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REVIEW

Treatment approaches and adherence to urate-lowering therapy for patients with gout

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Abstract: Gout is the most common inflammatory arthritis characterized by painful disabling acute attacks. It is caused by hyperuricemia and deposition of urate crystals in and around the joints. Long-standing untreated hyperuricemia can lead to chronic arthritis with joint damage, tophi formation and urate nephropathy. Gout is associated with significant morbidity and health care associated cost. The goal of long-term therapy is to lower the serum urate level to promote dissolution of urate crystals, reduce recurrent acute gout flares, resolve tophi and prevent joint damage. Despite the presence of established gout treatment guidelines and effective medications to manage gout, patient outcomes are often poor. Etiology for these shortcomings is multifactorial including both physician and patient characteristics. Poor adherence to urate-lowering therapy (ULT) is prevalent and is a significant contributor to poor patient outcomes. This article reviews the treatment strategies for the management of hyperuricemia in chronic gout, gaps in quality of care in gout management, factors contributing to poor adherence to ULT and discusses potential interventions to achieve improved gout-related outcomes. These interventions include initiation of prophylactic anti-inflammatory medication when starting ULT, frequent follow-ups, regular serum urate monitoring and improved patient education, which can be achieved through pharmacist- or nurse-assisted programs. Interventions such as these could improve adherence to ULT and, ultimately, result in optimal gout-related outcomes.

Keywords: gout, adherence, urate-lowering therapy

Introduction

Gout is the most common form of inflammatory arthritis, which results from the deposition of monosodium urate crystals in or around the joints due to chronic hyperuricemia.[1] The clinical consequences vary from episodes of disabling acute arthritis, chronic recurrent arthritis, persistent low-grade joint inflammation and potentially progressive disease joint damage. The acute gout flare is a self-limited condition, but chronic, recurrent gout flares can lead to deposits of monosodium urate crystals (described as tophus when clinically apparent) as well as irreversible arthritis and joint destruction.[2] Management of the ongoing manifestations of gout hinges upon lowering serum urate levels below the threshold for crystal formation with urate-lowering therapy (ULT). Higher serum urate levels are associated with increased frequency of recurrent gout attacks, deposition of crystals (tophus development) and joint damage.[3]

Disease burden of gout

Approximately 3.9% of adults in the USA (8.3 million Americans) suffer from gout, costing $27.4 million annually.[4] Caring for patients with gout is associated with an additional $3,000 per patient annual increase of health care cost, compared to patients without gout.[5] Individuals with gout are absent from work on average 5 additional

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days annually, compared to those without gout. As a result, estimates for indirect cost are in billions of dollars.[6]

Treatment strategies for the management of hyperuricemia in chronic gout

The goal of long-term therapy is to lower the serum urate level to promote dissolution of monosodium urate crystals, reduce recurrent acute gout flares, resolve tophi (if present) and prevent joint damage. Indications for ULT vary slightly across the specialty societies, but according to the 2012 American College of Rheumatology (ACR) Guideline, ULT is indicated for the following conditions: 1) frequent gout attacks (defined as two or more gout attacks per year), 2) clinically detectable tophi, 3) joint damage from gout, 4) concomitant urate nephrolithiasis, or 5) concurrent chronic kidney disease (stages 2–5, or end stage renal disease).[7] A "treat-to-target" strategy to achieve serum urate level <6 mg/dL is recommended for all the above patients who do not have clinically significant tophi or erosive arthropathy.[7] Urate level <5 mg/dL is recommended to improve the symptoms and signs of gout for patients with more severe or aggressive gout.[7] The ACR Guideline recommends monitoring serum urate level every 2–5 weeks during ULT dose escalation until the target level is achieved and at least once yearly thereafter (more frequently if the gout symptoms remain active).[7]

