Nonantimuscarinic treatment for overactive bladder: a systematic review

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The purpose of the study was to determine the efficacy and safety of nonantimuscarinic treatments for overactive bladder. Medline, Cochrane, and other databases (inception to April 2, 2014) were used. We included any study design in which there were 2 arms and an n > 100, if at least 1 of the arms was a nonantimuscarinic therapy or any comparative trial, regardless of number, if at least 2 arms were nonantimuscarinic therapies for overactive bladder. Eleven reviewers double-screened citations and extracted eligible studies for study: population, intervention, outcome, effects on outcome categories, and quality. The body of evidence for categories of interventions were summarized and assessed for strength. Ninety-nine comparative studies met inclusion criteria. Interventions effective to improve subjective overactive bladder symptoms include exercise with heat and steam generating sheets (1 study), diaphragmatic (1 study), deep abdominal (1 study), and pelvic floor muscle training exercises (2 studies). Pelvic floor exercises are more effective in subjective and objective outcomes with biofeedback or verbal feedback. Weight loss with diet and exercise, caffeine reduction, 25-50% reduction in fluid intake, and pelvic floor muscle exercises with verbal instruction and or biofeedback were all efficacious. Botulinum toxin A improves urge incontinence episodes, urgency, frequency, quality of life, nocturia, and urodynamic testing parameters. Acupuncture improves quality of life and urodynamic testing parameters. Extracorporeal magnetic stimulation improves urodynamic parameters. Mirabegron improves daily incontinence episodes, nocturia, number of daily voids, and urine volume per void, whereas solabegron improves daily incontinence episodes. Short-term posterior tibial nerve stimulation is more efficacious than pelvic floor muscle training exercises and behavioral therapy for improving: urgency, urinary incontinence episodes, daily voids, volume per void, and overall quality of life. Sacral neuromodulation is more efficacious than antimuscarinic treatment for subjective improvement of overactive bladder and quality of life. Transvaginal electrical stimulation demonstrates subjective improvement in overactive bladder symptoms and urodynamic parameters. Multiple therapies, including physical therapy, behavioral therapy, botulinum toxin A, acupuncture, magnetic stimulation, mirabegron, posterior tibial nerve stimulation, sacral neuromodulation, and transvaginal electrical stimulation, are efficacious in the treatment of overactive bladder.

Key words: overactive bladder, urinary incontinence, urgency, frequency, treatment

Overactive bladder (OAB) is a common problem affecting up to 17% of the female population.3 Anti-muscarinic medications are commonly used for treatment, and a significant number of outpatient visits in the United States annually are associated with one of these medications. One study found that 68 of 1000 ambulatory visits by women were affiliated with an OAB-related medication, and 8.1 million adult women in the United States were using an OAB-related anticholinergic medication in 2009.2 However, these medications are often marked by lack of efficacy, poor compliance, low patient satisfaction, and bothersome side effects.7 Furthermore, a recent systematic
review confirms that these medications often reduce voids by less than 2 episodes a day and only rarely result in complete resolution of symptoms.4 International guidelines for OAB emphasize behavioral modification and lifestyle therapy as first-line treatment, but there is a paucity of data regarding the effectiveness of these treatments.4-6

The expanding options for nonantimuscarinic treatment of OAB includes various forms of physical therapy, beta-3 agonist medications, neuromodulation, electrical or magnetic stimulation, acupuncture, and botulinum toxin injection.3,5 Many providers are unfamiliar with the evidence surrounding the efficacy and adverse events of these therapies. Emerging evidence demonstrates that nonantimuscarinic treatments, such as onabotulinum toxin A or nerve stimulation, may be as efficacious and acceptable as anticholinergics for OAB. Clinicians are often unsure where in the treatment paradigm to use these options, or consider them much later than ideal. Even the most commonly used nonantimuscarinic treatment for urgency symptoms, pelvic floor physiotherapy, has a lack of evidence regarding long-term outcomes and comparison with other treatments.10 The many women who have OAB would benefit greatly from their provider’s familiarity with the wide array of nonantimuscarinic options available for treatment.

In this systematic review, we aimed to determine the efficacy and safety of nonantimuscarinic treatments for women with OAB.

Methods
Eligibility criteria and study selection
We included adults (≥18 years old) with OAB symptoms of urgency, frequency, nocturia, urgency urinary incontinence (UUI), diagnoses of refractory OAB, refractory UUI, OAB syndrome (urgency, with or without UUI, frequency, and nocturia). We accepted any study (retrospective, prospective, cohort, randomized, controlled trials [RCT], case series, case control, cross-sectional, crossover) in which there were 2 arms and a number greater than 100, if at least 1 of the arms was a nonantimuscarinic therapy for overactive bladder. We also accepted any comparative study, regardless of number, if at least 2 arms were nonantimuscarinic therapies for overactive bladder. We excluded studies with participants having diabetic neuropathy or bladder dysfunction, greater than 50% of subjects with urodynamic stress incontinence, painful bladder syndrome, diabetes insipidus, nocturnal enuresis, vesico-ureteral reflux, neurogenic bladder, bladder cancer, and urinary tract infection (as an explicit eligibility criterion). We also excluded studies with >50% men or subjects who were restricted to residential facilities such as nursing homes.

The abstracts were collectively divided among the 11 group members. If there was a discrepancy between the 2 extrac tors regarding an abstract (ie, inclusion or not) the abstract was then reviewed by the principal investigator for the group to resolve the discrepancy. Online software (Abstrackr, http:abstrackr.cebm.brown.edu)11 was used for the screening process. Potentially eligible full-text articles were again screened in the same fashion.

Information sources
The Society of Gynecologic Surgeons Systematic Review Group, including gynecologic surgeons and systematic review methodologists, performed a systematic search to identify studies comparing nonantimuscarinic treatments for OAB. We searched Medline, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and Commonwealth Agricultural Bureaux Abstracts from inception until April 2, 2014. The search included numerous terms for OAB and possible treatments including: OAB, urinary incontinence, enuresis, urgency, frequency, nocturia, detrusor instability, diapers, mirabegron, botulinum toxins, neuromuscular agents, muscle/bladder training, exercises, biofeedback, electrical stimulation, behavioral therapy, related terms; and terms for comparative studies and systematic reviews. The search was restricted to English language publications.

**FIGURE 1**

Diagram of selected studies for systematic review

Identification
Abstracts identified through database searching (n=2975)

Screening
Double screened abstracts identified through database searching (n=2389)

Eligibility
Full-text articles assessed for eligibility (n=156)

Included
Studies included in qualitative synthesis (n=99)

Studies included in quantitative synthesis (n=99)

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<td>RCT</td>
<td>40</td>
<td>A</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>Low</td>
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<td>Emmons</td>
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<td>2005</td>
<td>RCT</td>
<td>74</td>
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<tr>
<td>Gordon</td>
<td>Israel</td>
<td>1998</td>
<td>RCT</td>
<td>40</td>
<td>B</td>
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<tr>
<td>Hassouna</td>
<td>Canada, USA, Netherlands</td>
<td>2000</td>
<td>RCT</td>
<td>51</td>
<td>B</td>
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<td>High</td>
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<td>Low</td>
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<tr>
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<tr>
<td>Schmidt</td>
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<tr>
<td>Van Kerrebrokeck</td>
<td>Netherlands, England, Canada, Germany, Sweden, Switzerland, USA</td>
<td>2007</td>
<td>Single arm, prospective</td>
<td>152</td>
<td>C</td>
<td>Unclear</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
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<td>Visco</td>
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<td>2012</td>
<td>RCT</td>
<td>249</td>
<td>A</td>
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<td>Low</td>
<td>Low</td>
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</table>

Search strategy
Searches of relevant databases initially identified 2975 citations that were screened. Figure 1 describes the flow of screened included and excluded abstracts. There were 156 manuscripts screened as full texts after abstract screening, and 99 of these manuscripts met all criteria for inclusion in the systematic review.

