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Rate of adherence to urate-lowering therapy among patients with gout: a systematic review and meta-analysis

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ABSTRACT

Introduction Reported adherence to urate-lowering therapy (ULT) in gout varies widely (17%–83.5%). Variability may partly be due to different adherence measurement methods. This review aimed to quantify ULT adherence in adult patients with gout.

Methods This analysis examined studies in PubMed, Web of Science, CNKI Scholar and WanFang databases from inception to January 2017. Papers were selected by inclusion and exclusion criteria in the context. Random-effect meta-analysis estimated adherence.

Results 22 studies were found by the inclusion criteria, which involved 1 37 699 patients with gout. Four ways to define adherence were reported. Meta-analysis revealed that the overall adherence rate was 47% (95% CI 42% to 52%, I^2=99.7%). Adherence rate to ULT was 42% (95% CI 37% to 47%, I^2=99.8%) for prescription claims, 71% (95% CI 63% to 79%) for pill count, 66% (95% CI 50% to 81%, I^2=86.3%) for self-report and 63% (95% CI 42% to 83%, I^2=82.9%) for interview, respectively. The influential factor on adherence rate was country of origin.

Conclusions Among adult patients with gout, overall adherence rate to ULT was as low as 47%, which suggested that clinicians should pay more attention to medication adherence in patients with gout to effectively improve adherence to ULT.

Strengths and limitations of this study

- ► To the best of our knowledge, this was the first meta-analysis quantifying the overall adherence rate to urate-lowering therapy (ULT) in patients with gout.
- ► This systematic review was composed of 22 studies, with 1 37 699 patients with gout.
- ► A substantial amount of heterogeneity among the studies remained unexplained by the variables examined.
- ► EMBASE database and Cochrane database library were not searched owing to lack of access.
- ► Several studies that referred to medications unspecified ULT were excluded, which could bias the findings.

INTRODUCTION

Gout, which is characterised by the deposition of monosodium urate monohydrate in the synovial fluid and other tissues, is the most common cause of inflammatory arthritis worldwide.[1] A treat-to-target serum urate (SU) strategy for patients with gout with an indication for urate-lowering therapy (ULT), such as allopurinol, febuxostat or probenecid, has been widely endorsed as a means of optimising clinical outcomes.[2] Previous studies have reported that effective ULT reduce SU levels sufficiently to prevent further crystal formation and to dissolve existing urate crystals, thus eliminating the causative agent, making gout the only chronic arthritis that can be 'cured'.[3–5] Therefore, lifelong ULT prescription, the key to successful long-term management of gout,[6] is usually advised. But the prospect of lifelong therapy may contribute to very low adherence rate.[7] A WHO report indicated that if patients with long-term therapies had poor adherence, the effectiveness of treatment may be impaired.[8] Therefore, it is significant to understand the measurement and determinants of adherence in gout. However, reported ULT adherence rates in patients with gout vary between 10% and 46% in different studies.[9] The vast interstudy difference may partly result from different adherence measurement methods, as well as definition of adherence. Our purpose was to establish pooled prevalence of adherence to ULT in patients with gout with regard to different measurement methods. This context assumed that measurement methods will affect the adherence rates obtained.

From what we know, this is the first attempt to estimate adherence rate to ULT in gout, for different adherence measurement methods. Variability of cut-points to define adherence is also explored across different studies.

METHODS

The meta-analysis was reported according to the recommendations of Preferred Reporting