Allopurinol, a purine analog and nonspecific competitive inhibitor of xanthine oxidase, is the most commonly used ULT.[8] The recommended starting dose is 100–150 mg/day (lower in the setting of chronic kidney disease) with titration as needed every 2–5 weeks to achieve a target urate level <6.0 mg/dL (maximum recommended US Food and Drug Administration dosing is 800 mg/day).[8] In clinical practice, 100 or 300 mg tablets are the most widely prescribed doses, but doses ≤300 mg are often insufficient to achieve the goal urate level in patients with normal renal function.[9] According to one observation study, 67% of patients on 100 mg required uptitration of medication vs 16% on 300 mg daily.[9] Febuxostat is an alternative nonpurine analog xanthine oxidase inhibitor (available in the USA at 40 or 80 mg/day, and in Europe available up to 120 mg/day).[10]

Probenecid, a uricosuric agent, is less commonly used. It is not recommended if creatinine clearance is below 50 mL/min and carries the risk of nephrolithiasis.[11] Lesinurad is a recently approved uricosuric that inhibits uric acid transporter 1.[12] It is indicated to be used in combination with a xanthine oxidase inhibitor.[12] Pegloticase is a urate-specific enzyme that metabolizes serum urate to allantoin, an inert, easily excreted metabolite.[13] Pegloticase is indicated for patients refractory to conventional ULT.[14] Neither lesinurad nor pegloticase is commonly used in the primary care setting.

Gaps in quality of care

Despite multiple guidelines for the management of hyperuricemia, therapy is often poorly monitored and treatment targets are often not achieved. There are multiple factors contributing to the discrepancy, including lack of monitoring in a primary care setting and disruption in treatment of hyperuricemia.

Failure to follow treat-to-target recommendations for the management of gout

The above guidelines recommend a treat-to-target strategy for the management of hyperuricemia. However, Wall et al showed in their study that in primary care settings, where most gout patients are treated, serum urate is monitored yearly in only one-quarter of patients.[15] Other studies have shown that fewer than 50% of patients met the goal urate level within 6 months or were flare free within 12 months.[16,17] Overall, there is a low adherence of primary care physicians to evidence-based treatment guidelines.[15] Absence of financial incentives to audit and improve standards of care might also contribute.[18]

Inconsistent use of urate-lowering medications (patient adherence)

In a study of 4,166 new users of ULT (97% received allopurinol), Harrold et al found that 70% had a significant interruption in medication, defined as a gap of >60 days between expected completion of last ULT prescription and no new refill. When these gaps in treatment occurred, it was most frequently (75% of the time) in the first year of therapy.[19] Also, a retrospective claims analysis from a managed care database found that one-third of patients with new ULT use had a medication possession ratio (MPR) of 10% or less. The median length of allopurinol therapy was 3 months, and ~88% of patients on ULT discontinued or had interrupted therapy.[20] When Halpern et al examined 18,243 subjects (mean age =54 years, male =84%) with gout, only 55% of all patients with gout were prescribed ULT (primarily allopurinol).[21] Among this 55% of patients, only 44% were found to be adherent to allopurinol based on MPR (>80%).[21] The mean MPR was 0.62, suggesting these individuals used allopurinol for 62% of the days of the given index period.[21] The Italian Health Search-Cegedim Strategic Data Longitudinal Patient Database showed that the proportion of patients adherent to

allopurinol was 45.9% in the interval 0–29 days and dropped to 16.7, 10.0 and 3.2% in 89, 149 and 365 days, respectively.[22]

Poor adherence is associated with suboptimal serum urate (sUA) control. Patients who were adherent to allopurinol were 2.5 times more likely to achieve an sUA of <6.0 mg/dL than nonadherent patients,[23] and in a separate study, post-allopurinol sUA of <6 mg/dL was achieved in a significantly higher proportion of subjects who were adherent to allopurinol (~50% vs 25%).[21]

Physician factors

In addition to patient adherence, there may be physician factors affecting patient outcomes. Compared with other conditions, there is less training given in medical school for gout.[18,24] Joint aspiration to detect mono-sodium urate (MSU) crystals may not be a viable option for the primary care physicians due to busy clinical schedules or lack of experience (particularly for smaller joints such as the first metatarsal phalange joint).[25] Even when ULT is initiated, it is often given at a fixed dose and not titrated appropriately to achieve a target serum uric acid level.[18] As a result, patients are undertreated. When the national administrative pharmacy claim database in Ireland was examined to identify adherence and persistence levels with urate-lowering therapies, only 14.6% were titrated to the 300 mg dose.[26]

