DOI: *10.4081/aiua.2023.11718*

SYSTEMATIC REVIEW - SUPPLEMENTARY MATERIAL

Treatment of urge incontinence in postmenopausal women: A systematic review

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[*] *U-merge Ltd. (Urology for Emerging Countries) is an academic urological platform dedicated to facilitate knowledge transfer in urology on all levels from developed to emerging countries. U-merge Ltd. is registered with the Companies House in London/UK. www.U-merge.com*

SUPPLEMENTARY MATERIALS TABLE 1. REASONS FOR DISCARDING PAPERS AFTER FULL TEXT LECTURE

- *a study dealing with patients with genitourinary syndrome (Archer 2018)*
- *evaluation of patients at enrollment (Brown 1999)*
- *a study dealing with postmenopausal patients with UTI (Brown 2001)*
- *a study dealing with patients with stress incontinence (Capobianco 2012)*
- *a study dealing with patients with stress incontinence (Capobianco 2014)*
- *meta-analysis (Cody 2009)*
- *comment about a paper (Easton 2001)*
- *a feasibility study without clinical data about urinary incontinence (Felsted 2019)*
- *a study of survivors from breast cancer (Ganz 2000)*
- *letter reporting about a series included in the review (Holroyd-Leduc 2005)*
- *a study not restricted to postmenopausal women (Ignacio Antonio 2022)*
- *a feasibility single-arm study (Mercier 2019)*
- *a study of self-efficacy as predictor to adherence to treatment (Messer 2007.*
- *duplicate study published by other Authors (Moore 2009)*
- *a study dealing with patients with stress incontinence (Pereira 2012)*
- *a study dealing with patients with stress incontinence (Pereira 2013)*
- *a study dealing with genitourinary syndrome (Ribeiro 2018)*
- *a study dealing with patients with stress incontinence (Wang 2019)*
- *a single-arm study without controls (Yaksi 2013)*

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Supplementary Materials Table 2. PICO Tables
Systemic estrogens

Cardozo 1993	Postmenopausal women with urodynamically confirmed urgency urinary incontinence N=64	Estriol orally 3 mg N=34 (31) placebo orally N=30 (25) 3 months	a structured doctor-administered questionnaire Urgency Oestriol 2.6 (0.5) vs l.5 (1.1)* Placebo 2.5 (0.8) vs 1.4 (1.1)* Nocturia Oestriol 1.6 (0.8) vs 1.0 (1.0)* Placebo 1.7 (1.1) vs 1.0 (1.1) Persistence of symptom Number not cured of urge urinary incontinence Estriol 14/25; Placebo 16/23;
Fanti 1996	Women > 45 with involuntary loss of urine N=83	0.625 mg/day conjugated equine estrogen plus 10 mg/day medroxyprogesterone acetate N=44 or placebo N=39 cyclically for 3 months	Perceived improvement of degree of incontinence Hormone treatment 54% Placebo 45% Incontinence (per week) PBO 16+12 vs 13+14 E+P 13+10 vs 10+10 Losses (g) PBO 63+88 vs 50+68 E+P 116+106 vs 101+150 Diurnal micturitions (per week) PBO 51+17 vs 49+15 E+P 53+13 vs 50+14 Nocturia (per week) PBO 9+5 vs 8+5 E+P 9+6 vs 9+6
Grady 2001 Heat and Estrogen/ Progestin Replacement Study,	Postmenopausal women N=2763 Paticipants at least one episode of incontinence per week at baseline N=1525	0.625 mg of conjugated estrogens plus 2.5 mg of medroxyprogesterone acetate in one tablet daily N=5768 or placebo N=5757 4.1 years	hormone group N=756 20.9% improved 38.8% worsened placebo group N=747 26.0% improved 27.0% worsened P < 0 .001
Hendrix 2005	Postmenopausal women at 40 US clinical centers based on hysterectomy status N=27347 women's Health Initiative	Estrogen plus progestin (E + P) 0.625 mg/d of conjugated equine estrogen + 2.5 mg/d medroxyprogesterone acetate (CEE + MPA) N=8506 Placebo N=8102	Combination CEE+MPA no significant effect on developing urge UI (RR, 1.15; 95% CI, 0.99-1.34) CEE alone increased the risk (RR, 1.32; 95% CI, 1.10-1.58) Patients with incontinence at baseline who perceived bother or disturbance attributed to UI

		estrogen alone 0.625 mg/d of conjugated equine estrogen (CEE) N=5310 Placebo N=5429	Risk of worsening Combined hormone treatment RR 1.22 (1.13-1.32) Estrogen alone RR 1.50 (1.37-1.65) Frequency worsened in both trials CEE+MPA RR, 1.38 [95% CI, 1.28- 1.49] CEE alone RR, 1.47 [95% CI, 1.35-1.61] Amount of UI worsened at 1 year in both trials CEE+MPA RR, 1.20 [95% CI, 1.06-1.36] CEE alone RR, 1.59 [95% CI, 1.39-1.82]
Rufford 2003	Postmenopausal women with the 'urge syndrome'	25 mg 17b-estradiol implant N=20 or placebo N=20 6 months	Micturitions/24h Estradiol 10.0 (8.8-11.3) vs 8.6 (6.5-11.4) Placebo 8.5 (7.2-10.0) vs 8.0 (7.0-9.8) Volume voided per micturition Estradiol 150 (113-213) vs 177 (143-209) Placebo 147 (134-175) vs 161 (107-200) Incontinence episodes/24 h Estradiol 0 (0-3) vs 0 (0-1.8) Placebo 0 (0-1.4) vs 0 (0-0.5)
Sherman 2003	Postmenopausal women with angiographically documented heart disease N=246 Estrogen Replacement and Atherosclerosis (ERA) trial	0.625 mg/day conjugated equine estrogen or estrogen plus 2.5 mg/day medroxyprogesterone acetate or placebo	The estrogen-only group reported more urinary incontinence than the placebo group ($p < 0.05$)
Steinauer 2005	Women with urinary incontinence data for at least 1 follow-up visit N=1.208 Heart Estrogen/ progestin Replacement Study	Daily oral conjugated estrogen (0.625 mg) plus medroxyprogesterone acetate (2.5 mg) N=597 or placebo N=611 4.2 years	Hormone treatment 64% weekly incontinence Placebo 49% weekly incontinence P < .001
Vestergaard 2003	Early postmenopausal women aged 45-58 years N=1006 Danish Osteoporosis Prevention Study (DOPS)	Hormonal Replacement Therapy (HRT) N= 502 or no HRT N=504 open label trial	Hormone treatment 100+42 (20+8%) incontinence (mild+moderate/severe) No treatment 100+47 (20+9%) incontinence (mild+moderate/severe)
Waetjen 2005	Postmenopausal women aged 60 to 80 years for prevention of osteoporosis	Ultralow-dose (0.014 mg/d) transdermal estradiol N=208	At 4 months improved placebo group 35.2% estradiol 25% worsened E2 group (23.8% compared with

