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D-mannose for preventing and treating urinary tract infections (Protocol)

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[Intervention Protocol]

D-mannose for preventing and treating urinary tract infections

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ABSTRACT

Objectives

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

This review aims to look at the benefits and harms of D-mannose for preventing and treating UTI in adults and children.

BACKGROUND

Description of the condition

Urinary tract infections (UTI) are common in general populations globally. Whilst many people may only experience a single episode in their lifetime (at least 50% of females), approximately 15% to 25% of adults and children (mostly adult women) are chronic symptomatic UTI sufferers under the categories of: recurrent (at least 2 episodes in 6 months or 3 episodes in 12 months); persistent (the same pathogen in urine culture); re-infected (new pathogen in urine culture); or relapsed (initial pathogen in urine culture after it had been eradicated) UTIs. Many cases in clinical practice do not respond to standard antibiotic treatments, creating a significant patient burden and high cost to healthcare systems (Altarac 2014; Rowe 2014).

Symptomatic bacteriuria is the combination of clinical UTI symptoms (including dysuria, urinary frequency, urgency and suprapubic pain, voiding issues, worsening of symptoms), with a positive quantitative urine culture (as confirmed by a catheter specimen of urine, midstream urine specimen if possible, or a clean-catch specimen and defined as > 10^5 colony-forming units (CFU)/mL, or as defined by authors) (Nicolle 2005; Rowe 2014).

Symptomatic UTI is the presence of clinical UTI symptoms (including dysuria, urinary frequency, urgency and suprapubic pain, voiding issues, worsening of symptoms), without a positive quantitative urine culture (Nicolle 2005; Rowe 2014).

Asymptomatic bacteriuria is the presence of bacteria in the urine without signs or symptoms of a UTI (Foxman 2014; Nicolle 2005). Current guidelines still recommend undertaking treatment because asymptomatic bacteriuria is most common in 1% to 6% of pregnant women, 1% to 25% in elderly women and men (mostly in long-term care facilities), or in people with diabetes, and is associated with pyelonephritis (US PSTF 2019).

The three most common pathogens found in the urogenital tract and bladder which cause UTIs are: *Escherichia coli* (*E coli*) (approximately 53%); Enterobacteriaceae (35%); Proteus (15%); Klebsiella (14%); and Providentia (4%) (Rowe 2014).

Currently available prophylactic therapy and treatments range from: antibiotics; methenamine hippurate salts; topical oestrogen; urine alkalisers; dietary supplements (cranberry or low acidic foods); and lifestyle and behavioural changes (altering sexual activity, personal hygiene, and clothing). Disadvantages of antibiotics, especially long-term antibiotic prophylaxis, are the risk of increasing bacterial resistance, high costs to the patient, and repeat visits to the healthcare professional (Altarac 2014). Whilst these therapies are available and recommended by healthcare professionals, not all are efficacious or evidence-based, hence the constant prevalence of chronic UTIs.

Description of the intervention

D-mannose is a sugar which is part of normal human metabolism and found within most diets. It plays an important role in particular in the glycosylation of most secretory proteins and certain glycoproteins in the human body (Hu 2016; Kranjčec 2014). It has been known for many years to impart beneficial effects on intestinal diseases, diabetes, the immune system, metabolic syndrome, and potentially UTI (Hu 2016).

Early pilot studies on animals and humans have trialled concentrated forms of D-mannose (tablets or sachets) in doses ranging from 200 mg (Lopes De Carvalho 2012) up to 2 g (Kranjčec 2014; Porru 2014; Salinas-Casado 2018). These trials investigate d-mannose in different combinations with other plant extracts or pharmacological agents such as: arbutin, berberine, birch, cranberry (*Vaccinium macrocarpaon*), proanthocyanidins, forskolin, nitrofurantoin, noxamicina (propolis extract), nitrofurantoin sulphamethoxazole, trimethoprim antibiotics, and vitamin C. Common treatment regimen appear to be daily doses ranging from 3 to 6 months duration. The known half-life of D-mannose is approximately 4 hours as it is known to be metabolised rapidly by the human digestive system (Hu 2016). Interactions with other treatments are currently uncertain.

