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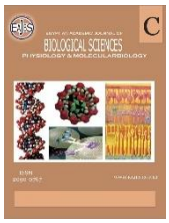

Gout: A Reviewing of The Recent Literature

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ABSTRACT

High-strength evidence supports the use of colchicine, nonsteroidal an anti-inflammatory drugs (NSAIDs), and systemic corticosteroids to reduce pain in patients with acute gout. Moderate-strength evidence supports the use of animal-derived ACTH formulation for this condition. Moderate-strength evidence supports the finding that low-dose colchicine is as effective as higher-dose colchicine for treating acute gout descent and has fewer side effects. Evidence is insufficient from randomized controlled trials that assess symptomatic out comes for specific dietary therapies. The evidence is also insufficient to support or refute the effectiveness of particular Traditional Chinese Medicine practices (e.g. Herbal mixtures, acupuncture, and moxibustion) for symptomatic outcomes. High-strength evidence supports that urate-lower therapy (ULT, with allopurinol or febuxostat) reduces serum urate levels.

However low-strength evidence supports the finding that treating to a specific target serum urate level reduces the risk of gout attacks. High-strength evidence supports the finding that ULT does not reduce the risk of acute gout attacks within the first 6 month of after directness. However, moderate-strength evidence supports the turn of ULT in reducing the risk of acute gout attacks after about 1 year of treatment. Low-strength evidence supports treating a specific target serum urate level to reduce the risk of gout attacks. High-strength evidence supports the finding that prophylactic therapy with low-dose colchicine or depressed dose NSAIDs reduces the risk of acute gout attacks when beginning ULT. No criteria for when to discontinue ULT have been validated.

INTRODUCTION

Gout is the most common form of inflammatory arthritis and is characterized by acute intermittent episodes of synovitis presenting with joint swelling and pain (referred to as acute gouty arthritis, acute gout attacks, or acute gout flares). It has been described as a disease of the foot since antiquity. Approximately 8 million patients in the United States have gout. Gout is caused when excess urate in the body crystalizes (as monosodium urate [MSU]) in joint fluid, cartilage, bones, tendons, bursas, or other sites. These crystals can directly stimulate an acute inflammatory attack. In some patients, acute gout attacks become progressively more frequent, protracted, and severe and may eventually progress to a chronic inflammatory condition n. Additionally, in some patient, the deposits of urate crystals grow into larger collections, called tophi (singular tophus) when clinically apparent. (ChoiHK, 2005)

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

Etiology of Gout:

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

Although the primary risk factor for gout is hyperuricemia, not all patients with hyperuricemia go on to develop clinical gout; hyperuricemia that does not progress to gout is known as asymptomatic hyperuricemia. Patients with asymptomatic hyperuricemia may or may not have evidence of urate deposits in their joints (as documented by advanced imaging methods). (Choi HK *et al.,* 2005)

The causes of gout are unclear but appear to be multifactorial, including a combination of genetic, hormonal, metabolic, and dietary factors. Family history, advancing age, male sex, or, in women, early menopause have been associated with a higher risk of gout and/or gout attacks. Some prescription medications such as thiazides are also to be risk factors for gout. (Lee SJ *et al.,*2009)

Diagnosis of Gout:

A number of methods have been proposed to establish the diagnosis of gout. The evidence supporting the various methods for the diagnosis of gout is the subject of a separate systematic review. (Gonzalez EB, 2012)

Clinical Presentation and Management:

Gout encompasses both acute and chronic phases.

Acute Gouty Arthritis:

The acute phase of gout is self-limited and characterized by recurrent attacks of synovitis (articular inflammation) that present with pain, erythema, and swelling, most frequently in the large toe but other joints, tendons, bursae, or other areas may be involved. Primary treatments for acute gout attacks have included non-steroidal anti-inflammatory agents (NSAIDs), corticosteroids (intraarticular), colchicine, and pituitary adrenocorticotropic hormone (ACTH, specifically animal-derived ACTH preparation) for the control of pain and inflammation. (Choi HK *et al.,* 2005).

