Adverse Events Associated with Nonsurgical Treatments for Urinary Incontinence in Women: a Systematic Review

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BACKGROUND: Urinary incontinence (UI) is a common malady in women. Numerous nonsurgical treatments are available, each associated with risk of adverse events (AEs).

METHODS: We systematically reviewed nonsurgical interventions for urgency, stress, or mixed UI in women, focusing on AEs. We searched MEDLINE®, Cochrane Central Trials Registry, Cochrane Database of Systematic Reviews, and Embase® through December 4, 2017. We included comparative studies and single-group studies with at least 50 women. Abstracts were screened independently in duplicate. One researcher extracted study characteristics and results with verification by another independent researcher. When at least four studies of a given intervention reported the same AE, we conducted random effects model meta-analyses of proportions. We also assessed the strength of evidence.

RESULTS: There is low strength of evidence that AEs are rare with behavioral therapies and neuromodulation, and that periurethral bulking agents may result in erosion and increase the risk of voiding dysfunction. High strength of evidence finds that anticholinergics and alpha agonists are associated with high rates of dry mouth and constitutional effects such as fatigue and gastrointestinal complaints. Onabotulinum toxin A (BTX) is also associated with increased risk of urinary tract infections (UTIs) and voiding dysfunction (moderate strength of evidence).

DISCUSSION: Behavioral therapies and neuromodulation have low risk of AEs. Anticholinergics and alpha agonists have high rates of dry mouth and constitutional effects. BTX is associated with UTIs and voiding dysfunction. Periurethral bulking agents are associated with erosion and voiding dysfunction. These AEs should be considered when selecting appropriate UI treatment options. AE reporting is inconsistent and AE rates across studies tended to vary widely. Trials should report AEs more consistently.

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Numerous nonsurgical interventions are available to improve the symptoms of urinary incontinence (UI) for women, including both nonpharmacologic and pharmacologic options. Most available nonsurgical options effectively achieve symptomatic cure (resolution of incontinence) or improvement.[1] Behavioral therapies are generally more effective than other treatments to achieve cure or improvement, but the relative effectiveness of other interventions is less clear.[1] While relief or improvement of UI symptoms may be the most important consideration for most women when selecting treatment,[2–5] many women also consider the balance between treatment benefits and the risks, severity, or types of adverse events (AEs) that may occur.[6] According to one survey, women with UI, in fact, put more emphasis on limiting the risk of side effects than on improving symptoms, in contrast with physicians who put more emphasis on increasing benefits.[2]

We conducted a broad systematic review of the clinical effects and harms of all nonsurgical treatments for typical stress, urgency, and mixed UI in nonpregnant women.[7] Here we summarize findings regarding AEs. We have separately summarized comparative effectiveness for cure and improvement.[1]

METHODS

The Brown Evidence-based Practice Center (EPC) conducted this review based on a systematic review of the scientific literature, using established methodologies.[8] The PROSPERO registration number is CRD42017069903. The literature search and screening methodology, overall eligibility criteria, strength of evidence, and interpretation of findings are

described in the full report.[7] In brief, the review was an update of a prior systematic review conducted in 2012.[9] We updated the review of adverse events through December 4, 2017. We included studies of adult women with stress, urgency, or mixed UI, excluding pregnant, hospitalized, or institutionalized women and those with UI attributable to urinary tract infection (UTI) or neurogenic bladder. We included pharmacological and nonpharmacological (but nonsurgical) interventions. We included randomized controlled trials with no minimum sample size and nonrandomized comparative studies with at least 50 women per intervention group. All studies had to have a minimum 4 weeks of follow-up.

DATA ANALYSIS

We calculated and summarized the percentage of people receiving each intervention who reported each AE as defined by the individual studies. We conducted restricted maximum likelihood meta-analyses of the arcsine of the square root proportions for AEs reported by at least four studies for a given intervention,[10] regardless of the degree of statistical heterogeneity. The degree of heterogeneity was taken into consideration when evaluating the strength of evidence for each conclusion.

