

Systematic Review: Randomized, Controlled Trials of Nonsurgical Treatments for Urinary Incontinence in Women

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Background: Urinary incontinence in women is a common problem that adversely affects quality of life.

Purpose: To synthesize evidence of management of urinary incontinence in women.

Data Sources: MEDLINE, CINAHL, and the Cochrane library.

Study Selection: 96 randomized, controlled trials (RCTs) and 3 systematic reviews published in English from 1990 through May 2007.

Data Extraction: Using standardized protocols, reviewers abstracted cases of continence, improvement of urinary incontinence, and prevalence of urinary incontinence to calculate risk difference.

Data Synthesis: Compared with regular care, pelvic floor muscle training plus bladder training resolved urinary incontinence (pooled risk difference, 0.13 [95% CI, 0.07 to 0.20]). Pelvic floor muscle training alone resolved or improved urinary incontinence compared with regular care, although the effect size was inconsistent across studies. Different injectable bulking agents and medical devices were associated with similar continence and improvement rates. Electrical stimulation failed to resolve urinary incontinence. Oral

hormone administration increased rates of urinary incontinence compared with placebo in most RCTs (1243 women). Transdermal or vaginal estrogen resulted in inconsistent improvement of urinary incontinence. Adrenergic drugs did not resolve or improve urinary incontinence. Oxybutynin or tolterodine resolved urinary incontinence compared with placebo (pooled risk difference, 0.18 [CI, 0.13 to 0.22]). Duloxetine compared with placebo improved (pooled risk difference, 0.11 [CI, 0.07 to 0.14]) but did not resolve urinary incontinence, with no significant dose–response association.

Limitations: Inconsistent measurements of outcomes limited the findings. Predictors of better effect have not been identified in RCTs.

Conclusions: Moderate levels of evidence suggest that pelvic floor muscle training and bladder training resolved urinary incontinence in women. Anticholinergic drugs resolved urinary incontinence, with similar effects from oxybutynin or tolterodine. Duloxetine improved but did not resolve urinary incontinence. The effects of electrostimulation, medical devices, injectable bulking agents, and local estrogen therapy were inconsistent.

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Prevalence estimates of urinary incontinence vary according to the definition and the method of data collection (1–13). In general, urinary incontinence affects about 19% of women age 19 to 44 years, 25% of those age 45 to 64 years, and 30% of those age 65 years and older. About 18% of younger women (19 to 44 years of age) (14) and 28% of women older than age 65 years (15) experience daily urinary incontinence, whereas 30% of women older than age 65 years (8, 16–20) and 27% of middle-aged women (17, 18, 21) report severe urinary incontinence. The severity of incontinence influences quality of life and treatment decisions (22, 23).

Clinical interventions to reduce urinary incontinence (24–34) have been extensively reviewed by the Cochrane Collaboration, the International Consultation on Incontinence (22, 23, 35), and the Agency for Healthcare Research and Quality (36, 37). Most studies examined short-term curative effects of treatment in participants with urinary incontinence. The basis for measuring successful treatment varied across the studies that examined different interventions.

The present review synthesizes evidence on the effectiveness of nonsurgical clinical interventions to treat urinary incontinence in community-dwelling women. This review was commissioned as background material for a National Institutes of Health Office of the Medical Applications of Research State of the Science Conference on Pre-

vention of Fecal and Urinary Incontinence. The full report can be found at www.ahrq.gov/clinic.

METHODS

Data Sources

We identified studies from MEDLINE (via PubMed), CINAHL, Cochrane databases, and manual searches of reference lists from systematic reviews and the proceedings of the International Continence Society (Appendix Table 1 available at www.annals.org).

Study Selection

Two investigators independently decided on study eligibility according to recommendations from the *Cochrane Handbook for Systematic Reviews of Interventions* (38) to include original publications of randomized, controlled trials (RCTs) that were published in English from 1990 to

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Appendix Tables

CME quiz

Conversion of graphics into slides

May 2007. Full texts of the RCTs that examined the effects of nonsurgical clinical interventions on urinary incontinence in community-dwelling women were eligible for the review. We excluded secondary data analyses, case reports, case series, and RCTs that did not report patient outcomes. We also excluded RCTs that analyzed surrogate outcomes as subjective and objective measures of severity of urinary incontinence, including continuous changes in the number of incontinence episodes or pad use, and urodynamic variables.

We excluded, but further assessed for selection bias, 17 RCTs published before 1990, 2 RCTs conducted in nursing homes residents (39, 40), and 2 RCTs that examined long-term indwelling catheters or bed pads (41, 42). One study of eligible medications was analyzed in the Cochrane review (43) and is included in our present analysis (44). Several RCTs examined drugs that were not eligible for our review (45–47). We concluded that we did not omit clinically important, relevant information by restricting our review to articles published from 1990 to May 2007. The information about all outcomes can be found in the full-text report, available at www.ahrq.gov/clinic.

Data Extraction and Quality Assessment

Two researchers abstracted the data by using standardized forms that elicited information about study samples, interventions, designs, and outcomes. Study quality was analyzed by using the following criteria: participant selection, length and loss of follow-up, use of intention-to-treat principle, masking of the treatment status, randomization scheme, adequacy of randomization and allocation concealment, and justification of sample sizes (evidence tables can be found at www.ahrq.gov/clinic and in **Appendix Table 2** and **Appendix Tables 4–10** [available at www.annals.org]) (48). We used the Grading of Recommendations Assessment, Development and Evaluation working group definitions to evaluate the overall strength of the evidence as high, moderate, low, very low, or insufficient (49, 50). The number of events, including prevalence of urinary incontinence, improvement of urinary incontinence, and continence after interventions in the active treatment and control groups, was abstracted to calculate relative risk and risk difference with 95% CIs among randomly assigned women; the intention-to-treat principle was applied (51, 52). The number of events among treatment groups was calculated from the reported rates among randomly assigned or analyzed women for intention-to-treat analysis. Baseline data were compared in the studies to test differences in the target population and unusual patterns in the data (53, 54). Errors in data extractions were assessed by comparing the established ranges for each variable and the data charts with the original articles. Reproducibility of the results was confirmed by repeating the calculations with different models. The analytic framework for the systematic review and meta-analyses was created according to the Quality of Reporting of Meta-Analyses statement (55).