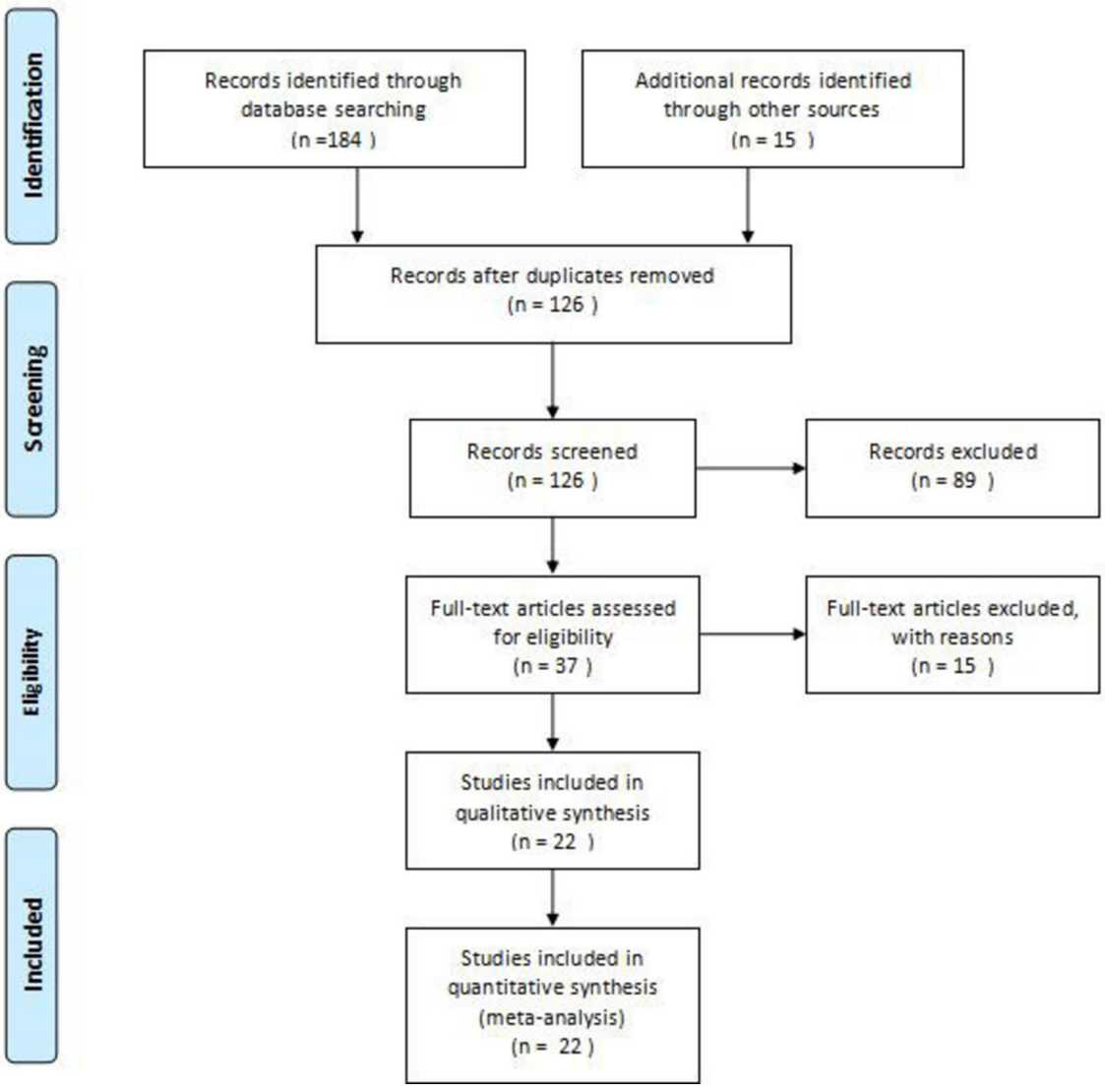

Figure 1 Flow chart illustrating the article search process. First, we obtained 184 records identified through database searching, and 15 additional records identified through other sources. Second, 126 records remained after duplicates were removed. Third, 89 studies were excluded after records screening. Then the remaining 37 studies were assessed for eligibility of which 15 studies were excluded. Finally, 22 studies were included in the quantitative synthesis (meta-analysis).

Items for Systemic Reviews and Meta-Analyses and the Meta-analysis of Observational Studies in Epidemiology as closely as possible.[10 11]

Search strategy

The systematic review examined the English-language databases of PubMed and Web of Science, and Chinese databases of the CNKI Scholar and WanFang (from inception to January 2017) to identify related studies; we also searched references that were listed in the studies. Reviews were used to identify relevant articles and to proof the search strategy. Case reports, letters and editorials were not included as primary data.

