Non-steroidal anti-inflammatory drugs for treating symptomatic uncomplicated urinary tract infections in non-pregnant adult women

DOI:
10.1002/14651858.CD014762

Document Version
Final published version

Cochrane Library

Cochrane Database of Systematic Reviews

Non-steroidal anti-inflammatory drugs for treating symptomatic uncomplicated urinary tract infections in non-pregnant adult women (Protocol)

Sachdeva A, Nambiar A, Rai BP, Veeratterapillay R, Harding C

Sachdeva A, Nambiar A, Rai BP, Veeratterapillay R, Harding C.
Non-steroidal anti-inflammatory drugs for treating symptomatic uncomplicated urinary tract infections in non-pregnant adult women (Protocol).
Cochrane Database of Systematic Reviews 2021, Issue 11. Art. No.: CD014762.
DOI: 10.1002/14651858.CD014762.

www.cochranelibrary.com

TABLE OF CONTENTS

[Intervention Protocol]

Non-steroidal anti-inflammatory drugs for treating symptomatic uncomplicated urinary tract infections in non-pregnant adult women

Ashwin Sachdeva[1,2], Arjun Nambiar[2], Bhavan Prasad Rai[2], Rajan Veeratterapillay[2], Christopher Harding[2]

[1]Division of Cancer Sciences, University of Manchester, Manchester, United Kingdom. [2]Department of Urology, Freeman Hospital, Newcastle upon Tyne, UK

Contact: Ashwin Sachdeva, ashwin.sachdeva@gmail.com.

Editorial group: Cochrane Kidney and Transplant Group.
Publication status and date: New, published in Issue 11, 2021.

Citation: Sachdeva A, Nambiar A, Rai BP, Veeratterapillay R, Harding C. Non-steroidal anti-inflammatory drugs for treating symptomatic uncomplicated urinary tract infections in non-pregnant adult women (Protocol). *Cochrane Database of Systematic Reviews* 2021, Issue 11. Art. No.: CD014762. DOI: 10.1002/14651858.CD014762.

ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

This review aims to investigate the benefits and risks associated with the use of NSAIDs in the treatment of symptomatic uncomplicated UTIs in non-pregnant adult women.

BACKGROUND

Description of the condition

Uncomplicated urinary tract infection (UTI) is defined as acute, sporadic, or recurrent cystitis limited to non-pregnant women in the absence of anatomical and functional abnormalities within the urinary tract, involvement of the upper renal tract, or vaginal discharge or irritation (Bonkat 2020). Symptoms of UTI include lower urinary tract symptoms such as dysuria (burning sensation while passing urine), increased urinary frequency, and urgency. The diagnosis of an uncomplicated UTI may be made either on clinical grounds alone or supported by laboratory tests including urinalysis and urine culture. The commonest microbial cause of uncomplicated UTI is *Escherichia coli* (75%), with occasional infections caused by *Klebsiella penumoniae* (6%), *Staphylococcus saprophyticus* (6%), *Enterococcus sp.* (5%), and *Proteus mirabilis* (2%) (Flores-Mireles 2015).

Almost half of all women will have at least one symptomatic UTI in their lifetime (Foxman 2000). Though the vast majority of uncomplicated UTIs are self-remitting, 74% of women contacting a health professional are prescribed an antibiotic (Butler 2015). In rare instances, uncomplicated UTIs may progress to more severe infections including pyrexia (body temperature > 38°C), flank pain or features of systemic illness (e.g. nausea, vomiting, rigors, fatigue), suggestive of development of complicated UTI. Therefore, the standard of care for treatment of symptomatic uncomplicated UTIs is oral antibiotic therapy, which aims to achieve symptom resolution and prevent development of complications such as pyelonephritis.

Description of the intervention

Increasing rates of antimicrobial resistance have prompted a greater need for antibiotic stewardship, and growing interest in the use of non-antibiotic alternatives for the management of UTIs. Previous studies have indicated a willingness amongst patients to delay or avoid antibiotic prescriptions for uncomplicated UTIs, when deemed safe to do so (Knottnerus 2013; Leydon 2010). Given that a number of UTIs are self-remitting, non-antibiotic treatments that may help reduce severity or duration of symptoms, or reduce the need for antibiotics are sometimes indicated.

