RHEUMATOLOGY

Original article

doi:10.1093/rheumatology/key155

Medication adherence among gout patients initiated allopurinol: a retrospective cohort study in the Clinical Practice Research Datalink (CPRD)

Lieke E. J. M. Scheepers[1,2,3], Andrea M. Burden[2,3,4], Ilja C. W. Arts[5], Bart Spaetgens[1,2], Patrick Souverein[2], Frank de Vries[2,3,4] and Annelies Boonen[1,3]

Abstract

Objectives. When urate lowering therapy is indicated in patients with gout, medication adherence is essential. This study assesses non-persistence and non-adherence in patients with newly diagnosed gout, and identifies factors associated with poor medication adherence.

Methods. A retrospective data analysis was performed within the UK Clinical Practice Research Datalink (1987–2014) among incident gout patients, aged $\geqslant$40 years and starting allopurinol (n = 48 280). The proportion of patients non-persistent (a first medication gap of $\geqslant$90 days) after 1 and 5 years, and median time until a first 90-day gap was estimated using Kaplan-Meier statistics in those starting allopurinol and restarting after a first interruption. Non-adherence (proportion of days covered <80%) over the full observation period was calculated. Multivariable Cox- or logistic regressions assessed factors associated with non-persistence or non-adherence, respectively.

Results. Non-persistence increased from 38.5% (95% CI: 38.1, 38.9) to 56.9% (95% CI: 56.4, 57.4) after 1 and 5 years of initiation. Median time until a first 90-day gap was 1029 days (95% CI: 988, 1078) and 61% were non-adherent. After a first gap, 43.3% (95% CI: 42.7, 43.9) restarted therapy within 1 year, yet only 52.3% (95% CI: 51.4, 53.1) persisted for 1 year. Being female and a current smoker increased the risk for non-persistence and non-adherence, while older age, overweight, receiving anti-hypertensive medication or colchicine and suffering from dementia, diabetes or dyslipidaemia decreased the risk.

Conclusion. Medication adherence among gout patients starting allopurinol is poor, particularly among females and younger patients and patients with fewer comorbidities. Medication adherence remains low in those reinitiating after a first gap.

Key words: gout, allopurinol, persistence, adherence, urate lowering therapy (ULT)

CLINICAL SCIENCE

Rheumatology key messages

- Persistence with and adherence to allopurinol treatment among newly diagnosed gout patients is poor.
- Adherence remains low in gout patients who restarted allopurinol therapy after a medication gap.

Introduction

Gout is the most prevalent form of inflammatory rheumatic disease, and caused by the deposition of monosodium urate crystals within the joint and surrounding tissues [1–3]. In patients with recurrent gout flares or tophi, it is recommended to start long-term urate lowering therapy (ULT) to reduce the number of gout flares and resolve tophi [4]. Despite proven efficacy of these drugs [5, 6], a substantial subgroup of patients fails to achieve optimal clinical benefit, partly because of poor medication adherence. Previous studies showed that non-adherence, usually defined as <80% of the total observation time covered by medication, is associated with higher serum urate concentrations and more gout flares [7–12]. While non-persistence, defined as the occurrence of a gap in use of therapy over time, may have little clinical effect in certain chronic diseases, a gap in ULT might actually trigger or prolong a gout flare [11]. Hence, poor medication

[1]Department of Internal Medicine, Division of Rheumatology, Maastricht University Medical Centre, Maastricht, [2]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute of Pharmaceutical Sciences, Utrecht University, Utrecht, [3]School for Public Health and Primary Care (CAPHRI), [4]Department of Clinical Pharmacy and Toxicology, Maastricht University Medical Centre and [5]Department of Epidemiology, CARIM School for Cardiovascular Diseases, MaCSBio Maastricht Centre for Systems Biology, Maastricht University, Maastricht, The Netherlands

Submitted 24 November 2017; revised version accepted 26 April 2018

Correspondence to: Frank de Vries, Department of Pharmacoepidemiology and Clinical Pharmacology, Universiteitsweg 99, Utrecht, The Netherlands.
E-mail: f.devries@uu.nl

adherence may lead to more severe disease for patients and to increased gout-related healthcare costs for society [10, 13].

Recently, a systematic review confirmed poor medication adherence among gout patients using ULT [14]. Adherence ranged from 18 to 44% and persistence from 12 to 44% [14]. Twelve out of 16 studies were conducted in the USA, hampering transferability to a European setting where general practitioners are often the main healthcare provider. Data were often derived from electronic prescription records databases and managed health care plans, which only include insured residents, which might have introduced selection bias. Furthermore, most studies focused on non-adherence, but little is known about non-persistence, time until non-persistence, restart of therapy and subsequent medication adherence after first discontinuation [15, 16].

To identify patients at high risk, factors associated with poor medication adherence should be determined. Several factors, such as older age or suffering from certain comorbidities like hypertension or diabetes, were associated with higher adherence rates [14]. Yet these factors have not, or poorly, been studied as determinants of non-persistence.

The objective of the current study was therefore to assess among newly diagnosed gout patients rates of non-persistence and non-adherence with allopurinol therapy, determinants of non-persistence and non-adherence, and the number of patients restarting therapy after the first occurrence of a gap in therapy and subsequent medication adherence.

Methods

A retrospective analysis was performed using the UK Clinical Practice Research Datalink (CPRD), including more than 11.3 million individuals from 674 general practices in England, Northern Ireland, Scotland and Wales, representing 6.9% of the British population [17]. The database provides detailed information on demographics, drug prescriptions, clinical events, specialist referrals and hospital admissions [17]. For this study we used data from 1987 through to June 2014.

Study population

The study population consisted of individuals aged $\geqslant$40 years, with a first ever Read code of gout and a prescription of allopurinol during the period of valid data collection. READ codes are a set of clinical codes used in primary care in the UK for the registration of clinical diagnosis, processes of care and medication. The use of READ codes has been validated for many diagnoses, including gout and common comorbidities [18, 19].

