Urate-Lowering Therapy for the Management of Gout: Summary of 2 Cochrane Reviews

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ABSTRACT. ***Objective.*** To systematically review the evidence on the efficacy, safety, and cost-effectiveness of urate-lowering therapy for gout: xanthine oxidase inhibitors (allopurinol and febuxostat), uricosuric medications (benzbromarone, probenecid and sulfinpyrazone), and uricases (pegloticase and rasburicase).

Methods. A systematic review was performed as part of the 3e (Evidence, Expertise, Exchange) Initiative on Gout. The primary efficacy outcomes were frequency of acute gout attacks, study participant withdrawal due to adverse events, and cost-effectiveness. Serum urate-lowering was a secondary outcome and was the most commonly reported outcome in the included trials.

Results. The search identified 17 articles for efficacy, 31 for safety, and 3 for cost-effectiveness. The main outcome described in these studies was serum urate-lowering. Allopurinol, febuxostat, and pegloticase are all effective at lowering serum urate compared to placebo and febuxostat (≥ 80 mg) was more effective at lowering serum urate than allopurinol. Compared to probenecid, benzbromarone was more effective at lowering serum urate. Regarding acute gout attacks, pegloticase and febuxostat (≥ 120 mg) resulted in more acute attacks than placebo. Regarding the primary safety outcome, more withdrawals due to adverse events were seen only when pegloticase was compared to placebo. The two trials of cost-effectiveness were inconclusive.

Conclusion. There is currently moderate quality data supporting the efficacy and safety of allopurinol, febuxostat, benzbromarone, and probenecid in gout. Pegloticase, while efficacious, is associated with more withdrawals due to adverse events and infusion reactions. There is insufficient evidence currently with respect to the cost-effectiveness or the most optimal sequencing of urate-lowering therapy. (J Rheumatol Suppl. 2014 Sept; 92:33–41; doi:10.3899/jrheum.140460)

Key Indexing Terms:

GOUT	TREATMENT	ALLOPURINOL
FEBUXOSTAT	URICOSURIC AGENTS	PEGLOTICASE

This article is part of the 3e (Evidence, Expertise, Exchange) Initiative on Diagnosis and Management of Gout[1]. The objective of the current work was to systematically review the available literature concerning the following one of 10 selected questions as an evidence base for generating the recommendations:

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What is the efficacy, cost efficacy and safety for urate-lowering therapy (allopurinol but also febuxostat, peguricase, benzbromarone, and probenecid) in the treatment of gout? Which sequence of urate-lowering drugs or combinations should be recommended?

This article includes a shortened version of 2 Cochrane reviews evaluating the efficacy and safety of allopurinol and uricosuric medications for chronic gout based upon randomized controlled trials (RCT) and controlled clinical trials (CCT)[2,3,4,5]. It also includes a safety review based on observational studies and a cost-effectiveness review.

MATERIALS AND METHODS

The systematic reviews performed to address the 3e research question proposed in this article followed the guidelines of the Cochrane Handbook[6].

Rephrasing the research question. The question formed by the expert panel was translated into epidemiologic terms using the PICO (Population, Intervention, Comparator, Outcome) format[6]. Separate PICO were created for efficacy, safety, and cost-effectiveness. The population was any adult (age ≥ 18 yrs) with gout. Interventions were xanthine oxidase inhibitors (allopurinol and febuxostat), uricosuric medications (benzbromarone, probenecid, and sulfinpyrazone), and uricases (pegloticase and rasburicase). Comparators were placebo, no treatment, nonpharmacologic treatment, and other urate-lowering therapy. Trials investigating combinations of 2 or more urate-lowering therapies or comparing different doses of the same medication were also included. Outcomes were based on those recommended by Outcome Measures in Rheumatology (OMERACT)[7,8]. For efficacy, the primary outcome was frequency of acute gout attacks. Secondary efficacy outcomes were pain reduction, health related quality of life, serum urate normalization, function (i.e., activity limitation), and tophus regression. The primary safety outcome was participant withdrawal due to adverse events (WAE) while secondary outcomes were total adverse events (AE) and serious adverse events (SAE). The primary outcome for the economic analysis was the incremental cost-effectiveness ratio (ICER) as cost per quality-adjusted life-years. Only RCT and CCT (i.e., where the method of allocation is quasi-random) were considered for efficacy, while for safety we also included cohort studies, case-control studies, and case series (> 20 patients). For cost-effectiveness we included full and partial economic evaluations, RCT that included economic data, and technology assessments.

