

**Title:** Long-term persistence and adherence on urate lowering treatment can be maintained in primary care – five year follow up of a proof-of-concept-study

**Authors:** Dr A Abhishek\*<sup>1</sup>, Mrs Wendy Jenkins<sup>1</sup>, Dr Jonathan Le-Carratt<sup>1,2</sup>, Dr Gwen Fernandes<sup>1,3</sup>, Prof. M Doherty<sup>1</sup>.

**Affiliation:** <sup>1</sup>Academic Rheumatology, University of Nottingham, Clinical Sciences Building, Nottingham City Hospital, Nottingham NG5 1PB, UK; <sup>2</sup> Department of Medicine, Nottingham University Hospitals NHS Trust, Nottingham, NG7 2UH; <sup>3</sup>Arthritis Research UK Centre for Sports, Exercise and Osteoarthritis

**Address for correspondence:** Dr. A. Abhishek, PhD; Academic Rheumatology, University of Nottingham, Nottingham NG5 1PB, United Kingdom

Phone: +44 115 8231392

Fax: +44 115 8231757

Email: [Abhishek.abhishek@nottingham.ac.uk](mailto:Abhishek.abhishek@nottingham.ac.uk)

**Word count:** 2000

## **ABSTRACT**

**Objectives:** To evaluate the persistence and adherence on urate lowering treatment (ULT) in the primary care five years after an initial nurse-led treatment of gout.

**Methods:** 100 gout patients initiated on up-titrated ULT between March-July 2010, last study visit March-July 2011, were sent a questionnaire that elicited information on current ULT, reasons for discontinuation of ULT if applicable, medication adherence, and generic and disease specific quality of life measures in 2015. They were invited for one visit at which height and weight were measured and blood was collected for serum uric acid (SUA) measurement.

**Results:** Seventy-five patients, mean (standard deviation (SD)) age and disease duration 68.13 (10.07) and 19.44 (13) years respectively returned completed questionnaires. The five-year persistence (95% (confidence interval (CI)) on ULT was 90.7 (81.4-91.6) %, and 85.3% responders self-reported taking ULT on  $\geq 6$  days/week. Of the 65 patients who attended for the study visit, the mean (SD) SUA was 292.8 (97.2)  $\mu\text{mol/L}$ .

**Conclusion:** An initial treatment that includes individualised patient education and involvement in treatment decisions, results in excellent adherence and persistence on ULT >4 years after the responsibility of treatment is taken over by the patients' GP, suggesting that this model of gout management should be adopted widely.

**Keywords:** Gout, urate lowering treatment, persistence, adherence

**Key messages:**

- Excellent long-term persistence and adherence on urate lowering treatment can be achieved if patients are initially educated about gout and its' treatment.
- The benefits of such an individualised education persists even after the responsibility of gout treatment is taken over by the patients' own GP.

**Introduction:** Gout is the commonest inflammatory arthritis with a prevalence of 2.5% (1). Although curable, its management is suboptimal as evidenced by low urate lowering treatment (ULT) initiation rates even in people who consult their GP for gout and fulfil the recommended criteria for ULT [1, 2]. Moreover, the persistence and adherence on ULT is generally poor [1, 3, 4]. For example, half of all men and women discontinued ULT by 358 and 379 days in a community based study, while another study reported the 12-month persistence on ULT to be even lower at 22.6% [4, 5]. Apart from this, adherence to ULT ranges from 10-46%; and is lower than medication adherence in other chronic illnesses including rheumatoid arthritis [1, 3, 4, 6, 7]. In the UK, only 34-38% gout patients get initiated on ULT, and of these, only 39% are adherent to ULT at 12 months [1, 2].

A proof-of-concept study from Nottingham, UK demonstrated that a predominantly nurse-led treatment package consisting of individually tailored patient information regarding gout and its management, and initiation and upward dose titration of ULT as per the British Society for Rheumatology (BSR) recommendations resulted in 92% gout patients persisting on ULT at 1 year [8]. However, whether these patients would persist on ULT in a real world setting, in the long-term, once the responsibility of prescribing ULT is taken over by the patients' own doctor at the end of the 12-month study period is not known.