Factors contributing to poor adherence to ULT

Increased gout flares during ULT initiation

When patients start ULT, they often experience increased frequency of gout flares during the first 6 months of ULT, as decreases in serum urate cause transient localized resorption and precipitation of monosodium urate crystals in the cartilage and soft tissues.[27]

A study of in-depth interviews of gout patients (N=26; 80% male) by Harrold et al demonstrated that among patients who discontinued ULT, 80% attributed acute gout flares and worsening of their gout to their ULT use, as reasons for discontinuation.[28] In the same study, several patients reported either increasing or decreasing the dose of allopurinol during an acute attack (which can increase the frequency or severity of gout attacks).[28] Similarly, a study by Becker et al showed that flares requiring treatment occurred in 10%–15% of patients in the first 2 months of starting febuxostat or allopurinol.[29] Pegloticase has uniquely high flare rates during the first 3 months of therapy (75% in pegloticase biweekly vs 81% in pegloticase monthly vs 53% in placebo groups).[13]

Patient fears of medication adverse effects

Patients' concern for side effects of gout medications and drug interaction were found to be another major challenge for treatment nonadherence in qualitative studies in both the UK and USA, with gout patients.[28,30,31] In the UK study on patients with gout (N=20; 75% male), several reported experiencing side effects of ULT, including frequent gout flares; also, a number of patients expressed unwillingness to take lifelong prescribed medication due to their concern for medication adverse effects.[31] In a US study of 26 patients (male =20, mean age =73 years), patients expressed concern that allopurinol triggered or worsened their gout.[28] Many patients were unclear about the duration of ULT management. In another US study (N=17, African American =12, female =9), patients' concerns about their gout medications was the top reason expressed for non-adherence. Patients were worried about the side effects of their gout medications including ULT and nonsteroidal anti-inflammatory drugs (NSAIDs), their long-term effects on vital organs and potential drug interactions with their other medications.[30]

Lack of information

Patients express concern about lack of information and/or misunderstanding about the treatment strategy, and this plays an important role in ULT nonadherence. In the in-depth telephone interviews conducted in gout patients (N=26) who started treatment with ULT, the patients claimed that lack of detailed information about the cause of gout and instructions on how to manage their gout from their providers was their major concern. Most importantly, patients had little appreciation of the risk of acute attacks related to variable adherence to ULT.[32] They also felt that visit time with their providers was too short, precluding sufficient discussion and understanding about their gout.[28] Patients often rely on Internet websites to obtain additional information. However, when 85 websites were selected and examined, 50% of the websites provided no information or had inaccuracies regarding the pathogenesis of gout and lacked emphasis on the importance of ULT.[33]

Other factors associated with low adherence

Patients' demographic factors, forgetfulness and financial issues were found to be associated with ULT adherence.

Age and gender

A study by Briesacher et al which examined drug adherence among more than 700,000 privately insured patients aged 18 or

older with chronic conditions demonstrated that the patient's age played an important role in treatment adherence.[34] The highest level of adherence was found in subjects with hypertension (72.3% of patients demonstrating MPRs ≥80%), whereas a lower level of adherence was found in subjects with gout (24.2% demonstrating MPRs ≤19%). The study showed that adherence ratios improved with increasing age in patients with gout (MPR >60% in patients aged 70 years or older, compared with <40% in those aged 18–29 years). In contrast, gender had little impact on adherence.[34]

Forgetfulness

A qualitative study of 43 African American patients with gout demonstrated that forgetting to take the ULT medication was one of the top barriers to adherence.[35] The reasons for forgetting to take the ULT included being busy with life, having the need to take many medications, or traveling. A similar study where in-depth telephone interviews were conducted for 26 Caucasian patients (mean age =73 years, 81% retired) with gout showed difficulties in remembering to take the ULT medication was a cause of treatment nonadherence.[28]