	N=417 Incontinence rate at baseline = 43% in both group	vs placebo patch N=209	19.3), but the differences between the groups were not statistically significa

Local estrogens

Cardozo 2001	Postmenopausal women with urinary frequency, urgency and/or urge incontinence with FSH > 40 iu/l and oestradiol (E2) < 220 pmol/l N=110	17-beta oestradiol 25-ug vaginal tablets or placebo daily 12 weeks N=56 N=54	No difference diary parameters Frequency Nocturia In subgroup with sensory uregency reduction of urgency No variation of urodynamic parameters
Dessole 2004	Postmenopausal women with urogenital aging symptoms N=88	Intravaginal estriol ovules (1 mg) once daily for 2 weeks + 2 ovules weekly for a total of 6 months N=44 vs placebo vaginal suppositories N=44	Estriol Before/After Placebo MUP (cm H20) 50.82 ± 6.15 vs 62.15 ± 8.64 52.35 ± 6.30 vs 49.40 ± 6.54 p < 0.05 MCUP (cm H20) 45.25 ± 7.20 56.87 ± 9.23 44.77 ± 6.86 43.32 ± 6.32 p < 0.05
Lose 2000	Postmenopausal women, with a mean age of 66 years, reporting at least one bothersome lower urinary tract symptom.	Estradiol-releasing ring for 24 weeks N=134 estriol pessaries 0.5 mg every second day N=117 24 weeks	Equally efficacious in alleviating urinary urgency (51% vs 56%) urge incontinence (58% vs 58%) stress incontinence (53% vs 59%) nocturia (51% vs 54%) dysuria (76% vs 67%)
Speroff 2003	Postmenopausal women with moderate to severe vasomotor symptoms (seven or more per day or 56 per week average)	Vaginal ring delivering 50 ug per day E2 N=113 or 100 ug per day E2 N=112 or placebo vaginal ring N=108 13 weeks	Questionnaire according to the following 4-point scale: 0 not at all, 1 a little, 2 quite a bit, and 3 extremely. P80 vs E2 50 vs E2 100 Urinary frequency (n) 60 54 53 Baseline 1.5 1.5 1.6 Week 4 - 0.6 - 0.7 - 0.8 Week 13 - 0.7 - 0.8 - 1.0 Urinary leakage (n) 42 47 45 Baseline 1.3 1.3 1.4 Week 4 -0.5 -0.6 -0.7 Week 13 -0.4 -0.6 -0.5 There was a general trend toward greater improvement of urogenital symptoms in both E2 vaginal ring groups compared with the placebo vaginal ring group
Mells 1997	Postmenopausal women	E3 vaginal treatment	Intensity of vaginal (itching, burning,

	suffering from vaginal and urologic symptoms N=50	Estriol (E3) (0,5 mg every day for 14 days followed by 0,5 mg every two days) Vs E3 plus benzidamine (E3 + B) 14 days	leucorrhea, dryness) and urologic (nocturia, incontinence, urgence incontinence) symptoms, such as the number of patients, significantly decreased after 3 months urologic symptoms did not differ between the treatments, whereas E3 + B showed to be more effective in reducing vaginal symptoms than E3 alone
Neiken 2011	Postmenopausal women with an overactive bladder	Ultralow-dose estradiol vaginal ring N=28 vs oral oxybutynin N=31 12 weeks	Oral oxybutynin -3.0 voids per day vaginal ring -4.5 voids per day no significant difference significant improvement in Urogenital Distress Inventory and Incontinence Impact Questionnaire in both groups no significant difference

ANTICHOLINERGICS

Chughtai 2016	Postmenopausal women N=23	Fesoterodine 4-8 mg + topical vaginal estrogen (combination) once daily (N=9) or fesoterodine once daily alone (N=9) 12 weeks	Combination Fesoterodine OAB-Q (symptom severity) 70.0 vs 10.0 0.006* 66.7 vs 23.3 < 0.0001* OAB-Q (HRQL) health-related quality of life 36.9 vs 96.9 0.029* 27.7 vs 84.6 0.0002* SQOL-F Sexual Quality of Life-Female 56.0 vs 99.0 0.0003* 51.0 vs 81.0 0.02* Micturitions (over 3 consecutive days) 45 vs 26 0.03* 29 vs 27 0.68
Jiang 2016	Overactive bladder treatment in postmenopausal women N=104	Solifenacin 5 mg once day promestriene vaginal capsules intravaginally N=52 vs solifenacin 5 mg N=52 12 weeks	Pre-post delta Urgency 2.00 (0.00; 5.00) vs 2.50 (0.00; 7.00) 0.6981 OAB-SS 6.0 (3.0; 8.0) vs 4.0 (1.0; 5.0) 0.016
Martin 2018	Postmenopausal women with complaints of frequency N=24	Fesoterodine conjugated estrogen vaginal cream vs fesoterodine placebo vaginal cream	Significant improvement in both groups OAB transformed scores (p=0.0041, n=24) increased HRQL transformed scores (p<.0001, n=24) decreased USIQ severity scores (p<.0001, n=24) decreased total USIQ scales (p=0.0015, n=24) subjective improvement during the follow-up interview (p=0.0007, n=22)

