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# The Rate of Adherence to Urate-Lowering Therapy among Gout Patients: A Systematic Review and Meta-analysis

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# The Rate of Adherence to Urate-Lowering Therapy among Gout Patients: A Systematic Review and Meta-analysis


## ABSTRACT

**Introduction** Reported adherence to urate-lowering therapy (ULT) in gout varies widely (17%-83.5%). Variability may result in part from different methods used to measure adherence. The aim was to quantify adherence to urate-lowering therapy (ULT) in adult gout patients.

**Methods** The systematic review examined PubMed, Web of Science, CNKI Scholar, WanFang databases and article reference lists from inception to January 2017. Papers with the data of adherence to ULT in adult patients with gout were included. Adherence rate was recorded for each method. Random-effect meta-analysis estimated adherence.

**Results** A total of 22 identified studies matched the inclusion criteria, reporting on a total of 137699 gout patients. Four methods of defining adherence were reported. Meta-analysis revealed that overall adherence rate was 47% (95% CI, 42%-52%, $I^2$ = 99.7%). The rate of adherence to ULT was 42% (95% CI, 37%-47%, $I^2$ = 99.8%) according to prescription claims. Adherence rate was 71% (95% CI, 63%-79%) for pill count, 66% (95% CI, 50%-81%, $I^2$=86.3%) for self-report and 63% (95% CI, 42%-83%, $I^2$ = 82.9%) for interview, respectively. The main influence on adherence rate was country of origin of the studies.

**Conclusions** Adherence to ULT was low in adult gout patients, with the overall adherence rate of 47%. It indicated that rheumatologists should

pay more attention to medication adherence in gout patients, in order to identify effective strategies for improving adherence to ULT among adult gout patients.

**KEYWORDS:** adherence; urate-lowering therapy; gout; meta-analysis

**ARTICLE SUMMARY**

**Strengths and limitations of this study**

- To our knowledge, this was the first meta-analysis quantifying the overall adherence rate to ULT in gout patients.
- This systematic review was composed of 22 studies, with 137699 gout patients.
- Some limitations should be considered: a substantial amount of the heterogeneity among the studies remained unexplained by the variables examined; our search did not include the EMBASE database and Cochrane database library. Moreover, several studies that referred to medications unspecified ULT were excluded, which could bias the findings.

## INTRODUCTION

Gout, which is characterised by deposition of monosodium urate monohydrate MSU in synovial fluid and other tissues, is the most common cause of inflammatory arthritis worldwide[1]. A treat-to-target serum urate (SU) strategy for gout patients with an indication for urate-lowering therapy (ULT), such as allopurinol, febuxostat, or probenecid, has been widely endorsed as a means of optimizing clinical outcomes[2]. It has been widely certified that treatment with ULT is key to successful long-term management of gout[3]. Therefore, lifelong ULT prescription is usually advised, but the prospect of lifelong therapy may contribute to very low adherence rate[4]. WHO report stated that poor adherence to long-term therapies severely compromises the effectiveness of treatment[5]. Therefore, it is important to have a firm understanding of measurement and determinants of adherence in gout. The exact prevalence of adherence to ULT in gout patients is unknown. Variability exists regarding apparent adherence among literature reports, and results vary from 10% to 46% across studies[6]. This variability may result in part from different methods used to measure adherence, as well as definition of adherence. Our purpose was to determine the rate of adherence to ULT in gout patients, according to the different methods used to measure adherence. We assumed that adherence rate is affected by the method used to measure it.

To the best of our knowledge, this is the first attempt to estimate adherence rate to ULT in gout, both cumulative and separately, for different methods used to measure adherence. We also demonstrate the variability of the cutpoints used to define adherence in different studies.

## METHODS

The meta-analysis was reported according to the recommendations of the Preferred Reporting Items for Systemic Review and Meta-Analyses (PRISMA) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) as closely as possible[7, 8].

### 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 databases (from inception to January 2017) to identify adherence studies to ULT in adult gout patients. Associated reference lists were searched. Reviews, case reports, letters, and editorials were not included as primary data. Reviews were used to identify relevant articles and to test the search strategy.

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])). For the Chinese databases, free text terms we used including the Chinese translations of terms meaning gout and adherence and ULT. References of

selected articles were also searched to identify additional reports.

**Inclusion and exclusion criteria**

Inclusion ctiteria were following: (1) patients with gout (either defined by the American College of Rheumatology criteria or as defined in the articles) and aged ≥ 18 years; (2) papers that reported adherence/compliance data with ULT; (3) observational studies.

Exclusion criteria were the following: (1) duplicates; (2) reviews, case reports, letters and editorials were excluded from the analysis, but used to search references lists; (3) studies on adherence to non-medication therapy or general recommendations (e.g., appointments, exercise, splints, or non-ULT (e.g., colchicine); (4) articles on persistence, discontinuation, switching, treatment gap, or retention rate; (5) articles that used the term "adherence," but actually measured persistence or retention rate or treatment gaps; (6) articles from which specific information on gout could not be extracted (e.g., papers contained data on a mix of medication, but there was not a breakdown of adherence by medication ); (7) papers from which adherence could not be extracted; (8) When adherence was defined only according to physician evaluation (level of compliance was determined by physician ratings of patients, but no corroborating method(s) such as questionnaires, pill counts, etc.).

**Data extraction and quality assessment**

Two researchers read the relative studies independently by the titles and abstracts to exclude the references which did not met the inclusion

criteria. Then, they read full texts in the remaining studies as mentioned above, and determined whether these references included were final studies or not. When multiple publications spanned the years of longitudinal studies, baseline adherence rate were reported. The following information was independently extracted from each article by other two trained investigators using a standardized form: 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, cutpoint for adherence/compliance, and reported prevalence of adherence/compliance. If we encountered multiple measurements from the same study, the most commonly 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 assessed using a modified version of the Newcastle-Ottawa Scale[9]. Studies were judged to be at low risk of bias (≥3 points) or high risk of bias (<3 points). Any disagreements in data extraction and quality assessment were resolved through discussion between the two reviewers or adjudication with a third reviewer.

**Outcome measures**

The outcomes were adherence or compliance assessed with prescription claims [e.g., medication possession ratio (MPR), proportion of days covered (PDC)], pill count, self-report or interview.

**Statistical analysis**

Because random-effects models tended to provide wider confidence intervals (CI) and were preferable in the presence of between-study heterogeneity, we used a random-effects meta-analysis to pool studies reporting adherence rate to ULT in gout patients[10]. Between-study heterogeneity was assessed by the $I^2$ with thresholds of ≥25%, ≥50% and ≥75% indicating low, moderate and high heterogeneity, respectively[11]. The influence of individual study on the overall prevalence estimate was explored by serially excluding each study in sensitivity analyses. Wherever possible, subgroup analyses were planned by measurement methods, publication year, country of origin, data sources, representativeness of the sample, sample size, cutpoint, and overall quality, if there was more than one study in the subgroup. Funnel plots and Egger's test were combined to explore the potential publication bias in this meta-analysis[12, 13]. Statistical analyses were performed with STATA version 12.0. The statistical significance level was 0.05, except for the test of between-study heterogeneity.

**RESULTS**

**Study selection**

A flowchart of the study selection process is shown in Figure 1. According to the selection criteria defined in Materials and methods, the meta-analysis finally included 22 articles, involving a total of 137699 adult gout patients.

## Study characteristics

Baseline characteristics of the included study, the methods employed to assess adherence to ULT and the frequency of their use were presented in Table 1A and 1B. Adherence was defined in 4 different ways. Fifteen studies assessed for adherence using prescription claims[14–28], with the cutpoint of ≥80%. One used prescripition claim and self report[29], one article used pill count[30]; two used self-report[31, 32] and three articles assessed by interview[33–35]. Among 22 identified studies, eleven took place in America, 2 in Oceania, 5 in Europe, and 4 in Asia. When evaluated by Newcastle-Ottawa quality assessment criteria, out of 5 possible points, 1 study received 5 points[31], 13 received 4 points[14–18, 21–28], 1 received 3 points[19], 5 received 2 points[20, 29, 30, 33, 34], and 2 received 1 point[32, 35].

**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 | 5942 | 2405 | Managed care database, USA | 57.4(14.1)* | 76.4* | NS | allopurinol | 4 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Briesacher et al, 2008 | | 9715 | MEDSTAT database, USA | 58.7(0.14) | 77.5 | NS | allopurinol, uricosurics | 4 |
| Harrold et al, 2009 | | 4166 | Integrated delivery Systems, USA | 62 (14) | 75 | NS | allopurinol, probenecid, sulfinpyrazone | 4 |
| Halpern et al, 2009 | 18243 | 10070 | Claims database, USA | Mean 53.9 | 84.2 | NS | allopurinol | 4 |
| Rashid et al, 2012 | | 9288 | KPSC health care, USA | Mean 60 | 78 | NS | allopurinol | 4 |
| Horsburgh et al, 2014 | 27,243 | 732 | Community pharmacy dispensing databases, New Zealand | NA | 39.5 † | NS | allopurinol | 4 |
| Singh, 2014 | | 43 | Outpatient clinic, USA | 63.9 (9.9) | 67 | NS | allopurinol, febuxostat | 2 |
| McGowan et al, 2016 | 34634 | 15908 | HSE-PCRS scheme database, Ireland | Mean 65.2* | 73* | NS | allopurinol, febuxostat, probenecid, sulfinpyrazone | 3 |
| Tan et al, 2016 | | 91 | Hospital clinics,Singapore | 53.5(16.9) | 92.3 | NS | allopurinol, probenecid | 2 |
| Solomon et al, 2008 | | 9823 | Medicare and PACE enrollees, USA | Mean 79 | 28 † | NS | allopurinol | 4 |

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|---|---|---|---|---|---|---|---|---|
| Park et al. 2012 | 352 | 242 | Scott & White Health Plan, USA | 61.02(15.33)* | 72.4* † | NS | allopurinol, febuxostat, probenecid | 4 |
| Zandman-Goddard et al, 2013 | | 7644 | MHS database, Israel | NA | 72 | NS | allopurinol | 4 |
| Mantarro et al, 2015 | | 3727 | HSD database, Italy | Mean 65 | 80 | NS | allopurinol | 4 |
| Rashid et al, 2015 | | 8288 | Clinical and administrative databases, USA | NA | 79.80 | NS | allopurinol, febuxostat, probenecid | 4 |
| Kuo et al, 2015 | | 49395 | GPRD database, UK | NA | NA | NS | ULT | 4 |
| Riedel et al, 2004 | 9482 | 5597 | IPA plans, USA | 51(11)* | 82.1* | NS | allopurinol | 4 |
| **Pill counts** | | | | | | | | |
| Lee et al, 2016 | | 132 | Outpatient clinic, Korea | 51.9 (10.4) | 100 | 100.0(89.1)[§] | allopurinol, febuxostat | 2 |
| **Self-report** | | | | | | | | |
| Silva et al, 2010 | | 34 | Outpatient, Spain | 57.1(11.8) | 94.1 † | NS | allopurinol, benzbromarone | 1 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Singh et al, 2016 | 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 | 60 | 56 | Community pharmacies, New Zealand | Mean 61* | 90* | NS | allopurinol | 2 |
| Sheng et al, 2014 | 161 | 80 † | Gout Clinic, China | NA | NA | NS | ULD | 1 |
| van Onna et al, 2015 | 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)

ULT:urate-lowering therapy; yr: year; mos: months; NS: not stated; NA: not applicable; cross: cross-sectional; ULD:urate-lowering drugs

**Table 1B.** Definitions, cutpoints, and percent adherence/compliance across studies. Studies were placed into subgroups according to the method used to measure adherence. Scale and cutpoints used to rate adherence are also shown.

| Studies | Outcome | Definition/scale | Cutpoint for Adherence/compliance | Adherence % |
|---|---|---|---|---|
| **Prescription claims** | | | | |
| Sarawate et al, 2006 | 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 | 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 | 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 | compliance | MPR: sum of days supply from first observed allopurinol fill during the 2-year observation period]/[number of days between the first observed fill and the end of the post-index period. | MPR ≥80 % | 44 |
| Rashid et al, 2012 | adherence | Adherence was measured using the MPR over the follow up time period. | MPR >80 % | 47.5† |

| | | | | |
|---|---|---|---|---|
| Horsburgh et al, 2014 | 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 | adherence | Self-report adherence to ULT. | MPR ≥0.80 | 32.6† |
| McGowan et al, 2016 | 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 | adherence | MPR summarized the proportion of days a patient has a supply of medications for. | MPR ≥80 % | 83.5 |
| Solomon et al, 2008 | 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 | adherence | PDC defined as the number of days during the study period (365 days) that the patient had at least 1 gout-specific medication on hand. | PDC ≥ 80% | 26.9† |
| Zandman-Goddard et al, 2013 | 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 | 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 | 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 | 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 | compliance | Compliance was defined for each prescription period as the presumed use of allopurinol on at least 80% of the days of that period.cc | Compliance rate ≥ 80% | 18 |
| **Pill count** | | | | |
| Lee et al, 2016 | compliance | Pill counts: noncompliance was defined as <80% of the prescribed dose taken. | Pill count ≥ 80% | 71.2 |
| **Self-report** | | | | |
| Silva et al, 2010 | compliance | Compliance defined as taking medication regularly, as prescribed. | NS | 53† |
| Singh et al, 2016 | adherence | Number of days the patient forgot to take ULT in the last month. | Adherence >0.80 | 78.5 |

| | | | | |
|---|---|---|---|---|
| Tan et al, 2016 | adherence | MMAS-8 used to measure medication adherence.(8 items, total score ranges 0-8) | MMAS-8 score≥6 (75%) | 61.9 |
| **Interview** | | | | |
| Martini et al, 2012 | compliance | Participants admitted to not taking ULTs as prescribed. | NS | 79 |
| Sheng et al, 2014 | 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 | 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.

MPR: medication possession ratio; ULT:urate-lowering therapy; UALT: uric acid lowering therapy; PDC:proportion of days covered; MMAS-8:8-item Morisky Medication Adherence Scale; NS: not stated

**The rate of adherence to ULT among gout patients.**

Adherence rate to ULT ranged from 17% to 83.5% in individual studies (Table 1B). Overall, 47% of gout patients were adherent to ULT (95% CI, 42%-52%, $I^2$ = 99.7%) (Figure not shown). The rate of adherence to ULT was 42% (95% CI, 37%-47%, $I^2$ = 99.8%) according to

prescription claims. Adherence rate was 71% (95% CI, 63%-79%) for pill count, 66% (95% CI, 50%-81%, $I^2 = 86.3\%$) for self-report and 63% (95% CI, 42%-83%, $I^2 = 82.9\%$) for interview, respectively (Figure 2).