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely available over-the-counter drugs often used to reduce pain, decrease fever, and reduce inflammation. They may be taken orally, applied topically, or administered intravenously. Their adverse effects include dyspepsia, gastroduodenal ulceration, upper gastrointestinal haemorrhage, and acute kidney injury. Common NSAIDs include ibuprofen, aspirin, diclofenac, and naproxen.

How the intervention might work

The arachidonic acid pathway is central to the inflammatory response, whereby cyclooxygenase (COX, or prostaglandin synthase) enzymes oxidise arachidonic acid to prostaglandins. There are two isoforms of the COX enzyme: COX-1 and COX-2, of which COX-2 plays a more dominant role in prostaglandin formation in inflammation. NSAIDs bind to and inhibit COX enzymes and thereby reduce the production of prostaglandins, which results in a reduced inflammatory response. Based on their specificity, there are two types of NSAIDs: (a) non-specific NSAIDs (such as ibuprofen, aspirin, diclofenac, naproxen, indomethacin), which inhibit both COX-1 and COX-2 enzymes; and (b) COX-2 specific NSAIDs (such as celecoxib), which only inhibits the COX-2 enzyme.

Since the onset of symptoms in uncomplicated UTI is strongly associated with prostaglandin levels (Farkas 1980), the anti-inflammatory effect of NSAIDs on the urothelium is hypothesised to alleviate symptoms of UTI. Furthermore, there is mixed evidence for anti-bacterial properties of NSAIDs (Elvers 1995; Obad 2015; Shah 2018; Whiteside 2019).

Why it is important to do this review

Uncomplicated UTIs are the most common bacterial infections in women, with approximately half of all women developing at least one UTI in their lifetime (Colgan 2011). About 20% to 30% of these women would go on to develop recurrent UTIs (Foxman 2003; Stamm 1991). UTIs in non-pregnant women are mostly self-remitting and rarely progress to upper UTIs, such as pyelonephritis (Czaja 2007; Naber 2011). Thus, the primary treatment goal is to reduce symptoms. Symptoms of UTI may arise from a local increase in inflammatory prostaglandins. Within this context, NSAIDs may be used to reduce symptoms of UTI.

Nevertheless, UTIs account for 10% to 20% of all antibiotic prescriptions in ambulatory care, with the inherent risk of the development of anti-microbial resistance (AMR). Thus, identification of non-antibiotic alternatives to the management of women with uncomplicated UTI may help improve antibiotic stewardship and thereby reduce the risk of development of AMR.

Over the past 10 years, a number of RCTs have reported mixed results regarding the use of NSAIDs in the treatment of uncomplicated UTIs in non-pregnant women. However, a meta-analysis of these studies has previously not been performed. Therefore, this review would help to more reliably estimate the true effect of NSAIDs in this context.

OBJECTIVES

This review aims to investigate the benefits and risks associated with the use of NSAIDs in the treatment of symptomatic uncomplicated UTIs in non-pregnant adult women.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) looking at the effectiveness of NSAIDs in the treatment of symptomatic uncomplicated UTIs.

Types of participants

We included adult non-pregnant women with symptomatic uncomplicated UTIs managed in the outpatient setting. Symptomatic UTI was defined as symptoms including dysuria, urinary frequency, urgency, and suprapubic discomfort. Participants were included regardless of whether the diagnosis was made based on positive urine dipstick results, positive urine culture, or symptoms alone.

Patients with complicated UTI, acute pyelonephritis, recurrent UTIs or other chronic conditions (including interstitial cystitis, painful bladder syndrome, chronic pelvic pain syndrome) were excluded. Complicated UTI was defined as UTI in patients with a structurally or functionally abnormal urinary tract, such as neuropathic bladder, associated urinary tract stones, or previous radiotherapy.

Types of interventions

We included studies where any NSAIDs were used, either alone, or in combination with antibiotics. Variable doses, routes of administration and duration of use were allowed. In addition, studies comparing NSAIDs with either a placebo or other pharmaceutical agents will also be considered.

The following comparisons will be considered.