Applicability of the population was estimated by evaluating the inclusion of women in clinical trials (56). Applicability of the intervention duration was high for studies with a follow-up of 1 year or more and was acceptable for studies with a follow-up of 6 to 12 months.

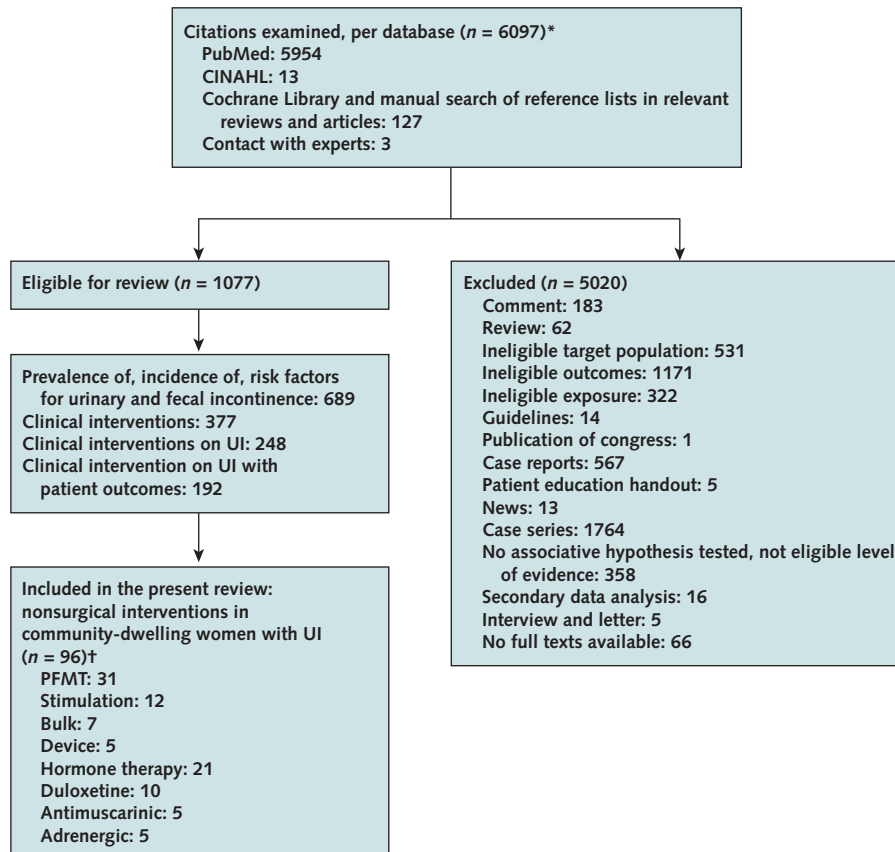
We used several strategies to reduce bias, including a comprehensive literature search of published and unpublished evidence in several databases, a search of reference lists of systematic reviews and proceedings of the International Continence Society, and contacts with experts for additional references.

Data Synthesis and Analysis

We report clinical definitions of urinary incontinence as they were used by the authors of the original studies and with calculated rates of continence and improvement for purposes of comparison: the number of participants continent after the clinical interventions, the number of participants with improvement in severity of urinary incontinence, and the number of participants with prevalent cases of urinary incontinence. We defined long-term (>6 months' duration at follow-up) continence as a primary outcome for the present review because continence is the better-defined and most important clinical outcome. In contrast, definitions of urinary incontinence and improvement in urinary incontinence included presence as well as frequency and severity of symptoms. The rates of continence could not always be interpreted as the reciprocal of the rates of incontinence if trials only reported cases of urinary incontinence but excluded cases of improved urinary incontinence. The efficacy of clinical interventions was analyzed from the trials that compared active treatments with placebo, regular care, or no active treatments. The comparative effectiveness of the interventions was analyzed from the trials with active controls, long-term follow-up, adequate sample size, and intention-to-treat analysis (57).

Pooling criteria included RCTs that reported outcomes after the same clinical interventions (58). Meta-analysis was used to assess the consistency of the association between treatments and urinary incontinence outcomes with random-effects models (59). Consistency in results was tested by comparing the direction and strength of the association. Chi-square tests and I^2 tests were used to assess heterogeneity in study results—a P value less than 0.01 and an I^2 value greater than 50% were considered high (60, 61). We conducted meta-regression analyses by using the dose of the drug tested in individual RCTs (62). We could not perform formal meta-analyses for all treatments and outcomes because of methodologic diversity among the trials and different measurements and definitions of the outcomes. The absolute risk difference in rates of outcomes in the active and control groups was calculated for each study and in pooled analysis (63, 64). To permit the studies with zero events in one group to have the correct CIs (65, 66), we used 0.5 zero-cell correction (65) and compared the

Figure 1. Study flow diagram.



*Literature search was conducted to examine diagnosis, prevalence of, incidence of, risk factors for, and clinical interventions for urinary and fecal incontinence. †Some randomized, controlled trials examined several interventions. PFMT = pelvic floor muscle training.

results of Peto, Mantel–Haenszel, and DerSimonian and Laird random-effects and fixed-effects method summary estimates (65, 66). Calculations were performed by using STATA software (STATA Corp., College Station, Texas) at a 95% confidence level (63).

Role of the Funding Source

The Agency for Healthcare Research and Quality suggested the initial questions and provided copyright release for this manuscript but did not participate in the literature search, data analysis, or interpretation of the results.

DATA SYNTHESIS

Of 248 RCTs on urinary incontinence interventions, we included 96 that examined nonsurgical treatments in women and reported patient outcomes (Figure 1). The Table shows evidence grades and a summary of the comparative conclusions. The studies included women with mixed urinary incontinence, predominant symptoms of stress urinary incontinence (67–78), urodynamic stress urinary incontinence (79–87), predominant urge urinary incontinence (88), overactive bladder with urge urinary in-

continence (89–94), or minimal urinary incontinence (95–97) (Appendix Table 2 and Appendix Tables 4–10). The studies did not explicitly exclude women with other types of urinary incontinence; therefore, the effects of the treatments can be applied to women with mixed urinary incontinence.

Urinary continence after various interventions was defined as self-reported ability to control urination according to voiding diaries and scales, negative results on a pad test, negative stress test results, or a combinations of these (Appendix Tables 2–6). The definitions of improvement in urinary incontinence varied across RCTs from perception of self-reported improvement to objective reduction by 50% to 75% in urinary incontinence episodes reported in a voiding diary.