**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, showed that our results were not driven by any single study (Figure not shown). The summary of meta-analysis and heterogeneity assessments was described in Table 2. The subgroup analysis of adherence rate to ULT estimates were conducted according to measurement methods, publication year, country of origin, data sources, representativeness of the sample, sample size, cutpoint, 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%–81%) vs 40% (95% CI, 33%-47%), vs 44%(95% CI, 40%-49%), vs 56% (95% CI, 17%-96%) from America, Europe and Asia, respectively]. The subgroup analysis for measurement methods, publication year, data sources, representativeness of the sample, sample size, cutpoint, and overall quality showed no clear patterns.

**Table 2**. Summary of adherence rate and heterogeneity findings.

| Outcomes | No. of studies | No. of participants | Adherence, % (95% confidence intervals) | Heterogeneity | | Test for overall effect | |
|---|---|---|---|---|---|---|---|
| | | | | *P*-value | $I^2$(%) | Z | *P*-value |
| **Overall** | 22 | 137699 | 47(42, 52) | 0.000 | 99.7 | 18.66 | 0.000 |
| **Measurement methods** | | | | | | | |
| Prescription claims | 16 | 137134 | 42(37, 47) | 0.000 | 99.8 | 15.61 | 0.000 |
| Pill count | 1 | 132 | 71(63, 79) | - | - | 18.06 | 0.000 |
| Self-report | 3 | 376 | 66(50, 81) | 0.001 | 86.3 | 8.40 | 0.000 |
| Interview | 3 | 148 | 63(42,83) | 0.003 | 82.9 | 6.09 | 0.000 |
| **Publication Year** | | | | | | | |
| 2010s | 6 | 41766 | 34(26, 43) | 0.000 | 99.7 | 8.22 | 0.000 |
| 2010- | 16 | 95923 | 53(47, 60) | 0.000 | 99.7 | 15.95 | 0.000 |
| **Country of origin** | | | | | | | |
| America | 11 | 59888 | 40(33, 47) | 0.000 | 99.6 | 11.82 | 0.000 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Oceania | 2 | 788 | 78(75, 81) | 0.860 | 0 | 52.97 | 0.000 |
| Europe | 5 | 69076 | 44(40, 49) | 0.000 | 98.0 | 19.62 | 0.000 |
| Asia | 4 | 7947 | 56(17, 96) | 0.000 | 99.4 | 2.81 | 0.000 |
| **Data sources** | | | | | | | |
| Database | 14 | 13700 | 40(34, 45) | 0.000 | 99.8 | 13.48 | 0.000 |
| Non-database | 8 | 699 | 65(54, 75) | 0.000 | 89.2 | 11.81 | 0.000 |
| **Representativeness** | | | | | | | |
| Mulitiple sites | 17 | 137319 | 44(39, 50) | 0.000 | 99.8 | 15.79 | 0.000 |
| A single site | 5 | 380 | 60(43, 76) | 0.000 | 92.1 | 7.04 | 0.000 |
| **Sample size** | | | | | | | |
| ≥ 200 | 15 | 137251 | 42(36, 48) | 0.000 | 99.8 | 14.55 | 0.000 |
| < 200 | 7 | 448 | 62(48, 75) | 0.000 | 89.3 | 9.12 | 0.000 |
| **Cutpoint** | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ≥80% | 18 | 137517 | 45(40, 51) | 0.000 | 99.7 | 16.70 | 0.000 |
| ≥75% | 1 | 19 | 62(52, 72) | 0.004 | 77.8 | 7.54 | 0.000 |
| NS | 4 | 182 | 60(45, 76) | - | - | 12.16 | 0.000 |
| **Quality** | | | | | | | |
| ≥3 points | 15 | 137251 | 42(36, 48) | 0.000 | 99.8 | 14.55 | 0.000 |
| <3points | 7 | 448 | 62(48, 75) | 0.000 | 89.3 | 9.12 | 0.000 |

**Publication bias**

According to the Egger's test, there was no significant evidence of publication bias in overall analyses, in study reporting adherence according to prescription claims, self report and interview [Egger: bias = 5.42 (95% CI: -6.55, 17.39), *P* = 0.356; Egger: bias = 4.32 (95% CI: -16.55, 25.18), *P* = 0.664; Egger: bias = -4.92 (95% CI: -20.50, 10.66), *P* = 0.155; Egger: bias = -2.02 (95% CI: -70.13, 66.08), *P* = 0.770, respectively] (Figure not shown).

**DISCUSSION**

This systematic review and meta-analysis of 22 studies involving 137699 adult gout patients demonstrated that overall, 47% of adult gout patients adhered to ULT. Majority of studies using prescription claims to report adherence to ULT were presented in 42% among gout patients. The rate of adherence to ULT was 71%, 66%, and 63% for pill count, self report and interview, respectively. Additionally, our analysis found no statistical differences among the different methods. To our knowledge, the meta-analysis is the first to quantify adherence and to seek a relationship between adherence and the method used to measure it.

A previous systematic review included 16 studies[6]. We identified an additional studies. Importantly, the previous review did not quantify adherence. In our meta-analysis, most studies used a cutpoint of ≥80% to define adherent patients. Data on persistence, discontinuation, switching, treatment gap or retention rate, and adherence to nonmedical therapy were excluded.

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

There are, however, additional important shortcomings in the evidence on adherence to ULT in adult gout patients that need to be addressed. First, a substantial amount of the heterogeneity among the studies remained unexplained by the variables examined. Unexamined factors, such as gender, age, disease duration, study design might contribute to the risk for adherence to ULT among gout patients. Second, our search did not include the EMBASE database and Cochrane database library, and several studies that referred to medications unspecified ULT were excluded, which could bias the findings.

## CONCLUSION

The rate of adherence to ULT was low in adult gout patients, with overall adherence rate of 47%. It indicated that rheumatologists should pay more attention to medication adherence in gout patients, in order to identify effective strategies for improving adherence to ULT among adult gout patients.

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## Competing interests

The authors declared that they have no competing interests.

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**Authors' contributions**

RY and LL searched and checked the databases according to the inclusion and exclusion criteria, extracted the data and assessed their quality, analyzed the data and wrote the draft of the paper. 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.

**Ethics approval and consent to participate**

Ethical approval and consent to participate are not required for this review.

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**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 remainder 37 studies were assessed for eligibility and 15 studies were excluded. Finally 22 studies were included in the quantitative synthesis (meta-analysis).

**Figure 2.** Meta-analysis of percent of adherent patients by method used to measure adherence.

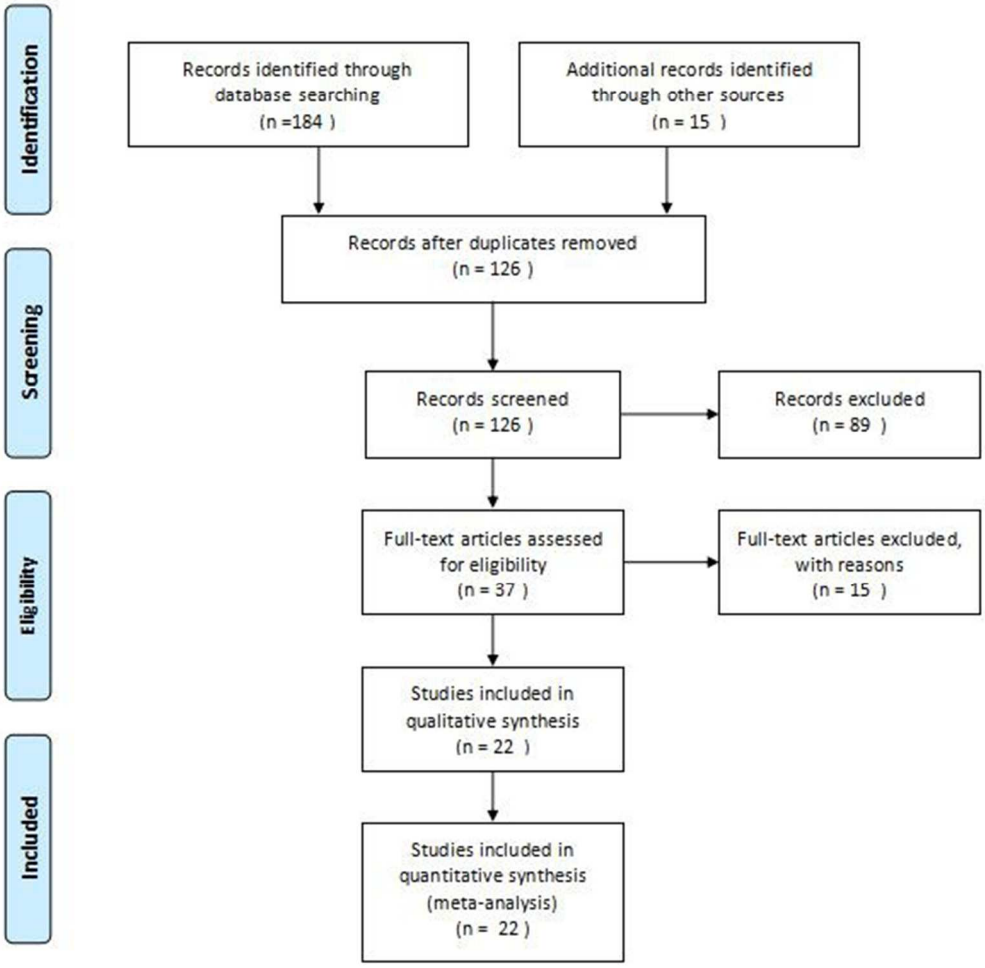


Figure 1. Flow-chart illustrating the article search process. First, we obtained 184 records identified through database searching, and 15 additional records identified through other sources. Second, 126 records remained after duplicates were removed. Third, 89 studies were excluded after records screening.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

155x151mm (96 x 96 DPI)

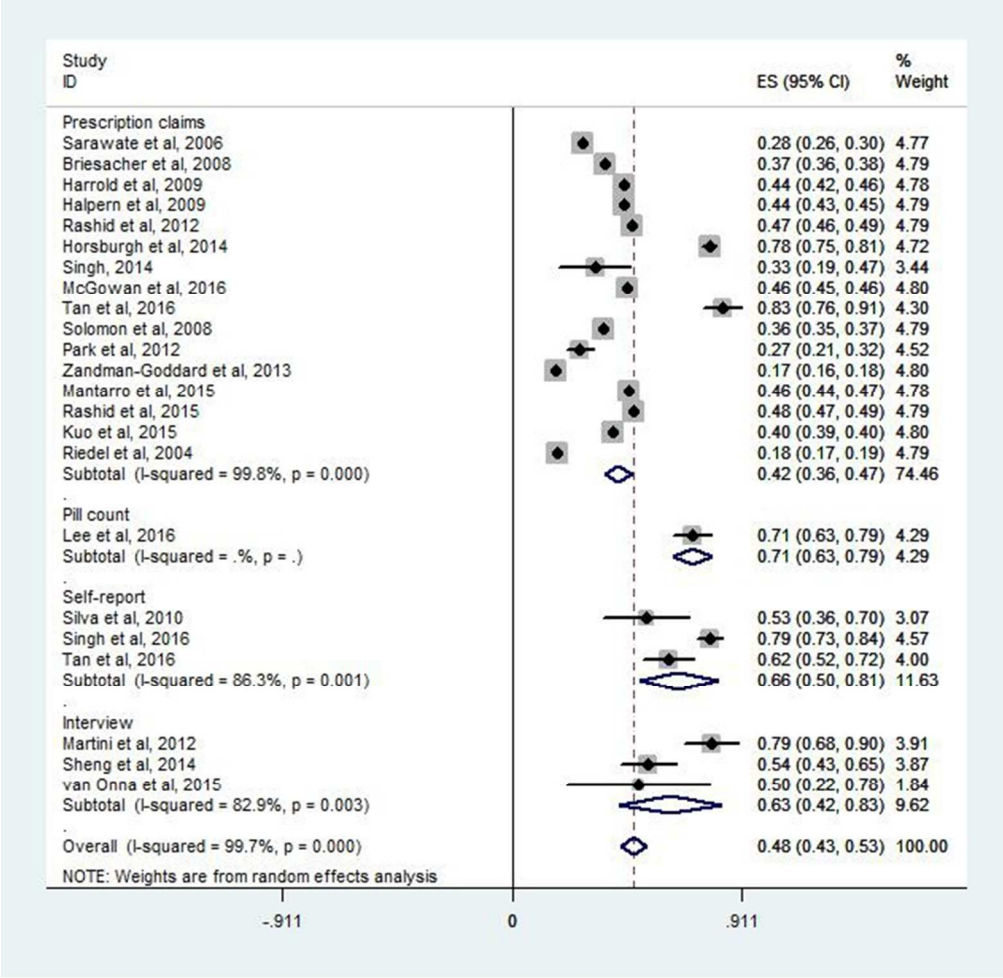


Figure 2. Meta-analysis of percent of adherent patients by method used to measure adherence.

166x162mm (96 x 96 DPI)

**PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol***

| Section and topic | Item No | Checklist item | Reported on Page # |
|---|---|---|---|
| **ADMINISTRATIVE INFORMATION** | | | |
| Title: | | | |
| Identification | 1a | Identify the report as a protocol of a systematic review | 1 |
| Update | 1b | If the protocol is for an update of a previous systematic review, identify as such | NO |
| Registration | 2 | If registered, provide the name of the registry (such as PROSPERO) and registration number | NO |
| Authors: | | | |
| Contact | 3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author | 1 |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review | 1 |
| Amendments | 4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | No |
| Support: | | | |
| Sources | 5a | Indicate sources of financial or other support for the review | 22-23 |
| Sponsor | 5b | Provide name for the review funder and/or sponsor | NO |
| Role of sponsor or funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol | NO |
| **INTRODUCTION** | | | |
| Rationale | 6 | Describe the rationale for the review in the context of what is already known | 4 |
| Objectives | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | |
| **METHODS** | | | |
| Eligibility criteria | 8 | Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review | 6 |
| Information sources | 9 | Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage | 5 |
| Search strategy | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated | 5-6 |

| | | | |
|---|---|---|---|
| Study records: | | | |
| Data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | 7 |
| Selection process | 11b | State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) | 6-7 |
| Data collection process | 11c | Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | 6-7 |
| Data items | 12 | List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications | 7 |
| Outcomes and prioritization | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | 7 |
| Risk of bias in individual studies | 14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | 8 |
| Data synthesis | 15a | Describe criteria under which study data will be quantitatively synthesised | 8 |
| | 15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$, Kendall's $\tau$) | 9-17 |
| | 15c | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) | 17-20 |
| | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned | NO |
| Meta-bias(es) | 16 | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) | 20 |
| Confidence in cumulative evidence | 17 | Describe how the strength of the body of evidence will be assessed (such as GRADE) | 9 |

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

*From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.*

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# The Rate of Adherence to Urate-Lowering Therapy among Gout Patients: A Systematic Review and Meta-analysis



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# The Rate of Adherence to Urate-Lowering Therapy among Gout Patients: A Systematic Review and Meta-analysis

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# The Rate of Adherence to Urate-Lowering Therapy among Gout Patients: A Systematic Review and Meta-analysis


## ABSTRACT

**Introduction** Reported adherence to urate-lowering therapy (ULT) in gout varies widely (17%-83.5%). Variability may result in part from different methods used to measure adherence. The aim was to quantify adherence to urate-lowering therapy (ULT) in adult gout patients.