Systematic literature search. For each review we performed searches from inception to October 2011 in MEDLINE, EMBASE, and Cochrane Central using a comprehensive search strategy developed in collaboration with an experienced librarian. For details on search strategies see the online Appendix available from www.3egout.com. Abstracts from the 2010 and 2011 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) conferences and the reference lists from retrieved articles and systematic reviews were also hand searched for additional studies. The original searches have been updated since the 3e recommendations were formulated and are discussed further in the associated Cochrane articles[4,5] updated May 13, 2013[4], and January 14, 2014[5]; the updated searches did not retrieve new information that would alter the 3e recommendations.

Selection of articles. Two reviewers (AK, RS) independently screened titles and abstracts retrieved from the searches and the full text as necessary to identify eligible studies. Included articles could be from any one of the languages spoken by the 3e bibliographic authors including English, French, Dutch, German, Spanish, or Portuguese (Cochrane reviews were unrestricted by language).

Data extraction and assessment of risk of bias. The same 2 reviewers independently extracted data of included studies into a standardized template, including trial characteristics, country and source of funding; participant characteristics and inclusion/exclusion criteria; and description of the interventions and outcomes reported. Raw data (means and standard deviations for continuous outcomes and number of events or participants for dichotomous outcomes) were extracted for outcomes of interest. Risk of bias (ROB) for RCT and CCT was assessed using the Cochrane ROB Tool[9], for cohort studies using Hayden, *et al*[10], and for case-control studies using the Newcastle-Ottawa Scale (NOS)[11].

Data analysis. For continuous data, results were analyzed as mean difference (MD) between the intervention and comparator group with 95% confidence intervals. For dichotomous data, a relative risk (RR) with corresponding 95% confidence intervals was calculated. Only data from studies considered sufficiently clinically homogeneous were pooled. Statistical heterogeneity was assessed using the I^2 statistic.

RESULTS

The literature searches identified 1594 efficacy abstracts, 2486 safety abstracts, and 244 cost-effectiveness abstracts (Figure 1). Of these, 17 trials met inclusion criteria for efficacy outcomes, 31 for safety outcomes, and 3 full-text articles (describing 2 studies) for cost-effectiveness outcomes. No additional studies were included from conference abstracts as none had been accepted for publication by our review deadline (February 1, 2012). Characteristics of included studies and study participants are summarized in Tables 1–3.

Allopurinol. Nine studies examined allopurinol efficacy (6 RCT[12-16,17] and 3 CCT[18,19,20]) and 20 examined allopurinol safety outcomes (Tables 1, 2). Gout prophylaxis was provided in all studies with either colchicine[14,15,20] or a choice of colchicine or nonsteroidal antiinflammatory drugs (NSAID)[12,13,16,17,18,19]. Prophylaxis duration varied between 1 month and duration of the study (up to 6 months). All but 3 studies[14,18,20] provided safety data. An additional 2 cohort studies[21,22], 1 open label extension[23], 1 case-control study[24], and 10 case series or other observational studies[25-29,30-34] also provided safety data.