Pelvic Floor Muscle Training Compared with Regular Care

We found moderate evidence from 4 RCTs ($n = 229$) of stress urinary incontinence (Table) that continence rates (Figure 2) and improvement in urinary incontinence were higher after pelvic floor muscle training, but the effect size

Table. Evidence of the Comparative Effectiveness of Clinical Interventions on Urinary Incontinence in Community-Dwelling Women

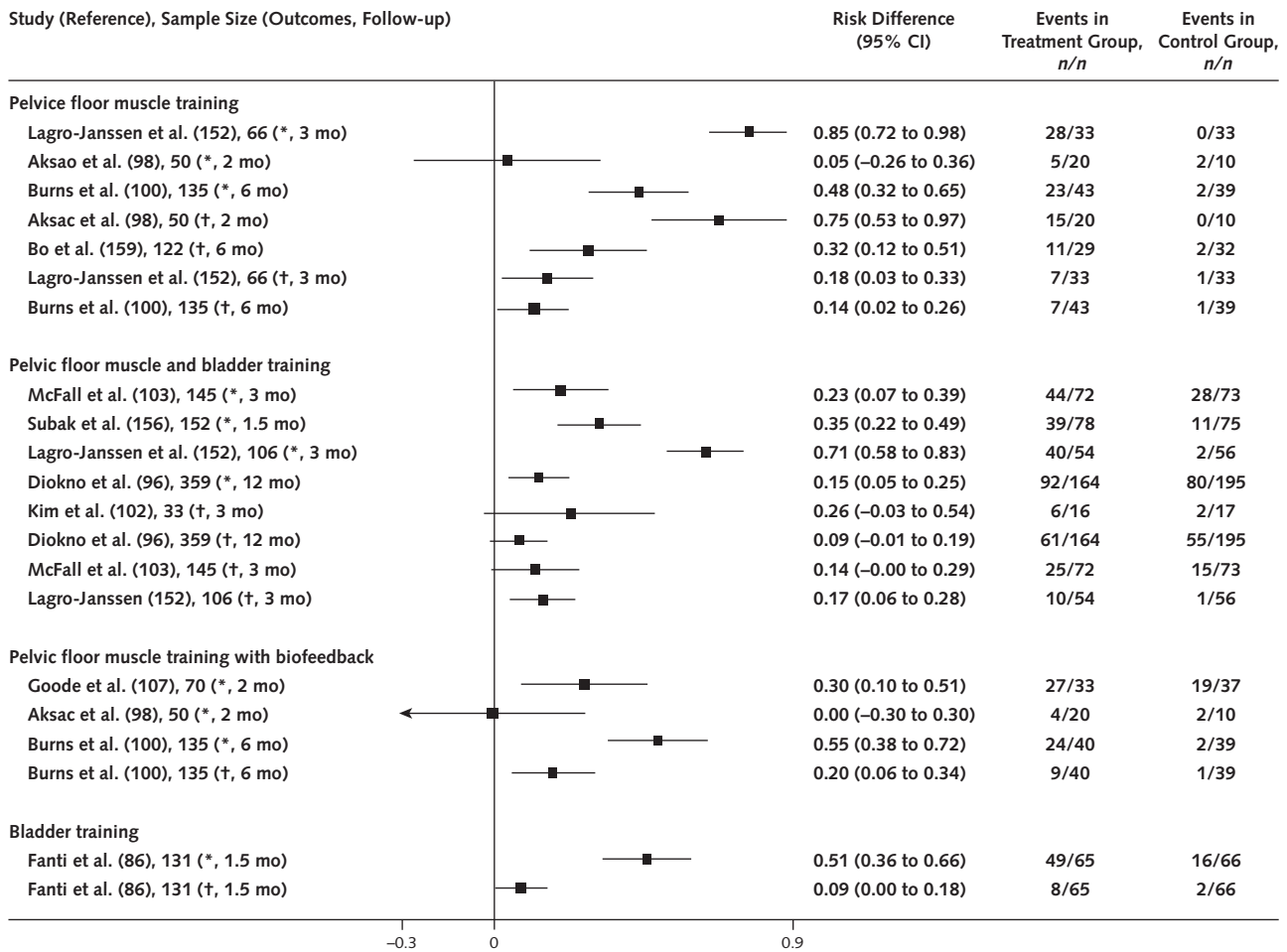
Clinical Interventions	RCTs, n (Women, n)	Level of Evidence	Conclusions
Pelvic floor muscle training compared with regular care	4 (229)	Moderate	Pelvic floor muscle training resulted in higher rates of continence and improvement in UI in all RCTs, but effect size was not consistent across the studies.
Bladder training compared with regular care	1 (131)	Low	Continence rate was not higher after bladder training (risk difference, 0.09 [CI, 0.00–0.18]), bladder training improved UI (risk difference, 0.51 [CI, 0.36–0.66]).
Pelvic floor muscle training and bladder training compared with regular care	4 (647)	Moderate	Pelvic floor muscle training and bladder training consistently increased continence rates (pooled risk difference, 0.13 [CI, 0.07–0.20]; $I^2 = 0\%$). Improvement in UI was higher in all RCTs, with inconsistent effect size across the studies.
Pelvic floor muscle training with biofeedback and bladder training compared with regular care	3 (179)	Low	Pelvic floor muscle training with biofeedback and bladder training improved but did not resolve UI. Pooled estimates was not valid because of significant heterogeneity in results across the studies.
Pelvic floor muscle training with biofeedback compared with active interventions (education and advice, bladder training, medical device, medications)	19 (2441)	Low	Continence and improvement rates did not differ when 2 active treatments were compared with each other. Individual pelvic floor muscle training cured (risk difference, 0.8 [CI, 0.001–0.16]) and improved UI (risk difference, 0.86 [CI, 0.02–0.13]) compared with group exercise (1 RCT of 530 women followed for 1 year). Complex behavioral training implemented by nurses improved urge UI (risk difference, 0.22 [CI, 0.07–0.37]) compared with self-administered pelvic muscle floor exercise in 222 older women followed for 2 mo (1 RCT). Behavioral training (biofeedback-assisted pelvic floor muscle training, bladder control strategies, and self-monitoring with bladder diaries) improved UI compared with self-administered behavioral training with a self-help booklet (risk difference, 0.24 [CI, 0.08–0.39]) in 200 women followed for 2 mo (1 RCT).
Electrical stimulation	12 (745)	Low	Continence rates were not greater after active compared with sham electrostimulation. Rates of resolved urge UI were higher in 1 RCT (risk difference, 0.04 [CI, 0.22–0.58]) of 52 women after 2 mo of treatment. Improvement in mixed UI was greater after active compared with sham stimulation (risk difference, 0.19 [CI, 0.03–0.34]) in 148 women after 2 mo of treatment. Active stimulation was not better than pelvic floor muscle training.
Injectable bulking agents	7 (882)	Low	Rates of continence and improvement were similar among different agents in most RCTs. Transurethral ultrasonography-guided injections of autologous myoblasts and fibroblasts resolved UI better than did collagen injections in 1 RCT of 63 women followed for 1 y (risk difference, 0.81 [CI, 0.66–0.96]). Periurethral or transurethral porcine dermal implant injection compared with silicone injection improved stress UI (risk difference, 0.28 [CI, 0.02–0.54]) in 50 women followed for 2 mo.
Medical device	5 (380)	Low	Continence and improvement rates did not differ among groups using vaginal cones, Hodge pessary, or disposable intravaginal devices.
Hormone therapy	Oral, 17 (1243) Transdermal or vaginal, 5 (710)	High Low	Oral hormone administration increased rates of UI compared with placebo. Transdermal or vaginal administration of estrogen resulted in inconsistent improvement in UI.
Adrenergic drugs	5 (482)	Low	Clenbuterol, norepinephrine, or phenylpropanolamine did not resolve or improve UI compared with placebo or pelvic floor muscle training.
Anticholinergic drugs	5 (2710)	Moderate	Oxybutynin (immediate-release, 5–10 mg) or tolterodine (extended-release, 4 mg) resulted in increased continence rates compared with placebo (pooled risk difference, 0.18 [CI, 0.13–0.22]; $I^2 = 0\%$). The data were not sufficient to allow conclusion about superiority of oxybutynin or tolterodine.
Duloxetine	10 (3633)	Moderate	Rates of improvement (pooled risk difference, 0.11 [CI, 0.04–0.11]; $I^2 = 6\%$) but not continence were higher after different doses of duloxetine compared with placebo. Improvement or cure did not demonstrate dose-response association when 20–80 mg of duloxetine were compared. Duloxetine combined with pelvic floor muscle training resulted in higher cure or improvement rates (risk difference, 0.36 [CI, 0.17–0.56]) in 1 RCT.

