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SYSTEMATIC REVIEW

Treatment of urge incontinence in postmenopausal women: A systematic review

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Summary

Background: *Urinary incontinence and other urinary symptoms tend to be frequent at menopause because of hormonal modifications and aging. Urinary symptoms are associated with the genitourinary syndrome of menopause which is characterized by physical changes of the vulva, vagina and lower urinary tract. The treatment strategies for postmenopausal urinary incontinence are various and may include estrogens, anticholinergics, and pelvic floor muscle training. A comparison of these treatments is difficult due to the heterogeneity of adopted protocols. We systematically reviewed the evidence from randomized controlled trials (RCTs) focusing on treatment of postmenopausal women with urge incontinence.*

Methods: *We conducted a systematic review and meta-analysis by searching PubMed and EMBASE databases for randomized controlled trials (RCTs) reporting results of treatments for postmenopausal urinary urge incontinence. Odds ratios for improvement of urinary incontinence were calculated using random effect Mantel-Haenszel statistics.*

Results: *Out of 248 records retrieved, 35 eligible RCTs were assessed for risk of bias and included in the meta-analysis. Compared with placebo, systemic estrogens were associated with decreased odds of improving urinary incontinence in postmenopausal women (OR = 0.74, 95% CI: 0.61-0.91, 7 series, 17132 participants, Z = 2.89, P = 0.004, I^2 = 72%). In most studies, no significant improvement in urinary symptoms was observed in patients treated with local estrogens, although they showed to be helpful in improving vaginal symptoms. Vitamin D, phytoestrogens and estrogen modulators were not effective in improving symptoms of incontinence and other symptoms of genitourinary menopause syndrome or yielded contradictory results. A randomized controlled trial demonstrated that oxybutynin was significantly better than placebo at improving postmenopausal urgency and urge incontinence. The combination of anticholinergics with local estrogens has not been shown to be more effective than anticholinergics alone in improving urinary incontinence symptoms in postmenopausal women. Physical therapy showed an overall positive outcome on postmenopausal urinary incontinence symptoms, although such evidence should be further validated in the frame of quality RCTs.*

Conclusions: *The evidence for effective treatment of postmenopausal urinary incontinence is still lacking. Well-designed large studies having subjective and objective improvement primary endpoints in postmenopausal urinary incontinence are needed. At present, a combination of different treatments tailored to the characteristics of the individual patient can be suggested.*

KEY WORDS: *Urinary incontinence; Urgency; Menopause; Estrogens; Anticholinergics; Vitamin D; Soy.*

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INTRODUCTION

Urinary incontinence affects 15-35% of community-dwelling postmenopausal women (1, 2). Urge inconti-

nence is the more common form of incontinence after menopause. It presents in association with a combination of urinary symptoms, including frequency, nocturia, urgency, and dysuria. Urge syndrome disorders are often misunderstood to be symptoms of urinary tract infection and, consequently, are not treated appropriately.

Estrogen deficiency is thought to play an important role in the etiology of the "*urge syndrome*", that tends to rise in prevalence and to enhance in intensity as the years of estrogen deficiency increase. In fact, estrogens affect the urethral mucosa, the smooth muscle, and the alpha-adrenergic tone in the urinary tract (3). Both oral and vaginal estrogens have been used in the management of urinary incontinence in postmenopausal women, although the effectiveness of hormonal therapy on urinary incontinence is controversial. Alternative treatments include anticholinergic medication, pelvic floor muscle exercise and bladder training. Combinations of anticholinergics and topical vaginal estrogen are also used for treatment of urge incontinence and female sexual dysfunction. In addition, posterior tibial nerve stimulation and acupuncture were used in the conservative treatment of these syndromes, in order to tackle the functional physiological changes associated with urge incontinence. Moreover, fractional CO_2 laser and *low intensity shock wave treatment* (LiSWT) have emerged as new treatment modalities, as these approaches may improve the atrophy of the urethral and bladder mucosa.

Evaluation of the efficacy of the treatment of urge incontinence is difficult due to heterogeneity of the protocols adopted, and to the paucity of randomized controlled studies. Our research was aimed to systematically review the available evidence resulting from randomized controlled trials (RCTs) aiming to treat postmenopausal women with urge incontinence.

Methods

Protocol and registration

This review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (5). The review protocol was registered on the PROSPERO platform (registration code: CRD42023405369).

Types of studies

We considered articles written in English, reporting the results of *randomized controlled trials* (RCTs) evaluating the efficacy of treatment of urge incontinence in postmenopausal women.

Types of patients

We included postmenopausal women of any ethnicity or age.

Types of interventions

We included studies focusing on any treatment aimed at addressing the signs and symptoms of urge incontinence.

Outcomes

The outcomes considered for this review were the rate and/or severity of symptoms and signs (urge incontinence, urgency, nocturia, pelvic floor muscle strength) evaluated by specific interview questions, or by administering questionnaires to patients (e.g., the *Revised Urinary incontinence Scale*, the *Overactive Bladder Questionnaire, the International Consultation on Incontinence Questionnaire*) or by recording the reports of structured bladder diaries. Microbiologic, cytologic and urodynamic findings were also evaluated. The outcomes were compared in patients receiving treatment compared to placebo or to no treatment.

Search strategy

Two electronic databases (*PubMed and EMBASE*) were searched for records reporting RCTs published up to 31 January 2023. The search was performed using strings based on broad MeSH terms (e.g., female AND menopause AND (dysuria OR urination disorders OR incontinence) AND treatment). Relevant data were also searched by browsing the reference lists of reviews and clinical trial reports, or through other sources (e.g., *clinicaltrials.gov*; *https://www.clinicaltrialsregister.eu/*).

Data collection and analysis (selection of studies and data extraction)

Title and abstract screening to exclude records that did not meet the inclusion criteria were performed independently by 4 authors (2 authors for *PubMed* and 2 for *EMBASE*). Duplicate references were deleted. Full texts were downloaded for a second round of screening and to extract relevant information. Controversies were resolved by the research coordinator (AT).

A PRISMA flow diagram was drawn to illustrate the results of the study selection process (Figure 1) (6).