STRENGTH OF EVIDENCE

We graded the strength of the total body of evidence as per the AHRQ Methods Guide on assessing the strength of evidence.[11] We assessed the strength of evidence for each outcome category (UI outcomes[1] and adverse events). For each strength of evidence assessment, we considered the number of studies, their study designs, the study limitations (i.e., risk of bias and overall methodological quality), the directness of the evidence to the Key Questions, the consistency of study results, the precision of any estimates of effect, the likelihood of reporting bias, other limitations, and the overall findings across studies. Based on these assessments, we assigned a strength of evidence rating as being either high, moderate, or low, or there being insufficient evidence to estimate an effect.

ROLE OF THE FUNDING SOURCE

This topic was nominated and funded by the Patient Centered Outcomes Research Institute (PCORI) for systematic review by an EPC in partnership with the Agency for Healthcare Research and Quality (AHRQ). AHRQ and PCORI program officers provided comments on draft versions of the protocol and full evidence report.[7] PCORI and AHRQ did not directly participate in the literature search; determination of study eligibility criteria; data analysis or interpretation; or preparation, review, or approval of the manuscript for publication.

RESULTS

The update searches returned 7840 new citations, of which we excluded 7117 during abstract screening (Fig. 1). Of the 723 abstracts accepted by initial screen and retrieved for full-text review, 613 were found to be irrelevant, primarily because they did not include the population of interest. Other reasons are listed in Figure 1. The 109 new studies were combined with the 134 studies from the original report that met eligibility criteria. Of these, 138 reported on AEs.[12–149] Across the 138 studies, analyzed sample sizes ranged between 6 and 4913, with a median of 123 (IQR 48 to 239). Sixty-five (47%) studies reported industry funding.

ADVERSE EVENTS

A wide range of AEs were reported, but studies were inconsistent in how and which AEs were reported. AE reporting was common among studies of anticholinergics, but sparser in studies of nonpharmacologic and other pharmacologic interventions. Excluding evaluations of vague AE outcomes (e.g., "adverse event," "serious adverse event"), only for four active intervention categories—five anticholinergics, the alpha agonist duloxetine, BTX, and periurethral bulking agents—did at least four studies report the same sets of outcomes; these are summarized in Table 1 (with more details in Supplement Tables 1 to 3). Notably, across studies, there were wide ranges of reported frequencies for most AEs, with correspondingly large statistical heterogeneity. In Table 1, less heterogeneous estimates ($I^2 < 75\%$) are highlighted in italicized text.

NONPHARMACOLOGIC INTERVENTIONS

Fifty-two studies reported on AEs in studies of nonpharmacological interventions (Supplement Table 1).[12–63] For no nonpharmacologic intervention did four of more studies report the same outcome. In general, the percentages of women with AEs were low. AE reporting was most common among studies of PFMT and TENS; 21 of 24 studies of PFMT and 7 of 11 studies of TENS reported no AEs. In three studies of TENS, between 10 and 18% of women reported a UTI.[15, 46, 50] No other specific outcome was reported by more than two studies for any intervention.

PHARMACOLOGIC INTERVENTIONS

There were 105 studies that reported on AEs in drugs (Supplement Table 2), 61 of which evaluated AEs in anticholinergics.[45–48, 64–120] In total, 71 studies reported on other drugs and placebo arms.[48–83, 114–118, 120–149] For most pharmacological interventions, "serious" AEs (as described by authors) were rare or did not occur, although few studies defined serious AEs. However, with periurethral bulking agents, 4.7% of 362 women in three studies had serious AEs,[137, 147,

