Title: Non-pharmacological, non-surgical interventions for urinary incontinence in older persons: a systematic review of systematic reviews. The SENATOR project ONTOP series.

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Highlights:

- There is sufficient evidence to warrant recommendation of group exercise therapy for stress incontinence in older women
- There is sufficient evidence to warrant recommendation of behavioural therapy for older women with any incontinence type
- Evidence was insufficient to recommend any non-pharmacological therapy for men with urinary incontinence
- Evidence was insufficient to recommend any other type of non-pharmacological therapy for older women with incontinence

Abstract

Background: Urinary incontinence is especially common in older age. Non-pharmacological therapies are particularly desirable in this group.

Objective: To define optimal evidence-based non-pharmacological, non-surgical therapies for urinary incontinence in older persons.

Methods: A Delphi process determined critical outcome measures of interest. Studies of any non-pharmacological intervention reporting critical outcomes were identified through database searches for relevant systematic reviews in Medline, Embase, CINAHL, PsycInfo and Cochrane by June 2018. Primary trials with a population mean age ≥65years were identified with subsequent data extraction and risk of bias assessment. Qualitative analysis and meta-analysis, when possible, were undertaken followed by grading of the evidence using GradePro software. Finally, bullet-point recommendations were formulated for the indications and contraindications for non-pharmacological interventions for urinary incontinence in older persons.

Results: Frequency of incontinence was identified as a critically important outcome. In total, 33 systematic reviews were identified with 27 primary trials meeting inclusion criteria. Evaluated therapies included exercise therapy, habit retraining, behavioural therapy, electrical stimulation, transcutaneous tibial nerve stimulation, magnetic stimulation, caffeine reduction and acupuncture. From meta-analysis, group exercise therapy and behavioural therapy in women were beneficial in reducing episodes of incontinence (mean reduction of 1.07 (95%CI 0.69-1.45) and 0.74 (95%CI 0.42-1.06) episodes per day respectively, evidence grade ‘moderate’). Evidence for other interventions was limited and of insufficient quality.

Conclusions: There is sufficient evidence to warrant recommendation of group exercise therapy for stress incontinence and behavioural therapy for urgency, stress or mixed urinary incontinence in older women. Evidence was insufficient to recommend any other non-drug therapy.

Keywords: Aging; Incontinence; Meta-analysis; Stress Incontinence; Urge Incontinence

Abbreviations:

ADR – adverse drug reaction

AUA – American Urological Association

CINAHL – Cumulative Index of Nursing and Allied Health Literature

EAU – European Association of Urology

GRADE - Grades of Recommendation, Assessment, Development and Evaluation

NICE – National Institute for Clinical Excellence

ONTOP – Optimal Non-Drug Therapy in Older People

PFMT – pelvic floor muscle training

PRISMA – Preferred Reporting Items for Systematic reviews and Meta-Analyses

QOL – quality of life

RCT – randomised controlled trial

SENATOR – Software engine for the Assessment and optimisation of drug and non-drug therapy in older persons

SUI – stress urinary incontinence

UUI – urinary urgency incontinence

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1.1 Introduction

Urinary incontinence primarily affects older people with current figures estimating that 46% of women and 34% of men over the age of 80 are affected [1-3]. It is often termed one of the "geriatric giants" due to its high prevalence and considerable social and economic impact [2-4]. Furthermore, an estimated 65.7% of women and 58.3% of men with urinary incontinence find symptoms impact to some degree on their quality of life (QoL), particularly in older age [5-10].

Older people are also much more likely to experience an adverse drug reaction (ADR) [11], accounting for up to 31% of hospital admissions [12], causing significant morbidity and mortality in this group. Despite this, about half of all ADRs are preventable [13]. The crude prevalence of ADRs dramatically increases with age for two main reasons - polypharmacy and the altered physiology associated with ageing. This means non-pharmacological treatments are particularly appealing to use in this patient group. Moreover, more people with incontinence prefer non-pharmacological approaches to medical or surgical options [14]. Therefore, providing evidence-based recommendations for the use of non-pharmacological treatments in this age group specifically is important.