The date of the first prescription of allopurinol after the start of valid data collection defined the index-date. Follow-up was defined from the index-date to either the end of data collection (30 June 2014), the date of transfer of the patient out of the practice area, or the patient's death, whichever came first. Because allopurinol is by far the most prescribed ULT, patients with a first prescription of febuxostat (0.2%) or probenecid (0.1%) were not included in the analyses. Patients who switched to probenecid or febuxostat during follow-up ($n = 729$) were censored for analyses. Patients with a prescription of ULT prior to the diagnosis of gout and those with follow-up $<$90 days after completion of the first prescription were excluded.

Measures of medication adherence

Non-persistence was defined as the occurrence of the first gap in time covered by an allopurinol medication prescription of at least 30 or 90 days after the end of each allopurinol prescription. In case of overlap between two prescriptions (i.e. a repeat prescription within the duration of use of a previous prescription), the overlap days was added to the duration of treatment time. In case of a missing length, the median value of all allopurinol prescriptions was assigned. Non-persistence rate was measured by calculating the proportion of patients who discontinued treatment, defined as a gap of at least 30 or 90 days in allopurinol prescription, over time.

Non-adherence was defined by the proportion of days covered (PDC). This was calculated as the number of days of prescribed medication divided by the total duration of follow-up, while truncating the possible overlap between two prescriptions. A PDC $<$0.80 was considered as non-adherence. The medication possession ratio (MPR) was determined by calculating the total number of days prescribed medication divided by the total duration of follow-up, while adding the days of overlap between two prescriptions to the number of days prescribed.

To improve insight into medication patterns, the proportion of patients restarting allopurinol therapy after the occurrence of a first gap of at least 90 days was calculated. Subsequently, in those patients restarting allopurinol therapy, non-persistence and non-adherence were once again calculated.

Potential determinants of non-adherence and non-persistence

Several determinants were explored for their association with non-persistence and non-adherence. These factors related first to patient characteristics at baseline including gender, age (40–49, 50–59, 60–69, 70–79 and $\geqslant$ 80 years), BMI ($<$20.0, 20.0–24.9, 25.0–29.9, 30.0–34.9 and $\geqslant$ 35.0 kg/m^2), smoking status (never, current, former), alcohol consumption (yes, no), socio-economic status (low, low-medium, medium, medium-high, high), calendar year start allopurinol (1987–99, 2000–05, 2006–09 and 2010–14), the number of days between gout diagnosis and initiation of allopurinol and the number of visits to general practitioners 12 months prior to the index date (0, 1–9, 10–19, 20–29, $\geqslant$30 visits).

Second, comorbidities prior to the index date were considered, including alcoholism chronic obstructive pulmonary disease, dementia, depression, diabetes mellitus, hypertension, ischaemic heart disease, myocardial infarction, OA, renal calculi and stroke. In the case of multiple records, the record most prior to the index-date was

Table 1 Baseline characteristics of allopurinol users with gout ($n = 48\,280$)

Male	75.7 (36.169)
Age, mean (S.D.), years	64.6 (13.2)
40–49	16.1 (7750)
50–59	21.3 (10 305)
60–69	24.2 (11 684)
70–79	23.6 (11 375)
80+	14.9 (7166)
BMI most recent prior to index date	
BMI, mean (S.D.), kg/m^2	29.7 (5.4)
<20.0	1.1% (536)
20.0–24.9	14.4 (6969)
25.0–29.9	38.1 (18 393)
30.0–34.9	25.5 (12 311)
⩾35.0	13.4 (6467)
Missing	7.5 (3604)
Smoking status	
Never	42.6 (20 573)
Current	12.1 (5865)
Ex	43.5 (20 998)
Missing	1.7 (844)
Alcohol use	
No	15.1 (7276)
Yes	78.0 (37 637)
Missing	7.0 (3367)
Alcoholism	4.5 (2150)
Calendar year start allopurinol, index date	
1987–99	17.5 (8430)
2000–05	29.1 (14 071)
2006–09	32.0 (15 464)
2010–14	21.4 (10 315)
Days between gout diagnosis and initiation allopurinol, mean (S.D.)	605 (1039)
0	24.3 (11 717)
1–90	26.7 (12 903)
91–365	14.1 (6789)
>366	34.9 (16 871)
Number of GP visits in year prior to index date	
0	18.8 (9062)
1–9	21.9 (10 576)
10–19	22.7 (10 975)
20–30	17.1 (8268)
⩾30	19.5 (9399)
Socio-economic status	
Low	13.6 (6557)
Low–medium	14.9 (7177)
Medium	11.9 (5760)
Medium–high	10.3 (4973)
High	8.0 (3875)
Missing	41.3 (19 938)
History of drug use within 6 months before index date	
Anti-hypertensive	40.6 (19 362)
Acute gout treatment	
Colchicine	22.2 (10 714)
Corticosteroid	7.6 (3647)
NSAIDs	67.0 (32 332)
History of comorbidity ever before index date	
COPD	15.1 (7296)
Dementia	0.5 (250)
Depression	15.5 (7480)
Diabetes	10.3 (4950)
Dyslipidaemia[a]	30.2 (14 603)
Hypertension	51.4 (24 830)
Ischaemic heart disease	17.7 (8561)
Myocardial infarction	8.9 (4304)
OA	23.8 (11 507)
Renal calculi	1.1 (517)
Stroke	6.4 (3111)
Most recent eGFR measurement (ml/min/1.73 m^2), mean (S.D.)	66.5 (22.2)
CKD 1	12.9 (6212)
CKD 2	38.6 (18 644)
CKD 3	35.8 (17 299)
CKD 4	2.9 (1420)
CKD 5	0.3 (141)
Missing	9.5 (4564)

Data are presented as percentage and number (n) unless otherwise indicated. [a]Medication prescriptions of statins 6 months prior to the index-date was used as a proxy indicator for dyslipidaemia. CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; GP: general practitioner. CKD 1: eGFR ⩾90; CKD 2: eGFR 60 < 90; CKD 3: eGFR 30 < 60; CKD 4: eGFR 15 < 30; CKD 5: eGFR < 15.

used. Renal function was evaluated by reviewing laboratory test data 6 months prior to index-date [estimated glomerular filtration rate (eGFR) modification of diet in renal disease where possible], and CPRD READ codes, which describe the stage of renal function. In case of multiple eGFR values on the same day, the mean value was used. CPRD READ codes were prioritized if there was a laboratory test on the same day.