Data extraction
We first extracted lists of reported outcomes from each article. Outcomes of potential interest (subjective, objective, voiding diary, validated questionnaires, urodynamic testing, catheterizations, and adverse event data) that appeared in at least 2 studies were included for final extraction (Appendix A). We extracted data on study characteristics, participant characteristics, intervention details, outcome definitions, length of follow-up, and results.

Assessment of risk of bias and strength of evidence
Each study was assessed on the basis of the Cochrane Risk of Bias Tool. This tool included questions regarding randomization, allocation concealment, outcome assessor and participant blinding, amount and handling of missing data, dropouts, crossovers, similarity of participants at baseline and of co-interventions, compliance, intention-to-treat analysis (evaluation of potential confounders), and clarity and accuracy of reporting (Table 1). Studies were graded as good (A), fair (B), or poor (C) quality, based on the likelihood of bias (Tables 1 and 2), and completeness of reporting, based on a system approved by the Agency for Healthcare Research and Quality. Outcome quality could vary within the same study. All extracted data, including quality assessment, were confirmed by a second reviewer. When a discrepancy between extracted outcome study qualities arose, that discrepancy was resolved by a third reviewer.

For each intervention, we generated an evidence profile by grading the strength of evidence for each outcome according to the Grades for Recommendation, Assessment, Development and Evaluation system. The process considered the methodologic quality, consistency of results across studies, directness of the evidence, and imprecision or sparseness of evidence to determine an overall quality of evidence. Four quality rating categories were possible: high (A), moderate (B), low (C), and very low (D). Strength of evidence was determined by group consensus.

Data synthesis
For reporting in this review, these outcomes were divided into the following categories: subjective, objective, voiding diary, validated symptom questionnaires, and quality of life, based on validated questionnaires, urodynamic testing, catheterizations, and adverse events.

Data from the completed data abstraction forms were used to develop evidence profiles. The evidence profiles were created for each of the major nonantimuscarinic forms of therapy for OAB. We compared interventions versus control, interventions versus antimuscarinic agent(s), and interventions versus other intervention(s). The final interventions and comparators were as follows: (1) behavioral therapy (including weight loss, fluid management, diet modification, bladder training, and pelvic floor muscle training exercises), (2) complementary and alternative medical therapy (most commonly acupuncture), (3) biofeedback, (4) botulinum toxin A formulations, (5) mirabegron, (6) magnetic stimulation, (7) vaginal electrical stimulation, (8) sacral neuromodulation, and (9) posterior tibial nerve therapy.

After the extraction forms were completed, a summary table was created. This table listed the complete list of manuscripts and all of the data in the various different study designs and outcome categories. After the summary table was created, we created evidence profiles. Each evidence profile was constructed for the individual treatment option. On the basis of the evidence in the literature, we attempted to make an evidence profile for each therapeutic option as noted above, comparing the intervention with control, antimuscarinic therapy, and other interventions. Evidence profiles were created for physical therapy, behavioral therapy, botulinum toxin A, complementary and alternative medicine, magnetic stimulation, mirabegron, posterior tibial nerve stimulation, sacral neuromodulation, and transvaginal electrical stimulation.

We developed guideline statements incorporating the balance between benefits and harms of the compared interventions when the data were sufficient to support these statements. Each guideline was graded into 2 parts: a strength of the recommendation and an

| TABLE 2 |
| Assessment of risk of bias |
| Bias type | Low (n = 99) | High (n = 99) | Unclear (n = 99) |
| Random sequence generation (selection bias) | 62.6% | 19.3% | 18.1% |
| Allocation concealment (selection bias) | 35.3% | 28.4% | 36.3% |
| Outcome assessment bias (detection bias) | 50.5% | 27.3% | 22.2% |
| Patient blinding bias (performance bias) | 44.4% | 45.5% | 10.1% |
| Incomplete outcome data (attrition bias) | 67.7% | 18.2% | 14.1% |
| Crossover bias | 69.7% | 5.0% | 25.3% |
| Baseline bias | 73.7% | 10.1% | 16.2% |
| Compliance bias | 60.6% | 11.1% | 28.3% |

Each risk of bias presented as percentage across all included studies.

overall quality of evidence. The strength of a recommendation indicates the extent to which one can be confident that adherence to the recommendation will do more good than harm. Grades for Recommendation, Assessment, Development, and Evaluation 1 recommendations are strong, worded as “we recommend,” and indicate that benefits do, or do not, outweigh risks, burden, and costs (what most practitioner[s] would do in a given clinical scenario). Grades for Recommendation, Assessment, Development, and Evaluation 2 recommendations are worded as “we suggest” and imply that the magnitude of the benefits, risks, burden, and costs are less certain. In either case, support for recommendations may come from high-quality, moderate-quality, or low-quality studies, labeled, respectively, A, B, and C. The review and guidelines were presented for public comment at the Society of Gynecologic Surgeons annual scientific meeting in April 2015 and posted on the Society of Gynecologic Surgeons website, after which comments were solicited for 4 weeks.

Results
Study selection
Eleven reviewers screened abstracts and titles in duplicate, with discrepancies resolved by a third reviewer, using online software (Abstrackr, http: abstrackr.cebm.brown.edu).11 Potentially eligible full-text articles were again screened in duplicate.

Risks of bias of included studies
Each study was assessed on the basis of the Cochrane Risk of Bias Tool.12 This included questions regarding randomization, allocation concealment, outcome assessor and participant blinding, amount and handling of missing data, dropouts, and crossovers, similarity of participants at baseline and of co-interventions, compliance, intention-to-treat analysis, handling of potential confounders, and clarity and accuracy of reporting. From these data, we were able to quantify various types of bias among the extracted manuscripts including selection, detection, performance, attrition, crossover, baseline, and compliance (Table 2). Studies were graded as good (A), fair (B), or poor (C) quality, based on the likelihood of bias and completeness of reporting, in accordance with the system approved by the Agency for Healthcare Research and Quality mentioned above13 (Table 1). Of the 99 manuscripts extracted, 45 of 99 (45.4%) were study quality (A), 27 of 99 (27.3%) were study quality (B), and 27 of 99 (27.3%) were study quality (C).

Synthesis of results
Physical therapy versus control. The heat- and steam-generating sheet is a thin, flexible filmed sheet (120 mm 204 mm; Kao, Tokyo, Japan) that generates heat and steam immediately after unsealing. When the sheet is placed on the body, the temperature of the skin surface rises to 38-40°C, and it continues to generate heat and steam for over 5 hours.14 The participants gathered at classes every 2 weeks, where heat- and steam-generating sheets were provided for 2 weeks, and the urinary diaries were collected. The participants in the heat- and steam-generating group were asked to place the heat- and steam-generating sheet on their lower back once a day immediately after waking up. The participants recorded the time of day that they placed and removed the sheet in their urinary diary (Table 3).

Exercises along with heat- and steam-generating sheets were superior to control for subjective cure of OAB symptoms in 1 RCT (1A)15 at 3 months, with no increase in adverse events.

Stretching, pelvic floor muscle exercises, and fitness exercises (with multidimensional approach) were superior to placebo at 3 months, based on 1 RCT (1B)16 for the objective outcomes (walking speed, grip strength, and adductor muscle strength), with no increase in adverse events.

Pelvic floor muscle exercises plus biofeedback were superior to control in 1 RCT (1B)17 for improvement in subjective outcomes (severity of incontinence symptoms) and objective outcomes (pad weight test) at 24 months with no adverse events.