The SENATOR consortium is an international collaborative group developing and trialing a Software ENgine for the Assessment and optimisation of drug and non-drug Therapy in Older peRsons (SENATOR) within an FP7 funded project[15]. This software will assess multi-morbidity in older people and deliver bespoke individualized recommendations on the optimal pharmacological and non-pharmacological treatment. Informing best practice for the SENATOR software recommendations on non-pharmacological therapy is the remit of the Optimal evidence based Non-drug Therapies

in Older Persons (ONTOP) project [16]. The ONTOP project evaluates non-drug therapies in older persons through a specially developed methodology involving systematic reviews of the literature on prevalent conditions affecting elderly patients, including urinary incontinence. The ONTOP methodology results in brief, bullet-point recommendations of non-pharmacological treatment of common geriatric syndromes that will inform the SENATOR software. Here, we describe the process for generation of SENATOR's recommendations on urinary incontinence.

2.1 Methods

2.1.1 ONTOP Methodology

The full methodology and protocol for the ONTOP series of reviews is published elsewhere [16]. Briefly, this involves using systematic reviews and meta-analyses as the source of evidence for clinical recommendations.

The first step is to identify those outcomes of highest clinical importance in order to focus the list of included studies. This was achieved by applying a Delphi Process to a list of outcomes deemed clinically relevant by a panel of 11 clinicians in geriatric medicine. Outcomes were rated anonymously and independently on a scale of 1-9 in the categories not important (1-3), important but not critical for making a decision (4-6) and critical for making a decision (7-9). Those outcomes rated as critical by the Delphi process were then used as the primary outcomes of interest in the literature being reviewed. Guidelines and review articles were included if they followed the set-up of a systematic review. The identified systematic reviews and meta-analyses were then used to identify primary studies for inclusion in this paper. Eligible papers had to include at least one primary study meeting inclusion criteria with the full text available in English. Primary studies had to be any type of comparative study, which included randomised controlled trails (RCTs) as well as quasi-experimental and pre/post intervention studies. Furthermore, only full texts in English were included as abstracts alone had insufficient evidence to allow assessment for inclusion as well as assessment of bias, meta-analysis and grading of evidence. In the event that data were not fully reported, attempts were made to contact the authors and request the additional information.

Systematic reviews including only male and female participants or both were included.

Since SENATOR software is intended for use in those aged 65 years or over only, a minimum mean age of ≥ 65 years was applied to participants of the primary studies. Studies investigating associated and specific conditions relating to incontinence were excluded, such as multiple sclerosis associated, post-prostatectomy and post-stroke urinary incontinence.

Systematic reviews relating to any non-pharmacological, non-surgical treatments were eligible for inclusion, e.g. pelvic floor muscle training (PFMT) or acupuncture. These interventions could be delivered in a multicomponent nature, independently, in the community or in a tertiary care setting. Studies detailing other aspects of urinary incontinence, such as risk factors and investigations, were excluded. Containment methods e.g. pads, were deemed inappropriate for inclusion, as they were not considered an intervention since they would not ultimately change incontinent episodes. Electrical stimulation with implantable electrodes e.g. percutaneous tibial nerve stimulation was also deemed inappropriate as this was regarded as an invasive technique.

2.1.2 Search Methods

Medline, Embase, PsycInfo, CINAHL and the Cochrane Library were used as the sources of systematic reviews for inclusion in this review. The source used to assist in defining the search strategies was the Cochrane Incontinence Group list for hand searchers [17] (see Supplementary Data, Appendix 1). There were no date restrictions set on the searches and records were searched from inception until 29th June 2018.

Database searches were limited to English language and humans. However, the Cochrane library cannot be limited in the same way so was simply limited to

Cochrane reviews only, with exclusion of protocols. However, on screening the Cochrane Library results, the same limits were placed on the results as the other databases.

Following duplicate removal, the results of the searches were screened by titles and abstracts, then by full texts to determine eligibility for inclusion. When there was an updated version of a systematic review, only the most recent publication was screened. On completion of screening of the systematic reviews, the primary studies included in the reviews were screened for inclusion eligibility and subsequently sourced. Furthermore, the reference lists of the included primary trials were also hand-searched to ensure thorough inclusion. Primary studies were included if they assessed any non-pharmacological, non-surgical intervention with any control intervention (no intervention, usual care, placebo or sham interventions) and measured any outcome deemed of critical importance by the Delphi group in a population of mean age 65 years or over.