Data extraction was conducted by 4 authors using a standardized form. The following data were obtained from each study: author(s), publication year, study design, population, intervention(s), results. In case of missing or insufficient information, we performed sensitivity analysis, in order to consider the impact of missing data on the meta-analysis results.

Quality evaluation on methodology

Three authors independently performed the quality assessment by identifying potential biases using the Cochrane risk of bias tool (9). The following potential sources of bias were considered: randomization process (D1), deviations from the intended interventions (D2), missing outcome data (D3), measurement of the outcome (D4) and selection of the reported result (D5). Disagreements were resolved by discussion. Risk of bias was not used to exclude studies.

Statistical analysis

Statistical analysis was performed using the RevMan5 software. Dichotomous data and number of subjects were extracted to calculate odds ratios (OR), confidence intervals (CI) to OR, and Z statistics (Random-effects model, Mantel-Haenszel method).

Assessment of heterogeneity

The heterogeneity of pooled results was assessed by the I^2 statistic, reported with 95% CIs, and interpreted as of lesser importance ($I2 \leq 40\%$), moderate ($I^2 = 30\%$-60%),

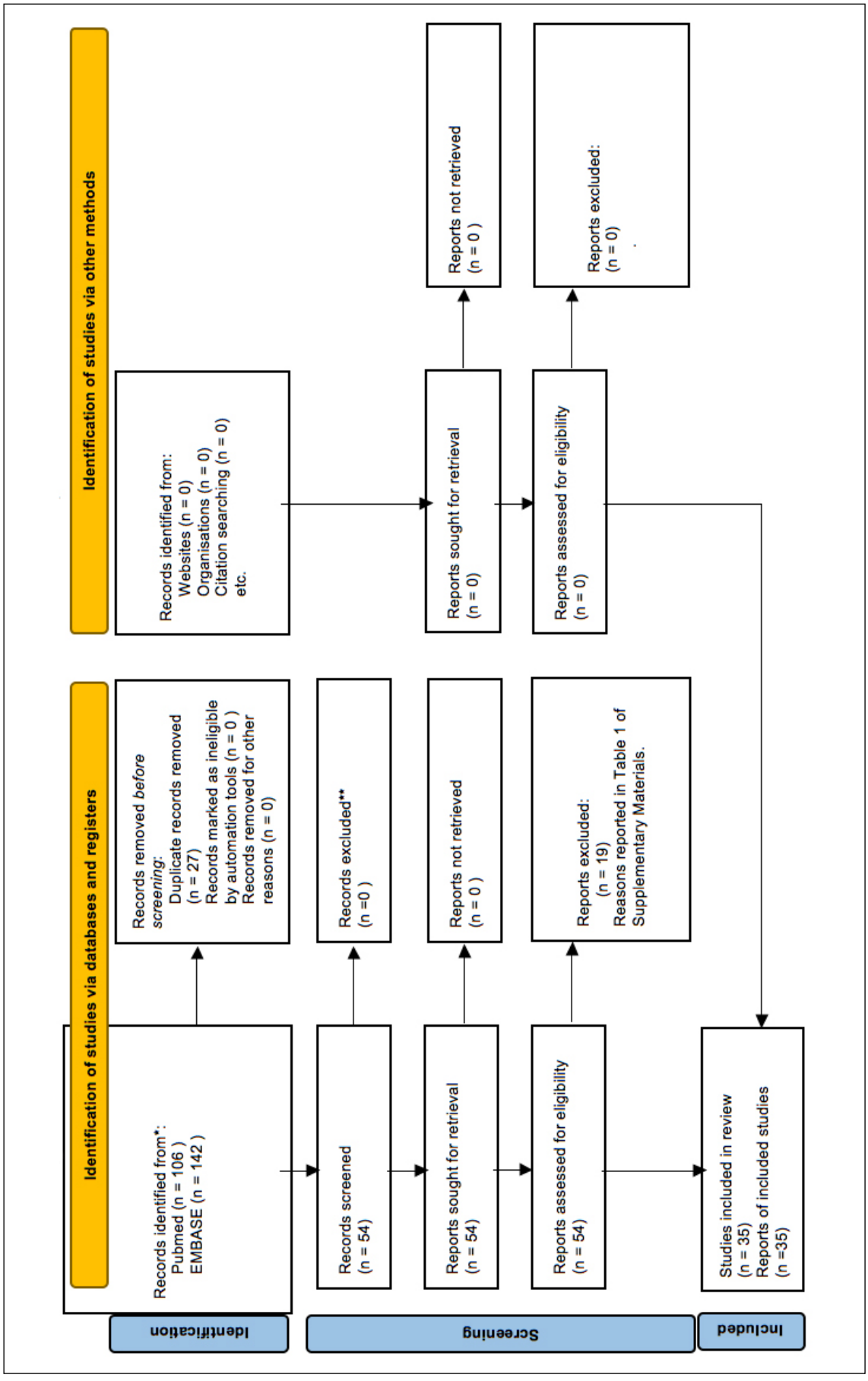


Figure 1.
PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources.

substantial (I^2 = 50%-90%) or considerable ($I^2 \geq 75\%$), according to Cochrane criteria. Sensitivity analysis was planned if considerable heterogeneity of pooled analyses including at least 4 studies was detected.

Assessment of publication bias

Publication bias was assessed by generating funnel plots if meta-analyses included at least 4 trials. The Begg's and Egger's tests were used to test funnel plot (a)symmetry and to confirm or exclude the presence of publication bias or small study effect. Data on funnel plots were presented as the natural logarithm of odds ratios.

The MetaEssential 2 software (*Rotterdam School of Management, Erasmus University, The Netherlands*) was used for funnel plot analysis.

Results

From 248 retrieved records ((Pubmed = 106, EMBASE = 142), and after removal of 27 duplicates, we selected 54 reports which were examined by full-text reading. After full-text examination, 19 reports were excluded for various reasons (***Supplementary Materials - Table 1***). The remaining 35 reports were classified according to different types of treatment, namely estrogen treatment, including systemic (N = 9) and local (N = 6) administration, anticholinergics (N = 5), other treatments (N = 6), and physical treatment (N = 9).

