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Interventions for treating urinary incontinence in older women: a network meta-analysis (Protocol)

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[Intervention Protocol]

Interventions for treating urinary incontinence in older women: a network meta-analysis

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ABSTRACT

Objectives

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

To compare the different treatments (conservative, pharmacological, and surgical) in terms of cure or cure and improvement of urinary incontinence, and adverse events, in women aged 60 and over through a network meta-analysis, and ranking the numerous interventions within one treatment network.

BACKGROUND

For a glossary of terms, see Appendix 1.

Description of the condition

Urinary incontinence (UI), defined as "any involuntary leakage of urine" (Haylen 2010), is one of the most prevalent health concerns facing women aged 60 and over, with overall prevalence reported as 38% in community-living women aged over 60, increasing to 77% in those residing in long-term care settings (Lukacz 2017). There are three types of UI: urgency (involuntary leakage accompanied or immediately preceded by an urgent need to urinate), stress (involuntary leakage related to effort, exertion, sneezing, or coughing), and mixed (both urgency and stress UI symptoms) (Haylen 2010). The prevalence of each type of UI varies according to age, with older women showing a predominance of mixed UI (Milsom 2017). Incontinence has a negative impact on quality of life (Milsom 2017).

A serious medical condition, UI can lead to urinary tract infections, pressure wounds, and perineal dermatosis (Resnick 1989; Wagg 2017). It is also associated with depression, social isolation, and physical deconditioning (Hunskaar 1991; Wagg 2017). Women with UI, particularly older women, often find themselves isolated and relatively inactive in the medium or long term (Johnson 1998). Because UI is often erroneously considered a normal part of ageing, women do not seek treatment and healthcare providers do not always recommend treatment (Abrams 2017). Untreated, UI can lead to significant social problems, embarrassment, and negative self-perception; reduces social interactions and physical activities and, among older women, increases the risk of falls and nursing-home admissions (Hunskaar 1991; Johnson 1998; Ko 2005; Resnick 1989; Sen 2006; Temml 2000). UI is also costly. The cost to the NHS in England and Wales is approximately GBP 80 million annually for UI containment products alone (i.e. absorbent pads) (NHS England 2018). Not surprisingly, the economic burden for patients, governments, and health insurance companies is enormous; it was projected that the costs of treatment and management of UI in the USA in 2020 would be USD 83 billion (Ganz 2010).

The World Health Organization reports that: "In 2020, the global population aged 60 years and over (older persons) is just over 1 billion people, representing 13.5% of the world's population of 7.8 billion. That number is 2.5 times greater than in 1980, and is projected to reach nearly 2.1 billion by 2050" (World Health Organization 2020). In 2019, there were 81 males per 100 females aged 80 years and older and it is expected that by 2050, inequalities will still be present with 71 males per 100 females at 80 years and older (United Nations 2020). Considering the persistent inequalities between sex in the future years and the high prevalence of UI in older women, a comparison of the effectiveness of different UI treatments in this population is needed. In line with healthy ageing, there is a need to optimise opportunities that enable older women to actively participate in society and remain independent.

Description of the intervention

A variety of treatments have been used in the management of female UI, including conservative interventions (Ayeleke 2015; Dumoulin 2018; Eustice 2000; Hay-Smith 2011; Herbison 2009; Herbison 2013; Herderschee 2011; Lipp 2014; Ostaszkiewicz 2004a; Ostaszkiewicz 2004b; Wallace 2004; Wang 2013), pharmacological interventions (Alhasso 2005; Cody 2012; Duthie 2011; Madhuvrata 2012; Mariappan 2005; Nabi 2006; Rai 2012; Roxburgh 2007), and surgical interventions (Abrams 2017; Ford 2017; Freites 2019; Glazener 2017a; Glazener 2017b; Kang 2015; Kirchin 2017; Lapitan 2017; Nambiar 2017; Saraswat 2020).

In this review, we will include a range of interventions that aim to cure or improve symptoms of all UI types, covering conservative, pharmacological, and surgical treatments. Generally, different interventions target specific types of UI, for example, pelvic floor muscle training (PFMT) (Dumoulin 2017), antidepressants such as duloxetine (Wagg 2017), and surgical sling procedures (Rovner 2017) are commonly used to cure or improve stress urinary incontinence, whereas urgency urinary incontinence is frequently managed with bladder training (Dumoulin 2017), antimuscarinic drugs (Wagg 2017), or augmentation cystoplasty (Rovner 2017).