Chronic Gout:

Although initial episodes may be brief and rare, acute episodes may increase in frequency and duration over time and lead to the development of chronic gout. In addition to more frequent attacks, chronic gout may be associated with deposits of uric acid crystals known as tophi. Tophi may develop in joints, cartilage, bone, and auricular or other cutaneous tissues. The average interval between the onset of gout and the manifestation of tophi, in the absence of treatment, is approximately 10 years. Management of chronic gout may include both pharmacologic and non-pharmacologic strategies. Historically, the treatment of chronic gout began with the identification of patients as overproducers‖ or underexcretors‖ of uric acid, 24-hour urine collection. Overproducers‖ were treated preferentially with allopurinol,whereas underexcretors‖ were treated preferentially with the uricosuria probenecid. However, uricosuria agents may increase the risk of renal stones, requiring increased fluid intake and alkalization for prevention. Probenecid use has fallen out of favor because allopurinol was found to be effective in underexcretors‖. Urate lowering strategies are the primary pharmacologic intervention for of long-term complications of gout. (Zhu Y *et al.,* 2011)

Lifestyle Changes:

Non-pharmacologic methods advocated for the administration of chronic gout include a combination of lifestyle changes, including weight loss, exercise, hydration, and dietary changes. Such changes include a decrease of dietary purines and alcohol intake, based on observational studies assessing associations between dietary components and risk for gout or trials assessing the effect of specific foods or supplements on serum uric acid levels. Dietary risk factors for gout have been postulated to include alcohol consumption, as well as consumption of meat, seafood, sugar-sweetened soft drinks, and foods high in fructose, whereas dairy foods and coffee have been associated with a lower risk of incident gout and in some cases a lower rate of gout attacks (flares). The evidence for the efficacy of specific dietary

changes in managing gout (preventing attacks) is a topic of this review (Singh JA, 2013).

Pharmacologic Agents:

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

Table 1. lists the drugs used to treat gout and notes the ones covered in this systematic review.Several interleukin-1ß-inhibitory anti-inflammatory agents currently approved for the medicament of rheumatoid arthritis are in Phase II and III trials for the medicament of gout, including anakinra, canakinumab, and rilonacept, and will not be included in this systematic review, because they are not prescribed in the primary care setting. These treatments do not act by lowering serum urate levels. (Roddy AND Dohert, 2010).

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

Scope of the Review;

The purpose of this review is to assess the evidence on the management of patients with gout, in both the acute and chronic phases, including patients with tophaceous gout, and to assess management therapies that are FDA-approved and within the scope of practice of typical primary care providers. A protocol for the review was accepted and publicly posted on the AHRQ Web site on November 3, 2014(Roddy, and Doherty, 2010).

Table 1. Pharmacologic agents used in the treatment of gout

Drug Class	Agent (generic/brand)	Manufacturer
Anti-inflammatory Agents For Gout Attacks	NSAIDS (including lbuprofen, naproxen, etodolac, diclofenac, indomethacin, COX-2 inhibitors)	Numerous
	-Corticosteroid/Animal-derived adrenocorticotropic hormone (ACTH) formulation	Numerous
	-Colchicine/Colcrys[IM], Colchicine tablets, USP authorized generic	Takeda pharmaceuticals, America, Inc
	-IL-1B Receptor Antagonists[a] Anakinra/kineret[R]	Sobi
Urate Lowering Agents	-Uricosurics;Probenecid/Benemid or Probalan	Multiple
	-Xanthine Oxidase lnhibitors: Allopurinol/Zyloprim[R]	Prometheus Labs
	-Febuxosta/Uloric[IM]	Teijin Pharma Ltd, Takeda
	-Uricase: Pegloticase/krystexxa[a]	Crealta
	-Combinatin agents: Colchicine-probenecid/Proben-C	Merck

Acute Gout Treatment:

In patients with acute gout, what are the benefits and harms of different pharmacological therapies?

a. Does effectiveness (benefits and harms) differ according to patient baseline demographic characteristics and co-morbid conditions (including renal function)?
b. Does effectiveness (benefits and harms) differ according to disease severity, including initial clinical presentation (e.g., the scope of joint involvement and time

since the outset of flare) and laboratory values (serum and/or urine UA levels)?.