How the intervention might work

The theoretical mechanism of action is to prevent bacterial adherence to uroepithelial cells (Hu 2016; Kranjčec 2014). The D-mannose attaches to the bacteria and prevents it from attaching to the urothelial cells. The D-mannose based inhibitors can block uropathogenic *E coli* (UPEC) adhesion and invasion of the uroepithelial cells (Kranjčec 2014). The bacteria are then understood to essentially be eliminated by urination.

Why it is important to do this review

D-mannose has been available on the non-prescription market in tablet and powder form in most western countries for some time. Although the anti-adhesive effects of D-mannose have been well-established, only recently have we seen a small number of pilot studies and small clinical trials being conducted. It is important to assess and summarise this emerging body of evidence to determine its efficacy (currently unknown) and to ensure high quality research is being conducted in this field.

OBJECTIVES

This review aims to look at the benefits and harms of D-mannose for preventing and treating UTI in adults and children.

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) will be included. Unblinded, single, and double-blind trials will be included.

Cross-over studies will be included and data from both phases will be considered if there is a minimum washout period of 7 days. Otherwise, the results of the first phase only will be considered for analysis.

Abstracts will be included. Unpublished clinical trials with online results available will be included.

Studies in any healthcare setting will be included, including hospitals.

Excluded study designs: single arm studies, commentaries, editorials, and clinical observations.

Types of participants

Inclusion criteria

- Adults and children, of any age and sex, in the general population.
- Pregnant, breastfeeding, and peri-menopausal women.
- Adults in residential and long-term care facilities.
- Adults and children seeking prophylaxis for UTI:
  - with an indwelling catheter or requiring intermittent catheterisation;
  - with an abnormal urinary tract (for example vesicoureteric reflux, urinary obstruction, dysfunctional voiding, pyelonephritis);
  - with asymptomatic bacteriuria.
- Adults and children seeking treatment of an existing UTI
  - symptomatic or asymptomatic UTI;
  - upper or lower, complicated or uncomplicated UTI.
- Studies exclusively involving critically ill, renal abnormalities, diagnosed chronic kidney disease (CKD), kidney transplant, or immunosuppressed patients will be included but analysed separately as subgroups where possible.
- Studies of patients who have co-morbidities such as diabetes, multiple sclerosis, cardiovascular diseases, neurological disorders, and serious or rare diseases will be included but analysed separately as subgroups where possible.
- Studies of perioperative nature where UTI prevention or treatment is involved will be included but analysed separately as subgroups where possible.
- Studies of mixed populations will be considered and applicable data for patients with our UTI criteria will be extracted where possible. If this is not possible, the study will be excluded with reasons provided.

Exclusion criteria

- Adults and children receiving concurrent pharmacological medications for co-morbidities including, but not limited to the following.
  - Blood glucose medications
  - Blood pressure medications
  - Immunosuppressants.
- Adults and children receiving simultaneous (or in the prior 7 days) pharmacological or non-pharmacological treatments for UTI prevention or treatment which are not of the study criteria including, but not limited to the following.
  - Antibiotics (either as prophylactic or for treatment of an existing UTI)
  - Prebiotics, probiotics, or synbiotics
  - Cranberry-based treatments (juice, concentrated tablets, fruit)
  - Diuretics or urinary alkalisation
  - Natural therapies or Traditional Chinese Medicine (TCM)
  - NOTE: these treatments will however be accepted as comparison interventions for D-mannose.
- Patients who have signs of systemic illness (such as fever, loin pain, toxicity).

Types of interventions

Studies of prophylaxis and studies of treating existing UTIs will be combined but analysed as subgroups.

