Therapeutic Class Overview
Colchicine

Therapeutic Class Overview/Summary:
This review will focus on the agent colchicine (Colcrys®, Mitigare®), which is used in the management of gout.[1,2] Gout is a complex inflammatory disease that occurs in response to the presence of monosodium urate monohydrate crystals in the joints, bones and soft tissues.[3,4] The disease consists of four clinical phases.[5] The first phase is asymptomatic hyperuricemia. Although hyperuricemia is a necessary predisposing factor, the presence of high serum urate levels alone does not automatically lead to gout.[3,5] One study reported that 78% of the men in the trial with serum urate levels greater than 9 mg/dL did not develop gout over a five year period.[6] Hyperuricemia can be caused by impaired renal excretion or overproduction of serum urate and/or overconsumption of purine-rich foods that are metabolized to urate.[3] Humans, lack the enzyme uricase and therefore cannot convert urate to the soluble allantoin as the end product of purine metabolism.[4] The deposition of monosodium urate monohydrate crystals into the joints and other areas of the body begin when serum urate levels are greater than 6.8 mg/dL. This concentration is the saturation point of urate in biological fluids and it is at this concentration where monosodium urate monohydrate crystals begin to precipitate. As mentioned previously the presence of hyperuricemia does not automatically lead to gout. Other factors, when combined with hyperuricemia that contribute to monosodium urate monohydrate deposition and the development of gout include trauma or irritation of joins, lower temperatures which favor crystal deposition and previously diseased joints.[6]

The second phase is characterized by intermittent acute gout attacks.[5] These attacks are due to the abrupt release of monosodium urate monohydrate crystals into the joint space where they initiate an acute inflammatory reaction characterized by painful inflammatory arthritis.[6] These attacks typically resolve spontaneously over a period of seven to 10 days.[4] The time interval separating these acute attacks is the third phase of the disease and is known as the intercritical gout period.[7] The time period separating acute gout attacks during this period vary widely between a few days to several years. Overtime, if the disease is left untreated it evolves into chronic tophaceous gout. This phase of the disease is characterized by the deposition of solid monosodium urate monohydrate crystal aggregates known as tophi in a variety of locations including joints, bursae and tendons.[7] In addition deposits of monosodium urate monohydrate crystals in the renal tubules can also lead to renal calculi and nephropathy.[5]

Treatment of gout consists of rapid relief of pain and disability caused by acute gout attacks and the reduction of serum urate levels. This reduction prevents further acute attacks and the progression of the disease to tophaceous gout.[4] Although acute attacks can be treated with anti-inflammatory medications, the underlying cause of the disease can only be treated by lowering serum urate levels.[6]

Colchicine is believed to exert a positive effect in gout by preventing the activation, degranulation and migration of neutrophils, implicated in the pathogenesis of gout symptoms. The mechanism by which colchicine acts in patients with Familial Mediterranean Fever has not been fully established; however, there is evidence suggesting that colchicine interferes with the assembly of the inflammasome complex found in neutrophils and monocytes that medicate the activation of interleukin-1β.[1,2] Colcrys® is the branded version of colchicine. In 2006, the Food and Drug Administration (FDA) launched the Unapproved Drugs Initiative. This initiative targeted drugs that had never formally received FDA-approval.[8] The initiative required manufacturers of the non-approved versions of colchicine to either apply for approval through the current FDA approval methods or cease manufacturing the agent. On September 30, 2010, the FDA informed manufacturers of these non-approved products that they were expected to stop manufacturing single-ingredient oral colchicine by October 14, 2010 and must stop shipping the product by December 30, 2010. Colchicine (Colcrys®), was approved by the FDA on July 30, 2009 and is the only currently approved and remaining colchicine product.[9] More recently, a new capsule formulation and generic version has been approved by the FDA.[2]

Table 1. Current Medications Available in the Therapeutic Class[1-2]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Colchicine (Colcrys®*, Mitigare®*)	Familial Mediterranean Fever†, Prophylaxis of gout glares, Treatment of gout flares†	Capsule: 0.6 mg Tablet: 0.6 mg	a

*Generic available in at least one dosage form or strength.
†Colcrys®

Evidence-based Medicine

- Clinical trials demonstrate the safety and efficacy of the colchicine for treatment of acute gout or for gout prophylaxis.[15-19]
- FDA-approval of brand colchicine for Familial Mediterranean Fever treatment was not based on new clinical studies but rather on previously published literature. This published literature consists of three double-blind, placebo-controlled, cross-over studies published in 1974 that evaluated a total of 48 adult patients with Familial Mediterranean Fever. These studies as well as others confirmed that the agent is efficacious in both reducing the number of attacks and in aborting acute attacks.[1,15,16]
- One study that evaluated brand colchicine for this indication was the AGREE trial which was the basis for FDA-approval. This study evaluated two different dosing regimens of colchicine; high dose (1.2 mg followed by 0.6 mg every hour for six hours), low dose (colchicine 1.2 mg followed by 0.6 mg in one hour followed by placebo doses every hour for five hours) and placebo in the treatment of acute gout attacks. The study demonstrated that the older traditional dosing regimen had the same efficacy as the new FDA-approved low dose regimen; however there were significantly more adverse drug events with the high dose.[18]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - The ACR, British Society of Rheumatology, and European League Against Rheumatism (EULAR) treatment guidelines all recommend a nonsteroidal anti-inflammatory drug (NSAID), colchicine, or a corticosteroid for the treatment of an acute gout attack.[10-13]
  - According to the more recent ACR guidelines for the management of gout, initiation of urate lowering therapy is recommended in patients with an established diagnosis of gout and tophus or tophi, frequent attacks of acute gouty arthritis (≥2 attacks/year), chronic kidney disease stage 2 or worse, and past urolithiasis.[16]
  - Goal is to achieve serum urate levels <300 mmol/L to ≤360 mmol/L.[10,12,13]
  - Of note, the ACR notes that serum urate lowering below 5 mg/dL may be needed to improve gout signs and symptoms.[10]
  - Agents used to lower serum urate levels include allopurinol, probenecid, and febuxostat. The main difference between these agents is that allopurinol and febuxostat inhibit urate production and probenecid promotes urate excretion.[10-14]
  - The 2012 ACR guideline, which was published after FDA approval of febuxostat, recommends either allopurinol or febuxostat as the first-line urate lowering therapy approach for the management of gout, with no preference stated between the two.[10]
  - During initiation of urate lowering therapy the guidelines recommend concurrent prophylaxis with either colchicine or an NSAID, although generally colchicine is the preferred, to prevent acute attacks while starting therapy.[11-13]
  - Concomitant therapy is generally recommended for up to six months at which point only the urate lowering agent is continued. Treatment with the urate lowering agent has the potential to be lifelong.[11,12]