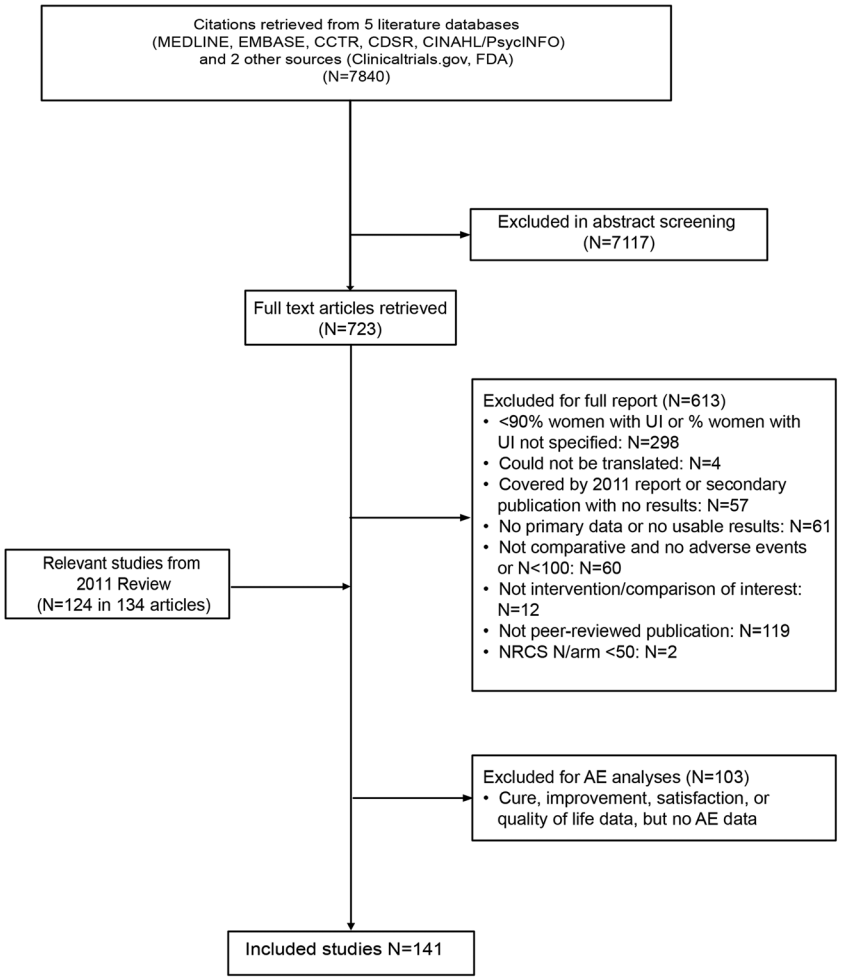

Figure 1 Literature flow. AE adverse events, NRCS nonrandomized comparative study, QoL quality of life, UI urinary incontinence, CCTR Cochrane Controlled Trials Register, CDSR Cochrane Database of Systematic Reviews, FDA Food and Drug Administration.

[149] including erosion and need for surgical excision of the bulking agents. The one study of a periurethral bulking agent currently available in the USA (macroplastique) reported 1.6% rate of erosion.[147] In seven studies of anticholinergics, overall 2.2% of 2469 women had serious AEs,[114–120] although the AEs were mostly undefined. In two studies, 0.6% of 1390 women taking the alpha agonist duloxetine had (undefined) serious AEs.[136, 138] By comparison, in 10 studies,[61–63, 115–118, 136–138] 1.0% of 2695 women taking placebo (or no treatment) had (mostly undefined) serious AEs.

The most commonly reported AE across interventions was dry mouth (Table 1). Approximately one-quarter or more of women using anticholinergic medications reported dry mouth; the summary estimate for oxybutynin was 44% (95% CI 31, 58) across 25 studies, but 24% (95% CI 15, 35) for tolterodine across 17 studies, with similar estimates for fesoterodine (5 studies), solifenacin (4 studies), and trospium (4 studies). In contrast, in 24 placebo arms, the summary estimate for placebo was 8% (95% CI 4, 12). Among 15 studies of the alpha agonist duloxetine, approximately 13% (95% CI 9, 16) complained of dry mouth. However, studies were highly heterogeneous, with within-study estimates ranging from 0 to 100% across studies (including placebo arms) and meta-analysis I^2 statistics all ≥ 92%.

Constipation was also commonly reported. For three anticholinergics—oxybutynin (19 studies), solifenacin (4 studies), and tolterodine (14 studies)—and duloxetine (14 studies), summary estimates of rates of constipation ranged from 8% (95% CI 4, 14) with tolterodine to 15% (95% CI 7, 26) for solifenacin, with lower rates among women given placebo (3%; 95% CI 2, 5; across 34 studies). Again, statistical heterogeneity was very wide, with within-study estimates ranging from 0 to 50% and I^2 statistics all ≥ 88%.

Other common AEs with anticholinergics, specifically oxybutynin, included summary estimates of voiding dysfunction/urinary retention in 16% (95% CI 8, 27; 6 studies) of women and visual AEs (mostly blurring) in 11% (95% CI 6, 18; 15 studies) of women, again with wide ranges of estimates across studies. Other common AEs with duloxetine included fatigue (summary estimate 10%; 95% CI 7, 13; 13 studies), nausea (19%; 95% CI 13, 26; 15 studies), and headache (11%, 95% CI 8, 14; 11 studies), also with wide ranges of estimates across studies.