Different search strategies were combined, as follows. For the English-language databases, search details were (adherence [All Fields] OR ('patient compliance' [MeSH Terms] OR ('patient' [All Fields] AND 'compliance' [All Fields] OR 'patient compliance' [All Fields] OR 'compliance' [All Fields] OR 'compliance' [MeSH Terms] AND (urate-lowering [All Fields] AND ('therapy' [Subheading] OR 'therapy' [All Fields] OR 'therapeutics' [MeSH Terms] OR 'therapeutics' [All Fields]) AND ('gout' [MeSH Terms] OR 'gout' [All Fields] (see online supplementary file 1). For the Chinese databases, we used Chinese translations of terms meaning gout and adherence and ULT as free-text terms in the Chinese databases.

Inclusion and exclusion criteria

Inclusion criteria were: (1) patients with gout (defined by the American College of Rheumatology or by the articles) older than 18; (2) papers that reported adherence/compliance data with ULT and (3) cross-sectional design or baseline cross-sectional data from a longitudinal study.

Exclusion criteria were: (1) duplicates; (2) studies on adherence to non-ULT related treatment; (3) articles on persistence, discontinuation, switching, treatment gap or

Table 1A Baseline characteristics

Studies	N (total)	n (ULT)	Population, country	Age, yrs, mean (SD)	Male,(%)	Disease duration, yrs, mean (SD)	Medications	Quality
Prescription claims								
Sarawate *et al*, 2006[17]	5942	2405	Managed care database, USA	57.4 (14.1)*	76.4*	NS	Allopurinol	4
Briesacher *et al*, 2008[18]		9715	MEDSTAT database, USA	58.7 (0.14)	77.5	NS	Allopurinol, uricosurics	4
Harrold *et al*, 2009[24]		4166	Integrated delivery Systems, USA	62 (14)	75	NS	Allopurinol, probenecid, sulfinpyrazone	4
Halpern *et al*, 2009[30]	18243	10070	Claims database, USA	Mean 53.9	84.2	NS	Allopurinol	4
Rashid *et al*, 2012[29]		9288	KPSC healthcare, USA	Mean 60	78	NS	Allopurinol	4
Horsburgh *et al*, 2014[19]	27243	732	Community pharmacy dispensing databases, New Zealand	NA	39.5†	NS	Allopurinol	4
Singh, 2014[23]		43	Outpatient clinic, USA	63.9 (9.9)	67	NS	Allopurinol, febuxostat	2
McGowan *et al*, 2016[22]	34634	15908	HSE-PCRS scheme database, Ireland	Mean 65.2*	73*	NS	Allopurinol, febuxostat, probenecid, sulfinpyrazone	3
Tan *et al*, 2016[32]		91	Hospital clinics, Singapore	53.5 (16.9)	92.3	NS	Allopurinol, probenecid	2
Solomon *et al*, 2008[21]		9823	Medicare and PACE enrollees, USA	Mean 79	28†	NS	Allopurinol	4
Park *et al*, 2012[26]	352	242	Scott & White Health Plan, USA	61.02 (15.33)*	72.4*†	NS	Allopurinol, febuxostat, probenecid	4
Zandman-Goddard *et al*, 2013[20]		7644	MHS database, Israel	NA	72	NS	Allopurinol	4
Mantarro *et al*, 2015[31]		3727	HSD database, Italy	Mean 65	80	NS	Allopurinol	4
Rashid *et al*, 2015[27]		8288	Clinical and administrative databases, USA	NA	79.80	NS	Allopurinol, febuxostat, probenecid	4
Kuo *et al*, 2015[28]		49395	GPRD database, UK	NA	NA	NS	ULT	4
Riedel *et al*, 2004[25]	9482	5597	IPA plans, USA	51(11)*	82.1*	NS	Allopurinol	4
Pill counts								
Lee *et al*, 2016[33]		132	Outpatient clinic, Korea	51.9 (10.4)	100	100.0 (89.1)‡	Allopurinol, febuxostat	2
Self-report								
Silva *et al*, 2010[35]		34	Outpatient, Spain	57.1 (11.8)	94.1†	NS	Allopurinol, benzbromarone	1
Singh *et al*, 2016[34]	499	251	People visiting the Gout and Uric Acid Education Society's website, USA	56.3 (12.6)*	73.7*	NS	Allopurinol, febuxostat	5
Interview								
Martini *et al*, 2012[36]	60	56	Community pharmacies, New Zealand	Mean 61*	90*	NS	Allopurinol	2
Sheng *et al*, 2014[38]	161	80†	Gout Clinic, China	NA	NA	NS	ULD	1
van Onna *et al*, 2015[37]	15	12	Outpatient clinic and primary care practices, The Netherlands	63 (12)*	93.3*†	11(7)*	ULT	2