			no significant difference in the data points between the fesoterodine with estrogen cream and fesoterodine with placebo
Tseng 2008	Postmenopausal women N=80	Tolterodine With Vaginal Estrogen Cream N=40 Versus Tolterodine Alone N=40	Combination Tolterodine Day time frequency/day 14.8+1.5 vs 5.8+0.9 14.1+1.3 vs 6.4+1.9 Urgency/24 hr 4.3+0.7 vs 3.3+0.6 4.5+0.8 vs 3.5+0.5 Nocturia/night 3.3+0.8 +2.6+0.7 3.5+0.8 +2.9+0.6 Urge incontinence/24 hr 2.1+1.1 +1.5+0.5 1.8+0.7 +1.5+0.5
Tapp 1990	Postmenopausal women suffering from detrusor instability	Oxybutynin chloride N=21 placebo N=33 cross-over 5 mg x 4 2 weeks	Visual analogue symptom scoring (urgency, urge incontinence, stress incontinence and enuresis) and uroflowmetry and videocystourethrography more effective than placebo at reducing the symptoms of urgency and urge incontinence and more effective at reducing the height of the highest unstable detrusor contraction

Other drugs

Markland 2019	Community-dwelling postmenopausal women, 50 years or older, with at least three UUI episodes on 7-day bladder diary and serum vitamin 25-hydroxyvitamin D (25[OH]D) of 30 ng/mL or less 56 women	Vitamin D supplementation Vs placebo 28 to vitamin D Vs 28 to placebo 51 completed treatments 12 weeks	UUI episodes per 24-hour day decreased by 43.0% with vitamin D3 compared to 27.6% with placebo (p=.22) no differences UI OAB severity perceived improvement of satisfaction with treatment no differences pelvic floor muscle strength anal sphincter muscle strength timed Up and Go testing
Oberg 2017	Vitamin D high dose Postmenopausal women with low bone mineral density N=297	20 000 IU vitamin D3 twice a week (high dose group) N=134 or placebo (standard dose group) N=139 all participants supplement of 500 mg of calcium and 400 IU of	Any urinary incontinence improved 20 vs 12 NS worsened 18 vs 10 Any LUTS improved 21 19 NS worsened 17 12 Any urinary incontinence improved 20 12 NS worsened 18 10 Severity index < 0.05 improved 7 2 worsened 3 10

		vitamin D3 twice daily	Significant UI improved 6 3 < 0.05 worsened 0 5 Urgency improved 25 18 NS worsened 11 13 UTI improved 4 6 NS worsened 8 11 Nocturia NS improved 4 3 worsened 7 7
Bumbu 2016	12 months and included 215 postmenopausal women who were divided into three groups: the first comprised T	Soy extract (40% isoflavones) (N=78) 1 mg oestradiol + 0.5 mg noretisterone acetate (NETA) p.o. daily (N=65) control group (N=72)	Without UI 68/78 52/65 62/72 Mild UI 9 11 8 Moderate UI 1 2 2
Manonai 2006	Soy-rich diet	Control diet (soy-free diet) isocaloric soy-rich diet (25 g soy protein in food containing more than 50 mg/day of isoflavones)	Urge incontinence Soy 0.17 ± 0.38 0.19 ± 0.47 Control 0.14 ± 0.35 0.25 ± 0.50* Urgency 0.64 ± 0.72 0.64 ± 0.68 0.58 ± 0.65 0.64 ± 0.68 Frequency 0.67 ± 0.76 0.61 ± 0.80 0.56 ± 0.61 0.61 ± 0.69
Waetjen 2004 Multiple Outcomes of Raloxifene trial	Women who were at least 2 years postmenopausal with osteoporosis N=963	Raloxifene 60 mg/day raloxifene 120 mg/day Placebo 3 years	Odds of worsening urinary incontinence severity after 3 years of raloxifene treatment were 1.05 (95% CI 0.75, 1.48) odds of developing new onset incontinence were 0.95 (95% CI 0.59, 1.52) raloxifene did not effect the odds of having stress (OR 1.01; 95% CI 0.71, 1.43) or urge (OR 1.20; 95% CI 0.86, 1.68) incontinence after 3 years of use
Green 2006	160 mg capsule of aprepitant (61) or placebo (64) once daily for 8 weeks		

Pelvic floor muscle training & Physical treatment

Alves 2015	Postmenopausal women N=46 30 completed study	Pelvic floor muscle training program (PFMT) group (n = 18) Control group (n = 12)	sEMG (p = 0.003) digital palpation (p=0.001) ICIQ-OAB scores (p<0.001) ICIQ UI-SF) (p=0.036 anterior pelvic organ prolapse (p=0.03) pelvic organ prolapse quantification (POP-Q)

