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Review Article

Clinical interventions to improve adherence to urate-lowering therapy in patients with gout: a systematic review

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Abstract

The aim of this study was to systematically review and compare the quantitative effect of clinical interventions designed to improve adherence to urate-lowering therapy. MEDLINE, Embase, CINAHL, Scopus and Web of Science were searched for interventional studies reporting quantitative adherence to urate-lowering therapy information as an endpoint. Intervention details, quantitative adherence information, clinical outcome and cost-effectiveness data were extracted. Risk of bias was assessed. From 4721 records, 11 studies (3 randomised and 8 observational) met the inclusion criteria. Pharmacist- and nurse-led interventions were described, involving a mixture of patient education, telephone or mobile texting reminders, and medication blister packing. Quantitative adherence information was obtained using methods such as patient self-reporting and pharmacy-dispensing data. Most studies had a moderate-to-high risk of bias. Two of the three randomised studies reported improvement in adherence between the intervention and control groups, including a 13% increase in the mean proportion of days covered >0.8 [341/681 participants (50%) versus 289/782 participants (37%)] and an 88% increase in achieving a high MedicineTaking Behaviour questionnaire score [37/42 participants (88.1%) versus 0/40 participants (0%)]. Four of the eight observational studies reported improved adherence from baseline (ranging from 33% to 91% based on the longitudinal change in adherence metrics reported). A comparison of the different types of interventions was not feasible due to the heterogeneity between study designs and adherence metrics used. These findings support the need for more interventional studies to be conducted to aid adherence management.

Keywords: gout; interventions; adherence; urate-lowering therapy; clinical management

Introduction

Gout is an acute inflammatory arthritis mainly affecting men and postmenopausal women.[1] It is caused by the deposition of monosodium urate crystals in and around joints resulting in an acute inflammatory response, known as a gout flare. They are characterised by swollen acutely painful joints, erythema and restricted movement.[1] Poorly managed gout can lead to joint destruction, deposition of urate crystals in joint spaces (tophi) and permanent disability.[1, 2]

One of the main risk factors for gout is prolonged and elevated serum urate concentrations (i.e. hyperuricemia). A sustained reduction of serum urate concentrations below the recommended target of 0.36 mmol/l (6 mg/dl) is critical to the long-term management of gout as it allows for dissolution of urate crystals, reduction in acute gout flares, and resolution of gouty tophi.[3, 4] With adequate treatment, including long-term use of urate-lowering medications (e.g. allopurinol, febuxostat), gout is an eminently curable condition.

Despite the availability of effective treatment options, however, there is a missed opportunity for successful gout management predominantly due to poor adherence to therapy. Gout is considered to have particularly poor adherence rates, even among chronic conditions with long asymptomatic phases.[5] One systematic review found that only 10-46% of patients took their urate-lowering therapy as prescribed >80% of the time, based on electronic prescription records.[6] Poor adherence has been shown to be a major source of between- and within-subject variability in urate-lowering therapy response contributing to inadequate urate control and poor treatment outcomes.[7] Faced with a patient who is not responding adequately to therapy, the treating clinician may decide to increase the dose or switch to a different medication. In the case of poor adherence, this management decision may be unnecessary and/or inappropriate.

To aid adherence management, there is a need to better understand clinical and behavioural interventions designed to improve adherence. It is currently unclear which interventions are most effective in improving adherence to urate-lowering therapy and which are economically sustainable. Therefore, the aims of this systematic review are to; (1) systematically review and assess the quantitative impact of clinical interventions on adherence to urate-lowering therapy and (2) determine which types of interventions are most effective for improving adherence.

Methods

A systematic review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.[8] The PRISMA 2020 checklist item is shown in Supplementary Table A1. The protocol was registered in the Prospero International Prospective Register of Systematic Reviews (registration number: CRD 42021268226).

Eligibility criteria

Studies were included in the systematic review if they (1) involved patients with an underlying confirmed diagnosis of gout who were prescribed urate-lowering therapy, (2) described an intervention with a stated outcome to improve patient adherence to urate-lowering therapy, (3) reported quantitative adherence information (examples of methods include participant-reported adherence, pill counts, pharmacy dispensing data, and electronic monitoring devices) and (4) reported within an original published journal article or conference abstract. Follow-up studies were also included. There was no limit set on the year of publication, language of publication and study design.

Studies that did not measure or report the outcome of interest (i.e. a quantitative adherence information), editorials and review papers were excluded. Review papers and editorials were however used for citation mining.

Information sources

The following databases were searched for any relevant literature (including grey literature): Ovid MEDLINE, Ovid Embase, EBSCOhost CINAHL, Scopus and Web of Science. The searches were conducted from the start date of the respective databases to March 2021. Alerts were set up in each database to keep updated with newly published articles corresponding to the saved search strategies. Each database was last searched or consulted in October 2021. Database searches were complemented by citation searching from relevant reports identified from the screening process. Types of references examined included citations in systematic reviews covering a similar topic.

The following registers were searched in April 2021 for registered trials or studies that may be otherwise unpublished: Australian New Zealand Clinical Trials Registry (ANZCTR), Clinicaltrials.gov, and the Cochrane Central Register of Controlled Trials (CENTRAL). Each source was last consulted in October 2021.