Risk of bias

Of the 35 reports, only 8 were rated as having a low risk of bias, whereas 5 reports presented slight concerns and 23 high concerns of bias. The randomization process was associated to risk of bias in most reports (n = 24) and to unclear risk in 10. Only one study presented high concerns of bias with respect to the randomization process. Risk of deviations from the intended intervention (blinding) was rated as low in 18 reports, unclear in 4 and high in 13. The risk for missing outcome data was judged low in 20 reports, unclear in 4 and high in 11. The risk of bias in measurement of outcome was considered low in 27 reports, unclear in 1 and high in 7. The risk of bias in selection of the reported results was judged low in 34 and unclear in 1 (***Supplementary Materials - Figure 1***).

Systemic estrogens

The effect of estrogen administration on urinary incontinence in postmenopausal women was compared to placebo or no treatment in 9 studies. Most studies date back to the 1990s or early 2000s, and some relate to programs that had women's general health after menopause as their main outcome, namely the *Women's Health Initiative*, the *Heart and Estrogen/Progestin Replacement Study* (HERS), the *Estrogen Replacement and Atherosclerosis* (ERA) trial, the *Danish Osteoporosis Prevention Study* (DOPS).

In a study, estriol produced not significant subjective and objective changes of the lower urinary tract function compared with placebo (8).

In three studies (9-11), administration of combined estrogen and progestogen therapy (0.625 mg/day conjugated equine estrogen plus 10 mg/day medroxyprogesterone acetate) was compared with placebo.

Fantl et al. observed no significant changes in the number of incontinence episodes, weight of fluid losses and number of diurnal or nocturnal voids (9).

Conversely, *Grady et al.* showed that oral estrogen plus progestin treatment was associated with a worsening of urinary incontinence in postmenopausal women of the HERS (10).

An article by *Steinauer et al.*, reporting about some results of HERS, confirmed a higher rate of weekly incontinence in patients on hormone treatment compared to a placebo group (64% *vs* 49%) (11). In two other studies (12, 13), both estrogens alone and a combination of estrogen and progestinics were compared with placebo. Oral estrogen plus progestinic treatment had no significant effects on the de novo development of urge urinary incontinence in patients who were asymptomatic at baseline (RR 1.15) but increased the frequency of urinary incontinence (RR 1.38) and worsened the amount of urinary incontinence episodes (RR 1.20) in patients who reported urinary incontinence at baseline compared to placebo. Oral estrogens alone increased the risk of the de novo development of urinary incontinence (RR 1.32), worsened the urinary frequency (RR 1.47) and increased the amount of urinary incontinence episodes in patients with incontinence at baseline (RR 1.59) (12). A similar study showed significantly higher rates of urinary incontinence in the estrogen-only group compared to the placebo group (13). In two studies, the effect of an estrogen implant, or of transdermal estrogen, was compared with placebo (14, 15). After two years of treatment with ultralow-dose transdermal estriol (0.014 mg/d), the prevalence of incontinence symptoms did not differ in treated women compared to placebo. The odds ratio for incontinence worsening in women with incontinence at baseline was 1.35 in the estradiol treated compared with placebo group, and the odds of developing at least one weekly incontinence episode in women without incontinence at baseline was 1.20 (14). In neither case were odds ratios statistically significant. *Rufford et al.* evaluated the effect of systemic estrogen replacement by a 25 mg 17b-estradiol implant compared to placebo implant. No significant differences between the groups were observed by videocystourethrography, frequency volume chart, visual analogue score of symptoms, and *King's Health Care Quality of life Questionnaire* (15). Finally, an open label study had a more complex design, as it included a group that was randomized to receive hormonal treatment versus no treatment and a second group in which patients chose whether to receive hormonal treatment or no treatment (16). First-line hormonal treatments were: (a) sequential oral estrogen and progestogen (2 mg estradiol for the first 12 days, 2 mg estradiol plus 1 mg norethisterone acetate for 10 days, and 1 mg estradiol for 6 days) in women with intact uterus and (b) oral continuous estradiol, 2 mg per day, in hysterectomized women. Hormonal treatment did not seem to influence the degree of voiding frequency, or the severity of incontinence (16).

The effect of hormone therapy both as combination of estrogens with progestogens or estrogens alone was quantitatively evaluated In 7 studies.

Meta-analysis

Treatment of incontinence was considered successful

when the Authors defined the patients as cured (absence of the symptom(s) present at baseline) (8, 15) or improved (9, 10, 14) or without worsening of the degree of bother or disturbance attributed to urinary incontinence (12).

The odds of successful treatment were significantly lower in the hormone treatment group compared to the placebo or control groups (OR = 0.74, 95% CI: 0.61-0.91, 7 series, 17132 participants, Z = 2.89, P = 0.004, I^2 = 72%, Figure 2). Funnel plot analysis for detection of publication bias produced uncertain results (***Supplementary Materials Figure 2***). Visual analysis of the plot suggest a significant degree of asymmetry, which was confirmed by the Egger regression test (p = 0.016), but not to the Begg's test (p = 0.88).

When women treated with a combined hormonal protocol were analyzed separately, the odds of success of incontinence treatment were confirmed to be significantly lower than the control group (OR = 0.78, 95% CI: 0.68-0.90, 3 series, 10707 participants, Z = 3.53, p = 0.0004, I^2 = 21%, Figure 3), while the odds ratios of success of treatment with estrogen alone were not significantly different from controls (OR = 0.72, 95% CI: 0.49-1.06, 4 series, 6425 participants, Z = 1.65, p = 0.10, I^2 = 54%, Figure 4, panel A). Visual analysis of the funnel plot suggested the presence of asymmetry, which was not confirmed by the Egger

Figure 2.
Odds for success of systemic hormone treatment of urinary postmenopausal incontinence.