			Control treatment Digital palpation 2.25 (±1.05) 2.58 (±0.99) 2.17 (±0.98) 3.16 (±1.09) 0.001 Modified Oxford Grading Scale (zero to five points) sEMG 25.38 (±13.76) 27.80 (±13.96) 15.44 (±8.22) 28.12 (±16.80) 0.003
Borges Aguiar 2020	Postmenopausal women aged 50 years or older N=72	Fractional CO2 laser 10 mg of vaginal promestriene, three times weekly for 12 weeks topical lubricant gel	ICIQ – UI SF Basal vs Week 14 8.92 (6.55) vs 6.45 (4.67) P=0.004 8.92 (7.11) vs 7.79 (5.24) P=0.235 9.89 (5.90) vs 11.47 (5.95) P=0.812 stress urinary loss, increased urinary frequency, nocturia, urgency, and urgency incontinence
Diokno 2004	Postmenopausal, continent women (0 to 5 days of incontinent episodes in the previous year) 55 years and older	Pelvic floor muscle training (PMT) and bladder training (BT) N=164 N=195 12 months	Continence status (p 0.01), 37 vs 28% pelvic muscle strength (pressure score) p 0.0003 displacement score p 0.0001), frequency (day) 7.3 vs 6.1 7.4 vs 7.5 (p<0.0001) nocturia (day) 0.9 vs 0.7 0.8 vs 0.9 (p=0.00) intervoid interval 3.19 vs 3.69 3.09 vs 3.09 (p 0.0001)
Eftekhar 2021	Mixed urinary incontinence (MUI) and vulvovaginal atrophy (VVA)	Radiofrequency (RF) N=80 vs Laser N=78 vs Placebo N=79	VAS RF group 26.5±12.6 vs 13.5±9.9 < 0.001 Laser group 23.3±12.6 vs 17.6±12.2 < 0.001 Placebo group 24.5±15.8 vs 23.3±15.3 0.006 VHI RF group 10.1±2.1 vs 20.9±1.5 < 0.001 Laser group 10.9±3.4 vs 12.7±4.8 0.002 Placebo group 10.6±4.6 vs 10.5±4.0 0.636 MUI RF group 7.6±5.1 vs 4.1±3.6 < 0.001 Laser group 6.5±3.3 vs 4.9±3.1 < 0.001 Placebo group 6.7±4.0 vs 6.1±3.9 0.067
Fuentes-Aparicio 2022	Climacteric women aged between 40-75 years old who presented with SUI	PFMT Vs PFMT + postural instructtions N=23 N=24 12 weeks	PFMs electromyographical (EMG) activity strength (Oxford Grading Scale) 3-day bladder diary post-intervention higher values for the AEPPI compared to the AEP group

→

			At 3-months follow-up, statistically significant differences were only obtained in strength No significant differences were obtained in terms of UI symptoms
Lin 2010	Postmenopausal women with ovary hormone deficiency (OHD) with OAB	58 participants to investigate the therapeutic efficacy of LIESWT (0.25 mJ/mm², 3000 pulses, 3 pulses/second) N=39 vs Sham N=19 8 weeks	Sham LIESWT Daytime frequency (times) 11.38 ± 0.33 11.09 ± 0.30 11.83 ± 0.46 10.24 ± 0.35 *,† Nocturia (times) 1.73 ± 0.12 1.51 ± 0.11 1.68 ± 0.14 1.27 ± 0.10 *,† Urgency (times) 2.90 ± 0.23 2.69 ± 0.24 3.10 ± 0.35 2.22 ± 0.36 **,† Q_{max} (mL/s) 25.30 ± 1.54 26.65 ± 1.18 24.21 ± 1.09 27.58 ± 1.43 * PVR (mL) 42.79 ± 4.58 44.00 ± 4.66 46.67 ± 5.27 35.06 ± 4.63 *,† OABSS score (points) Urge incontinence 1.73 ± 0.16 1.67 ± 0.16 1.61 ± 0.18 1.00 ± 0.14
Spruijt 2003	Postmenopausal women (age 65 years or older)	Vaginal electrical stimulation vs PFMT N=24 N=11	Standardized PAD test (mg/24 h) 65 (0-489) vs 63 (14-630) 25 (11-93) vs 26 (4-157) P=0.081 Pelvic muscle strength (measured by a perineometer) (mmHg) 10.75 (0.75-35.00) vs 15.375 (1.75-40.00) 12.50 (3.25-21.50) vs 10.00 (3.25-23.00) Detrusor instability (on ambulant urodynamic registration) Improvement (%) 22.2 vs 28.6 p0 0.853 urinary symptoms based on the PRAFAB score Improved (%) 45.8 vs 45.4 p=0.893
Sran 2016	Postmenopausal women aged 55 years and over with osteoporosis or low bone density and urinary incontinence	Physical therapy group with individual sessions of physical therapy (once per week) N=24 control group receiving osteoporosis education session N=24 12 weeks	At one year follow up treatment group favored number of leakage episodes on the 7-day bladder diary (p=0.018) amount of leakage on the 24-hour pad test (p=0.011) impact of UI as measured by the UDI (p=0.026)
Wu 2021	Women aged 55 years or more with no urinary incontinence	PFMT program 2 h (2-hrClass) N=276	Class vs Video nocturia never

	TULIP study	or DVD showing essentially the same information as a 20-minute video (20-minVideo) N=268 24 months	60 vs 66<% 44 vs 72% urinary urgency never 67 vs 55 57 vs 54 urinary frequency < 2 h 70 vs 17 70 vs 14

Supplementary Materials Table 3. Summary of findings

Effect of hormone treatment versus placebo or no treatment on post-menopausal incontinence

Patient or population: post-menopausal women
Settings: outpatient
Intervention: various hormone therapy protocols
Comparison: placebo or no treatment
Outcome: urinary incontinence