Thus, the overall aim of this study was to explore the effects of an initial nurse-led gout treatment on ULT continuation in the long-term. The specific objectives were to [1] examine the persistence and adherence on ULT, [2] calculate the proportion of patients who meet the British Society for Rheumatology and European League Against Rheumatism treatment target for serum uric acid (SUA) at 5 years [9].

## **Methods:**

*Study design* Cross-sectional study

*Setting* Primary care

*Case definition* Crystal-proven gout patients previously participated in the proof-of-concept study, recruited March to July 2010, and last study visit July 2011 [8].

*Recruitment* 100 of the 106 gout cases (5 dead, 1 moved out of the area) were sent a postal questionnaire in September 2015. The questionnaire elicited information about demographic characteristics, current ULT, reason(s) for ULT discontinuation (if applicable), self-reported adherence to ULT, and quality of life assessed by the Short Form 36 version 2 (SF-36v2) and the Gout Impact Scale (GIS) of the Gout Assessment Questionnaire version 2 (GAQv2) [10, 11]. Responders were invited to attend for a hospital visit at which height, weight, and blood pressure were measured; and blood was collected for SUA measurement. Data on SUA, serum creatinine measurements requested by GPs between July 2011 and September 2015 were obtained from Clinical Chemistry Department, Nottingham University Hospitals NHS Trust.

The postcode of each study participant was used to obtain their Index of Multiple Deprivation (IMD), a composite measure of socioeconomic and healthcare deprivation, from the Department for Communities and Local Government, England (<http://imd-by-postcode.opendatacommunities.org>). The IMD ranks each postcode (n = 32,844) in England according to their relative deprivation, with lower ranks being the most deprived. This study was approved by the Medical School Ethics Committee, University of Nottingham, UK, Ref: B18062015 SoM ROD.

*Statistical Analysis* N(%) and mean (standard deviation (SD)) were used for descriptive statistics. Persistence and adherence rates and their 95% confidence

intervals (95% CIs) were calculated. Independent sample T-test and chi-square test were used to compare the baseline disease and demographic characteristics of questionnaire responders and non-responders. The SF-36v2 scores were standardised using population norms generated from a large UK community sample [11]. Scores of each domain of SF-36v2 at baseline and five year follow up were compared using paired T-test. Odds ratio (OR) and 95%CI were used to examine associations. Binary logistic regression was used to calculate the OR. All statistical analyses were carried out using STATA.  $p \leq 0.05$  was statistically significant.

**Results:** 75 of the 100 questionnaires were returned and 65 patients attended for the study visit. The mean (SD) age, disease duration, and BMI were 68.13 (10.07) years, 19.44 (13) years, and 31.12(4.51) kg/m<sup>2</sup> respectively. 12% responders were women, and 14.7% had tophaceous gout. Questionnaire responders were older than non-responders at the baseline visit in 2010 (Table 1). However, this was not statistically significant and other disease and demographic characteristics, including SF-36 scores and IMD were comparable between the two groups (Table 1).

Sixty-eight of the 75 responders were on ULT at the time of follow-up questionnaire survey, giving a persistence (95% CI) of 90.7(81.4-91.6)%. Reasons for discontinuing ULT were: felt to be no longer required (3); fed-up with taking ULT (2); temporary discontinuation for unrelated reasons (1); and unclear (1). Five-year persistence was comparable in those on allopurinol (93.1%), febuxostat (81.8%), and benzbromarone (100%) (p=0.47). The dose of ULT was reduced in 11 participants (Allopurinol 400 mg/day to 300 mg/day (n=9) and 500 mg/day to 400mg/day (n=1), Febuxostat 120mg/day to 80 mg/day (n=1)), remained the same in 52 participants, and was increased in three participants. Two participants were commenced on a different ULT. A median of 1 (inter-quartile range 0-3) SUA measurements, and 4 (2-7) serum creatinine measurements were requested by the GPs between the end of the proof of concept study and September 2015, and only 37.5% patients had  $\geq 2$  SUA measurements during this period.