Febuxostat. There were 4 RCT that assessed efficacy[12,13,17,35] (Tables 1, 2). As detailed above, 2 RCT compared febuxostat to allopurinol[12,13], and 1 compared febuxostat to both allopurinol and placebo[17]. A fourth study compared febuxostat to placebo[35]. Allopurinol was given in a dose of 300 mg daily[13] or 300 mg daily in participants with normal renal function and 100 mg or 200 mg daily in participants with impaired renal function[12,17]. Flare prophylaxis was with colchicine[35] or either colchicine or NSAID[12,13,17]. Safety data were provided by all 4 RCT as well as 2 open-label extension studies[23,36], 2 posthoc analyses[37,38], and 1 observational study[39].

Uricosurics. There were 4 trials that assessed uricosuric efficacy[15,16,20,40] (Tables 1, 2). Two RCT compared benzbromarone to allopurinol[15,16], 1 RCT compared benzbromarone to probenecid in participants who had failed allopurinol[40], and 1 CCT compared probenecid to allopurinol therapy[20]. No studies of sulfinpyrazone met

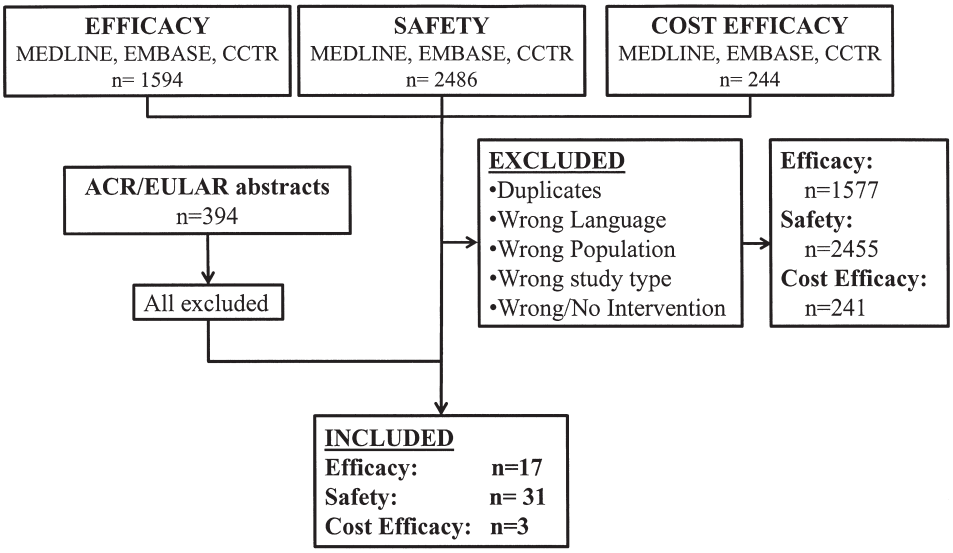

Figure 1. Procedure of the literature searches with included and excluded studies.

inclusion criteria. Acute gout prophylaxis was used in all studies with either colchicine[15,20] or a choice of colchicine or NSAID[16,40]. Where compared, allopurinol was used at doses up to 600 mg/day in 2 studies[16,20] and 300 mg/day in 1 study[15]. Safety data were provided by all trials and 2 additional observational studies[21,34].

Uricases. Three RCT of pegloticase (described in 2 reports[41,42] and 1 posthoc analysis[43]) met inclusion criteria for efficacy, while 2 additional phase 1 studies of pegloticase were included in the safety assessment[44,45]. No studies met inclusion criteria for rasburicase. Two replication RCT assessed the efficacy and safety of pegloticase 8 mg vs placebo for 6 months; pegloticase was given either every 2 weeks or every month[41]. A third study randomized participants to different pegloticase doses (between 4 mg and 12 mg) given either every 2 weeks or every month[42]. Colchicine or NSAID prophylaxis was provided for the duration of the replication RCT[41] but was provided at the discretion of the investigator in the earlier Phase 2 study[42].

Economic search results. Two full or partial economic analyses (3 reports, but 2 of them covered the same study) met inclusion criteria (Table 3).