- Any D-mannose treatment administered for the prevention or treatment of symptomatic or asymptomatic UTI compared to an active comparator, placebo or no treatment.
- Any route of administration, any dose, duration, or frequency will be accepted.
- Formulations such as oral tablets, liquids, and effervescent powders will be accepted.
- Combination pharmacotherapies (such as d-mannose plus vitamin, or d-mannose plus cranberry) will be accepted and considered as separate treatment arms.

Comparison pairs for analysis

- D-mannose (dose A) versus D-mannose (dose B)
- D-mannose versus placebo
- D-mannose versus no treatment
- D-mannose versus another pharmacological active comparator such as: antibiotics, prebiotics, probiotics, synbiotics, cranberry-base treatments (juice, concentrated tablets, fruit)
- D-mannose versus diuretics or urinary alkalisation
- D-mannose versus non-pharmacological active comparator such as: vitamin or herbal supplements, Traditional Chinese Medicine (TMC), or natural therapies
- D-mannose versus combination pharmacotherapies (two or more of any of the above in one treatment arm)
- D-mannose in combination with another treatment (two or more of any of the above in one treatment arm) versus any of the above.

Treatment arms where the intervention is in combination with an analgesic will not be accepted such as: D-mannose plus paracetamol, opioids, or an NSAID.

Types of outcome measures

This review will not exclude studies based on non-reporting of outcomes of interest or availability of data.

Primary outcomes

1. Symptomatic bacteriuria UTI according to defined clinical symptomatic criteria (including dysuria, urinary frequency, urgency and suprapubic pain, voiding issues, worsening of symptoms), plus a positive quantitative urine culture (as confirmed by a catheter specimen of urine, midstream urine specimen if possible, or a clean catch specimen and defined as

> 10^5 CFU/mL, or as defined by authors), as any of the following measures.
- Total number of symptomatic bacteriuria (> 10^5 CFU/mL) (cystitis or pyelonephritis) in each group following treatment (all time points included).
- Recurrent symptomatic bacteriuria (> 10^5 CFU/mL) (cystitis or pyelonephritis) following treatment (all time points included).
- Persistent symptomatic bacteriuria (> 10^5 CFU/mL) (cystitis or pyelonephritis) following treatment (all time points included).
- Re-infection symptomatic bacteriuria (> 10^5 CFU/mL) (cystitis or pyelonephritis) following treatment (all time points included).
- Relapse symptomatic bacteriuria (> 10^5 CFU/mL) (cystitis or pyelonephritis) following treatment (all time points included).
- Short term reduction in symptomatic bacteriuria episodes and bacteriologically confirmed up to 2 weeks after the start of treatment.
- Long term reduction in symptomatic bacteriuria episodes and bacteriologically confirmed up to 8 weeks after the start of treatment.

2. Symptomatic UTI (dysuria, urinary frequency, urgency and suprapubic pain, voiding issues, worsening of symptoms), with negative urine specimen, as any of the following measures.
   - Total number of patients who develop urinary symptoms following treatment (all time points included).
   - Recurrent urinary symptoms following treatment (all time points included).
   - Persistence of urinary symptoms following treatment (all time points included).
   - Re-infection of urinary symptoms following treatment (all time points included).
   - Relapse of urinary symptoms following treatment (all time points included).
   - Short term symptomatic cure: the absence of urinary symptoms up to 2 weeks after start of treatment.
   - Long term symptomatic cure: the absence of urinary symptoms up to 8 weeks after start of treatment.
3. Asymptomatic bacteriuria (irrespective of the presence of symptoms suggestive of UTI). *"The number of UTI confirmed by appropriate microbiological criteria. Bacteriuria on quantitative urine analysis of more than 100,000 organisms of a single species per mL is the accepted standard - however, the colony count may vary from 100 to 100,000 depending on the clinical setting* (Stamm 1988). *Therefore in some situations, (such as a clean suprapubic tap) a colony count of less than 100,000 is acceptable."* (Nicolle 2005).
4. Any changes to previous treatment regimen prior to study including: antibiotic regimen; reduction in analgesics; or number of return visits to the GP; probiotics; alternative therapies; reduction in the use of acute and prophylactic antibiotics.
5. Pain (any scale VAS) including: neuropathic pain; abdominal or pelvic pain (suprapubic pain, loin pain); other measures of pain.