How the intervention might work

Most conservative management treatments focus on modifying risk factors (termed lifestyle interventions) or improving pelvic floor muscle function in order to prevent urine leakage (pelvic floor muscle training; PFMT). These interventions can be performed with or without electrical stimulation (EStim), biofeedback and cones, bladder training or tibial nerve stimulation (TNS) (Dumoulin 2017). In addition to these groups of interventions, there are mechanical devices that aim to increase the support or occlude the urethra, including pessaries, vaginal inserts and urethral plugs, as well as complementary therapies such as acupuncture. Conservative management is often, but not exclusively, delivered by specifically-trained healthcare professionals (Dumoulin 2017).

Pharmacological interventions aim to either reduce the intensity of urinary urgency (anticholinergic and β-3agonist drugs such as botulinum toxin) or to encourage contraction of the peri-urethral striated muscle of the urethral sphincter, which promotes urine storage and continence (serotonin and noradrenaline reuptake inhibitors) (Wagg 2017).

Surgical interventions aim to restore bladder capacity or storage, or to stimulate the nerves controlling bladder motor and sensory function, by improving urethro-vesical-junction support or correcting deficient urethral closure (or both) (Rovner 2017).

Although there are a considerable number of treatments for UI and the relief of UI symptoms might be the main goal of treatment, it is important to achieve the balance between favourable outcomes (i.e. efficacy) and safety (i.e. adverse events) in all the varying interventions.

Why it is important to do this review

Although previous Cochrane Reviews have examined the effectiveness of UI interventions in women as a general population, they may react differently to specific interventions or interventions' intensity, or manifest adverse effects that differ in type and incidence (Abrams 2017). Owing to the additional vulnerabilities of ageing, there is competing evidence that this population is afflicted with an increased risk of adverse events related to the treatment (Finlayson 2001; Goldfischer 2015; Hong 2020). This raises questions about the efficacy and safety of treatments for older women in existing reviews (Dumoulin 2017). The lack of evidence and clinical guidelines for older women may be

a significant factor in treatment provision and could lead to suboptimal outcomes for this group of women (Schlögl 2021).

Furthermore, most systematic reviews have conducted independent pairwise meta-analyses of interventions that have been directly compared, and few attempts have been made to compare a wide range of interventions with each other. Network meta-analysis (NMA), which uses a combination of direct and indirect comparisons, is an extension of the traditional pairwise meta-analysis that allows a large number of interventions to be compared simultaneously in a single analysis, as well as indirect comparison between interventions that have not been directly compared in studies (Higgins 2021a). Two previous NMAs compared surgical interventions (Imamura 2019), and pharmacological and conservative interventions (Balk 2019), but to our knowledge, no attempts have been made to synthesise the results using all interventions combined.

There is still uncertainty surrounding whether treatments that are effective and safe in younger and middle-aged women may be as effective or as appropriate in older women given the effects of menopause and ageing on pelvic floor muscle function, and the association of comorbidities such as increased body mass index, constipation, diabetes, mobility and cognitive impairment (Dumoulin 2019; Dumoulin 2020). Thus, the effects and safety of UI treatments in older women must be addressed and carefully considered among patients and healthcare professionals.

OBJECTIVES

To compare the different treatments (conservative, pharmacological, and surgical) in terms of cure or cure and improvement of urinary incontinence, and adverse events, in women aged 60 and over through a network meta-analysis, and ranking the numerous interventions within one treatment network.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) of conservative, pharmacological, or surgical interventions for the treatment of urinary incontinence (UI) in older women, or in women in general where data specific to older women are available. We will also include cluster-RCTs and the first phase of cross-over trials.

Types of participants

We will include studies of women aged 60 years and over with stress, urgency, mixed or unclassified types of UI according to symptoms, signs and/or urodynamic evaluation, as defined by the trial investigators. The cut-off of 60 years is in line with the United Nations 2020 definition and was chosen to maximise the inclusion of relevant studies with older adults (Shenkin 2017). Studies that recruited different age ranges will be eligible if they provide outcomes and demographic data separately for older women. Studies of healthy, frail older women and women with comorbidities (e.g. diabetes), living in either the community or institutional care will be eligible.

We will include studies involving participants with symptoms of overactive bladder and pelvic organ prolapse only if UI is present. We will also include studies involving participants who have undergone previous interventions if UI is still present.