- NSAIDs versus placebo
- NSAIDs versus antibiotics
- NSAIDs and antibiotics versus antibiotics alone
- NSAIDs versus other pharmaceutical agents
- NSAIDs versus any other treatments.

Types of outcome measures

Primary outcomes

1. Short term resolution of symptoms (days 1 to 4 from randomisation)
2. Medium term resolution of symptoms (days 5 to 10 from randomisation)
3. Incidence of adverse events (including progression to sepsis or complicated UTI, hospitalisation or need for intravenous antibiotics, gastrointestinal complications, or death) up to 30 days from randomisation

Secondary outcomes

1. Duration of symptoms
2. Severity of symptoms
3. Microbiological resolution (by day 10 from randomisation)
4. Use of antibiotic treatment by 30 days of randomisation
5. Emergence of antibiotic resistant bacteria

Search methods for identification of studies

Electronic searches

We will search the Cochrane Kidney and Transplant Register of Studies through contact with the Information Specialist using search terms relevant to this review. The Register contains studies identified from the following sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Searches of kidney and transplant journals, and the proceedings and abstracts from major kidney and transplant conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney and transplant journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of search strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available on the Cochrane Kidney and Transplant website.

See Appendix 1 for search terms used in strategies for this review.

Searching other resources

1. Reference lists of review articles, relevant studies, and clinical practice guidelines.
2. Contacting relevant individuals/organisations seeking information about unpublished or incomplete studies.
3. Grey literature sources (e.g. abstracts, dissertations, and theses), in addition to those already included in the Cochrane Kidney and Transplant Register of Studies, will not be searched.

Data collection and analysis

Selection of studies

The search strategy described will be used to obtain titles and abstracts of studies that may be relevant to the review. The titles and abstracts will be screened independently by two authors, who will discard studies that are not applicable, however studies and reviews that might include relevant data or information on trials will be retained initially. Two authors will independently assess retrieved abstracts and, if necessary, the full text, of these studies to determine which studies satisfy the inclusion criteria. Disagreements will be resolved in consultation with a third author.

Data extraction and management

Data extraction will be carried out independently by two authors using standard data extraction forms. Disagreements will be resolved in consultation with a third author. Studies reported in non-English language journals will be translated before assessment. Where more than one publication of one study exists, reports will be grouped together and the publication with the most complete data will be used in the analyses. Where relevant outcomes are only published in earlier versions these data will be used. Any discrepancy between published versions will be highlighted.

Assessment of risk of bias in included studies

The following items will be independently assessed by two authors using the risk of bias assessment tool (Higgins 2020) (see Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?

- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

For dichotomous outcomes (e.g. presence or absence of symptoms, presence or absence of adverse effects) results will be expressed as risk ratio (RR) with 95% confidence intervals (CI). Where continuous scales of measurement are used to assess the effects of treatment (e.g. severity of symptoms), the mean difference (MD) will be used, or the standardised mean difference (SMD) if different scales have been used.

Unit of analysis issues

Studies with non-standard designs will be analysed in accordance with the Cochrane Handbook of Systematic Reviews of Intervention (Higgins 2020). In studies using a cross-over design, only the first randomisation period will be included as cross-over data would not be appropriate to study the intervention under review. Where trials include multiple treatment groups, data will be split and analysed as individual pair-wise comparisons.

Dealing with missing data

Any further information required from the original author will be requested by written correspondence (e.g. emailing and/or writing to corresponding author) and any relevant information obtained in this manner will be included in the review. Evaluation of important numerical data such as screened, randomised patients as well as intention-to-treat, as-treated and per-protocol population will be carefully performed. Attrition rates, for example drop-outs, losses to follow-up and withdrawals will be investigated. Issues of missing data and imputation methods (for example, last-observation-carried-forward) will be critically appraised (Higgins 2020).

Assessment of heterogeneity

We will first assess the heterogeneity by visual inspection of the forest plot. We will quantify statistical heterogeneity using the I^2 statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than sampling error (Higgins 2003). A guide to the interpretation of I^2 values will be as follows.

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity.

The importance of the observed value of I^2 depends on the magnitude and direction of treatment effects and the strength of evidence for heterogeneity (e.g. P-value from the Chi^2 test, or a confidence interval for I^2) (Higgins 2020).