Search strategy

Search keywords and strategies were developed with the assistance of a librarian and included 'gout', 'inflammatory arthritis', 'uric acid', 'urate', 'urate lowering therapy', 'gout suppressant', 'allopurinol', 'febuxostat', 'probenecid', 'benzbromarone', 'intervention', 'management' and 'self-management'. The search was intended to capture all gout-related intervention studies in the screening process, even where adherence was not a primary outcome, therefore search terms pertaining to 'adherence' were not included in the search keywords. Respective database-specific vocabulary (e.g. Medical Subject Headings) were used where permitted in databases such as Ovid MEDLINE, Ovid Embase, and CINAHL. Advanced search strategies were used for all searches conducted. The database searches were also limited to only human studies.

The search strategy for each of the five databases is presented in the supplemental material (Supplemental tables, Tables A2, A3, A4, A5, and A6). The search strategy for each of the three registers is provided in the supplemental material (Supplemental tables, Tables A7, A8, and A9).

All searches were conducted by one of the authors (KS) and subsequently checked by a co-author (DW). The EndNote X9 Reference Manager software (Clarivate Analytics, Philadelphia, PA, USA) was used to manage all records exported from the database and register searches. Any duplicate reports were removed. The duplicate removal process was conducted by KS.

Selection process

Following the duplicate removal process, records were screened based on the relevance of the study title and abstract to the research question. Reports that met the inclusion criteria were subjected to a full-text review and assessed against the inclusion/exclusion criteria. Authors were contacted by email if further information was needed to clarify the inclusion decision.

Two reviewers (KS and JSC) independently screened each record retrieved based on the study title and abstract. If required, any disagreements were resolved by referral to a third independent reviewer (DW) until consensus was reached.

The full text of eligible reports was independently assessed by two reviewers (KS and DW). If necessary, any disagreements were resolved by referral to a third independent reviewer (SS) until consensus was reached. There were no records screened or assessed by full text that required translation into the English language to determine eligibility.

Data collection process

An electronic data extraction form was created to capture and record all applicable information from each eligible study. Two independent

reviewers (KS and JSC) captured all pertinent data from included studies directly into the customised form. If needed, any disagreements were resolved by referral to a third independent reviewer (DW) until consensus was reached.

Data items

Any quantitative adherence information for patients taking urate-lowering therapy was considered an eligible outcome. For the purposes of this review, we distinguish the methods used to collect adherence information and the metric used to express the quantitative outcome.

The following are examples of common methods for collecting medication adherence information:

1. Participant-reported adherence.
2. Pharmacy dispensing data or prescription claims data [metric: proportion of days covered (PDC) or medication possession ratio (MPR)].[9]
3. Pill counts.
4. Electronic monitoring devices such as a Medication Event Monitoring System (MEMS) consisting of micro-circuitry incorporated into medication packages to detect and record the time and date of opening pill bottles.
5. Measurement of a biological marker (e.g. serum urate concentrations) of treatment response.
6. Direct observed therapy.

There were no restrictions placed on the minimum follow-up time for the outcome measures.

The following data were extracted from the included studies:

1. Article information such as name of the first author, year of publication, study title and country where the study was conducted.
2. Demographics of study participants (age, gender, body mass index and ethnicity).
3. Urate-lowering medication prescribed for the study participants.
4. Details of the study intervention, study design, health professionals involved, duration of the study period and number of study participants.
5. Quantitative adherence metrics reported.
6. Clinical outcomes related to gout therapy including percentage of participants achieving target serum urate concentration, absolute reduction in serum urate concentrations, time to reach target serum urate concentration and frequency of self-reported gout flares.
7. Any cost-effectiveness data.

Relevant authors were contacted to provide clarification of any missing or unclear information. If authors were uncontactable or did not respond, the information was recorded as not available.

Study risk of bias assessment

The Cochrane Risk of Bias tool for randomised trials (RoB 2.0 tool)[10] was used to assess the risk of bias of included randomised studies. The tool addressed five specific domains: (1) bias arising from the randomisation process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in measurement of the outcome and (5) bias in the selection of the reported result. Risk of bias judgements for each domain was recorded as either low, some concerns or high. The overall risk of bias judgement for each study was determined by the highest risk of bias level in any of the assessed domains. Two reviewers (KS, JSC) independently applied the tool to each included randomised study. Any discrepancies in judgements of risk of bias were resolved by referral to independent reviewers (DW, SS and DH) until consensus was reached.

The ROBINS-I (Risk of Bias in Non-randomised Studies – of Interventions) tool[11] was used to assess the risk of bias in non-randomised studies (observational studies). The tool addressed seven specific domains: (1) bias due to confounding; (2) bias due to selection of participants; (3) bias in classification of interventions; (4) bias due to deviations from intended interventions; (5) bias due to missing data; (6) bias in the measurement of outcomes and (7) bias in the selection of the reported result. Risk of bias judgements for each domain was recorded as either low, moderate, serious, critical or no information. The overall risk of bias judgement for each study was determined using the guidance in the ROBINS-I tool document. Two reviewers (KS, JSC) independently applied the tool to each included non-randomised study. Any discrepancies in judgements of risk of bias were resolved by referral to independent reviewers (DW, SS and DH) until consensus was reached.