Two independent reviewers undertook the searches and selections, with any disagreements between reviewers resolved by discussion, to produce a final list of literature for detailed review. Studies that used data that had already been included in another study were excluded. If any differences could not be resolved by discussion between the reviewers, a third reviewer was asked to determine eligibility for inclusion. All individuals involved completed training in the ONTOP methodology to ensure consistency of approach.

2.1.3 Data Extraction and Analysis

Following identification of primary papers for inclusion, data extraction was undertaken by two reviewers using a standard data extraction form including general information about

the study design and participants as well as critical appraisal questions, allowing an initial assessment of the risk of bias in the included studies.

The risk of bias in each study was assessed as per the Cochrane Handbook for systematic reviews [18] using risk of bias tables on RevMan5.3. The tables addressed the following seven sources of bias:

- Random sequence generation
- Allocation concealment
- Blinding of participants and personnel
- Blinding of outcome assessment
- Incomplete outcome data
- Selective reporting
- Other biases

These areas of bias were assigned low, high or, if there was insufficient evidence, unclear risk and allowed assessment of selection, performance, detection, attrition reporting and other biases.

Meta-analysis was undertaken when possible, by intervention and outcome following the clinical questions previously mentioned. For eligibility for meta-analysis, studies had to be a comparative study and in the case of pre/post intervention studies the pre and post results were considered as control and experimental groups respectively. Furthermore, only studies where data were fully reported, or had been accessed through contacting authors, with a sample size, mean and standard deviation, were included. Individual forest plots were created if there was more than one study for an intervention and outcome.

Grading of the evidence was done by intervention and outcome using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) Working Group approach on the GradePro Software, allowing subsequent recommendations regarding care to be made [19-22]. The GRADE approach involves assessing four areas of evidence, i.e. risk of bias, inconsistency, indirectness and imprecision. A summary of findings table was prepared using GradePro software and evidence was rated as high, moderate, low or very low quality allowing for an objective decision to be made regarding recommendations for care. From grading of evidence, practical bullet-point recommendations were made regarding the care of older people with urinary incontinence to be used in the ONTOP section of the SENATOR software.

3.1 Results

The results of the Delphi Process, applied to 11 identified outcomes, are shown in Supplementary Data Appendix 2. The number of episodes of incontinence per day was the only outcome rated as critical and hence was the only outcome of interest in this review. In the event that episodes of incontinence were reported per week, this was converted to episodes per day.

The results from the database searches and the screening process are shown in the PRISMA flow diagram (Fig. 1). From the 2496 articles identified through database searching following duplicate removal, a total of 33 systematic reviews were identified with 27 primary articles on eight different interventions were eligible for inclusion in this systematic review (see Supplementary data, Appendix 3 and 4).

Of the 27 studies, 17 were RCTs, four were non-randomised quasi-experimental studies, five were pre/post intervention studies and one was a prospective case series. All the studies were community based, including outpatient clinics and nursing homes, and had sample sizes varying from 13 to 222 participants. The majority (N=19) were based in the USA and the others in Australia, China, Hong Kong, Iran, Japan, Portugal and Sweden. A total of 17 studies consisted of women participants only, with men being the minority in the remaining 10 studies. There were varying diagnoses among participants, with five studies including participants with urinary urgency incontinence (UUI) or urgency predominant mixed urinary incontinence only, three studies investigating participants with stress urinary incontinence (SUI) only and the rest investigating any type of urinary incontinence. The risk of bias assessment is shown in Supplementary data, Appendix 5. The highest risk areas of bias were in the blinding of participants and personnel and the blinding of outcome assessment. Due to

the nature of the majority of the interventions, it would have been impossible to blind participants and personnel to the group allocation, hence major weight was given to the blinding of the outcome assessor during evidence assessment.