Cost

In a study by Singh, patients also reported concerns about the cost of medications[35] (particularly for febuxostat) and the need to fill multiple prescriptions.[35] They also described losing job insurance, retirement or limited income as causes of their financial restraints.[35] Financial concerns were also reported as a motivation for skipping or discontinuing medications by a few patients in the study by Harrold et al.[28]

Potential interventions to improve medication adherence

Use of prophylaxis to prevent gout flares while taking ULT

Better patient education about the expected increase in flares and use of colchicine prophylaxis could improve ULT adherence. Use of concurrent colchicine with ULT initiation has shown benefits in preventing flares since the 1960s.[36,37] In 2004, the first randomized, placebo-controlled trial of colchicine prophylaxis showed that among 43 subjects those who were treated with colchicine experienced fewer total flares compared to those who did not use colchicine (0.52 vs 2.91, P=0.008).[27] In this study, placebo-controlled patients had an average of two attacks and colchicine-treated patients had an average of 0.5 attacks during the first 3 months of ULT initiation.[27]

For the three randomized control trials comparing the efficacy of febuxostat and allopurinol (APEX,[10] FACT[38] and CONFIRMS[29]), colchicine or low-dose NSAID was used as prophylaxis. In APEX[10] and FACT[38] trials where patients were randomized to different doses of allopurinol and febuxostat, subjects were continued on either colchicine 0.6 mg once daily or naproxen 250 mg twice daily during the washout period and the first 8 weeks of ULT treatment, as prophylaxis for gout flare. Whereas, in the CONFIRMS trial, patients were continued on prophylaxis for 6 months.[29] In a post hoc reanalysis of FACT, APEX and CONFIRMS trials, the rate of flares increased sharply up to 40% at the end of 8 weeks of prophylaxis in FACT and APEX studies, when prophylaxis was discontinued.[39] However, the flare rates were consistently low (3%–5%) throughout the 6 months of prophylaxis in the CONFIRMS study.[39]

Colchicine's known side effects include diarrhea, abdominal cramps, nausea and vomiting. Rarely, it can cause bone marrow suppression as well as neuromyopathy.[27] Naproxen and colchicine should be given with caution in patients with renal impairment, and naproxen should be avoided in patients with gastric ulceration. Currently, the European League Against Rheumatism and ACR guidelines suggest the use of prophylaxis, either colchicine or NSAIDs.[11,40] The ACR recommends at least 3 months beyond achieving target serum urate for nontophaceous patients and at least 6 months for tophaceous patients.[11]

Frequent follow-ups

A UK study led by Rees et al demonstrated that frequent reinforcement with telephone calls is an effective way for gout patients to achieve target sUA.[41] Frequent follow-ups, either by telephone or face to face, particularly for those with high-risk characteristics for nonadherence, such as newly diagnosed patients or younger patients, can improve patients' adherence to therapy. Frequent follow-ups are known to improve adherence in other conditions. A phone call made to patients to ensure blood pressure goals were achieved with home blood pressure monitoring revealed significantly greater adherence rate in hypertension medications.[42]

Utilization of nurse- and pharmacist-led programs to educate patients

The above reports indicate that lack of patient education and misperceptions of disease and gout therapy result in treatment nonadherence. It is important to educate patients that gout can be managed through the dissolution of MSU crystals and that ULT is key in this process. Rees et al examined the effectiveness of a nurse-delivered intervention that included education, individualized lifestyle advice and appropriate ULT over a 12-month period (N=106, male =94) and found 92% had achieved the therapeutic target SUA ≤360 µmol (6.05 mg/dL)

at 12 months.[41] They also demonstrated reduction in acute gout flares with this intervention. The study showed that patients could be encouraged to be compliant with ULTs and to practice self-management with gout therapy.