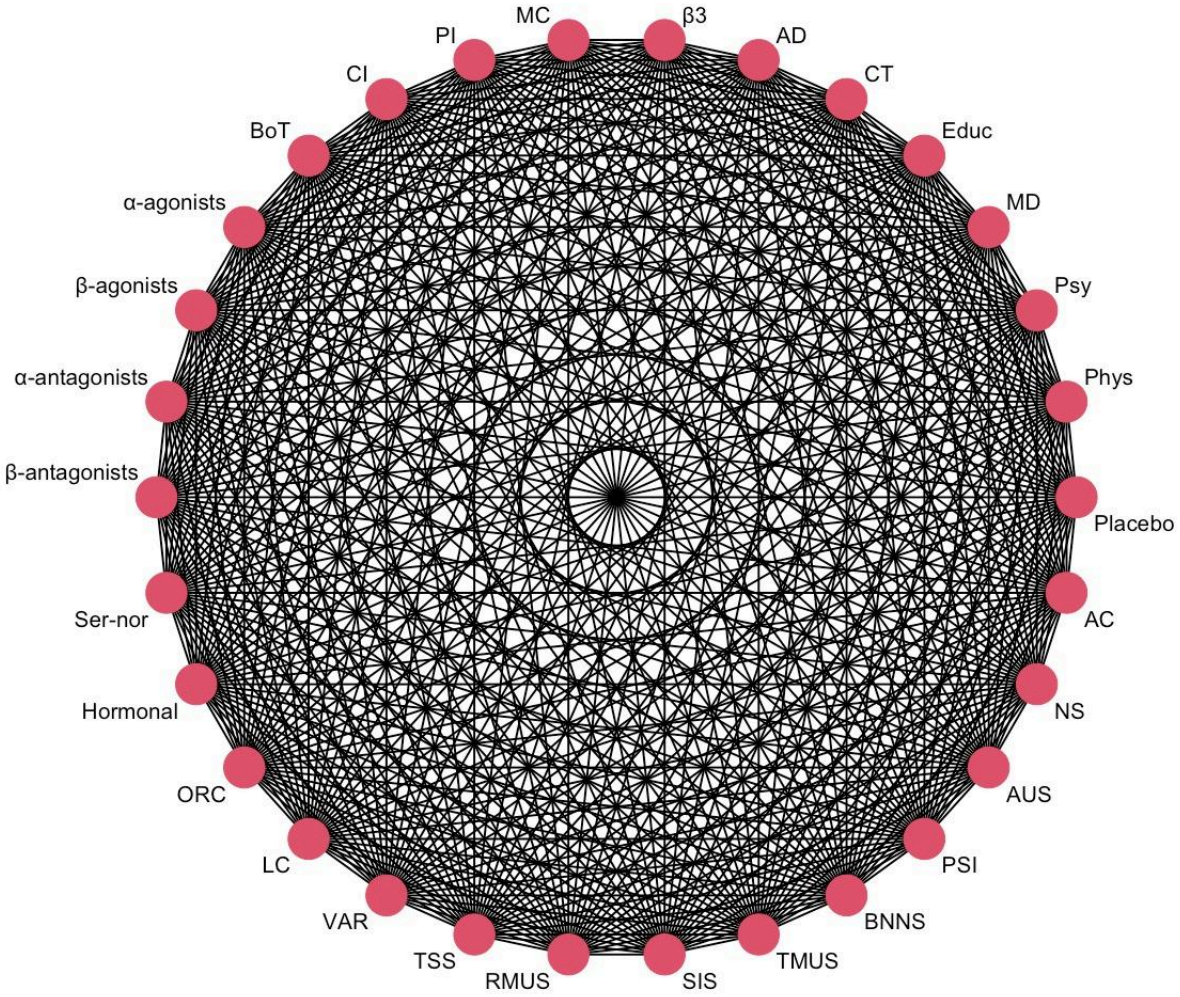
We will exclude studies of participants with nocturnal enuresis or serious pathologies (e.g. psychiatric disorders, cognitive impairment, and cancer). Due to uncertainties about the effects of the interventions investigated in this review on people with damage or diseases of the central peripheral and automatic nervous systems (Panicker 2015), we will exclude studies of participants with UI related to factors outside the urinary tract such as neurological disease.

Types of interventions

The treatment options are based on UI type, patient preference, severity, and presence of comorbidity. Usually, conservative treatments are the first line of care (initial), escalating to medication and ultimately surgery (specialised) (Abrams 2017). However, there are significant differences in management across different healthcare systems depending on patient preference and professional advice. One arm of the trial will include one or more of the following interventions: conservative, pharmacological, and/or surgical.

We will use a splitting approach to classify the interventions because each included intervention is complex and heterogeneous by nature. For example, different trials using conservative interventions may focus on using different methods or strategies (e.g. individual versus group pelvic floor muscle training (PFMT)) and incorporate different additional co-interventions (e.g. PFMT added to neuromuscular electrical stimulation (NMES)). If present, the combination of interventions will form a separate treatment node (e.g. PFMT plus another active treatment). Given the heterogeneity of the interventions, we will scrutinise the description of the intervention in the trials to classify them according to the pre-defined treatment nodes based on used approaches for the treatment of UI. We will include trials that allocate participants to any category of treatments listed in Additional Table 1 compared to placebo, no treatment, and any other comparator listed. Figure 1 represents all theoretically possible network comparisons of treatment nodes.