- Other Key Facts:
  - Colchicine tablets and colchicine capsules have different FDA-approved indications and ages approved.[1,2]
  - Colchicine tablets are approved for use in children ≥4 years of age for the treatment of Familial Mediterranean Fever (tablets)[1]

References

1. Colcrys® [package insert]. Deerfield (IL): Takeda Pharmaceuticals America, Inc.; 2012 Nov.
2. Mitigare® [package insert]. Memphis (TN): Hikma Americas, Inc.; 2015 July.
3. Monach P, Becker MA. Pathophysiology of gouty arthritis. In: Basow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2012 [cited 2012 Jun 27]. Available from: http://www.utdol.com/utd/index.do.
4. Neogi T. Gout. N Engl J Med. 2011;364:443-52.
5. Hardy E. Gout diagnosis and management: what NPs need to know. The Nurse Practitioner. 2011 Jun;159.
6. Schumacher HR. The pathogenesis of gout. Cleveland Clinic Journal of Medicine. 2008 Jul;75(supplement 5);S2-S4.
7. Grassi W, De Angelis R. Clinical features of gout. Reumatismo. 2011;63(4):238-45.
8. Unapproved Drugs Initiative [press release on the Internet]. Rockville (MD): Food and Drug Administration (US): 2009 Mar 03 [cited 2012 Jun 27]. Available from: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/SelectedEnforcementActionsonUnapprovedDrugs/ucm118990.htm.
9. FDA orders halt to marketing of unapproved single-ingredient oral colchicine [press release on the Internet]. Rockville (MD): Food and Drug Administration (US): 2010 Sep 30 [cited 2012 Jun 27]. Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm227796.htm.
10. Khanna D, Fitzgerald JD, Khanna PP, Bae S, Singh MK, Neogi T, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: Systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care & Research. 2012 Oct;64(10):1431-46.
11. Khanna D, Khanna PP, Fitzgerald JD, Singh MK, Bae S, Neogi T, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and antiinflammatory prophylaxis of acute gouty arthritis. Arthritis Care & Research. 2012;64(10):1447-61.
12. Jordan KM, Cameron JS, Snaith M, et al. British Society for Rheumatology and British Health Professionals in rheumatology guideline for the management of gout. The British Society for Rheumatology (BSR). Rheumatology. 2007;46:1372-4;doi:10.1093/rheumatology/kem056a.
13. Zhang W, Doherty M, Bardin T, et al. EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis. 2006;doi:10.1136/ard.2006.055269.
14. National Institute for Health and Clinical Excellence (NICE). Febuxostat for the management of hyperuricemia in people with gout. NICE technology appraisal guidance 164. London (England): 2008. [cited 2012 June 27]. Available from: http://guidance.nice.org.uk/TA164/Guidance/pdf/English.
15. Goldstein RC, Schwabe AD. Prophylactic colchicine therapy in familial Mediterranean fever. Annals of Internal Medicine. 1974;81:792-4.
16. Wright DG, Wolff SM, Fauci AS, Alling DW. Efficacy of intermittent colchicine therapy in familial Mediterranean fever. Annals of Internal Medicine. 1977;86:162-5.
17. Ahern MJ, Reid C, Gordon TP, McCredie M, Brooks PM, Jones M. Does colchicine work? The results of the first controlled study in acute gout. Aust NZ J Med. 1987;17:301-4.
18. Terkeltaub RA, Furst DE, Bennett K, Kook KA, Crockett RS, Davis MW. High vs low dosing of oral colchicine for early acute gout flare. Arthritis and Rheumatism. 2010;62:1060-8.
19. Paulus HE, Schlosstein LH, Godfrey RG, Klinenberg JR, Bluestone R. Prophylactic colchicine therapy of intercritical gout a placebo-controlled study of probenecid-treated patients. Arthritis and Rheumatism.1974 Sep-Oct;17(5):609-14.

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The second phase is characterized by intermittent acute gout attacks.[5] These attacks are due to the abrupt release of monosodium urate monohydrate crystals into the joint space where they initiate an acute inflammatory reaction characterized by painful inflammatory arthritis.[6] These attacks typically resolve spontaneously over a period of seven to 10 days.[4] The time interval separating these acute attacks is the third phase of the disease and is known as the intercritical gout period.[7] The time period separating acute gout attacks during this period vary widely between a few days to several years. Overtime, if the disease is left untreated it evolves into chronic tophaceous gout. This phase of the disease is characterized by the deposition of solid monosodium urate monohydrate crystal aggregates known as tophi in a variety of locations including joints, bursae and tendons.[7] In addition deposits of monosodium urate monohydrate crystals in the renal tubules can also lead to renal calculi and nephropathy.[5]

Treatment of gout consists of rapid relief of pain and disability caused by acute gout attacks and the reduction of serum urate levels. This reduction prevents further acute attacks and the progression of the disease to tophaceous gout.[4] Although acute attacks can be treated with anti-inflammatory medications, the underlying cause of the disease can only be treated by lowering serum urate levels.[6]

Colchicine is believed to exert a positive effect in gout by preventing the activation, degranulation and migration of neutrophils, implicated in the pathogenesis of gout symptoms. The mechanism by which colchicine acts in patients with Familial Mediterranean Fever has not been fully established; however, there is evidence suggesting that colchicine interferes with the assembly of the inflammasome complex found in neutrophils and monocytes that medicate the activation of interleukin-1β.[1,2] Colcrys® is the branded version of colchicine. In 2006, the Food and Drug Administration (FDA) launched the Unapproved Drugs Initiative. This initiative targeted drugs that had never formally received FDA-approval.[8] The initiative required manufacturers of the non-approved versions of colchicine to either apply for approval through the current FDA approval methods or cease manufacturing the agent. On September 30, 2010, the FDA informed manufacturers of these non-approved products that they were expected to stop manufacturing single-ingredient oral colchicine by October 14, 2010 and must stop shipping the product by December 30, 2010. Colchicine (Colcrys®), was approved by the FDA on July 30, 2009 and is the only currently approved and remaining colchicine product.[9] More recently, a new capsule formulation and generic version has been approved by the FDA.[2]