Drug discontinuation rates were generally higher with duloxetine (20%; 95% CI 14, 26; 5 studies) and oxybutynin

Table 1 Specific Adverse Events Reported by at Least Four Studies

Adverse event	Summary percent (95% CI) I^2 value {Median [full range]} No. of studies (total *N*) Fesoterodine	Oxybutynin	Solifenacin	Tolterodine	Trospium	Duloxetine	Onabotulinum toxin A	Periurethral bulking	Placebo†
CNS: dizziness		5.9 (2.7, 10.1) I^2 93% {3.3 [0, 42.6]} 14 (2642)		*2.0 (1.4, 2.8)* *$I^2$55%* *{1.8 [1.1, 16.7]}* *12 (3694)*		8.7 (6.5, 11.3) I^2 91% {10.6 [2.2, 18.3]} 14 (9217)			*2.2 (1.7, 2.7)* *$I^2$32%* *{2.4 [0, 9.8]}* *25 (6724)*
Discontinue due to adverse event		9.9 (4.1, 17.6) I^2 87% {6.7 [3.2, 31.6]} 6 (743)		*4.6 (3.4, 6.0) $I^2$1%* *{4.6 [2.5, 8.0]}* *5 (977)*		19.5 (13.6, 26.2) I^2 85% {16.2 [14.7, 32.7]} 5 (1929)			*3.3 (2.5, 4.3)* *$I^2$43%* *{3.6 [0, 6.6]}* *10 (3393)*
Dry mouth	24.3 (15.5, 34.4) I^2 97% {22.8 [6.0, 54.5]} 5 (2667)	44.1 (30.5, 58.1) I^2 99% {39.5 [2, 100]} 25 (4147)	28.4 (14.3, 45.1) I^2 93% {31.1 (9.7, 45.7)} 4 (654)	24.0 (14.7, 34.8) I^2 98% {20.1 [2.0, 74.5]} 17 (2868)	23.2 (13.0, 35.3) I^2 92% {28.4 [11.4, 33,3]} 4 (1080)	12.6 (9.4, 16.1) I^2 94% {12.9 [1.5, 21.8]} 15 (9370)			7.5 (4.1, 11.9) I^2 97% {4.2 [0, 86.2]} 34 (7515)
Fatigue: asthenia						2.5 (0.8, 5.2) I^2 88% {3.5 [0.7, 5.8]} 4 (2500)			*0.3 (0, 0.7)* *$I^2$42%* *{0.2 [0, 1.6]}* *4 (2493)*
Fatigue or drowsiness		*4.3 (1.0, 9.7)* *$I^2$55%* *{2.8 [0, 12.5]}* *4 (187)*		*2.8 (1.9, 3.8) $I^2$0%* *{3.3 [2.2, 3.8]}* *4 (1128)*		10.0 (7.2, 13.1) I^2 94% {10.1, [1.6, 20.1]} 13 (9130)			2.5 (1.7, 3.5) I^2 74% {2.7 [0, 11.1]} 20 (5690)
Fatigue: somnolence		8.9 (2.4, 18.8) I^2 97% {2.5 [0, 44.7]} 8 (1394)		1.8 (0.6, 3.5) I^2 84% {2.1 [0, 16.7]} 8 (2428)		4.3 (2.6, 6.5) I^2 84% {8.6 [2.0, 12.7]} 12 (4186)			*0.8 (0.5, 1.2)* *$I^2$51%* *{0.9 [0, 4.2]}* *19 (5736)*
GI: abdominal pain		*2.5 (1.3, 4.1)* *$I^2$35%* *{2.0 [1.1, 4.9]}* *5 (790)*		*3.5 (2.4, 4.8)* *$I^2$64%* *{3.7 [1.0, 6.2]}* *6 (2543)*					*1.3 (0.7, 2.1)* *$I^2$37%* *{1.7 [0, 3.3]}* *82 (112)*
GI: appetite decreased						*3.0 (2.0, 4.3)* *$I^2$35%* *{3.9 [2.0, 6.7]}* *5 (1695)*			*0.3 (0.1, 0.6)* *$I^2$0%* *{0.2 [0, 1.6]}* *5 (1684)*
GI: constipation		12.6 (7.3, 19.2) I^2 96% {7.8 [0.8, 50]} 19 (2981)	15.2 (6.9, 26.0) I^2 88% {15.0 [6.9, 28.3]} 4 (654)	8.0 (3.7, 13.7) I^2 97% {5.8 [1.0, 40.9]} 14 (4642)		9.6 (7.2, 12.4) I^2 92% {11 [1.3, 16.7]} 14 (9315)			3.4 (1.9, 5.2) I^2 94% {2.3 [0, 44.8]} 34 (8131)
GI: diarrhea				*2.7 (1.8, 3.8)* *$I^2$48%* *{3.1 [1.3, 11.8]}* *8 (2493)*		3.2 (1.1, 6.3) I^2 95% {5.1 [0.7, 16.7]} 8 (6880)			*2.5 (2.0, 3.0)* *$I^2$0%* *{2.7 [0, 8.3]}* *14 (3785)*
GI: dyspepsia				*2.7 (1.7, 3.8)* *$I^2$62%* *{3.0 [0.8, 6.1]}* *6 (2538)*					*1.2 (0.8, 1.7)* *$I^2$0%* *{1.4 [0.7, 4.2]}* *7 (19,850)*
GI: nausea		7.1 (4.3, 10.7) I^2 86% {6.3 [0, 26.3]} 13 (2252)		*1.6 (1.2, 2.1)* *$I^2$58%* *{1.7 [0, 8.8]}* *9 (2954)*		19.4 (13.3, 26.4) I^2 98% {23.2 [7.6, 45.5]} 15 (9370)			2.9 (2.1, 4.0) I^2 81% {2.3 [0, 15.0]} 30 (7569)