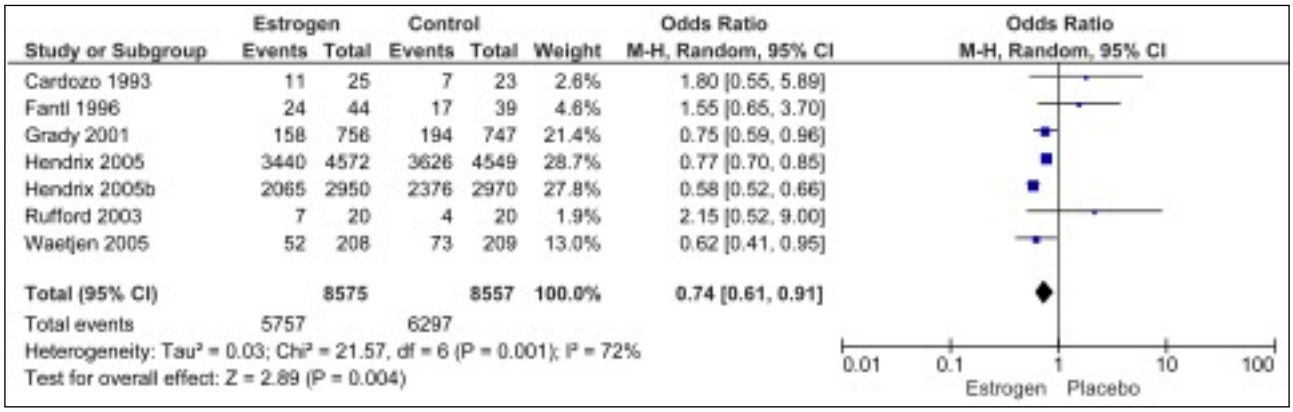


Figure 3.
Odds for success of combined systemic hormone treatment of urinary postmenopausal incontinence.

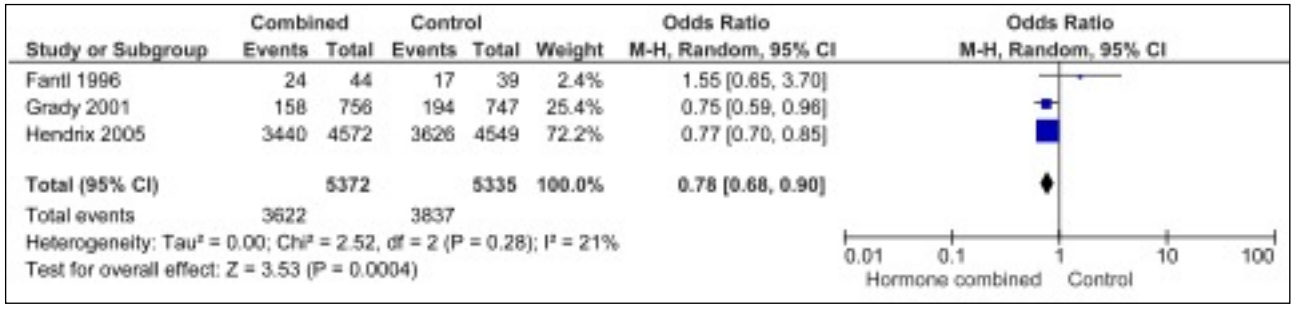


Figure 4.
Odds for success of treatment for urinary postmenopausal incontinence with systemic estrogens alone.

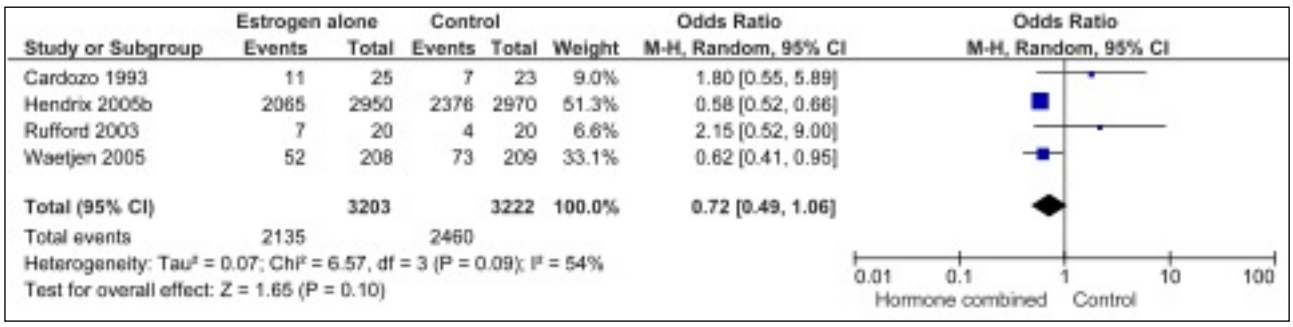
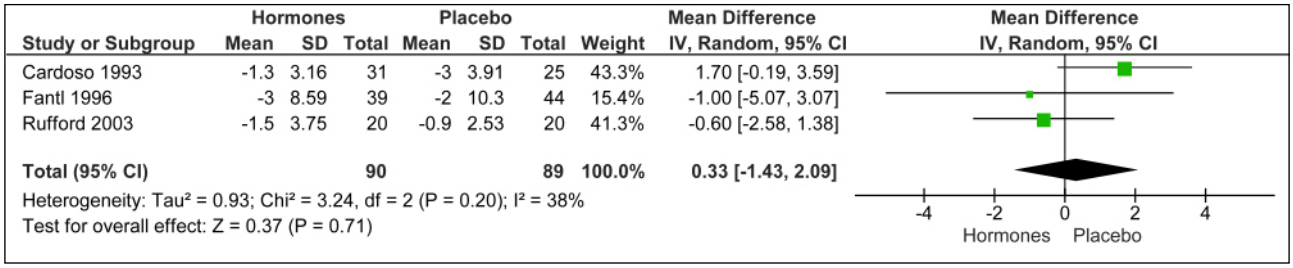
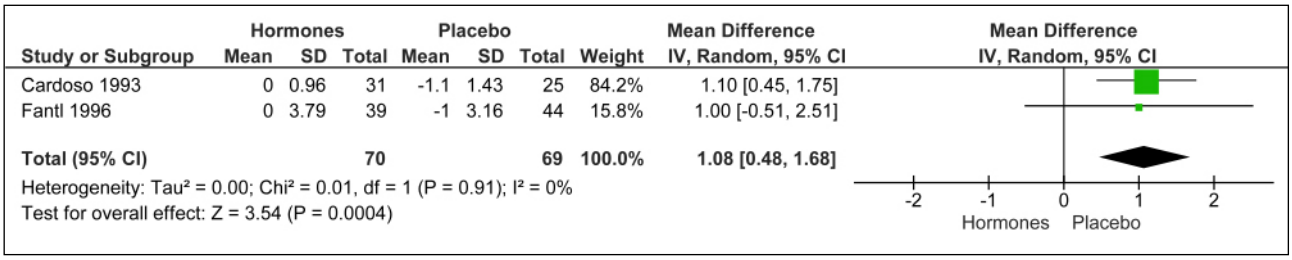


Figure 5.
Odds for urgency, nocturia and urinary incontinence in patients on systemic hormone treatment.