In a separate study, a pharmacist-based gout management pilot program was implemented in the USA with 100 participants. This study used telephone-delivered intervention to provide educational and dietary guideline materials and to titrate ULT to a target sUA level ≤6 mg/dL using a protocol. Seventy-eight completed the program and successfully achieved two consecutive target sUA levels.[43] Similarly, Fields et al led a nursing educational intervention program followed by calls from pharmacists emphasizing adherence to management programs. Eighty-one percent of 40 subjects reported the helpfulness of the nursing education program and 50% of subjects reported the helpfulness of the calls from the pharmacists.[44] These findings suggest that ULT therapy compliance can be improved with a multidisciplinary program. The importance of education is also highlighted in other medical conditions such as hypertension. Effects on interventions to improve medication adherence were similar, whether delivered by physicians or pharmacists.[45]

Due to the complex nature of gout, information regarding the short-term and long-term effects of ULT and the risk of acute flares during titrating ULT doses may need to be reinforced to patients at multiple time points in various modes (ie, orally and in print).[28] In addition, medication reminder tools such as a pillbox with alarm may help improve patients' adherence to ULT, as was found to be the case in tuberculosis patients.[46]

Concurrent management of comorbidities

Hypertension, alcohol use and obesity are the risk factors for developing gout.[47] Patients who have metabolic syndrome often also have chronic kidney diseases, which prevent utilization of gout prophylaxis and uptitration of ULT. A meta-analysis of ten prospective studies showed that the relative risks of gout increased to 1.78, 2.67, 3.62 and 4.64 for persons with body mass index 25, 30, 35 and 40 compared to those with a body mass index of 20.[48] Patients who are diagnosed with gout should be closely followed for the management of hypertension, diabetes, hyperlipidemia and obesity. A study has shown the relationship between dietary habits and hyperuricemia.[49] As a result, lifestyle modifications, including weight control, regular exercise and less consumption of red meat, alcohol and high fructose corn syrup, should also be emphasized.[11]

Conclusion

In summary, gout is a common inflammatory arthritis associated with excruciating pain, poor quality of life and significant health care associated cost. Despite the presence of guidelines and effective medications to manage gout, optimal outcomes are often not achieved in gout. Etiology for these shortcomings is multifactorial, but includes inadequate patient education, management and lack of adherence to ULT. Many factors contribute to nonadherence, including increased gout flares with initiation of ULTs, patients' concerns for medication adverse effects, inadequate disease and drug counseling and inadequate time to educate patients. Initiation of prophylactic anti-inflammatory medication with ULT, frequent follow-ups, regular serum urate monitoring and pharmacist- or nurse-assisted programs to promote patients' education could well improve adherence to ULT and, ultimately, help in optimal gout management.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Kim KY, Schumacher HR, Hunsche E, Wertheimer AI, Kong SX. A literature review of the epidemiology and treatment of acute gout. *Clin Ther*. 2003;25(6):1593–1617.
2. Nasser-Ghodsi N, Harrold LR. Overcoming adherence issues and other barriers to optimal care in gout. *Curr Opin Rheumatol*. 2015; 27(2):134–138.
3. Perez-Ruiz F. Treating to target: a strategy to cure gout. *Rheumatology (Oxford)*. 2009;48(Suppl 2):ii9–ii14.
4. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the national health and nutrition examination survey 2007–2008. *Arthritis Rheum*. 2011;63(10):3136–3141.
5. Wertheimer A, Morlock R, Becker MA. A revised estimate of the burden of illness of gout. *Curr Ther Res Clin Exp*. 2013;75:1–4.
6. Kleinman NL, Brook RA, Patel PA, et al. The impact of gout on work absence and productivity. *Value Health*. 2007;10(4):231–237.
7. Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American college of rheumatology guidelines for management of gout. part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res (Hoboken)*. 2012;64(10):1431–1446.
8. Zyloprim® tablet [Package insert]. San Diego, CA: Prometheus Laboratories Inc; 2003.
9. Jennings CG, Mackenzie IS, Flynn R, et al. Up-titration of allopurinol in patients with gout. *Semin Arthritis Rheum*. 2014;44(1):25–30.
10. Schumacher HR, Becker MA, Wortmann RL, et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial. *Arthritis Rheum*. 2008;59(11):1540–1548.
11. Khanna D, Khanna PP, Fitzgerald JD, et al. 2012 American college of rheumatology guidelines for management of gout. Therapy and antiinflammatory prophylaxis of acute gouty arthritis. *Arthritis Care Res (Hoboken)*. 2012;64(10):1447–1461.
12. Saag KG, Fitz-Patrick D, Kopicko J, et al. Lesinurad combined with allopurinol: a randomized, double-blind, placebo-controlled study in gout subjects with inadequate response to standard of care allopurinol (A US-based study). *Arthritis Rheumatol*. 2017;69(1):203–212.
13. Sundy JS, Baraf HSB, Yood RA, et al. Efficacy and tolerability of pegloticase for the treatment of chronic gout in patients refractory to conventional treatment two randomized controlled trials. *JAMA*. 2011;306(7):711–720.