**Methods** The systematic review examined PubMed, Web of Science, CNKI Scholar, WanFang databases and article reference lists from inception to January 2017. Papers with the data of adherence to ULT in adult patients with gout were included. Adherence rate was recorded for each method. Random-effect meta-analysis estimated adherence.

**Results** A total of 22 identified studies matched the inclusion criteria, reporting on a total of 137699 gout patients. Four methods of defining adherence were reported. Meta-analysis revealed that overall adherence rate was 47% (95% CI, 42%-52%, $I^2$ = 99.7%). The rate of adherence to ULT was 42% (95% CI, 37%-47%, $I^2$ = 99.8%) according to prescription claims. Adherence rate was 71% (95% CI, 63%-79%) for pill count, 66% (95% CI, 50%-81%, $I^2$=86.3%) for self-report, and 63% (95% CI, 42%-83%, $I^2$ = 82.9%) for interview, respectively. The main influence on adherence rate was country of origin of the studies.

**Conclusions** Adherence to ULT was low in adult gout patients, with the overall adherence rate of 47%. It indicated that clinicians should pay

more attention to medication adherence in gout patients, in order to identify effective strategies for improving adherence to ULT among adult gout patients.

**Strengths and limitations**

- To our knowledge, this was the first meta-analysis quantifying the overall adherence rate to ULT in gout patients.
- This systematic review was composed of 22 studies, with 137699 gout patients.
- A substantial amount of the heterogeneity among the studies remained unexplained by the variables examined.
- EMBASE database and Cochrane database library were not searched due to lack of access.
- Several studies that referred to medications unspecified ULT were excluded, which could bias the findings.

**KEYWORDS:** adherence; urate-lowering therapy; gout; meta-analysis

## INTRODUCTION

Gout, which is characterised by deposition of monosodium urate monohydrate (MSU) in synovial fluid and other tissues, is the most common cause of inflammatory arthritis worldwide[1]. A treat-to-target serum urate (SU) strategy for gout patients with an indication for urate-lowering therapy (ULT), such as allopurinol, febuxostat, or probenecid, has been widely endorsed as a means of optimizing clinical outcomes[2]. Previous studies have reported that effective ULT to 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]. WHO report stated that poor adherence to long-term therapies severely compromises the effectiveness of treatment[8]. Therefore, it is important to have a firm understanding of measurement and determinants of adherence in gout. The exact prevalence of adherence to ULT in gout patients is unknown. Variability exists regarding apparent adherence among literature reports, and results vary from 10% to 46% across studies[9]. This variability may result in part from different methods used to measure adherence, as well as definition of adherence. Our purpose was to determine the rate of adherence to ULT in gout patients, according to the different methods used to measure adherence. We assumed that adherence rate is affected by the method used to measure it.

To the best of our knowledge, this is the first attempt to estimate adherence rate to ULT in gout, both cumulative and separately, for different methods used to measure adherence. We also demonstrate the variability of the cutpoints used to define adherence in different studies.

## METHODS

The meta-analysis was reported according to the recommendations of the Preferred Reporting Items for Systemic Review and Meta-Analyses (PRISMA) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) 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 databases (from inception to January 2017) to identify adherence studies to ULT in adult gout patients. Associated reference lists were searched. Reviews, case reports, letters, and editorials were not included as primary data. Reviews were used to identify relevant articles and to test the search strategy.

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])). For the Chinese databases, free text terms we used including the Chinese translations of terms meaning gout and adherence and ULT. References of selected articles were also searched to identify additional reports.

**Inclusion and exclusion criteria**

Inclusion ctiteria were following: (1) patients with gout (either defined by the American College of Rheumatology criteria or as defined in the articles) and aged ≥ 18 years; (2) papers that reported adherence/compliance data with ULT; (3) observational studies.

Exclusion criteria were the following: (1) duplicates; (2) reviews, case reports, letters and editorials were excluded from the analysis, but used to search references lists; (3) studies on adherence to non-medication therapy or general recommendations (e.g., appointments, exercise, splints, diet), or non-ULT (e.g., colchicine); (4) articles on persistence, discontinuation, switching, treatment gap, or retention rate; (5) articles that used the term "adherence," but actually measured persistence or retention rate or treatment gaps; (6) articles from which specific information on gout could not be extracted (e.g., papers contained data on a mix of medication, but there was not a breakdown of adherence by medication ); (7) papers from which adherence could not be extracted; (8) When adherence was defined only according to physician evaluation (level of compliance was determined by physician ratings of patients, but no corroborating method(s) such as questionnaires, pill counts, etc.).

**Data extraction and quality assessment**

Two researchers read the relative studies independently by the titles and abstracts to exclude the references which did not met the inclusion criteria. Then, they read full texts in the remaining studies as mentioned above, and determined whether these references included were final studies or not. When multiple publications spanned the years of longitudinal studies, baseline adherence rate were reported. The following information was independently extracted from each article by other two trained investigators using a standardized form: 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, cutpoint for adherence/compliance, and reported prevalence of adherence/compliance. If we encountered multiple measurements from the same study, the most commonly 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 assessed using a modified version of the Newcastle-Ottawa Scale[12]. Studies were judged to be at low risk of bias (≥3 points) or high risk of bias (<3 points). Any disagreements in data extraction and quality assessment were resolved through discussion between the two reviewers or adjudication with a third reviewer.

**Outcome measures**

The outcomes were adherence or compliance assessed with prescription claims [e.g., medication possession ratio (MPR), proportion of days covered (PDC)], pill count, self-report or interview.

**Statistical analysis**

Because random-effects models tended to provide wider confidence intervals (CI) and were preferable in the presence of between-study heterogeneity, we used a random-effects meta-analysis to pool studies reporting adherence rate to ULT in gout patients[13]. Between-study heterogeneity was assessed by the $I^2$ with thresholds of ≥25%, ≥50% and ≥75% indicating low, moderate and high heterogeneity, respectively[14]. The influence of individual study on the overall prevalence estimate was explored by serially excluding each study in sensitivity analyses. Wherever possible, subgroup analyses were planned by measurement methods, publication year, country of origin, data sources, representativeness of the sample, sample size, cutpoint, and overall quality, if there was more than one study in the subgroup. Funnel plots and Egger's test were combined to explore the potential publication bias in this meta-analysis[15, 16]. Regression analysis was performed to test the difference among methods used to measure percentages of adherence. Statistical analyses were performed with STATA version 12.0. The statistical significance level was 0.05, except for the test of between-study heterogeneity.

**RESULTS**

**Study selection**

A flowchart of the study selection process is shown in Figure 1. According to the selection criteria defined in Materials and methods, the meta-analysis finally included 22 articles, involving a total of 137699 adult gout patients.

**Study characteristics**

Baseline characteristics of the included study, the methods employed to assess adherence to ULT and the frequency of their use were presented in Table 1A and 1B. Adherence was defined in 4 different ways. Fifteen studies assessed for adherence using prescription claims[17–31], with the cutpoint of ≥80%. One used prescripition claim and self report[32], one article used pill count[33]; two used self-report[34, 35] and three articles assessed by interview[36–38]. Among 22 identified studies, eleven took place in America, 2 in Oceania, 5 in Europe, and 4 in Asia. When evaluated by 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].

**Table 1A.** Baseline characteristics.

| Studies | N (total) | N (ULT) | Population, Country | Age, Yrs, Mean (SD) | Male,(%) | Disease Duration,Yrs, | Medications | Quality |
|---|---|---|---|---|---|---|---|---|

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Mean (SD) | | | |
| **Prescription claims** | | | | | | | | |
| Sarawate et al, 2006 | 5942 | 2405 | Managed care database, USA | 57.4(14.1)* | 76.4* | NS | allopurinol | 4 |
| Briesacher et al, 2008 | | 9715 | MEDSTAT database, USA | 58.7(0.14) | 77.5 | NS | allopurinol, uricosurics | 4 |
| Harrold et al, 2009 | | 4166 | Integrated delivery Systems, USA | 62 (14) | 75 | NS | allopurinol, probenecid, sulfinpyrazone | 4 |
| Halpern et al, 2009 | 18243 | 10070 | Claims database, USA | Mean 53.9 | 84.2 | NS | allopurinol | 4 |
| Rashid et al, 2012 | | 9288 | KPSC health care, USA | Mean 60 | 78 | NS | allopurinol | 4 |
| Horsburgh et al, 2014 | 27,243 | 732 | Community pharmacy dispensing databases, New Zealand | NA | 39.5 † | NS | allopurinol | 4 |
| Singh, 2014 | | 43 | Outpatient clinic, USA | 63.9 (9.9) | 67 | NS | allopurinol, febuxostat | 2 |
| McGowan et al, 2016 | 34634 | 15908 | HSE-PCRS scheme database, Ireland | Mean 65.2* | 73* | NS | allopurinol, febuxostat, probenecid, | 3 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | sulfinpyrazone | |
| Tan et al, 2016 | | 91 | Hospital clinics,Singapore | 53.5(16.9) | 92.3 | NS | allopurinol, probenecid | 2 |
| Solomon et al, 2008 | | 9823 | Medicare and PACE enrollees, USA | Mean 79 | 28 † | NS | allopurinol | 4 |
| Park et al. 2012 | 352 | 242 | Scott & White Health Plan, USA | 61.02(15.33)* | 72.4* † | NS | allopurinol, febuxostat, probenecid | 4 |
| Zandman-Goddard et al, 2013 | | 7644 | MHS database, Israel | NA | 72 | NS | allopurinol | 4 |
| Mantarro et al, 2015 | | 3727 | HSD database, Italy | Mean 65 | 80 | NS | allopurinol | 4 |
| Rashid et al, 2015 | | 8288 | Clinical and administrative databases, USA | NA | 79.80 | NS | allopurinol, febuxostat, probenecid | 4 |
| Kuo et al, 2015 | | 49395 | GPRD database, UK | NA | NA | NS | ULT | 4 |
| Riedel et al, 2004 | 9482 | 5597 | IPA plans, USA | 51(11)* | 82.1* | NS | allopurinol | 4 |
| **Pill counts** | | | | | | | | |
| Lee et al, 2016 | | 132 | Outpatient clinic, Korea | 51.9 (10.4) | 100 | 100.0(89.1)[§] | allopurinol, febuxostat | 2 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Self-report** | | | | | | | | |
| Silva et al, 2010 | | 34 | Outpatient, Spain | 57.1(11.8) | 94.1 † | NS | allopurinol, benzbromarone | 1 |
| Singh et al, 2016 | 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 | 60 | 56 | Community pharmacies, New Zealand | Mean 61* | 90* | NS | allopurinol | 2 |
| Sheng et al, 2014 | 161 | 80 † | Gout Clinic, China | NA | NA | NS | ULD | 1 |
| van Onna et al, 2015 | 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)

ULT:urate-lowering therapy; yr: year; mos: months; NS: not stated; NA: not applicable; cross: cross-sectional; ULD:urate-lowering drugs

**Table 1B.** Definitions, cutpoints, and percent adherence/compliance across studies. Studies were placed into subgroups according to the method used to measure adherence. Scale and cutpoints used to rate adherence are also shown.

| Studies | Outcome | Definition/scale | Cutpoint for Adherence/compliance | Adherence % |
|---|---|---|---|---|
| **Prescription claims** | | | | |
| Sarawate et al, 2006 | 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 | 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 | 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 | compliance | MPR: sum of days supply from first observed allopurinol fill during the 2-year | MPR ≥80 % | 44 |

| | | | | |
|---|---|---|---|---|
| | | observation period]/[number of days between the first observed fill and the end of the post-index period. | | |
| Rashid et al, 2012 | adherence | Adherence was measured using the MPR over the follow up time period. | MPR >80 % | 47.5† |
| Horsburgh et al, 2014 | 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 | adherence | Self-report adherence to ULT. | MPR ≥0.80 | 32.6† |
| McGowan et al, 2016 | 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 | adherence | MPR summarized the proportion of days a patient has a supply of medications for. | MPR ≥80 % | 83.5 |
| Solomon et al, 2008 | 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 | adherence | PDC defined as the number of days during the study period (365 days) that the patient had at least 1 gout-specific medication on hand. | PDC ≥ 80% | 26.9† |

| | | | | |
|---|---|---|---|---|
| Zandman-Goddard et al, 2013 | 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 | 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 | 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 | 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 | compliance | Compliance was defined for each prescription period as the presumed use of allopurinol on at least 80% of the days of that period.cc | Compliance rate ≥ 80% | 18 |
| **Pill count** | | | | |
| Lee et al, 2016 | compliance | Pill counts: noncompliance was defined as <80% of the prescribed dose taken. | Pill count ≥ 80% | 71.2 |

| | | | | |
|---|---|---|---|---|
| **Self-report** | | | | |
| Silva et al, 2010 | compliance | Compliance defined as taking medication regularly, as prescribed. | NS | 53† |
| Singh et al, 2016 | adherence | Number of days the patient forgot to take ULT in the last month. | Adherence >0.80 | 78.5 |
| Tan et al, 2016 | adherence | MMAS-8 used to measure medication adherence.(8 items, total score ranges 0-8) | MMAS-8 score≥6 (75%) | 61.9 |
| **Interview** | | | | |
| Martini et al, 2012 | compliance | Participants admitted to not taking ULTs as prescribed. | NS | 79 |
| Sheng et al, 2014 | 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 | 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.

MPR: medication possession ratio; ULT:urate-lowering therapy; UALT: uric acid lowering therapy; PDC:proportion of days covered; MMAS-8:8-item Morisky Medication Adherence Scale; NS: not stated

**The rate of adherence to ULT among gout patients.**

Adherence rate to ULT ranged from 17% to 83.5% in individual studies (Table 1B). Overall, 47% of gout patients were adherent to ULT (95% CI, 42%-52%, $I^2$ = 99.7%) (Figure not shown). The rate of adherence to ULT was 42% (95% CI, 37%-47%, $I^2$ = 99.8%) according to prescription claims. Adherence rate was 71% (95% CI, 63%-79%) for pill count, 66% (95% CI, 50%-81%, $I^2$ = 86.3%) for self-report and 63% (95% CI, 42%-83%, $I^2$ = 82.9%) for interview, respectively (Figure 2). Regression analysis revealed no statistically significant difference among methods used to measure percentage of adherence ($P$ = 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, showed that our results were not driven by any single study (Figure not shown). The summary of meta-analysis and heterogeneity assessments was described in Table 2. The subgroup analysis of adherence rate to ULT estimates were conducted according to measurement methods, publication year, country of origin, data sources, representativeness of the sample, sample size, cutpoint, 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%–81%) vs 40% (95% CI, 33%-47%), vs 44%(95% CI, 40%-49%), vs 56% (95% CI, 17%-96%) from America, Europe and Asia, respectively]. The

subgroup analysis for measurement methods, publication year, data sources, representativeness of the sample, sample size, cutpoint, and overall quality showed no clear patterns.