The included studies investigated eight types of non-pharmacological, non-surgical interventions, which were:

- Pelvic floor muscle training (7 studies)
    - Group exercise therapy (4 studies)
    - Individual pelvic floor muscle training (3 studies)
- Bladder training (5 studies)
- Behavioural therapy (10 studies)
- Electrical stimulation (1 study)
- Transcutaneous tibial nerve stimulation (1 study)
- Non-invasive magnetic stimulation (1 study)
- Minimising caffeine consumption (1 study)
- Acupuncture (1 study)

Of these interventions, only group pelvic floor muscle training, behavioural therapy and bladder training provided sufficient evidence for use in meta-analysis of reducing the number of episodes of urinary incontinence in elderly people (Figures 2-4). Two studies on behavioural therapy (Burton et al 1998 and Jirovec et al 2017) and one on bladder training (Colling et al 1992) could not be included in the meta-analyses as their results were not presented as mean and standard deviations of episodes of incontinence per day. The quality of evidence according to the GRADE classification is shown in Supplementary Data, Appendix 6. All the other interventions provided insufficient evidence to warrant their use in

treating urinary incontinence mainly due to a limitation in the number of studies, such that grading was only low or very low quality evidence.

Therefore, a small number of ONTOP recommendations were produced from this review for use in the SENATOR software. The instructions are based on the interventions in the included studies.

Recommendation 1- Group exercise therapy consisting of stretching exercises, PFMT and fitness exercises are recommended for older women with SUI in weekly sessions (strong recommendation based on moderate quality evidence).

Recommendation 2- Combination behavioural therapy consisting of PFMT, bladder training and methods for managing SUI and UUI is recommended for older people with urinary incontinence (strong recommendation based on moderate quality evidence).

- Bladder training consists of prompted or scheduled voiding every 1-hour, increasing by half an hour each week to a target of two and a half to three hours between voids.
- PFMT consists of at least 15 contractions of pelvic floor muscles three times/day each lasting as close to 10 seconds as possible for the patient. This can be with/without biofeedback of any form, at the discretion of the clinician.
- Instructions for managing incontinence:
    - UUI- Do not rush to toilet on sensation of urgency. Sit down and attempt relaxation plus 3-4 quick contractions of the pelvic floor muscles. When sensation passes, continue to toilet at a normal pace.
    - SUI- Contract pelvic floor muscles before and whilst carrying out activity associated with incontinence e.g. coughing and sneezing.

4.1 Discussion

This study found limited evidence for the use of eight types of non-pharmacological intervention for reducing daily episodes of urinary incontinence in older people. With the exception of group exercise therapy, there was generally little evidence of effect when these were used in isolation. However, when PFMT and bladder training were delivered in combination as a behavioural therapy, they appeared to provide greater benefit, leading to stronger evidence of effect in reducing episodes of incontinence. The relatively high degree of heterogeneity in the meta-analysis for behavioural therapy and bladder training probably reflects the range of different treatment protocols and study populations. Meta-analysis showed group exercise therapy reduced mean episodes of incontinence by 1.07 per day (95%CI 0.69-1.45) and behavioural therapy by 0.74 per day (95%CI 0.42-1.06), based on moderate quality of evidence according to GRADE. This makes these interventions approximately equally efficacious as antimuscarinic therapy for urgency incontinence [23] but without risking their adverse effects [24]. We therefore concluded the SENATOR software should make strong recommendations for both these therapies in the treatment of urinary incontinence in older persons.

The findings from this review differ to a degree from current guidelines, perhaps because guidelines are not usually focused on older people's needs specifically. The European Association of Urology (EAU) guidelines are, commendably, one of the few to include separate recommendations for older people [25], but these mostly emphasise the need for person-centred management rather than comprehensively reviewing and analysing the evidence-base in older people specifically. The National Institute for Health and Care Excellence (NICE) guidelines [26] recommends behavioural therapy only if bladder training is unsuccessful, while the EAU only makes recommendations for specific components of

behavioural therapy. The American Urological Association (AUA) guidelines for stress urinary incontinence does not make any evidence-based recommendations at all, but recommends PFMT based on expert opinion [27]. Our findings suggest behavioural therapy should be more widely recommended for older people. Both EAU and NICE recommend bladder training for all women with incontinence but studies in older people are lacking. Our analysis suggest bladder training reduces daily episodes of incontinence by 0.77 episodes per day (95%CI 0.15-1.38) but the quality of evidence was down-graded to 'low' due to included studies having high risk of bias and inconsistency. This means future studies are likely to influence recommendations for practice and we could not make a recommendation for including bladder training in SENATOR recommendations. Our results are consistent with other similar systematic reviews that used different methodology or inclusion criteria but also found insufficient evidence to recommend bladder training [28-31]. AUA, EAU and NICE recommend supervised PFMT for all patients while this review found insufficient evidence of efficacy in older people, except where PFMT is delivered within a programme of group exercise therapy. A recent Cochrane review of PFMT also supports its use as first line therapy, but did not consider older people separately, nor did it differentiate between individual and group exercise [32]. In common with other reviews, we found little evidence to recommend other lifestyle interventions, such as reducing caffeine intake [33], despite their inclusion in the EAU and NICE guidelines [25,26].