14. Hussar DA. New therapeutic agents marketed in the second half of 2010. *Pharmacy Today*. 2011;17(3):69–80.
15. Wall GC, Koenigsfeld CF, Hegge KA, Bottenberg MM. Adherence to treatment guidelines in two primary care populations with gout. *Rheumatol Int*. 2010;30(6):749–753.
16. Becker MA, Fitz-Patrick D, Choi HK, et al. An open-label, 6-month study of allopurinol safety in gout: the LASSO study. *Semin Arthritis Rheum*. 2015;45(2):174–183.
17. Khanna D, Khanna PP, Hagerty D, et al. Patients that continue to flare despite apparent optimal urate lowering therapy. *Arthritis Rheum*. 2012; 64(Suppl 10):140.
18. Doherty M, Jansen TL, Nuki G, et al. Gout: why is this curable disease so seldom cured? *Ann Rheum Dis*. 2012;71(11):1765–1770.
19. Harrold LR, Andrade SE, Briesacher B, et al. The dynamics of chronic gout treatment: medication gaps and return to therapy. *Am J Med*. 2010;123(1):54–59.
20. Sarawate CA, Brewer KK, Yang W, et al. Gout medication treatment patterns and adherence to standards of care from a managed care perspective. *Mayo Clin Proc*. 2006;81(7):925–934.
21. Halpern R, Mody RR, Fuldeore MJ, Patel PA, Mikuls T. Impact of noncompliance with urate-lowering drug on serum urate and gout-related healthcare costs: administrative claims analysis. *Curr Med Res Opin*. 2009;25(7):1711–1719.
22. Mantarro S, Capogrosso-Sansone A, Tuccori M, et al. Allopurinol adherence among patients with gout: an Italian general practice database study. *Int J Clin Pract*. 2015;69(7):757–765.
23. Rashid N, Coburn BW, Wu YL, et al. Modifiable factors associated with allopurinol adherence and outcomes among patients with gout in an integrated healthcare system. *J Rheumatol*. 2015;42(3): 504–512.
24. Ogdie AR, Hoch S, Dunham J, Von Feldt JM. A roadmap for education to improve the quality of care in gout. *Curr Opin Rheumatol*. 2010; 22(2):173–180.
25. Roddy E, Zhang W, Doherty M. Concordance of the management of chronic gout in a UK primary-care population with the EULAR gout recommendations. *Ann Rheum Dis*. 2007;66(10):1311–1315.
26. McGowan B, Bennett K, Silke C, Whelan B. Adherence and persistence to urate-lowering therapies in the Irish setting. *Clin Rheumatol*. 2016;35(3):715–721.
27. Borstad GC, Bryant LR, Abel MP, Scroggie DA, Harris MD, Alloway JA. Colchicine for prophylaxis of acute flares when initiating allopurinol for chronic gouty arthritis. *J Rheumatol*. 2004;31(12):2429–2432.
28. Harrold LR, Mazor KM, Velten S, Ockene IS, Yood RA. Patients and providers view gout differently: a qualitative study. *Chronic Illn*. 2010;6(4):263–271.
29. Becker MA, Schumacher HR, Espinoza LR, et al. The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial. *Arthritis Res Ther*. 2010;12(2):R63.
30. Singh JA. Challenges faced by patients in gout treatment: a qualitative study. *J Clin Rheumatol*. 2014;20(3):172–174.
31. Spencer K, Carr A, Doherty M. Patient and provider barriers to effective management of gout in general practice: a qualitative study. *Ann Rheum Dis*. 2012;71(9):1490–1495.
32. Vaccher S, Kannangara D, Baysari M, et al. Barriers to care in gout: from prescriber to patient. *J Rheumatol*. 2016;43(1):144–149.