Dietary and Lifestyle Management of Gout:

a. In adults with gout, what are the benefits and harms of different dietary therapies and life style measures on intermediate (serum and/or urine UA levels) and final health outcomes (including recurrence of gout episodes and progression [e.g., development of tophi])? (Lic, *et al.,* 2013).
b. Doses efficiency and comparative effectiveness of dietary modification differ according to disease severity (including the existence of tophi and baseline serum UA), underlying mechanisms of hyperuricemia, or baseline demographic and co-morbid characteristics. (Khanna *et al.,* 2012).

Pharmacologic Management of Hyperuricemia in Gout Patients:

a. In adults with gout, what are the benefits and harms of different pharmacological therapies on intermediate (serum and/or urine UA levels) and long-term clinical health outcomes (including recurrence of gout episodes and progression)?.
b. Doses efficiency and comparative effectiveness of urate decrease therapy differ according to disease severity (including the presence of tophi and baseline serum UA), underlying mechanisms of hyperuricemia, or baseline demographic and co-morbid characteristics.
c. What is the effect of dietary modification in combination With pharmacologic therapy? (Khanna *et al.,* 2012).

Treatment Monitoring of Patients with Gout:

a. In adults with gout, does monitoring serum urate levels with pharmacologic treatment and/or dietary and/or lifestyle change measures (e.g., compliance) improve treatment outcomes.
b. Is achieving lower subsequent serum urate levels (less than 5 vs. 5– 7mg/dL) associated with decreased risk for a frequent acute gout attack, progression to chronic arthritis or disability, resolution of tophi, or other clinical outcomes (including risk for comorbidities or progression of comorbidities) or patient-reported outcomes.

Discontinuation of Pharmaceutical Management for Patients on Acute or Chronic Gout Medications:

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

a. urate lessening therapy.
b. anti-inflammatory prophylaxis against acute gout attack for patients on urate lessening therapy after an acute gout attack. (ChoiHK, 2005)

Diagnosis, Treatment, and Prevention of Gout:

Gout is characterized by painful joint inflammation, most commonly in the first metatarsophalangeal joint, resulting from the precipitation of monosodium urate crystals in a joint space. Gout is typically diagnosed using clinical criteria from the American College of Rheumatology. Diagnosis may be confirmed by the identity of monosodium urate crystals in the synovial fluid of the affected joint. Acute gout may be treated with nonsteroidal anti-inflammatory drugs, corticosteroids, or colchicine. To reduce the likelihood of recurrent flares, patients should limit their consumption of certain purine-rich foods (e.g., organ meats, shellfish) and avoid alcoholic drinks (especially beer) and beverages sweetened with high-fructose corn syrup.

Consumption of vegetables and low-fat or nonfat dairy products should be encouraged. The use of loop and thiazide diuretics can increase uric acid levels, whereas the use of the angiotensin receptor blocker losartan increases urinary excretion of uric acid.

Reduction of uric acid levels is key to avoiding gout flares. Allopurinol and febuxostat are first-line medications for the prevention of recurrent gout, and colchicine and/or probenecid are reserved for patients who cannot tolerate first-line agents or in whom first-line agents are ineffective. Patients receiving urate- lessening medications should be treated concurrently with nonsteroidal

anti-inflammatory drugs, colchicine, or low-dose corticosteroids to prevent flares. Treatment should continue for at least three months after uric acid levels fall below the (ChoiHK *et al.,* 2005) target goal in those without tophi, and for six months in those with a history of tophi.Gout is the most common inflammatory arthroplasty, affecting more than 8 million Americans. Gout accounts for approximately 7 million (ChoiHK *et al.,* 2004), ambulatory visits in the United States annually at a cost of nearly 1 billion. Risk factors include genetics, age, sex, and diet. These factors may contribute to a high serum uric acid level, which is currently defined as a value of at least 6.8 mg per dL (405 µmol per L). Pathophysiology and Risk Factors Genetic mutations may be (Gonzalez, 2012) associated with overproduction or more often under excretion of uric acid because of defects in the renal urate transporter system.6 The prevalence of gout increases with age and peaks at more than 12% in persons older than 80 years.1 Because female sex hormones increase urinary excretion of uric acid, pre-menopausal women have a substantially lower prevalence of gout compared with men (2.0% vs. 5.9%). Black persons have a higher risk. Consuming alcoholic drinks (particularly beer), meat (especially red meat, wild game, and organ meat), some seafood (e.g., shellfish, some large saltwater fish), fruit juice, and beverages sweetened with high-fructose corn syrup increases the risk of gout. Purine-rich foods such as nuts, asparagus, legumes, and mushrooms do not seem to increase the risk. Consumption of dairy products appears to confer slight protection from gout. Gout results from the precipitation of monosodium urate crystals in a joint space. Crystal deposition then triggers immune activation with the release of several inflammatory cytokines and Other common sites include the midtar- sal joints, ankles, knees, fingers wrists, and elbows. Urate crystals may also be (Lee SJ *et al.,* 2009) deposited throughout the body (e.g., vertebrae, skin, soft tissues), mimicking other disease states. Clinical Presentation Gout is typically diagnosed clinically based on the rapid development of monoarticular arthritis marked by swelling and redness usually involving the first metatarsophalangeal joint. The American College of (Neogi, 2011) Rheumatology criteria are the most widely used for the diagnosis of gout. An online risk calculator is also available it uses sex, uric acid level, and five findings from the history and physical examination to predict the likelihood of an acute gout. Microscopy of joint fluid is used less often, primarily in equivocal cases. In these situations, the diagnosis is established by aspiration of a joint or tophus and identification of needle-shaped monosodium urate crystals, preferably intracellular, with bright, negative birefringence on compensated polarized light microscopy.