The American College of Rheumatology (ACR) published updated guidelines for the management of gout in 2012.[10,11] The ACR, British Society of Rheumatology, and European League Against Rheumatism (EULAR) treatment guidelines all recommend a nonsteroidal anti-inflammatory drug (NSAID), colchicine, or a corticosteroid for the treatment of an acute gout attack.[10-13] According to the more recent ACR guidelines for the management of gout, initiation of urate lowering therapy is recommended in patients with an established diagnosis of gout and tophus or tophi, frequent attacks of acute gouty arthritis (≥2 attacks/year), chronic kidney disease stage 2 or worse, and past urolithiasis.[16] The main goal of therapy is to promote monosodium urate monohydrate crystal dissolution and prevent further crystal formation which will lead to a reduction in acute gout flairs as well as the prevention of tophi development.[2,19] In order to achieve this goal serum urate levels must be reduced and maintained below the monosodium urate monohydrate crystal saturation point. Thus, the treatment serum urate goal recommended in the ACR and EULAR guidelines is <6 mg/dL (360 mmol/L) and slightly less in the British Society of Rheumatology guideline (≤300 mmol/L).[10,12,13] Of note, the ACR notes that serum urate lowering below 5 mg/dL may be needed to improve gout signs and symptoms.[10] Agents used to lower serum urate levels include allopurinol, probenecid, and febuxostat. The main difference between these agents is that allopurinol and febuxostat inhibit urate production and probenecid promotes urate excretion.[10-14] The 2012 ACR guideline, which was published after FDA approval of febuxostat, recommends either allopurinol or febuxostat as the first-line urate lowering therapy approach for the management of gout, with no preference stated between the two.[10] In comparison, older guidelines, published prior to approval of febuxostat, recommend allopurinol first-line and note febuxostat as a second-line option when allopurinol is not effective or not appropriate.[12-14] The ACR recommends probenecid as an alternative first-line urate lowering therapy option in patients with a contraindication or intolerance to either allopurinol or febuxostat.[16] During initiation of urate lowering therapy the guidelines recommend concurrent prophylaxis with either colchicine or an NSAID, although generally colchicine is the preferred, to prevent acute attacks while starting therapy.[11-13] Concomitant therapy is generally recommended for up to six months at which point only the urate lowering agent is continued. Treatment with the urate lowering agent has the potential to be lifelong.[11,12]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade Name)	Medication Class	Generic Availability
Single Entity Agents		
Colchicine (Colcrys®*, Mitigare®*)	Antigout Agents	a

*Generic available in at least one dosage form or strength.

Indications

Table 2. Food and Drug Administration Approved Indications[1,2]

Indication	Colchicine	
	Colcrys®	Mitigare®
Familial Mediterranean Fever	a	
Prophylaxis of gout glares	a	a
Treatment of gout flares*	a	

*When taken at the first sign of a flare

Pharmacokinetics

Table 3. Pharmacokinetics[1,2]

Generic Name	Bioavailability (%)	Volume of distribution	Metabolism	Half-Life (hours)
Colchicine	45	5 to 8 L/kg	CYP3A4 (16 %), Glucuronidation (% not reported)	26.6 to 31.2

Clinical Trials

The clinical trials demonstrating the safety and efficacy of the colchicine are outlined in Table 4. Of note no head-to-head clinical trials comparing colchicine to alternatives (i.e., non-steroidal anti-inflammatory drugs) for treatment of acute gout or for gout prophylaxis could be identified.[15-19]

Regarding Familial Mediterranean Fever, studies that have examined the use of colchicine for this disease state are limited. It should be noted, that approval of brand colchicine for Familial Mediterranean Fever treatment was not based on new clinical studies but rather on previously published literature. This published literature consists of three double-blind, placebo-controlled, cross-over studies published in 1974 that evaluated a total of 48 adult patients with Familial Mediterranean Fever. These studies as well as others confirmed that the agent is efficacious in both reducing the number of attacks and in aborting acute attacks.[1,15,16]

There is a paucity of colchicine trials for the treatment of acute gout flares. One study that evaluated brand colchicine for this indication was the AGREE trial which was the basis for FDA-approval. This study evaluated two different dosing regimens of colchicine; high dose (1.2 mg followed by 0.6 mg every hour for six hours), low dose (colchicine 1.2 mg followed by 0.6 mg in one hour followed by placebo doses every hour for five hours) and placebo in the treatment of acute gout attacks. The study demonstrated that the older traditional dosing regimen had the same efficacy as the new FDA-approved low dose regimen; however there were significantly more adverse drug events with the high dose.[18] One other, older placebo controlled study that evaluated generic colchicine was also identified. This study also demonstrated that treatment with colchicine resulted in a significantly faster improvement in pain when compared to placebo.[17]