85.3 (74.4 - 92.0)% of responders self-reported taking ULT on  $\geq 6$  days in an average week (Figure 1a). The mean (SD) SUA at the five year visit was 292.8 (97.2)  $\mu\text{mol/L}$ . The SUA was significantly lower in those on ULT than in those not on ULT (mean (SD) SUA 269.4 (50.4)  $\mu\text{mol/L}$  vs. 577.2 (63.6)  $\mu\text{mol/L}$ , p <0.001). Of the patients for whom the five-year SUA levels were available, 86.4% (75.5-92.9) had SUA  $\leq 360$   $\mu\text{mol/L}$  and

69.7% had SUA  $\leq$ 300  $\mu$ mol/L. Those who self-reported forgetting ULT on  $\geq$ 2 days/week were significantly less likely have SUA  $\leq$ 300  $\mu$ mol/L (OR (95%CI) 0.19 (0.04-0.84),  $p=0.029$ ) (Figure 1b).

The bodily pain domain score of SF-36v2 improved over five years, with mean (SD) baseline and five year scores of 42.55 (10.47) and 46.01 (11.32) respectively, a mean (95% CI) improvement of 3.46 (0.69-6.23),  $p=0.015$ . There were no statistically significant differences in the other SF-36v2 domain scores over five years (data not shown). Similarly, study participants had excellent scores on each of the five GIS domains, and in the overall GIS score. The mean (95% CI) gout concern overall, gout medication side effects, unmet gout treatment need, well-being during attack, and gout concern during attack were 34.88 (28.51-41.25), 37.84 (32.15-43.53), 22.30 (17.98-26.62), 40.47 (34.75-46.19), 32.42 (27.34-37.47).



**Discussion:** This study examined the effects of a one-year initial nurse led treatment of gout on long-term persistence and adherence to ULT after the responsibility for prescribing ULT was handed-over to the patients' own doctor. It reports that >90% patients persisted on ULT at five years with excellent adherence, and that >86% patients met the EULAR treatment target for SUA at five years. These findings suggest that a personalized interactive education about gout, and full involvement of patients in management decisions results in improved long-term persistence on ULT even after the responsibility of prescribing ULT is handed over to the patients' own GP. This concurs with the findings of a systematic review which concluded that patient education improves medication adherence [12]. As reported previously, three of the six patients who discontinued ULT did so because they felt that long-term ULT was no longer necessary [13, 14]. These findings suggest that the need for long-term ULT should be reinforced periodically.

In a cross sectional study from New Zealand, patients' determination to maintain a normal SUA was the only psychological determinant of treatment success [15]. It is possible that the individualized patient education during the proof-of-concept study increased their commitment to reduce the SUA to below treatment target, and that progressive reductions in SUA during treat to target ULT provided the requisite positive feedback to maintain this. Thus, the key components that resulted in excellent five year persistence on ULT are an experienced rheumatologist with an interest and expertise in gout (MD) fully assessing the patient and providing initial explanations concerning gout, its possible effects, and available treatment options; nurse led disease monitoring and ULT dose escalation and reinforcement of patient education over the first year; and subsequent continued prescription of ULT by the GP. Although

not directly measured, it is likely that the excellent adherence to ULT is at least in part due to ongoing follow-up and encouragement to adhere to ULT by the GP.

In keeping with the findings of a previous study, we found that poor adherence to ULT associated with high SUA [16]. This study also shows that long-term ULT improves bodily pain in gout. The magnitude of improvement in our study is smaller than that reported previously, in studies undertaken predominantly in patients from secondary care [17], and this may be due to participants in the other studies having more severe disease, resulting in a greater improvement in quality of life with ULT. Similarly, the scores on gout concern overall, unmet gout treatment need, and gout concern during an attack domains of GIS in this well treated gout cohort are 25.9% to 44.7%, 20.9% to 41.6%, and 35.5% to 40.8% lower than that observed in other gout cohorts, providing further evidence of long-term beneficial effects from an initial nurse-led treatment of gout [18-20]. Smaller differences were present in gout medication side effects (13.3% to 21.7%), and well-being during attack (14.2% to 27.4%) domains (18-20). **(Figure S1)**