Third, medication prescriptions 6 months prior to the index-date for hypertension, use of statins (a proxy indicator for dyslipidaemia) and acute gout medication (NSAIDs, colchicine and oral corticosteroids) were considered.

Ethical approval

The CPRD Group holds research ethics and has obtained ethical approval from a National Research Ethics Service Committee for all purely observational research using anonymized CPRD data. The present study is based on anonymized and unidentifiable CPRD data and the study protocol was approved by the CPRD Independent Scientific Advisory Committee (protocol number 15_130R2AR). The CPRD complies with the Declaration of Helsinki. Because our study does not include patient involvement, no further ethical approval and patient consents are deemed necessary by Independent Scientific Advisory Committee (ISAC).

Statistical analysis

Descriptive statistics were used to characterize the study population. Kaplan–Meier life table analyses were applied to estimate proportion of patients with a first 30- or 90-day medication gap within the 1st and the first 5 years after starting allopurinol and the median time (days) until

non-persistent. Average PDC and MPR during the total observation time and the proportion of patients considered non-adherent (PDC or MPR <0.80) were calculated. Kaplan–Meier life table analyses were also used to estimate the proportion of patients restarting allopurinol therapy after a first 90-day gap and the median number of days until restarting allopurinol therapy. In this sub-sample, subsequent persistence and adherence were again assessed.

Multivariable Cox-regression analyses were performed to study the strength of the association between determinants and non-persistence (90-day gap), by entering all above described variables into the regression model. The proportional hazards assumption was tested by including time interaction terms into the model. In case of violation ($P < 0.05$), hazard ratios (HRs) for the association between the covariate and non-persistence were calculated for the first year after the index date. Multivariable logistic-regression analyses were performed to study the strength of the association between determinants and non-adherence (PDC < 0.80). All analyses were conducted using SAS software (Version 9.3; SAS Institute Inc., Cary, NC, USA).

Results

Study population

Of the 131 565 newly diagnosed gout patients a total of 48 438 (38.8%) patients initiated allopurinol as the first ULT during the observation period. Of the 48 438 allopurinol users, 158 patients were excluded for analyses because follow-up was shorter than 90 days after the first prescription, resulting in a study population of 48 280 gout patients.

Table 1 shows the characteristics of the study population. The mean (S.D.) age of the study population was 64.6 (13.2) years and 76% were male. Comorbidities were common, the most frequent being hypertension (51%), dyslipidaemia (30%), OA (24%) and depression (16%), and 41% received anti-hypertensive medication.

Medication adherence

Non-persistence estimates for treatment with allopurinol are displayed in Fig. 1. Considering a gap-length of 30 days, non-persistence with allopurinol therapy increased from 57.8% (95% CI: 57.3, 58.2) at year 1 to 80.9% (95% CI: 80.4, 81.2) at 5 years following initiation (Table 2). The median time until discontinuation was 225 days (95% CI: 220, 231). Increasing the gap length up to 90-days, non-persistence estimates were 38.5% (95% CI: 38.1, 38.9) at year 1 and 56.9% (95% CI: 56.4, 57.4) at 5 years following initiation, with a median time until discontinuation of 1029 days (95% CI: 988, 1078).

Regarding non-adherence, the average PDC was 0.57 (S.D. 0.43), indicating that patients had an allopurinol prescription for 57% of the total observation time. The proportion of patients non-adherent to allopurinol therapy

Fig. 1 Kaplan-Meier curve for persistence (90-day gap) to treatment with allopurinol medication in the total study population

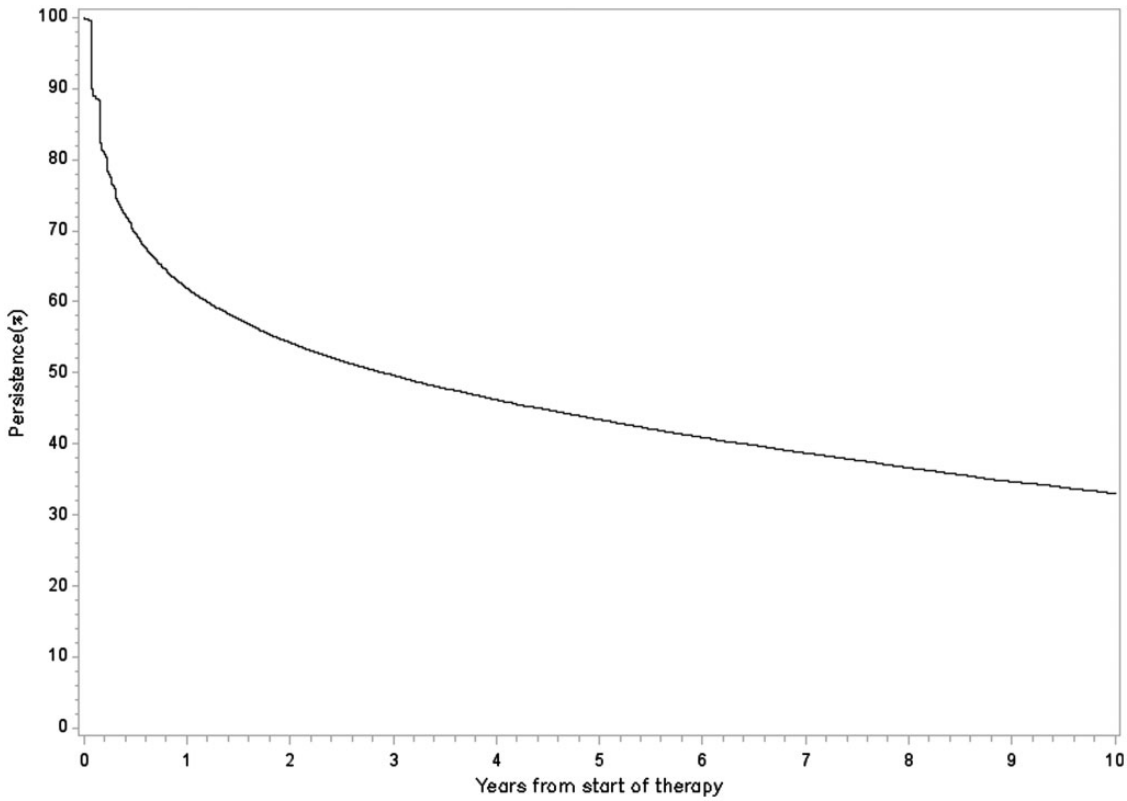


Table 2 Medication adherence among gout patients initiated allopurinol ($n = 48\,280$)