*Data for total population.
†Calculated based on data provided in the article.
‡Disease duration (months).
cross, cross-sectional; NA, not applicable; NS, not stated; ULD, urate-lowering drugs; ULT, urate-lowering therapy; yr, year.

Table 1B Definitions, cut-points and per cent adherence/compliance across studies. Studies were placed into subgroups according to the method used to measure adherence. Scale and cut-points used to rate adherence are also shown.

Studies	Outcome	Definition/scale	Cut-point for adherence/ compliance	Adherence %
Prescription claims				
Sarawate *et al*, 2006[17]	Compliance	MPR was calculated as medication supply actually received divided by medication supply that could have been received.	MPR≥80%	28
Briesacher *et al*, 2008[18]	Adherence	MPR defined as the days supply of the drug dispensed during the follow-up year divided by the number of days in the year.	MPR≥80%	36.8
Harrold *et al*, 2009[24]	Adherence	MPR defined as the days supply of medication dispensed during the follow-up year divided by the number of days in the year and is a reliable measure of adherence.	MPR≥80%	44
Halpern *et al*, 2009[30]	Compliance	MPR: sum of days supply from first observed allopurinol fill during the 2-year observation period divided by the number of days between the first observed fill and the end of the postindex period.	MPR≥80%	44
Rashid *et al*, 2012[29]	Adherence	Adherence was measured using the MPR over the follow-up time period.	MPR>80%	47.5*
Horsburgh *et al*, 2014[19]	Adherence	MPR defined as the ratio of days supplied from initial dispensing to the number of days to the end of the study period or the patient's date of death.	MPR≥80%	78*
Singh, 2014[23]	Adherence	Self-report adherence to ULT.	MPR≥0.80	32.6*
McGowan *et al*, 2016[22]	Adherence	MPR defined as the number of doses filled by the pharmacist divided by the number of days in the defined period (6 or 12 months).	MPR≥80%	45.5
Tan *et al*, 2016[32]	Adherence	MPR summarised the proportion of days a patient has a supply of medications for.	MPR≥80%	83.5
Solomon *et al*, 2008[21]	Adherence	PDC was calculated as the days with available UALT divided by the total number of days of follow-up.	PDC≥80%	36*
Park *et al*, 2012[26]	Adherence	PDC defined as the number of days during the study period (365 days) that the patient had at least one gout-specific medication on hand.	PDC≥80%	26.9*
Zandman-Goddard *et al*, 2013[20]	Adherence	Mean PDC calculated by dividing the quantity of allopurinol dispensed by the total time interval from index date to drug cessation, death, leaving MHS or 31 December 2009, whichever occurred first.	PDC≥80%	17
Mantarro *et al*, 2015[31]	Adherence	PDC defined as dividing the cumulative days of medication use by the length of follow-up.	PDC≥80%	45.9
Rashid *et al*, 2015[27]	Adherence	PDC was defined as the number of days with ULT drug dispensed divided by the number of days in the specified time interval (365 days).	PDC≥80%	48.2*
Kuo *et al*, 2015[28]	Adherence	PDC defined as the period from the latest of registration date or 1 January to the earliest of transfer-out, death date or 31 December of the calendar year specified.	PDC≥80%	39.66
Riedel *et al*, 2004[25]	Compliance	Compliance was defined for each prescription period as the presumed use of allopurinol on at least 80% of the days of that period.	Compliance rate≥80%	18
Pill count				
Lee *et al*, 2016[33]	Compliance	Pill counts: non-compliance was defined as <80% of the prescribed dose taken.	Pill count≥80%	71.2
Self-report				
Silva *et al*, 2010[35]	Compliance	Compliance defined as taking medication regularly, as prescribed.	NS	53*
Singh *et al*, 2016[34]	Adherence	Number of days the patient forgot to take ULT in the last month.	Adherence>0.80	78.5
Tan *et al*, 2016[32]	Adherence	MMAS-8 used to measure medication adherence (eight items, total score ranges 0–8).	MMAS-8 score≥6 (75%)	61.9
Interview				
Martini *et al*, 2012[36]	Compliance	Participants admitted to not taking ULTs as prescribed.	NS	79
Sheng *et al*, 2014[38]	Adherence	Adherence was defined as sustained use of ULD in the prior 12 months, otherwise non-adherence.	NS	53.8*
van Onna *et al*, 2015[37]	Adherence	Non-adherence at some point in time was defined as admission in the interview.	NS	50.0*

