each), but these rates were not statistically significantly different from those in placebo-treated patients. Rare skin reactions also occur with febuxostat.
- High-strength evidence supports a lack of difference in overall adverse events between allopurinol 300mg and febuxostat 40mg. A systematic review that identified four RCTs comparing the safety of urate lowering therapies found no statistically significant differences in overall adverse events between allopurinol and febuxostat.

Key Questions 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 KQ 4a, we identified one SR⁹¹ from which 16 original studies were referenced mined.⁹²⁻¹⁰⁷

For KQ 4b, we identified one SR¹⁰⁸ and eight studies that addressed the question.¹⁰⁹⁻¹¹⁶

Key Findings and SoE for Key Question 4

- Evidence is insufficient to support or refute that monitoring serum urate improves outcomes.
- Low-strength evidence supports the finding that treating to a specific target serum urate level reduces the risk of gout attacks. However, the only way to know if urate lowering therapy affects serum urate is by monitoring serum urate levels. Therefore, this logic supports some monitoring, although how often and to what target have not been experimentally tested.

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 three observational (prospective cohort) studies¹¹⁷⁻¹¹⁹ and also used data from three RCTs that addressed duration of anti-inflammatory prophylaxis in urate lowering therapy trials.¹²⁰⁻¹²²

Key Findings and SoE for Key Question 5

- The evidence is insufficient that discontinuing urate lowering therapy results in no increase in risk of acute gout attacks in gout patients who have completed 5 years of urate lowering therapy that kept serum urate levels < 7mg/dl, and in whom subsequent annual serum urate levels (off of urate lowering therapy) stayed < 7mg/dl.
- Moderate-strength evidence supports the finding that prophylaxis for acute gout with low dose colchicine or NSAIDs when initiating urate lowering therapy results in fewer gout attacks when treatment is given for longer than 8 weeks.

Discussion

Key Findings and SoE

We found a large number of research studies about gout, yet only a relatively modest number of these studies

provided evidence for some of our KQs, 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 were able to reach strong conclusions about the usefulness of these drugs because of some specific features of gout: Symptoms result from an inflammatory reaction to the deposition of urate crystals, which occurs when serum urate rises above its saturation point in the blood. Hence, in an era that predated the widespread practice of placebo-controlled trial testing of therapies, medications aimed at blocking the inflammatory response were tried as treatments. Steroids are one of the most powerful and effective anti-inflammatory medications available. Although no placebo-controlled RCTs have tested their use in acute gout, steroids have proven efficacy in other inflammatory conditions, which gives us confidence that they are 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 would mean withholding therapies of known effectiveness (e.g., colchicine) from the placebo-treated group. Indeed, a recent, high profile study of the use of steroids in acute gout compared their use not to placebo, but to NSAIDs. Because 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 SoE as high that their use relieves symptoms by a clinically important amount—despite the lack of placebo-controlled RCT evidence.

With regard to chronic gout, we similarly used evidence from a number of sources to reach conclusions about the effectiveness of ULT at reducing the risk of acute gout attacks over time, despite the fact that this outcome has not been studied in any placebo-controlled trial of longer than a few months. We based our moderate SoE rating on the high strength evidence that ULT reduces serum urate, that serum urate level is a strong predictor of the risk of acute gout attacks, and that the open-label extension studies of randomized controlled trials of ULT have shown a graded relationship between the serum urate level achieved and the risk of acute gout attacks. We thus concluded that over time, possibly by 1 year from initiation of therapy, ULT reduces the risk of acute gout attacks. We also concluded, based on a comparison of the timing of the occurrence of acute gout attacks in the weeks following initiation of

ULT, that longer courses of prophylactic treatment with colchicine or NSAIDs (greater than 8 weeks) are more effective than courses of treatment with durations of 8 weeks or less, since in the one RCT of urate lowering therapy where prophylactic colchicine or NSAIDs were continued for 6 months, no “spike” in acute gout attacks coincided temporally with the discontinuation of the prophylactic therapy, like that seen in other RCTs where prophylaxis was stopped at 8 weeks.

A third key finding of our review is that there is scant direct evidence about how much ULT to give (e.g. the concept of treating-to-a-target) and for how long to give it (are there any criteria about when ULT can be stopped, or if once started is treatment needed for life?).

The key findings and SoE are in Table B.