Non-persistence[a]	**30-day gap**	**90-day gap**
First year, median (95% CI)	57.8 (57.3, 58.2)	38.5 (38.1, 38.9)
First 5 years, median (95% CI)	80.8 (80.4, 81.2)	56.9 (56.4, 57.4)
Time until discontinuation (days), median (95% CI)	225 (220, 231)	1029 (988, 1078)
Adherence (PDC)		
Mean (S.D.)	0.57 (0.34)	
Median (IQR)	0.67 (0.64)	
Categories, *n* (%)		
<0.20	23.1 (11.136)	
0.20–0.40	10.9 (5.242)	
0.40–0.60	11.9 (5.756)	
0.60–0.80	15.8 (7.611)	
0.80–1.00	38.4 (18.535)	
Estimates for restarting therapy after a gap of at least 90 days, median (95% CI)		
First year	43.3 (42.7, 43.9)	
First 5 years	64.2 (63.5, 64.9)	
Time until restart (days), median (95% CI)	643 (617, 678)	
Medication adherence after restarting therapy (*n* = 14 084), median (95% CI)		
Non-persistence	**30-day gap**	**90-day gap**
First year	75.7 (75.0, 76.4)	52.3 (51.4, 53.1)
First 5 years	91.1 (90.5, 91.7)	71.6 (70.7, 72.5)
Time until second discontinuation (days), median (95% CI)	87 (84, 94)	313 (294, 334)
Adherence (PDC)		
Mean (S.D.)	0.49 (0.31)	
Adherence (PDC ⩾ 0.80)		
No	76.8 (10.819)	
Yes	23.2 (3.265)	

Data are presented as percentage and number (*n*) unless otherwise indicated. [a]Kaplan-Meier estimates for non-persistence at (%) at different time periods following initiation, by 30-day and 90-day gap lengths. IQR: interquartile range.

was 61%. The average MPR was 0.66 (S.D. 0.40), 47.6% of the patients had an MPR ⩾0.80 and 23.2% reached a MPR >1.00.

Of the 26 235 patients who experienced a 90-day gap during observation time, 15 013 (57%) restarted allopurinol therapy; 43.3% (95% CI: 42.7, 43.9) of them within 1 year and 64.2% (95% CI: 63.5, 64.9) within 5 years (Fig. 2A). Median time until restart was 643 days (95% CI: 617, 678). Following allopurinol re-starters, 75.7% (95% CI: 75.0, 76.4) experienced a 30-day gap and 52.3% (95% CI: 51.4, 53.1) a 90-day gap in the first year. The median time until discontinuation was 88 days (95% CI: 84, 97) for a 30-day and 319 days (95% CI: 301, 340) for a 90-day gap (Fig. 2B). Average PDC was 0.49 (S.D. 0.31) and only 10.3% were considered adherent.

Factors associated with medication adherence

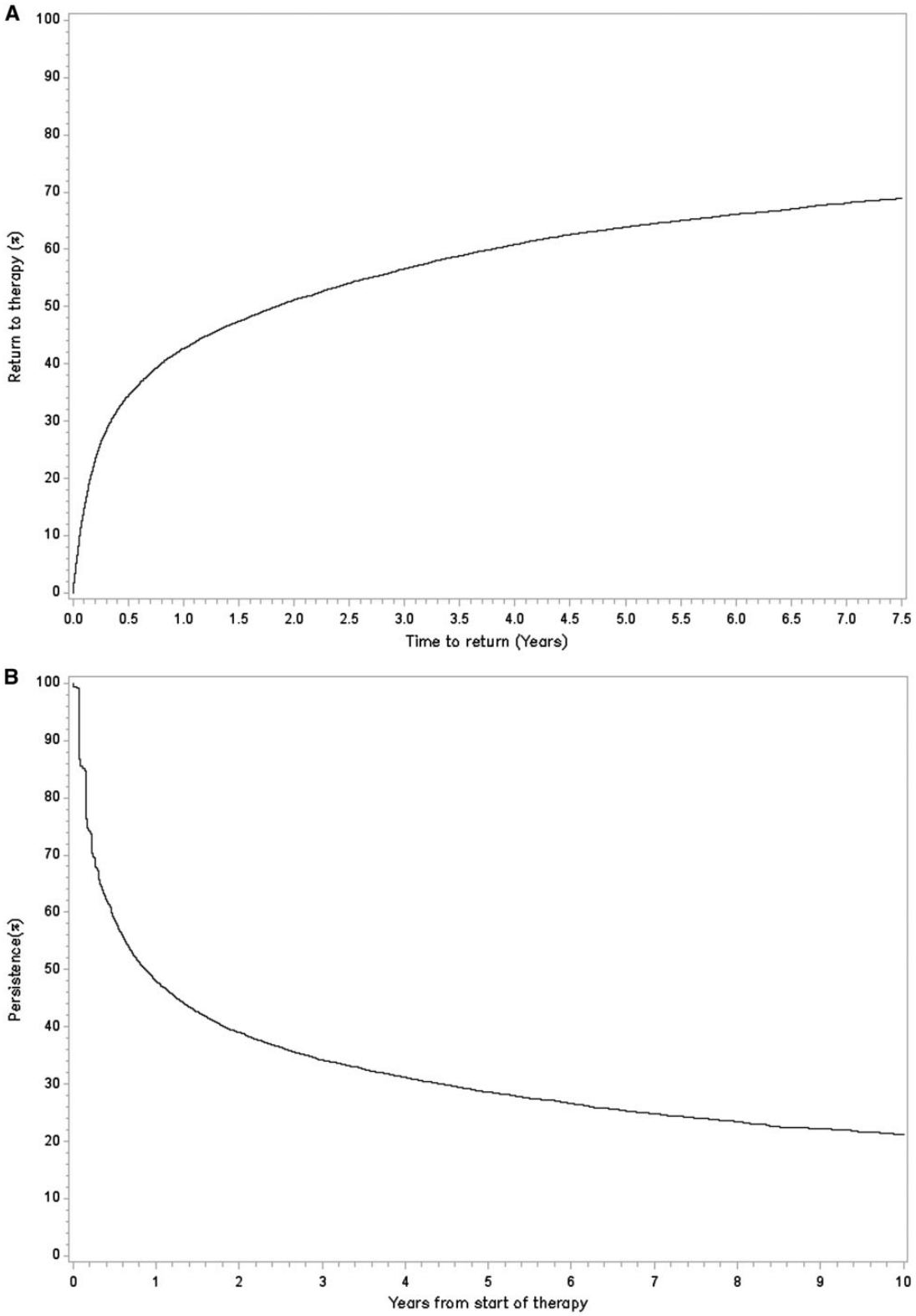
Factors associated with non-persistence or non-adherence are presented in Table 3. In the multivariable adjusted model, female gender and current smoking increased the risk of non-persistence and non-adherence. While older age (⩾50 years as compared with those 40–49 years), overweight (*vs* a normal weight), former smoking (*vs* never), use of colchicine, not starting allopurinol at time of diagnosis with gout and suffering from dementia, diabetes mellitus or dyslipidaemia decreased the risk of non-persistence and non-adherence.