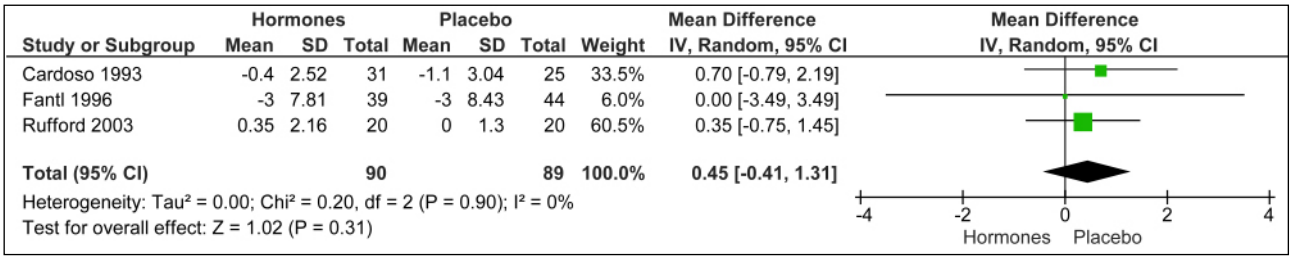
a) diurnal voids



b) nocturia



c) urinary incontinence



regression test (p = 0.078) or by the Begg's test (p = 0.17) (***Supplementary materials Figure 2***).

On the other hand, meta-analyses of three studies demonstrated that the odds for diurnal voids and urinary incontinence in women on systemic hormone treatment were not different from those in women treated with placebo, while in two studies the odds for nocturia worsened for women on hormonal treatment compared to controls (Figure 5).

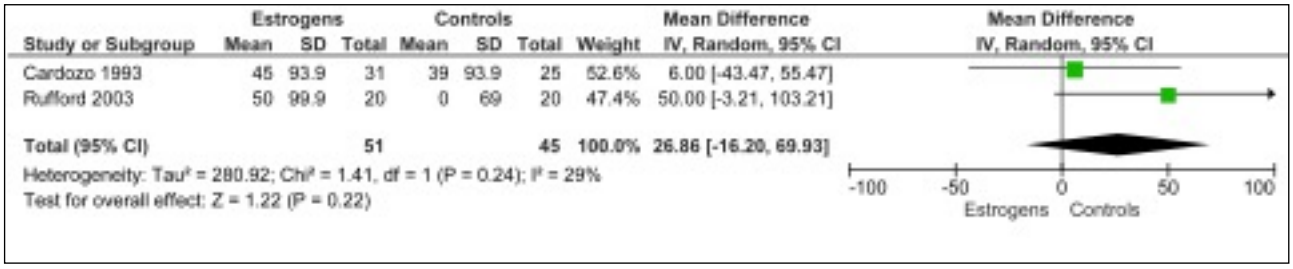
Similarly, in two studies, the odds of improvement in urodynamic parameters (volume at first desire to void, cystometric capacity, and detrusor pressure) were not significantly different in patients receiving hormone treatment compared to controls (Figure 6).

Local estrogens

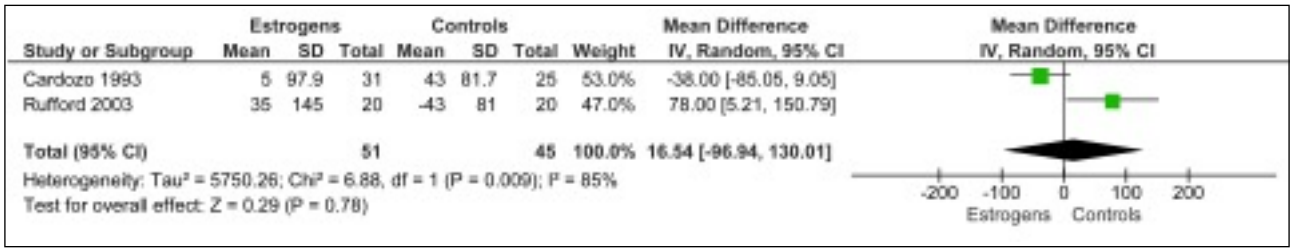
Three studies compared the use of local estrogens with placebo (17-19). One study compared local estrogens alone with local estrogens combined with benzydamine (20). Another study compared estrogen delivery via a vaginal ring with an estriol pessary (21). Finally, a study compared ultralow-dose estradiol vaginal ring with oral oxybutynin (22).

Figure 6.
Odds for improvement of urodynamic parameters in patients on systemic hormone treatment compared to controls.

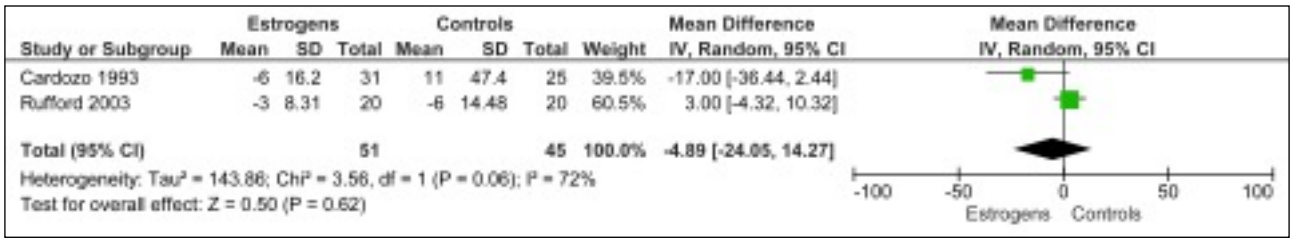
a) volume at first desire to void



b) cystometric capacity



c) detrusor pressure



Cardozo et al. evaluated the effect of 17-beta estradiol 25 mg vaginal tablets or placebo daily for 12 weeks (17). No significant improvement was observed in urinary frequency and urgency following treatment with intravaginal 17-beta estradiol. The only statistically significant difference was a greater reduction in urinary urgency in women with a urodynamic diagnosis of sensory urgency. In this subgroup, urgency was related to urogenital atrophy secondary to estrogen deficiency.