Colchicine is also indicated for prophylaxis against gout attacks. It should be noted that the basis for FDA-approval of brand colchicine for gout attack prophylaxis was derived from the published literature.[1]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Familial Mediterranean Fever				
Goldstein et al[15] Colchicine 0.6 mg TID vs placebo	DB, PC, RCT, XO Patients with FMF and at least 1 attack/month for ≥1 year without amyloidosis or concurrent disease with no chronic steroid or narcotic use and no evidence of pregnancy	N=15 6 months (XO was done after 90 days of treatment and patients were reexamined at 30-day intervals)	Primary: Patient reported record of attacks Secondary: Not reported	Primary: In the colchicine treatment group eight patients experienced no attacks and two patients had a reduction in frequency from 10 and five attacks to two and three attacks respectively. In the placebo group nine patients reported a total of 59 attacks. One patient did not have an attack during either treatment arm. Overall, 80% of patients did not have attacks while being treated with colchicine compared to 10% of patients while treated with placebo. The decrease in attacks during colchicine therapy compared to placebo was statistically significant (P<0.002). Secondary: Not reported
Wright et al[16] Colchicine 0.6 mg vs placebo Separate courses of both colchicine and placebo were supplied to the patient. The order of therapy was determined by a randomized scheme. Each course consisted of 10 total tablets; six tablets on day 1 and 2 tablets on each of the following 2 days.	DB, PC, RCT, XO Patients with a history of FMF attacks that were characterized by acute short lived episodes of peritonitis or pleuritis and usually with fever	N=9 10 months	Primary: Patient reported number of attacks aborted with colchicine Secondary: Time interval between attacks, safety	Primary: Five patients completed their treatment assignments and colchicine was effective in aborting the attacks of three patients and was ineffective in two patients. The remaining four patients could not be assessed due to the insufficient number of courses. During the 10 months of the trial, 28 courses of colchicine and 31 courses of placebo were taken during the early stages of FMF attacks. Of the colchicine courses 21 (75%) were followed by attacks that were considered to have been aborted compared to only three (10%) courses with placebo (P value not reported). Secondary: No significant differences were seen in the time interval between attacks after colchicine treatment was compared to placebo. The mean interval between attacks after colchicine treatment was 15.1±1.8 days compared to 20.1±5.0 days in the placebo group (P value not reported). Two patients experienced diarrhea early in the trial and their treatment was reduced. Further adverse events attributed to colchicine did not occur.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Patients were told to begin medication at the earliest suspicion that an attack was about to occur.				
Treatment of Gout Flares				
Ahern et al[17] Colchicine 1 mg followed by 0.5 mg every 2 hours until complete response or toxicity vs placebo	PC, RCT Patients with joint aspiration proven acute gout	N=45 Patients were assessed every 6 hours for 48 hours	Primary: Percentage of joints with a 50% decrease in baseline pain and clinical score measures Secondary: Safety	Primary: The percentage of joints with a 50% decrease in baseline pain score was 23, 41, 73, and 73% in the colchicine group compared to 9, 9, 32, and 36% in the placebo group for 12, 24, 36 and 48 hours after starting treatment respectively. The difference between the two groups was statistically significant at the 36-hour (P<0.05) and 48-hour (P<0.05) marks. The percentage of joints with a 50% decrease in baseline clinical score were 5, 23, 50, and 64% in the colchicine group compared to 0, 0, 5, and 23% in the placebo group for 12, 24, 36 and 48 hours after starting treatment respectively. The difference between the two groups was statistically significant only at the 36-hour (P<0.01) and 48-hour (P<0.05) marks. Secondary: Diarrhea and/or vomiting occurred in all patients taking colchicine at a median time of 24 hours and at a median total dose of 6.7 mg. Five patients developed nausea while on the placebo (P values not reported).
Terkeltaub et al[18] (AGREE) Colchicine 1.2 mg followed by 0.6 mg every hour for 6 hours (High-dose) vs colchicine 1.2 mg followed by 0.6 mg in 1 hour followed by placebo doses every hour	DB, MC, PC, PG RCT Male and postmenopausal female patients ≥18 years of age with a confirmed gout diagnosis who had ≥2 gout flares within the prior 12 months	N=575 24 hours	Primary: The proportion of patients in the high dose group compared to placebo group who responded to treatment (defined as a having a pretreatment pain score within	Primary: In the ITT population (N=184), 32.7% of patients in the high-dose group were responders compared to 15.5% in the placebo group. The difference between these two groups was statistically significant (P=0.034). Secondary: In the ITT population (N=184), 37.8% of patients in the low-dose group were responders compared to 15.5% in the placebo group. The difference between these two groups was statistically significant (P=0.005). In the placebo group 50% of patients required rescue medication within the first 24 hours compared to 34.6% in the high-dose group and 31.1% in the low

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
for 5 hours (Low-dose) vs placebo Study drug used was the branded version of colchicine colchicine/probenecid			12 hours of flare onset and a ≥50% reduction in pain within 24 hours without rescue medication Secondary: The proportion of patients in the low dose group compared to the placebo group who responded (defined above) to treatment, proportion of patients who required rescue medication, safety	dose group. The difference between the high-dose group and the placebo group was not statistically significant (P=0.103). The difference between the low-dose group and the placebo group was statistically significant (P=0.027). There were no deaths, serious adverse events, or patient withdrawals due to adverse events. All adverse events in the low-dose group were mild to moderate in intensity, while 19.2% of the high dose group had severe adverse events, all of which were diarrhea. The overall rate for adverse events was 76.9, 36.5, and 27.1% in the high-dose, low-dose and placebo groups respectively. The most common adverse event was diarrhea which occurred in 76.9, 23.0% and 13.6% of patients in the high-dose, low-dose and placebo groups respectively. The difference was statistically significant between the high-dose and low-dose groups (OR, 11.2; 95% CI, 4.8 to 25.9) and the high-dose and placebo groups (OR, 21.3; 95% CI, 7.9 to 56.9). The difference was not statistically significant between the low-dose and placebo groups (OR, 1.9; 95% CI, 0.8 to 25.9) (P values not reported). Nausea occurred in 17.3, 4.1 and 5.1% of patients in the high-dose, low dose and placebo groups respectively. The difference was statistically significant between the high-dose and low-dose groups only (OR, 5.0; 95% CI, 1.3 to 19.3) (P values not reported). Vomiting occurred in 17.3% of patients in the high-dose group compared to 0% in both the low dose and placebo groups; P values not reported.
Prophylaxis of Gout Flares				
Paulus et al[19] Colchicine/probenecid 0.5/500 mg TID vs probenecid/placebo 500 mg TID In the event of an acute gout attack patients were	DB, MC, PC, PG, RCT Male patients with confirmed gout	N=52 6 months	Primary: Gout attack rate Secondary: Gout attack rate in patients with sUA levels <6.5 mg/dL, safety	Primary: The data from 38 members was analyzed. In the colchicine/probenecid group there were a total of 23 acute attacks during a combined 109 months of therapy. In the probenecid/placebo group there were a total of 35 acute attacks during a combined 94 months of therapy. For the colchicine/ probenecid group the rate of attacks per month per patient were 0.19±0.05 compared to 0.48±0.12 attacks per month per patient in the probenecid/placebo group. The difference between the two groups was statistically significant (*P*<0.05). Secondary: For patients with sUA levels <6.5 mg/dL in the colchicine/probenecid group the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
instructed to take additional colchicine, indomethacin or phenylbutazone until the attack subsided.				rate of attacks per month per patient were 0.13±0.06 compared to 0.49±0.13 attacks per month per patient in the probenecid/placebo group. The difference between the two groups was statistically significant (*P*<0.05). Adverse events were reported by 15 of the 20 patients in the colchicine/ probenecid group compared to eight of the 18 patients in the probenecid/placebo group. The difference between these two groups was not statistically significant (*P*>0.05). In the colchicine/probenecid group adverse events included, diarrhea in nine patients, vomiting or anorexia in 11 patients and steadily increasing AST/ALT in one patient. In the probenecid/placebo group, diarrhea was reported in six patients, and nausea, vomiting or anorexia in five patients (*P* values not reported).