Diaphragmatic, deep abdominal and pelvic floor muscle retraining were superior to control at 4 months for subjective outcomes, general health and well-being (avoiding activities due to needing to use a toilet), daily incontinence episodes, daily voids, and leakage volume with no increase in adverse events, based on a single RCT (1A).18

Physical therapy versus antimuscarinic. Pelvic floor muscle exercises were similar to oxybutynin in 1 RCT (1B)19 at 12 weeks for the subjective outcome of urgency and objective outcomes (number of daily pad use and post void residual volumes). However, in the same RCT (1B),19 oxybutynin was superior to pelvic floor muscle exercises in urodynamical outcomes (maximum cystometric capacity values) and the subjective outcome of nocturia symptoms. In this trial, oxybutynin was associated with more dry mouth, blurry vision, constipation, confusion, and dizziness.

Physical therapy versus other intervention. On the basis of 1 RCT (1A),20 electrical stimulation was superior to pelvic floor muscle exercises for improving quality of life, based on the International Consultation on Incontinence Questionnaire short form for short-term follow-up (12 weeks). No data were available on adverse events.

On the basis of 1 RCT (1B),21 biofeedback-assisted pelvic floor muscle exercises were superior to electrical stimulation combined with pelvic floor muscle exercises for improvement in objective outcomes (pelvic floor muscle contraction strength at 12 weeks), but that effect was not seen in a single separate RCT at 3 months (1B).22 No data on adverse events were available in either of these studies.

On the basis of 1 RCT (1B),21 biofeedback-assisted pelvic floor muscle exercises combined with electrical stimulation was superior to pelvic floor muscle exercises alone for improvement in quality of life (Kings Health Questionnaire at 12 weeks). No data on adverse events were available in this trial.

Biofeedback or verbal feedback were superior to a self-help book based on 1 RCT (1A)23 for improvement in
## TABLE 3
Summary of evidence

<table>
<thead>
<tr>
<th>Therapy group</th>
<th>Outcome</th>
<th>Intervention vs comparator</th>
<th>Follow-up time</th>
<th>Quality of evidence</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical therapy vs control</td>
<td>Subjective outcome: cure of overactive bladder symptoms</td>
<td>Exercises with heat and steam generating sheets were superior to control</td>
<td>3 Months</td>
<td>1A Study</td>
<td>None</td>
</tr>
<tr>
<td>Physical therapy vs control</td>
<td>Objective outcomes: walking speed, grip strength, adductor muscle strength</td>
<td>Stretching, pelvic floor muscle exercises and fitness exercises (with multidimensional approach) were superior to control</td>
<td>24 Months</td>
<td>1B Study</td>
<td>None</td>
</tr>
<tr>
<td>Physical therapy vs control</td>
<td>Subjective outcomes: severity of incontinence symptoms objective outcomes: pad weight</td>
<td>Pelvic floor muscle exercises plus biofeedback were superior to control for improvement in outcomes</td>
<td>24 Months</td>
<td>1B Study</td>
<td>None</td>
</tr>
<tr>
<td>Physical therapy vs control</td>
<td>Subjective outcomes: general health and well-being (less need to avoid activities due to need to use toilet) -daily incontinence episodes -daily voids -leakage volume</td>
<td>Diaphragmatic, deep abdominal and pelvic floor muscle re-training were superior to control for improvement in outcomes</td>
<td>4 Months</td>
<td>1A Study</td>
<td>None</td>
</tr>
<tr>
<td>Physical therapy vs antimuscarinic</td>
<td>Subjective outcomes: urgency and objective number of daily voids, pad use, and post-void residual volumes</td>
<td>Pelvic floor muscle exercises were similar to oxybutynin for improvement in outcomes</td>
<td>12 Weeks</td>
<td>1B Study</td>
<td>Oxybutynin was associated with more dry mouth, blurry vision, constipation, confusion, and dizziness</td>
</tr>
<tr>
<td>Physical therapy vs antimuscarinic</td>
<td>Subjective outcomes: nocturia symptoms objective outcomes: maximum cystometric capacity on urodynamic testing</td>
<td>Oxybutynin was superior to pelvic floor muscle exercises for improvement in outcomes</td>
<td>12 Weeks</td>
<td>1B Study</td>
<td>Oxybutynin was associated with more dry mouth, blurry vision, constipation, confusion, and dizziness</td>
</tr>
<tr>
<td>Physical therapy vs other intervention</td>
<td>Quality-of-life outcome: International Consultation on Incontinence Questionnaire</td>
<td>Electrical stimulation was superior to pelvic floor muscle exercises for improvement in outcomes</td>
<td>12 Weeks</td>
<td>1A Study</td>
<td>No data</td>
</tr>
<tr>
<td>Physical therapy vs other intervention</td>
<td>Objective outcome: pelvic floor muscle contraction strength</td>
<td>Biofeedback-assisted pelvic floor muscle exercises were similar to electrical stimulation combined with pelvic floor muscle exercises</td>
<td>3 months</td>
<td>2B studies</td>
<td>No data</td>
</tr>
<tr>
<td>Physical therapy vs other intervention</td>
<td>Quality-of-life outcome: Kings Health Questionnaire</td>
<td>Biofeedback-assisted pelvic floor muscle exercises combined with electrical stimulation was superior to pelvic floor muscle exercises alone for improvement in outcomes</td>
<td>12 Weeks</td>
<td>1B Study</td>
<td>No data</td>
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<td>Physical therapy vs other intervention</td>
<td>Subjective outcome: overactive bladder symptoms</td>
<td>Biofeedback or verbal feedback were superior to self-help book for improvement in outcomes</td>
<td>12 Weeks</td>
<td>1A Study</td>
<td>None</td>
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<tr>
<td>Physical therapy vs other intervention</td>
<td>Objective outcomes: daily pad use and in visual analog scale scores</td>
<td>Biofeedback with pelvic floor muscle exercises were superior to pelvic muscle exercises alone for improvement in outcomes</td>
<td>6 Weeks</td>
<td>1C Study</td>
<td>No data</td>
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</table>


(continued)
<table>
<thead>
<tr>
<th>Therapy group</th>
<th>Outcome</th>
<th>Intervention vs comparator</th>
<th>Follow-up time</th>
<th>Quality of evidence</th>
<th>Adverse events</th>
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<tbody>
<tr>
<td>Physical therapy vs other intervention</td>
<td>Quality-of-life outcome: Kings Health Questionnaire</td>
<td>Electrical stimulation and biofeedback assisted pelvic floor muscle exercises were superior to pelvic floor muscle exercises alone in one study and similar in one study</td>
<td>12 Weeks</td>
<td>2B Studies</td>
<td>No data</td>
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<td>Physical therapy vs other intervention</td>
<td>Subjective outcome: wearing less protection, overactive bladder symptoms, improved muscle strength</td>
<td>Vaginal weighted cones were similar to pelvic muscle exercises</td>
<td>12 Weeks</td>
<td>1C Study</td>
<td>No data</td>
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<tr>
<td>Behavioral therapy vs control</td>
<td>Subjective outcomes and improvement in voiding diary outcomes</td>
<td>Bladder training with pelvic floor muscle exercises were similar to control for subjective outcomes, and superior to control for voiding diary outcomes</td>
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<td>1C Study</td>
<td>None</td>
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<td>Behavioral therapy vs control</td>
<td>Bladder diary outcomes: daily voids and daily urgency episodes</td>
<td>Education on caffeine reduction was superior to control for improvement in outcomes</td>
<td>No data</td>
<td>1B Study</td>
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<td>Behavioral therapy vs control</td>
<td>Voiding diary outcomes: daily urge incontinence episodes, stress incontinence episodes, and smaller volume accidents</td>
<td>Weight loss with diet and exercise were superior to control for improvement in outcomes</td>
<td>No data</td>
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<tr>
<td>Behavioral therapy vs control</td>
<td>Voiding diary outcomes: daily urgency and nocturia</td>
<td>A 25-50% reduction in fluid intake was associated with improvement in outcomes</td>
<td>No data</td>
<td>1B Study</td>
<td>None</td>
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<tr>
<td>Behavioral therapy vs antimuscarinic</td>
<td>Bladder diary outcome: 24-hour incontinence episodes</td>
<td>Bladder training plus terodiline were similar to control</td>
<td>6 Weeks</td>
<td>1B Study</td>
<td>Increased rate of dry mouth noted when terodiline was used</td>
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<tr>
<td>Behavioral therapy vs other intervention</td>
<td>Objective: Visual Analog Scale score</td>
<td>Outpatient bladder training and physiotherapy were superior to inpatient bladder training alone for improvement in outcomes</td>
<td>3 Months</td>
<td>1B Study</td>
<td>None</td>
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<tr>
<td>Behavioral therapy vs other intervention</td>
<td>Subjective outcomes: nocturia symptoms Quality-of-life outcomes: International Consultation on Incontinence Questionnaire-short form Bladder diary outcomes: stress incontinence episodes and daily urgency urinary incontinence episodes</td>
<td>Pelvic floor muscle exercises (instruction to perform without physiotherapy guidance) plus bladder training and posterior tibial nerve stimulation were superior pelvic floor muscle exercises and bladder training alone for improvement in outcomes</td>
<td>12 Weeks</td>
<td>1B Study</td>
<td>None</td>
</tr>
<tr>
<td>Behavioral therapy vs other intervention</td>
<td>Voiding diary outcome: daily stress incontinence and urge incontinence episodes Quality-of-life outcome: Short Form-36 health survey</td>
<td>Immediate intervention weight loss was superior to delayed intervention weight loss for improvement in outcomes</td>
<td>No data</td>
<td>1A Study</td>
<td>None</td>
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</table>
### TABLE 3
**Summary of evidence** (continued)