Figure 1. Network plot of all theoretically possible network comparisons.
Abbreviations: AC: augmentation cystoplasty; AD: antimuscarinic drugs; α-agonists: α-adrenoceptor agonists; α-antagonists: α-adrenoceptor antagonists; AUS: artificial urethral sphincters; β-agonists: β-adrenoceptor agonists; β-antagonists: β-adrenoceptor antagonists; β3: β3-adrenergic agonists; BNNS: bladder neck needle suspension; BoT: botulinum toxins; CI: cyclooxygenase inhibitors; CT: complementary therapies; Educ: education/ behavioural/lifestyle; Hormonal: hormonal treatment of urinary incontinence; LC: laparoscopic colposuspension; MC: drugs acting on membrane channels; MD: mechanical devices; NS: nerve stimulation; ORC: open retropubic colposuspension; Phys: physical therapies; PI: phosphodiesterase inhibitors; PSI: periurethral sphincter injection; Psy: psychological therapies; RMUS: retropubic mid-urethral sling; Ser-nor: serotonin-noradrenaline uptake inhibitors; SIS: single incision sling; TMUS: transobturator mid-urethral sling; TSS: traditional suburethral sling; VAR: vaginal anterior repair.



Following current clinical practice and evidence, we will categorise interventions based on a previous network meta-analysis (NMA) (Balk 2019). For this analysis, we will categorise interventions on the basis of whether they are classified as initial and specialised management for UI following the 7th International Consultation on Incontinence (Abrams 2022).

We plan to summarise different sets of comparisons.

- All stress UI interventions compared to no treatment.
- Initial and specialised management used for stress UI compared to each other.
- All urgency UI interventions compared to no treatment.
- Initial and specialised management used for urgency UI compared to each other.
- All mixed UI interventions compared to no treatment.
- Initial and specialised management used for mixed UI compared to each other.
- All UI interventions compared to no treatment.
- Initial and specialised management used for UI compared to each other.

Types of outcome measures

We will assess the following outcome measures.

Primary outcomes

- Number of women with cure, defined as complete absence of any symptoms of UI as reported by the participant or clinician.
- Number of women with self- or clinician-reported cure or improvement. Improvement will be considered as any indication of improvement in UI symptoms.

For the primary outcomes, we will use the original definition used by the trialists (e.g. no UI symptoms, negative testing, continent, dry, satisfied, very much improved). We will extract data using a hierarchy of measures as follows: women-reported cure or improvement or both, including validated symptoms questionnaires (e.g. Patient Global Impression of Improvement, International Consultation of Incontinence Questionnaire, King's Health Questionnaire) or a direct question about UI symptoms with 'yes' or 'no' answer. For improvement, we will consider women's satisfaction rate. When such measures are not available, we will use objective measures for quantification of symptoms including diaries (reported number of incontinence episodes per day) and pad test (based on pad weights in grams per hour (short pad test) or per day (long pad test). The outcomes reported in categorised measures (i.e. slight, moderate, and severe) will not be included in the quantitative analysis.

Secondary outcomes

Secondary outcomes will comprise.

- Number of participants with serious adverse events.

Adverse events will be defined as the number of participants who experience serious adverse events (i.e. death, disability, bleeding, nerve injury, hospitalisation, temporary or permanent sequelae, persistent pain, and serious infections) during the intervention period that results in discontinuation of treatment. We will use the definition of serious adverse events as reported by trial investigators.

Timing of outcome assessment

There will be no restriction on the duration of follow-up for the outcomes. To evaluate the effects of different interventions with different time points, we plan to assess the short- and long-term symptomatic cure and improvement (< than 12 months and ≥ 12 months post-randomisation).

Main outcomes for summary of findings tables

All primary and secondary outcomes will be included in summary of findings tables.

Search methods for identification of studies

This review will draw on the search strategy developed for Cochrane Incontinence. No language or other limitations will be imposed on the search procedures described below.

Electronic searches

We will search the Cochrane Incontinence Specialised Register that includes searches of the following electronic bibliographic databases:

- Cochrane Central Register of Controlled Trials (CENTRAL);
- MEDLINE;
- MEDLINE In-Process, In-Data-Review and Other Non-Indexed Citations;
- MEDLINE Epub Ahead of Print;
- MEDLINE Daily;
- ClinicalTrials.gov;
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP).

For full details of all the sources searched in the development and maintenance of the Cochrane Incontinence Specialised Register please see the 'Specialised Register' section of the Cochrane Incontinence webpages.

The terms that will be used to search the Cochrane Incontinence Specialised Register are given in Appendix 2.

Additionally, we will search PEDro (the Physiotherapy Evidence Database).

Searching other resources

We will identify relevant studies by.

1. Handsearching the conference proceedings of the annual Latin American Pelvic Floor Association Congress (ALAPP).
2. Searching the reference lists of included trials and review articles about conservative management, pharmacological and surgical interventions in older women with UI.
3. Contacting experts in the field (including authors of included trials and excluded studies identified as possible preliminary or pilot work).