The review had a number of strengths and limitations relating to both the methods employed and the studies included in the review. Using the Delphi process helped identify the outcome of the highest importance to clinicians was included in the review. However, a major limitation is that the panel did not include patient representatives and not all clinicians had a special interest in incontinence specifically. Therefore, other important outcomes may have been excluded. The standardised method employed in all the ONTOP reviews ensures

consistency and has already resulted in published evidence-based recommendations for non-drug management in delirium [34], falls [35,36], stroke [37], pressure sores [38,39], behavioural disturbances in dementia [40], malnutrition [41] and sarcopenia [42]. This method also has the advantage of not pre-specifying interventions in the search terms, allowing evaluation of lesser-known interventions. However, by identifying current systematic reviews as a source of primary trials, the risk of missing potentially informative trials was increased. Nevertheless, no further studies were found by hand-searching bibliographies of included reports, suggesting the search methods were robust. Only studies with a population mean age over 65 years were included. This is arguably a strength of the study in making its findings more relevant to a large proportion of people with incontinence, but it also risks neglecting potentially useful interventions that have only been tested in younger people. This is particularly important because only one study solely investigated older people. We also acknowledge that older people are a heterogenous group and it may have arguably been more clinically relevant to consider frailty or multi-morbidity rather than age. However, definitions of frailty vary and the management of incontinence in frailty is already considered in the latest International Consultation on Incontinence [43]. The current review includes limited evidence in men and a number of studies did not stratify populations by sex. This restricted the evidence and subsequent recommendations largely to women only. Excluding trials in specific conditions relating to incontinence may have resulted in selection bias. Finally, we limited the search to studies published in English but we did not identify any important trials in other languages during our search.

5.1 Conclusions

Group exercise therapy for stress incontinence and behavioural therapy incorporating bladder training, pelvic floor muscle training and practical tips to manage stress and urgency incontinence are beneficial in the management of urinary incontinence in older women. There was insufficient evidence to make recommendations in men or to recommend other forms of non-pharmacological therapy in older women.