<table>
<thead>
<tr>
<th>Therapy group</th>
<th>Outcome</th>
<th>Intervention vs comparator</th>
<th>Follow-up time</th>
<th>Quality of evidence</th>
<th>Adverse events</th>
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</thead>
<tbody>
<tr>
<td><strong>Toxin A vs control</strong></td>
<td>Subjective outcomes: urgency, frequency, quality of life</td>
<td>Onabotulinum and abobotulinum toxin A was superior to placebo for improvement in outcomes</td>
<td>30 Days to 6 months</td>
<td>10A Studies</td>
<td>Onabotulinum and abobotulinum toxin A had greater: urinary retention, elevated post-void residual volumes, need for self-intermittent catheterization, and urinary tract infections</td>
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<tr>
<td><strong>Onabotulinum toxin A vs control</strong></td>
<td>Subjective outcomes: urgency, frequency, and nocturia</td>
<td>100 Units of onabotulinum toxin A was more effective than 50 units for improvement in outcomes</td>
<td>30 Days to 6 months</td>
<td>10A Studies</td>
<td>Onabotulinum toxin A had greater urinary retention, elevated post-void residual volumes, need for self-intermittent catheterization, and urinary tract infections</td>
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<td><strong>Onabotulinum toxin vs antimuscarinic</strong></td>
<td>Subjective outcome: cure</td>
<td>Both anticholinergics and onabotulinumtoxin A were similar in efficacy for reduction in UUI episodes and OAB scores, but onabotulinumtoxin A was superior to anticholinergics for subjective cure of UUI</td>
<td>6 Months</td>
<td>1A Study</td>
<td>Onabotulinum toxin A: increased risk of urinary retention, need for self-catheterization, and urinary tract infections. Antimuscarinic medication was associated with an increased risk of dry mouth</td>
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<tr>
<td><strong>Onabotulinum toxin vs other intervention</strong></td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
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<tr>
<td><strong>Acupuncture vs control</strong></td>
<td>Quality-of-life outcome: Incontinence impact questionnaire-7, and urodynamic distress inventory-6</td>
<td>Acupuncture was superior to control for improvement in quality of life for improvement in outcomes</td>
<td>No data</td>
<td>1A Study 1C Study</td>
<td>Arthralgia, lead migration, blurry vision, dry eyes, nasopharangitis, itching, dizziness, nausea, headache, bruising at the needle site, and insomnia noted with acupuncture</td>
</tr>
<tr>
<td><strong>Acupuncture vs control</strong></td>
<td>Quality-of-life outcomes: International Consultation on Incontinence Questionnaire, Kings Health Questionnaire, bladder diary outcomes: 24-hour voiding frequency, urgency</td>
<td>Acupuncture was similar to for improvement in outcomes</td>
<td>8 Weeks</td>
<td>1A Study</td>
<td>None</td>
</tr>
<tr>
<td><strong>Acupuncture vs antimuscarinic</strong></td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td><strong>Antimuscarinic vs other intervention</strong></td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
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</thead>
<tbody>
<tr>
<td>Magnetic stimulation vs control</td>
<td>Quality-of-life outcome: International consultation on incontinence questionnaire-short form Voiding diary outcomes: overactive bladder cure, daily urge incontinence episodes</td>
<td>Functional magnetic stimulation was superior to control for improvement in outcomes</td>
<td>8-24 Weeks</td>
<td>1C Study 1B Study</td>
<td>None</td>
</tr>
<tr>
<td>Magnetic stimulation vs control</td>
<td>Urodynamic outcomes: increasing the volume of first contraction, maximum detrusor pressure, and maximum cystometric capacity</td>
<td>Extracorporeal magnetic stimulation was superior to sham chair for improvement in outcomes</td>
<td>10-24 Weeks</td>
<td>1A Study 1B Study</td>
<td>None</td>
</tr>
<tr>
<td>Magnetic stimulation vs control</td>
<td>Functional magnetic stimulation vs functional electrical stimulation</td>
<td>Functional magnetic stimulation was similar functional electrical stimulation for improvement in outcomes</td>
<td>8 Weeks</td>
<td>1C Study</td>
<td>None</td>
</tr>
<tr>
<td>Mirabegron vs control</td>
<td>Voiding diary outcome: daily incontinence episodes</td>
<td>Mirabegron (25-50 mg) was superior to control for improvement in outcomes</td>
<td>12 Weeks</td>
<td>1A Study</td>
<td>None</td>
</tr>
<tr>
<td>Mirabegron vs control</td>
<td>Voiding diary outcome: daily incontinence episodes</td>
<td>Mirabegron (50-100 mg) was superior to control for improvement in outcomes</td>
<td>12 Months</td>
<td>1A Study</td>
<td>Increase in upper respiratory tract infections, dizziness, nausea, and back pain</td>
</tr>
<tr>
<td>Solebegron vs control</td>
<td>Subjective outcome: daily incontinence episodes</td>
<td>Solebegron (125 mg) was superior to placebo for improvement in outcomes</td>
<td>4 Weeks</td>
<td>1A Study</td>
<td>Increase in headache, nasopharangitis, dry mouth, constipation, nausea, increase in urinary tract infections, arthralgia, hypertension, abdominal pain, dizziness, extremity pain, depression, general pain, musculoskeletal chest pain</td>
</tr>
<tr>
<td>Mirabegron vs antimuscarinic</td>
<td>Subjective outcome: nocturia Bladder diary outcomes: daily incontinence episodes, number of daily voids, urine volume per void</td>
<td>Mirabegron (100 mg) was similar to tolterodine extended release (4 mg) for improvement in outcomes</td>
<td>12 Weeks</td>
<td>1A Study</td>
<td>There were similar rates of hypertension, urinary tract infection, dry mouth, nasopharangitis, headache, influenza, constipation, arthralgia, tachycardia, back pain, dizziness, diarrhea, and sinusitis</td>
</tr>
<tr>
<td>Therapy group</td>
<td>Outcome</td>
<td>Intervention vs comparator</td>
<td>Follow-up time</td>
<td>Quality of evidence</td>
<td>Adverse events</td>
</tr>
<tr>
<td>--------------------------------------------------</td>
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<td>Mirabegron vs other intervention</td>
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<tr>
<td>Posterior tibial nerve stimulation vs control</td>
<td>Subjective outcome: urgency</td>
<td>Posterior tibial nerve stimulation was superior to control for improvement in outcomes</td>
<td>4-13 Weeks</td>
<td>2A Studies</td>
<td>Posterior tibial nerve stimulation was associated with ankle bruising, discomfort at needle site, bleeding at needle site, and tingling in the leg</td>
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<tr>
<td></td>
<td>Quality-of-life outcomes: overactive bladder questionnaire score and Short Form-36 bladder diary outcomes: reduction in urgency urinary incontinence, daily voids, daily incontinence episodes, volume per void</td>
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<td>Posterior tibial nerve stimulation vs antimuscarinic</td>
<td>Subjective outcome: improvement in symptoms</td>
<td>Posterior tibial nerve stimulation was similar to oxybutynin</td>
<td>5 Weeks</td>
<td>1B Study</td>
<td>None</td>
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<td>Posterior tibial nerve stimulation vs other intervention</td>
<td>Bladder diary outcomes: daily voids</td>
<td>Posterior tibial nerve stimulation was superior to pelvic floor muscle exercises and behavioral therapy for improvement in outcomes</td>
<td>12 Weeks</td>
<td>1B Study</td>
<td>None</td>
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<td>Sacral neuromodulation vs control</td>
<td>Subjective outcomes: cure, wearing less protection, urgency intensity</td>
<td>Sacral neuromodulation was superior to control for improvement in outcomes</td>
<td>6 Months</td>
<td>2B Studies</td>
<td>Pain at the implantable pulse generator site, extremity pain, adverse change in bowel function, cardiac arrhythmia, vaginal pain, anal pain, and skin irritation at the implantation site</td>
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<td></td>
<td>Bladder diary outcomes: reduction in daily incontinence episodes, daily voids, urine volume per void</td>
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<td></td>
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<tr>
<td></td>
<td>Quality of life: Short Form-36</td>
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<tr>
<td>Sacral neuromodulation vs control</td>
<td>Bladder diary outcome: daily voids</td>
<td>Transelectrical modulation/sacral neuromodulation were similar to control for improvement in outcomes</td>
<td>3 Weeks</td>
<td>1C Study</td>
<td>No data</td>
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<tr>
<td>Sacral neuromodulation vs antimuscarinic</td>
<td>Bladder diary outcomes: number of pads used in 24 hours, daily incontinence episodes, leakage volume, Urodynamic outcomes: first sensation, improved involuntary detrusor contraction volume, and quality of life</td>
<td>Sacral neuromodulation was superior to anticholinergics for improvement in outcomes</td>
<td>6 Months</td>
<td>1B Study</td>
<td>Sacral neuromodulation was associated with an adverse change in bowel habits, electrically induced discomfort, pain at the implantable pulse generator site, infection</td>
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<td>Transelectrical stimulation vs control</td>
<td>Subjective outcome: improvement in overactive bladder symptoms</td>
<td>Transvaginal electrical stimulation was superior to control for improvement in outcomes</td>
<td>8 Weeks to</td>
<td>1A Study</td>
<td>Uncomfortable stimulator and back pain</td>
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<td></td>
<td>Objective outcome: 24-hour voiding diary frequency</td>
<td></td>
<td>3 Months</td>
<td>1C Study</td>
<td></td>
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<td></td>
<td>Urodynamic outcome: detrusor overactivity</td>
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subjective outcomes (improvement in OAB symptoms) at 8 weeks, with no increase in adverse events.

