Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Literature Scan: Analgesics for Gout

Month/Year of Review: April 2015 **Date of Last Review:** January 2014

Current Status of PDL Class:
See Appendix 1

Conclusions and Recommendations:

- There is low quality evidence a greater proportion of patients respond to treatment, defined as a 50% or greater decrease in pain score, with high-dose (4.8 mg over six hours) colchicine compared to placebo (absolute risk difference 28%; RR 2.16; 95% CI 1.28 to 3.65; NNT 4) and low quality evidence significantly decreases inflammation scores more than placebo (absolute risk difference 45%; RR 10.50; 95% CI 1.48 to 74.38).
- There is low quality evidence of no significant difference between high- (4.8 mg over six hours) and low-dose (1.8 mg over one hour) colchicine in treatment response (RR 0.86; 95% CI 0.53 to 1.41) with fewer gastrointestinal events with low-dose colchicine.
- There remains insufficient evidence of any significant difference between allopurinol and febuxostat for treatment of acute gout flares.
- There is low-quality evidence of uncertainty around the difference in prevention of acute gout attacks between probenecid and allopurinol after 18 months of treatment (53% vs. 55%; RR 0.96; 95% CI 0.53 to 1.75) with no significant difference found.
- Continue to include one xanthine oxidase inhibitor as preferred on the PDL for the treatment of chronic gout and hypeuricemia.
- No further review or research needed; evaluate comparative costs in executive session.

Previous Conclusions and Recommendation:

- Therapy with xanthine oxidase inhibitors remains first-line therapy for chronic gout and hyperuricemia.
- There is insufficient evidence of any significant difference between allopurinol and feboxostat on clinical outcomes such as gout flares. The American College of Rheumatology guidelines give no preference to either agent and both are recommended as first line treatment.
- There is insufficient evidence for the treatment of intra-articular corticosteroids for the treatment of gout.
- There is moderate quality evidence of no difference in efficacy/effectiveness or safety between agents.
- Colchicine is the only agent for gout and Familial Mediterranean Fever.
- Febuxostat reduces serum urate below 6 mg/dL in a significantly greater proportion of patients with gout and hyperuricemic compared to patients receiving allopurinol but there was no difference in gout flares.
- Block pharmacy claims for pegloticase.

Author: M. Herink, Pharm.D. Date: May 2015

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to placebo or active controls were conducted. A summary of the clinical trials is available in **Appendix 2**. The Medline search strategy used for this literature scan is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drugs, indications, and safety alerts. Finally, the AHRQ National Guideline Clearinghouse was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

1. A systematic review was completed to evaluate current evidence for the treatment of acute gout.[1] A high quality literature search was done and the methodological quality of the trials was assessed using the Jadad scale. Thirty RCTs were included in the analysis, of which 21 were double blinded. The majority of the trials assessed evaluated NSAIDs, including indomethacin, and cox-2 inhibitors for the treatment of acute gout and will not be discussed here. Two trials were identified evaluating the use of colchicine for acute gout. Compared to placebo, colchicine had greater efficacy in reducing pain when administered within 12 hours of an acute attack. Compared to high dose colchicine (4.8 mg over six hours), low dose colchicine (1.8 mg over one hour) had a significantly greater tolerability profile and were similar in efficacy.

2. The Cochrane Collaboration recently evaluated colchicine for the treatment of acute gout with a literature search up to April 2014.[2] Only two trials were identified (n=618) which resulted in low quality evidence of a greater proportion of patients responding to treatment, defined as a 50% or greater decrease in pain score, with high-dose colchicine (total 4.8 mg over six hours) compared to placebo (absolute risk difference 28%; RR 2.16; 95% CI 1.28 to 3.65; NNT 4) and low quality evidence for a greater decrease in inflammation score compared to placebo (absolute risk difference 45%; RR 10.50; 95% CI 1.48 to 74.38). There was no evidence to evaluate quality of life, functioning, or withdrawals due to adverse events. The smaller study evaluated a high-dose regimen that is no longer recommended in clinical practice (1 mg colchicine, then 0.5 mg every two hours until relief or side effects) and the mean dose given was not included. The second trial compared colchicine 1.8 mg over one hour, 4.8 mg over 6 hours, and placebo. Those on the lower dose of colchicine also had a significantly greater response compared to placebo (RR 2.74; 95% CI 1.05 to 7.13) and there was low quality evidence of no significant difference between the higher and lower doses of colchicine in response to treatment (RR 0.86; 95% CI 0.53 to 1.41). There was a significantly higher rate of total adverse events and gastrointestinal side effects with the high-dose colchicine compared to low-dose.

   The authors concluded that, based on only two trials, there is low-quality evidence that low-dose colchicine is likely to be an effective treatment for acute gout with some uncertainty around the estimated effect. There are no studies comparing colchicine in populations with comorbidities or in comparison with other commonly used medications, such as NSAIDs and glucocorticoids.

3. Another systematic review and meta-analysis from the Cochrane Collaboration evaluated the use of allopurinol for the treatment of chronic gout.[3] All RCTs comparing allopurinol to placebo or active treatment in adults with chronic gout were included. The primary outcomes were frequency of acute gout attacks, achievement of normal serum urate levels, pain, function, tophus regression, withdrawals due to adverse events, and serious adverse events.