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Figure Legends

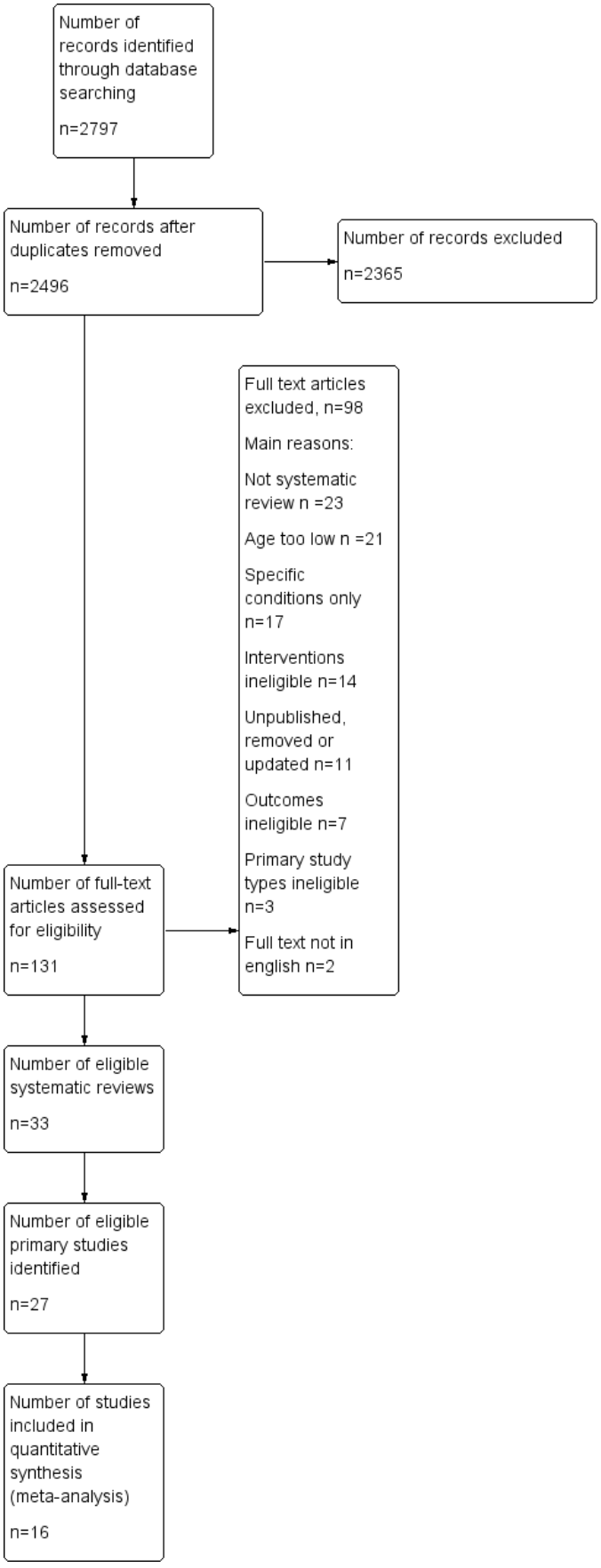
Figure 1: PRISMA Flow Diagram

Figure 2- Effect of group exercise therapy on number of episodes of incontinence/day

Figure 3- Effect of behavioural therapy on number of episodes of incontinence/day

Figure 4- Effect of bladder training on number of episodes of incontinence/day (Hu et al reported as mean change in episodes per day from baseline).

Figure 1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Number of records after duplicates removed
n=2496
Number of records excluded
n=2365
Full text articles excluded, n=98
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Not systematic review n =23
Age too low n =21
Specific conditions only n=17
Interventions ineligible n=14
Unpublished, removed or updated n=11
Outcomes ineligible n=7
Primary study types ineligible n=3
Full text not in english n=2
Number of full-text articles assessed for eligibility
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Number of eligible systematic reviews
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Number of eligible primary studies identified
n=27
Number of studies included in quantitative synthesis (meta-analysis)
n=16

Figure 2

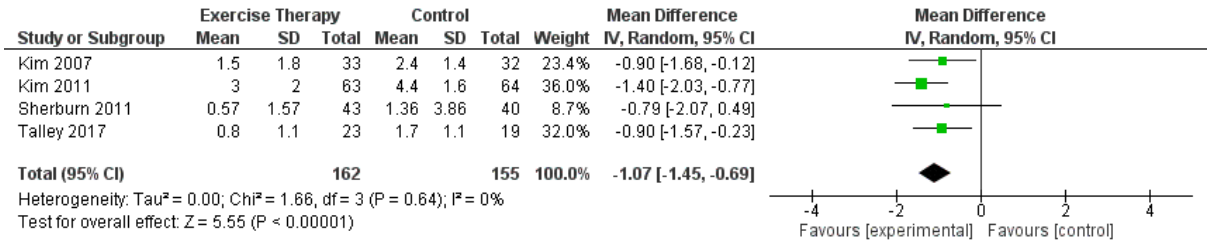

Exercise Therapy
Control
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Kim 2007 1.5 1.8 33 2.4 1.4 32 23.4% -0.90 [-1.68, -0.12]
Kim 2011 3 2 63 4.4 1.6 64 36.0% -1.40 [-2.03, -0.77]
Sherburn 2011 0.57 1.57 43 1.36 3.86 40 8.7% -0.79 [-2.07, 0.49]
Talley 2017 0.8 1.1 23 1.7 1.1 19 32.0% -0.90 [-1.57, -0.23]
Total (95% CI) 162 155 100.0% -1.07 [-1.45, -0.69]
Heterogeneity: Tau² = 0.00; Chi² = 1.66, df = 3 (P = 0.64); I² = 0%
Test for overall effect: Z = 5.55 (P < 0.00001)
-4
-2
0
2
4
Favours [experimental]
Favours [control]