There are several strengths of this study, namely, a very high response rate to the questionnaire, and long follow up period. However, there are several caveats to this study. Firstly, we do not have information about persistence and adherence on ULT in those who did not respond to the follow-up questionnaire. Additionally, the questionnaire non-responders were 4.6 years younger than responders. Since persistence on ULT is lower in the younger age group, it is possible that the overall long-term adherence and persistence on ULT in the proof-of-concept study participants is lower than that estimated in this study. Similarly, non-responders had slightly worse disease at baseline, which could relate to socio-economic deprivation, which associates with reduced medication adherence. However, responders and non-

responders had similar socio-economic deprivation scores (Table 1). Nevertheless, even if all non-responders are assumed to be not taking ULT, the five year persistence on ULT would be 68%. Even this is much better than other reports of long-term persistence on ULT. Unfortunately we did not collect information on GIS during the proof-of-concept study in 2010-2011, and are unable to measure any long-term improvements in disease specific quality of life from the initial nurse-led package of care. Due to the small sample size, and high persistence and adherence rates, we did not perform multivariate analysis to identify the disease and demographic predictors of non-persistence or non-adherence to ULT, as any such analysis would be prone to type II error. Additionally, we do not have data on the number of times a patient was seen by their GP for gout between the final study visit in 2011 and the questionnaire survey in 2015. These data are likely to be inaccurate when captured retrospectively in a questionnaire survey after four years because a review of gout would have been part of broader periodic medical review, and the patient may not remember being asked by their GP about gout several years later.

In conclusion, this study demonstrates that an initial package of care that includes individualised education, patient involvement in management decisions and a treat-to-target approach to ULT results in the best long-term ULT adherence and persistence reported so far. Such treatment may be initiated by a suitably trained nurse or by any other allied healthcare professional like a community pharmacist. Further research is required to find out if persistence and adherence to long-term ULT is due to retained knowledge of gout and its treatment, and if such treatment improves renal function and reduces the risk of cardiovascular disease.

**Financial disclosures:** The authors report that no financial support or other benefits were used from commercial sources for the work reported in the manuscript. MD has received research funding from AstraZeneca and AA has received research funding from AstraZeneca and OxfordImmunotech. The authors do not have any other financial interests which could create a potential conflict of interest or the appearance of a conflict of interest with regard to the work.

**Funding:** This research was funded by Nottingham University Hospitals NHS Trust Charity.

## References:

1. Kuo CF, Grainge MJ, Mallen C, Zhang W, Doherty M. Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study. *Ann Rheum Dis.* 2015;74(4):661-7.
2. Cottrell E, Crabtree V, Edwards JJ, Roddy E. Improvement in the management of gout is vital and overdue: an audit from a UK primary care medical practice. *BMC family practice.* 2013;14:170.
3. De V. Medication adherence in gout: A systematic review. *Arthritis Care and Research.* 2014;66(10):1551-9.
4. Zandman-Goddard G, Amital H, Shamrayevsky N, Raz R, Shalev V, Chodick G. Rates of adherence and persistence with allopurinol therapy among gout patients in Israel. *Rheumatology (Oxford, England).* 2013;52(6):1126-31.
5. McGowan B, Bennett K, Silke C, Whelan B. Adherence and persistence to urate-lowering therapies in the Irish setting. *Clinical Rheumatology.* 2014; 35(3):715-21.
6. Briesacher BA, Andrade SE, Fouayzi H, Chan KA. Comparison of drug adherence rates among patients with seven different medical conditions. *Pharmacotherapy.* 2008;28(4):437-43.
7. Harrold LR, Andrade SE. Medication adherence of patients with selected rheumatic conditions: a systematic review of the literature. *Semin Arthritis Rheum.* 2009;38(5):396-402.
8. 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):826-30.