Risk of Bias

Risk of bias of included studies is shown in Tables 1 and 2; and further details are reported in the Cochrane reviews[4,5]. For allopurinol the 9 RCT and CCT had unclear[12,13,16,17] or high risk of bias[14,15,18,19,20]; the 14 observational studies had moderate[22,24] or high risk of bias[21,23,25-29,30,31,32,33]. For febuxostat, the 4 RCT had unclear risk of bias[12,13,17,35], and the 5 observational studies had unclear[37] and high[23,36,38,39] risk of bias. For uricosurics, 6 RCT of uricosuric efficacy had unclear[16,40] or high risk of bias[15,20,21,34]. The 2 replication RCT of pegloticase[41] and the posthoc analysis of these studies[43] had low risk of bias. The other Phase 2 and Phase 1 studies had high risk of bias[42,44,45].

Efficacy of Interventions

For full results of the data analyses see online appendix, available from www.3egout.com.

Allopurinol vs placebo. In the first 2 months of therapy, while all patients were taking acute gout prophylaxis, there was no statistically significant difference in the frequency of acute gout attacks between allopurinol at the studied doses (up to 300 mg/day) and placebo (1 trial; unclear ROB). Significantly more participants taking allopurinol achieved a serum urate level < 6.0 mg/dl (0.36 mmol/l) (1 trial; unclear ROB; RR 49.3; 95% CI 7.0 to 349.0; absolute risk difference (ARD) 38% more achieved target)[5]. There was no between-group difference in number of tophi following therapy (but results were not presented)[17].

Febuxostat versus placebo. Frequency of acute gout attacks was similar for placebo and febuxostat 40 mg (1 trial; unclear ROB) and 80 mg/day (2 trials; unclear ROB), while higher doses of febuxostat were more likely than placebo to be associated with acute gout attacks: 120 mg febuxostat/day (2 trials; unclear ROB; pooled RR 1.7; 95% CI 1.3 to 2.3; ARD 16% more likely) and 240 mg febuxostat/day (1 trial; unclear ROB; RR 2.6; 95% CI 1.8 to 3.7; ARD 31% more likely). All doses of febuxostat studied were more likely than placebo to achieve a serum urate level of < 6.0 mg/dl (0.36 mmol/l): febuxostat 40 mg/day (1 trial; unclear ROB; RR 44.1; 95% CI 2.8 to 702.9; ARD 57% more achieved target), febuxostat 80 mg/day (2 trials; unclear ROB; pooled RR 78.8; 95% CI 16.0 to 388.2; ARD 72% more achieved target), febuxostat 120 mg/day (2 trials;

Table 1. Summary of clinical trials assessing efficacy and safety of urate lowering medications in gout.