Biofeedback with pelvic floor muscle exercises was superior to pelvic floor muscle exercises alone, based on 1 non-randomized, prospective comparative trial (1C) for improvement in subjective (daily pad use) and objective outcomes (Visual Analog Scale scores) at 6 weeks, with no adverse event data reported.

Electrical stimulation and biofeedback-assisted pelvic floor muscle exercises were superior to pelvic floor muscle exercises alone in a single RCT (1B) for improved quality of life (Kings Health Questionnaire at 12 weeks), but no effect in the Kings Health Questionnaire was seen at 3 months in a separate RCT (1B).

On the basis of 1 RCT (1C), there was no evidence that vaginal weighted cones were superior to pelvic floor muscle exercises for subjective or objective outcomes (wearing less protection, improved OAB symptoms, or improved pelvic muscle strength) at 12 weeks, with no adverse event data reported.

Behavioral therapy

*Behavioral therapy versus control.* Bladder training with pelvic floor muscle exercises were similar to control for all outcomes in a single RCT (1C) but superior to control in 1 RCT (1B) for improvement in voiding diary outcomes, with no increase in adverse events.

On the basis of 1 RCT (1B), education on caffeine reduction was superior to control for improvement in bladder diary outcomes (daily voids and daily urgency episodes), with no adverse events noted.

Weight loss with diet and exercise was superior to control in 1 RCT (1A) for the improvement of voiding diary outcomes (daily urge incontinence episodes, stress incontinence episodes, and smaller volume accidents), with no adverse events noted.

On the basis of 1 RCT (1B), a 25-50% reduction in fluid intake was associated with improved daily urgency and nocturia episodes, with no increase in adverse events.
Behavioral therapy versus antimuscarinic. Bladder training plus terodiline was similar to control in 1 RCT (1B) for the improvement of bladder diary outcomes (24-hour incontinence episodes) at 6 weeks, with an increased rate of dry mouth noted when terodiline was used.

Behavioral therapy versus other intervention. One RCT (1B) demonstrated that outpatient bladder training and physiotherapy were superior to inpatient bladder training alone at 3 months to improve objective outcomes (Visual Analog Scale scores), with no increase in adverse events.

Pelvic floor muscle exercises (instructed to perform without physiotherapist guidance) plus bladder training and posterior tibial nerve stimulation was superior to pelvic floor muscle exercises and bladder training alone for improvement in subjective outcomes (nocturia symptoms), quality of life (International Consultation on Incontinence Questionnaire short form), and bladder diary symptoms (stress urinary incontinence episodes and daily urgency urinary incontinence episodes), based on 1 RCT (1B) at 12 weeks’ follow-up, with no increase in adverse events.

Immediate intervention weight loss was superior to delayed intervention weight loss in 1 RCT (1A) for improvement in voiding diary outcomes (daily stress incontinence and urge incontinence episodes) and quality of life (Short Form-36 health survey), with no adverse events noted.

Botulinum toxin A

Botulinum toxin versus control. Comparing onabotulinum toxin A formulations (Botox) and abobotulinum toxin A (Dysport) with placebo in a population of OAB patients, botulinum toxin A is more effective than placebo in subjective outcomes and urodynamic testing parameters in 4 RCTs. Botulinum toxin A is superior to placebo in the specific subjective outcomes of urgency as supported by a total of 7 RCTs and the particular symptom of frequency as supported by 9 RCTs, with quality-of-life outcomes supported by 9 RCTs as well. Botulinum toxin A preparations have had the following adverse events reported: increased incidence of retention in 10 RCTs (10A), elevated post-void residual >150 mL in 9 RCTs (9A), need for self-intermittent catheterization in 10 RCTs (10A), and urinary tract infection in 10 RCTs (10A) during the interval of therapy.

In several RCTs, 100 units of onabotulinum toxin A was more effective than 50 units of onabotulinum toxin A for improvement in subjective outcome (UII in 5 RCTs, urgency in 3 RCTs, frequency in 3 RCTs, and nocturia in 1 RCT). However, 200 or more units of onabotulinum toxin A was associated with the following adverse events: retention in 3 RCTs (3A), elevated post-void residual in 3 RCTs (3A), and need for clean intermittent catheterization in 3 RCTs (3A).