Findings in Relationship to What is Already Known

In general, our findings support the results of existing SRs. 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 115 studies assessed in detail (not counting SRs), only 9 studies explicitly stated that patients came only from, or the study included patients from, primary care sites (including the ED and urgent care settings). Furthermore, it is likely that patients enrolled in clinical trials differ from those commonly seen in primary care settings. In the major trials of ULT, the proportion of patients with tophi is greater than 20 percent¹²⁰⁻¹²³ whereas in a trial that explicitly enrolled patients from primary care, the proportion of patients with tophi was 10 percent. A population-based study of more than 50,000 gout patients in English primary care practices reported the proportion with tophi as 0.5 percent¹²⁴ Patients enrolled in clinical trials usually have fewer comorbidities than those seen in practice, because clinical trials have exclusion criteria. Thus, in most trials, enrolled patients probably had more advanced gout, but were 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 KQs of interest, data were not reported on the subgroups or outcomes of interest as specified in the KQs and analytic frameworks, limiting the comparative effectiveness review. For the portion of the review on Traditional Chinese Medicine (TCM), the variability in tested interventions made comparisons across studies not justified.

Limitations of the Evidence Base

The lack of studies specifically stating that they enrolled patients in primary care settings is a limitation, as is the lack of randomized controlled studies assessing clinical outcomes for ULT (such as recurrent acute gout flare after 1 year) and intervention studies of dietary therapies for management of chronic gout. Longer term studies will be needed to assess the degree to which 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, for example, < 6mg/dL for all gout patients versus < 5mg/dL for patients with significant gout morbidity. However, for many gout patients in primary care practice whose gout is well controlled on ULT, no data support such targets. In fact, the results of one cohort study suggest that once gout has been asymptomatic for 5 years, ULT might be discontinued for many years (as long as serum urate levels remain acceptable, e.g., < 7mg/dL).¹¹⁷ Therefore, the most important research gap is a RCT 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 (for example, 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 versus a 5 percent chance of a skin rash and a less than 1 percent chance of a very serious skin rash).

Likewise, in spite of the many observational studies linking dietary factors with risk for gout, 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 RCTs for specific dietary changes (such as reducing or eliminating sugar-sweetened beverages or high-fructose foods, adequate hydration, restriction of alcohol, increase in low fat dairy consumption, and even restriction of high purine foods) compared with standard healthy diet advice and weight loss in reducing the risk of gout attacks.

A third research gap is the better characterization of adverse events from ULT and how they may be minimized.

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

Key Question	Prior Knowledge Used in Determining Strength of Evidence	Sources of Evidence Included in This Systematic Review	Strength of Evidence
KQ1 Acute Gout Treatment			
Colchicine reduces pain	N/A	<ul style="list-style-type: none"> 2 placebo-controlled RCTs (N=45 and N=184) both with low risk of bias 	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"> 1 head-to-head RCT with low risk of bias (N=184) 	Moderate
NSAIDs reduce gout pain	<ul style="list-style-type: none"> Biologic rationale (anti-inflammatory action) Placebo-controlled RCT evidence that NSAIDs provide temporary pain relief for numerous conditions 	<ul style="list-style-type: none"> 1 placebo-controlled RCT with high risk of bias (N=30) High strength observational data (NSAID use as prophylaxis against gout flare) (see below under KQ3) 	High
No difference between NSAIDs in effectiveness	<ul style="list-style-type: none"> Equivalence in effectiveness among NSAIDs in numerous other conditions 	<ul style="list-style-type: none"> 16 head-to-head RCTs 	Moderate
Systemic corticosteroids reduce pain	<ul style="list-style-type: none"> Biologic rationale (anti-inflammatory action) 	<ul style="list-style-type: none"> No placebo-controlled RCTs Equivalence to NSAIDs in 4 RCTs (N=27, N=90, N=120, and N=60). Three of four RCTs had low risk of bias. 	High
Animal-derived ACTH formulation reduces pain	<ul style="list-style-type: none"> Biologic rationale (anti-inflammatory action) 	<ul style="list-style-type: none"> No placebo-controlled RCTs Equivalence to NSAIDs and intramuscular steroids in RCTs (one RCT of each, N=76 and N=31 both at high risk of bias) 	Moderate
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

Table B. Summary of prior knowledge, findings from the systematic review, and strength of evidence, by KQ (continued)