Study	Population	Interventions & Comparators	Dose per day, mg	Outcome (s)	Study Design & Duration, mo	Risk of Bias
Schumacher 2008[17]	1067 patients with gout, mean age 51–54 yrs, 94% male	A F Pl	300 or 100 (RI) 80, 120, or 240 NA	Efficacy, Safety	RCT, 7 mo	Unclear
Becker 2010[12]	2268 patients with gout, mean age 52–53 yrs, 94% male	A F	300 or 200 (RI) 40 or 80	Efficacy, Safety	RCT, 6 mo	Unclear
Becker 2005[13]	760 patients with gout, mean age 51–52 yrs, 96% male	A F	300 80 or 120	Efficacy, Safety	RCT, 12 mo	Unclear
Bull 1989[18]	50 patients with gout, mean age 53–56 yrs	A	Continuous vs intermittent; variable dose	Efficacy	CCT, 24-28 mo	High
Gibson 1982[14]	59 patients with gout, mean age 49 yrs, 98% male	A None	200 NA	Efficacy	RCT, 12–24 mo	High
Rodnan 1975[19]	20 male patients with gout	A	100 three times daily vs 300 once daily	Efficacy, Safety	CCT, 1.75 mo	High
Reinders 2009[34]	65 patients with gout, mean age 59–60 yrs, 81–83% male	A B	300 to 600 100 to 200	Efficacy, Safety	RCT, 4 mo	Unclear
Perez-Ruiz 1999[15]	37 patients with gout, mean age 65 yrs, 86% male	A B	100 (RI) to 300 100 to 200	Efficacy, Safety	RCT, 9–24 mo	High
Scott 1966[20]	40 patients with gout, mean age 54 yrs, 100% male	A P	300 to 600 2000	Efficacy	CCT, 10–24 mo	High
Becker 2005 A[35]	153 patients with gout, mean age 52–55 yrs	F Pl	40, 80, or 120 NA	Efficacy, Safety	RCT, 1 mo	Unclear
Reinders 2009A[40]	62 gout patients who had failed allopurinol, mean age 55–58 yrs	B P		Efficacy, Safety	RCT, 2 mo	Unclear
Sundy 2011[41]	225 gout patients, mean age 54–58 yrs	Peg, Peg/Pl, Pl		Efficacy, Safety	2 replication RCT, 6 mo	Low
Singh 2011[43]	212 gout patients, mean age 55 yrs, 82% male	Peg, Peg/Pl, Pl		Efficacy	Post-hoc of RCT, 6 mo	Low
Sundy 2008[42]	41 gout patients, mean age 58 yrs, 85% male	Peg 2 doses at 2–4 weeks		Efficacy, Safety	Phase 2 RCT, 3–3.5 mo	High

Pl: placebo; A: allopurinol; F: febuxostat; B: benzbromarone; P: probenecid; S: sulfinpyrazone; Peg: pegloticase; R: rasburicase; RCT: randomized controlled trial; CCT: controlled clinical trial; OLE: open-labelled Extension; ND: not discussed; NA: not applicable; RI: renal insufficiency.

unclear ROB; pooled RR 90.1; 95% CI 18.3 to 443.4; ARD 86% more achieved target), and febuxostat 240 mg/day (1 trial; unclear ROB; RR 116.9; 95% CI 16.6 to 824.2; ARD 91% more achieved target).

Allopurinol versus febuxostat. During the first 8 weeks of therapy, while taking gout prophylaxis, no significant difference in acute gout attacks was detected comparing allopurinol at studied doses (up to 300 mg/day) and febuxostat 80 mg/day (2 trials; unclear ROB)[5]. Allopurinol was less likely to be associated with an acute gout attack when compared with higher doses of febuxostat: 120 mg/day (2 trials; unclear ROB; pooled RR 0.6; 95% CI 0.5 to 0.8; ARD 14% less likely) or 240 mg/day (1 trial; unclear ROB; RR 0.4; 95% CI 0.3 to 0.6; ARD 29% less likely). There was no significant difference between allopurinol and febuxostat 40 mg/day with respect to serum urate normalization (1 trial; unclear ROB). Compared with higher doses of febuxostat, however, allopurinol was less likely to achieve the serum urate target of < 6.0 mg/dl (0.36 mmol/l): febuxostat 80 mg/day (3 trials; unclear ROB; pooled RR 0.6; 95% CI 0.5 to 0.7; ARD 32% fewer achieved target), febuxostat 120 mg/day (2 trials; unclear ROB; pooled RR 0.5; 95% CI 0.4 to 0.5; ARD 42% fewer achieved target), or febuxostat 240 mg/day (1 trial; unclear ROB; RR 0.4; 95% CI 0.4 to 0.5; ARD 53% fewer achieved target)[5].

Allopurinol versus uricosurics. There was no significant difference between 4 months of allopurinol and benzbromarone in frequency of acute gout attacks (1 trial; unclear

Table 2. Summary of observational studies included in safety analysis.