**Table 2**. Summary of adherence rate and heterogeneity findings.

| Outcomes | No. of studies | No. of participants | Adherence, % (95% confidence intervals) | Heterogeneity | | Test for overall effect | |
|---|---|---|---|---|---|---|---|
| | | | | *P*-value | $I^2$(%) | Z | *P*-value |
| **Overall** | 22 | 137699 | 47(42, 52) | 0.000 | 99.7 | 18.66 | 0.000 |
| **Measurement methods** | | | | | | | |
| Prescription claims | 16 | 137134 | 42(37, 47) | 0.000 | 99.8 | 15.61 | 0.000 |
| Pill count | 1 | 132 | 71(63, 79) | - | - | 18.06 | 0.000 |
| Self-report | 3 | 376 | 66(50, 81) | 0.001 | 86.3 | 8.40 | 0.000 |
| Interview | 3 | 148 | 63(42,83) | 0.003 | 82.9 | 6.09 | 0.000 |
| **Publication Year** | | | | | | | |
| 2010s | 6 | 41766 | 34(26, 43) | 0.000 | 99.7 | 8.22 | 0.000 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 2010- | 16 | 95923 | 53(47, 60) | 0.000 | 99.7 | 15.95 | 0.000 |
| **Country of origin** | | | | | | | |
| America | 11 | 59888 | 40(33, 47) | 0.000 | 99.6 | 11.82 | 0.000 |
| Oceania | 2 | 788 | 78(75, 81) | 0.860 | 0 | 52.97 | 0.000 |
| Europe | 5 | 69076 | 44(40, 49) | 0.000 | 98.0 | 19.62 | 0.000 |
| Asia | 4 | 7947 | 56(17, 96) | 0.000 | 99.4 | 2.81 | 0.000 |
| **Data sources** | | | | | | | |
| Database | 14 | 13700 | 40(34, 45) | 0.000 | 99.8 | 13.48 | 0.000 |
| Non-database | 8 | 699 | 65(54, 75) | 0.000 | 89.2 | 11.81 | 0.000 |
| **Representativeness** | | | | | | | |
| Mulitiple sites | 17 | 137319 | 44(39, 50) | 0.000 | 99.8 | 15.79 | 0.000 |
| A single site | 5 | 380 | 60(43, 76) | 0.000 | 92.1 | 7.04 | 0.000 |
| **Sample size** | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ≥ 200 | 15 | 137251 | 42(36, 48) | 0.000 | 99.8 | 14.55 | 0.000 |
| < 200 | 7 | 448 | 62(48, 75) | 0.000 | 89.3 | 9.12 | 0.000 |
| **Cutpoint** | | | | | | | |
| ≥80% | 18 | 137517 | 45(40, 51) | 0.000 | 99.7 | 16.70 | 0.000 |
| ≥75% | 1 | 19 | 62(52, 72) | 0.004 | 77.8 | 7.54 | 0.000 |
| NS | 4 | 182 | 60(45, 76) | - | - | 12.16 | 0.000 |
| **Quality** | | | | | | | |
| ≥3 points | 15 | 137251 | 42(36, 48) | 0.000 | 99.8 | 14.55 | 0.000 |
| <3points | 7 | 448 | 62(48, 75) | 0.000 | 89.3 | 9.12 | 0.000 |

**Publication bias**

According to the Egger's test, there was no significant evidence of publication bias in overall analyses, in study reporting adherence according to prescription claims, self report and interview [Egger: bias = 5.42 (95% CI: -6.55, 17.39), *P* = 0.356; Egger: bias = 4.32 (95% CI: -16.55, 25.18),

*P* = 0.664; Egger: bias = -4.92 (95% CI: -20.50, 10.66), *P* = 0.155; Egger: bias = -2.02 (95% CI: -70.13, 66.08), *P* = 0.770, respectively] (Figure not shown).

## DISCUSSION

To our knowledge, this systematic review and meta-analysis of 22 studies involving 137699 adult gout patients is the first to quantify adherence and to seek a relationship between adherence and the method used to measure it.

Overall, 47% of adult gout patients adhered to ULT. Majority of studies using prescription claims to report adherence to ULT were presented in 42% among gout patients (16 of 22). The rate of adherence to ULT was 71%, 66%, and 63% for pill count, self report and interview, respectively. According to the adherence rate from high to low on the measurement methods to sort, followed by pill count, 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% are 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 an additional studies. Importantly, the previous review did not quantify adherence. In our meta-analysis, most studies used a cutpoint of ≥80% to define adherent patients. Data on persistence, discontinuation,

switching, treatment gap or retention rate, and adherence to nonmedical therapy (e.g., diet recommendations) were excluded.

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

This meta-analysis indicated significant difference in adherence in claims database, especially from the USA, and also from 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) vs. government funded; primary care vs. secondary care, as well as severity of gout and age of patients (older typically will have higher adherence). This could also have an impact on the findings.

Because of the low adherence with ULT, it is particularly important to carry out 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[39]. Abhishek 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 interventions such as these could improve adherence to ULT and, ultimately, result in optimal gout-related outcomes.

There are, however, additional important shortcomings in the evidence on adherence to ULT in adult gout patients that need to be addressed. First, a substantial amount of the heterogeneity among the studies remained unexplained by the variables examined. Unexamined factors, such as gender, age, disease duration, study design might contribute to the risk for adherence to ULT among gout patients. Second, due to lack of access, our search did not include the EMBASE database and Cochrane database library, and several studies that referred to medications unspecified ULT were excluded, which could bias the findings.

## CONCLUSION

The rate of adherence to ULT was low in adult gout patients, with overall adherence rate of 47%. It indicated that clinicians should pay more attention to medication adherence in gout patients, in order to identify effective strategies for improving adherence to ULT among adult gout patients.

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**Competing interests**

The authors declared that they have no competing interests.

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**Authors' contributions**

RY and LL searched and checked the databases according to the inclusion and exclusion criteria, extracted the data and assessed their quality, analyzed 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.

**Ethics approval and consent to participate**

Ethical approval and consent to participate are not required for this review.

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**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 remainder 37 studies were assessed for eligibility and 15 studies were excluded. Finally 22 studies were included in the quantitative synthesis (meta-analysis).

**Figure 2.** Meta-analysis of percent of adherent patients by method used to measure adherence.

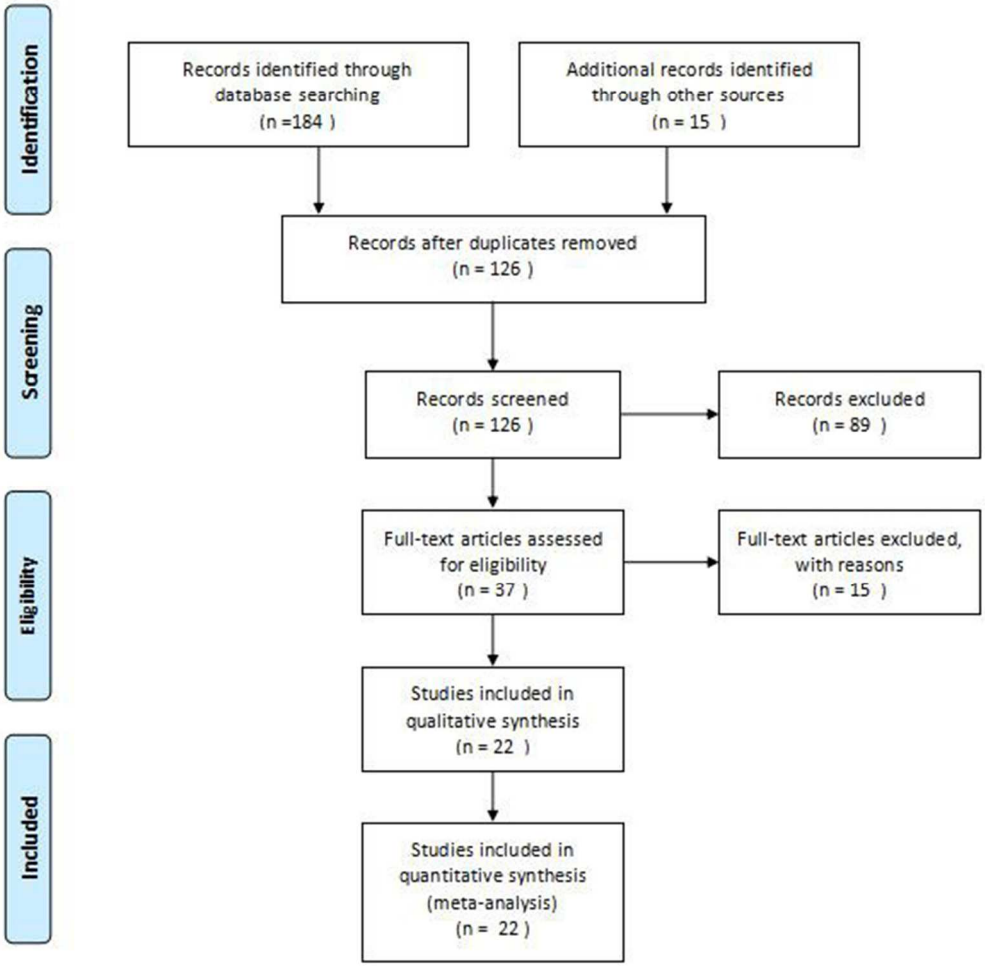


Figure 1. Flow-chart illustrating the article search process. First, we obtained 184 records identified through database searching, and 15 additional records identified through other sources. Second, 126 records remained after duplicates were removed. Third, 89 studies were excluded after records screening.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

49x48mm (300 x 300 DPI)

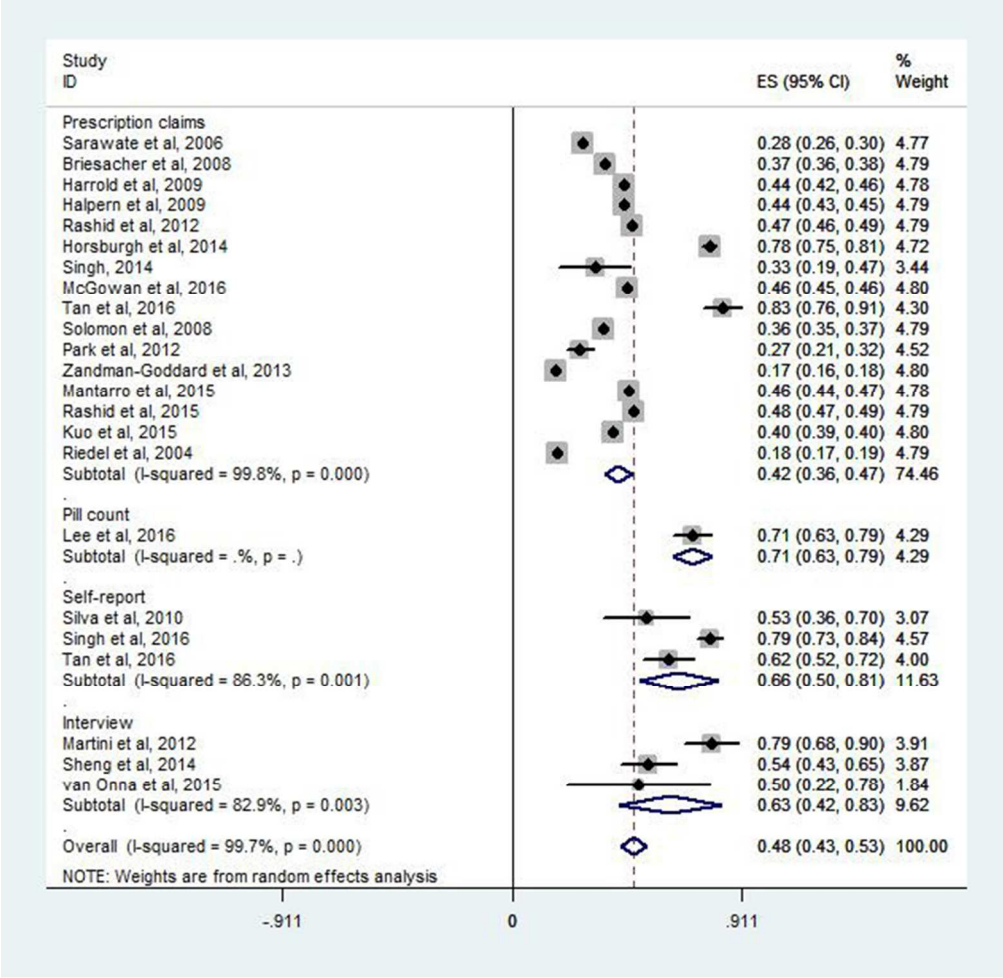


Figure 2. Meta-analysis of percent of adherent patients by method used to measure adherence.

53x52mm (300 x 300 DPI)

**PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol***

| Section and topic | Item No | Checklist item | Reported on Page # |
|---|---|---|---|
| **ADMINISTRATIVE INFORMATION** | | | |
| Title: | | | |
| Identification | 1a | Identify the report as a protocol of a systematic review | 1 |
| Update | 1b | If the protocol is for an update of a previous systematic review, identify as such | NO |
| Registration | 2 | If registered, provide the name of the registry (such as PROSPERO) and registration number | NO |
| Authors: | | | |
| Contact | 3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author | 1 |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review | 1 |
| Amendments | 4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | NO |
| Support: | | | |
| Sources | 5a | Indicate sources of financial or other support for the review | 24 |
| Sponsor | 5b | Provide name for the review funder and/or sponsor | NO |
| Role of sponsor or funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol | NO |
| **INTRODUCTION** | | | |
| Rationale | 6 | Describe the rationale for the review in the context of what is already known | 4 |
| Objectives | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | 4 |
| **METHODS** | | | |
| Eligibility criteria | 8 | Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review | 6 |
| Information sources | 9 | Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage | 5 |
| Search strategy | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated | 5-6 |

| | | | |
|---|---|---|---|
| Study records: | | | |
| Data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | 7 |
| Selection process | 11b | State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) | 7 |
| Data collection process | 11c | Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | 7 |
| Data items | 12 | List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications | 7 |
| Outcomes and prioritization | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | 7-8 |
| Risk of bias in individual studies | 14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | 8 |
| Data synthesis | 15a | Describe criteria under which study data will be quantitatively synthesised | 8 |
| | 15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$, Kendall's $\tau$) | 9-17 |
| | 15c | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) | 17-20 |
| | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned | NO |
| Meta-bias(es) | 16 | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) | 20-21 |
| Confidence in cumulative evidence | 17 | Describe how the strength of the body of evidence will be assessed (such as GRADE) | 7 |

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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BMJ Open

# The Rate of Adherence to Urate-Lowering Therapy among Gout Patients: A Systematic Review and Meta-analysis



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| | |

# The Rate of Adherence to Urate-Lowering Therapy among Gout Patients: A Systematic Review and Meta-analysis

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# The Rate of Adherence to Urate-Lowering Therapy among Gout Patients: A Systematic Review and Meta-analysis


## ABSTRACT

**Introduction** Reported adherence to urate-lowering therapy (ULT) in gout varies widely (17%-83.5%). Variability may result in part from different methods used to measure adherence. The aim was to quantify adherence to urate-lowering therapy (ULT) in adult gout patients.