We will search for trials in any language and arrange for translation of potentially eligible trials published in languages other than English.

Data collection and analysis

We will process data as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021a), and analyse data using Review Manager 2020.

Selection of studies

We will merge and import references identified by each database into Covidence and remove duplicates. Two review authors (Giovana Vesentini (GV) and Nicole O'Connor (NOC)) will independently screen titles and abstracts. We will exclude any reports that do not fulfil the inclusion criteria and are categorised as irrelevant by both review authors. We will retrieve the full reports of studies deemed to be suitable trials and those whose eligibility is unclear. Subsequently, the same two review authors will independently read the full text of relevant records to determine their inclusion in the review according to the eligibility criteria. We will resolve disagreements through discussion between review authors or, where consensus is not reached, through consultation with a third review author (Chantale Dumoulin (CD)). We will report the study selection process of the studies according to the PRISMA flow chart (Page 2021) and the PRISMA extension for NMA (PRISMA-NMA) (Hutton 2015).

Data extraction and management

Two review authors (GV and NOC) will independently undertake data extraction of the included studies. We will resolve any disagreements by discussion or through referral to a third review author, if needed. We plan to use a standardised data extraction form adapted from Cochrane Incontinence. We plan to extract and record key features of each study, including the following.

- Trial methodology (e.g. design, randomisation sequence, stratification, allocation concealment, blinding, recruitment details).
- Participants (e.g. setting, number, eligibility, diagnostic criteria, baseline characteristics: age, comorbidities, socioeconomic status).
- Interventions investigated. We will use the TIDieR framework to describe components of interventions, including characteristics of drug treatment (e.g. types of drugs, dose, route of administration), characteristics of surgery (e.g. type, length of hospital stay), characteristics of comparison (placebo, other intervention associated), duration of intervention, intensity and number of sessions (Hoffman 2014).
- Outcomes: we will extract the number of participants allocated to each intervention group and the proportion of patients for primary and secondary outcomes, effect modifiers, and time points reported. We plan to categorise time points as short-term (< than 12 months after randomisation) and long-term (≥ 12 months and more after randomisation) follow-up.
- Notes (contact with study author, sponsorship/funding, conflicts of interest, translation).

From each study, we will extract the following characteristics that may act as effect modifiers: UI type, residential status, comorbidity, UI severity, age and frailty.

We will extract data from graphs using WebPlotDigitizer if the results are provided in figures only. If multiple publications of the same study are identified, we will collect data from all related reports for complete data extraction. If clarification is needed regarding unclear data in the included studies, we will attempt to contact primary authors.

Assessment of risk of bias in included studies

At least two review authors (GV and NOC) will independently assess the risk of bias of included studies using Cochrane's RoB 2 tool for the primary outcomes and short-term follow-up (Higgins 2019) using the most recently developed RoB2 Excel tool. We will use the variants of the RoB 2 tool for cluster-RCTs and cross-over RCTs (Eldridge 2021; Higgins 2021b). The domains of bias assessed will include the following: bias arising from randomisation process; bias due to deviations from the intended intervention; bias due to missing outcome data; bias in measurement of the outcome; and bias in selection of the reported results. We will assess the outcomes and time points included in the summary of findings tables, and will focus on the assessment of the effect of assignment to the interventions at baseline. Using the signalling questions, we will categorise each domain as yes, probably yes, no, probably no, and no information (Higgins 2021a). The judgement for each domain will be classified as low risk of bias, some concerns, or high risk of bias.

The overall judgement about risk of bias will be made based on the five domains judgements (Sterne 2019), as the following.

- Low risk of bias: the outcome is considered to be at low risk of bias.
- Some concerns: a few concerns are expected to be associated with the outcome in at least one domain, but it does not warrant categorisation as a study with a high risk of bias with regard to any domain.
- High risk of bias: the outcome is considered to be at high risk of bias in at least one domain, or has a few concerns with regard to multiple domains are observed in the study such that these concerns significantly lower confidence in the study results.

We will summarise our findings in the risk of bias tables. The complete data of consensus decisions for the signalling questions will be presented in a supplemental appendix with the review. We will express the percentage of agreement about the judgement of risk of bias, and we will resolve any disagreements by consulting a third review author (CD and Ashraf F Nabhan (AFN)).

Measures of treatment effect

We will calculate risk ratios (RR) and 95% confidence intervals (CIs) for dichotomous data. For continuous data, where studies report outcomes using the same measurement we will calculate mean difference (MD) and 95% CIs. Where studies report outcomes using different measurements, we will calculate standardised mean difference (SMD) and 95% CIs. We will interpret the SMD using generic effect size estimates as follows: small or slight (SMD ≥ 0.20 to < 0.50), moderate (SMD ≥ 0.50 to < 0.80), or large or substantial (SMD ≥ 0.80) (Cohen 1988). Furthermore, the effect estimate of treatment will be used to generate relative treatment ranking to the included interventions for each outcome measure.