The effect of use of anti-hypertensive medication, calendar year start allopurinol and kidney function on non-persistence, was not constant over time and did not met the proportional hazard assumption ($P < 0.05$). Therefore, follow-up was restricted to the first 365 days following initiation. The use of anti-hypertensive medication decreased the risk of non-persistence (HR = 0.73; 95% CI: 0.70, 0.77). Patients starting allopurinol between 2010 and 2014 were more likely to be persistent compared with patients who started between 1987 and 1999 (HR = 0.96; 95% CI: 0.87, 0.99). Kidney function was not significantly associated with non-persistence in the first year after initiation.

Discussion

The present study showed poor medication adherence among incident gout patients starting allopurinol treatment. Non-persistence (⩾90-day gap) with allopurinol was 57% after 1 year and increased to 77% at 5 years following initiation. After the occurrence of a gap, 54% of the patients restarted therapy; yet less than half of the patients persisted with treatment for 1 year following restarting therapy. During the entire observation period only 39% of the patients were considered adherent (PDC ⩾ 0.80). Medication adherence was better among

Fig. 2 Kaplan-Meier curves for cumulative incidence of restarters and persistence after restarting therapy to allopurinol treatment



Kaplan-Meier curves for (**A**) cumulative incidence of restart with allopurinol medication after first discontinuation and (**B**) persistence to treatment with allopurinol medication after restarting therapy after first discontinuation—discontinuation was defined as a treatment gap of at least 90 days.

Table 3 Determinants of non-persistence (gap of ⩾90 days) and non-adherence (PDC < 0.80)