*Calculated based on data provided in the article.
MMAS-8, 8-item Morisky Medication Adherence Scale; MPR, medication possession ratio; NS, not stated; PDC, proportion of days covered; UALT, uric acid-lowering therapy; ULD, urate-lowering drug; ULT, urate-lowering therapy.

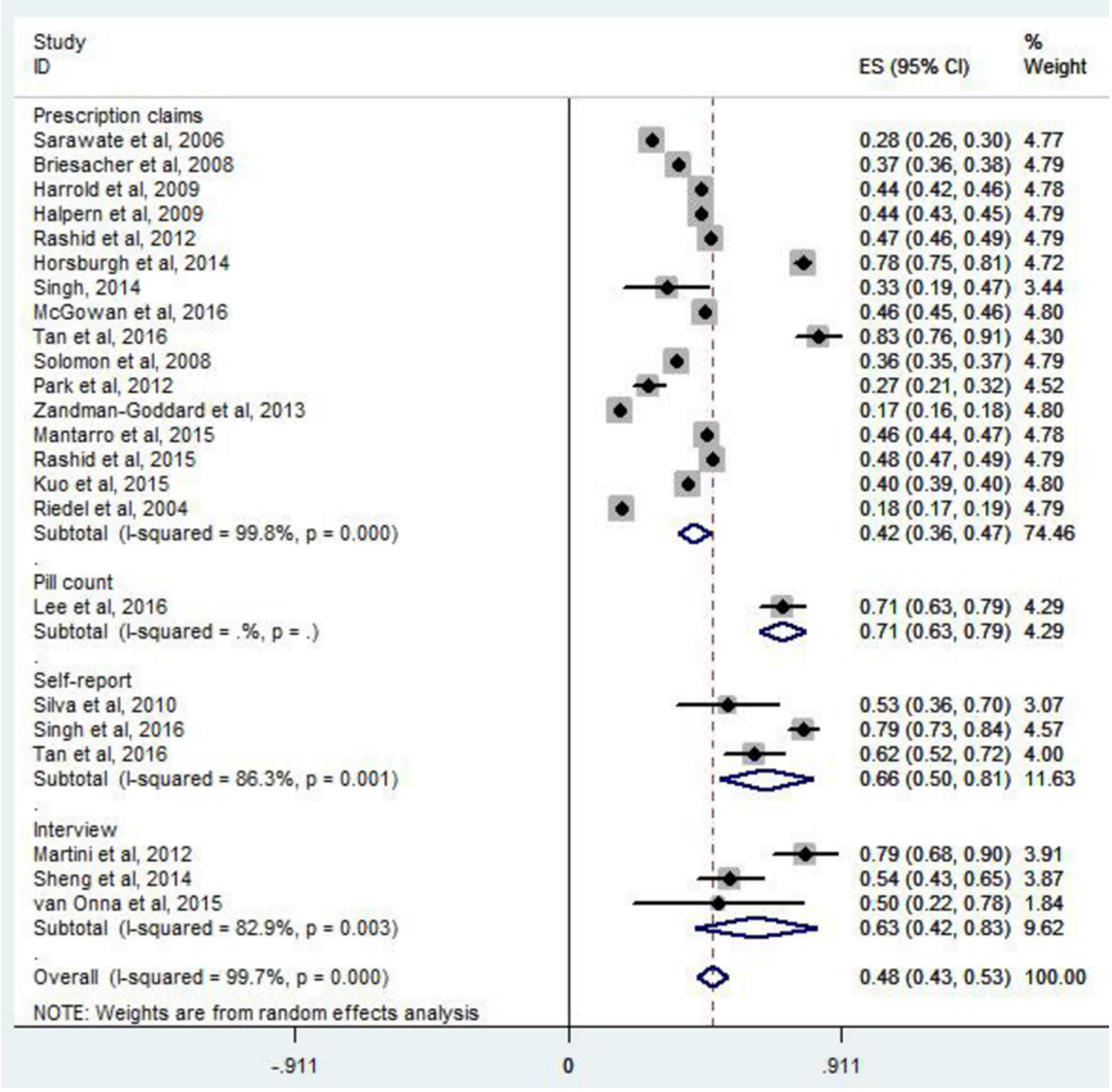

Figure 2 Meta-analysis of per cent of adherent patients by method used to measure adherence. ES, effective size.

retention rate; (4) data not independently available (eg, papers that contained data on a mix of medications, but there was no breakdown of adherence by medication) and (5) data from physicians' subject evaluation instead of objective and quantified methods.

Data extraction and quality assessment

According to the titles and abstracts, two authors (RY and LL) read the relative studies independently, and decided whether to include articles by reading the abstract and further full-text examination. Two trained investigators extracted the following information from each article independently: year, sample size, population, country, average age of participants, percentage of male participants, mean disease duration, type of medication, outcome, criteria for detection of adherence/compliance, cut-point for adherence/compliance, and reported prevalence of adherence/compliance. If we encountered multiple measurements from the same study, the most common evaluation method was used to carry out analysis. All the methods were used for subgroup analysis if not in the same subgroup. The methodological quality of each study included in the present meta-analysis was evaluated using a modified version of the Newcastle–Ottawa Scale,[12] where studies with more than or equal to 3 points were considered having low risk of bias while those with less than 3 points were considered having high risk of bias. All discrepancies were resolved by discussion and adjudication of a third reviewer (GZ).