Comparison (condition)	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of Participants (studies or comparisons)	Quality of the evidence (GRADE)	Comments
	Assumed control risk	Corresponding intervention risk				
	Comparison	Intervention				
Hormone treatment vs. placebo	**735.88 per 1000**	**673.40 per 1000** (629.57 to 717.15)	**OR** 0.74 (0.61 to 0.91)	17132 (7)	⊕⊝⊝⊝ **Very low**	*Reasons for downgrading:* none *Reasons for downgrading:* - probable publication bias - risk of bias - inconsistency due to substantial heterogeneity
Systemic estrogen treatment *vs.* placebo	**719.21 per 1000**	**666.43 per 1000** (635.27 to 697.45)	**OR** 0.78 (0.68 to 0.90)	10707 (3)	⊕⊕⊕⊝ **Moderate**	*Reasons for upgrading:* none *Reasons for downgrading:* - risk of bias
Combined systemic hormone treatment *vs.* placebo	**763.50 per 1000**	**699.19 per 1000** (612.68 to 773.86)	**OR** 0.72 (0.49 to 1.06)	6425 (4)	⊕⊕⊕⊝ **Moderate**	*Reasons for downgrading:* none *Reasons for downgrading:* - risk of bias

The corresponding intervention risk (and its 95% confidence interval) is based on the assumed control risk in the comparison group and the relative effect of the intervention (and its 95% CI).
It is calculated from the odds ratio using the formula:
OR x ACR/[1-ACR + (OR x ACR)]
CI: Confidence Interval; OR: Odds Ratio; ACR: Assumed Control Risk

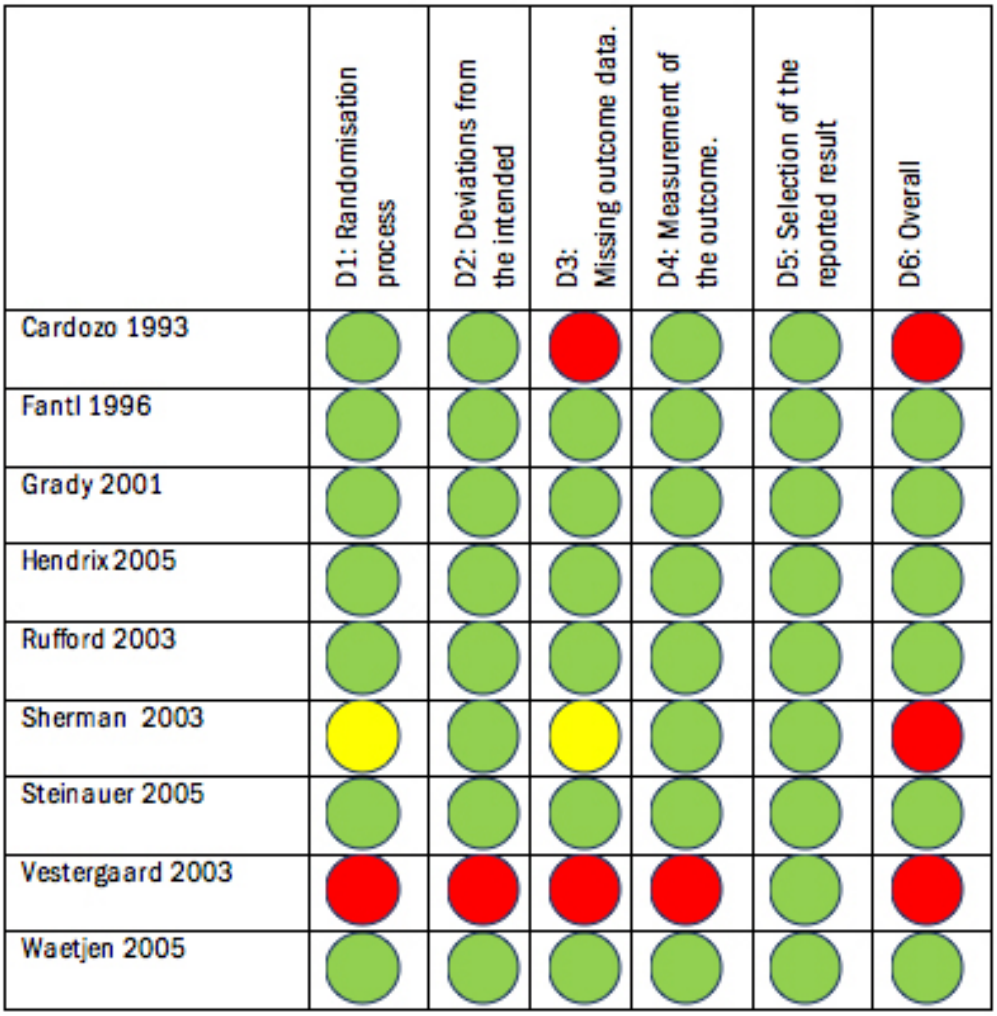
GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Supplementary Materials Figure 1. Risk of Bias (RoB) 2 assessment

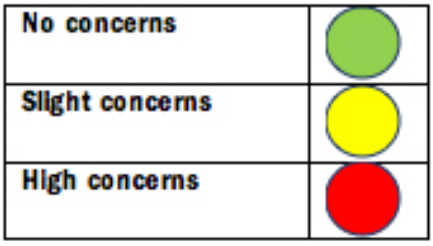
1. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019; 366:l4898.

2. Lundh A, Gotzsche PC. Recommendations by Cochrane Review Groups for assessment of the risk of bias in studies. BMC Med Res Methodol 2008; 8:22.

Systemic estrogens



D1: Randomisation process.
D2: Deviations from the intended interventions.
D3: Missing outcome data.
D4: Measurement of the outcome.
D5: Selection of the reported result



1. Cardozo 1993: randomization was held centrally and there was code; double blinded; 50 patients per arm were needed though recruitment was 64 and 8 of them were lost during follow-up (> 10%).

2. Fantl 1996: randomization ok, double blinded, lost during follow-up < 10%.

3. Grady 2001: randomization ok, double blinded, although not all patients were followed-up to 3 years the majority of them had at least one follow-up visit and they were counted in follow-up so it was rated as low risk.

4. Hendrix 2005: randomization ok, double blinded, not quite sure about the follow-up but most patients had at least one follow-up visit so rated as low risk.