Assessment of reporting biases

If possible, funnel plots will be used to assess for the potential existence of small study bias (Higgins 2020).

Data synthesis

Data will be pooled using the random-effects model, but the fixed-effect model will also be used to ensure robustness of the model chosen and susceptibility to outliers.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis will be used to explore possible sources of heterogeneity (e.g. participants, interventions, and study quality). Heterogeneity among participants could be related to age, urine culture results, menopausal status, and causative pathogen. Heterogeneity in treatments could be related to prior agent(s) used and the agent, dose, and duration of therapy (e.g. short versus long course of NSAID use, use for non-selective vs COX-2-selective NSAIDs). Adverse effects will be tabulated and assessed with descriptive techniques, as they are likely to be different for the various agents used. Where possible, the risk difference with 95% CI will be calculated for each adverse effect, either compared to no treatment or to another agent.

If the data allows and sufficient studies are identified, we will perform the following subgroup analyses:

- **By patient population**
  - Age (under 65 years versus over 65 years)
  - Urine culture positive versus negative
  - Pre-menopausal vs post-menopausal women
- **By NSAID**
  - Type of NSAIDs (non-selective versus COX-2 selective)
  - Dose and frequency
  - Duration of NSAIDs use
- **By urinary pathogen (in culture positive cases)**
  - *E. coli* versus non-*E. coli* pathogens

Sensitivity analysis

We will perform sensitivity analyses to explore the influence of the following factors on effect size:

- Repeating the analysis excluding unpublished studies
- Repeating the analysis taking account of risk of bias, as specified
- Repeating the analysis excluding any very long or large studies to establish how much they dominate the results
- Repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), and country.

Summary of findings and assessment of the certainty of the evidence

We will present the main results of the review in 'Summary of findings' tables. These tables present key information concerning the certainty of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schunemann 2020a). The 'Summary of findings' tables also include an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach (GRADE 2008; GRADE 2011). The GRADE approach defines the certainty of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. This will be assessed by two

authors. The certainty of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (Schunemann 2020b). We plan to present the following outcomes in the 'Summary of findings' tables.

- Short-term resolution of symptoms (days 1 to 4)
- Medium-term resolution of symptoms (days 5 to 10)
- Incidence of adverse effects
- Duration of symptoms
- Severity of symptoms
- Microbiological resolution
- Use of antibiotic treatment.

ACKNOWLEDGEMENTS

The authors would like to thank the Cochrane Kidney and Transplant group for their help and support in preparing this review protocol.

We wish to thank the peer reviewers for their comments: Lindsay Nicolle, University of Manitoba, Winnipeg Canada; Professor Hugo N Catalano, Hospital Universitario Austral, Argentina; Professor Tom Fahey, RCSI University of Medicine and Health Sciences, Dublin Ireland; Professor Magnus J Grabe, Urology, Lund University, Lund, Sweden.

The Methods section of this protocol is based on a standard template used by Cochrane Kidney and Transplant.

REFERENCES

Additional references

Bonkat 2020

Bonkat G, Bartoletti R, Bruyére F, Cai T, Geerlings SE, Köves B, et al. European Association of Urology Guidelines. 2020 Edition. www.uroweb.org/guideline/urological-infections/ (accessed 25 October 2021).

Butler 2015

Butler CC, Hawking MK, Quigley A, McNulty CA. Incidence, severity, help seeking, and management of uncomplicated urinary tract infection: a population-based survey. *British Journal of General Practice* 2015;**65**(639):e702-7. [MEDLINE: 26412847]

Colgan 2011

Colgan R, Williams M. Diagnosis and treatment of acute uncomplicated cystitis. *American Family Physician* 2011;**84**(7):771-6. [MEDLINE: 22010614]

Czaja 2007

Czaja CA, Scholes D, Hooton TM, Stamm WE. Population-based epidemiologic analysis of acute pyelonephritis. *Clinical Infectious Diseases* 2007;**45**(3):273-80. [MEDLINE: 17599303]

Elvers 1995

Elvers KT, Wright SJ. Antibacterial activity of the anti-inflammatory compound ibuprofen. *Letters in Applied Microbiology* 1995;**20**(2):82-4. [MEDLINE: 7765904]