Outcome measures

The outcomes were adherence or compliance assessed with prescription claims (eg, medication possession ratio, proportion of days covered), pill count, self-report or interview.

Statistical analysis

We used a random-effects meta-analysis, which was preferable and can provide wider CIs, to pool studies reporting adherence rates to ULT in patients with gout.[13] I^2 was used

Table 2 Summary of adherence rate and heterogeneity findings

Outcomes	No of studies	No of participants	Adherence, % (95% CIs)	Heterogeneity		Test for overall effect	
				P-value	I^2 (%)	Z	P-value
Overall	22	137 699	47 (42 to 52)	0.000	99.7	18.66	0.000
Measurement methods							
Prescription claims	16	137 134	42 (37 to 47)	0.000	99.8	15.61	0.000
Pill count	1	132	71 (63 to 79)	–	–	18.06	0.000
Self-report	3	376	66 (50 to 81)	0.001	86.3	8.40	0.000
Interview	3	148	63 (42 to 83)	0.003	82.9	6.09	0.000
Publication year							
2010	6	41 766	34 (26 to 43)	0.000	99.7	8.22	0.000
2010–	16	95 923	53 (47 to 60)	0.000	99.7	15.95	0.000
Country of origin							
USA	11	59 888	40 (33 to 47)	0.000	99.6	11.82	0.000
Oceania	2	788	78 (75 to 81)	0.860	0	52.97	0.000
Europe	5	69 076	44 (40 to 49)	0.000	98.0	19.62	0.000
Asia	4	7947	56 (17 to 96)	0.000	99.4	2.81	0.000
Data sources							
Database	14	13 700	40 (34 to 45)	0.000	99.8	13.48	0.000
Non-database	8	699	65 (54 to 75)	0.000	89.2	11.81	0.000
Representativeness							
Multiple sites	17	137 319	44 (39 to 50)	0.000	99.8	15.79	0.000
Single site	5	380	60 (43 to 76)	0.000	92.1	7.04	0.000
Sample size							
≥200	15	137 251	42 (36 to 48)	0.000	99.8	14.55	0.000
<200	7	448	62 (48 to 75)	0.000	89.3	9.12	0.000
Cut-point							
≥80%	18	137 517	45 (40 to 51)	0.000	99.7	16.70	0.000
≥75%	1	19	62 (52 to 72)	0.004	77.8	7.54	0.000
NS	4	182	60 (45 to 76)	–	–	12.16	0.000
Quality							
≥3 points	15	137 251	42 (36 to 48)	0.000	99.8	14.55	0.000
<3 points	7	448	62 (48 to 75)	0.000	89.3	9.12	0.000