* Evidence was rated as follows: high—further research is very unlikely to change our confidence in the estimates; moderate—further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low—further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low—any estimate of effect is very uncertain; insufficient—not graded if there were too few comparisons and not a key comparison of interest. RCT = randomized, controlled trial; UI = urinary incontinence.

was not consistent because of 2 trials with sparse data (98, 99). Neither of the latter 2 RCTs (Appendix Table 2) planned intention-to-treat analysis, justified the sample size, or reported no continence (98) or improvement in urinary incontinence (99) after regular care. We compared pooled relative risk, risk difference, and odds ratios of resolved and improved urinary incontinence to seek consistent estimates of statistically significant overall effects from

the same treatments on different scales (Appendix Table 3). We consider valid only the results that were consistent across RCTs and showed significant benefit from the treatments according to multiple (relative risk and odds ratio) and absolute (absolute risk difference) measures. Pooled relative risk for continence after pelvic floor muscle training (7.1 [95% CI, 2.8 to 18.4]) (80, 98–100) and pelvic floor muscle training with biofeedback (11.2 [CI, 2.2 to

Figure 2. Effects of pelvic floor muscle training compared with regular care on resolving or improving urinary incontinence in community-dwelling women (risk difference from individual randomized, controlled trials).



*Improved urinary incontinence. †Resolved urinary incontinence.

56.4]) (98, 100) were significant and consistent across the studies. Pooled Peto odds ratios, used for RCTs with no events or small rates of the outcomes, showed consistent benefits from both treatments for resolved but not improved urinary incontinence (Appendix Table 3). However, pooled absolute risk differences of resolved or improved urinary incontinence were inconsistent across the studies. Considering that relative risk and absolute risk difference, but not odds ratios, are the most appropriate measures of clinically important effects of the treatments in RCTs (58, 101), available data did not show that pelvic floor muscle training alone or with biofeedback provided consistent valid benefit for urinary incontinence.

Only 1 trial (86) examined bladder training in 131 women with urodynamic stress urinary incontinence and reported higher rates of improvement, but not continence, compared with regular care (Figure 2). The results of this RCT may be compromised because the study did not use intention-to-treat analysis, mask the treatment status, jus-

tify the sample size, or clearly describe allocation concealment (Appendix Table 2).

Moderate consistent evidence from 4 RCTs suggested that women with both types of urinary incontinence were continent more often after pelvic floor muscle training and bladder training compared with regular care (Figure 2) (96, 99, 100, 102, 103). Despite baseline differences in age, type of urinary incontinence, methods to measure continence, and quality of the studies (Appendix Table 2), a pooled risk difference of 13% (0.13 [CI, 0.07 to 0.20]) was consistent across the studies (Appendix Table 3). Pelvic floor muscle training and bladder training also improved urinary incontinence (absolute risk difference, 0.36 [CI, 0.10 to 0.61]), but improvement was not consistent across the studies. Pelvic floor muscle training showed consistent benefit for resolving but not improving urinary incontinence, confirming that long-term continence is the most clinically desirable and valid patient outcome.