Relative treatment ranking

We will determine ranking of treatments for the primary outcomes in order of effectiveness using mean ranks and summarise with rankograms, along with surface under the cumulative ranking curves (SUCRAs) and P scores (Rücker 2015; Salanti 2011).

Unit of analysis issues

We will include patient randomised trials in this review and the unit of analysis will be per participant randomised.

For cross-over RCTs, we intend to use data from paired analyses when available. If not reported, we will use data from the first trial period if presented separately using the methods described in section 23.2.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021a).

For cluster-RCTs, we plan to include them provided that the effect estimate is adjusted for the correlation between participants within clusters. When this information is not available, we will try to contact trial authors to obtain an estimate of the intracluster correlation or impute using estimates from other included studies of similar external trials.

In the case of multi-arm studies, we will combine intervention groups as long as they are considered the same treatment node. If this is not the case, the same trial will be included in the same pairwise meta-analysis avoiding double counting. For this, we will split the intervention group as multiple independent comparisons. For dichotomous data, the number of events and total number of patients will be divided, and for continuous data, the sample size will be divided keeping the same means and standard deviation.

Dealing with missing data

Where feasible, we intend to carry out analyses according to the intention-to-treat basis for all outcomes (that is, by the randomised groups irrespective of whether women received the treatment according to the allocation). We will contact trial authors if we identify important missing data or unclear data. For studies with continuous outcomes where means are reported, but standard deviations are not that cannot be derived or obtained from contacting authors, we will calculate these from P values, t values, CIs, or standard errors using approaches described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021a).

Assessment of heterogeneity

We will assess heterogeneity between trials in the pairwise meta-analysis by comparing characteristics across all included trials, visual inspection of forest plots, the Chi^2 test for heterogeneity with statistical heterogeneity set as $P < 0.1$, and the I^2 statistic. We will define the thresholds for interpretation of the I^2 statistic as follows (section 10.10.2; Higgins 2021a):

- low: less than 40%;
- moderate: 30% to 60%;
- substantial: 50% to 90%; and
- considerable: greater than 75%.

We will explore potential sources of clinical and methodological heterogeneity by performing subgroup and sensitivity analysis (see Subgroup analysis and investigation of heterogeneity).

Assessment of transitivity across treatment comparisons

We will evaluate the transitivity assumption by visual inspection of tables, evaluating the distribution of potential sources of intransitivity (i.e. effect modifiers) across relevant studies (see Subgroup analysis and investigation of heterogeneity). We will assess heterogeneity or inconsistency in the NMA among primary outcomes, incorporating an inconsistency model. To evaluate the presence of heterogeneity and inconsistency in the entire network, we will use network meta-regression. To evaluate the presence of inconsistency locally, we will incorporate a loop-specific approach that evaluates inconsistency in all closed loops of evidence by contrasting direct with indirect estimates (Higgins 2012).

Assessment of reporting biases

We plan to investigate the possibility of publication bias and related biases in meta-analyses involving 10 or more studies. If applicable, we will investigate publication bias through visual inspection of funnel plots and evaluate funnel plot asymmetry using Egger's tests (Egger 1997).

For NMA, we will use the new tool, ROB-MEN (Risk Of Bias due to Missing Evidence in Network meta-analysis) (Chiocchia 2021), implemented within CINeMA (Confidence in Network Meta-Analysis) that evaluates the impact of publication bias on the results of NMA of interventions.

Data synthesis

We will use a combination of direct and indirect comparisons of interventions in the statistical analysis. We will include all studies that provide data regardless of the overall risk of bias as assessed by the RoB 2 tool in the main analysis.

Methods for pairwise meta-analyses

For every comparison with at least two studies, we will conduct pairwise meta-analysis of available direct evidence for all primary and secondary outcomes using Review Manager 2020. We will estimate RRs for binary outcomes and MDs (or SMD) for continuous outcomes, with 95% CIs using a random-effects model as we expect heterogeneity across studies in trial design, interventions, and outcome measurements.

Methods for network meta-analyses

We will conduct indirect comparisons of interventions that have not been compared directly with each other within the same trial. The indirect comparisons will estimate intervention effects whilst preserving the randomisation of the originally assigned patient groups. Where possible, we will perform indirect comparisons for the primary outcomes and combined with available direct evidence, applying frequentist methods for NMA using the netmeta package in R software (Rücker 2022). We will estimate relative intervention effects from random-effects models fitted with a single heterogeneity parameter.