**Methods** The systematic review examined PubMed, Web of Science, CNKI Scholar, WanFang databases and article reference lists from inception to January 2017. Papers with the data of adherence to ULT in adult patients with gout were included. Adherence rate was recorded for each method. Random-effect meta-analysis estimated adherence.

**Results** A total of 22 identified studies matched the inclusion criteria, reporting on a total of 137699 gout patients. Four methods of defining adherence were reported. Meta-analysis revealed that overall adherence rate was 47% (95% CI, 42%-52%, $I^2$ = 99.7%). The rate of adherence to ULT was 42% (95% CI, 37%-47%, $I^2$ = 99.8%) according to prescription claims. Adherence rate was 71% (95% CI, 63%-79%) for pill count, 66% (95% CI, 50%-81%, $I^2$=86.3%) for self-report, and 63% (95% CI, 42%-83%, $I^2$ = 82.9%) for interview, respectively. The main influence on adherence rate was country of origin of the studies.

**Conclusions** Adherence to ULT was low in adult gout patients, with the overall adherence rate of 47%. It indicated that clinicians should pay

more attention to medication adherence in gout patients, in order to identify effective strategies for improving adherence to ULT among adult gout patients.

**Strengths and limitations**

- To our knowledge, this was the first meta-analysis quantifying the overall adherence rate to ULT in gout patients.
- This systematic review was composed of 22 studies, with 137699 gout patients.
- A substantial amount of the heterogeneity among the studies remained unexplained by the variables examined.
- EMBASE database and Cochrane database library were not searched due to lack of access.
- Several studies that referred to medications unspecified ULT were excluded, which could bias the findings.

**KEYWORDS:** adherence; urate-lowering therapy; gout; meta-analysis

## INTRODUCTION

Gout, which is characterised by deposition of monosodium urate monohydrate (MSU) in synovial fluid and other tissues, is the most common cause of inflammatory arthritis worldwide[1]. A treat-to-target serum urate (SU) strategy for gout patients with an indication for urate-lowering therapy (ULT), such as allopurinol, febuxostat, or probenecid, has been widely endorsed as a means of optimizing clinical outcomes[2]. Previous studies have reported that effective ULT to 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]. WHO report stated that poor adherence to long-term therapies severely compromises the effectiveness of treatment[8]. Therefore, it is important to have a firm understanding of measurement and determinants of adherence in gout. The exact prevalence of adherence to ULT in gout patients is unknown. Variability exists regarding apparent adherence among literature reports, and results vary from 10% to 46% across studies[9]. This variability may result in part from different methods used to measure adherence, as well as definition of adherence. Our purpose was to determine the rate of adherence to ULT in gout patients, according to the different methods used to measure adherence. We assumed that adherence rate is affected by the method used to measure it.

To the best of our knowledge, this is the first attempt to estimate adherence rate to ULT in gout, both cumulative and separately, for different methods used to measure adherence. We also demonstrate the variability of the cutpoints used to define adherence in different studies.

## METHODS

The meta-analysis was reported according to the recommendations of the Preferred Reporting Items for Systemic Review and Meta-Analyses (PRISMA) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) 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 databases (from inception to January 2017) to identify adherence studies to ULT in adult gout patients. Associated reference lists were searched. Reviews, case reports, letters, and editorials were not included as primary data. Reviews were used to identify relevant articles and to test the search strategy.

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 Additional file 1). For the Chinese databases, free text terms we used including the Chinese translations of terms meaning gout and adherence and ULT. References of selected articles were also searched to identify additional reports.

**Inclusion and exclusion criteria**

Inclusion ctiteria were following: (1) patients with gout (either defined by the American College of Rheumatology criteria or as defined in the articles) and aged ≥ 18 years; (2) papers that reported adherence/compliance data with ULT; (3) observational studies.

Exclusion criteria were the following: (1) duplicates; (2) reviews, case reports, letters and editorials were excluded from the analysis, but used to search references lists; (3) studies on adherence to non-medication therapy or general recommendations (e.g., appointments, exercise, splints, diet), or non-ULT (e.g., colchicine); (4) articles on persistence, discontinuation, switching, treatment gap, or retention rate; (5) articles that used the term "adherence," but actually measured persistence or retention rate or treatment gaps; (6) articles from which specific information on gout could not be extracted (e.g., papers contained data on a mix of medication, but there was not a breakdown of adherence by medication ); (7) papers from which adherence could not be extracted; (8) When adherence was defined only according to physician evaluation (level of compliance was determined by physician ratings of patients, but no corroborating method(s) such as questionnaires, pill counts, etc.).

**Data extraction and quality assessment**

Two researchers read the relative studies independently by the titles and abstracts to exclude the references which did not met the inclusion criteria. Then, they read full texts in the remaining studies as mentioned above, and determined whether these references included were final studies or not. When multiple publications spanned the years of longitudinal studies, baseline adherence rate were reported. The following information was independently extracted from each article by other two trained investigators using a standardized form: 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, cutpoint for adherence/compliance, and reported prevalence of adherence/compliance. If we encountered multiple measurements from the same study, the most commonly 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 assessed using a modified version of the Newcastle-Ottawa Scale[12]. Studies were judged to be at low risk of bias (≥3 points) or high risk of bias (<3 points). Any disagreements in data extraction and quality assessment were resolved through discussion between the two reviewers or adjudication with a third reviewer.

**Outcome measures**

The outcomes were adherence or compliance assessed with prescription claims [e.g., medication possession ratio (MPR), proportion of days covered (PDC)], pill count, self-report or interview.

**Statistical analysis**

Because random-effects models tended to provide wider confidence intervals (CI) and were preferable in the presence of between-study heterogeneity, we used a random-effects meta-analysis to pool studies reporting adherence rate to ULT in gout patients[13]. Between-study heterogeneity was assessed by the $I^2$ with thresholds of ≥25%, ≥50% and ≥75% indicating low, moderate and high heterogeneity, respectively[14]. The influence of individual study on the overall prevalence estimate was explored by serially excluding each study in sensitivity analyses. Wherever possible, subgroup analyses were planned by measurement methods, publication year, country of origin, data sources, representativeness of the sample, sample size, cutpoint, and overall quality, if there was more than one study in the subgroup. Funnel plots and Egger's test were combined to explore the potential publication bias in this meta-analysis[15, 16]. Regression analysis was performed to test the difference among methods used to measure percentages of adherence. Statistical analyses were performed with STATA version 12.0. The statistical significance level was 0.05, except for the test of between-study heterogeneity.

**RESULTS**

**Study selection**

A flowchart of the study selection process is shown in Figure 1. According to the selection criteria defined in Materials and methods, the meta-analysis finally included 22 articles, involving a total of 137699 adult gout patients.

**Study characteristics**

Baseline characteristics of the included study, the methods employed to assess adherence to ULT and the frequency of their use were presented in Table 1A and 1B. Adherence was defined in 4 different ways. Fifteen studies assessed for adherence using prescription claims[17–31], with the cutpoint of ≥80%. One used prescripition claim and self report[32], one article used pill count[33]; two used self-report[34, 35] and three articles assessed by interview[36–38]. Among 22 identified studies, eleven took place in America, 2 in Oceania, 5 in Europe, and 4 in Asia. When evaluated by 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].

**Table 1A.** Baseline characteristics.

| Studies | N (total) | N (ULT) | Population, Country | Age, Yrs, Mean (SD) | Male,(%) | Disease Duration,Yrs, | Medications | Quality |
|---|---|---|---|---|---|---|---|---|

| | | | | | Mean (SD) | | | |
|---|---|---|---|---|---|---|---|---|
| **Prescription claims** | | | | | | | | |
| Sarawate et al, 2006 | 5942 | 2405 | Managed care database, USA | 57.4(14.1)* | 76.4* | NS | allopurinol | 4 |
| Briesacher et al, 2008 | | 9715 | MEDSTAT database, USA | 58.7(0.14) | 77.5 | NS | allopurinol, uricosurics | 4 |
| Harrold et al, 2009 | | 4166 | Integrated delivery Systems, USA | 62 (14) | 75 | NS | allopurinol, probenecid, sulfinpyrazone | 4 |
| Halpern et al, 2009 | 18243 | 10070 | Claims database, USA | Mean 53.9 | 84.2 | NS | allopurinol | 4 |
| Rashid et al, 2012 | | 9288 | KPSC health care, USA | Mean 60 | 78 | NS | allopurinol | 4 |
| Horsburgh et al, 2014 | 27,243 | 732 | Community pharmacy dispensing databases, New Zealand | NA | 39.5 † | NS | allopurinol | 4 |
| Singh, 2014 | | 43 | Outpatient clinic, USA | 63.9 (9.9) | 67 | NS | allopurinol, febuxostat | 2 |
| McGowan et al, 2016 | 34634 | 15908 | HSE-PCRS scheme database, Ireland | Mean 65.2* | 73* | NS | allopurinol, febuxostat, probenecid, | 3 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | sulfinpyrazone | |
| Tan et al, 2016 | | 91 | Hospital clinics,Singapore | 53.5(16.9) | 92.3 | NS | allopurinol, probenecid | 2 |
| Solomon et al, 2008 | | 9823 | Medicare and PACE enrollees, USA | Mean 79 | 28 † | NS | allopurinol | 4 |
| Park et al. 2012 | 352 | 242 | Scott & White Health Plan, USA | 61.02(15.33)* | 72.4* † | NS | allopurinol, febuxostat, probenecid | 4 |
| Zandman-Goddard et al, 2013 | | 7644 | MHS database, Israel | NA | 72 | NS | allopurinol | 4 |
| Mantarro et al, 2015 | | 3727 | HSD database, Italy | Mean 65 | 80 | NS | allopurinol | 4 |
| Rashid et al, 2015 | | 8288 | Clinical and administrative databases, USA | NA | 79.80 | NS | allopurinol, febuxostat, probenecid | 4 |
| Kuo et al, 2015 | | 49395 | GPRD database, UK | NA | NA | NS | ULT | 4 |
| Riedel et al, 2004 | 9482 | 5597 | IPA plans, USA | 51(11)* | 82.1* | NS | allopurinol | 4 |
| **Pill counts** | | | | | | | | |
| Lee et al, 2016 | | 132 | Outpatient clinic, Korea | 51.9 (10.4) | 100 | 100.0(89.1)[§] | allopurinol, febuxostat | 2 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Self-report** | | | | | | | | |
| Silva et al, 2010 | | 34 | Outpatient, Spain | 57.1(11.8) | 94.1 † | NS | allopurinol, benzbromarone | 1 |
| Singh et al, 2016 | 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 | 60 | 56 | Community pharmacies, New Zealand | Mean 61* | 90* | NS | allopurinol | 2 |
| Sheng et al, 2014 | 161 | 80 † | Gout Clinic, China | NA | NA | NS | ULD | 1 |
| van Onna et al, 2015 | 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)

ULT:urate-lowering therapy; yr: year; mos: months; NS: not stated; NA: not applicable; cross: cross-sectional; ULD:urate-lowering drugs

**Table 1B.** Definitions, cutpoints, and percent adherence/compliance across studies. Studies were placed into subgroups according to the method used to measure adherence. Scale and cutpoints used to rate adherence are also shown.

| Studies | Outcome | Definition/scale | Cutpoint for Adherence/compliance | Adherence % |
|---|---|---|---|---|
| **Prescription claims** | | | | |
| Sarawate et al, 2006 | 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 | 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 | 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 | compliance | MPR: sum of days supply from first observed allopurinol fill during the 2-year | MPR ≥80 % | 44 |

| | | | | |
|---|---|---|---|---|
| | | observation period]/[number of days between the first observed fill and the end of the post-index period. | | |
| Rashid et al, 2012 | adherence | Adherence was measured using the MPR over the follow up time period. | MPR >80 % | 47.5† |
| Horsburgh et al, 2014 | 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 | adherence | Self-report adherence to ULT. | MPR ≥0.80 | 32.6† |
| McGowan et al, 2016 | 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 | adherence | MPR summarized the proportion of days a patient has a supply of medications for. | MPR ≥80 % | 83.5 |
| Solomon et al, 2008 | 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 | adherence | PDC defined as the number of days during the study period (365 days) that the patient had at least 1 gout-specific medication on hand. | PDC ≥ 80% | 26.9† |

| | | | | |
|---|---|---|---|---|
| Zandman-Goddard et al, 2013 | 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 | 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 | 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 | 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 | compliance | Compliance was defined for each prescription period as the presumed use of allopurinol on at least 80% of the days of that period.cc | Compliance rate ≥ 80% | 18 |
| **Pill count** | | | | |
| Lee et al, 2016 | compliance | Pill counts: noncompliance was defined as <80% of the prescribed dose taken. | Pill count ≥ 80% | 71.2 |

| | | | | |
|---|---|---|---|---|
| **Self-report** | | | | |
| Silva et al, 2010 | compliance | Compliance defined as taking medication regularly, as prescribed. | NS | 53† |
| Singh et al, 2016 | adherence | Number of days the patient forgot to take ULT in the last month. | Adherence >0.80 | 78.5 |
| Tan et al, 2016 | adherence | MMAS-8 used to measure medication adherence.(8 items, total score ranges 0-8) | MMAS-8 score≥6 (75%) | 61.9 |
| **Interview** | | | | |
| Martini et al, 2012 | compliance | Participants admitted to not taking ULTs as prescribed. | NS | 79 |
| Sheng et al, 2014 | 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 | 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.

MPR: medication possession ratio; ULT:urate-lowering therapy; UALT: uric acid lowering therapy; PDC:proportion of days covered; MMAS-8:8-item Morisky Medication Adherence Scale; NS: not stated

**The rate of adherence to ULT among gout patients.**

Adherence rate to ULT ranged from 17% to 83.5% in individual studies (Table 1B). Overall, 47% of gout patients were adherent to ULT (95% CI, 42%-52%, $I^2$ = 99.7%) (Figure not shown). The rate of adherence to ULT was 42% (95% CI, 37%-47%, $I^2$ = 99.8%) according to prescription claims. Adherence rate was 71% (95% CI, 63%-79%) for pill count, 66% (95% CI, 50%-81%, $I^2$ = 86.3%) for self-report and 63% (95% CI, 42%-83%, $I^2$ = 82.9%) for interview, respectively (Figure 2). Regression analysis revealed no statistically significant difference among methods used to measure percentage of adherence ($P$ = 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, showed that our results were not driven by any single study (Figure not shown). The summary of meta-analysis and heterogeneity assessments was described in Table 2. The subgroup analysis of adherence rate to ULT estimates were conducted according to measurement methods, publication year, country of origin, data sources, representativeness of the sample, sample size, cutpoint, 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%–81%) vs 40% (95% CI, 33%-47%), vs 44%(95% CI, 40%-49%), vs 56% (95% CI, 17%-96%) from America, Europe and Asia, respectively]. The

subgroup analysis for measurement methods, publication year, data sources, representativeness of the sample, sample size, cutpoint, and overall quality showed no clear patterns.