Figure 3

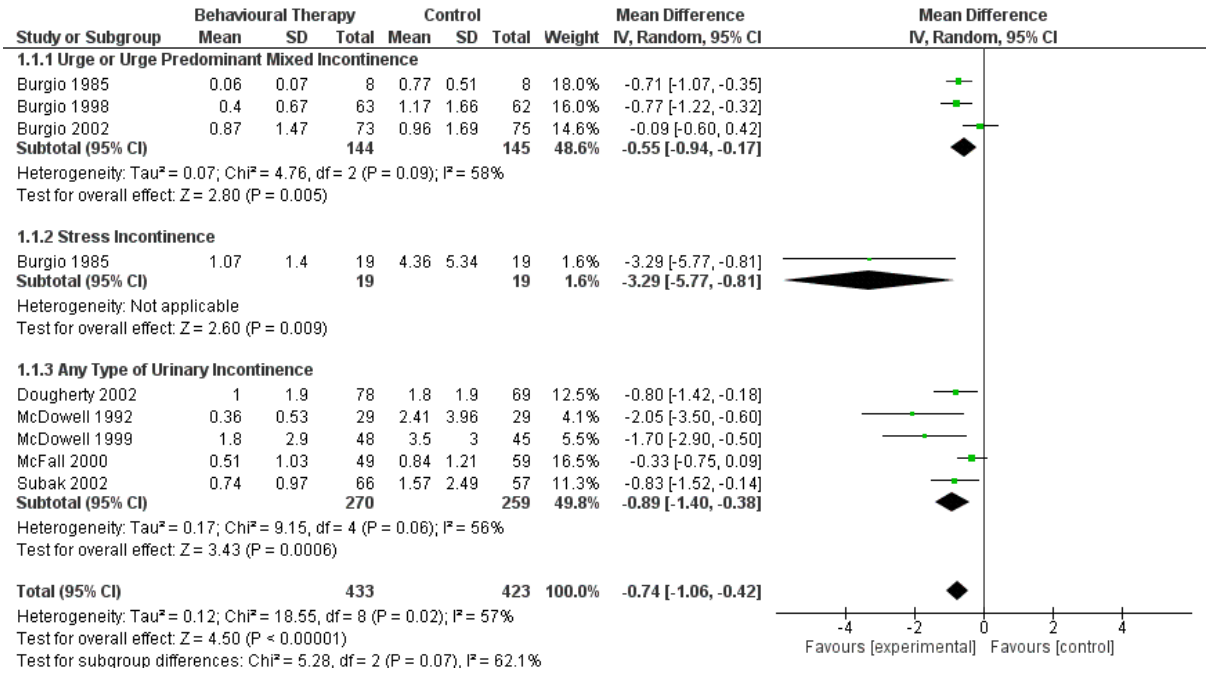
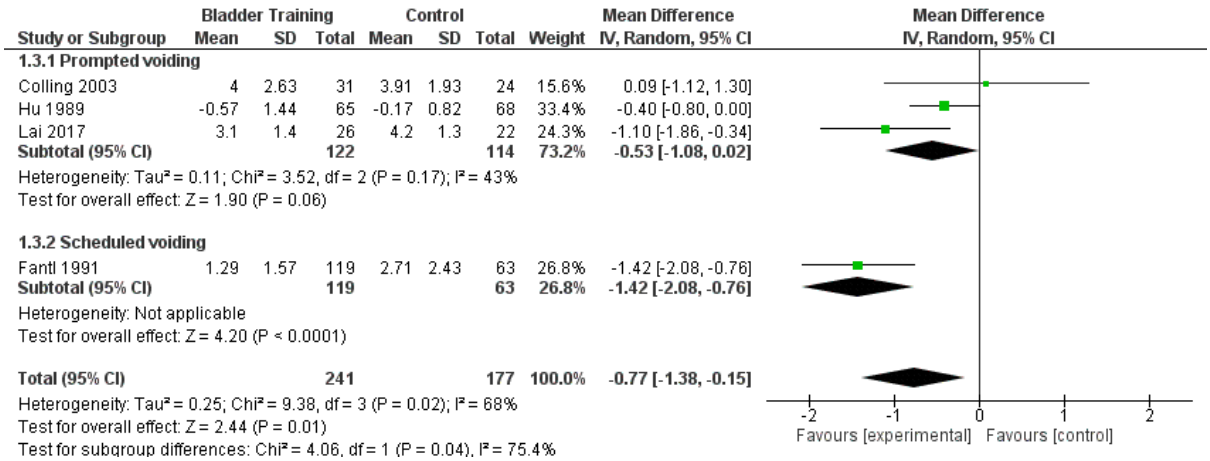