Drug regimen abbreviations: BID=twice daily, IV=intravenous, QD=once daily, TID=three times daily
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, ITT=intent to treat, MC=multicenter, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, XO=crossover
Miscellaneous abbreviations: FMF=Familial Mediterranean Fever, sUA=serum uric acid, VAS=visual analog scale

Special Populations

Table 5. Special Populations[1,2]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Colchicine	Safety and efficacy in elderly patients have not been established. Approved for use in children ≥4 years of age for the treatment of Familial Mediterranean Fever (tablets) Approved for use in children ≥16 years of age for the prophylaxis of gout and for the treatment of gout flares (tablet). Safety and efficacy for use in children <18 have not been established for the prophylaxis of gout and for the treatment of gout flares (capsule).	Renal dose adjustment is required. Prophylaxis of gout and FMF: Severe renal impairment (CrCl <30 mL/min), use 0.3 mg daily Treatment of gout flairs: Severe renal impairment (CrCl <30 mL/min), no dose adjustment required, however do not repeat course of therapy more than once every two weeks.	Hepatic dose adjustment may be required. Patients with severe hepatic impairment should not repeat a course of therapy for the treatment of gout flairs more than once every two weeks.	C	Yes (<10%)

CrCl=creatinine clearance, FMF=Familial Mediterranean Fever

Adverse Drug Events

Table 6. Adverse Drug Events (%)[1,2]

Adverse Event	Colchicine
Abdominal cramping	a
Abdominal pain	a
Acute attacks of gout	4
Alopecia	a
Aplastic anemia	a
Azoospermia	a
Diarrhea	23
Elevated alanine aminotransferase	a
Elevated aspartate aminotransferase	a
Elevate creatine phosphokinase	a
Fatigue	1
Granulocytopenia	a
Headache	1
Lactose intolerance	a
Leukopenia	a
Maculopapular rash	a
Muscle pain	a

Adverse Event	Colchicine
Muscle weakness	a
Myopathy	a
Myotonia	a
Nausea	4
Oligospermia	a
Pancytopenia	a
Pharyngolaryngeal pain	3
Purpura	a
Rash	a
Rhabdomyolysis	a
Sensory motor neuropathy	a
Thrombocytopenia	a
Vomiting	a

-Incidence not reported.
a Percent not specified.

Contraindications

Table 7. Contraindications[1,2]

Contraindication	Colchicine
Concomitant use of a P-glycoprotein or a strong CYP3A4 inhibitor in the presence of renal or hepatic impairment	a

Warnings and Precautions

Table 8. Warnings and Precautions[1,2]

Warning/Precaution	Colchicine
Blood dyscrasias have been reported at therapeutic doses	a
Fatal overdoses both intentional and accidental have been reported in both adults and children	a
Life-threatening and fatal drug interactions have been reported with concomitant use of colchicine and a P-glycoprotein or a strong CYP3A4 inhibitor; if treatment with either is required in patients with normal renal and hepatic function then the dose of colchicine may need to be reduced or interrupted	a
Neuromuscular toxicity and rhabdomyolysis have been reported with chronic treatment in therapeutic doses; concomitant use of statins, fibrates or cyclosporine can potentiate these adverse events	a

Drug Interactions

Table 9. Drug Interactions[1,2]

Generic Name	Interacting Medication or Disease	Potential Result
Colchicine	Cyclosporine	Severe adverse reactions, including gastrointestinal, hepatic, renal, and neuromuscular toxicity, may occur during coadministration.
Colchicine	Macrolides and related antibiotics	Increased colchicine serum concentrations with toxicity (including death) may occur.
Colchicine	Nefazodone	Colchicine plasma concentrations may be elevated, increasing the risk of toxicity.
Colchicine	Protease inhibitors	Colchicine plasma concentrations may be elevated, increasing the risk of toxicity.
Colchicine	Verapamil	Elevated colchicine serum and cerebrospinal concentrations

Generic Name	Interacting Medication or Disease	Potential Result
		with toxicity may occur.

Dosage and Administration

Table 10. Dosing and Administration[1,2]

Generic Name	Adult Dose	Pediatric Dose	Availability
Colchicine	Prophylaxis of gout flares: Capsule, Tablet: 0.6 mg QD to 0.6 mg BID; maximum, 0.6 mg BID Treatment of gout flares: Tablet: 1.2 mg at the first sign of flare followed by 0.6 mg one hour later Treatment of Familial Mediterranean Fever: Tablet: 1.2 to 2.4 mg/day as a single or divided dose (BID); maximum, 2.4 mg/day	Treatment of Familial Mediterranean Fever (four to six years of age): Tablet: 0.3 to 1.8 mg/day as a single or divided dose (BID); maximum, 1.8 mg/day Treatment of Familial Mediterranean Fever (six to 12 years of age): Tablet: 0.9 to 1.8 mg/day as a single or divided dose (BID); maximum, 1.8 mg/day Treatment of Familial Mediterranean Fever (12 years of age or older): Tablet: 1.2 to 2.4 mg/day as a single or divided dose (BID); maximum, 2.4 mg/day Prophylaxis of gout flares (16 years of age or older): Tablet: 0.6 mg QD to 0.6 mg BID; maximum, 0.6 mg BID	Capsule: 0.6 mg Tablet: 0.6 mg

BID=twice daily, QD=once daily, QID=four times daily, TID=three times daily

Clinical Guidelines

Table 11. Clinical Guidelines

Clinical Guideline	Recommendations
American College of Rheumatology: **Guidelines for the Management of Gout. Part 1: Systematic Nonpharmacologic and Pharmacologic Therapeutic Approaches to Hyperuricemia (2012)**[10]	· Patient education on diet, lifestyle, treatment objectives, and management of comorbidities is a recommended core therapeutic measure in gout. · Xanthine oxidase inhibitor therapy with either allopurinol or febuxostat is recommended as the first-line pharmacologic urate lowering therapy approach in gout. · Probenecid is recommended as an alternative first-line pharmacologic urate lowering therapy option in the setting of contraindication or intolerance to at least one xanthine oxidase inhibitor agent. · Serum urate level should be lowered sufficiently to durably improve signs and symptoms of gout, with a target <6 mg/dL at a minimum, and often <5 mg/dL. · Combination oral urate lowering with one xanthine oxidase inhibitor and one uricosuric agent is appropriate when the serum urate target has not