Definitions
- Re-infection rate: new pathogen in urine culture.
- Relapse rate: initial pathogen in urine culture after it had been eradicated.
- Cure rates: no clinical signs, bacteriological cure rate defined as eradication of bacteria, combined clinical and bacteriological cure rate defined as no clinical signs and eradication of bacteria.

Secondary outcomes

1. Cure/complete remission of symptomatic and asymptomatic UTI.
2. Quality of life using any validated scale including: mental and functional status (e.g. confusion, weakness, falls).
3. Life participation (lifestyle impact): days absent from work or school; return to normal activities (or ability to do usual activities).
4. Treatment satisfaction: patient-reported; healthcare provider-reported.
5. Treatment adherence.
6. Decline in kidney functional measures including: reduction in estimated glomerular filtration rate; proteinuria; albuminuria.
7. Adverse events: total adverse events, serious adverse events; withdrawals due to adverse events.
   - These include but not limited to: rash; diarrhoea; gastrointestinal symptoms; pyelonephritis; urosepsis; liver or renal toxicity; worsening of UTI, progression to complicated UTI; any renal parenchymal damage on DMSA, four to six months following UTI; pregnancy-related outcomes such as preterm birth, stillbirth, small birthweight, or gestational age.
   - Serious adverse events are considered: fatal, life-threatening, requiring hospitalisation, intravenous antibiotics, bacteraemia, or fungaemia.
   - Death (any cause); sepsis-related deaths.

*Cure rates (defined as no clinical signs, bacteriological cure rate defined as eradication of bacteria, combined clinical and bacteriological cure rate defined as no clinical signs and eradication of 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. Results of the search will be displayed in a PRISMA study flow chart.

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 2011) (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. death, or positive UTI episodes) results will be expressed as risk ratio (RR) to establish statistical difference, and number needed to treat for an additional beneficial outcome (NNT) and pooled percentages as absolute measures of effect with 95% confidence intervals (CI).

Where continuous scales of measurement are used to assess the effects of treatment (e.g. pain or decline in kidney function), the mean difference (MD) will be used, or the standardised mean difference (SMD) if different scales have been used.

Where possible, we will use the mean change score from baseline. We anticipate that some studies may only report the mean endpoint score of which we will use the final time point available and combine these results with the mean change in score, as long as they are of similar scales.

Unit of analysis issues

We will only accept randomisation of the individual participant. For multiple dose studies, we will use data for the first dose only. For cross-over studies, we will use the first phase only, unless a minimum washout period of 7 days has been applied to the trial design. The unit of analysis for UTI will be either events or patients analysed separately, depending on what type of data is available.

Dealing with missing data

Any further information required from the original author will be requested by written correspondence (e.g. emailing 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 2011).

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 2011).

Assessment of reporting biases

If possible, funnel plots will be used to assess for the potential existence of small study bias (Higgins 2011).

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, where there are sufficient data. Heterogeneity among participants could be related to age, co-morbidities, and renal pathology (e.g. with or without CKD). Heterogeneity in treatments could be related to prior agent(s) used and the agent, dose and duration of therapy. 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.

Planned subgroups where sufficient data are available.

- Dose
- Time point
- Prevention versus treatment of UTI
- CKD present
- Age.

Sensitivity analysis

We will perform sensitivity analyses in order 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' tables

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 2011a).

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. A summary of the assessment process is in Appendix 3. 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 2011b). We plan to present the following outcomes in the 'Summary of findings' tables.