Behavioural Therapy
Control
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
1.1.1 Urge or Urge Predominant Mixed Incontinence
Burgio 1985 0.06 0.07 8 0.77 0.51 8 18.0% -0.71 [-1.07, -0.35]
Burgio 1998 0.4 0.67 63 1.17 1.66 62 16.0% -0.77 [-1.22, -0.32]
Burgio 2002 0.87 1.47 73 0.96 1.69 75 14.6% -0.09 [-0.60, 0.42]
Subtotal (95% CI) 144 145 48.6% -0.55 [-0.94, -0.17]
Heterogeneity: Tau² = 0.07; Chi² = 4.76, df = 2 (P = 0.09); I² = 58%
Test for overall effect: Z = 2.80 (P = 0.005)
1.1.2 Stress Incontinence
Burgio 1985 1.07 1.4 19 4.36 5.34 19 1.6% -3.29 [-5.77, -0.81]
Subtotal (95% CI) 19 19 1.6% -3.29 [-5.77, -0.81]
Heterogeneity: Not applicable
Test for overall effect: Z = 2.60 (P = 0.009)
1.1.3 Any Type of Urinary Incontinence
Dougherty 2002 1 1.9 78 1.8 1.9 69 12.5% -0.80 [-1.42, -0.18]
McDowell 1992 0.36 0.53 29 2.41 3.96 29 4.1% -2.05 [-3.50, -0.60]
McDowell 1999 1.8 2.9 48 3.5 3 45 5.5% -1.70 [-2.90, -0.50]
McFall 2000 0.51 1.03 49 0.84 1.21 59 16.5% -0.33 [-0.75, 0.09]
Subak 2002 0.74 0.97 66 1.57 2.49 57 11.3% -0.83 [-1.52, -0.14]
Subtotal (95% CI) 270 259 49.8% -0.89 [-1.40, -0.38]
Heterogeneity: Tau² = 0.17; Chi² = 9.15, df = 4 (P = 0.06); I² = 56%
Test for overall effect: Z = 3.43 (P = 0.0006)
Total (95% CI) 433 423 100.0% -0.74 [-1.06, -0.42]
Heterogeneity: Tau² = 0.12; Chi² = 18.55, df = 8 (P = 0.02); I² = 57%
Test for overall effect: Z = 4.50 (P < 0.00001)
Test for subgroup differences: Chi² = 5.28, df = 2 (P = 0.07), I² = 62.1%
-4
-2
0
2
4
Favours [experimental]
Favours [control]

Figure 4


Bladder Training
Control
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
1.3.1 Prompted voiding
Colling 2003 4 2.63 31 3.91 1.93 24 15.6% 0.09 [-1.12, 1.30]
Hu 1989 -0.57 1.44 65 -0.17 0.82 68 33.4% -0.40 [-0.80, 0.00]
Lai 2017 3.1 1.4 26 4.2 1.3 22 24.3% -1.10 [-1.86, -0.34]
Subtotal (95% CI) 122 114 73.2% -0.53 [-1.08, 0.02]
Heterogeneity: Tau² = 0.11; Chi² = 3.52, df = 2 (P = 0.17); I² = 43%
Test for overall effect: Z = 1.90 (P = 0.06)
1.3.2 Scheduled voiding
Fantl 1991 1.29 1.57 119 2.71 2.43 63 26.8% -1.42 [-2.08, -0.76]
Subtotal (95% CI) 119 63 26.8% -1.42 [-2.08, -0.76]
Heterogeneity: Not applicable
Test for overall effect: Z = 4.20 (P < 0.0001)
Total (95% CI) 241 177 100.0% -0.77 [-1.38, -0.15]
Heterogeneity: Tau² = 0.25; Chi² = 9.38, df = 3 (P = 0.02); I² = 68%
Test for overall effect: Z = 2.44 (P = 0.01)
Test for subgroup differences: Chi² = 4.06, df = 1 (P = 0.04), I² = 75.4%
-2
-1
0
1
2
Favours [experimental]
Favours [control]