Eleven trials were identified from the literature search and included in the review. The most relevant active comparison was allopurinol compared to febuxostat (four trials). Only one trial was found to have a low risk of bias in all domains.

There was moderate quality evidence from 1 study (n=51) that compared to placebo, allopurinol did not significantly reduce acute gout attacks (7.7% in allopurinol group vs. 12% in placebo; RR 0.64; 95% CI 0.12 to 3.52) but did significantly increase the proportion of subjects achieving target serum urate levels (RR 49.11; 95% CI 3.15 to 765.58) with no significant difference in withdrawals due to adverse events (RR 1.36; 95% CI 0.61 to 3.08) or serious adverse events (RR 1.93; 95% CI 0.48 to 7.80).

Data from four trials with unclear to high risk of bias were pooled and showed low quality evidence of no difference in the frequency of acute gout attacks with allopurinol compared to febuxostat 80 mg (RR 0.89; 95% CI 0.71 to 1.10). Subjects taking allopurinol had significantly fewer acute gout attacks compared with those on higher doses of febuxostat 120 mg (RR 0.62; 95% CI 0.51 to 0.76). Compared to febuxostat 80 mg, those on allopurinol were less likely to achieve target serum urate levels (RR 0.55; 95% CI 0.48 to 0.63). There was moderate quality evidence of no difference in withdrawals due to adverse events between allopurinol and feboxostat 80 mg (RR 0.89; 95% CI 0.62 to 1.26). Trials did not report pain reduction or functioning.

All other comparisons were based only on small studies. The authors concluded there was low- to moderate- quality evidence demonstrating similar effects on withdrawals due to adverse events and incidence of acute gout attacks when allopurinol was compared to placebo or febuxostat 80 mg daily. Allopurinol seemed more effective than placebo and less effective than febuxostat in achieving a target serum urate level of 6 mg/dL or less based on low- to moderate-quality evidence.

4. Lastly, a Cochrane Collaboration systematic review evaluated the evidence for uricosuric medications for the treatment of chronic gout.[4] Controlled clinical trials comparing uricosuric agents (probenecid, sulphinpyrazone or benzbromarone) to other treatments or placebo were included. Probencid is the only agent available in the US and only data for probencid will be summarized here. Five trials were identified; however, only one of these included probenecid. A single center, controlled clinical trial compared probecid to allopurinol in 40 subjects with chronic gout. Study outcomes were acute gout attacks, serum urate, and tophus regression. This small study with high risk of bias provided low-quality evidence of uncertainty around the difference in acute gout attacks between probenecid and allopurinol after 18 months of treatment (53% vs. 55%; RR 0.96; 95% CI 0.53 to 1.75). The study did not report proportion of patients achieving target serum urate levels, pain reduction, functioning, withdrawals due to adverse events or total adverse events. In addition, 29% (5/17) of subjects treated with probenicid changed therapy to sulphinpyrazone due to minor adverse events.

Guidelines:
None identified.

New drugs:
None identified.

New Formulations/Indications:
None identified.

New FDA safety alerts:
None identified.

References:
1. Khanna PP, Gladue HS, Singh MK, et al. Treatment of acute gout: a systematic review. *Semin Arthritis Rheum*. 2014;44(1):31-38. doi:10.1016/j.semarthrit.2014.02.003.

2. Van Echteld I, Wechalekar MD, Schlesinger N, Buchbinder R, Aletaha D. Colchicine for acute gout. *Cochrane Database Syst Rev*. 2014;8:CD006190. doi:10.1002/14651858.CD006190.pub2.

3. Seth R, Kydd ASR, Buchbinder R, Bombardier C, Edwards CJ. Allopurinol for chronic gout. *Cochrane Database Syst Rev*. 2014;10:CD006077. doi:10.1002/14651858.CD006077.pub3.

4. Kydd ASR, Seth R, Buchbinder R, Edwards CJ, Bombardier C. Uricosuric medications for chronic gout. *Cochrane Database Syst Rev*. 2014;11:CD010457. doi:10.1002/14651858.CD010457.pub2.

Author: M. Herink, Pharm.D. Date: May 2015

Appendix 1: Current Status on Preferred Drug List

- Preferred Agents: ALLOPURINOL, COLCHICINE/PROBENECID
- Non-Preferred Agents: COLCHICINE (COLCRYRS®), FEBUXOSTAT (ULORIC®), PROBENECID, PEGLOTICASE (KRYSTEXXA)

Appendix 2: New Clinical Trials

Seventeen potentially relevant articles were evaluated from the literature search. After further review, all articles were either post-hoc analyses of older trials, non relevant comparisons, meta-analyses of select studies, or studies without evaluation of clinical outcomes, and were therefore excluded.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to April 20 2015
1 Allopurinol.mp. 4133
2 colchicine.mp 5988
3 probenecid.mp. 1287
4 febuxostat.mp. 261
5 pegloticase.mp. 72
6 Gout 2816
7 Hyperuricemia 1769
8 1or 2o r 3 or 4 or 5 11279
9 6 or 7 4071
10 8 and 9 1017
11 limit 10 to (english language and humans and yr="2014 -Current" and (clinical trial, phase iii or clinical trial or controlled clinical trial or guideline or meta analysis or randomized controlled trial or systematic reviews)) 17

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