Ultrasonography,magnetic resonance imaging, and computed tomography are typically not necessary for diagnosis. The differential diagnosis for acute (Reginato *et al.,* 2012) monoarticular joint includes pseudo gout, infection, and trauma. Pseudogout, or calcium pyrophosphate deposition disease, can mimic gout in clinical appearance and may respond to nonsteroidal anti-inflammatory drugs (NSAIDs).

Findings of calcium pyrophosphate crystals and normal serum uric acid levels on joint fluid analysis can differentiate pseudo gout from gout. Septic arthritis may present without a fever or elevated white blood cell count; arthrocentesis is required to distinguish this condition from acute gout. Gout and septic arthritis can occur concomitantly, but this is rare. Trauma-associated joint swelling is typically (ChoiHK *et al.,* 2005) identified by the history; however, trauma may result in an acute gout flare caused by increased concentrations of synovial urate. Imaging may be necessary to rule out fracture in a patient with gout-like symptoms after a joint injury. Treatment To achieve rapid and complete resolution of symptoms, treatment of acute gout should commence within. hours of symptom onset. Oral corticosteroids, intravenous corticosteroids, NSAIDs, and colchicine are equally effective in treating acute flares of gout. NSAIDs are the first-line treatment. Indomethacin (Indocin) has historically been the preferred choice; however, there is no

evidence it is more effective than any other NSAID. Intramuscular ketorolac appears to have similar effectiveness. Any oral NSAID may be given at the maximal dosage and continued for one to two days after the reduction of symptoms. Corticosteroids are an appropriate alternative for patients who cannot tolerate NSAIDs or colchicine. Patients with diabetes mellitus can be given corticosteroids for short-term use with appropriate monitoring for hyperglycemia. When gout is limited to a single joint, intra-articular corticosteroid injections may be favorite to systemic corticosteroids because of their lower adverse effect profile. Rebound flares are common after discontinuation of corticosteroid therapy for acute gout. To reduce the risk of a rebound flare, preventive treatment and initiation of a tapered course of cortico-steroids over 10 to 14 days is recommended after the solution of symptoms. Colchicine is another treatment option for acute gout. Generic colchicine, which has been used for decades, did not undergo a official review by the U.S. Food and Drug Administration (FDA) for this indication until 2009, when branded colchicine (Colcrys) was approved. However, Colcrys is expensive, and generic colchicine is no longer available. In addition, colchicine does not have analgesic properties and may be less effective in treating acute flares when given beyond 72 to 96 hours after symptom onset. Common adverse effects include nausea, vomiting, and diarrhea. Colchicine should be used with caution in (Terkelta, 2010) patients with hepatic or renal impairment.

Prevention:

Serum urate-lowering therapy should be initiated to prevent recurrences in persons with a history of gout and any one of the following: at least two flares per year (one per year in persons with chronic kidney disease stage 2 or greater), tophi, or a history of nephrolithiasis. Serum urate should be lowered to a target of less than 5 to 6 mg per dL (297 to 357 µmol per L), depending on the crystal and tophaceous burden. Normal serum urate levels do not exclude the diagnosis of gout. They should be monitored periodically to assess preventive therapy in patients with recurrent gout and a history of elevated urate levels. Urate-lowering therapy should be continued for three to six months after a flare if there are no ongoing symptoms.