Study	Population	Interventions & Comparators	Study Design & Duration, mo	Risk of Bias	Summary of Outcomes
Stamp 2011[22]	90 gout patients, mean age 59 yrs, 88% male	A	Cohort, 12 m	Moderate	Allopurinol dose escalation: 89% achieved target serum urate (< 0.36 mmol/l); no serious adverse events recorded
Perez-Ruiz 2010[21]	546 investigator defined gout patients, mean age 58-59 yrs	A, B	Cohort, ND	High	Risk factors for nephrolithiasis: clearance of uric acid at baseline and undissociated uric acid concentration during followup
Becker 2009[23]	1086 patients with gout	A, F	OLE, of 2 RCT 31–40 m	High	No significant difference in overall adverse events rate comparing febuxostat to allopurinol in OLE
Foong 2009[24]	379 investigator defined gout patients, 41% male	A	Case control, ND	Moderate	Allopurinol most frequently associated with Stevens-Johnson syndrome or toxic epidermal necrolysis in an outpatient setting: 66 exposed patients (17.4%) and 28 exposed control subjects (1.9%) (adjusted OR = 18; 95% CI 11 to 32)
Lee 2008[33]	28 patients of whom 16 had gout, mean age 69 yrs, 32% male	A	Case series, ND	High	Allopurinol hypersensitivity syndrome cases
Arellano 1993[25]	101 investigator defined gout patients, mean age 58 yrs, 67% male	A	Case series, NA	High	Allopurinol hypersensitivity syndrome cases
Singer 1986[31]	80 investigator defined gout patients (8 cases and 72 cases from literature)	A	Case series, NA	High	Allopurinol hypersensitivity syndrome cases
Hande 1984[28]	78 investigator defined gout patients (6 cases and 72 from literature)	A	Case series, NA	High	Allopurinol hypersensitivity syndrome cases
Fraunfelder 1982[27]	30 investigator defined gout patients	A	Case series, NA	High	30 cases of cataracts in patients taking allopurinol
Lang 1979[29]	20 investigator defined gout patients	A	Case series, NA	High	20 patients with severe hypersensitivity reactions to allopurinol
Reinders 2007[34]	50 gout patients	A or A/P combination	Observational, NA	High	10% withdrawal due to adverse events for allopurinol step of therapy
Liu 1988[30]	53 investigator defined gout patients, mean age 59 yrs	A	Observational, NA	High	Lens changes in allopurinol treated patients
Dalbeth 2006[26]	250 gout patients, mean age 56 yrs, 82% male	A	Observational, NA	High	1.6% patients with rash to allopurinol; none taking higher than recommended allopurinol based on renal dosing
Vazquez-Mellado 2001[32]	120 investigator defined gout patients, mean age 53, 98% male	A	Observational, NA	High	4% allopurinol related adverse reactions; not increased in patients treated above recommended dose for creatinine clearance
Goldfarb 2011[37]	138 patients with gout	F Pl	Posthoc of RCT, 1 m	Unclear	Most common adverse event diarrhea (11%) or pain (10%)
Whelton 2011[38]	116 patients with gout, mean age 53 yrs, 91% male	F	Posthoc of OLE of RCT, 260 m	High	18% of participants experienced a serious adverse event, of which, atrial fibrillation was the most commonly reported (5%)
Schumacher 2009[36]	116 patients with gout, mean age 53 yrs, 91% male	F	OLE of RCT, 260 m	High	

Table 2. Continued.