In a study by *Dessole et al.*, the treatment cohort received intravaginal estriol ovules (1 mg ovule once-daily for 2 weeks and subsequently 2 ovules once-weekly for a 6 months), and the control group received inert placebo vaginal suppositories in a similar regimen. A subjective improvement of incontinence was observed in 68% of the treated participants in comparison to 16% of the controls.

Speroff et al. assessed the efficacy of a vaginal ring, delivering the equivalent of 50 or 100 mcg per day of estradiol compared with placebo (19). There was a general trend towards the improvement of urogenital symptoms in patient with active rings, although a significant improvement compared with placebo was observed only for certain vaginal symptoms (vaginal dryness, pain during intercourse).

Melis et al. compared vaginal administration of a low dose of estriol (0.5 mg daily for 14 days, followed by 0.5 mg every two days for 3 months) with the same regimen plus an anti-inflammatory and antibacterial compound (benzidamine) (20). The efficacy on urinary symptoms (nocturia, incontinence, urge incontinence) was not different between the two groups, although the combination of estriol with benzidamine was more effective in reducing vaginal symptoms (itching, burning, leucorrhea, dryness).

Lose et al. compared the efficacy of an estradiol-releasing vaginal ring with an estriol pessary, showing that these strategies were equally efficacious in reducing urinary urgency, urge incontinence, stress incontinence and nocturia (21). The vaginal ring showed higher patient acceptability compared to estriol pessaries.

Nelken et al. evaluated women who were randomized to receive either a vaginal ring releasing ultralow-dose estradiol (2 mg of 17beta-estradiol released at a rate of 7.5 Kg microgr daily) or oral oxybutynin (5 mg twice daily) for 12 weeks (22). Both treatments achieved a reduction in the number of voids per day, with no significant difference between the groups.

Anticholinergics

Only one study compared anticholinergics with placebo (23). In four studies (24-27) the efficacy of anticholinergics alone was compared with anticholinergics in combination with local estrogens.

Tapp et al. performed a placebo controlled cross over study of oxybutynin chloride in postmenopausal women suffering from detrusor instability (23). Oxybutynin therapy significantly reduced the symptoms of urgency, urge incontinence, and nocturia. Oxybutynin therapy was significantly better than placebo at improving urgency and urge incontinence.

Chughtai et al. compared fesoterodine with topical vaginal estrogen once daily with fesoterodine once daily alone for 12 weeks (24). Both treatments were associated with a significant improvement in urinary symptom severity and quality of life. Compared to fesoterodine alone, the combination treatment showed a reduced symptom severity (*OAB score*) and higher quality of life (HRQL and SQOL-F score). Urinary frequency was significantly reduced from baseline in the combination group alone.

Jiang et al. randomized patients to receive solifenacin 5 mg plus promestriene vaginal capsules, or solifenacin 5 mg alone for 12 weeks (25). There were no significant intergroup differences in the number of daily voids, urgency episodes, urge incontinence episodes and nocturia.

Martin et al. randomized patients to treatment with fesoterodine in combination with either a conjugated estrogen vaginal cream or a placebo vaginal cream (26). Both treatments decreased the severity of urinary symptoms (OAB and USIQ scores) and increased the quality of life (HRQL score). No significant intergroup differences were

observed. In addition, there was no significant improvement in data recorded in bladder diaries.
Tseng et al. randomized patients to treatment with 2 mg tolterodine twice daily compared to 2 mg tolterodine twice daily associated to vaginal conjugated equine estrogen 0.625 mg twice a week for 12 weeks (27). The comparison between groups showed a significantly greater improvement in daytime frequency and voided volume after combination treatment. Other symptoms, including nocturia, urgency and urge incontinence were improved with both treatments, though intergroup differences were not reported. The quality of life was significantly improved after combination treatment compared to the single-agent protocol.

Other treatments
Two reports presented the results of treatment with soy extracts (28, 29).
Bumbu et al. compared the effect of long-term administration of soy extracts (40% isoflavones) with the results of continuous combined hormonal treatment based on 1 mg estradiol and 0.5 mg noretisterone acetate daily, with a control no-treatment group (28). After 12 months, symptom scores, according to the *Revised Urinary Incontinence Scale* (RUIS), and the incidence of urinary incontinence, were influenced neither by soy nor by hormone treatment compared to placebo.
Manorai et al. compared the effect of a soy-rich diet (25 g soy protein in various forms of soy food, containing more than 50 mg/day of isoflavones) with an isocaloric control diet (soy-free diet) (29). The symptoms of urge incontinence and vaginal dryness significantly increased after 12-weeks of soy-free diet.
Two studies evaluated the effect of vitamin D supplementation on urinary incontinence symptoms (30, 31).
Markland et al. conducted a randomized trial in women with serum 25-hydroxyvitamin D (25[OH]D) of 30 ng/mL or less, comparing treatment with weekly oral 50.000 IU vitamin D3 or placebo for 12 weeks (30). Vitamin D treatment demonstrated a greater than 40% decrease in urinary incontinence episodes, which however did not reach statistical significance compared to placebo.
Oberg at al. (31) allocated patients to 20 000 IU of vitamin D3 twice a week, or to a similarly looking placebo. After 12 months, a statistically significant reduction in the severity of urine incontinence in the high dose vitamin D group was observed, compared to placebo.
Other pharmacological treatments were evaluated in two studies (32, 33).
Waetjen et al. assigned patients to raloxifene or placebo (32). After 3 years of treatment, there was no significant difference between raloxifene and placebo groups in terms of urinary incontinence severity (OR 1.02). In addition, the odds of worsening urinary incontinence severity were 1.05 and the odds of developing new onset incontinence were 0.95.
Green et al. assigned women to treatment with aprepitant at a daily dose of 160 mg versus placebo for 8 weeks (33). Aprepitant is a neurokinin-1 receptor antagonist that may be efficacious in the treatment of urge urinary incontinence, since preclinical evidence suggested that incontinence may be associated to up-regulation of the tachykinin mediated bladder/spinal reflex signaling. Treatment significantly decreased the number of daily voids and urgency episodes compared with placebo at 8 weeks, although the daily number of urge urinary incontinence and the total urinary incontinence episodes were not significantly reduced.