Farkas 1980

Farkas A, Alajem D, Dekel S, Binderman I. Urinary prostaglandin E2 in acute bacterial cystitis. *Journal of Urology* 1980;**124**(4):455-7. [MEDLINE: 6999176]

Flores-Mireles 2015

Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. *Nature Reviews. Microbiology* 2015;**13**(5):269-84. [MEDLINE: 25853778]

Foxman 2000

Foxman B, Barlow R, D'arcy H, Gillespie B, Sobel J. Urinary tract infection: self-reported incidence and associated costs. *Annals of Epidemiology* 2000;**10**(8):509-15. [MEDLINE: 11118930]

Foxman 2003

Foxman B, Brown P. Epidemiology of urinary tract infections Transmission and risk factors, incidence, and costs. *Infectious Disease Clinics of North America* 2003;**17**(2):227-41. [MEDLINE: 12848468]

GRADE 2008

Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**(7650):924-6. [MEDLINE: 18436948]

GRADE 2011

Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology* 2011;**64**(4):383-94. [MEDLINE: 21195583]

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60. [MEDLINE: 12958120]

Higgins 2020

Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). Cochrane, 2020. Available from www.training.cochrane.org/handbook.

Knottnerus 2013

Knottnerus BJ, Geerlings SE, Moll van Charante EP, ter Riet G. Women with symptoms of uncomplicated urinary tract infection are often willing to delay antibiotic treatment: a prospective cohort study. *BMC Family Practice* 2013;**14**:71. [MEDLINE: 23721260]

Leydon 2010

Leydon GM, Turner S, Smith H, Little P, UTIs Team. Women's views about management and cause of urinary tract infection: qualitative interview study. *BMJ* 2010;**340**:c279. [MEDLINE: 20139217]

Naber 2011

Naber KG, Wullt B, Wagenlehner FM. Antibiotic treatment of uncomplicated urinary tract infection in premenopausal women. *International Journal of Antimicrobial Agents* 2011;**38 Suppl**:21-35. [MEDLINE: 22000072]

Obad 2015

Obad J, Suskovic J, Kos B. Antimicrobial activity of ibuprofen: new perspectives on an "old" non-antibiotic drug. *European Journal of Pharmaceutical Sciences* 2015;**71**:93-8. [MEDLINE: 25708941]

Schunemann 2020a

Schünemann HJ, Higgins JP, Vist GE, Glasziou P, Akl EA, Skoetz N, et al. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). Cochrane, 2020. www.training.cochrane.org/handbook.

Schunemann 2020b

Schünemann HJ, Vist GE, Higgins JP, Santesso N, Deeks JJ, Glasziou P, et al. Chapter 15: Interpreting results and drawing conclusions. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). Cochrane, 2020. Available from www.training.cochrane.org/handbook.

Shah 2018

Shah PN, Marshall-Batty KR, Smolen JA, Tagaev JA, Chen Q, Rodesney CA, et al. Antimicrobial activity of ibuprofen against cystic fibrosis-associated gram-negative pathogens. *Antimicrobial Agents & Chemotherapy* 2018;**62**(3):e01574-17. [MEDLINE: 29311081]

Stamm 1991

Stamm WE, McKevitt M, Roberts PL, White NJ. Natural history of recurrent urinary tract infections in women. *Reviews of Infectious Diseases* 1991;**13**(1):77-84. [MEDLINE: 2017637]

Whiteside 2019

Whiteside SA, Dave S, Reid G, Burton JP. Ibuprofen lacks direct antimicrobial properties for the treatment of urinary tract infection isolates. *Journal of Medical Microbiology* 2019;**68**(8):1244-52. [MEDLINE: 31184571]