Reporting bias assessment

Risk of bias due to missing results (arising from reporting biases) was assessed using existing tools: RoB 2.0 tool (relevant domain: bias due to missing outcome data) and ROBINS-I tool (relevant domains: (1) bias due to missing data and (2) bias in the selection of reported result).[10, 11]

For the RoB 2.0 tool, risk of bias judgements for each domain was recorded as either low, some concerns or high. The overall risk of bias judgement for each study was determined by the highest RoB level in any of the assessed domains. In the ROBINS-I tool, risk of bias judgements for each domain was recorded as either low, moderate, serious, critical or no information. The overall risk of bias judgement for each study was determined using the guidance provided in the ROBINS-I tool document.

Two reviewers (KS, JSC) independently applied the tools to each included study. Any discrepancies in judgements of reporting bias assessment were resolved by referral to independent reviewers (SS, DW and DH) until consensus was reached.

Certainty assessment

The certainty of evidence (i.e. similarity of measured effect on adherence to the true adherence) for each adherence outcome in the randomised studies was evaluated independently by two researchers (KS, DW) using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[12] Five domains were used for assessing the certainty of evidence by each outcome: (1) risk of bias, (2) inconsistency, (3) indirectness, (4) imprecision and (5) publication bias. The final level of certainty was assessed as either very low, low, moderate, or high. The following criteria were considered for upgrading the certainty of evidence, if applicable: large effects, dose–response, and opposing plausible residual bias and confounding. Decisions to up- or down-grade the certainty of studies were justified using footnotes. Any disagreements in judgements were resolved by referral to a third independent reviewer (SS) until consensus was reached.

Synthesis methods and data analysis

Randomised studies were analysed separately from observational studies

Quantitative adherence information was analysed by meta-analysis if feasible. Should a meta-analysis not be possible, the quantitative adherence information was synthesised narratively.

Differences between different types of interventions on adherence were assessed by grouping the interventions into related services (educational, point of care, technology-based applications, reminder services) and comparing the reported adherence rates.

Clinical outcomes related to gout management from included studies were summarised. These included the percentage of participants achieving target serum urate concentrations, absolute reduction in serum urate concentrations, time to reach target serum urate concentration and frequency of self-reported gout flares.

Unpublished trials were reviewed, however were not eligible for inclusion.

Results

Study selection

A total of 8147 records were identified from databases, registers, and citation searching. Following the duplicate removal process, 4721 records were screened based on the study title and abstract. A total of 80 reports qualified for full-text assessment; of which, 18 reports consisting of 11 studies and four unpublished trials met the eligibility criteria. A total of 62 reports were excluded after full-text assessment, details as follows: (1) 47 reports did not provide quantitative adherence information, (2) 13 reports were review papers and (3) two reports had no response from authors when contacted (multiple attempts) for further clarification on intervention details and therefore were excluded. Of the 11 included studies,[13–23] three were randomised studies (two as conference abstracts), and eight were observational (one conference abstract). Details of the study selection workflow are presented in Figure 1.

Study characteristics

Details of the included studies are summarised in Table 1. The studies were conducted in New Zealand, the UK, Thailand, Canada, the USA, Singapore, Spain and South Korea. The study duration ranged from 3 to 36 months. Interventions were administered by pharmacists, nurses and rheumatologists. The clinical interventions included gout education, telephone and mobile texting reminders, and medication blister packing. Two studies[13, 17] were follow ups from original interventions that assessed urate-lowering therapy persistence rates. Out of 11 studies, 4 used allopurinol as their urate-lowering therapy,[14, 15, 19, 20] while 3 studies used a combination of allopurinol and other therapies such as febuxostat, benzbromarone and probenecid.[13, 18, 22] The remaining four studies did not report the specific urate-lowering therapies prescribed for participants.[16, 17, 21, 23] The baseline demographics of participants across the included studies are presented in Supplementary Table A10.

Adherence metrics used in the studies included participant self-reported data from questionnaires (eight studies), proportion of days covered (PDC) >0.8 (one study) and medication possession ratio (MPR) >0.8 (one study). PDC and MPR were calculated based on pharmacy dispensing data obtained in the respective studies. Some studies designed their own questionnaires to assess participant adherence behaviour while others used validated questionnaires that produced composite scores from ordinal scales (e.g. Medicine Taking Behaviour-Thai, Morisky Compliance Questionnaire, Compliance Questionnaire Rheumatology 5-item and Medication Adherence Report Survey). Details of the questionnaires used across respective studies are summarised in Supplemental Table A11.