Study	Population	Interventions & Comparators	Study Design & Duration, mo	Risk of Bias	Summary of Outcomes
Chohan 2011[39]	13 gout patients with previous serious allopurinol reactions	F	Observational, NA	High	1 of 13 patients developed hypersensitivity type cutaneous vasculitis when changed to febuxostat
Sundy 2007[45]	24 gout patients, mean age 57 yrs, 83% male	Peg	Phase 1, 35 days	High	58% of participants had gout flares. 38% of participants developed IgG antibodies to peguricase
Ganson 2006[44]	13 gout patients, mean age 56 yrs, 76% male	Peg	Phase 1, 21 days	High	3 of 13 participants had injection site reactions and 6 had gout attacks

Pl: placebo; A: allopurinol; F: febuxostat; B: benzbromarone; P: probenecid; S: sulfinpyrazone; P: pegloticase; rasburicase (Ras); RCT: randomized controlled trial; OLE: open-labelled extension; ND: not discussed; NA: not applicable.

Table 3. Summary of economic evaluations of urate lowering therapies in gout.

Study	Study Design	Study Details	Risk of Bias
Stevenson 2011 & NICE 2008[47,48]	Cost-effectiveness analysis	Manufacturer supplied febuxostat economic analyses	High
Ferraz 1995[49]	Cost-effectiveness analysis	1993 Canadian population, decision analysis model analysing initiation of urate lowering drug (ULD) vs non ULD initiation from a societal perspective regarding costs with a 1 year time horizon	Low

ROB) or 2 months of probenecid (1 trial; high ROB). Four months of allopurinol or benzbromarone with dose escalation resulted in no significant difference in whether patients achieved a target serum urate level (2 trials; unclear and high ROB)[4].

Uricosuric comparison. Benzbromarone demonstrated no statistically significant difference in the frequency of acute gout attacks when compared with 2 months of probenecid (1 trial; unclear ROB). Benzbromarone, however, was more likely to achieve a target serum urate of < 0.3 mmol/l (5 mg/dl) (1 trial; unclear ROB; RR 1.4; 95% CI 1.0 to 2.0; ARD 24% more achieved target)[4].

Uricases versus placebo. Pegloticase, given either biweekly or monthly, was associated with more acute gout attacks in the first 3 months of therapy than placebo (2 replication trials; low ROB; biweekly pooled RR 1.4; 95% CI 1.0 to 1.9 and monthly pooled RR 1.5; 95% CI 1.1 to 2.0; ARD 22% and 27% more likely, respectively). Both biweekly and monthly pegloticase administration were more likely to achieve a target serum urate level of < 6 mg/dl (< 0.36 mmol/l) than placebo (2 replication trials; low ROB; biweekly pooled RR 37.4; 95% CI 2.4 to 594.3 and monthly pooled RR 30.5; 95% CI 1.9 to 488.1; ARD 42% and 35% more achieved target, respectively). Pegloticase was associated with greater improvement in disability (measured by the HAQ-DI) when compared to placebo: monthly (2 replication trials; low ROB; mean difference –0.2; 95% CI –0.4 to –0.1), and biweekly (2 replication trials; low ROB; mean difference –0.2; 95% CI –0.4 to –0.1). Resolution of 1 or more tophi was more likely to occur after 6 months of therapy with either monthly pegloticase (2 replication trials; low ROB; pooled RR 2.9; 95% CI 0.7 to 12.0) or biweekly pegloticase (2 replication trials; low ROB; pooled RR 5.5; 95% CI 1.4 to 21.6) when compared to placebo. Pegloticase given biweekly was also associated with greater improvement in participant pain compared with placebo (2 replication trials; low ROB; mean difference –14.2; 95% CI –24.4 to –4.0 on a 0–100 VAS). Monthly pegloticase was not associated with greater improvement in pain compared with placebo.

Safety of interventions. There were no differences in withdrawals due to AE between allopurinol, placebo, or febuxostat. However, allopurinol was associated with more AE than 80 mg (3 trials; unclear ROB; pooled RR 1.1; 95% CI 1.0 to 1.1; ARD 4% more individuals experienced adverse events) and 120 mg/day febuxostat (2 trials; unclear ROB; pooled RR 1.1; 95% CI 1.1 to 1.2; ARD 9% more individuals).