5. Rufford 2003: randomization ok, double blinded, none lost at follow up at 3 months.

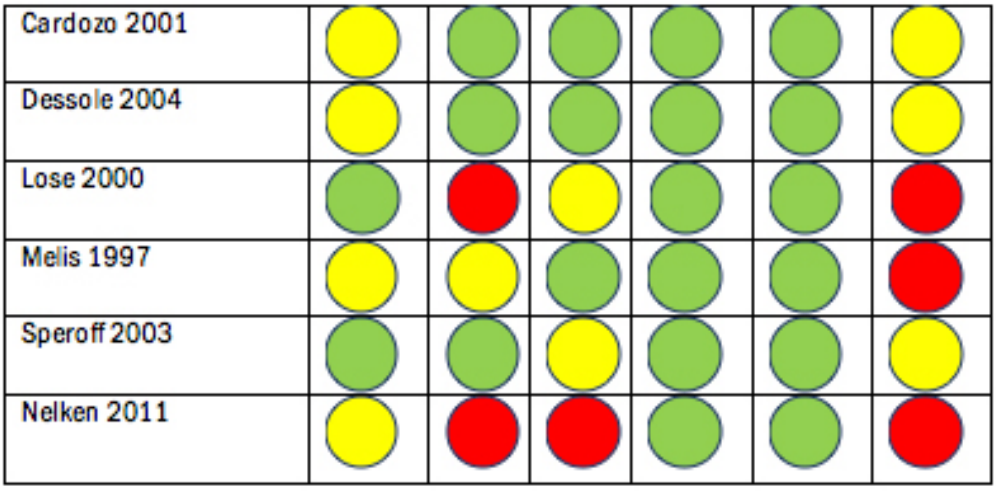
6. Sherman 2003: randomized unclear, double blinded, follow-up not shown.

7. Steinauer 2005: randomization ok, double blinded, lost during follow-up < 10%.

8. Vestergaard 2003: partial randomization, no blinding, change of hormone type during trial; limited reporting on voiding disturbances; follow-up < 10%.

9. Waetjen 2005: randomization ok, double blinded, 90% completed the study.

Local estrogens



1. Cardozo 2001: randomization not described in detail, double blinded, < 10% lost during follow-up.

2. Dessole 2004: randomization ok, blinding ok, > 10% lost at follow up (4/44 treatment, 7/44 control).

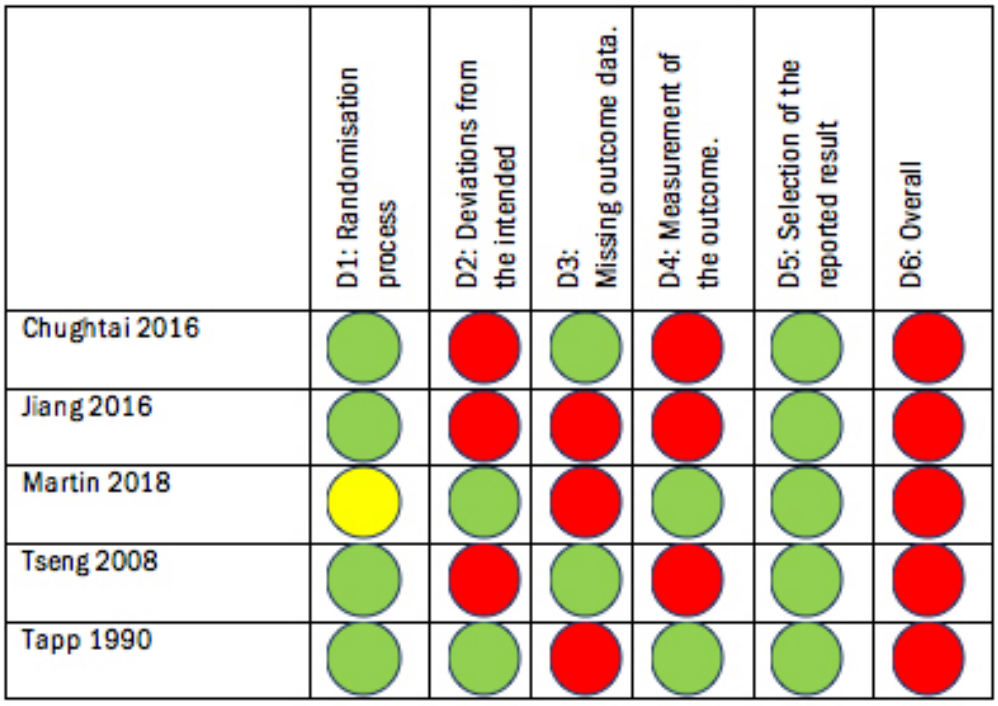
3. Lose 2000: randomization ok, no blinding, different number of participants in the two groups.

4. Melis 1997: randomization not described in detail, blinding not described, < 10% lost during follow-up.

5. Speroff 2003: randomization ok, blinding ok, lost at follow-up 12.4% and 9.8% in the treatment groups and 26.9% in the placebo.

6. Nelken 2011: randomization not described in detail, no blinding, loss to follow-up > 10% (oxybutinin group).

ANTICHOLINERGICS



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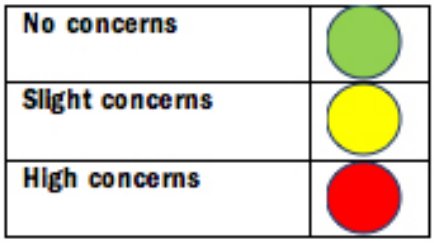


1. Chughtai, et al. 2016: randomization described, unblinded study, significant number of patients stopped treatment but due to side effects and not lost during follow-up, therefore rated as low risk.