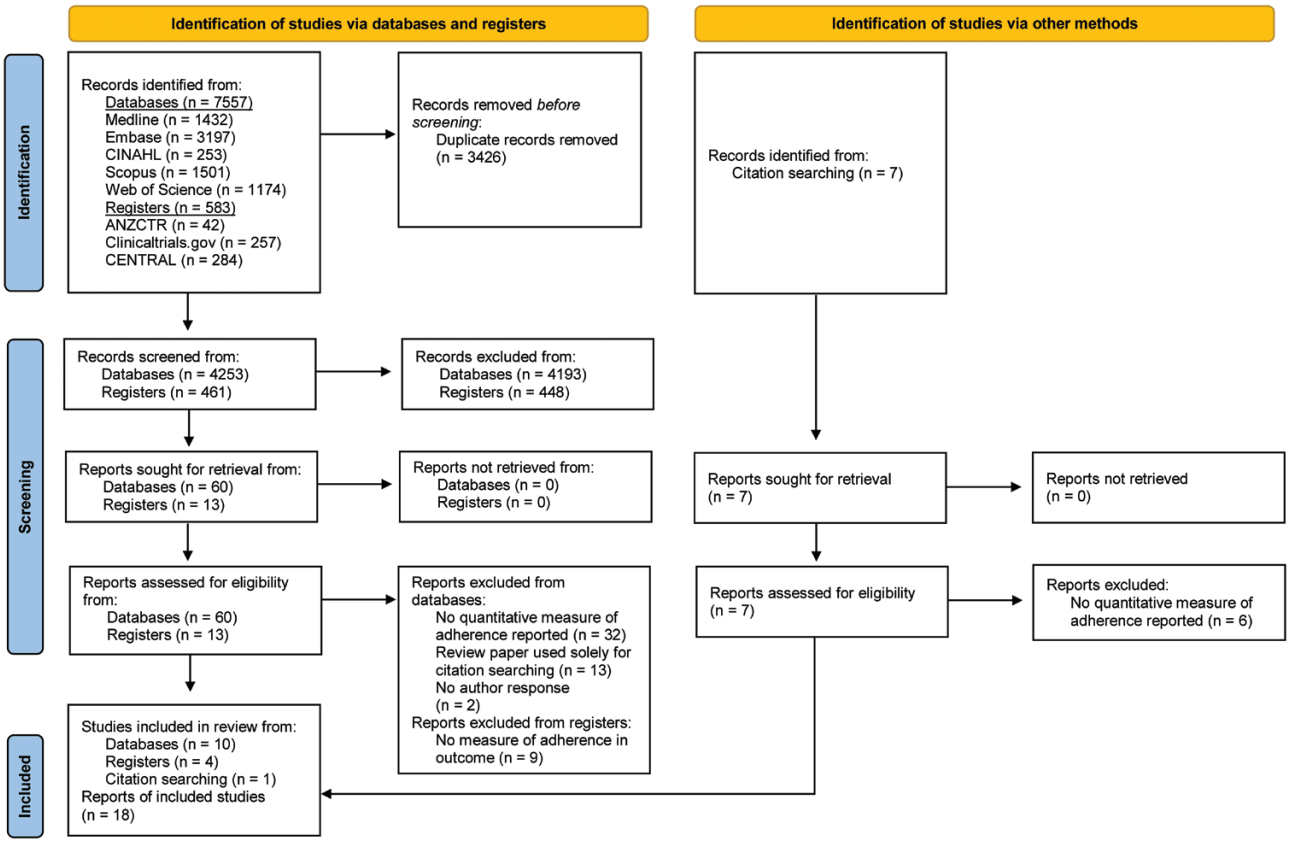

Figure 1. PRISMA 2020 flow diagram for systematic reviews that includes searches from databases, registers and other methods.

Table 1. Details of the interventional studies assessing the impact on adherence to urate-lowering therapy included in the systematic review.

Author, year, country	Design	*N*	Duration, months	Health professional(s)	Intervention details	Quantitative adherence information	Adherence outcome: intervention versus control	Clinical outcome
Bunphong and Narongroeknawin, 2018, Thailand[14]	RCT (Abstract)	82	3	Not reported	Intervention group: daily text message reminders. Control group: weekly messages about non-pharmacological gout treatment.	Method: Patient reported adherence Metric: MTB-Thai score > 21	37/42 (88.1%) versus 0/40 (0%); RR 71.5; 95% CI 4.54, 1126.80; $P = 0.002$. *GRADE rating: Low*[1]	Greater reduction of serum urate concentrations in intervention versus control group −0.09 ± 0.05 versus -0.02 ± 0.02 mmol/l (−1.47 ± 0.86 versus -0.28 ± 0.39 mg/dl), $P < 0.001$.
Mikuls *et al*, 2019, US[20]	RCT	1463	24	Pharmacist	Patient-focused gout education, and allopurinol dose adjustment in intervention group versus usual care in controls. Intervention delivered through a telephone interactive voice recognition system.	Method: Pharmacy dispensing data Metric: Proportion of days covered (PDC)> 0.8 at 1 year.	341/681 (50%) versus 289/782 (37%); OR 1.68; 95% CI 1.30, 2.17; $P < 0.001$. *GRADE rating: Moderate*[2]	Intervention group was more likely to reach target serum urate concentration < 0.36 mmol/l (<6.00 mg/dl) than control group (30% versus 15%; OR 2.37; CI 1.83, 3.05). There was no significant difference between groups in gout flare reduction.
Yoo *et al*, 2017, South Korea[23]	RCT (Abstract)	100	2-3	Nurse	Intervention group: nurse-led education session on the first and second visit. Control group: education session on the second visit (2-3 months from the first visit). Both groups: leaflet for lifestyle advice.	Not reported.*	Improvement in adherence in intervention group from baseline (88.76%) to second visit (92.91%); $P > 0.05$. Control group results were not reported.* *GRADE rating: Very low*[3]	Serum urate concentrations decreased in intervention group; baseline: 0.34 ± 0.10 mmol/l (5.73 ± 1.72 mg/dl) versus second visit: 0.31 ± 0.10 mmol/l (5.09 ± 1.62 mg/dl), $P = 0.032$. Control group results not reported.*
Abhishek *et al*, 2017, UK[13]	Observational (Cross-sectional)	75	60	Nurse	Questionnaire sent to gout patients from another nurse-led intervention study consisting of education, lifestyle advice and an individualised management plan[24] to examine long-term adherence.	Method: Patient-reported adherence Metric: Questionnaire Δ	Five-year ULT persistence was 90.7% (95% CI 81.4, 91.6). 85.3% of participants self-reported taking ULT≥6 days/week.	65/75 participants had mean serum urate concentrations of 0.20 mmol/l (3.31 mg/dl).