NS, not stated.

to assess between-study heterogeneity, I^2 with thresholds of ≥25% (low heterogeneity), ≥50% (moderate heterogeneity) and ≥75% (high heterogeneity).[14] A sensitivity analyses was performed for sequential omission of each study to explore individual study's impact on the overall prevalence estimate. Wherever possible, subgroup analyses were planned by measurement methods, publication year, country of origin, data sources, representativeness of the sample, sample size, cut-point and overall quality, if there was more than one study in the subgroup. We combined Funnel plots and Egger's test to explore the potential publication bias in this meta-analysis.[15 16] We performed regression analysis to test the difference among methods that was used to measure rate of adherence. Statistical analyses were performed with STATA V.12.0. The statistical significance level was 0.05.

RESULTS

Study selection

After having assessed the studies by selection criteria, we included data from 22 studies, involving a total of 137 699 adult patients with gout. A flow chart of the study selection process is shown in figure 1.

Study characteristics

Baseline characteristics of the included study, the methods used to evaluate adherence to ULT and the frequency of their use are presented in table 1A and B. All included

studies assessed adherence in four different ways. Fifteen studies were assessed for adherence using prescription claims,[17–31] with the cut-point of ≥80%. One study used prescription claim and self-report,[32] one article used pill count,[33] two used self-report[34 35] and three articles were assessed by interview.[36–38] Among the 22 identified studies, 11 took place in USA, 2 in Oceania, 5 in Europe and 4 in Asia. When evaluated using the Newcastle–Ottawa quality assessment criteria, out of 5 possible points, 1 study received 5 points,[34] 13 received 4 points,[17–21 24–31] 1 received 3 points,[22] 5 received 2 points[23 32 33 36 37] and 2 received 1 point.[35 38]

Rate of adherence to ULT among patients with gout

The adherence rate to ULT ranged from 17% to 83.5% in individual studies (table 1B). Overall, 47% of patients with gout were adherent to ULT (95% CI 42% to 52%, I^2=99.7%) (figure not shown). According to prescription claims, the rate of adherence to ULT was 42% (95% CI 37% to 47%, I^2=99.8%). The adherence rate was 71% (95% CI 63% to 79%) for pill count, 66% (95% CI 50% to 81%, I^2=86.3%) for self-report and 63% (95% CI 42% to 83%, I^2=82.9%) for interview, respectively (figure 2). According to regression analysis, no significant difference was found for adherence measurement methods (p=0.535).

Sensitivity and subgroup analyses

Sensitivity analysis indicated that all of the estimated values were in regions of the lower CI limit and upper CI limit, which showed that no single study affected our results (figure not shown). A summary of meta-analysis and heterogeneity assessments is described in table 2. The subgroup analysis of adherence rate to ULT estimates was conducted according to the measurement methods, publication year, country of origin, data sources, representativeness of the sample, sample size, cut-point and overall quality. The results of the meta-analysis affected by the country of origin in those included studies showed that studies from the Oceania had higher adherence estimates (78% (95% CI 75% to 81%) vs 40% (95% CI 33% to 47%) vs 44% (95% CI 40% to 49%) vs 56% (95% CI 17% to 96%) from USA, Europe and Asia, respectively). The subgroup analysis for measurement methods, publication year, data sources, representativeness of the sample, sample size, cut-point and overall quality showed no clear patterns.

Evaluation of publication bias

No significant evidence of publication bias was found in overall analyses through the Egger's test, in any study reporting adherence according to prescription claims, self-report and interview (Egger: bias=5.42 (95% CI −6.55 to 17.39), p=0.356; Egger: bias=4.32 (95% CI −16.55 to 25.18), p=0.664; Egger: bias=−4.92 (95% CI −20.50 to 10.66), p=0.155; Egger: bias=−2.02 (95% CI −70.13 to 66.08), p=0.770, respectively) (figure not shown).