Characteristics	Non-persistence (90-day gap)		Non-adherence (PDC < 0.80)	
	Age and sex adjusted OR (95% CI)	Fully adjusted[a] OR (95% CI)	Age and sex adjusted OR (95% CI)	Fully adjusted[a] OR (95% CI)
Females (ref: male)	1.14 (1.11, 1.18)	**1.18 (1.14, 1.23)**	1.18 (1.13, 1.23)	**1.21 (1.14, 1.28)**
Age (ref: 40–49 years)				
50–59	0.74 (0.71, 0.77)	**0.81 (0.78, 0.84)**	0.60 (0.56, 0.64)	**0.70 (0.65, 0.75)**
60–69	0.59 (0.57, 0.62)	**0.70 (0.67, 0.73)**	0.41 (0.38, 0.43)	**0.55 (0.51, 0.59)**
70–79	0.60 (0.58, 0.62)	**0.74 (0.71, 0.78)**	0.40 (0.38, 0.43)	**0.57 (0.53, 0.62)**
80+	0.59 (0.56, 0.62)	**0.70 (0.66, 0.74)**	0.40 (0.37, 0.43)	**0.55 (0.51, 0.60)**
BMI (ref: 20.0–24.9 kg/m^2)				
<20.0	1.19 (1.06, 1.34)	1.10 (0.98, 1.24)	1.30 (1.07, 1.57)	1.15 (0.95, 1.39)
25.0–29.9	0.88 (0.85, 0.91)	**0.93 (0.89, 0.96)**	0.84 (0.80, 0.89)	**0.92 (0.87, 0.98)**
30.0–34.9	0.81 (0.78, 0.84)	**0.89 (0.85, 0.93)**	0.73 (0.69, 0.78)	**0.86 (0.81, 0.92)**
⩾35.0	0.73 (0.69, 0.76)	**0.84 (0.80, 0.88)**	0.62 (0.58, 0.67)	**0.79 (0.73, 0.85)**
Smoking status (ref: never)				
Current	1.14 (1.10, 1.19)	**1.15 (1.11, 1.19)**	1.19 (1.12, 1.27)	**1.19 (1.12, 1.27)**
Ex	0.89 (0.87, 0.92)	**0.97 (0.94, 0.99)**	0.82 (0.79, 0.85)	**0.94 (0.90, 0.98)**
Alcohol use (ref: no)				
Yes	0.94 (0.91, 0.97)	**0.92 (0.89, 0.95)**	0.93 (0.89, 0.99)	**0.91 (0.86, 0.96)**
Calendar year start allopurinol[b] (ref: 1987–99)				
2000–05	0.94 (0.90, 0.98)	1.02 (0.97, 1.08)	0.80 (0.76, 0.85)	**0.91 (0.84, 0.98)**
2006–09	0.91 (0.87, 0.95)	1.06 (1.00, 1.12)	0.69 (0.65, 0.73)	**0.86 (0.80, 0.94)**
2010–14	0.78 (0.75, 0.82)	**0.93 (0.87, 0.99)**	0.59 (0.56, 0.63)	**0.75 (0.69, 0.82)**
Days between gout diagnosis and initiation allopurinol (ref: 0)				
1–90	0.88 (0.85, 0.91)	**0.89 (0.86, 0.93)**	0.84 (0.80, 0.89)	**0.87 (0.82, 0.92)**
91–365	0.91 (0.88, 0.95)	**0.94 (0.91, 0.98)**	0.86 (0.86, 0.92)	**0.90 (0.85, 0.96)**
>366	0.93 (0.90, 0.96)	0.97 (0.94, 1.00)	0.86 (0.82, 0.91)	**0.93 (0.89, 0.98)**
Number of GP visits (ref: 0)				
1–9	1.06 (1.02, 1.10)	**1.11 (1.06, 1.16)**	1.05 (0.98, 1.11)	**1.17 (1.09, 1.27)**
10–19	0.89 (0.85, 0.92)	**1.06 (1.01, 1.11)**	0.77 (0.73, 0.81)	1.06 (0.99, 1.15)
20–29	0.81 (0.77, 0.84)	1.01 (0.96, 1.06)	0.67 (0.63, 0.71)	0.99 (0.91, 1.08)
⩾30	0.77 (0.74, 0.80)	0.99 (0.94, 1.05)	0.62 (0.59, 0.66)	0.96 (0.88, 1.04)
Socio-economic status (ref: medium)				
Low	0.99 (0.95, 1.04)	0.99 (0.94, 1.04)	1.04 (0.96, 1.12)	1.04 (0.96, 1.12)
Low–medium	0.95 (0.90, 0.99)	0.96 (0.91, 1.00)	0.93 (0.87, 1.00)	0.94 (0.88, 1.02)
Medium–high	1.01 (0.96, 1.06)	1.02 (0.97, 1.07)	1.02 (0.94, 1.10)	1.03 (0.95, 1.12)
High	1.04 (0.99, 1.10)	1.05 (0.99, 1.10)	1.08 (0.99, 1.17)	1.08 (0.99, 1.18)
Medication (ref: no)				
Anti-hypertensive[b]	0.65 (0.63, 0.67)	**0.73 (0.70, 0.77)**	0.54 (0.52, 0.56)	**0.67 (0.63, 0.71)**
Acute gout treatment				
Colchicine	0.86 (0.83, 0.89)	**0.94 (0.90, 0.97)**	0.81 (0.78, 0.85)	0.95 (0.91, 1.00)
Corticosteroid	0.93 (0.89, 0.98)	0.98 (0.93, 1.03)	0.92 (0.85, 0.98)	0.99 (0.92, 1.07)
NSAIDs	1.08 (1.05, 1.11)	**1.05 (1.02, 1.08)**	1.10 (1.06, 1.14)	1.04 (0.99, 1.08)
Comorbidities (ref: no)				
Alcoholism	1.04 (0.98, 1.10)	1.06 (0.99, 1.13)	1.04 (0.95, 1.14)	1.06 (0.99, 1.13)
COPD	0.99 (0.96, 1.03)	1.02 (0.98, 1.06)	1.01 (0.96, 1.07)	1.02 (0.98, 1.06)
Dementia	0.64 (0.50, 0.81)	**0.58 (0.46, 0.74)**	0.63 (0.49, 0.82)	**0.56 (0.43, 0.72)**
Depression	0.99 (0.95, 1.02)	1.03 (0.99, 1.07)	0.96 (0.91, 1.01)	1.03 (0.97, 1.08)
Diabetes	0.77 (0.74, 0.81)	**0.94 (0.89, 0.98)**	0.68 (0.64, 0.73)	**0.92 (0.86, 0.98)**
Dyslipidaemia[c]	0.73 (0.71, 0.75)	**0.87 (0.84, 0.90)**	0.62 (0.60, 0.65)	**0.84 (0.80, 0.89)**
Hypertension	0.77 (0.75, 0.79)	1.00 (0.96, 1.03)	0.66 (0.63, 0.68)	0.95 (0.91, 1.01)
Ischaemic heart disease	0.94 (0.90, 0.97)	1.04 (1.00, 1.08)	0.92 (0.88, 0.97)	1.05 (0.99, 1.11)
Myocardial infarction	0.90 (0.86, 0.94)	0.99 (0.94, 1.05)	0.87 (0.81, 0.93)	0.99 (0.92, 1.07)
OA	0.97 (0.94, 1.00)	1.00 (0.97, 1.03)	0.96 (0.91, 1.00)	1.02 (0.97, 1.07)
Renal calculi	0.94 (0.83, 1.06)	1.00 (0.88, 1.13)	0.83 (0.70, 0.99)	0.92 (0.77, 1.11)
Stroke	0.96 (0.91, 1.01)	0.99 (0.94, 1.05)	1.02 (0.95, 1.10)	1.07 (0.99, 1.15)
Renal function[b] (ref: CKD 1)				
CKD 2	1.02 (0.97, 1.08)	0.98 (0.93, 1.03)	0.95 (0.86, 1.05)	1.00 (0.94, 1.07)
CKD 3	1.07 (1.02, 1.13)	1.05 (0.99, 1.11)	0.95 (0.86, 1.06)	1.04 (0.97, 1.12)
CKD 4	1.00 (0.90, 1.11)	1.01 (0.90, 1.12)	1.01 (0.88, 1.15)	1.10 (0.97, 1.25)
CKD 5	1.07 (0.81, 1.41)	1.14 (0.86, 1.50)	1.22 (0.90, 1.64)	**1.45 (1.01, 2.07)**

Bold indicates statistical significant in multivariable analyses. [a]Adjusted for sex, age, BMI, smoking status, alcohol use, socio-economic status at index date, calendar year start allopurinol, number of GP visits 12 months prior the index date, use of anti-hypertensive, colchicine, corticosteroids, NSAIDs and statins in the 6 months prior to the index date, and comorbidities ever before the index date (COPD, dementia, depression, diabetes, hypertension, ischaemic heart disease, myocardial infarction, OA, stroke and renal function), except the variables that are the explanatory variable in the analysis. [b]Follow-up was restricted to 1 year for the Cox-regression analyses, because of violating the proportional hazard assumption. [c]Medicationprescriptions of statins 6 months prior to the index-date was used as a proxy indicator for dyslipidaemia. COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; GP: general practitioner; HR: hazard ratio; PDC: proportion of days covered.

older patients and those being overweight and suffering from comorbidities such as diabetes and hypertension.