Table 1. Continued

Author, year, country	Design	*N*	Duration, months	Health professional(s)	Intervention details	Quantitative adherence information	Adherence outcome: intervention versus control	Clinical outcome
Callear *et al*, 2017, UK[15]	Observational (Quality improvement project)	115	12	General practitioner Nurse Pharmacist	Three phase improvement cycles involving patient education, serum urate monitoring, and medication compliance support.	Method: Patient reported adherence Metric: Interviews	Adherence improved from 63% to 91% (p=0.0001) at baseline and 1 year respectively.	Serum urate concentrations of participants decreased from 0.40 mmol/l (6.67 mg/dl) to 0.32 mmol/l (5.41 mg/dl), *P* = 0.14.
Fields *et al*, 2017,US[16]	Observational	40	12	Nurse Pharmacist Rheumatologist Social worker	Nurse educational intervention through structured gout curriculum and monthly phone calls from pharmacist.	Method: Patient reported adherence Metric: Morisky Compliance Questionnaire	Median Morisky scores at enrolment, 6 months, and 12 months were 3, 4, and 4 respectively with 4 indicating best compliance.	Median serum urate concentrations decreased throughout intervention; baseline: 0.46 mmol/l (7.60 mg/dl), 6 months: 0.33 mmol/l (5.50 mg/dl), and 12 months: 0.31 mmol/l (5.10 mg/dl). Median gout flares decreased from 2 flares at baseline to 1 flare at 6- and 12-month visits.
Fuller *et al*, 2020, UK[17]	Observational (Cross-sectional)	438	Not reported	Nurse General practitioner	Questionnaire sent to gout patients from previous intervention study (nurse-led versus GP-led care)[25].	Method: Patient reported adherence Metric: Questionnaire Δ	ULT persistence higher in nurse-led care group versus GP-led care group (92.7% versus 76.6%). Self-reported adherence of taking ULT≥ 6 days/week was high in both nurse and GP-led groups (97.7% versus 95.8%, *P* = 0.345).	Nurse-led care group had less participants with 2 or more gout flares compared to those in the GP-led care group (8.25% versus 35.10%). Greater reduction in serum urate concentrations in the nurse-led group versus GP-led group -0.11 mmol/l (-1.90 mg/dl) versus -0.10 mmol/l (-1.72 mg/dl).
Howren *et al*, 2017, Canada[18]	Observational (Abstract)	29	12	Rheumatologist Pharmacist Dietician	Follow up consults with rheumatologist, monthly telephone calls from pharmacist, and one telephone consult with a dietician.	Method: Patient reported adherence Metric: CQR5	27 participants completed the CQR5 questionnaire at baseline and 50% were classified as adherent. By 6months, 71% of the participants were considered adherent.	Mean serum urate concentrations decreased over baseline, 3 months, and 6 months from 0.30 mmol/l (5.08 mg/dl), to 0.25 mmol/l (4.24 mg/dl), and 0.24 mmol/l (4.04 mg/dl) respectively.
Lawrence *et al*, 2019, NZ[19]	Observational (Open evaluation)	887	3	Prescriber Pharmacist Community support worker	Free medication blister packing, gout education, and communication with prescribers to address inequitable health outcomes for Māori and Pacific patients.	Method: Patient reported adherence Metric: Interviews	450/887 participants completed the programme. 66% (299/450) continued taking allopurinol following programme completion.	40% of Māori and Pacific participants and 51% of non-Māori and Pacific participants reached their target serum urate concentration < 0.36 mmol/l (< 6.00 mg/dl).

Table 1. Continued

Author, year, country	Design	*N*	Duration, months	Health professional(s)	Intervention details	Quantitative adherence information	Adherence outcome: intervention versus control	Clinical outcome
Perez-Ruiz *et al*, 2020, Spain, France & Ireland[21]	Observational	336	36	Rheumatologist	Rheumatologist-led education sessions to empower and educate patients.	Method: Electronic database Metric: Medication possession ratio (MPR) > 0.8	MPR> 0.8 at baseline, 1 year, 2 years, and beyond 2 years of follow-up were 82.1%, 74.6%, 87% and 86.4%.	None reported.
Phang *et al*, 2020, Singapore[22]	Observational (Quality improvement project)	127	Not reported	Nurse Rheumatologist	Telemedicine intervention to assist in dose escalation of ULT, education, and monitoring of adverse effects.	Method: Patient reported adherence Metric: MARS-5	41/127 participants completed MARS-5. The median MARS-5 score post intervention was 24 with the highest score being 25. No baseline MARS-5 scores were taken.	Median time to reach target serum urate concentration was 19 weeks (IQR 11-31).