There were no differences between the 4-month comparison of allopurinol and benzbromarone therapy or 2-month comparison of benzbromarone and probenecid with respect to number of withdrawals due to AE or total number of AE.

Compared with placebo, participants treated with pegloticase were more likely to withdraw due to AE (2 replication trials; low ROB; biweekly RR 7.6; 95% CI 1.0 to 55.6 and monthly RR 8.2; 95% CI 1.1 to 59.7; ARD 15% and 17% more withdrew, respectively), but there was no significant difference between pegloticase and placebo with respect to total AE. Pegloticase was noted to have a significantly higher number of infusion reactions than placebo: biweekly 26% ($p = 0.002$), monthly 42% ($p < 0.0001$), and placebo 5%[41]. Based on postmarketing surveillance, an ACR Hotline 2012[46] indicated that pegloticase should not be used concurrently with urate-lowering medications as there may be a higher risk of infusion reactions.

Table 2 summarizes the safety outcomes from the included observational studies.

Economic outcomes. One of the included articles was an evaluation of the manufacturer of febuxostat's submission to the National Institute for Health and Clinical Excellence (NICE) single technology appraisal process[47,48]. Although the NICE technology appraisal concluded that the economic analysis submitted by the manufacturer was full of uncertainties — precluding its use in assessing the cost-effectiveness of febuxostat in the management of hyperuricemia in patients with gout — no model details were presented to enable review[47]. The other study, by Ferraz, *et al*[49], is a decision analysis model from a 1993 Canadian population analysing the initiation of urate-lowering drug (allopurinol) versus non-urate-lowering drug initiation from a societal perspective regarding costs with a 1-year period. Although this study was judged to be at low ROB (per NICE guideline methodology for economic evaluations[50]), its assumptions regarding medication adherence, acute attack rate, and effectiveness of different urate-lowering medications are now known to be erroneous, making it difficult to draw any conclusions from this study.

DISCUSSION

The objective of this systematic review was to summarize the evidence for the efficacy, safety, and cost-effectiveness of urate-lowering therapies in patients with gout. We identified 17 studies addressing efficacy, 31 studies addressing safety, and 2 studies addressing cost-effectiveness.

The most well documented outcome was serum urate normalization. Acute gout attacks, the primary outcome of this systematic review, are more difficult to interpret because the incidence of these attacks is higher in the course of urate-lowering therapy (mobilization gout). The short-term nature of the included studies did not allow assessment of the longterm reduction in acute gout attacks. Very few of the studies addressed the other OMERACT gout outcomes, such as pain reduction, health related quality of life, function (i.e., activity limitation), and tophus regression.

There have recently been 2 other systematic reviews of urate-lowering therapy in gout[51,52]. The first is summarized in the ACR Gout Guidelines[51,53]. The conclusions of both reviews are broadly consistent with our review although they differed with respect to study inclusion. The review on which the ACR guidelines were based included observational studies[40,54,55], while Hamburger, *et al* included uncontrolled trials[34,56], and studies of people with asymptomatic hyperuricemia[57]. As well Hamburger, *et al* limited the review to include only studies published from 2005, and excluded uricosurics other than probenecid because these are not currently available in the US[14,15,18,19,20,40].

In summary, there is currently moderate quality evidence for the efficacy and safety of a number of urate-lowering therapies including allopurinol, febuxostat, benzbromarone, and probenecid. Pegloticase, while efficacious, results in a greater number of withdrawals due to AE and infusion reactions compared with placebo. It is thought that these infusion reactions may occur more frequently in individuals with higher anti-pegloticase antibody levels[41]. At the time of this review, there was insufficient economic evidence from full or partial economic evaluations with which to support or refute treatment decisions regarding urate-lowering therapy. Future research would be beneficial in examining higher doses of allopurinol, combination therapy, longer duration of urate-lowering therapy, and economic analyses, as well as reporting other outcome measures such as health related quality of life, pain reduction, and tophus regression.

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