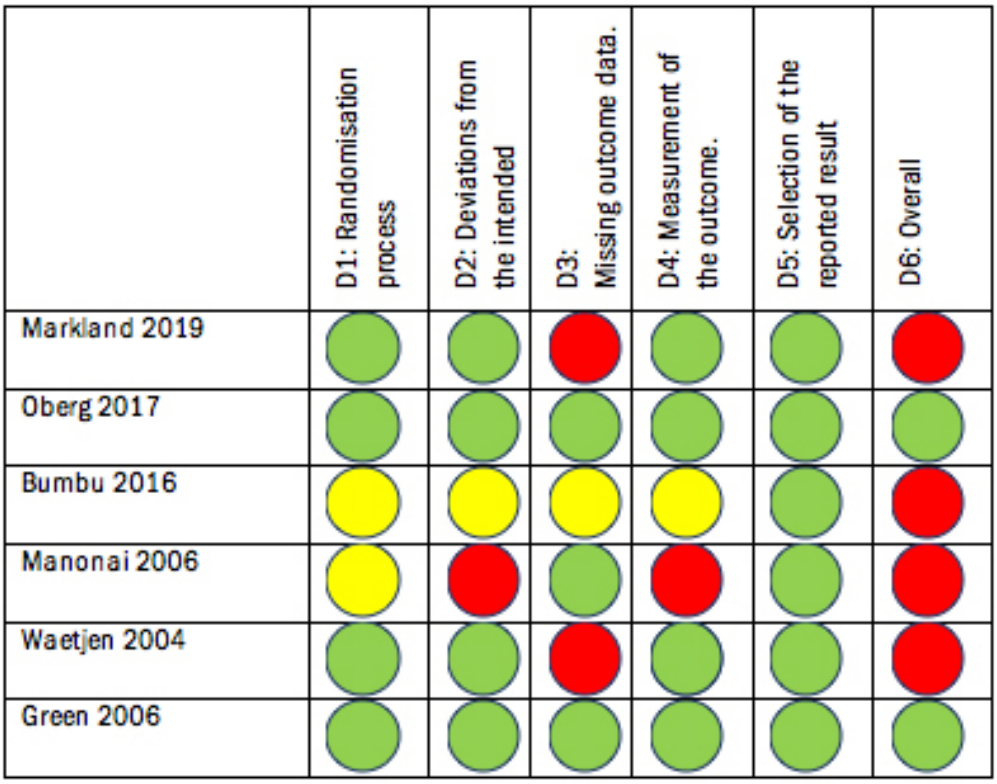
2. Jiang et al 2016: randomization described, open label study, very large number of patients dropped out in both groups.

3. Martin, et al. 2018: randomization not described in detail: unblinded study, increased number of dropouts mentioned (63 enrolled, 24 completed the study).

4. Tseng et al. 2008: randomization described, unblinded study, all patients completed the study.

5. Tapp et al. 1990: randomization described (cross-over design), double blinded study, increased number of patients lost during follow-up (> 10%).

Others



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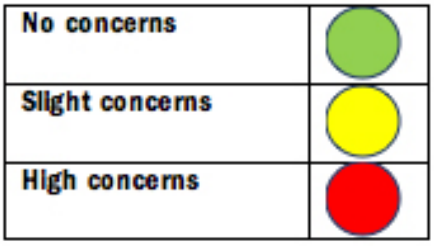


1. Markland 2019: randomization ok, double blinded study, high number of patients who did not complete bladder diary in both groups.

2. Oberg 2017: randomization described in detail in other study, double blinded study, lost during follow-up < 10% in both groups.

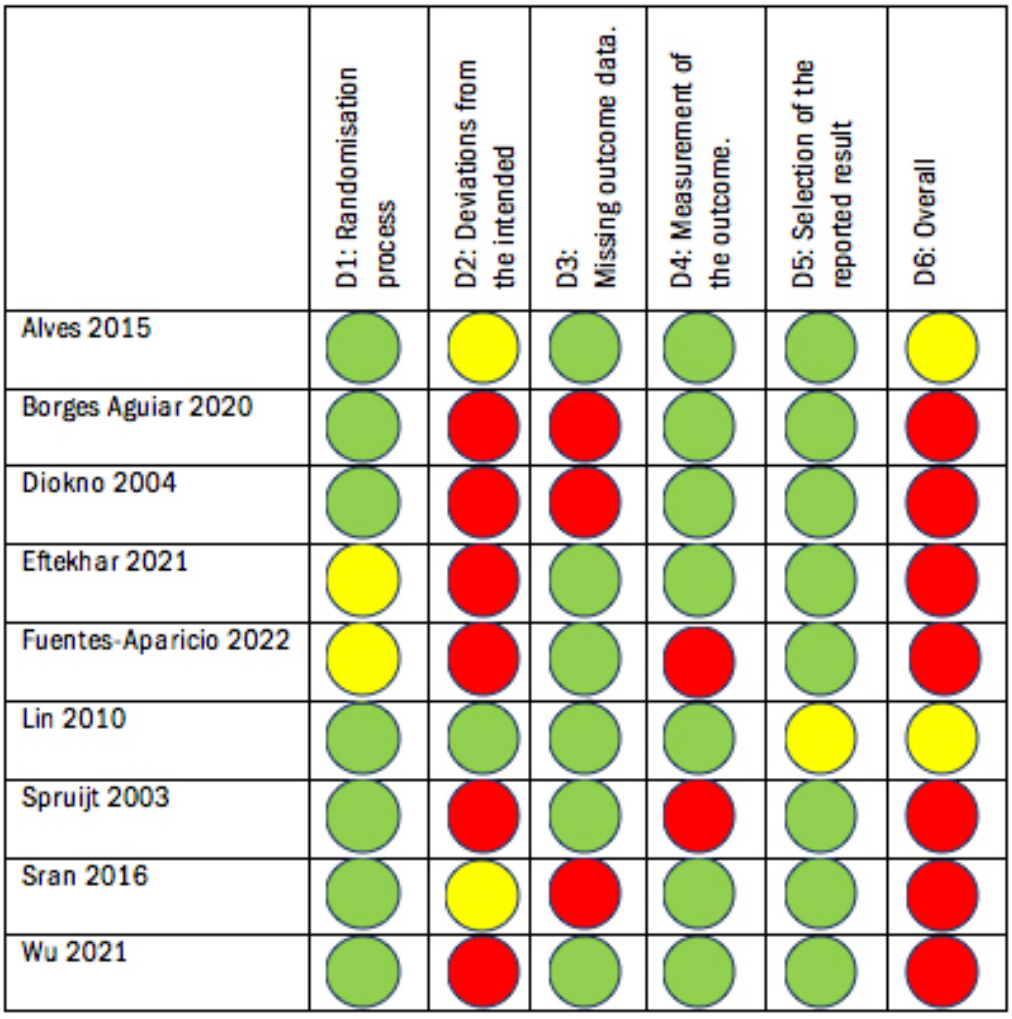
3. Bumbu 2016: mentions randomization but no details, no mentioning of patients lost during follow-up and blinding, therefore rated them as moderate risk.