The trials did not examine the predictors of better

responses to pelvic floor muscle training. We compared the results from individual studies to analyze the effectiveness of pelvic floor muscle training depending on population and treatment characteristics (**Appendix Table 2**). Pelvic floor muscle training in groups with skilled physical therapists increased subjective cure from stress urinary incontinence at 6 months of follow-up (relative risk, 15.4 [CI, 2.2 to 110.3]) (80). Women with stress urinary incontinence experienced objective cure after this treatment 6 times more often compared with untreated controls (relative risk, 6.1 [CI, 1.5 to 25.1]) (80). Older women with urodynamically diagnosed stress urinary incontinence reported cure 8 times more often than those in regular care at 6 months of follow-up (relative risk, 8.8 [CI, 1.2 to 66]) (100). Individualized behavioral intervention with pelvic floor muscle training for stress urinary incontinence or bladder training for urge urinary incontinence resulted in continence in 19% of women at 3 months of follow-up, with substantial relative benefit compared with regular care (relative risk, 10.4 [CI, 1.4 to 78.3]) (99). Community-based interventions, including education about self-regulation of continence, bladder training, and pelvic floor muscle training, resulted in continence in 35% of women at 3 months of follow-up compared with 30% of those receiving usual care (103). Some evidence suggested the preventive effects of clinical interventions on urinary incontinence. At 12 months of follow-up, the continence rates after a behavioral modification program (including pelvic floor muscle training and bladder training) implemented in 359 postmenopausal, continent women 55 years of age and older were the same as those in patients receiving usual care (continence rate, 37% vs. 28%) (96, 97) (**Appendix Table 2**). Intensive lifestyle therapy to maintain loss of at least 7% of initial body weight and to engage in moderate-intensity physical activity reduced stress urinary incontinence by 15% after 2.9 years of follow-up in the Diabetes Prevention Program RCT among 2191 overweight prediabetic women with a mean body mass index of 24 kg/m² or greater (relative risk, 0.85 [CI, 0.73 to 0.99]) (95).

Comparative Effectiveness of Pelvic Floor Muscle Training

The results from 19 RCTs of pelvic floor muscle training with biofeedback compared with other treatments (including education, bladder training, medical device, or medications) suggested similar effects on continence and improvement of urinary incontinence in women, without statistically significant relative benefit (**Appendix Table 2**). A rehabilitation program implemented by nurse continence advisors and consulting urogynecologists, which included bladder training, gradual increase in fluid intake, pelvic floor muscle training, and transvaginal electrical stimulation, resulted in urinary continence in 50% of women at 3 months, but with no statistically significant differences compared with short-term consultation and bladder training (104). Women with urodynamically diag-

nosed stress urinary incontinence were continent 4 times more often 15 years after intensive pelvic floor muscle training that was supervised by a physical therapist compared with women participating in home exercise (relative risk, 4.02 [CI, 1.54 to 10.53]) (105). Individualized pelvic floor muscle training and bladder training increased continence rates by 158% compared with group exercises in 530 women after 12 months of follow-up (relative risk, 1.58 [CI, 1.05 to 2.36]) (106). Behavioral training (biofeedback-assisted pelvic floor muscle training, bladder control strategies, and self-monitoring with bladder diaries) improved urinary incontinence compared with self-administered behavioral training administered with a self-help booklet (relative risk, 1.42 [CI, 1.1 to 1.8]; risk difference, 0.24 [CI, 0.08 to 0.39]) in 200 women followed for 2 months (1 RCT) (107).

Physical Rehabilitation Therapies

Inconsistent low-level evidence from 12 RCTs did not show that magnetic or electrical stimulation cured or improved urinary incontinence in women better than did sham stimulation or pelvic floor muscle training (**Appendix Table 4**).

Electrical stimulation resulted in continence in about 20% of women (84, 108). However, 2 RCTs that assessed continence at 6 months or more of follow-up failed to show statistically significant benefit from electrical stimulation compared with continence services or medications (80, 108). Other RCTs also did not demonstrate significant relative benefit of electrical stimulation compared with Kegel exercises (108), biofeedback-assisted training (79), or placebo (109–112).

The cure rates for urge urinary incontinence after functional magnetic stimulation were more than 70% in 1 RCT (113). The statistically significant relative benefit of active magnetic stimulation over sham stimulation was shown in only 1 trial at 2 months of follow-up (relative risk, 3.5 [CI, 1.6 to 7.8]; risk difference, 0.57 [CI, 0.35 to 0.8]) (113).

The effectiveness of stimulation to improve urinary incontinence depended on the type of urinary incontinence and administered therapy. The improvement after magnetic stimulation varied from 23% in women with urge urinary incontinence (113) to 74% in those with stress urinary incontinence (110). The greatest improvement in urge urinary incontinence (85%) was observed after intravaginal electrical stimulation in women with predominantly urge urinary incontinence (88). The design of the studies may alter the interpretations of the results; most of the studies had short-term follow-up, and only few justified the sample size (80, 84, 88, 109, 114). Trials were designed to show a decrease in the frequency or severity of urinary incontinence rather than long-term continence after stimulation therapy.

Injectable Bulking Agents

The effects of different bulking agents were examined in 4 RCTs; 1 study included more than 100 women (67), and the other 3 had smaller sample sizes (82, 83, 115). Follow-up lasted 6 (83) to 12 (67, 82, 115) months (**Appendix Table 5**). Curative effects were shown after intra-urethral collagen injection in women with stress urinary incontinence (51.5% were dry during a 24-hour pad test) (67). Transurethral injection of a porcine dermal implant resulted in negative pad test results (cure) in 60% of women with urodynamically proven stress urinary incontinence (83). Transurethral injection of the bulking agent dextran copolymer resulted in objective cure in 15% of women with stress or mixed incontinence (minor and controlled urge component) in whom previous conservative treatments had failed (82).

However, only 1 RCT reported statistically significant relative benefit. This occurred in 63 women with stress urinary incontinence at 12 months of follow-up after transurethral ultrasonography-guided injections of autologous myoblasts and fibroblasts compared with conventional endoscopic injections of collagen (relative risk, 9.5 [CI, 2.53 to 35.63]; risk difference, 0.81 [CI, 0.66 to 0.96]) (115). Other injectable bulking agents did not result in better improvement compared with control treatments.

Medical Devices

Devices studied included a Hodge pessary (81), disposable intravaginal devices (69, 116, 117), urethral plug (118), and vaginal cones (80, 119, 120) (**Appendix Table 6**). Blocking urinary leakage by using a urethral insert device with disposable applicator resulted in continence in 67% of women with mixed or stress urinary incontinence but showed no relative benefit compared with a urethral insert with a sterile balloon device (117). A disposable intravaginal device (Conveen Continence Guard, Coloplast, Humlebaek, Denmark) resolved urinary incontinence in 36% of women with stress urinary incontinence compared with 48% of those using a continence tampon (Contrelle Continence Tampon, Coloplast), with no significant difference between treatments (69). One RCT of 122 women with stress urinary incontinence showed no differences in continence rates after use of vaginal cones compared with continence guard services at 6 months of follow-up (80).