**Table 2**. Summary of adherence rate and heterogeneity findings.

| Outcomes | No. of studies | No. of participants | Adherence, % (95% confidence intervals) | Heterogeneity | | Test for overall effect | |
|---|---|---|---|---|---|---|---|
| | | | | *P*-value | $I^2$(%) | Z | *P*-value |
| **Overall** | 22 | 137699 | 47(42, 52) | 0.000 | 99.7 | 18.66 | 0.000 |
| **Measurement methods** | | | | | | | |
| Prescription claims | 16 | 137134 | 42(37, 47) | 0.000 | 99.8 | 15.61 | 0.000 |
| Pill count | 1 | 132 | 71(63, 79) | - | - | 18.06 | 0.000 |
| Self-report | 3 | 376 | 66(50, 81) | 0.001 | 86.3 | 8.40 | 0.000 |
| Interview | 3 | 148 | 63(42,83) | 0.003 | 82.9 | 6.09 | 0.000 |
| **Publication Year** | | | | | | | |
| 2010s | 6 | 41766 | 34(26, 43) | 0.000 | 99.7 | 8.22 | 0.000 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 2010- | 16 | 95923 | 53(47, 60) | 0.000 | 99.7 | 15.95 | 0.000 |
| **Country of origin** | | | | | | | |
| America | 11 | 59888 | 40(33, 47) | 0.000 | 99.6 | 11.82 | 0.000 |
| Oceania | 2 | 788 | 78(75, 81) | 0.860 | 0 | 52.97 | 0.000 |
| Europe | 5 | 69076 | 44(40, 49) | 0.000 | 98.0 | 19.62 | 0.000 |
| Asia | 4 | 7947 | 56(17, 96) | 0.000 | 99.4 | 2.81 | 0.000 |
| **Data sources** | | | | | | | |
| Database | 14 | 13700 | 40(34, 45) | 0.000 | 99.8 | 13.48 | 0.000 |
| Non-database | 8 | 699 | 65(54, 75) | 0.000 | 89.2 | 11.81 | 0.000 |
| **Representativeness** | | | | | | | |
| Mulitiple sites | 17 | 137319 | 44(39, 50) | 0.000 | 99.8 | 15.79 | 0.000 |
| A single site | 5 | 380 | 60(43, 76) | 0.000 | 92.1 | 7.04 | 0.000 |
| **Sample size** | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ≥ 200 | 15 | 137251 | 42(36, 48) | 0.000 | 99.8 | 14.55 | 0.000 |
| < 200 | 7 | 448 | 62(48, 75) | 0.000 | 89.3 | 9.12 | 0.000 |
| **Cutpoint** | | | | | | | |
| ≥80% | 18 | 137517 | 45(40, 51) | 0.000 | 99.7 | 16.70 | 0.000 |
| ≥75% | 1 | 19 | 62(52, 72) | 0.004 | 77.8 | 7.54 | 0.000 |
| NS | 4 | 182 | 60(45, 76) | - | - | 12.16 | 0.000 |
| **Quality** | | | | | | | |
| ≥3 points | 15 | 137251 | 42(36, 48) | 0.000 | 99.8 | 14.55 | 0.000 |
| <3points | 7 | 448 | 62(48, 75) | 0.000 | 89.3 | 9.12 | 0.000 |

**Publication bias**

According to the Egger's test, there was no significant evidence of publication bias in overall analyses, in study reporting adherence according to prescription claims, self report and interview [Egger: bias = 5.42 (95% CI: -6.55, 17.39), *P* = 0.356; Egger: bias = 4.32 (95% CI: -16.55, 25.18),

*P* = 0.664; Egger: bias = -4.92 (95% CI: -20.50, 10.66), *P* = 0.155; Egger: bias = -2.02 (95% CI: -70.13, 66.08), *P* = 0.770, respectively] (Figure not shown).

## DISCUSSION

To our knowledge, this systematic review and meta-analysis of 22 studies involving 137699 adult gout patients is the first to quantify adherence and to seek a relationship between adherence and the method used to measure it.

Overall, 47% of adult gout patients adhered to ULT. Majority of studies using prescription claims to report adherence to ULT were presented in 42% among gout patients (16 of 22). The rate of adherence to ULT was 71%, 66%, and 63% for pill count, self report and interview, respectively. According to the adherence rate from high to low on the measurement methods to sort, followed by pill count, 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% are 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 an additional studies. Importantly, the previous review did not quantify adherence. In our meta-analysis, most studies used a cutpoint of ≥80% to define adherent patients. Data on persistence, discontinuation,

switching, treatment gap or retention rate, and adherence to nonmedical therapy (e.g., diet recommendations) were excluded.

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

This meta-analysis indicated significant difference in adherence in claims database, especially from the USA, and also from 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) vs. government funded; primary care vs. secondary care, as well as severity of gout and age of patients (older typically will have higher adherence). This could also have an impact on the findings.

Because of the low adherence with ULT, it is particularly important to carry out 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[39]. Abhishek 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 interventions such as these could improve adherence to ULT and, ultimately, result in optimal gout-related outcomes.

There are, however, additional important shortcomings in the evidence on adherence to ULT in adult gout patients that need to be addressed. First, a substantial amount of the heterogeneity among the studies remained unexplained by the variables examined. Unexamined factors, such as gender, age, disease duration, study design might contribute to the risk for adherence to ULT among gout patients. Second, due to lack of access, our search did not include the EMBASE database and Cochrane database library, and several studies that referred to medications unspecified ULT were excluded, which could bias the findings.

## CONCLUSION

The rate of adherence to ULT was low in adult gout patients, with overall adherence rate of 47%. It indicated that clinicians should pay more attention to medication adherence in gout patients, in order to identify effective strategies for improving adherence to ULT among adult gout patients.

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**Competing interests**

The authors declared that they have no competing interests.

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**Authors' contributions**

RY and LL searched and checked the databases according to the inclusion and exclusion criteria, extracted the data and assessed their quality, analyzed 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.

**Ethics approval and consent to participate**

Ethical approval and consent to participate are not required for this review.

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**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 remainder 37 studies were assessed for eligibility and 15 studies were excluded. Finally 22 studies were included in the quantitative synthesis (meta-analysis).

**Figure 2.** Meta-analysis of percent of adherent patients by method used to measure adherence.

**Additional file 1**: Search strategy.

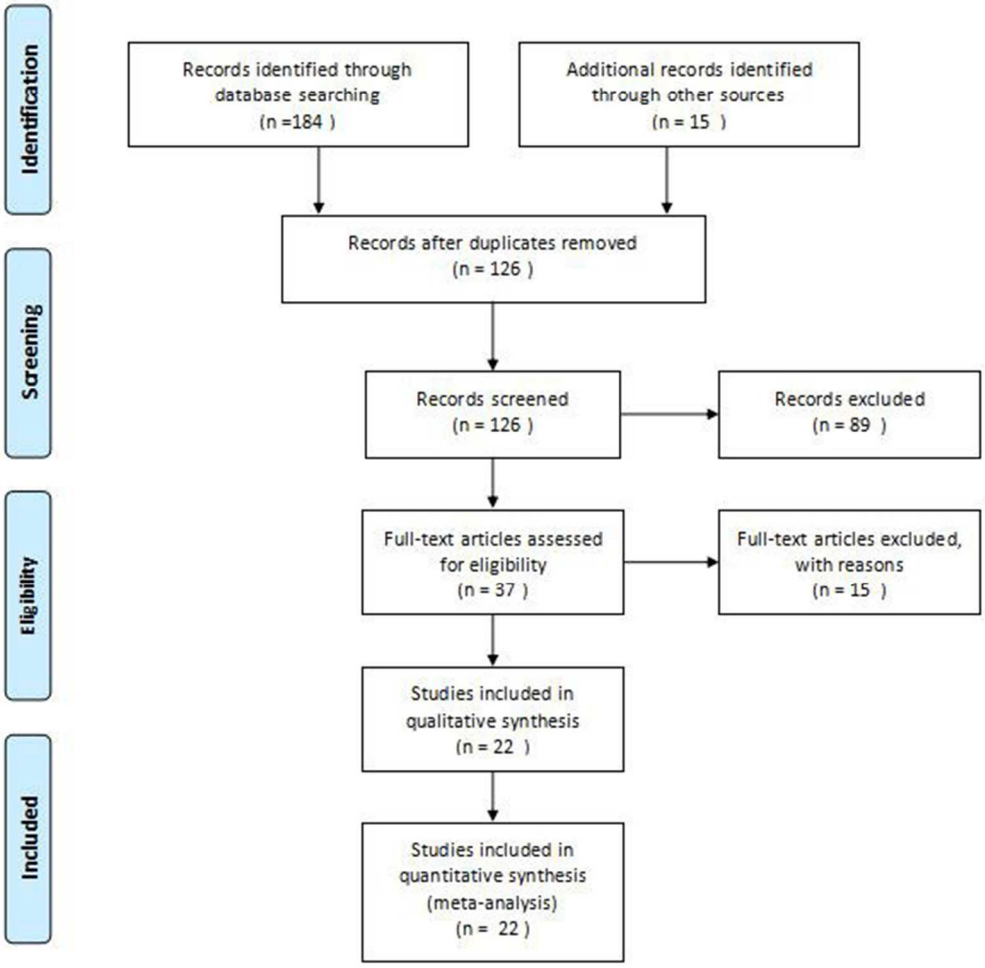


Figure 1. Flow-chart illustrating the article search process. First, we obtained 184 records identified through database searching, and 15 additional records identified through other sources. Second, 126 records remained after duplicates were removed. Third, 89 studies were excluded after records screening.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

49x48mm (300 x 300 DPI)

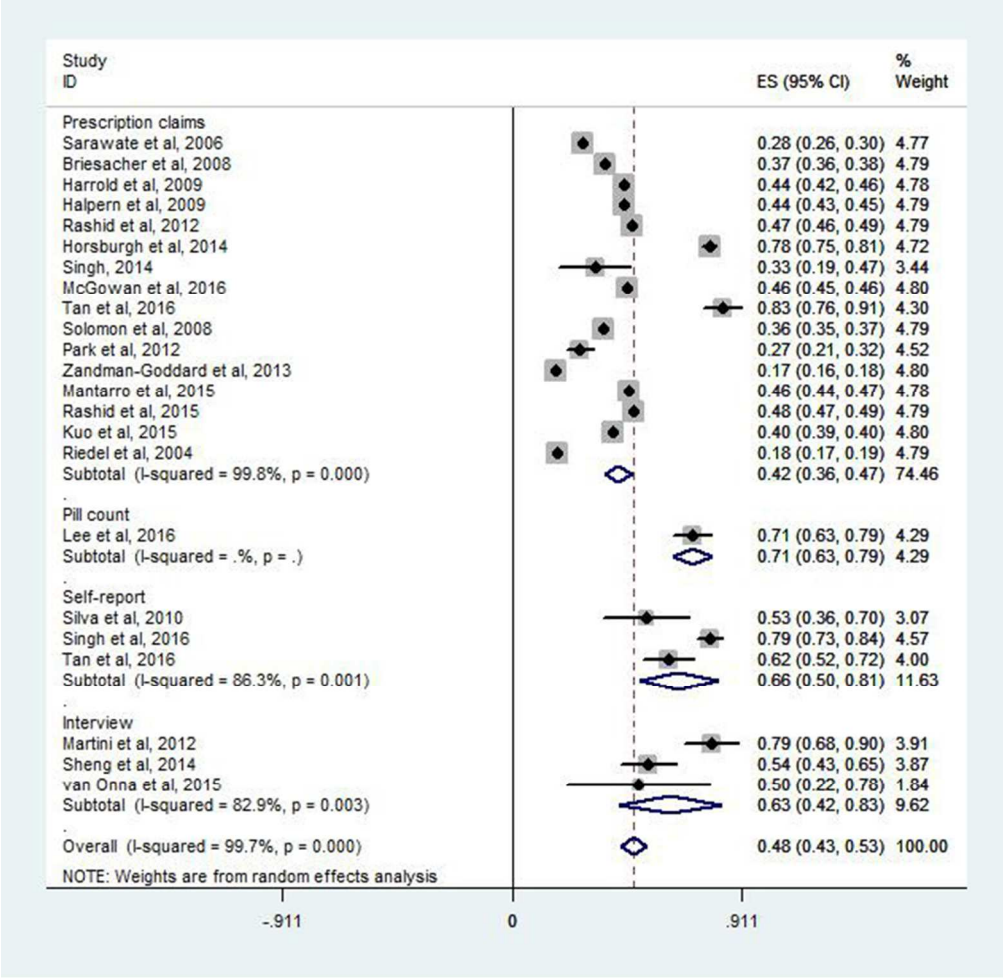


Figure 2. Meta-analysis of percent of adherent patients by method used to measure adherence.

53x52mm (300 x 300 DPI)

# **Additional file 1**: Search strategy

PubMed/Web of Science:

（adherence OR compliance）AND urate-lowering therapy AND gout

**PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol***

| Section and topic | Item No | Checklist item | Reported on Page # |
|---|---|---|---|
| **ADMINISTRATIVE INFORMATION** | | | |
| Title: | | | |
| Identification | 1a | Identify the report as a protocol of a systematic review | 1 |
| Update | 1b | If the protocol is for an update of a previous systematic review, identify as such | NO |
| Registration | 2 | If registered, provide the name of the registry (such as PROSPERO) and registration number | NO |
| Authors: | | | |
| Contact | 3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author | 1 |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review | 1 |
| Amendments | 4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | NO |
| Support: | | | |
| Sources | 5a | Indicate sources of financial or other support for the review | 24 |
| Sponsor | 5b | Provide name for the review funder and/or sponsor | NO |
| Role of sponsor or funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol | NO |
| **INTRODUCTION** | | | |
| Rationale | 6 | Describe the rationale for the review in the context of what is already known | 4 |
| Objectives | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | 4 |
| **METHODS** | | | |
| Eligibility criteria | 8 | Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review | 6 |
| Information sources | 9 | Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage | 5 |
| Search strategy | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated | 5-6 |

| | | | |
|---|---|---|---|
| Study records: | | | |
| Data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | 7 |
| Selection process | 11b | State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) | 7 |
| Data collection process | 11c | Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | 7 |
| Data items | 12 | List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications | 7 |
| Outcomes and prioritization | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | 7-8 |
| Risk of bias in individual studies | 14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | 8 |
| Data synthesis | 15a | Describe criteria under which study data will be quantitatively synthesised | 8 |
| | 15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$, Kendall's $\tau$) | 9-17 |
| | 15c | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) | 17-20 |
| | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned | NO |
| Meta-bias(es) | 16 | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) | 20-21 |
| Confidence in cumulative evidence | 17 | Describe how the strength of the body of evidence will be assessed (such as GRADE) | 7 |

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

*From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.*

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# The Rate of Adherence to Urate-Lowering Therapy among Gout Patients: A Systematic Review and Meta-analysis



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| Keywords: | adherence, urate-lowering therapy, gout, meta-analysis |
| | |

# The Rate of Adherence to Urate-Lowering Therapy among Gout Patients: A Systematic Review and Meta-analysis

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# The Rate of Adherence to Urate-Lowering Therapy among Gout Patients: A Systematic Review and Meta-analysis


## ABSTRACT

**Introduction** Reported adherence to urate-lowering therapy (ULT) in gout varies widely (17%-83.5%). Variability may result in part from different methods used to measure adherence. The aim was to quantify adherence to urate-lowering therapy (ULT) in adult gout patients.