Key Question	Prior Knowledge Used in Determining Strength of Evidence	Sources of Evidence Included in This Systematic Review	Strength of Evidence
KQ2 Diet and Lifestyle Management			
Specific dietary changes (including reducing intakes of dietary purines, protein, or alcohol; increasing intakes of cherries, modified milk products, or supplemental vitamin C; or achieving weight loss) in gout management may affect symptomatic outcomes	N/A	<ul style="list-style-type: none"> 3 RCTs (two at high risk of bias) (N=67, N=120, N=40) 3 observational studies (N=20, N=120, N=633) 	Insufficient
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) compared with nonspecific dietary advice (counseling about the importance of weight loss and reduced alcohol intake) for reducing serum urate levels in patients with gout	N/A	<ul style="list-style-type: none"> 1 RCT with high risk of bias (N=30) 	Insufficient
Effectiveness of Traditional Chinese Medicine (TCM) (acupuncture, herbal mixtures, moxibustion) on symptomatic outcomes	N/A	<ul style="list-style-type: none"> 86 RCTs, all of idiosyncratic therapies, with conflicting results 	Insufficient
KQ3 Management of Hyperuricemia			
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"> 2 placebo-controlled RCTs, with low risk of bias (N=1,072 and N=57) 	High
Urate lowering therapy reduces the risk of acute gout attacks after 1- year	<ul style="list-style-type: none"> Acute gout attacks are caused by elevated serum urate concentrations 	<ul style="list-style-type: none"> No placebo-controlled RCTs assess long-term risk of acute gout attacks RCTs with low risk of bias show that ULT reduces serum uric acid 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 	Moderate
Urate lowering therapy reduces serum urate	N/A	<ul style="list-style-type: none"> 4 placebo-controlled RCTs all with low risk of bias (N=1,072, N=96, N=153, and N=57) 	High
40 mg febuxostat and 300mg allopurinol show no differences in serum urate lowering	N/A	<ul style="list-style-type: none"> 1 head-to-head RCT with low risk of bias (N=2,269) 	High

Table B. Summary of prior knowledge, findings from the systematic review, and strength of evidence, by KQ (continued)

Key Question	Prior Knowledge Used in Determining Strength of Evidence	Sources of Evidence Included in This Systematic Review	Strength of Evidence
Effectiveness and comparative effectiveness of allopurinol and febuxostat depending on the presence of tophi	N/A	<ul style="list-style-type: none"> Subgroup analyses of included trials did not report consistent results when stratified on the presence of tophi. 	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"> Subgroup analyses of 1 head-to-head RCT with low risk of bias (N=2,269) 	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"> 1 placebo-controlled RCT of colchicine with low risk of bias (N=43) Strong observational evidence across 3 RCTs with low risk of bias that included different durations of prophylaxis (N=762, N=2,269, and N=1,072) 	High
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"> Indirect evidence from comparisons across 3 RCTs of differing durations of prophylaxis 1 RCT with high risk of bias (N=190) 	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"> 1 RCT with high risk of bias (N=30) 	Insufficient
KQ4 Treatment Monitoring			
Serum urate monitoring improves outcomes	N/A	<ul style="list-style-type: none"> No direct evidence An argument can be made indirectly, based on the evidence that elevated serum urate levels cause gout 	Insufficient
Treating to a specific target serum urate level reduces the risk of gout attacks	<ul style="list-style-type: none"> Lower serum urate levels are associated with reduced risk of gout attacks 	<ul style="list-style-type: none"> No RCT evidence Variable targets proposed or assessed in the literature 	Low

Table B. Summary of prior knowledge, findings from the systematic review, and strength of evidence, by KQ (continued)

Key Question	Prior Knowledge Used in Determining Strength of Evidence	Sources of Evidence Included in This Systematic Review	Strength of Evidence
KQ5 Criteria for Discontinuation of Pharmaceutical Management			
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"> 3 prospective cohort studies (N=211, N=33, N=100) 	Insufficient
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"> 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) 	Moderate

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

If the rare but serious adverse events from ULT could be further minimized, for example by HLA typing for predisposition, then the benefit/risk profile of ULT would further improve and make more patients eligible for treatment.

An additional research gap concerns prophylaxis when initiating ULT therapy. The optimal duration of such therapy has not been experimentally tested, and the comparative benefits/risks of all three agents used for acute attacks (colchicine, NSAIDs, oral steroids) have not been established.

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 the benefits and harms of long term urate lowering therapy have yet to be demonstrated directly. 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.

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Full Report

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