DISCUSSION

To the best of our knowledge, this systematic review and meta-analysis of 22 studies involving 137 699 adult patients with gout is the first to quantify adherence and to seek a relationship between adherence and the method used to measure it.

Totally, 47% adult patients with gout adhered to ULT. Majority of studies using prescription claims to report adherence to ULT were present in 42% among patients with gout (16 of 22). The rate of adherence to ULT was 71%, 66% and 63% for pill count, self-report and interview, respectively. The highest adherence rate measured by pill count, followed by self-report, interview and prescription claims. Although no statistical differences were found among the different methods, suboptimal medication adherence was clear across the included studies. It is particularly shocking that the adherence rate of 42% based on prescription claims and the overall adherence rate of 47% is below the well-quoted WHO estimate that 50% of adults adhere to long-term therapies.

A previous systematic review included 16 studies.[9] We identified additional studies. It is important that previous reviews did not quantify adherence. In our meta-analysis, a cut-point of ≥80% to define adherent patients, was used in most studies. Data on persistence, discontinuation, switching, treatment gap or retention rate, as well as adherence to non-medical therapy (eg, diet recommendations) were excluded.

The results demonstrated an overall adherence rate to ULT in adult patients with gout of 47%. However, heterogeneity was large. By subgroup analyses for measurement methods, publication year, country of origin, data sources, representativeness of the sample, sample size, cut-point and overall quality in those included studies, country of origin was found to have contributed to the heterogeneity between studies, with heterogeneity of 0% among studies from Oceania, 99.6% from USA, 98.0% from Europe and 99.4% from Asia. Although studies varied widely in terms of quality, our sensitivity analyses suggested that the adherence rate estimates were reasonably stable.

This meta-analysis indicated significant difference in adherence in claims database, especially from the USA, and also from the UK. The reasons for this could be that interview studies or postal surveys are prompting patients to self-report higher adherence. Additionally, adherence also depends on the healthcare system in which the study is done—private (with billing for drugs used) versus government funded; primary care versus secondary care, as well as severity of gout and age of patients (older patients typically will have higher adherence). This could also have an impact on the findings.

The adherence rate is surprisingly low considering that ULT does not have significant side effects or require taking tablets several times a day. It could be that patients do not think it is necessary to always take urate-lowering agents (ULAs) since they may feel asymptomatic most of the time. It could also be that ULA are not included in the medical insurance; because the price of ULA is

higher, long-term use of ULA will cause a greater financial burden on patients with gout.

Owing to the low adherence with ULT, carrying out potential and effective interventions is vital to improve gout-related outcomes. There are some interventions that can be achieved through pharmacist-assisted or nurse-assisted programmes, that may be effective, which include initiation of prophylactic anti-inflammatory medications when starting ULT, monitoring SU regularly, frequent follow-ups and improved patient education.[39] Abhishek *et al*[40] and Rees *et al*[41] have confirmed that there are excellent adherence rates after nurse-led treatment of gout, which means that these interventions could improve adherence to ULT in patients with gout and, eventually, improving gout-related outcomes.

However, we still need to address additional shortcomings in this systematic review and meta-analysis. First, heterogeneity which was high among the studies remained unexplained by the variables examined. Unexamined factors, such as gender, age, disease duration and study design might contribute to the risk for adherence to ULT among patients with gout. Second, owing to lack of access, we did not include the studies from EMBASE database and Cochrane database library in our search, and several studies that referred to medications unspecified ULT were excluded, which could bias the findings.

CONCLUSION

Among adult patients with gout, overall adherence rate to ULT was as low as 47%, which suggested that clinicians should pay more attention to medication adherence in patients with gout to effectively improve adherence to ULT.

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Contributors RY and LL searched and checked the databases according to the inclusion and exclusion criteria, extracted the data and assessed their quality, analysed the data and wrote the draft of the paper. GZ, YC, LZ, QZ, TF, HC, LL and ZG gave advice on meta-analysis methodology and revised the paper. All authors contributed to reviewing or revising the paper. LL and ZG were the guarantors of this work and had full access to all the data in the study and took responsibility for its integrity and the accuracy of the data analysis. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient consent Not required.

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Data sharing statement No additional data are available.

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