9. Jordan KM, Cameron JS, Snaith M, Zhang W, Doherty M, Seckl J, et al. British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of gout. *Rheumatology* (Oxford, England). 2007;46(8):1372-4.
10. Hirsch JD, Lee SJ, Terkeltaub R, Khanna D, Singh J, Sarkin A, et al. Evaluation of an instrument assessing influence of Gout on health-related quality of life. *J Rheumatol*. 2008;35(12):2406-14.
11. Jenkinson C, Stewart-Brown S, Petersen S, Paice C. Assessment of the SF-36 version 2 in the United Kingdom. *Journal of epidemiology and community health*. 1999;53(1):46-50.
12. Galo JS, Mehat P, Rai SK, Avina-Zubieta A, De Vera MA. What are the effects of medication adherence interventions in rheumatic diseases: a systematic review. *Ann Rheum Dis*. 2016;75(4):667-73.
13. 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):1490-5.
14. Singh JA. Facilitators and barriers to adherence to urate-lowering therapy in African-Americans with gout: a qualitative study. *Arthritis Research & Therapy*. 2014;16(2):R82.
15. Dalbeth N, House ME, Horne A, Petrie KJ, McQueen FM, Taylor WJ. Prescription and dosing of urate-lowering therapy, rather than patient behaviours, are the key modifiable factors associated with targeting serum urate in gout. *BMC Musculoskeletal Disorders*. 2012;13:174.
16. Halpern R, Mody RR, Fuldeore MJ, Patel PA, Mikuls TR. Impact of noncompliance with urate-lowering drug on serum urate and gout-related healthcare

costs: administrative claims analysis. *Current medical research and opinion*. 2009;25(7):1711-9.

17. Khanna PP, Perez-Ruiz F, Maranian P, Khanna D. Long-term therapy for chronic gout results in clinically important improvements in the health-related quality of life: short form-36 is responsive to change in chronic gout. *Rheumatology (Oxford, England)*. 2011;50(4):740-5.

18. Hirsch JD, Terkeltaub R, Khanna D, Singh J, Sarkin A, Shieh M, et al. Gout disease-specific quality of life and the association with gout characteristics. *Patient related outcome measures*. 2010;2010:1-8.

19. Khanna PP, Shiozawa A, Walker V, Bancroft T, Essoi B, Akhras KS, et al. Health-related quality of life and treatment satisfaction in patients with gout: results from a cross-sectional study in a managed care setting. *Patient preference and adherence*. 2015;9:971-81.

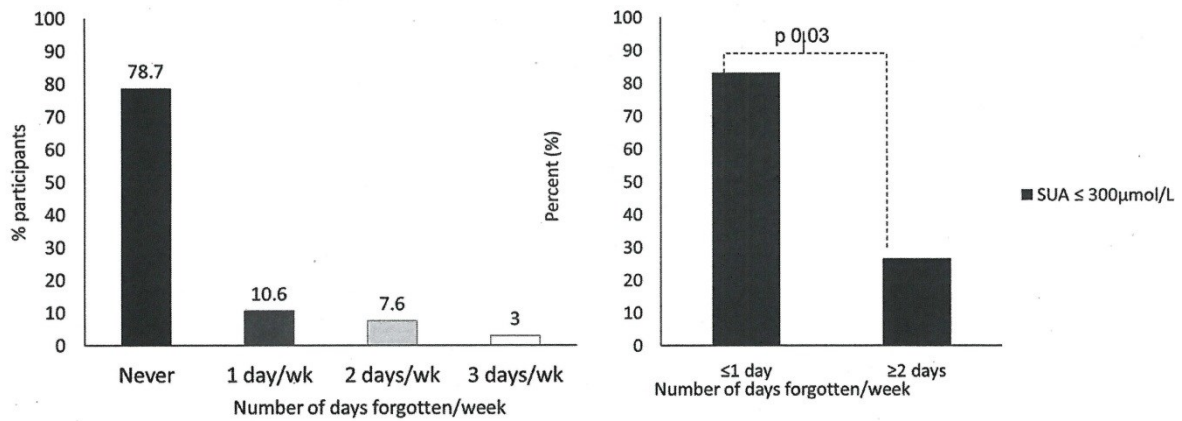
20. Wallace B, Khanna D, Aquino-Beaton C, Singh JA, Duffy E, Elashoff D, et al. Performance of Gout Impact Scale in a longitudinal observational study of patients with gout. *Rheumatology (Oxford, England)*. 2016; 55(6):982-90.