Network meta-analysis assumes that any treatment being investigated is the same from one comparison to another, and we assume that all participants who meet our inclusion criteria will be jointly randomisable across each intervention. We will investigate this transitivity assumption by examining the distribution of potential effect modifiers between comparisons (e.g. UI type, residential status, comorbidity, UI severity, age and frailty). We will assess other assumptions relating to heterogeneity and consistency using methods described by Song 2009 and Veroniki 2013. For each comparison, we will give the estimated treatment effect along with its 95% CI. We will investigate inconsistency by splitting the direct and indirect evidence and using design-by-interaction consistency models, if appropriate (Higgins 2021a). A

senior statistician with extensive experience in NMA (Andrew Elders (AE)) will provide support and input for conducting all analyses.

Subgroup analysis and investigation of heterogeneity

In anticipation of differences of effect and where the data will allow, we plan to undertake the following separate subgroup analyses for primary outcomes.

- Different types of incontinence.
  - Stress UI alone (symptoms, signs, urodynamic diagnosis).
  - Urgency UI alone (symptoms, signs, urodynamic diagnosis).
  - Mixed UI (symptoms, signs, urodynamic diagnosis).
  - Unclassified types of UI (symptoms, signs, urodynamic diagnosis).
- Setting.
  - Living in the community (e.g. elderly people living independently).
  - Living in an institution (e.g. care home, sheltered home, nursing home).
- UI severity.
- Co-existing pelvic organ prolapse and comorbidities (e.g. diabetes and cardiovascular diseases).
- Age.
  - Aged between 60 and < 80 years.
  - ≥ 80 years.
- Frailty.

We will use the test for differences between subgroups in Review Manager 2020, the subgroups being defined by the different comparisons being made, and we will estimate the difference between the subgroups and determine their statistical and clinical significance. For NMA, we will assess the differences in the effect estimates between the subgroups using network meta-regression.

Sensitivity analysis

For both pairwise meta-analysis and NMA, we will perform sensitivity analyses to investigate the effect of methodological quality by restricting analyses to include only the studies with a low risk of bias, as determined by the RoB 2 tool, and to include only the studies with no missing reported summary data. We plan to present the detailed analysis along with the codes used as supplemental data.

Summary of findings and assessment of the certainty of the evidence

We will include a summary of findings table following the template by Yepes-Nuñez 2019 for all primary outcomes. For each outcome, we plan to present as follows: (i) initial management versus no treatment; (ii) specialised management versus no treatment; (iii) initial management versus specialised management.

Following the guidelines of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021a), we will assess the certainty of the evidence by using the CINeMA approach (Salanti 2014) and the CINeMA web application (Nikolakopoulou 2020). We will consider the six domains of the CINeMA framework: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence. Each domain will be judged to have no concerns, some concerns, or major concerns. Judgements across the domains will be summarised to obtain the levels of confidence classified as very low, low, moderate, or high. The certainty of the evidence will be assessed independently by two review authors (GV and NOC) with disagreements resolved by discussion or by involving a third review author (CD and AFN).

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ADDITIONAL TABLES

Table 1. Categories of interventions for urinary incontinence in older women

Intervention	Category	Characteristics
Conservative	Physical therapies	Pelvic floor muscle training (PFMT), manual therapies, biofeedback, stimulation, tibial nerve stimulation (TNS), and electrical stimulation (EStim)
	Psychological therapies	Behavioural therapies, humanist therapies, cognitive behavioural therapies, mindfulness
	Mechanical devices	Intra-vaginal (pessaries), intra-urethral and external urethral
	Education/behavioural/lifestyle	Diet, exercise advice, activities of daily living (ADL) advice, fluid management, void interventions, weight loss/obesity, scheduled voiding regimens, smoking cessation, bowel management, anatomy and physiology education
	Complementary therapies	Hypnotherapy, acupuncture, Bowen technique, reflexology, pilates, and yoga
Pharmacological	Antimuscarinic drugs	Darifenacin, fesoterodine, imidafenacin, propantheline, solifenacin, tolterodine, trospium, oxybutynin, propiverine, flavoxate
	β3-adrenergic agonists	Mirabegron, vibegron
	Drugs acting on membrane channels	Calcium antagonists, potassium channel openers
	Phosphodiesterase inhibitors	-
	Cyclooxygenase inhibitors	Indomethacin, flurbiprofen
	Botulinum toxins	-
	α-adrenoceptor agonists	-
	β-adrenoceptor agonists	-
	α-adrenoceptor antagonists	Alfuzosin, doxazosin, prazosin, terazosin, tamsulosin, silodosin, naftopidil
	β-adrenoceptor antagonists	Terbutaline (β2), salbutamol (β2), mirabegron (β3)
	Serotonin-noradrenaline uptake inhibitors	Imipramine, duloxetine
	Hormonal treatment of urinary incontinence	Oestrogen and other hormones
Surgical	Open retropubic colposuspension	-
	Laparoscopic colposuspension	-
	Vaginal anterior repair	Pacey, Kelly
	Traditional suburethral sling	-