Pharmacologic Agents

Hormone Therapy

Oral hormone administration (17 RCTs; $n = 1243$) resulted in higher rates of urinary incontinence in most studies, with a 50% relative increase in incident mixed urinary incontinence (relative risk, 1.5 [CI, 1.1 to 2.2]) and an 80% increase in incident stress urinary incontinence in postmenopausal women (relative risk, 1.8 [CI, 1.6 to 2.2]) (121) (**Appendix Table 7** available at www.annals.org). Incident urge urinary incontinence increased by 30% (relative risk, 1.3 [CI, 1.2 to 1.5]) and total urinary incontinence by 40% (relative risk, 1.4 [CI, 1.3 to 1.6]) after

participants received estrogen combined with progestin (122). Oral estrogen alone without progestin increased incident stress urinary incontinence by 210% (relative risk, 2.1 [CI, 1.7 to 2.5]) (121) and worsened urinary incontinence by 530% (relative risk, 5.3 [CI, 1.2 to 23.5]) (123).

In contrast, transdermal or vaginal administration of estrogen resulted in inconsistent improvement in urinary incontinence in 5 RCTs ($n = 710$) (116, 124–127). The highest rates of continence were reported after transdermal administration of an estrogen patch (100%) and estrogen gel (90%) among postmenopausal women with self-reported urinary symptoms (126). Topical estrogen in suppositories or creams combined with physiotherapy and electrical stimulation resolved urinary incontinence in 22% of women age 50 to 74 years with regular mild incontinence (>2 leakage episodes per month) compared with 0% in the control group, which did not receive hormone treatment (116).

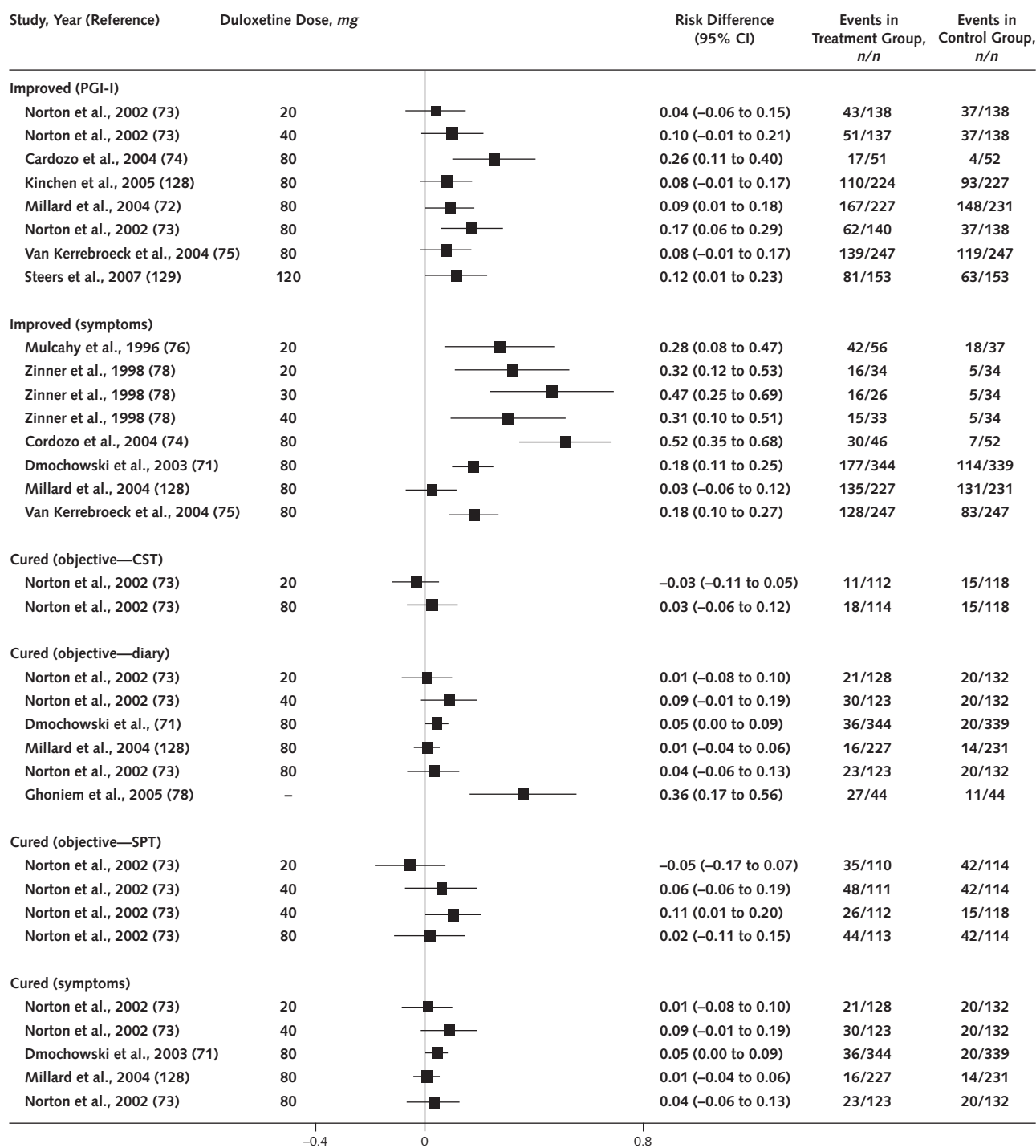
Other Pharmacologic Agents

We updated 3 systematic Cochrane reviews that reported the effects of drug treatment for urinary incontinence in women. The reviews analyzed randomized trials of anticholinergic drugs for overactive bladder (90), of adrenergic drugs for urinary incontinence (43), and of serotonin and noradrenaline reuptake inhibitors for stress urinary incontinence (70). We estimated the relative risk and risk difference of cure, improvement, or progression from the RCTs published after 1990 (**Appendix Tables 8–10**).

Review of 10 RCTs (71–78, 128, 129) ($n = 3633$) of duloxetine administered for 3 to 12 weeks in women with predominantly stress urinary incontinence concluded that the drug failed to show better curative effects than placebo (**Figure 3**) (**Appendix Table 8**). However, improvement rates and quality-of-life scores were better after duloxetine than after placebo (pooled risk difference, 0.11 [CI, 0.07 to 0.14]; $I^2 = 6\%$). The improvement or cure did not demonstrate a dose-response association when 20 to 80 mg of duloxetine were compared (**Figure 4**). Duloxetine combined with pelvic floor muscle training resulted in higher cure or improvement rates (risk difference, 0.36 [CI, 0.17 to 0.56]) in 1 RCT. Common side effects of duloxetine that were analyzed from the database of 1913 women (130) included nausea (23.2%), dry mouth (13.4%), fatigue (12.7%), insomnia (12.6%), constipation (11.0%), headache (9.7%), dizziness (9.5%), somnolence (6.8%), and diarrhea (5.1%). Approximately 20% of women stopped taking duloxetine because of adverse effects.