Physical treatment
Three studies compared postmenopausal women treated with *pelvic floor muscle training* (PFTM) with a control group (34-36).An increase of pelvic floor muscle contractility after PFMT, as evaluated by *surface electromyography* (sEMG) and digital palpation, was observed in two reports (34,35). *Alves et al.* demonstrated an improvement of incontinence symptom scores (ICIQ-OAB, ICIQ UI-SF, MESA), as well as of the anterior pelvic organ prolapse score (POP-Q System) after PFTM, compared to controls (34). *Sran et al.* reported an improvement of symptoms as measured by *Urogenital Distress Inventory* (UDI) after PFTM ($p = 0.026$), whereas changes of *Incontinence Impact Questionnaire* (IIQ) and *Geriatric Self-Perceived Efficacy* scores were not significantly improved (36).
Results of bladder diaries showed a reduction of nocturia and frequency together with an increase of intervoid intervals (35), and a reduction of weekly leakage episodes (36). Finally, the same group demonstrated that physical treatment significantly reduced the amount of leakage on the 24-hour pad test.
A study compared PFMT alone with PFMT combined with postural instructions and demonstrated that addition of the latter improved pelvic muscle strength as evaluated by *Oxford Grading Scale*. However, incontinence symptoms were not improved (37).
Another study compared two formats of unsupervised PFMT programs (2-hr Class or 20 min Video instruction), showing no difference in terms of nocturia and urinary urgency episodes reduction and inter-void interval extension (38).
Other studies evaluated the effectiveness of other physical treatments (vaginal electrostimulation, radiofrequency, fractional CO_2 laser, LiESWT) in reducing urinary incontinence in post-menopausal women.
The effect of vaginal electrostimulation was compared with the outcome of PFMT; no significant improvement in subjective and objective outcome variables were reported in the population treated with electrostimulation compared with the population treated with PFMT. The rates of women reporting improvements in urinary leakage were 29.2% *vs.* 27.3% (39).
A study compared radiofrequency treatment and fractional CO_2 laser treatment (4 weeks apart, about 1-2 minute(s) per session) with a control group. It was demonstrated that mixed urinary incontinence decreased after the intervention including radiofrequency and laser compared to the control group. However, the changes in the laser group were not statistically significant (40).
Borges Aguiar et al. compared the efficacy of CO_2 laser treatment with local estrogen treatment and a control treatment (vaginal lubricant) (41). The laser group showed a more significant reduction in the total ICIQ-UI SF score and nocturia compared to controls.

Finally, a study investigated the therapeutic efficacy of *low intensity extracorporeal shock wave treatment* (LiESWT) on urinary incontinence of postmenopausal women in comparison to sham treatment (42). LiESWT decreased urinary frequency, nocturia, urgency, urgency incontinence, and post-voided residual urine volume and increased voided urine volume and maximal flow rate compared to the sham control.

Summary of findings

A *Summary of Findings* (SOF) table prepared according to GRADE criteria is shown in the ***Supplementary materials (Table 2)***. The quality of the evidence ranged between moderate (presence of Risk of Bias) and very low (publication bias, risk of bias and inconsistency due to substantial heterogeneity).

Discussion

The prevalence of bladder symptoms, such as frequency, urgency and incontinence, tends to increase around the menopause, although it is still debated whether these disorders are due to menopause, or aging, or a combination of the two.

Urinary symptoms are associated with the *genitourinary syndrome of menopause* (GSM) which is characterized by physical changes of the vulva, of the vagina and of the lower urinary tract, including the presence of pallor or erythema of the genital mucosa, loss of vaginal wrinkles, introital retraction, vaginal dryness and the prolapse of the urethral mucosa.

These genital alterations have been all correlated with local estrogen deficiency, and were shown to benefit from local estrogen administration. However, the effects of local estrogens on urinary symptoms such as urgency, frequency and urinary incontinence are still unclear (43-45).

For these reasons, the treatment of postmenopausal incontinence remains not well defined by therapeutic guidelines, which sometimes do not consider postmenopausal incontinence as an independent and specific condition, but as a subtype of other clinical disorders (overactive bladder, lower urinary tract symptoms, urge and urinary incontinence).

Our search and literature review retrieved the results of studies focusing on various forms of treatment or combinations of different treatments.

Estrogens

High affinity estrogen receptors are present in the female urinary tract and in the structures of the pelvic floor. Clinical and urodynamic modifications are observed during pregnancy, the menstrual cycle and following the onset of the menopause. In animal studies, pretreatment with estrogens enhanced detrusor contractility in response to alpha-adrenoceptor agonists, cholinomimetics and prostaglandins, and contractile response to alpha-agonists in the ureter and urethra, conversely, progesterone decreases the muscle tone in the ureter, bladder and urethra by enhancing beta-adrenergic responses (46). In postmenopausal women, atrophic mucosal changes respond well to low-dose estrogen replacement therapy (43).

Two meta-analyses by *Cody et al.* extensively evaluated the role of estrogen therapy for urinary incontinence in post-menopausal women (44, 45). The authors concluded that systemic treatment with conjugated equine estrogen may worsen urinary incontinence. However, too few data were retrieved to extensively evaluate the effects of estrogen type, different dosage, and route of administration. Furthermore, the authors highlighted the potential risk of endometrial and breast cancer onset associated with long-term high-dose estrogen treatment and suggested cautious and limited in time use of estrogen, especially in non-hysterectomized women.