*No response from authors when contacted for clarification.

ΔSelf-designed questionnaires.

UK, United Kingdom; US, United States; RCT, randomised controlled trial; N, number of participants; ULT, urate-lowering therapy; MTB-Thai, Medicine Taking Behaviour Thai questionnaire; CQR5, Compliance Questionnaire Rheumatology 5-item; MARS-5, Medication Adherence Report Survey; CI, confidence interval; RR, relative risk; OR, odds ratio; GP, general practitioner; IQR, interquartile range; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation approach.

[1]Level of evidence downrated from high to low due to risk of bias and imprecision.

[2]Level of evidence downrated from high to moderate due to risk of bias.

[3]Level of evidence downrated from high to very low due to risk of bias, imprecision, and publication bias.

Details of included unpublished clinical trials are presented in Supplemental tables, Table A12. Most of the interventions targeted adherence to urate-lowering therapy as their primary outcome. Examples of interventions currently being investigated in registered (but unpublished) studies include (1) participant access to a technology-based application tailored to support long-term adherence and gout self-management, (2) a behavioural cue-reward intervention that targets healthy habit formation to improve medication adherence, (3) use of urate self-testing kits to support self-management of gout and (4) a storytelling intervention/narrative video to improve medication adherence through gout education. Two out of four trials are examining adherence to urate-lowering therapy using the Medication Event Monitoring System (MEMS) consisting of microcircuitry incorporated into medication packages to detect and record the time and date of opening of pill bottles.[26] Other quantitative methods for determining adherence behaviour included plasma oxypurinol concentrations (the active metabolite of allopurinol, used as a measure of drug exposure), and participant-reported adherence. The status of most trials is currently active (not recruiting) with estimated completion dates within 2022. Note that these studies were not included in the synthesis reported below.

Synthesis of studies

Due to the paucity of randomised studies (n = 3) and high heterogeneity across interventions and adherence metrics, a meta-analysis was not performed. Data were tabulated and synthesised narratively. Randomised studies were analysed separately from observational studies. A comparison of the different types of interventions to determine the effect in improving adherence was not feasible due to high heterogeneity between studies and adherence metrics used (not one study used the same adherence metric).

The findings from the three randomised studies are provided in Table 1. In one study, a pharmacist-led educational and allopurinol dose-adjustment intervention, delivered through a telephone interactive voice recognition system, was found to improve the mean proportion of days covered (PDC) by 13% (50% versus 37%, P < 0.001) compared with the control group, and participants receiving the intervention had an increased likelihood of reaching target serum urate concentrations (<0.36 mmol/l) compared with the control group (30% versus 15%, P < 0.001).[20] When estimating PDC, it was not reported if this metric was able to distinguish between participants who persisted with treatment versus those who discontinued therapy. Another study found that 88% of participants in the intervention group managed to achieve a Medicine Taking Behaviour-Thai score of >21 (the threshold for 'good' adherence) after receiving a text reminder service, compared with 0% in the control group.[14] Participants in the same study also had a greater reduction in serum urate concentrations versus the control group (–0.08 versus –0.02 mmol/l, P < 0.001).[14] A nurse-led face-to-face gout education intervention was found to improve adherence by about 4% (88.76% versus 92.91%, P > 0.05) from baseline in the intervention group (results for control group not reported).[23] Unfortunately, the methods and metrics used to determine adherence improvement in this study were not stated.

Results from the eight observational studies are also shown in Table 1. Four out of eight studies reported improved adherence from baseline ranging from 33 to 91% based on the longitudinal change in adherence metrics reported, including questionnaire scores and medication possession ratio (MPR) > 0.8. As an indicative example, a study involving the intervention 'Gout Stop Programme' found that following programme completion of 3 months, 66% of their participants continued taking their urate-lowering therapy (i.e. allopurinol).[19] Another nurse-led, rheumatologist-assisted telemedicine intervention that assessed urate-lowering therapy adherence using the Medication Adherence Report Survey (MARS-5) did not take any baseline scores (confirmed through author contact), however did report a relatively high median MARS-5 score of 24 out of 25 post-intervention.[22]

A cost-effectiveness analysis was conducted in an intervention[25] from one included study.[17] Doherty et al found that each Quality-Adjusted Life Year (QALY) gained in a nurse-led intervention would cost over £5000 (approximately $6600 US).[25]

Risk of bias assessment

The risk of bias results for randomised studies (n = 3) obtained using the RoB 2.0 tool is shown in Figure 2. Two of the three studies scored a high risk of bias[14, 23] while the remaining study was deemed to have 'some concerns' related to risk of bias.[20] The study conducted by Yoo et al.[23] was judged to be at high risk of bias in multiple domains (i.e. domains 2, 3 and 4) as information regarding the study was limited and contact attempts with the authors were unsuccessful. Details in reaching judgements for individual domains are shown in Supplementary Table A13.