**Table 1** Disease and demographic characteristics at the beginning of the proof-of-concept study (2010) according to response to follow-up questionnaire in 2015

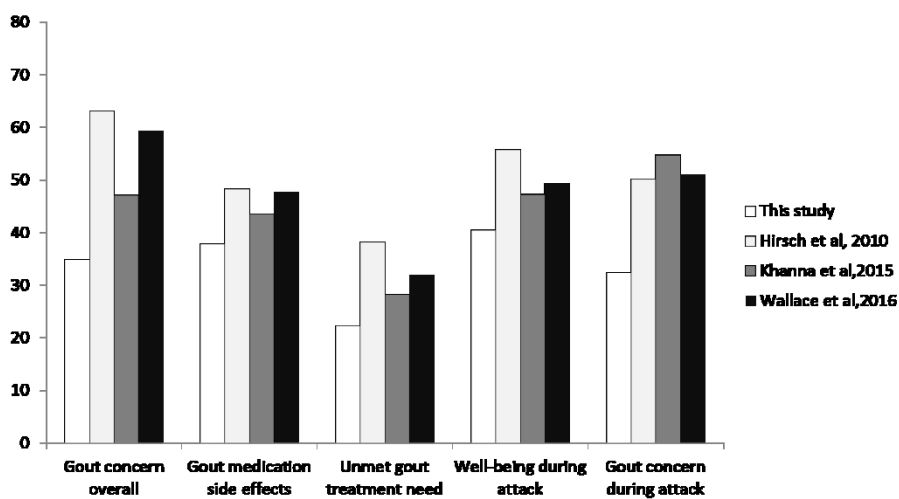
	Questionnaires returned (n=75)	No response or not mailed (n=31)	<i>p</i>
Age, years mean (SD <sup>1</sup> )	62.2 (10.1)	57.6 (13.2)	0.06
Sex, % female	12%	9.7%	0.73
BMI <sup>2</sup> , kg/m <sup>2</sup> mean (SD)	31.1 (4.5)	30.2 (5.2)	0.34
Age at first attack, years mean (SD)	48.7 (15)	43.5 (16.7)	0.12
Number of attacks in 12 months, mean (SD)	3.8 (3.6)	4.3 (3.0)	0.52
Tophi, % present	14.7%	19.4%	0.55
Serum uric acid, µmol/L mean (SD)	456.6 (11.4)	453.6 (18.6)	0.88
SF-36v2 domain scores			
Physical function	41.4 (14.1)	40.8 (15.3)	0.80
Role physical	44.0 (12.9)	43.7 (13.0)	0.93
Bodily pain	42.5 (10.5)	44.4 (13.2)	0.44
General health	44.4 (11.1)	43.6 (12.1)	0.74
Vitality	51.4 (10.6)	47.4 (12.5)	0.10
Social functioning	49.3 (10.8)	48.7 (12.0)	0.81
Role emotional	49.1 (11.7)	46.2 (12.4)	0.25
Mental health	53.3 (9.5)	49.5 (13.1)	0.10
Index of multiple deprivation rank, median decile (inter quartile range)	6 (3-8)	5 (3-7)	0.33

<sup>1</sup>SD standard deviation <sup>2</sup>BMI body mass index





**Figure 1 (a)** Self-reported adherence to urate lowering treatment in those currently on urate lowering treatment (left panel); **(b)** Proportion of patients meeting the treatment targets for serum uric acid according to self-reported adherence to urate lowering treatment (right panel)



**Figure S1** Gout Impact Scale domain scores in this study, and in other cohorts (18-20)