**Methods** The systematic review examined PubMed, Web of Science, CNKI Scholar, WanFang databases and article reference lists from inception to January 2017. Papers with the data of adherence to ULT in adult patients with gout were included. Adherence rate was recorded for each method. Random-effect meta-analysis estimated adherence.

**Results** A total of 22 identified studies matched the inclusion criteria, reporting on a total of 137699 gout patients. Four methods of defining adherence were reported. Meta-analysis revealed that overall adherence rate was 47% (95% CI, 42%-52%, $I^2$ = 99.7%). The rate of adherence to ULT was 42% (95% CI, 37%-47%, $I^2$ = 99.8%) according to prescription claims. Adherence rate was 71% (95% CI, 63%-79%) for pill count, 66% (95% CI, 50%-81%, $I^2$=86.3%) for self-report, and 63% (95% CI, 42%-83%, $I^2$ = 82.9%) for interview, respectively. The main influence on adherence rate was country of origin of the studies.

**Conclusions** Adherence to ULT was low in adult gout patients, with the overall adherence rate of 47%. It indicated that clinicians should pay more attention to medication adherence in gout patients, in order to identify effective strategies for improving adherence to ULT among adult gout patients.

**Strengths and limitations**

- To our knowledge, this was the first meta-analysis quantifying the overall adherence rate to ULT in gout patients.
- This systematic review was composed of 22 studies, with 137699 gout patients.
- A substantial amount of the heterogeneity among the studies remained unexplained by the variables examined.
- EMBASE database and Cochrane database library were not searched due to lack of access.
- Several studies that referred to medications unspecified ULT were excluded, which could bias the findings.

**KEYWORDS:** adherence; urate-lowering therapy; gout; meta-analysis

## INTRODUCTION

Gout, which is characterised by deposition of monosodium urate monohydrate (MSU) in synovial fluid and other tissues, is the most common cause of inflammatory arthritis worldwide[1]. A treat-to-target serum urate (SU) strategy for gout patients with an indication for urate-lowering therapy (ULT), such as allopurinol, febuxostat, or probenecid, has been widely endorsed as a means of optimizing clinical outcomes[2]. Previous studies have reported that effective ULT to 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]. WHO report stated that poor adherence to long-term therapies severely compromises the effectiveness of treatment[8]. Therefore, it is important to have a firm understanding of measurement and determinants of adherence in gout. The exact prevalence of adherence to ULT in gout patients is unknown. Variability exists regarding apparent adherence among literature reports, and results vary from 10% to 46% across studies[9]. This variability may result in part from different methods used to measure adherence, as well as definition of adherence. Our purpose was to determine the rate of adherence to ULT in gout patients, according to the different methods used to measure adherence. We assumed that adherence rate is affected by the method used to measure it.

To the best of our knowledge, this is the first attempt to estimate adherence rate to ULT in gout, both cumulative and separately, for different methods used to measure adherence. We also demonstrate the variability of the cutpoints used to define adherence in different studies.

## METHODS

The meta-analysis was reported according to the recommendations of the Preferred Reporting Items for Systemic Review and Meta-Analyses (PRISMA) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) 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 databases (from inception to January 2017) to identify adherence studies to ULT in adult gout patients. Associated reference lists were searched. Reviews, case reports, letters, and editorials were not included as primary data. Reviews were used to identify relevant articles and to test the search strategy.

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 Additional file 1). For the Chinese databases, free text terms we used including the Chinese translations of terms meaning gout and adherence and ULT. References of selected articles were also searched to identify additional reports.

**Inclusion and exclusion criteria**

Inclusion ctiteria were following: (1) patients with gout (either defined by the American College of Rheumatology criteria or as defined in the articles) and aged ≥ 18 years; (2) papers that reported adherence/compliance data with ULT; (3) observational studies.

Exclusion criteria were the following: (1) duplicates; (2) reviews, case reports, letters and editorials were excluded from the analysis, but used to search references lists; (3) studies on adherence to non-medication therapy or general recommendations (e.g., appointments, exercise, splints, diet), or non-ULT (e.g., colchicine); (4) articles on persistence, discontinuation, switching, treatment gap, or retention rate; (5) articles that used the term "adherence," but actually measured persistence or retention rate or treatment gaps; (6) articles from which specific information on gout could not be extracted (e.g., papers contained data on a mix of medication, but there was not a breakdown of adherence by medication ); (7) papers from which adherence could not be extracted; (8) When adherence was defined only according to physician evaluation (level of compliance was determined by physician ratings of patients, but no corroborating method(s) such as questionnaires, pill counts, etc.).

**Data extraction and quality assessment**

Two researchers read the relative studies independently by the titles and abstracts to exclude the references which did not met the inclusion criteria. Then, they read full texts in the remaining studies as mentioned above, and determined whether these references included were final studies or not. When multiple publications spanned the years of longitudinal studies, baseline adherence rate were reported. The following information was independently extracted from each article by other two trained investigators using a standardized form: 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, cutpoint for adherence/compliance, and reported prevalence of adherence/compliance. If we encountered multiple measurements from the same study, the most commonly 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 assessed using a modified version of the Newcastle-Ottawa Scale[12]. Studies were judged to be at low risk of bias (≥3 points) or high risk of bias (<3 points). Any disagreements in data extraction and quality assessment were resolved through discussion between the two reviewers or adjudication with a third reviewer.

**Outcome measures**

The outcomes were adherence or compliance assessed with prescription claims [e.g., medication possession ratio (MPR), proportion of days covered (PDC)], pill count, self-report or interview.

**Statistical analysis**

Because random-effects models tended to provide wider confidence intervals (CI) and were preferable in the presence of between-study heterogeneity, we used a random-effects meta-analysis to pool studies reporting adherence rate to ULT in gout patients[13]. Between-study heterogeneity was assessed by the $I^2$ with thresholds of ≥25%, ≥50% and ≥75% indicating low, moderate and high heterogeneity, respectively[14]. The influence of individual study on the overall prevalence estimate was explored by serially excluding each study in sensitivity analyses. Wherever possible, subgroup analyses were planned by measurement methods, publication year, country of origin, data sources, representativeness of the sample, sample size, cutpoint, and overall quality, if there was more than one study in the subgroup. Funnel plots and Egger's test were combined to explore the potential publication bias in this meta-analysis[15, 16]. Regression analysis was performed to test the difference among methods used to measure percentages of adherence. Statistical analyses were performed with STATA version 12.0. The statistical significance level was 0.05, except for the test of between-study heterogeneity.

**RESULTS**

**Study selection**

A flowchart of the study selection process is shown in Figure 1. According to the selection criteria defined in Materials and methods, the meta-analysis finally included 22 articles, involving a total of 137699 adult gout patients.

**Study characteristics**

Baseline characteristics of the included study, the methods employed to assess adherence to ULT and the frequency of their use were presented in Table 1A and 1B. Adherence was defined in 4 different ways. Fifteen studies assessed for adherence using prescription claims[17–31], with the cutpoint of ≥80%. One used prescripition claim and self report[32], one article used pill count[33]; two used self-report[34, 35] and three articles assessed by interview[36–38]. Among 22 identified studies, eleven took place in America, 2 in Oceania, 5 in Europe, and 4 in Asia. When evaluated by 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].

**Table 1A.** Baseline characteristics.

| Studies | N (total) | N (ULT) | Population, Country | Age, Yrs, Mean (SD) | Male,(%) | Disease Duration,Yrs, | Medications | Quality |
|---|---|---|---|---|---|---|---|---|

| | | | | | Mean (SD) | | | |
|---|---|---|---|---|---|---|---|---|
| **Prescription claims** | | | | | | | | |
| Sarawate et al, 2006 | 5942 | 2405 | Managed care database, USA | 57.4(14.1)* | 76.4* | NS | allopurinol | 4 |
| Briesacher et al, 2008 | | 9715 | MEDSTAT database, USA | 58.7(0.14) | 77.5 | NS | allopurinol, uricosurics | 4 |
| Harrold et al, 2009 | | 4166 | Integrated delivery Systems, USA | 62 (14) | 75 | NS | allopurinol, probenecid, sulfinpyrazone | 4 |
| Halpern et al, 2009 | 18243 | 10070 | Claims database, USA | Mean 53.9 | 84.2 | NS | allopurinol | 4 |
| Rashid et al, 2012 | | 9288 | KPSC health care, USA | Mean 60 | 78 | NS | allopurinol | 4 |
| Horsburgh et al, 2014 | 27,243 | 732 | Community pharmacy dispensing databases, New Zealand | NA | 39.5 † | NS | allopurinol | 4 |
| Singh, 2014 | | 43 | Outpatient clinic, USA | 63.9 (9.9) | 67 | NS | allopurinol, febuxostat | 2 |
| McGowan et al, 2016 | 34634 | 15908 | HSE-PCRS scheme database, Ireland | Mean 65.2* | 73* | NS | allopurinol, febuxostat, probenecid, | 3 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | sulfinpyrazone | |
| Tan et al, 2016 | | 91 | Hospital clinics,Singapore | 53.5(16.9) | 92.3 | NS | allopurinol, probenecid | 2 |
| Solomon et al, 2008 | | 9823 | Medicare and PACE enrollees, USA | Mean 79 | 28 † | NS | allopurinol | 4 |
| Park et al. 2012 | 352 | 242 | Scott & White Health Plan, USA | 61.02(15.33)* | 72.4* † | NS | allopurinol, febuxostat, probenecid | 4 |
| Zandman-Goddard et al, 2013 | | 7644 | MHS database, Israel | NA | 72 | NS | allopurinol | 4 |
| Mantarro et al, 2015 | | 3727 | HSD database, Italy | Mean 65 | 80 | NS | allopurinol | 4 |
| Rashid et al, 2015 | | 8288 | Clinical and administrative databases, USA | NA | 79.80 | NS | allopurinol, febuxostat, probenecid | 4 |
| Kuo et al, 2015 | | 49395 | GPRD database, UK | NA | NA | NS | ULT | 4 |
| Riedel et al, 2004 | 9482 | 5597 | IPA plans, USA | 51(11)* | 82.1* | NS | allopurinol | 4 |
| **Pill counts** | | | | | | | | |
| Lee et al, 2016 | | 132 | Outpatient clinic, Korea | 51.9 (10.4) | 100 | 100.0(89.1)[§] | allopurinol, febuxostat | 2 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Self-report** | | | | | | | | |
| Silva et al, 2010 | | 34 | Outpatient, Spain | 57.1(11.8) | 94.1 † | NS | allopurinol, benzbromarone | 1 |
| Singh et al, 2016 | 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 | 60 | 56 | Community pharmacies, New Zealand | Mean 61* | 90* | NS | allopurinol | 2 |
| Sheng et al, 2014 | 161 | 80 † | Gout Clinic, China | NA | NA | NS | ULD | 1 |
| van Onna et al, 2015 | 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)

ULT:urate-lowering therapy; yr: year; mos: months; NS: not stated; NA: not applicable; cross: cross-sectional; ULD:urate-lowering drugs

**Table 1B.** Definitions, cutpoints, and percent adherence/compliance across studies. Studies were placed into subgroups according to the method used to measure adherence. Scale and cutpoints used to rate adherence are also shown.

| Studies | Outcome | Definition/scale | Cutpoint for Adherence/compliance | Adherence % |
|---|---|---|---|---|
| **Prescription claims** | | | | |
| Sarawate et al, 2006 | 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 | 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 | 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 | compliance | MPR: sum of days supply from first observed allopurinol fill during the 2-year | MPR ≥80 % | 44 |

| | | | | |
|---|---|---|---|---|
| | | observation period]/[number of days between the first observed fill and the end of the post-index period. | | |
| Rashid et al, 2012 | adherence | Adherence was measured using the MPR over the follow up time period. | MPR >80 % | 47.5† |
| Horsburgh et al, 2014 | 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 | adherence | Self-report adherence to ULT. | MPR ≥0.80 | 32.6† |
| McGowan et al, 2016 | 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 | adherence | MPR summarized the proportion of days a patient has a supply of medications for. | MPR ≥80 % | 83.5 |
| Solomon et al, 2008 | 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 | adherence | PDC defined as the number of days during the study period (365 days) that the patient had at least 1 gout-specific medication on hand. | PDC ≥ 80% | 26.9† |

| | | | | |
|---|---|---|---|---|
| Zandman-Goddard et al, 2013 | 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 | 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 | 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 | 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 | compliance | Compliance was defined for each prescription period as the presumed use of allopurinol on at least 80% of the days of that period.cc | Compliance rate ≥ 80% | 18 |
| **Pill count** | | | | |
| Lee et al, 2016 | compliance | Pill counts: noncompliance was defined as <80% of the prescribed dose taken. | Pill count ≥ 80% | 71.2 |

| | | | | |
|---|---|---|---|---|
| **Self-report** | | | | |
| Silva et al, 2010 | compliance | Compliance defined as taking medication regularly, as prescribed. | NS | 53† |
| Singh et al, 2016 | adherence | Number of days the patient forgot to take ULT in the last month. | Adherence >0.80 | 78.5 |
| Tan et al, 2016 | adherence | MMAS-8 used to measure medication adherence.(8 items, total score ranges 0-8) | MMAS-8 score≥6 (75%) | 61.9 |
| **Interview** | | | | |
| Martini et al, 2012 | compliance | Participants admitted to not taking ULTs as prescribed. | NS | 79 |
| Sheng et al, 2014 | 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 | 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.