Clinical Guideline	Recommendations
	been met by appropriate dosing of a xanthine oxidase inhibitor. · Pegloticase is appropriate for patients with severe gout disease burden and refractoriness to, or intolerance of, appropriately dose oral urate lowering options. <u>Indications for pharmacologic urate lowering therapy</u> · Any patient with established diagnosis of gouty arthritis and: o Tophus or tophi by clinical exam or imaging study. o Frequent attacks of acute gouty arthritis (≥2 attacks/year). o Chronic kidney disease stage 2 or worse. o Past urolithiasis. · Treat to serum urate target defined for individual patient. o The minimum serum urate target is <6 mg/dL. o Serum urate lowering below 5 mg/dL may be needed to improve gout signs and symptoms. o If serum urate target is achieved, the following is recommended for the long-term management of gout: § Continue gout attack prophylaxis if there are ongoing gout symptoms and/or signs (≥1 tophus on physical exam). § Continue to regularly monitor serum urate and monitor for side effects of urate lowering therapy. § After palpable tophi and all acute and chronic gouty arthritis gout symptoms have been resolved, continue all measures (including pharmacologic urate lowering therapy) needed to maintain serum urate <6 mg/dL indefinitely. § Consider referral to a specialist when there is unclear etiology of hyperuricemia; refractory signs or symptoms of gout; difficulty in reaching target serum urate, particularly with renal impairment and a trial of xanthine oxidase inhibitor treatment; and multiple and/or serious adverse events from pharmacologic urate lowering therapy. o If serum urate target is NOT achieved, the following is recommended: § Increase intensity of urate lowering therapy and re-evaluate serum urate. § When serum urate target is achieved, recommendations for long-term management of gout should be followed. <u>General health, diet, and lifestyle measure for gout patients</u> · Weight loss for obese patients, to achieve body mass index that promotes general health; healthy overall diet; exercise; smoking cessation; and hydration are all recommended. · Patients should avoid organ meats high in purine content (e.g., sweetbreads, liver, kidney); high fructose corn syrup-sweetened sodas, other beverages, or food; alcohol overuse (>2 servings per day for a male and >1 serving per day for a female); and any alcohol use in gout during period of frequent gout attacks, or advanced gout under poor control. · Patients should limit serving sizes of beef, lamb, pork, and seafood with high purine content (e.g., sardines, shellfish); servings of naturally sweet

Clinical Guideline	Recommendations
	fruit juices, table sugar and sweetened beverages and desserts, and table salt, including in sauces and gravies; and alcohol (particularly beer, but also wine and spirits). · Patients should be encouraged to consume low-fat or non-fat dairy products and vegetables. <u>Core recommendations for the use of allopurinol</u> · Starting dosage should be no greater than 100 mg/day for any patient. Patients with stage 4 or worse chronic kidney disease should be started on 50 mg/day. · The maintenance dose should be gradually titrated upward every two to five weeks to appropriate maximum dose in order to treat chosen serum uric acid target. · Dose can be raised >300 mg/day, even in patients with renal impairment, provided adequate patient education and monitoring for drug toxicity is present. · Prior to initiation, consider HLA-B*5801 in selected patients. Specific subpopulations at higher risk for allopurinol hypersensitivity include Koreans with stage 3 or worse chronic kidney disease, and Han Chinese and Thai irrespective of renal function. <u>Core recommendations for the use of uricosuric therapy</u> · Probenecid is the first choice among uricosuric agents for urate lowering therapy monotherapy. Probenecid is not recommended as first-line monotherapy urate lowering therapy in patients with a creatinine clearance <50 mL/minute. · Use of other agents other than probenecid with clinically significant uricosuric effects, such as fenofibrate and losartan, can be therapeutically useful as components of a comprehensive urate lowering therapy strategy. · History of urolithiasis contraindicates first-line uricosuric urate lowering monotherapy. · Urinary uric acid should be measured before initiation of uricosuric urate lowering therapy. · Elevated urine uric acid indicative of uric acid overproduction contraindicates uricosuric urate lowering therapy. · Continue to monitor urinary uric acid during uricosuric urate lowering therapy. · Consider urine alkalinization with monitoring of urine pH, in addition to increased fluid intake, as a risk management strategy for urolithiasis. <u>Pharmacologic urate lowering therapy escalation</u> · Step 1: single agent xanthine oxidase inhibitor, titrated to maximum appropriate dose. Probenecid should be used as an alternative if xanthine oxidase inhibitor is contraindicated or not tolerated. · If serum urate target is not achieved, and there is continuing disease activity go to Step 2. · Step 2: add uricosuric to xanthine oxidase inhibitor with both agents titrated to maximum appropriate dose. · If serum urate target is not achieved, and there is continuing disease activity go to Step 3. · Step 3: pegloticase.

Clinical Guideline	Recommendations
	Recommendations for refractory disease in gout · Attempt upward dose titration of one xanthine oxidase inhibitor to respective maximum appropriate dose. · Febuxostat can be substituted for allopurinol or vice versa in the event of drug intolerance and adverse events, and such a substitution should be considered after initial failure of upward dose titration of one xanthine oxidase inhibitor. · Effective therapeutic options include addition of a uricosuric agent (e.g., probenecid, fenofibrate, or losartan) to a xanthine oxidase inhibitor drug or vice versa. · Pegloticase is appropriate for patients with severe gout disease burden and refractoriness to, or intolerance of, conventional and appropriately dosed urate lowering therapy. · Pegloticase therapy is not recommended as first-line urate lowering therapy agent for any case scenarios. · There is a lack of consensus on the appropriate duration of pegloticase therapy relative to intended and achieved decrease in symptoms and signs of gout, including decrease in tophus size.
American College of Rheumatology: **Guidelines for the Management of Gout. Part 2: Therapy and Antiinflammatory Prophylaxis of Acute Gouty Arthritis (2012)**[11]	· An acute gouty arthritis attack should be treated with pharmacologic therapy, initiated within 24 hours of onset. · Established pharmacologic urate lowering therapy should be continued, without interruption, during an acute attack of gout. · Nonsteroidal antiinflammatory drugs (NSAIDs), corticosteroids, or oral colchicine are appropriate first-line options for treatment of acute gout. Certain combinations can be employed for severe or refractory attacks. · Pharmacologic antiinflammatory prophylaxis is recommended for all gout patients when pharmacologic urate lowering is initiated, and should be continued if there is any clinical evidence of continuing gout disease activity and/or the serum urate target has not yet been achieved. · Oral colchicine is an appropriate first-line gout attack prophylaxis therapy, including with appropriate dose adjustment in chronic kidney disease and for drug interactions, unless there is a lack of tolerance or medical contraindication. · Low-dose NSAID therapy is an appropriate choice for first-line gout attack prophylaxis, unless there is a lack of tolerance or medical contraindication. Management of an acute gout attack · General principles include the following: o Acute gouty arthritis attacks should be treated with pharmacologic therapy. o To provide optimal care, pharmacologic treatment should be initiated within 24 hours of acute gout attack onset. o Ongoing pharmacologic urate lowering therapy should not be interrupted during an acute gout attack. · Monotherapy with an NSAID, corticosteroids, or colchicine is recommended first-line. o If the patient is experiencing severe pain, particularly for a polyarticular attack or an attack affecting multiple large joints, initial combination therapy is an appropriate option. · If there is an inadequate outcome, switch to an alternate monotherapy or add-on combination therapy. · If there is a successful outcome, consider indications for urate lowering