The risk of bias for eight observational studies using the ROBINS-I tool are presented in Figure 3. Five out of eight studies were judged to have serious concerns for the overall risk of bias. One study, that was only available in the abstract form, scored a judgement of 'no information'. Attempts to contact the authors for

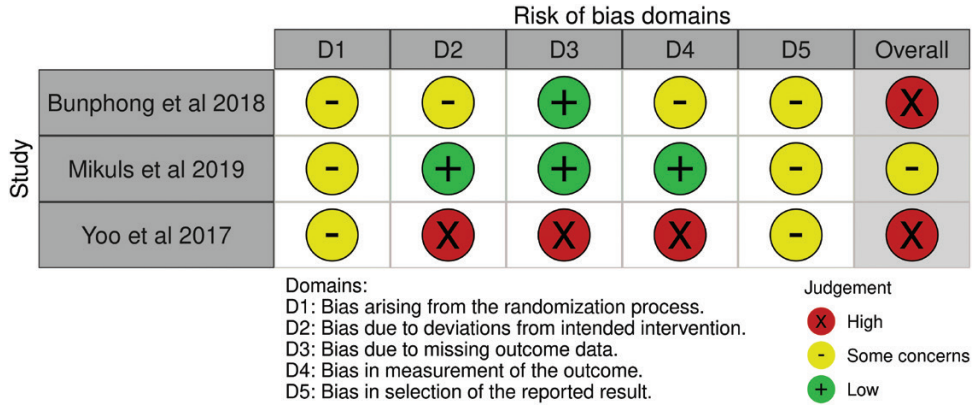

Figure 2. Risk of bias results for randomised studies obtained using the Cochrane Risk of Bias tool for randomised trials (RoB 2.0).

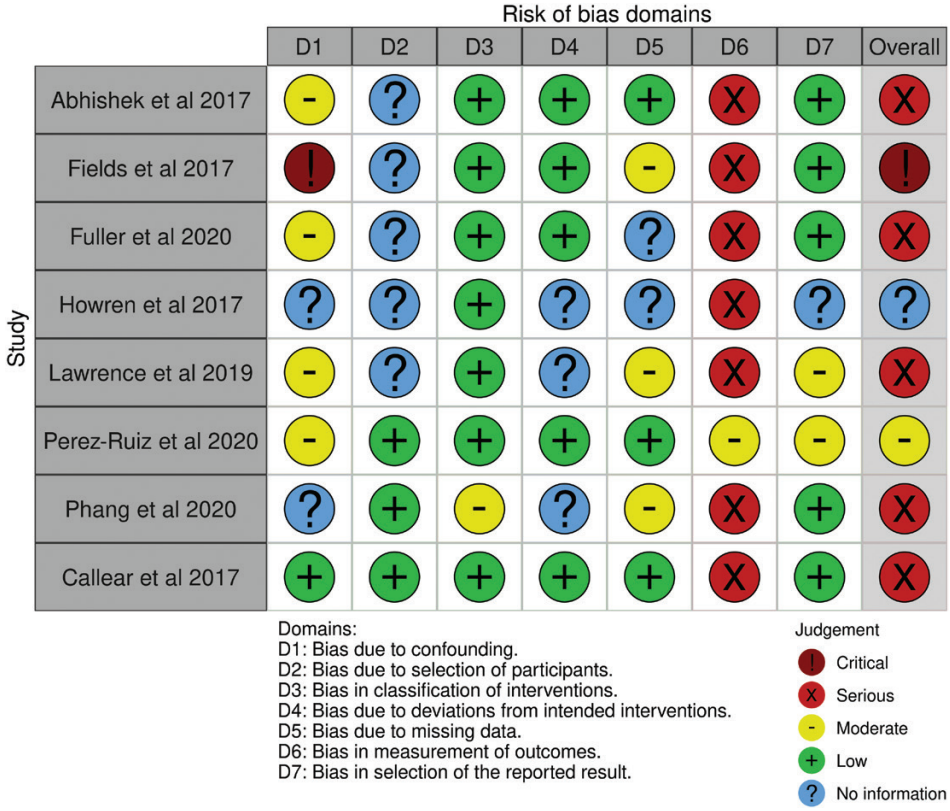

Figure 3. Risk of bias results for non-randomised studies obtained using the ROBINS-I (Risk of Bias in Non-randomised Studies – of Interventions) tool.

more information were unsuccessful. One study was judged to have critical concerns for risk of bias mainly due to the risk of bias from confounding.[16] The details of how judgements were reached for the individual domains including the respective answers from the ROBINS-I tool are shown in Supplementary Table A14.

Reporting biases

Results of reporting biases from included studies are presented in Supplementary Figure A1 and A2 for randomised and observational studies, respectively.

Certainty of evidence

The GRADE ratings for adherence outcomes from the included randomised studies are presented in Table 1. Reasons for downgrading the certainty of studies were justified using footnotes. All three studies[14, 20, 23] downrated at least one level of certainty due to risk of bias. Other reasons for downgrading certainty included imprecision and publication bias. No studies qualified for upgrading of certainty. More details on reaching judgements for certainty of evidence using the GRADE approach are shown in Supplementary Table A15.

Discussion

Although the clinical interventions implemented to date appear to improve adherence to urate-lowering therapy, the evidence base is of low-to-moderate quality. Pharmacist-led, nurse-led and rheumatologist-assisted services have been implemented, with interventions including a mixture of patient education, telephone or text reminders, and free medication blister packing. In addition, a moderate-to-high risk of bias among the studies reviewed was found as well as a large heterogeneity between studies in terms of the interventions used, study designs and outcome measures.