MPR: medication possession ratio; ULT:urate-lowering therapy; UALT: uric acid lowering therapy; PDC:proportion of days covered; MMAS-8:8-item Morisky Medication Adherence Scale; NS: not stated

**The rate of adherence to ULT among gout patients.**

Adherence rate to ULT ranged from 17% to 83.5% in individual studies (Table 1B). Overall, 47% of gout patients were adherent to ULT (95% CI, 42%-52%, $I^2$ = 99.7%) (Figure not shown). The rate of adherence to ULT was 42% (95% CI, 37%-47%, $I^2$ = 99.8%) according to prescription claims. Adherence rate was 71% (95% CI, 63%-79%) for pill count, 66% (95% CI, 50%-81%, $I^2$ = 86.3%) for self-report and 63% (95% CI, 42%-83%, $I^2$ = 82.9%) for interview, respectively (Figure 2). Regression analysis revealed no statistically significant difference among methods used to measure percentage of adherence ($P$ = 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, showed that our results were not driven by any single study (Figure not shown). The summary of meta-analysis and heterogeneity assessments was described in Table 2. The subgroup analysis of adherence rate to ULT estimates were conducted according to measurement methods, publication year, country of origin, data sources, representativeness of the sample, sample size, cutpoint, 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%–81%) vs 40% (95% CI, 33%-47%), vs 44%(95% CI, 40%-49%), vs 56% (95% CI, 17%-96%) from America, Europe and Asia, respectively]. The

subgroup analysis for measurement methods, publication year, data sources, representativeness of the sample, sample size, cutpoint, and overall quality showed no clear patterns.

**Table 2**. Summary of adherence rate and heterogeneity findings.

| Outcomes | No. of studies | No. of participants | Adherence, % (95% confidence intervals) | Heterogeneity | | Test for overall effect | |
|---|---|---|---|---|---|---|---|
| | | | | *P*-value | $I^2$(%) | Z | *P*-value |
| **Overall** | 22 | 137699 | 47(42, 52) | 0.000 | 99.7 | 18.66 | 0.000 |
| **Measurement methods** | | | | | | | |
| Prescription claims | 16 | 137134 | 42(37, 47) | 0.000 | 99.8 | 15.61 | 0.000 |
| Pill count | 1 | 132 | 71(63, 79) | - | - | 18.06 | 0.000 |
| Self-report | 3 | 376 | 66(50, 81) | 0.001 | 86.3 | 8.40 | 0.000 |
| Interview | 3 | 148 | 63(42,83) | 0.003 | 82.9 | 6.09 | 0.000 |
| **Publication Year** | | | | | | | |
| 2010s | 6 | 41766 | 34(26, 43) | 0.000 | 99.7 | 8.22 | 0.000 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 2010- | 16 | 95923 | 53(47, 60) | 0.000 | 99.7 | 15.95 | 0.000 |
| **Country of origin** | | | | | | | |
| America | 11 | 59888 | 40(33, 47) | 0.000 | 99.6 | 11.82 | 0.000 |
| Oceania | 2 | 788 | 78(75, 81) | 0.860 | 0 | 52.97 | 0.000 |
| Europe | 5 | 69076 | 44(40, 49) | 0.000 | 98.0 | 19.62 | 0.000 |
| Asia | 4 | 7947 | 56(17, 96) | 0.000 | 99.4 | 2.81 | 0.000 |
| **Data sources** | | | | | | | |
| Database | 14 | 13700 | 40(34, 45) | 0.000 | 99.8 | 13.48 | 0.000 |
| Non-database | 8 | 699 | 65(54, 75) | 0.000 | 89.2 | 11.81 | 0.000 |
| **Representativeness** | | | | | | | |
| Mulitiple sites | 17 | 137319 | 44(39, 50) | 0.000 | 99.8 | 15.79 | 0.000 |
| A single site | 5 | 380 | 60(43, 76) | 0.000 | 92.1 | 7.04 | 0.000 |
| **Sample size** | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ≥ 200 | 15 | 137251 | 42(36, 48) | 0.000 | 99.8 | 14.55 | 0.000 |
| < 200 | 7 | 448 | 62(48, 75) | 0.000 | 89.3 | 9.12 | 0.000 |
| **Cutpoint** | | | | | | | |
| ≥80% | 18 | 137517 | 45(40, 51) | 0.000 | 99.7 | 16.70 | 0.000 |
| ≥75% | 1 | 19 | 62(52, 72) | 0.004 | 77.8 | 7.54 | 0.000 |
| NS | 4 | 182 | 60(45, 76) | - | - | 12.16 | 0.000 |
| **Quality** | | | | | | | |
| ≥3 points | 15 | 137251 | 42(36, 48) | 0.000 | 99.8 | 14.55 | 0.000 |
| <3points | 7 | 448 | 62(48, 75) | 0.000 | 89.3 | 9.12 | 0.000 |

**Publication bias**

According to the Egger's test, there was no significant evidence of publication bias in overall analyses, in study reporting adherence according to prescription claims, self report and interview [Egger: bias = 5.42 (95% CI: -6.55, 17.39), *P* = 0.356; Egger: bias = 4.32 (95% CI: -16.55, 25.18),

*P* = 0.664; Egger: bias = -4.92 (95% CI: -20.50, 10.66), *P* = 0.155; Egger: bias = -2.02 (95% CI: -70.13, 66.08), *P* = 0.770, respectively] (Figure not shown).

## DISCUSSION

To our knowledge, this systematic review and meta-analysis of 22 studies involving 137699 adult gout patients is the first to quantify adherence and to seek a relationship between adherence and the method used to measure it.

Overall, 47% of adult gout patients adhered to ULT. Majority of studies using prescription claims to report adherence to ULT were presented in 42% among gout patients (16 of 22). The rate of adherence to ULT was 71%, 66%, and 63% for pill count, self report and interview, respectively. According to the adherence rate from high to low on the measurement methods to sort, followed by pill count, 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% are 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 an additional studies. Importantly, the previous review did not quantify adherence. In our meta-analysis, most studies used a cutpoint of ≥80% to define adherent patients. Data on persistence, discontinuation,

switching, treatment gap or retention rate, and adherence to nonmedical therapy (e.g., diet recommendations) were excluded.

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

This meta-analysis indicated significant difference in adherence in claims database, especially from the USA, and also from 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) vs. government funded; primary care vs. secondary care, as well as severity of gout and age of patients (older typically will have higher adherence). This could also have an impact on the findings.

The adherence rate is surprisingly low considering ULT does not have significant side effects or require taking tablets several times a day. It could be that patients don't think it is necessary to always take urate-lowering agents (ULA) since they may feel asymptomatic most of the time.

It could also be that ULA are not included in the medical insurance, while the price is higher, long-term use of ULA will cause a greater financial burden on gout patients.

Because of the low adherence with ULT, it is particularly important to carry out 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[39]. Abhishek 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 interventions such as these could improve adherence to ULT and, ultimately, result in optimal gout-related outcomes.

There are, however, additional important shortcomings in the evidence on adherence to ULT in adult gout patients that need to be addressed. First, a substantial amount of the heterogeneity among the studies remained unexplained by the variables examined. Unexamined factors, such as gender, age, disease duration, study design might contribute to the risk for adherence to ULT among gout patients. Second, due to lack of access, our search did not include the EMBASE database and Cochrane database library, and several studies that referred to medications unspecified ULT were excluded, which could bias the findings.

**CONCLUSION**

The rate of adherence to ULT was low in adult gout patients, with overall adherence rate of 47%. It indicated that clinicians should pay more attention to medication adherence in gout patients, in order to identify effective strategies for improving adherence to ULT among adult gout patients.

**Acknowledgments**

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**Competing interests**

The authors declared that they have no competing interests.

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**Authors' contributions**

RY and LL searched and checked the databases according to the inclusion and exclusion criteria, extracted the data and assessed their quality, analyzed 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.

**Ethics approval and consent to participate**

Ethical approval and consent to participate are not required for this review.

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**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 remainder 37 studies were assessed for eligibility and 15 studies were excluded. Finally 22 studies were included in the quantitative synthesis (meta-analysis).

**Figure 2.** Meta-analysis of percent of adherent patients by method used to measure adherence.

**Additional file 1**: Search strategy.

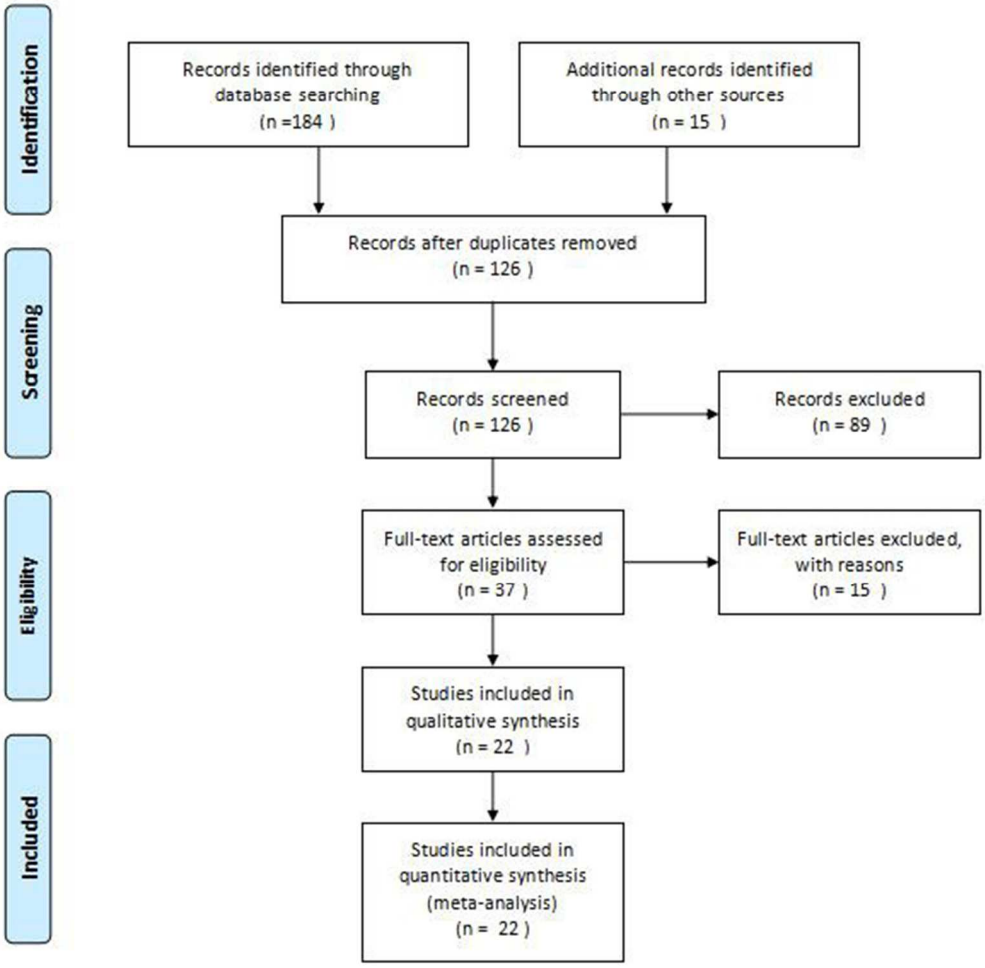


Figure 1. Flow-chart illustrating the article search process. First, we obtained 184 records identified through database searching, and 15 additional records identified through other sources. Second, 126 records remained after duplicates were removed. Third, 89 studies were excluded after records screening.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

49x48mm (300 x 300 DPI)

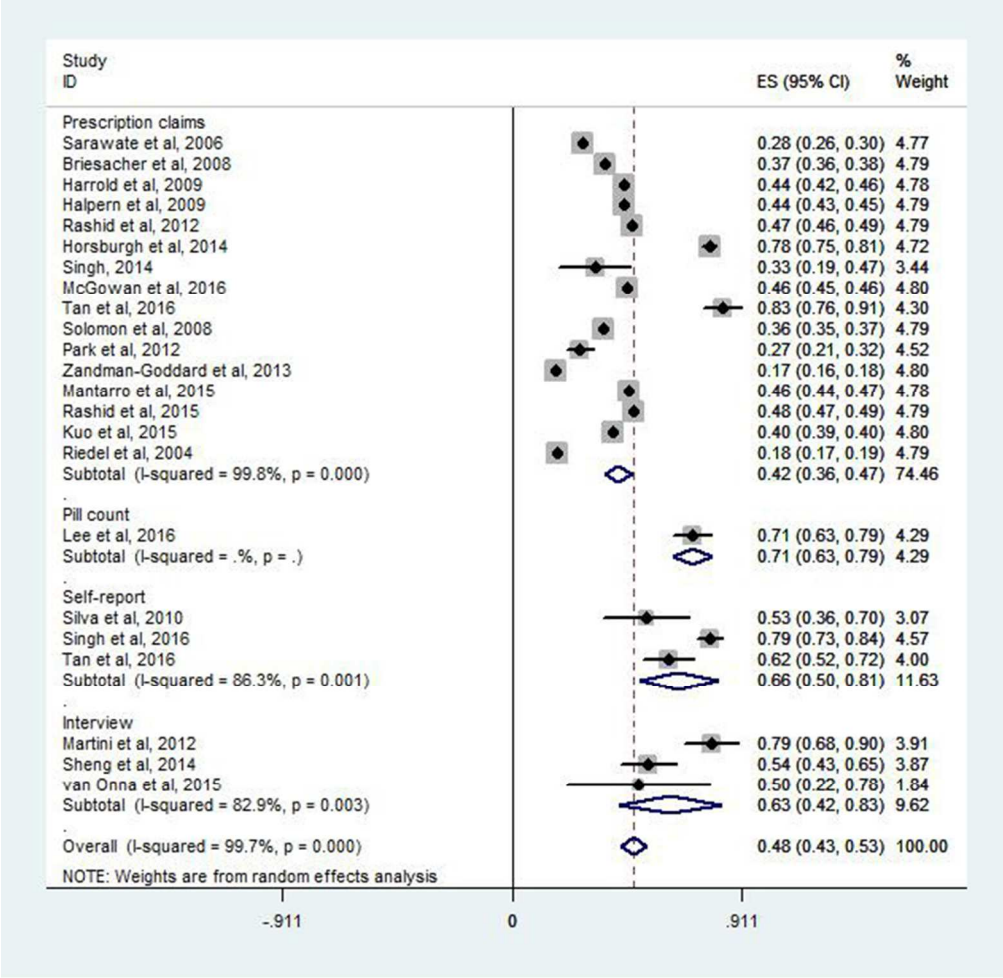


Figure 2. Meta-analysis of percent of adherent patients by method used to measure adherence.

53x52mm (300 x 300 DPI)

# **Additional file 1**: Search strategy

PubMed/Web of Science:

（adherence OR compliance）AND urate-lowering therapy AND gout

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2-3 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 4 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 4 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 5 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 6 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 5 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 5-6 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 6 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 7 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 7 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 7 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 8 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 8 |

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 8 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 8 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 9 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 9-13 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 9-13 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 13-16 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 17 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 20-21 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 17-20 |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 21-23 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 23 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 23-24 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 24 |

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