Estriol has less uterotrophic effect compared to other estrogens; conversely, the addition of a progestogen to long-term estrogen therapy to reduce the risk of endometrial cancer may increase the risk of incontinence due to a decrease in urethral pressure induced by the latter.

Local treatment with estrogen was considered safer and was deemed to improve urinary incontinence, though the optimal duration of treatment and long-term effects have been poorly studied (44, 45).

EAU guidelines suggest offering vaginal estrogen therapy to women with *lower urinary tract symptoms* (LUTS) and associated symptoms of genitourinary syndrome of menopause (47). Our analysis showed that no significant improvements in urinary symptoms were observed in patients treated with local estrogens, except for a reduction in urgency severity in a subgroup of patients presenting with sensory urgency. Similarly, no significant changes in urodynamic parameters were observed. Local estrogens do not seem to give a substantial benefit of urinary symptoms in postmenopausal patients, although they may be helpful in improving vaginal irritation symptoms.

Vitamin D, phytoestrogens and estrogens modulators

An alternative to estrogen treatment is the use of other drugs acting on estrogen receptors or on other receptors present in the genitourinary organs.

Phytoestrogens, such as the isoflavones of soy, show structural similarities to natural and synthetic estrogens and antiestrogens, acting as estrogen agonists and producing estrogen-like effects. Consumption of a phytoestrogen-rich diet has been suggested to alleviate menopausal symptoms without increasing the risk of cancer (48). Conversely, studies retrieved by our review showed that a soy-rich diet was not effective in improving the symptoms of incontinence and other symptoms of the genitourinary menopause syndrome (28, 29).

Raloxifene is a second-generation selective estrogen receptor modulator that is used for the prevention and treatment of osteoporosis in postmenopausal women because of its estrogenic effect on the bone, associated to an antiestrogenic effect on breast, and a neutral effect on the endometrium and the vaginal mucosa. In the RCT included in this review, raloxifene had no significant effect on urinary incontinence in postmenopausal women after 3 years of treatment (32).

The use of vitamin D for the treatment of urinary incontinence in postmenopausal women is supported by the finding of vitamin D receptors on the bladder detrusor and striated muscle (48). Vitamin D could act on stromal and smooth muscle cells by improving the muscle response to bladder filling in women with low vitamin D intake (50).

In our review, two studies (30, 31) evaluated the effects of vitamin D administration on urinary incontinence in menopausal women, but the results appear to be contradictory, and no conclusive statement can be made on this matter.

Anticholinergics

Anticholinergics are successfully used in the treatment of neurogenic or idiopathic overactive bladder symptoms, although their use is limited by side effects such as dry mouth and constipation (51). In addition, a specific limitation of the use of anticholinergics in the treatment of postmenopausal urinary incontinence could be the potential risk of cognitive impairment in older women. In fact, treatment with anticholinergics in elderly people could be associated with cognitive impairment, as has been demonstrated in recent longitudinal cohort studies (52, 53). Cognitive impairment could be a consequence of central nervous system metabolism alterations and brain atrophy.

EAU guidelines (47) confirm the efficacy of anticholinergic drugs in elderly patients with overactive bladder and urinary incontinence but warn of the risk of a cognitive impact with a cumulative effect related to the length of treatment. Worsening of cognitive function has been observed in patients taking oxybutynin (52, 54), but not in short-term studies with darifenacin, fesoterodine, solifenacin and trospium. Although a previous meta-analysis (55) found inconclusive evidence of the impact of anticholinergics on cognition, a cautious use of long-term anticholinergics has been recommended, especially in patients at risk or with pre-existing cognitive dysfunction or on treatment with other drugs with anticholinergic effects (54).

Mirabegron

A possible alternative to anticholinergics could be β3-adrenoceptor agonists, which have demonstrated efficacy and safety in elderly patients. In patients aged ≥ 65 years, dry mouth occurred much less frequently with mirabegron than with tolterodine. Mirabegron also had a low incidence of central nervous system effects, and a systematic review of the cardiovascular safety profile has shown no clinically significant effects on blood pressure or pulse rate amongst patients aged ≥ 65 years (56, 57).

Our literature review found no RCT comparing mirabegron or other β3-adrenoceptor agonists with placebo for the treatment of postmenopausal incontinence. Further studies are warranted in this respect. A recent study (58), published after the conclusion of our literature search, compared two β3-adrenoceptor agonists, mirabegron and vibegron, in postmenopausal women with treatment naive overactive bladder. After 12 weeks of treatment, both drugs significantly improved symptom scores, micturition frequency, urgency and incontinence episodes, as well as the voided volume per 24 hours, compared with baseline, without significant difference in postvoid residual urine volume. Severe side effects requiring the discontinuation of treatment were observed in 6.2% of patients in the mirabegron group and in 6.8% in the vibegron group.

Physical therapy

The studies included in our review demonstrated an overall positive outcome of *pelvic floor muscle training* (PFMT) on postmenopausal urinary incontinence symptoms, although in most studies no effort was made to distinguish between the different types of incontinence. Similarly, a recent systematic review demonstrated that PFMT in combination with physical training was effective in reducing urinary incontinence and improving quality of life in elderly patients (> 65 years) (59). Moreover, an ICI consensus paper stated that age and frailty alone did not represent a contraindication for PFMT in selected patients with sufficient cognition to comply with treatment (60).

Other forms of physical treatment for urinary incontinence need to be validated by quality, adequately powered RCTs.

EAU guidelines report slight, short-term improvement of overactive bladder symptom after vaginal laser therapy, but data about long-term efficacy and safety are missing. Vaginal laser therapy is not recommended outside the frame of well-designed controlled clinical trials (61).

Conclusions

In conclusion, the results of our review demonstrate that there is no robust evidence of an effective treatment for postmenopausal urinary incontinence. There is still a need of large, adequately powered and well-designed studies, focusing on subjective and objective improvements in urinary incontinence as their primary outcome. Currently, no treatment by itself has been shown to be fully effective and superior to another. From the limited evidence available, a combined approach, including different forms of treatment tailored to the characteristics of the individual patient can be suggested.

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