Clinical Guideline	Recommendations
	therapy or adjustment of ongoing urate lowering therapy (see Part 1 of guidelines). <u>Recommendations for combination therapy approach to acute gouty arthritis</u> · Initial combination therapy is an appropriate option for an acute, severe gout attack, particularly with involvement of multiple large joints or polyarticular arthritis. · Acceptable combination therapy approaches include the initial simultaneous use of full doses (or, where appropriate, prophylaxis doses) of either: o Colchicine and NSAIDs. o Oral corticosteroids and colchicine. o Intra-articular steroids with all other modalities. · For patients not responding adequately to initial pharmacologic monotherapy, adding a second appropriate agent is an acceptable option. Recommendations for pharmacologic antiinflammatory prophylaxis of attacks of acute gout · Initiate prophylaxis: o With, or just prior to initiating urate lowering therapy: § First-line: low dose colchicine (0.6 mg once or twice daily) or low dose NSAIDs (with proton pump inhibitor where indicated). § Second-line: low dose prednisone or prednisolone (≤10 mg/day) (if colchicine and NSAIDs both are not tolerated, contraindicated, or ineffective). · Continue pharmacologic gout attack prophylaxis if there is any clinical evidence of continuing gout disease activity (such as one or more tophi detected on physical examination, recent acute gout attacks, or chronic gouty arthritis, and/or the serum urate target has not been achieved. o Continue prophylaxis for the greater of: § Six months' duration. Or § Three months after achieving the target serum urate level for the patient without tophi detected on physical examination Or § Six months after achieving the target serum urate level, where there has been resolution of tophi previously detected on physical examination.
The European League Against Rheumatism: **European League Against Rheumatism Evidence Based Recommendations for Gout. Part II: Management. Report of a Task Force of the European League Against Rheumatism Standing Committee**	· Urate lowering therapy is recommended in patients with recurrent acute attacks, arthropathy, tophi, or radiographic changes of gout. · The therapeutic goal of urate lowering therapy is to promote crystal dissolution and prevent crystal formation. The goal is to achieve and maintain serum uric acids <u>≤</u>6 mg/dL. · Oral colchicine and/or NSAIDs are first line agents for the systemic treatment of acute gouty attacks. In the absence of contraindications, an NSAID is a convenient and well accepted option. · Low doses of colchicine (0.5 mg three times daily) may be sufficient for some patients with acute gout. Higher doses may lead to side effects such as diarrhea and gastrointestinal discomfort. · Intra-articular aspirations and injection of long acting steroids is an

Clinical Guideline	Recommendations
For International Clinical Studies Including Therapeutics (2006)[13]	effective and safe treatment for an acute gouty attack. · Allopurinol is an appropriate long-term urate-lowering agent. It is recommended that allopurinol be started at 100 mg daily and increased by 100 mg every two to four weeks if required. The dose must be adjusted in patients with renal impairment. If toxicity occurs, alternatives to allopurinol include other xanthine oxidase inhibitors, a uricosuric agent, or allopurinol desensitization, in cases of mild rash only. · Uricosuric agents such as probenecid and sulphinpyrazone* can be used as an alternative to allopurinol in patients with normal renal function. The agents are contraindicated in patients with urolithiasis. · Prophylaxis against acute attacks during the first months of urate lowering therapy can be achieved by colchicine (0.5 to 1 mg daily) and/or an NSAID (with gastro-protection if indicated). · When gout is associated with diuretic therapy, stop the diuretic if possible. For the treatment of hypertension and hyperlipidemia consider the use of losartan and fenofibrate, respectively (both have modest uricosuric effects).
National Institute for Health and Clinical Excellence: **Febuxostat for the Management of Hyperuricemia in People With Gout. National Institute for Health and Clinical Excellence Technology Appraisal Guidance 164 (2008)[14]**	· Febuxostat is recommended as an option for the management of chronic hyperuricemia in gout only for patients who cannot tolerate allopurinol or in whom allopurinol is contraindicated. · Intolerance to allopurinol is defined as adverse effects that are sufficiently severe or warrant its discontinuation, or prevent full dose escalation for optimal effectiveness.
British Society for Rheumatology and British Health Professionals in Rheumatology: **Guideline for the Management of Gout (2007)[12]**	<u>Management of acute gout</u> · After an acute gout episode, affected joints should be rested and analgesic and anti-inflammatory drug therapy should be commenced immediately and continued for one to two weeks. · Fast-acting oral NSAIDs at maximum doses are the drugs of choice in gout when there are no contraindications. · Physicians should follow standard guidelines for the use of NSAIDs and cyclooxygenase-2 (COX-2) inhibitors in patients with increased risk of peptic ulcers, bleeds or perforations. · Colchicine can be an effective alternative but it has a slower onset of action than NSAID therapy. · Allopurinol should not be commenced during an acute attack. It should be continued if used when an acute attack occurs and the acute attack should be treated conventionally. · Opiate analgesics can be used as adjunct therapy. · Intra-articular corticosteroids are highly effective in acute gouty mono-arthritis and can be effective in patients unable to tolerate NSAIDs or in patient's refractory to other treatments. <u>Diet, lifestyle modification and non-pharmacological therapy</u> · In overweight patients, dietary modification should be attempted to achieve ideal body weight. However, "crash dieting" and high protein/low carbohydrate diets should be avoided. Patients should be instructed on proper diet to avoid precipitation of an acute gout attack.