- Symptomatic bacterial UTI
- Symptomatic UTI
- Asymptomatic bacteriuria
- Any changes to previous treatment regimen
- Pain
- Cure/complete remission
- Adverse effects.

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

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APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. "d-mannose":ti,ab,kw 2. mannose:ti,ab,kw 3. mannoside*:ti,ab,kw 4. {OR #1-#3} 5. (urinary next tract next infection*):ti,ab,kw 6. (UTI or UTIs):ti,ab,kw 7. bacteriuri*:ti,ab,kw 8. pyuri*:ti,ab,kw 9. cystitis:ti,ab,kw 10.pyelonephritis:ti,ab,kw 11.{OR #5-#10} 12.#4 and #11 in Trials
MEDLINE	1. Mannose/ 2. mannosides/ 3. d-mannose.tw. 4. mannose.tw. 5. mannoside*.tw. 6. or/1-5 7. Urinary Tract Infections/ 8. Bacteriuria/ 9. Pyuria/ 10.Cystitis/ 11.exp Pyelonephritis/ 12.urinary tract infection*.tw. 13.(UTI or UTIs).tw. 14.bacteriuria.tw. 15.pyuria.tw. 16.cystitis.tw. 17.pyelonephritis.tw. 18.or/7-17 19.and/6,18
EMBASE	1. mannose/ 2. mannoside/ 3. d-mannose.tw. 4. mannose.tw. 5. mannoside*.tw. 6. or/1-5 7. urinary tract infection/ 8. cystitis/ 9. pyelonephritis/ or acute pyelonephritis/ or chronic pyelonephritis/ 10.bacteriuria/ 11.asymptomatic bacteriuria/ 12.pyuria/ 13.urinary tract infection*.tw

(Continued)

	14.(UTI or UTIs).tw. 15.cystitis.tw. 16.bacteriuria.tw. 17.pyuria.tw. 18.pyelonephritis.tw. 19.or/7-18 20.and/6,19

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
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.

(Continued)

	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 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.

Appendix 3. The GRADE approach (Grades of Recommendation, Assessment, Development, and Evaluation)

The GRADE approach assesses the certainty of a body of evidence, rating it into one of four grades (GRADE 2008).

- **High**: we are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate**: we are moderately confident in the effect estimate; the true effect is likely to be close the estimate of effect, but there is a possibility that it is substantially different.
- **Low**: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- **Very low**: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

We decreased the certainty of evidence if there was (Balshem 2011):

- serious (-1) or very serious (-2) limitation in the study design or execution (risk of bias);
- important inconsistency of results (-1);
- some (-1) or major (-2) uncertainty about the directness of evidence;
- imprecise or sparse data (-1) or serious imprecision (-2); or
- high probability of publication bias (-1).

We increased the certainty of evidence if there was (GRADE 2011):

- a large magnitude of effect (direct evidence, relative risk (RR) = 2 to 5 or RR = 0.5 to 0.2 with no plausible confounders) (+1); very large with RR > 5 or RR < 0.2 and no serious problems with risk of bias or precision; more likely to rate up if effect is rapid and out of keeping with prior trajectory; usually supported by indirect evidence (+2);
- evidence of a dose response gradient (+1); or
- all plausible residual confounders or biases would reduce a demonstrated effect, or suggest a spurious effect when results show no effect (+1).

HISTORY

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CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: TC; CT; MH; ATP; AT; GW
2. Study selection: TC; CT
3. Extract data from studies: TC; CT
4. Enter data into RevMan: TC; CT
5. Carry out the analysis: TC; CT
6. Interpret the analysis: TC; CT; ATP
7. Draft the final review: TC; CT; MH; ATP; AT; GW
8. Disagreement resolution: MH; ATP; AT; GW
9. Update the review: TC; GW

DECLARATIONS OF INTEREST

- TC: none known
- CT: none known
- MH: none known
- ATP: none known
- AT: none known
- GW: none known

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