Non-persistence estimates found in the present study were comparable to previous studies, which showed rates between 56 and 88% [15, 20–22]. All studies used pharmacy-claims data and three out of four were conducted in the USA [15, 21, 22]. Despite these differences in study population, sampling method and design, it seems that the variation in non-persistence estimates in claims databases mainly depends on the permissible gap-length and observation time. For example, McGowan *et al.* [20] showed among 15 908 Irish gout patients that 81% experienced a gap of 5 weeks, while 54% experienced a gap of 9 weeks in the first year after initiation of ULT.

The dynamics in medication use is less frequently studied, such as whether patients return to therapy after the occurrence of a first gap and if they remain on therapy after restarting. We found that almost half of the patients returned to therapy after a 90-day gap in the first year. This finding is in line with a study conducted by Harrold *et al.* [15] who showed that 70% had a gap of at least 60 days in therapy and, among those with a gap, an estimated 50% returned to treatment within 8 months, and by 4 years, 75% had restarted. As it might be that a proportion of persons with a first episode of non-persistence might not have a strict indication to start ULT, persistence after re-initiation was expected to be better. However, we found that only 50% remained on therapy in the first year after reinitiating. Of note, multiple and extended gaps in therapy can lead to less efficiency in achieving the target level of serum urate, allowing accumulation of monosodium urate crystals, recurrent gout flares and the formation of tophi [23].

In the present study, only 39% of the gout patients were considered adherent during the entire observation time. Although, our reliance on a PDC $\geqslant$0.80 to be considered adherent is arbitrary, the mean PDC was 0.57, which is far from optimal. In 2012, a systematic review reported mean adherence rates all below 0.80 and the proportion of adherent patients ranged from 10 to 46% [14]. This was based on 10 claims/electronic records of which nine were conducted in the USA [14]. Recently, two European studies have been conducted. Among Irish patients 35.8% had an MPR $\geqslant$0.80 in the first 12 months, using pharmacy claims data [20]. In an Italian study the rates were even more alarming, 10% of the 3727 gout patients were adherent to allopurinol in the first 150 days and just 3% in the first year [9]. Our data from the UK and the studies conducted in Ireland [20] and Italy [9] indicate that poor medication adherence among gout patients not only occurs in patients from the USA, but also in Europeans.

To improve medication adherence, patients at risk should be identified. In our study, females were more prone to have poor medication adherence; this is in line with other previous research [12, 20], while others found the opposite [7, 24, 25], or no effect of gender on persistence or adherence [9, 22]. In agreement with our findings, older patients and those being overweight [12] and suffering from comorbidities such as diabetes and hypertension were more likely to be persistent and adherent [7, 9, 12, 21, 24, 26]. Although not investigated, these patients appear to be less healthy and might have more severe gout or are aware of the negative consequences of poor medication adherence on their health than younger and healthier gout patients [10, 21, 22, 27]. Somewhat contra-intuitively, persons registered with dementia had a lower risk of non-persistence (HR = 0.58) and non-adherence [Odds ratio (OR) = 0.56], most likely because they will be supervised when taking their medication. Likely, general practitioners register dementia only in the clear and more severe cases [28]. Finally, it was reassuring that patients who started allopurinol more recently had better medication adherence than those who started between 1987 and 1999. As indicated by Kuo *et al*. [1], although adherence to allopurinol improves over the years, it remains poor.

This study represents a comprehensive analysis of medication adherence among newly diagnosed gout patients from a representative primary care data-set from the UK. There were certain limitations to this study. First, medication adherence was estimated retrospectively by analysing allopurinol prescriptions of general practitioners. Therefore, we could not ascertain if patients purchased and took the prescribed medication. On the other hand, by using prescription data, any distortion caused by patient recall or desire to give socially accepted answers can be eliminated [29] and is therefore considered as an acceptable and accurate measure of persistence and adherence [30]. Second, although we identified patients at high risk for poor medication adherence, the reason for stopping or interrupting therapy could not be traced and might be physician-directed. An investigation into whether experiencing a gout flare after the initiation of allopurinol influenced medication adherence is of interest and requires further investigation. Additionally, if true, the need for prophylaxis treatment should be emphasized when initiating allopurinol. Of note, we showed that gout patients with a colchicine prescription in the 6 months prior to allopurinol initiation had a lower risk to become non-persistent. However, it is impossible to distinguish whether colchicine was prescribed for treatment of a severe attack or initiated as prophylaxis. Third, only prescription of allopurinol was considered. A low number of patients switching to probenecid or febuxostat were censored. Likely these drugs are prescribed to patients with different health characteristics, who might receive more attention in the healthcare system influencing their medication adherence. Fourth, non-adherence was defined as a PDC or MPR $<$ 0.80. Even though the dichotomization of adherence is widely used in the literature, this cut-off is arbitrary and not clinically validated in gout.

In conclusion, our study showed poor persistence and adherence among incident gout patients initiating allopurinol. Although patients experiencing a gap in therapy are likely to return, the chance of a backlash is likely. This highlights the need for research on medication adherence

to ULT. One adherence intervention study in gout has been conducted, and showed that a nurse-delivered 'package of care' leads to improved persistence and adherence compared with usual care, even after 5 years of follow-up [31, 32], emphasizing that personalized care [33–36] is important to improve medication adherence and to tackle this complex problem. Target groups for such or other adherence interventions may be those who are at higher risk, so patients who are younger and considered healthier.