Therapy should continue indefinitely if there are ongoing signs or symptoms (e.g., one or more tophi on examination). (ChoiHK, 2005)

Dietary Modifications:

Weight gain is a significant risk factor for gout in men, whereas weight loss reduces the risk. Intake of high-fructose corn syrup should be restricted because fructose contributes to increased uric acid production as a byproduct of adenosine triphosphate catabolism. Patients with gout should limit their intake of purine rich animal protein (e.g., organ meats, beef, lamb, pork, shellfish) and avoid alcohol (especially beer). Purine-rich vegetables do not increase the risk of gout. Consumption of vegetables and low-fat or nonfat dairy products should be encouraged. **(**Gonzalez**,** 2012).

Pharmacologic Options:

Pharmacologic options for the protection of chronic gout are outlined. Although avoidance of loop and thiazide diuretics has been recommended for patients with hypertension and gout because these agents can increase uric acid levels, a systematic review found only small increases in the risk of gouty flares. Calcium channel blockers and the angiotensin receptor blocker losartan (Cozaar) are associated with a decreased risk of incident gout. Losartan is the only angiotensin receptor blocker with this property. Historically, urate-lowering medication was thought to worsen acute gout flares, but recent evidence suggests that allopurinol (Zyloprim) can be started during an acute flare if it is used in conjunction with an NSAID (Lee *et al.*, 2009) and colchicine. Patients receiving a urate-lowering drug should be treated concurrently with an NSAID, colchicine, or low-dose corticosteroid to prevent a flare. Treatment should continue for at least three months after uric acid levels fall below the target goal in those without tophi, or for six months in those with a history of tophi. NSAIDs and corticosteroids should not be used for long periods without a urate-lowering

medication because uric acid crystals continue to accumulate and damage the joint, despite a lack of pain or clinical signs of inflammation. If a patient has a gout flare while receiving a urate-lowering agent, the medication should be continued while the flare is treated acutely. Allopurinol. Allopurinol, a xanthine oxidase (Neoga T, 2011) inhibitor, is a first-line agent to prevent recurrent gout. In patients with gout and chronic kidney disease or congestive heart failure, allopurinol has the added benefit of preventing chronic disease. The starting dosage is 100 mg per day, and 300 mg per day is a common maintenance dosage. Dosing is guided by the target serum uric acid level. In patients with chronic kidney disease, low initial doses are recommended with slow titration to achieve target uric acid levels. Dosages higher than 300 mg may be used even in those with renal impairment as long as patients are closely monitored for adverse effects. Certain ethnic groups have a higher risk of a severe hypersensitivity skin reaction when starting allopurinol (Neogi,2011) therapy. Screening for the human leukocyte antigen genotype is recommended before initiating treatment in patients of Han Chinese or Thai descent, regardless of kidney function, or in Koreans with chronic kidney disease stage 3 or greater. Febuxostat. Febuxostat (Uloric) is a xanthine oxidase inhibitor that was approved by the FDA in 2009. Although febuxostat is superior to 300 mg allopurinol at lowering serum uric acid levels, it is not more effective at reducing the frequency of gout flares. Febuxostat is considered a first-line agent to prevent recurrent gout, but it is considerably more expensive than allopurinol. Colchicine. Colchicine prevents gout flares at a dosage of 0.6 to 1.2 mg per day. The dose should be adjusted in (ZhuY *et al.*, 2011) patients with chronic kidney disease and when used with cytochrome or P- glycoprotein inhibitors. The long-term adverse effects of colchicine include reversible axonal neuromyopathy (less than 1%). Patients should be advised to stop taking colchicine and tell their physician if they experience leg weakness or pain. Treatment should be discontinued if any signs or symptoms of nerve or muscle damage are present. The rare risk of rhabdomyolysis is increased when colchicine is used (Terkelta, 2010) concomitantly with statins or clarithromycin (Biaxin), especially in older adults or those with chronic kidney disease; therefore, close monitoring is recommended. Probenecid. Probenecid increases urinary excretion of uric acid and is typically used as a second-line treatment because of numerous drug interactions. Of particular concern, probenecid increases blood levels of methotrexate and ketorolac, which may result in severe toxicity. Probenecid may be used in combination with allopurinol or febuxostat when one drug does not independently lower serum uric acid to target (Singh, 2013) levels. Nephrolithiasis is a common adverse effect that may be avoided by high fluid intake and urine alkalization with potassium citrate. Pegloticase. Pegloticase (Krystexxa) is an intravenous uricase approved by the FDA in 2010. The mechanism of action involves the metabolism of uric acid to allantois. It is a third-line agent and is indicated for the medicament of refractory gout. It is usually administered by a rheumatologist and is given every two weeks at a cost of more than $5,000 per dose. Data Sources: We searched PubMed, the Cochrane database, Essential Evidence Plus, and the National Guideline Clearinghouse. The search included expert (Lee *et al.*, 2009) consensus statements, clinical reviews, and clinical trials. Search terms included gout, gouty arthritis, gout prevention, and gout therapy. Search date: May 2014.