This systematic review should be interpreted in light of some important limitations. The inferences were limited by the quality of the data in the studies reviewed, including a high risk of bias, and inconsistency around the methods used to determine the intervention effect on adherence. It was therefore not possible to identify which types of interventions facilitate sustainable improvements in adherence to urate-lowering therapy and therefore might be preferred in the clinical setting. We observed a large diversity in the metrics used to quantify adherence (e.g. questionnaires), a lack of robust adherence tools to quantify medicine-taking behaviour (e.g. MEMS) and differences in the interventions used. As a result, we were unable to conduct a comparison between different interventions and were unable to conduct a meta-analysis. Our narrative overview of the current state of the literature is therefore limited to an indicative understanding of how interventions will impact the management of adherence. Future work to identify the methods for measuring and reporting adherence in interventional studies seems warranted. Our review was susceptible to publication bias as this was not accounted for during the initial literature search process.

Two recent systematic reviews by Ramsubeik et al.[27] and Gill et al.[28] examined the impact of behavioural and educational interventions on the uptake of urate-lowering therapy in gout patients. Unlike the present review, these reviews focused on clinical endpoints (e.g. absolute reduction in serum urate concentrations, time to reach target serum urate concentration and reduction in gout flares) as the primary outcome of interest. While improved clinical outcomes are paramount in patient care, and increased adherence could be inferred as the driver, there are other factors that could contribute

to improved patient outcomes, such as major alterations in diet and lifestyle, or changes in how comorbidities are managed. Our review was purposely designed to summarise the quantitative impact of interventions on changing adherence behaviour. These data are required to help understand how health services might be implemented to increase drug exposure or improve urate control and will help to identify the typical patterns of poor adherence that might be expected in gout patients. In addition, quantitative adherence data can provide the basis for pharmacometric and pharmacoeconomic models that can predict the pharmacological and economic impacts of clinical services designed to improve adherence.[29] This information is required to enable researchers to determine which services are likely to provide scalable and sustainable adherence support in the clinical setting.

Gout education was incorporated in most of the interventions. Improved knowledge and health literacy in other chronic conditions have been associated with better clinical outcomes and improved adherence to long-term therapy.[30] Indeed, the European League against Rheumatism (EULAR) considers patient education to be a fundamental component of gout management.[31] Notably, the studies reviewed did not include technology-based adherence applications for mobile phones or the use of urate self-testing, designed to empower the patient and support long-term adherence. However, some unpublished studies reviewed in the clinical trial registers (see Supplementary Table A12) are assessing this. These adherence aids are expected to have a positive impact on patient engagement with their gout treatment and may support a long-term improvement in adherence.[32]

Medication adherence is recognised as a behaviour that changes over time, and that encompasses recognisable overall patterns including initiation (when the first dose of a prescribed medication is taken), implementation (a measure of how well a patient's actual dosing regimen matches the prescribed regimen), and discontinuation (marks the end of treatment when a dose is missed and no more doses are taken thereafter).[33] The metrics used to quantify adherence (e.g. proportion of days covered (PDC) > 0.8, medication possession ratio (MPR) > 0.8 or adherence questionnaire scores) in the studies reviewed provide an aggregate summary of adherence behaviour over a period of time and are unfortunately unable to distinguish these different patterns. The pattern of adherence may influence the type of clinical intervention required. For example, a patient who is taking their medicines erratically (either purposely or not) may require a different intervention from one who has decided to stop taking the medicine. Adherence measurement methods such as a Medication Event Monitoring System (MEMS), which can detect and record the opening of pill bottles through a microcircuitry system, would help distinguish between these recognisable patterns of adherence and ultimately aid in designing interventions targeting the specific phases. The studies reviewed here used self-reported adherence methods which are not considered Gold standard.[34]

Several gaps in knowledge related to adherence research have been identified through this review. There was limited information on the long-term cost-effectiveness of the interventions implemented. Cost-effectiveness analysis will support the scalability and sustainability of any proposed intervention to support adherence management. In general, the long-term impact on health costs for adherence interventions has not been well studied, although there is evidence to suggest that in the field of gout, adherence rates are not sustained post-study suggesting that long-term patient engagement is critical.[20] In this case, joint pharmacometric-pharmacoeconomic modelling offers a promising methodological approach for exploring the viability of gout adherence interventions.[29, 35]

Conclusions

Several clinical interventions designed to improve adherence to urate-lowering therapy have been implemented. Most interventions were focused on increasing contact between the patient and health provider through telephone reminders and visits, providing education and support, and increasing the opportunity for self-care among patients. Outcome measures such as adherence rates have been found to be improved in participants who received the interventions, with low to moderate quality evidence. These findings support the need for more studies to be conducted, including efforts to standardise adherence methods and metrics used across interventions, to enable the comparison of different service models and aid adherence management.

Authors contributions

KAS, DAH and DFBW conceived and designed the systematic review; KAS conducted the literature review; KAS and DFBW drafted the manuscript; KAS and JSC conducted the screening, data extraction, and risk of bias assessments; DFBW reviewed the screening results; SLS, DAH, DFBW reviewed the risk of bias assessments; KAS, SLS, JSC, DAH, DFBW reviewed and drafted the final manuscript.

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Conflict of interest

The author(s) declare that there are no conflicts of interest.

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