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

Disclosure statement: L.E.J.M.S. has worked at AstraZeneca, Mölndal, Sweden (Biometrics - Department of Early Clinical Development, R&D Respiratory, Inflammation and Autoimmunity) since October 2017; the statistical analysis and writing of the first draft of the manuscript were conducted before October 2017 and work at AstraZeneca is unrelated to the scope of the current manuscript. F.dV. currently supervises a PhD student who is employed at F. Hoffmann la Roche Ltd, Basel, Switzerland; they do not receive any fees for this and the topic of this PhD is outside the scope of the current manuscript. A.B. received research grants to their department from Celgene and Friesland-Campina, and honoraria for consultancy or lectures from University College Dublin, Janssen, Novartis and Lilly. All other authors have declared no conflicts of interest.

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;74:661–7.

2 Wijnands JM, Viechtbauer W, Thevissen K *et al*. Determinants of the prevalence of gout in the general population: a systematic review and meta-regression. Eur J Epidemiol 2015;30:19–33.

3 Kuo CF, Grainge MJ, Zhang W, Doherty M. Global epidemiology of gout: prevalence, incidence and risk factors. Nat Rev Rheumatol 2015;11:649–62.

4 Richette P, Doherty M, Pascual E *et al*. 2016 updated EULAR evidence-based recommendations for the management of gout. Ann Rheum Dis 2017;76:29–42.

5 Shoji A, Yamanaka H, Kamatani N. A retrospective study of the relationship between serum urate level and recurrent attacks of gouty arthritis: evidence for reduction of recurrent gouty arthritis with antihyperuricemic therapy. Arthritis Rheum 2004;51:321–5.

6 Schumacher HR, Jr, 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;59:1540–8.

7 Rashid N, Levy GD, Wu YL *et al*. Patient and clinical characteristics associated with gout flares in an integrated healthcare system. Rheumatol Int 2015;35:1799.

8 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;42:504–12.

9 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;69:757–65.

10 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. Curr Med Res Opin 2009;25:1711–9.

11 Park H, Rascati KL, Prasla K, McBayne T. Evaluation of health care costs and utilization patterns for patients with gout. Clin Ther 2012;34:640–52.

12 Zandman-Goddard G, Amital H, Shamrayevsky N *et al*. Rates of adherence and persistence with allopurinol therapy among gout patients in Israel. Rheumatology 2013;52:1126–31.

13 Wu EQ, Patel PA, Yu AP *et al*. Disease-related and all-cause health care costs of elderly patients with gout. J Manag Care Pharm 2008;14:164–75.

14 De Vera MA, Marcotte G, Rai S, Galo JS, Bhole V. Medication adherence in gout: a systematic review. Arthritis Care Res 2014;66:1551–9.

15 Harrold LR, Andrade SE, Briesacher B *et al*. The dynamics of chronic gout treatment: medication gaps and return to therapy. Am J Med 2010;123:54–9.

16 Scheepers LEJM, van Onna M, Stehouwer CDA *et al*. Medication adherence among patients with gout: a systematic review and meta-analysis. Semin Arthritis Rheum 2018;47:689–702.

17 Herrett E, Gallagher AM, Bhaskaran K *et al*. Data Resource Profile: clinical Practice Research Datalink (CPRD). Int J Epidemiol 2015;44:827–36.

18 Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. Br J Clin Pharmacol 2010;69:4–14.

19 Meier CR, Jick H. Omeprazole, other antiulcer drugs and newly diagnosed gout. Br J Clin Pharmacol 1997;44:175–8.

20 McGowan B, Bennett K, Silke C, Whelan B. Adherence and persistence to urate-lowering therapies in the Irish setting. Clin Rheumatol 2016;35:715–21.

21 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;81:925–34.

22 Solomon DH, Avorn J, Levin R, Brookhart MA. Uric acid lowering therapy: prescribing patterns in a large cohort of older adults. Ann Rheum Dis 2008;67:609–13.

23 Pascual E, Sivera F. Time required for disappearance of urate crystals from synovial fluid after successful hypouricaemic treatment relates to the duration of gout. Ann Rheum Dis 2007;66:1056–8.

24 Riedel AA, Nelson M, Joseph-Ridge N *et al*. Compliance with allopurinol therapy among managed care enrollees with gout: a retrospective analysis of administrative claims. J Rheumatol 2004;31:1575–81.

25 Horsburgh S, Norris P, Becket G *et al*. Allopurinol use in a New Zealand population: prevalence and adherence. Rheumatol Int 2014;34:963–70.

26 Lee S, So MW. Adherence with urate-lowering therapies among male patients with gout in a routine clinical setting. Mod Rheumatol 2016;26:950–5.

27 Harrold LR, Andrade SE, Briesacher BA *et al*. Adherence with urate-lowering therapies for the treatment of gout. Arthritis Res Ther 2009;11:R46.

28 Bradford A, Kunik ME, Schulz P, Williams SP, Singh H. Missed and delayed diagnosis of dementia in primary care: prevalence and contributing factors. Alzheimer Dis Assoc Disorders 2009;23:306–14.

29 Choo PW, Rand CS, Inui TS *et al*. Validation of patient reports, automated pharmacy records, and pill counts with electronic monitoring of adherence to antihypertensive therapy. Med Care 1999;37:846–57.

30 Lau HS, de Boer A, Beuning KS, Porsius A. Validation of pharmacy records in drug exposure assessment. J Clin Epidemiol 1997;50:619–25.

31 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;72:826–30.

32 Abhishek A, Jenkins W, La-Crette J, Fernandes G, Doherty M. Long-term persistence and adherence on urate-lowering treatment can be maintained in primary care—5-year follow-up of a proof-of-concept study. Rheumatology 2017;56:529–33.

33 Harrold LR, Mazor KM, Velten S, Ockene IS, Yood RA. Patients and providers view gout differently: a qualitative study. Chronic Illn 2010;6:263–71.

34 Singh JA. Facilitators and barriers to adherence to urate-lowering therapy in African-Americans with gout: a qualitative study. Arthritis Res Ther 2014;16:R82.

35 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;71:1490–5.

36 Harrold LR, Mazor KM, Peterson D *et al*. Patients' knowledge and beliefs concerning gout and its treatment: a population based study. BMC Musculoskelet Disord 2012;13:180.