Onabotulinum toxin versus antimuscarinic. Onabotulinumtoxin A was similar in efficacy to antimuscarinics over 6 months when considering daily UUI episodes on a voiding diary and quality of life via the OAB questionnaire short form in 1 RCT (1A). Onabotulinumtoxin A was superior to antimuscarinics when evaluating subjective cure over that same time period (1A). Antimuscarinics were associated with a greater risk of dry mouth, whereas onabotulinumtoxin A was associated with greater risk of urinary retention, urinary tract infections, and need for clean intermittent catheterization.

Onabotulinum toxin versus other intervention. There was no evidence comparing botulinum toxin A with another nonantimuscarinic intervention found during screening for this systematic review.

Magnetic stimulation

Magnetic stimulation versus control. Functional magnetic stimulation was superior to control/sham at 2 months in 1 RCT (1C) for subjective outcomes, and a single randomized crossover trial (1B) at 10-24 weeks found functional magnetic stimulation superior for objective and voiding diary outcomes as well as quality of life: International Consultation on Incontinence Questionnaire-short form (1B), with no increase in adverse events.

Extracorporeal magnetic stimulation was superior to sham chair in 1 RCT (1A) for the urodynamic outcomes (increasing the volume at first contraction and increasing maximum detrusor pressure), and in a crossover RCT, the urodynamic parameter of maximum cystometric capacity was improved at 10 and 24 weeks with the use of extracorporeal magnetic stimulation (1B), with no increase in adverse events noted with the stimulation.
Magnetic stimulation versus anti-muscarinic. There was no evidence comparing magnetic stimulation with an anti-muscarinic agent found in this systematic review.

Magnetic stimulation versus other intervention. There was no difference in improvement in severity symptoms when functional magnetic stimulation was compared with functional electrical stimulation at 2 months in 1 non-randomized, prospective comparative trial (1C)\textsuperscript{,53} with no increase in adverse events noted.

Mirabegron

Mirabegron versus control. Mirabegron (25–50 mg) was superior to control in 1 RCT (1A)\textsuperscript{,54} for improved voiding diary outcomes (daily incontinence episodes) at 12 months, and mirabegron (50–100 mg) was superior to control in another RCT (1A)\textsuperscript{,55} for improvement in the same outcome at 12 weeks, with an increase in the adverse events of upper respiratory tract infection, dizziness, nausea, and back pain noted in the 12-month trial (1A)\textsuperscript{,55}.

Solabegron (125 mg) was superior to placebo for improvement in daily incontinence episodes at 4 weeks in a single RCT (1A)\textsuperscript{,56} with an increase in the following adverse events: headache, nasopharyngitis, dry mouth, constipation, nausea, increase in urinary tract infections, arthralgia, hypertension, abdominal pain, dizziness, extremity pain, depression, general pain, and musculoskeletal chest pain.

Mirabegron versus antimuscarinic. Mirabegron (100 mg) was similar to tolterodine extended-release (4 mg) at 12 weeks in an RCT (1A)\textsuperscript{,57} for subjective outcomes (nocturia) and bladder diary outcomes (daily incontinence episodes, number of daily voids, and urine volume per void). The following adverse events were reported and found to be similar between mirabegron and tolterodine in this RCT: hypertension, urinary tract infections, dry mouth, nasopharyngitis, headache, influenza, constipation, arthralgia, tachycardia, back pain, dizziness, diarrhea, and sinusitis.

Mirabegron versus other intervention. There was no evidence in the literature comparing mirabegron with any intervention other than tolterodine found in this systematic review.

Posterior tibial nerve stimulation

Posterior tibial nerve stimulation versus control. Posterior tibial nerve stimulation was superior to control for improvement in subjective outcomes (urgency), validated questionnaire outcomes (OAB questionnaire score), and improved quality of life (Short Form-36) at 13 weeks in 1 RCT (1A)\textsuperscript{,58} Posterior tibial nerve stimulation was also superior to control at 4 weeks in a separate RCT (1A)\textsuperscript{,59} for improvement in bladder diary outcomes (reduction in UUI episodes >50%), daily voids, daily incontinence episodes, improvement in volume per void), and improved quality of life via the Incontinence Quality of Life questionnaire. Posterior tibial nerve stimulation was associated with a higher incidence of ankle bruising, discomfort at the needle site, bleeding at the needle site, and tingling in the legs.

Posterior tibial nerve stimulation versus antimuscarinic. It was unclear if posterior tibial nerve stimulation or oxybutynin was superior to control in the single RCT that investigated this question (1B)\textsuperscript{,60}.

Posterior tibial nerve stimulation versus other intervention

In 1 RCT (1B)\textsuperscript{,33} posterior tibial nerve stimulation was superior to pelvic floor muscle exercises and behavioral therapy at 12 weeks for the improvement in bladder diary outcomes (daily voids), with no adverse events noted.

Sacral neuromodulation

Sacral neuromodulation versus control. Sacral neuromodulation was superior to control at 6 months in 1 RCT (1B)\textsuperscript{,61} for improvement in subjective outcomes (subjective cure, wearing less protection) and bladder diary outcomes (reduction in daily incontinence episodes). Sacral neuromodulation was superior to control at 6 months in another RCT (1B)\textsuperscript{,62} for improvement in the bladder diary outcomes (daily voids, urine volume per void), the subjective outcome of urgency intensity, and improved quality of life (Short Form-36). The following adverse events were noted in the 6-month RCT (1B)\textsuperscript{,61}: pain at the implantable pulse generator site, extremity pain, adverse change in bowel function, cardiac arrhythmia, vaginal pain, anal pain, and skin irritation at the implantation site.

Transvaginal electrical stimulation/sacral neuromodulation were similar to control at 3 weeks for the bladder diary outcome of daily voids, based on a single RCT (1C)\textsuperscript{,63}.

Sacral neuromodulation versus antimuscarinic. Although sacral neuromodulation was superior to anticholinergics at 6 months in a single RCT (1B)\textsuperscript{,64} for improvement in bladder diary outcomes (number of pads used in 24 hours, daily incontinence episodes, and leakage volume), urodynamic outcomes (first sensation and improvement in involuntary detrusor contraction volume) and quality of life, these benefits must be weighed against potential adverse events documented such as adverse change in bowel habits, electrically induced discomfort, pain at the implantable pulse generator site, and infection.

Transvaginal electrical stimulation

Transvaginal electrical stimulation versus control. Transvaginal electrical stimulation was superior to control at 8 weeks, based on 1 RCT (1A)\textsuperscript{,65} for adequate improvement in subjective (OAB symptoms), objective (24-hour voiding frequency), and urodynamic outcomes (detrusor overactivity). Transvaginal electrical stimulation was not clearly superior to control at 3 months in 1 single-arm prospective study (1C)\textsuperscript{,66} comparing long-term vaginal stimulation (patient report) with control (physician report). Adverse events of uncomfortable stimulator and back pain were noted in this single arm study (1C)\textsuperscript{,66}.

Bladder diary outcomes (voids per 24 hours) were reported on in 2 RCTs (1B, 1A)\textsuperscript{,67,68} comparing transvaginal electrical stimulation with placebo, and
transvaginal electrical stimulation was not superior at 1 month (1A) but was superior to placebo at 2 months in the second trial (1B), with no adverse events data reported in either trial. In the second trial (1B), transvaginal electrical stimulation was superior to control at 2 months for subjective (improvement in nocturia), bladder diary (daily urgency episodes), and urodynamic outcomes (maximum cystometric capacity).

Transvaginal electrical stimulation versus antimuscarinic. There was no evidence in the literature found during screening for this systematic review comparing transvaginal electrical stimulation with an antimuscarinic agent.