Clinical Guideline	Recommendations
	· Affected joints should be elevated and exposed in a cool environment. · Moderate physical exercise should be encouraged. <u>Management of recurrent, intercritical and chronic gout</u> · The plasma urate should be maintained below 300 µmol/L. · Uric acid lowering drug therapy should be started if further attacks occur within one year and should also be offered to patients with tophi, renal insufficiency, and uric acid stones and to patients who need to continue treatment with diuretics. · Uric acid-lowering drug therapy should be delayed until one to two weeks after inflammation has settled. · Long-term treatment of recurrent uncomplicated gout should be initiated with allopurinol at a starting dose of 50 to 100 mg daily and increased by 50 to 100 mg increments every few weeks, adjusted if necessary for renal function, until the therapeutic target (plasma urate <300 µmol/L) or maximum dose (900 mg daily) is reached. · Uricosuric agents can be used as second-line drugs in patients who excrete sufficient uric acid in those resistant to, or intolerant of, allopurinol. Preferred drugs include: sulfinpyrazone in patients with normal renal function or benzbromarone* in patients with mild to moderate renal insufficiency. · Colchicine should be co-prescribed following initiation of treatment with allopurinol or uricosuric drugs, and continued for up to six months. An NSAID or COX-2 inhibitor can be substituted if colchicine cannot be used (provided that there are no contraindications). However, the duration of therapy should be limited to six weeks. · Aspirin in low doses (75 to 150 mg daily) has insignificant effects on the plasma urate and can be used; however, aspirin in analgesic doses (600 to 2,400 mg daily) interferes with uric acid excretion and should be avoided.

*Agent not available in the United States.

Conclusions

Gout is a complex inflammatory disease that occurs in response to the presence of monosodium urate monohydrate crystals in the joints, bones and soft tissues.[3,4] In general there are four phases of gout.[5] The first is asymptomatic hyperuricemia which can be caused by either overproduction of urate or by renal urate underexcretion. Hyperuricemia is defined as serum urate levels greater than 6.8 mg/dL. It is at this concentration where monosodium urate crystals begin to precipitate and deposit in the synovial fluid and other tissues.[4-6] It is important to note that hyperuremia predisposes to gout; however it does not necessarily cause gout as many people can have hyperuricemia without any gout symptoms. In some patients with hyperuricemia the abrupt release of monosodium urate monohydrate crystals into the joint space will initiate a painful acute inflammatory reaction. This is known as an acute gout attack and is the second phase of the disease. Acute attacks are self-limiting and can resolve on their own even without treatment.[6] The time period between acute attacks is known as the intercritical gout period.[7] If left untreated the patient will enter the fourth phase known as chronic tophaceous gout. This phase is characterized by the deposition of solid monosodium urate monohydrate crystal aggregates known as tophi which can deposit on a variety of tissues including the joints. Tophaceous gout can lead to significant morbidity if untreated as it can cause permanent joint damage and can also lead to nephropathy.[5,7]

Clinical consensus guidelines indicate that acute gout attacks should be treated with an non-steroidal anti-inflammatory drug (NSAID), colchicine, or a corticosteroid; however the disease can and often will continue to progress unless the serum urate level is normalized.[6,10-14] Agents used for the treatment of

hyperuricemia are allopurinol, febuxostat, and probenecid. The main difference between these agents is that allopurinol and febuxostat inhibit urate production and probenecid promotes urate excretion. In general consensus guidelines indicated that allopurinol is the first line agent. According to more recent guidelines, allopurinol and febuxostat are considered first-line urate lowering therapy approaches, with probenecid considered an alternate first-line option.[10] It should be noted that colchicine tablets (Colcrys®) are also indicated for Familial Mediterranean Fever[1]

References

1. Colcrys® [package insert]. Deerfield (IL): Takeda Pharmaceuticals America, Inc.; 2012 Nov.
2. Mitigare® [package insert]. Memphis (TN): Hikma Americas, Inc.; 2015 July.
3. Monach P, Becker MA. Pathophysiology of gouty arthritis. In: Basow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2012 [cited 2012 Jun 27]. Available from: http://www.utdol.com/utd/index.do.
4. Neogi T. Gout. N Engl J Med. 2011;364:443-52.
5. Hardy E. Gout diagnosis and management: what NPs need to know. The Nurse Practitioner. 2011 Jun;159.
6. Schumacher HR. The pathogenesis of gout. Cleveland Clinic Journal of Medicine. 2008 Jul;75(supplement 5);S2-S4.
7. Grassi W, De Angelis R. Clinical features of gout. Reumatismo. 2011;63(4):238-45.
8. Unapproved Drugs Initiative [press release on the Internet]. Rockville (MD): Food and Drug Administration (US): 2009 Mar 03 [cited 2012 Jun 27]. Available from: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/SelectedEnforcementActionsonUnapprovedDrugs/ucm118990.htm.
9. FDA orders halt to marketing of unapproved single-ingredient oral colchicine [press release on the Internet]. Rockville (MD): Food and Drug Administration (US): 2010 Sep 30 [cited 2012 Jun 27]. Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm227796.htm.
10. Khanna D, Fitzgerald JD, Khanna PP, Bae S, Singh MK, Neogi T, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: Systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care & Research. 2012 Oct;64(10):1431-46.
11. Khanna D, Khanna PP, Fitzgerald JD, Singh MK, Bae S, Neogi T, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and antiinflammatory prophylaxis of acute gouty arthritis. Arthritis Care & Research. 2012;64(10):1447-61.
12. Jordan KM, Cameron JS, Snaith M, et al. British Society for Rheumatology and British Health Professionals in rheumatology guideline for the management of gout. The British Society for Rheumatology (BSR). Rheumatology. 2007;46:1372-4;doi:10.1093/rheumatology/kem056a.
13. Zhang W, Doherty M, Bardin T, et al. EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis. 2006;doi:10.1136/ard.2006.055269.
14. National Institute for Health and Clinical Excellence (NICE). Febuxostat for the management of hyperuricemia in people with gout. NICE technology appraisal guidance 164. London (England): 2008. [cited 2012 June 27]. Available from: http://guidance.nice.org.uk/TA164/Guidance/pdf/English.
15. Goldstein RC, Schwabe AD. Prophylactic colchicine therapy in familial Mediterranean fever. Annals of Internal Medicine. 1974;81:792-4.
16. Wright DG, Wolff SM, Fauci AS, Alling DW. Efficacy of intermittent colchicine therapy in familial Mediterranean fever. Annals of Internal Medicine. 1977;86:162-5.
17. Ahern MJ, Reid C, Gordon TP, McCredie M, Brooks PM, Jones M. Does colchicine work? The results of the first controlled study in acute gout. Aust NZ J Med. 1987;17:301-4.
18. Terkeltaub RA, Furst DE, Bennett K, Kook KA, Crockett RS, Davis MW. High vs low dosing of oral colchicine for early acute gout flare. Arthritis and Rheumatism. 2010;62:1060-8.
19. Paulus HE, Schlosstein LH, Godfrey RG, Klinenberg JR, Bluestone R. Prophylactic colchicine therapy of intercritical gout a placebo-controlled study of probenecid-treated patients. Arthritis and Rheumatism.1974 Sep-Oct;17(5):609-14.