4. Manonai 2006: mentions randomization but no details, I think not blinded since not mentioned and also is a diet study, lost during follow-up 1 due to loss of contact but some more who discontinued Tx (marked it as low risk though).

5. Waetien 2004: randomization ok, double blinded, 21% lost from baseline to 3 years of final questionnaire completion.

6. Green 2006: randomization ok, double blinded, 7% lost during follow-up.

Pelvic floor muscle training & Physical treatment



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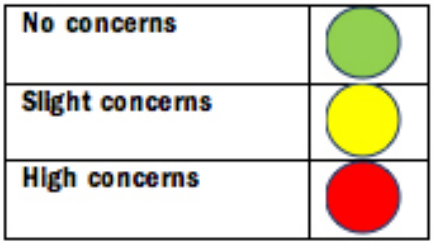


Reasons

D2: in most studies patients, carers and people delivering the interventions were aware of the group assignment, but the study of Lin et al which submitted controls to sham treatment. In some studies assessors were blinded to treatment (Alves et al, Sran et al.) (scored as "some concerns").

Alves et al: no double blinding-only assessor, 12 missing patients (> 10%), otherwise well designed.

Borges Aguiar et al: no blinding, 14 patients lost during follow-up (> 10%) although ITT analysis was performed.

Diokno et al: single blinding (although not entirely clear in the text), 41 missing patients (> 10%).

Eftekhar et al: no information on randomization (only refer to it as a RCT), no blinding mentioned thus assumed it was an open trial.

Fuentes-Aparicio et al: no blinding thus marked as high-risk in the relevant domains.

Lin et al: single blinded (I understand patients were blinded since there was a sham procedure), adequately described randomization process.

It's a rather confusing paper. It's hard to see if all the results are reported.

Spruijt et al: no blinding is mentioned thus assumed that this is an open-label study, patients lost to follow-up 2 (< 10%) and randomization done with blocks.

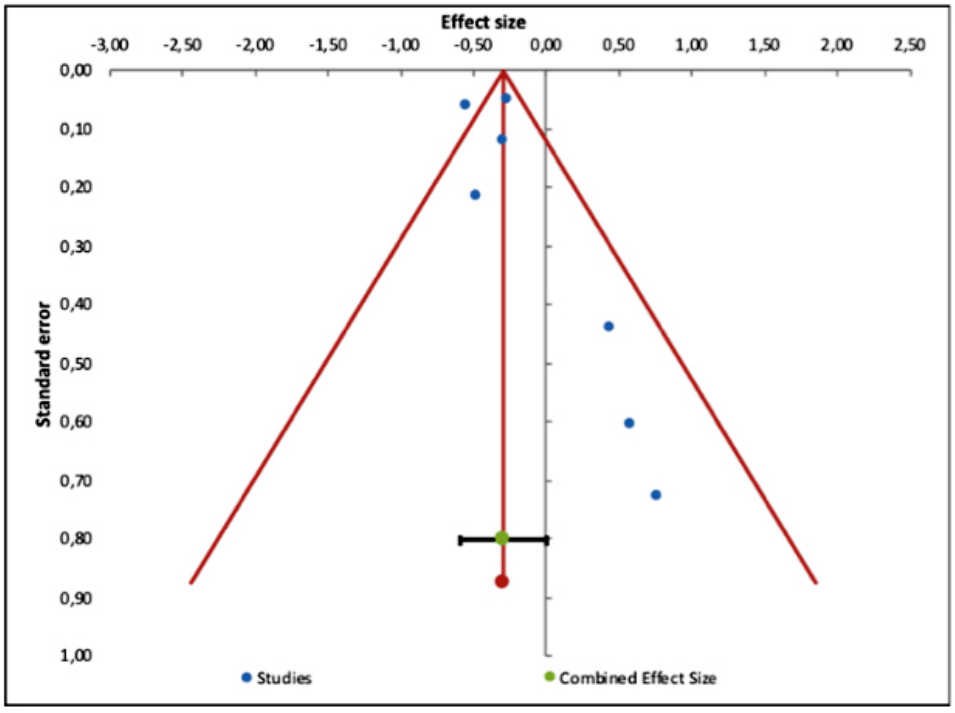
patients knew which group that they were being allocated to. A large number of patients rejected the trial because of this. I think this is a major bias that affects the outcome.

Sran et al: single-blinded for researchers, 5 patients lost to follow-up (> 10%).

Wu et al: patients lost during follow-up but < 10%, single blinded for researchers, randomization adequately described.

Supplementary Materials Figure 2 – Funnel plots for publication bias analysis
A) success of systemic hormone treatment of urinary postmenopausal incontinence
B) success of systemic estrogens alone

A



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