Transvaginal electrical stimulation versus other intervention. Functional electrical stimulation was similar to functional magnetic stimulation at 2 months in a prospective, nonrandomized study (1C) regarding subjective (improvement or cure of OAB symptoms), objective (pad weight test), and bladder diary outcomes (voids per 24 hours), with no increase in adverse events reported.

Comment
The Society of Gynecologic Surgeons systematic review group reviewed the data and produced clinical practice guidelines.

Main findings
1. Physical therapy
   We suggest the use of exercise along with heat- and steam-generating sheets, diaphragmatic deep abdominal and pelvic floor muscle retraining for subjective improvement in OAB symptoms (Grade 2A).
   We suggest if prescribing pelvic floor exercises for patients with OAB symptoms, using biofeedback or verbal feedback over written information alone (Grade 2A).

2. Behavioral therapy
   We suggest the following lifestyle modifications for improvement in subjective OAB symptoms: weight loss with diet and exercise, caffeine reduction, 25-50% reduction in fluid intake for eligible patients, and pelvic floor muscle exercises with verbal instruction and or biofeedback (Grade 2B).

3. Botulinum Toxin
   We recommend botulinum toxin A onabotulinum toxin A (Botox) and/or abobotulinum toxin A (Dysport) for improvement in urge incontinence episodes, urgency, frequency, health-related quality of life, nocturia, and urodynamic testing parameters, although benefits must be weighed against adverse events, including urinary retention, post-void residual volumes greater than 150 mL, need for clean intermittent self-catheterization, and urinary tract infections (Grade 1A).
   We recommend 100 units of onabotulinum toxin A over 50 units for improvement in urge incontinence, urgency, frequency, and nocturia (Grade 1A).
   We recommend using less than 200 units of onabotulinum toxin A when treating patients with OAB to reduce the incidence of urinary retention, elevated post-void residual volumes, and need for clean intermittent self-catheterization (Grade 1A).

4. Complementary and Alternative Medicine (Acupuncture)
   We suggest acupuncture for improved quality of life and improved urodynamic testing parameters, with benefits being weighed against side effects of arthralgia, lead migration, blurry vision, dry eyes, nasopharyngitis, itching, dizziness, nausea, headache, bruising at the needle site, and insomnia (Grade 2B).

5. Magnetic stimulation
   We suggest extracorporeal magnetic stimulation to improve urodynamic parameters such as volume at first contraction, maximum detrusor pressure, and maximum cystometric capacity, as well as improved quality of life (Grade 2B).

6. Mirabegron
   We suggest mirabegron in (25-100 mg daily doses) for improved daily incontinence episodes, but the benefits must be weighed against potential adverse events such as upper respiratory infections, dizziness, nausea, and back pain noted in patients followed (Grade 2A).
   We suggest solabegron (125 mg) for improvement in daily incontinence episodes at 4 weeks of use with benefits being weighed against potential adverse events such as headache, nasopharyngitis, dry mouth, constipation, nausea, increase in urinary tract infections, arthralgia, hypertension, abdominal pain, dizziness, extremity pain, depression, general pain, and musculoskeletal chest pain (Grade 2A).
   We suggest mirabegron (50-100 mg) use to improve nocturia, daily incontinence episodes, number of daily voids, and urine volume per void, with the benefits being weighed against potential adverse events of each medication (Grade 2A).

7. Posterior Tibial Nerve Stimulation
   We suggest the use of posterior tibial nerve stimulation up to 13 weeks over pelvic floor muscle exercises and behavioral therapy to improve urgency, urinary incontinence episodes, daily voids, volume per void, and overall quality of life (Grade 2A).

8. Sacral Neuromodulation
   We suggest sacral neuromodulation over anticholinergics for the subjective improvement of OAB and overall quality of life. These benefits must be weighed against potential adverse events such as pain at the implantable pulse generator site, extremity pain, adverse change in bowel function, cardiac arrhythmia, vaginal pain, anal pain, skin irritation, and infection at the implantation site (Grade 2B).

9. Transvaginal electrical stimulation
   We suggest transvaginal electrical stimulation for at least 8 weeks of use for subjective improvement in OAB symptoms and improved urodynamic parameters. These benefits must be weighed against potential adverse events such as uncomfortable stimulator and back pain (Grade 2B).
Strengths and limitations
The strengths of this systematic review are that it provides a comprehensive evaluation of the literature on the topic and evaluates the risk of bias in the literature. We also performed extraction from past related systematic reviews when possible, allowing a more complete assessment of the available evidence and adverse events possibly related to these therapies. Adverse event data were also obtained on all body systems on which the literature reported.

The limitation of this systematic review is largely due to the limitations of the evidence in the literature. There were very few studies comparing one intervention to another, and relatively few studies report on outcomes in the same manner consistently. Furthermore, the heterogeneity of study methods, particularly in behavioral and physiotherapy interventions, make meta-analysis of the literature difficult. Also, we were only able to collect adverse event data and outcome data on those reported by the studies, so this risks the non-detection of differences in outcomes or adverse events that may exist between treatments (type II error).

Therefore, it is difficult to draw conclusions in support of one treatment protocol over another for the nonantimuscarinic treatment of OAB.

Comparison with existing literature
Our study is consistent with other systematic reviews and confirms that there is a paucity of long-term data (greater than 12 months) regarding pelvic floor muscle exercises or behavioral modification.\(^{10,69}\) Despite the difficulty this poses, our study also confirms that even short-duration interventions, such as 1-3 months of guided or unguided pelvic floor muscle exercises, can significantly improve patient symptoms. Furthermore, our results further the conclusion of recent systematic reviews that more guided supervision of pelvic floor muscle exercises\(^{69,70}\) (such as individualized appointments or biofeedback) may have added benefit for patients. We concur with past reviews that indicate that evidence is insufficient to recommend one form of therapy over another.\(^{10,69,70}\)

This review systemically evaluated the evidence indicating that nonantimuscarinic treatments may be equivalent to or, in some cases, preferable to typical antimuscarinic medications. Randomized trials have demonstrated that both posterior tibial nerve stimulation and sacral neuromodulation are equivalent to antimuscarinic therapy and may be associated with less bothersome side effects.\(^{7,8}\) This being stated, it is known that the long-term side effects of sacral neuromodulation include a very high subsequent surgical intervention rate of 39.5%,\(^{71}\) whereas posterior tibial nerve stimulation appears to be efficacious with minimal side effects.\(^{72}\) Therefore, patients desiring less invasive therapy may be best served with posterior tibial nerve stimulation. Our review also indicates that onabotulinum toxin A use, which is offset by the risks of urinary retention and low return to baseline after injection, has a higher cure rate and similar subjective improvement in quality of life for overactive bladder symptoms as antimuscarinic medication.\(^{9}\) Overall, patients probably will receive the most benefit from reversible treatments with minimal side effects that are proven to have good efficacy in short time frames. This may be best demonstrated by physiotherapy, (optimally with biofeedback) and posterior tibial nerve stimulation.

Conclusions and Implications
This systematic review determined that there are a variety of nonantimuscarinic treatments available for women with overactive bladder, and many of them have been determined by RCTs to be effective versus placebo or no treatment. These include the interventions of physical therapy, behavioral modification, botulinum toxin A, acupuncture, magnetic stimulation, mirabegron, posterior tibial nerve therapy, sacral nerve neuromodulation, and vaginal stimulation. Some of these therapies, such as pelvic floor muscle training exercises, mirabegron, and posterior tibial nerve stimulation, and onabotulinumtoxin A, have also been compared with an antimuscarinic agent and found to be equally effective in improving overactive bladder symptoms, with some therapies potentially associated with less risk. On the basis of the gaps in the literature and the prevalence of antimuscarinic drug use for overactive bladder (up to 2% in this population),\(^{73}\) it would appear that OAB patients would benefit from a greater number of high-quality trials comparing other nonantimuscarinic treatments with antimuscarinic drugs (ie, comparison of acupuncture or certain types of biofeedback with commonly used anticholinergic medications).