Conclusion:

Treatment and initiation of a tapered course of cortico-steroids over 10 to 14 days are recommended after the solution of symptoms. Colchicine is another treatment option for acute gout. Generic colchicine, which has been used for decades, did not undergo a official review by the U.S. Food and Drug Administration (FDA) for this indication until 2009 when branded colchicine (Colcrys) was approved. However, Colcrys is expensive, and generic colchicine is no longer available. In addition, colchicine does not have analgesic properties and may be less effective in treating acute flares when given beyond 72 to 96 hours after symptom onset. Common adverse effects

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REFERENCES

Choi H.K., Atkinson K., Karlson E.W., Curhan G. (2005) , Obesity, weight change, hypertension, diuretic use, and risk of gout in men: the health profes-sionals follow-up study. *Archives of Internal Medicine;*165(7):742-748.

Choi H.K., Atkinson K., Karlson E.W., Willett W., Curhan G. (2004), Purine-rich foods, dairy and protein intake, and the risk of gout in men. *The New England Journal of Medicine;*350(11):1093-1103.

Choi H.K. (2005) Diet, alcohol, and gout: how do we advise patients given recent developments? *Current Rheumatology Reports;*7(3):220-226.

Gonzalez EB. (2012) An update on the pathology and clinical management of gouty arthritis. *Clinical Rheumatology;*31(1):13-21.

Khanna D., Fitzgerald J.D., Khanna P.P., *et al.* (2012), 2012 American College of Rheumatology guidelines for management of gout. Part 1: system-atic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Research (Hoboken);*64(10):1431-1446.

Lee S J , Hirsch J D , Terkeltaub R , *et al.* (2009), Perceptions of disease and health-related quality of life among patients with gout.*Rheumatology(Oxford).;*48(5):582-586.

Li C**.,** Martin B.C., Cummins D.F., Andrews L.M, Frech-Tamas F., Yadao A.M. (2013), Ambulatory resource utilization and cost for gout in United States. *American Journal Pharmacy Benefits;*5(2):e46-e54.

Neogi T., (2011), Clinical practice. Gout. *The New England Journal of Medicine;*364(5):443-452.

Ning T,C,, Keenan R,T. (2010), Unusual clinical presentations of gout. *Current Opinion in Rheumatology;*22(2):181-187

Reginato A.M., Mount D.B., Yang I., ChoiHK. (2012), The genetics of hyperuricae-mia and gout. *Nature Reviews Rheumatology;*8(10):610-621.

Roddy E., Doherty M. (2010), Epidemiology of gout. *Arthritis Research Therapy;* 12(6):223.

Schlesinger N., Thiele R.G. (2010), The pathogenesis of bone erosions in gouty arthritis. *Annals of The Rheumatic Diseases;*69(11):1907-1912.

Singh J.A., (2013) Racial and gender disparities among patients with gout.*Current Rheumatology Reports;*15(2):307.

Terkelta Z.h.R., (2010), Update on gout: new therapeutic strategies and options. *Nature Reviews Rheumatology,* 6(1):30-38.

Zhu Y., Pandya B.J., Choi H.K. (2011), Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examina-tion Survey 2007-2008. *Arthritis Rheumatology*;63(10):3136-3141.