Table 1. Categories of interventions for urinary incontinence in older women *(Continued)*

Retropubic mid-urethral sling	-
Single incision sling	-
Transobturator mid-urethral sling	-
Bladder neck needle suspension	Pereyra, Stamey, Raz
Periurethral sphincter injection	-
Artificial urethral sphincters	-
Nerve stimulation	-
Augmentation cystoplasty	-

APPENDICES

Appendix 1. Glossary of plain terms

Acupuncture:	Insertion of very thin needles through the skin at strategic points on the body.
Augmentation cystoplasty:	A surgical procedure to make the bladder larger.
Behavioural therapies:	A term that describes a broad range of techniques used to change harmful behaviours.
Biofeedback:	An external sensor that can be combined with pelvic floor muscle training as a way of enhancing the therapy providing feedback.
Bladder neck needle suspension:	A surgical procedure that ties sutures between the vagina and the abdominal wall.
Bowen technique:	Complementary therapy that works on the soft connective tissue (fascia) of the body.
Cognitive:	Involves thinking, reasoning, or remembering.
Electrical stimulation:	The use of electrical potential or electrical currents to encourage therapeutic responses.
Humanist therapies:	A type of mental health treatment that centres around your unique experience and perspective.
Hypnotherapy:	The use of hypnosis to try to treat conditions or change habits.
Mindfulness:	A type of meditation.
Pelvic floor muscle training:	Training and exercises that include a correct contraction of the pelvic floor muscles.
Periurethral sphincter injection:	A procedure in which drugs are injected around the urethra and bladder neck.
Pessaries:	Devices that fits into the vagina and provide pelvic support.

(Continued)

Pilates:	Exercise that aims to strengthen muscles while improving postural alignment and flexibility.
Reflexology:	Type of massage that involves applying pressure to the feet, hands, or ears.
Retropubic colposuspension:	A surgical procedure for lifting the tissues near the bladder neck and proximal urethra in the area behind the pubic bones.
Scheduled voiding regimens:	Toileting on a planned schedule.
Sphincters:	Circular muscles that open and close certain body parts.
Suburethral sling procedures:	A surgical procedure using a sling that is placed around the urethra to lift it back into a normal position and to exert pressure on the urethra.
Tibial nerve stimulation:	The use of electrical potential or electrical currents to encourage therapeutic responses placed on the tibial nerve.
Vaginal anterior repair:	A surgical procedure to repair or reinforce the weakened layers between the bladder and the vagina.
Yoga:	Exercises that involve physical poses, concentration, and deep breathing.

Appendix 2. Search terms - Cochrane Incontinence Specialised Register

The search terms that will be used to search the Cochrane Incontinence Specialised Register are given below:

(design.cct* OR design.rct*)
AND
(topic.urine.incon*)
AND
(intvent.phys* OR intvent.psych* OR intvent.mech* OR intvent.educ* OR intvent.lifestyle* OR intvent.complementary* OR intvent.chem.drug* OR intvent.chem.horm* OR intvent.surg*)

All searches will be of the keywords field of EndNote 2018.

CONTRIBUTIONS OF AUTHORS

- Giovana Vesentini: drafted the protocol, reviewed and approved the final protocol.
- Andrew Elders: reviewed and approved the final protocol.
- Ashraf F Nabhan: reviewed and approved the final protocol.
- Mélanie Le Berre: reviewed and approved the final protocol.
- Adrian Wagg: reviewed and approved the final protocol.
- Nicole O'Connor: reviewed and approved the final protocol.
- Licia Cacciari: reviewed and approved the final protocol.
- Chantale Dumoulin: drafted the protocol, reviewed and approved the final protocol.

DECLARATIONS OF INTEREST

In accordance with Cochrane's Commercial Sponsorship Policy, the following declarations are applicable for the 3 years prior to the registration of this title.

- Giovana Vesentini: none known.
- Andrew Elders: none known.
- Ashraf F Nabhan: none known.
- Mélanie Le Berre: none known.
- Adrian Wagg: none known.

- Nicole O'Connor: is Assistant Managing Editor for Cochrane Incontinence. She played no part in the editorial process for this protocol.
- Licia Cacciari: none known.
- Chantale Dumoulin: none known.

Where members of the review team are authors on an included trial (Licia Cacciari, Andrew Elders, Ashraf F Nabhan, Adrian Wagg, Chantale Dumoulin), they will not be involved in decisions about the eligibility of the study, or extract data from, carry out the risk of bias assessment for, or perform GRADE assessments of that study. This will be done independently by two other review authors.

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