In general, some themes emerge from this systematic review. It appears that adding biofeedback or “hands-on” intervention to a behavioral therapy such as pelvic floor muscle training exercises is beneficial for the patient. It is evident that some effective interventions such as physical therapy with biofeedback and posterior tibial nerve stimulation are only associated with mild adverse events, which are unlikely to cause long-term morbidity. Other interventions such as botulinum toxin A or sacral neuromodulation may be associated with more significant adverse events such as urinary tract infections or urinary retention. Therefore, when considering therapies for the overactive bladder patient, risks versus benefits must be carefully weighed and therapy individualized after the needs and expectations of the patient are considered.

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Appendix A

Subjective Responses
Subj. 1: Urgency
Subj. 2: Satisfaction (categorical)
Subj. 3: Adequate improvement (categorical)
Subj. 4: Wear less protection
Subj. 5: Quality of life (good/bad)
Subj. 6: Patient perception of bladder condition
Subj. 7: Severity of incontinence symptoms
Subj. 8: General health and well-being (good/bad)
Subj. 9: Cure
Subj. 10: Improvement

Objective Findings
Obj. 1: Cure/improvement
Obj. 2: Number of pads/24 hours
Obj. 3: Pad weight test
Obj. 4: Post-void residual volume
Obj. 5: Digital pelvic floor muscle contraction strength (power)
Obj. 6: Pelvic floor strength (Oxford scale)
Obj. 7: Pelvic muscle strength (perineometry value)
Obj. 8: OAB questionnaire score
Obj. 9: Objective (visual analog scale)
Obj. 10: Physical exam by digital score (pressure, displacement, duration)
Obj. 11: Grip strength
Obj. 12: Adductor muscle strength
Obj. 13: Walking speed (usual, minimum, maximum)
Obj. 14: Reduction in urgency and UUI >50%
Obj. 15: Reduction in urgency and UUI >75%
Obj. 16: Incontinence episodes per 24 hours
Obj. 17: Number of micturations per 24 hours
Obj. 18: Severity index
Obj. 19: Urgency severity score
Obj. 20: Urinary tract infection
Obj. 21: Costs

Voiding Diary
Diary 1: Voids/24 hours
Diary 2: Voiding frequency (interval)/24 hours
Diary 3: Incontinence episodes/24 hours
Diary 4: Nocturnal voids/24 hours (nocturia)
Diary 5: Urine volume/micturation (void)
Diary 6: Fluid intake/24 hours
Diary 7: Urgency episodes/24 hours
Diary 8: Urgency intensity
Diary 9: UUI episodes/24 hours
Diary 10: Leakage volume
Diary 11: Fewer accidents (categorical)
Diary 12: Accidents are smaller (categorical)
Diary 13: Eneuresis episodes/night (24 hours)
Diary 14: Urinary volume/24 hours
Diary 15: Stress urinary incontinence episodes
Diary 16: Urinary incontinence increase
Diary 17: Urgency increase
Diary 18: Stress incontinence increase
Diary 19: Urinary retention
Diary 20: Micturation difficulty

Validated Questionnaires
Q.1: Incontinence quality of life
Q.2: Incontinence impact questionnaire-7
Q.3: Kings health questionnaire
Q.4: Short Form-36 health survey
Q.5: Treatment benefit scale
Q.6: Urogenital distress inventory-6
Q.7: International consultation on incontinence questionnaire (short form)
Q.8: Incontinence impact questionnaire (long form)
Q.9: Urinary distress inventory (long form)

Urodynamic Testing
UDT. 1: First desire to void
UDT. 2: Maximum cystometric capacity
UDT. 3: Involuntary detrusor contraction volume
UDT. 4: Involuntary detrusor contraction maximal pressure
UDT. 5: Number of uninhibited contractions
UDT. 6: Pressure detrusor (maximum)
UDT. 7: Q maximum
UDT. 8: Volume at 1st contraction (mL)
UDT. 9: Volume at strong desire to void (mL)
UDT. 10: Detrusor pressure
UDT. 11: Voiding efficiency (%)
UDT. 12: Volume at urgent desire to void/urgency
UDT. 13: Detrusor overactivity
UDT. 14: Vesical pressure
UDT. 15: First sensation
UDT. 16: Detrusor pressure at first sensation
UDT. 17: Detrusor pressure at first desire
UDT. 18: Detrusor pressure at maximum fill
UDT. 19: Detrusor activity index

Catheterizations
Cath. 1: Frequency of self-catheterizations
Cath. 2: Patients initiating clean intermittent self-catheterization
Cath. 3: Catheterized volume per catheterization (urinary retention group)
Cath. 4: Post-void residual >150 mL

Adverse Events
Head
1: Headache
2: Hydrocephalus

Eyes
1: Blurry vision
2: Dry eyes
Nose
1: Nasopharyngitis
2: Sinusitis

Mouth
1: Dry mouth

Heart
1: Cardiac arrhythmia
2: Tachycardia
3: QT interval prolongation
4: Atrial fibrillation
5: ECG changes

Lungs
1: Metastatic lung adenocarcinoma
2: Malignant lung neoplasm
3: Upper respiratory tract infection
4: Bronchopneumonia

Chest
1: Muscular-skeletal chest pain

Breast
1: Breast cancer
2: Breast tenderness

Back
1: Back pain
2: Uncomfortable stimulator

Gastrointestinal
1: Nausea
2: Diarrhea
3: Constipation
4: Intestinal symptoms
5: Adverse change in bowel function

Liver
1: Hepatotoxicity

Kidneys
1: Pyelonephritis
2: Bilateral hydronephrosis

Spine
1: Lead migration
2: Electrically induced discomfort

Abdomen
1: Seroma
2: Gastroabdominal pain

Pelvis
1: Pelvic pain

Vagina
1: Herpes flare
2: Vaginal pain
3: Vaginal cramps
4: Vaginal spotting

Bladder
1: Number of urinary tract infections
2: Number of urinary retention episodes
3: Increased urinary incontinence
4: Increase in urgency
5: Increase in stress incontinence
6: Clean intermittent self-catheterization
7: Difficulty on micturition
8: Urinary retention
9: Urinary tract infection
10: Dysuria
11: Bacteruria
12: Hematuria
13: Leukocyturia
14: Bladder clots
15: Large post-void residual >150 mL

Anus
1: Anal pain

Legs
1: Pain in extremities
2: Tingling in legs
3: Numbness

Ankle
1: Ankle pain

Neurology
1: Syncope
2: Seizures
3: Dizziness
4: Suspected neuropraxia

Skin
1: Hypersensitivity
2: Itching
3: Bruising at needle site
4: Rash
5: Pain at implantable pulse generator site
6: Skin irritation at implantation site

Systemic
1: Hypertension
2: Vital sign changes
3: Anaphylaxis

Mental state
1: Drowsiness
2: Somnolence
3: Depression
4: Confusion
5: Psychological distress
6: Insomnia
7: Sleep disturbance

Joints
1: Arthralgia

General
1: Pain
2: Incident and severity of treatment; emergent adverse events
3: Fatigue
4: Influenza
5: Perisurgical visual analog scale pain scale
6: Discontinuation
7: General symptoms and weakness
8: Sexual impairment
9: Social practical inconvenience
10: Expensive treatment
11: Failure of stimulator
12: Surgical revision
13: Lack of efficacy
14: Loss of efficacy
15: Battery depletion
16: Trouble with metal detectors
17: Reoperation
18: Unable to perform CISC
19: Inability to undergo MRI
20: Need for magnetic resonance imaging

Bladder
1: Urinary incontinence increase
2: Urgency increase