The Cochrane review of 61 trials of adults with overactive bladder syndrome that compared anticholinergic drugs with placebo or no treatment reported the combined outcome of cure or improvement in urinary incontinence in women and men. We updated the review by analyzing RCTs that included women only (**Figure 5**). **Appendix Table 9**. Oxybutynin (immediate-release, 5 to 10 mg) or

Figure 3. Effects of duloxetine compared with placebo on resolving or improving urinary incontinence in community-dwelling women (risk difference from individual randomized, controlled trials).

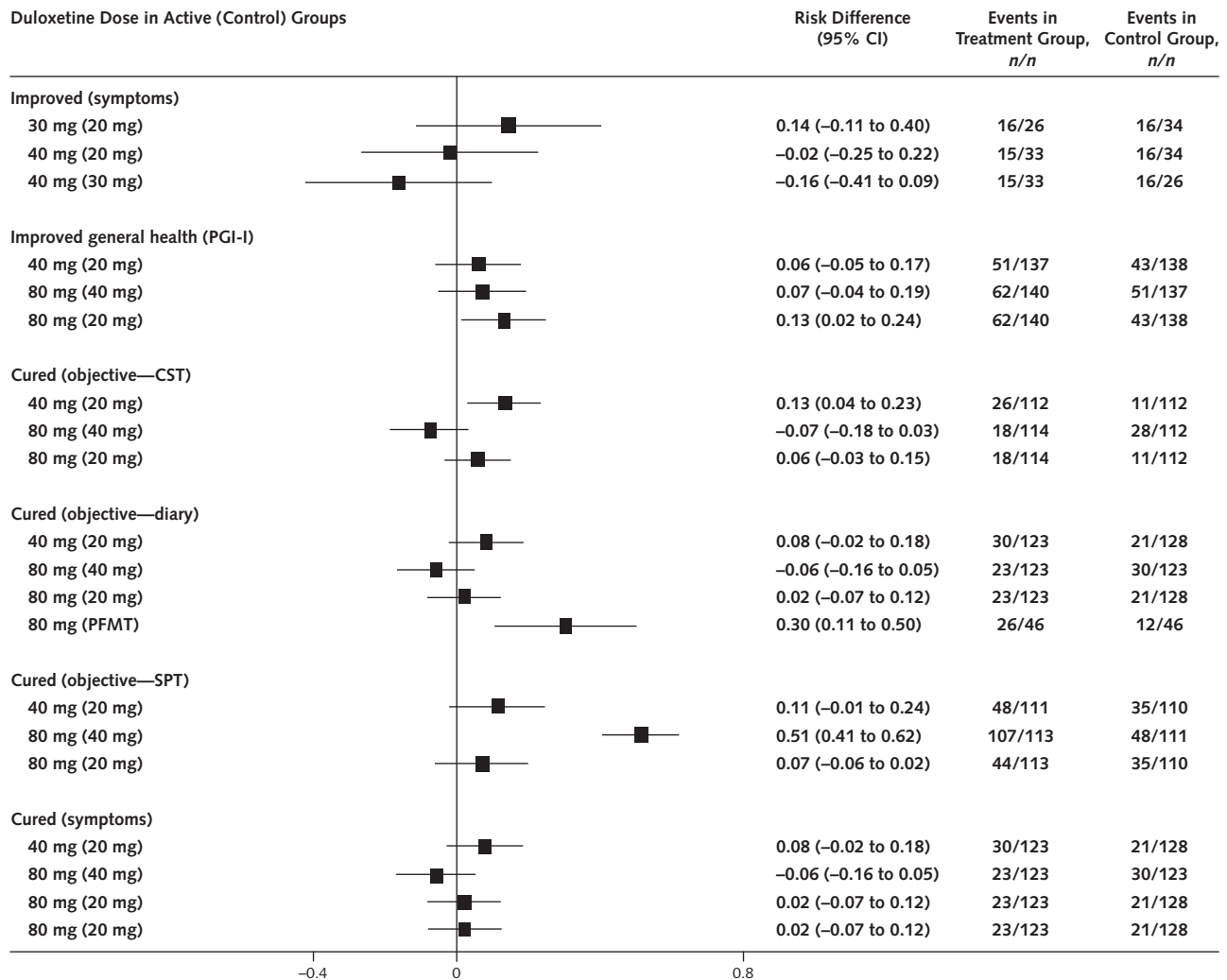


CST = cough stress test; PGI-I = Patient Global Impression of Improvement; SPT = stress pad test.

tolterodine (extended-release, 4 mg) resulted in increased continence rates compared with placebo (pooled risk difference, 0.18 [CI, 0.13 to 0.22]; $I^2 = 0\%$) (91–94, 131). The data were not sufficient for the authors to conclude

superiority of oxybutynin or tolterodine. Pooled analysis of 6 RCTs of different drugs resulted in 139% higher rates of cure or improvement in both men and women (relative risk, 1.4 [CI, 1.3 to 1.5]) (90). The authors also reported

Figure 4. Effects of different doses of duloxetine on resolving or improving urinary incontinence in community-dwelling women (risk difference from individual randomized, controlled trials).



CST = cough stress test; PGI-I = Patient Global Impression of Improvement; SPT = stress pad test.

statistically significant reduction in daily leakage episodes (mean difference, −0.5 episode [CI, −0.7 to −0.4 episode]) after drug administration. The most common adverse effect, dry mouth, was 3 times more common in the medication groups than in the placebo groups (relative risk, 3.00 [CI, 2.70 to 3.34]), with similar rates of withdrawal due to adverse effects (relative risk, 1.11 [CI, 0.91 to 1.36]) (90).