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor: [Anti-Inflammatory Agents, Non-Steroidal] explode all trees 2. (non-steroid* next anti-inflammatory next agent*):ti,ab,kw 3. (nonsteroid* next antiinflammatory next agent*):ti,ab,kw 4. (nonsteroid* next anti-inflammatory next agent*):ti,ab,kw 5. (non-steroid* next antiinflammatory next agent*):ti,ab,kw 6. NSAID*:ti,ab,kw 7. aspirin:ti,ab,kw 8. ibuprofen:ti,ab,kw 9. naproxen:ti,ab,kw 10.indomethacin:ti,ab,kw 11.celecoxib:ti,ab,kw 12.salicylate*:ti,ab,kw 13.(salicylic next acid*):ti,ab,kw 14.{OR #1-#13} 15.(urinary next tract next infection*):ti,ab,kw 16.cystitis:ti,ab,kw 17.pyelonephritis:ti,ab,kw 18.bacteriuria:ti,ab,kw 19.pyuria:ti,ab,kw 20.("UTI" or "UTIs"):ti,ab,kw 21.{OR #15-#20} 22.#14 and #21
MEDLINE	1. exp Anti-Inflammatory Agents, Non-Steroidal/ 2. non-steroidal anti-inflammatory agent*.tw. 3. nonsteroidal antiinflammatory agent*.tw. 4. nonsteroidal anti-inflammatory agent*.tw. 5. non-steroidal antiinflammatory agent*.tw. 6. NSAID*.tw. 7. aspirin.tw. 8. ibuprofen.tw. 9. naproxen.tw. 10.indomethacin.tw. 11.celecoxib.tw. 12.salicylate*.tw. 13.(salicylic acid*):ti,ab,kw

(Continued)

	14.or/1-13 15.Urinary Tract Infections/ 16.Bacteriuria/ 17.Pyuria/ 18.Cystitis/ 19.Pyelonephritis/ 20.urinary tract infection*.tw. 21.bacteriuria.tw. 22.pyuria.tw. 23.cystitis.tw. 24.pyelonephritis.tw. 25.(UTI or UTIs).tw. 26.or/15-25 27.and/14,26
EMBASE	1. exp nonsteroid antiinflammatory agent/ 2. non-steroid* anti-inflammatory agent*.tw. 3. nonsteroid* antiinflammatory agent*.tw. 4. nonsteroid* anti-inflammatory agent*.tw. 5. non-steroid* antiinflammatory agent*.tw. 6. NSAID*.tw. 7. aspirin.tw. 8. ibuprofen.tw. 9. naproxen.tw. 10.indomethacin.tw. 11.celecoxib.tw. 12.salicylate*.tw. 13.salicylic acid*.tw. 14.or/1-13 15.urinary tract infection/ 16.cystitis/ 17.pyelonephritis/ or acute pyelonephritis/ or chronic pyelonephritis/ 18.bacteriuria/ 19.asymptomatic bacteriuria/ 20.pyuria/ 21.urinary tract infection*.tw. 22.cystitis.tw. 23.bacteriuria.tw. 24.pyuria.tw. 25.pyelonephritis.tw. 26.(UTI or UTIs).tw. 27.or/15-26 28.and/14,27

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria

(Continued)

Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimisation (minimisation may be implemented without a random element, and this is considered to be equivalent to being random).
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.
	Unclear: Insufficient information about the sequence generation process to permit judgement.
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear: Randomisation stated but no information on method used is available.
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with

(Continued)

	substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. sub-scales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: AS, AN, BPR, RV, CKH
2. Study selection: AS, AN
3. Extract data from studies: AS, AN
4. Enter data into RevMan: AS
5. Carry out the analysis: AS, AN
6. Interpret the analysis: AS, AN, BPR, RV, CKH
7. Draft the final review: AS, CKH
8. Disagreement resolution: CKH
9. Update the review: AS, AN, BPR, RV, CKH

DECLARATIONS OF INTEREST

In accordance with Cochrane's Commercial Sponsorship Policy, the following declarations are applicable for the three years prior to the publication date of this protocol.

- Ashwin Sachdeva has declared that they have no conflict of interest
- Arjun Nambiar has declared that they have no conflict of interest
- Bhavan Prasad Rai has declared that they have no conflict of interest
- Rajan Veeratterapillay has declared that they have no conflict of interest
- Christopher Harding: Allergan Consultant Speaker Honorarium, Medtronic Speaker Honorarium, Proctor Astellas Speaker Honorarium, Teleflex Medical (none of which concern NSAIDs in patients with UTI).

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- No sources of support provided