33. Jimenez-Linan LM, Edwards L, Abhishek A, et al. Online patient information resources on gout provide inadequate information and minimal emphasis on potentially curative urate lowering treatment. *Arthritis Care Res (Hoboken)*. Available from: https://www.ncbi.nlm.nih.gov/labs/articles/27390083/. Accessed March 6, 2017.
34. Briesacher BA, Ph D, Andrade SE, Sc D, Fouayzi H, Chan A. Comparison of drug adherence rates among patients with seven different medical conditions. *Pharmacotherapy*. 2009;28(4):437–443.
35. Singh JA. Facilitators and barriers to adherence to urate-lowering therapy in African-Americans with gout: a qualitative study. *Arthritis Res Ther*. 2014;16(2):R82.
36. Paulus HE, Schlosstein LH, Godfrey RG, Klinenberg JR, Bluestone R. Prophylatic colchicine therapy of intercritical gout. A placebo-controlled study of probenecid-treated patients. *Arthritis Rheum*. 1974;17(5): 609–614.
37. Yu T, Gutman A. Efficacy of colchicine prophylaxis. Prevention of recurrent gouty arthritis over a mean period of 5 years in 208 gouty subjects. *Ann Intern Med*. 1961;55:179–191.
38. Becker MA, Schumacher HR, Wortmann RL, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *N Engl J Med*. 2005;353(23):2450–2461.
39. Wortmann RL, Macdonald PA, Hunt B, Jackson RL. Effect of prophylaxis on gout flares after the initiation of urate-lowering therapy: analysis of data from three phase III trials. *Clin Ther*. 2010;32(14):2386–2397.
40. Richette P, Doherty M, Pascual E, et al. Updated EULAR evidence-based recommendations for the management of gout. *Ann Rheum Dis*. 2014;73:1–14.
41. Rees F, Jenkins W, Doherty M. Patients with gout adhere to curative treatment if informed appropriately: proof-of-concept observational study. *Ann Rheum Dis*. 2013;72(6):826–830.
42. Márquez-Contreras E, Martell-Claros N, Gil-Guillén V, et al. Efficacy of a home blood pressure monitoring programme on therapeutic compliance in hypertension: the EAPACUM-HTA study. *J Hypertens*. 2006;24(1):169–175.
43. Goldfien RD, Ng MS, Yip G, et al. Effectiveness of a pharmacist-based gout care management programme in a large integrated health plan: results from a pilot study. *BMJ Open*. 2014;4(1):e003627.
44. Fields TR, Rifaat A, Yee AMF, et al. Pilot study of a multidisciplinary gout patient education and monitoring program. *Semin Arthritis Rheum*. In press 2016.
45. Conn VS, Ruppar TM, Chase JA, Enriquez M, Cooper PS. Interventions to improve medication adherence in hypertensive patients: systematic review and meta-analysis. *Curr Hypertens Rep*. 2015;17(12):94.
46. Liu X, Lewis JJ, Zhang H, et al. Effectiveness of electronic reminders to improve medication adherence in tuberculosis patients: a cluster-randomised trial. *PLoS Med*. 2015;12(9):1–18.
47. Choi HK, Atkinson K, Karlson EW, Curhan G. Obesity, weight change, hypertension, diuretic use, and risk of gout in men: the health professionals follow-up study. *Arch Intern Med*. 2005;165(7):742–748.
48. Aune, D, Norat, T, Vatten L. Body mass index and the risk of gout: a systemic review and dose-response meta-analysis of prospective studies. *Eur J Nutr*. 2014;53(8):1591–1601.
49. Miao Z, Li C, Chen Y, et al. Dietary and lifestyle changes associated with high prevalence of hyperuricemia and gout in the Shandong coastal cities of Eastern China. *J Rheumatol*. 2008;35(9):1859–1864.