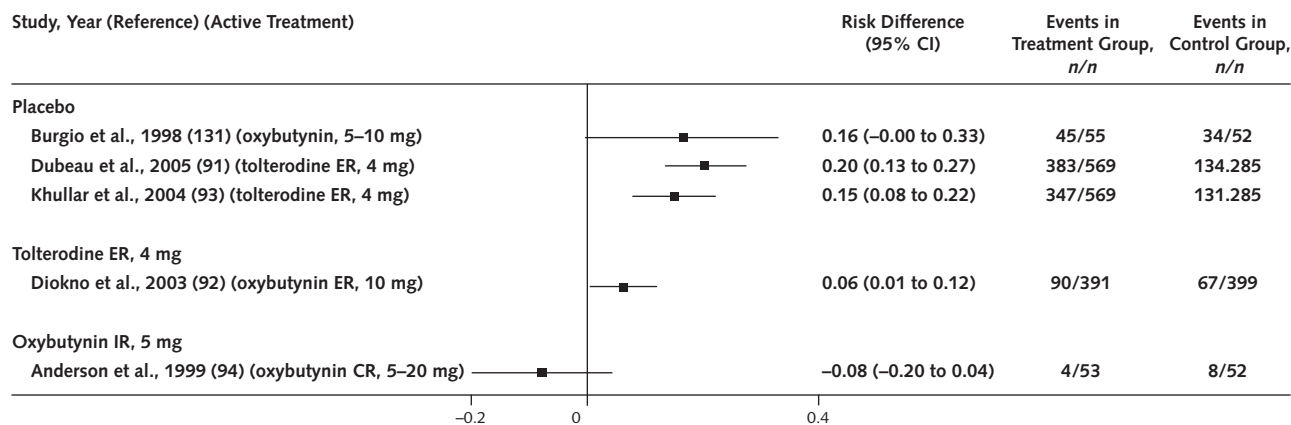
Adrenergic drugs (clenbuterol, norepinephrine, or phenylpropranolamine) did not resolve or improve urinary incontinence compared with placebo or pelvic floor muscle training (76, 91–94, 130–136) (Appendix Table 10). Clenbuterol resulted in continence 2 to 4.6 times more often than placebo in 2 trials but was not more effective than pelvic floor muscle training. The rates of adverse effects after adrenergic drugs were similar to those seen with

placebo; 4% of women stopped treatments because of severe insomnia, restlessness, and vasomotor stimulation (43).

DISCUSSION

Our review confirms the diversity of interventions used, populations, sampling strategies, definitions, and outcome measurements (22, 137). The quality of most of the RCTs was good; participants were not excluded from the analysis of outcomes, and randomization was adequate. However, allocation concealment was inadequate in a large proportion of RCTs (Appendix Table 2 and Appendix Tables 4–10). Variations in populations, interventions, and outcome measures, rather than RCT quality, resulted in heterogeneity between studies.

Figure 5. Effects of anticholinergic drugs on resolving or improving urinary incontinence in community-dwelling women (risk difference from individual randomized, controlled trials).



CR = controlled release; ER = extended release; IR = immediate release.

Studies of behavioral interventions, including pelvic floor muscle training, bladder training, and biofeedback among community-dwelling women, relied largely on convenience samples that involved recruiting participants in clinics (104, 138); few studies reported population-based recruitment (95). Selection criteria varied for the same interventions. For example, only women with intact uteri were included in some (122, 139–141), but not all (123), RCTs of hormone therapy. Baseline characteristics of the participants were balanced, with stratified randomization in few RCTs (125, 142). However, some clinical trials reported statistically significant differences at baseline among treatment groups despite randomization (143, 144). Pooling analysis was questionable because of clinical and methodologic differences across the studies included in the present report and previous systematic reviews (28, 31). Future research is required to determine the predictors of the long-term curative effects of treatments in women from different age and ethnic groups.

Despite extensive efforts to standardize outcome assessment for urinary incontinence (145), the included RCTs measured a variety of outcomes, including self-reported symptoms, signs, and improvement; severity of urinary incontinence as assessed by voiding diaries; pad test weights; and condition-specific quality of life. The measurement of outcomes was inconsistent within and across the studies (Appendix Table 2 and Appendix Tables 4–10). Objective improvements in selected physiologic measures were not consistent after the same interventions and did not correlate with self-reported continence and reduction in severity of urinary incontinence. These improvements were excluded from the present review but are available in the full report (www.ahrq.gov/clinic). The effects on quantitative measures of incontinence, including frequency and amount of leakage as measured by a voiding diary, were smaller than qualitative improvements in symp-

toms. Other systematic reviews analyzed predominantly self-reported cure and improvement in urinary incontinence and concluded that the data are not sufficient to permit proposing invasive and costly urodynamic testing as a measure of success (33).

The criteria for deeming a treatment successful are not well established. Pooled analyses showed substantial heterogeneity across interventions and reported outcomes. Patients and clinicians need to know comparative effectiveness of available treatments on valid and clinically meaningful outcomes. Long-term continence should be the primary outcome for future clinical trials. Consistently significant benefits across the studies from available treatments on absolute rates of cured urinary incontinence should be used for clinical decisions to improve the quality of life in community-dwelling women.

Despite substantial heterogeneity among studies, attributable benefit for public health can be estimated from individual RCTs. Intensive lifestyle changes would avoid 54 cases of stress urinary incontinence per 1000 treated women (95). Pelvic floor muscle training would resolve 490 cases of stress urinary incontinence (105), 80 cases of any urinary incontinence (106), and 167 cases of stress or urge urinary incontinence (99) per 1000 treated women. Magnetic stimulation therapy would resolve 390 cases of urge urinary incontinence (113) and the administration of tolterodine (extended-release, 4 mg), 202 cases of urge urinary incontinence (91) per 1000 treated women.

We analyzed the available information on participant characteristics, randomization, and outcomes that were selected for publication. Well-designed RCTs of pharmacologic agents did not report long-term continence. We did not review RCTs of solifenacin, darifenacin, or trospium because they included participants of both sexes with over-reactive bladder and did not report resolved or improved urinary incontinence in women (Appendix Table 1) (90).

Pelvic floor muscle training combined with bladder training effectively resolved urinary incontinence in women. The long-term effects of combined behavioral and drug therapies on continence rather than surrogate tests need further investigation. Administrative databases can provide useful information on comparative treatment effectiveness, but the results can be biased if provider characteristics are ignored.

The effectiveness of clinical interventions in subgroups of participants by race, comorbid conditions and concomitant treatments, and baseline pelvic floor dysfunction has not yet been well established. Larger trials with recruitment of high-priority populations could yield enough participants among treatment groups to support a subgroup analysis that would provide valid estimations of treatment effects in different populations. The choice of outcomes should reflect participant perception of cure and quality of life rather than provider evaluation and instrumental testing.

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