(continued on next page)

Table 1. (continued)

Adverse event	Summary percent (95% CI) I^2 value {Median [full range]} No. of studies (total *N*) Fesoterodine	Oxybutynin	Solifenacin	Tolterodine	Trospium	Duloxetine	Onabotulinum toxin A	Periurethral bulking	Placebo†
GI: vomiting						4.9 (3.0, 7.3) I^2 92% {5.5 [1.2, 12.7]} 8 (8155)			*1.7 (1.3, 2.2)* *$I^2$0%* *{2.0 [0, 3.5]}* *10 (3376)*
Headache		*4.8 (2.8, 7.5)* *$I^2$70%* *{4.0 [0, 32.3]}* *9 (1275)*		*4.7 (3.6, 5.9)* *$I^2$64%* *{4.8 [1.0, 16.7]}* *14 (4187)*		10.9 (8.4, 13.6) I^2 77% {8.3 [1.6, 27.3]} 11 (8775)			*4.5 (3.6, 5.3)* *$I^2$62%* *{4.6 [0, 10.0]}* *26 (7401)*
Infection, urinary tract				2.8 (1.5, 4.7) I^2 83% {3.2 [0.4, 5.9]} 6 (2629)			35.4 (28.6, 42.5) I^2 80% {36.9 [17.0, 54.5]} 6 (1447)	7.5 (3.5, 12.8) I^2 91% {7.4 [1.3, 23.8]} 5 (1365)*	6.4 (2.7, 11.6) I^2 95% {4.3 [0, 40]} 12 (2723)
Sleep disorder: insomnia				*1.5 (0.9, 2.1) $I^2$0%* *{1.8 [0.8, 3.3]}* *6 (1718)*		8.9 (5.9, 12.4) I^2 95% {12.6 [0.8, 14.7]} 13 (9179)			*2.1 (1.5, 2.8)* *$I^2$52%* *{2.2 [0, 5.7]}* *15 (5358)*
Sweating, excessive						4.1 (2.3, 6.4) I^2 92% {5.3 [1.2, 8.3]} 7 (4891)			*0.8 (0.5, 1.2)* *$I^2$0%* *{0.6 [0, 0.9]}* *6 (2988)*
Urinary: voiding dysfunction		16.2 (7.6, 27.3) I^2 91% {22.6 [3.3, 34.2]} 6 (656)						6.9 (0.6, 19.5) I^2 98% {4.0 [0, 28.2]} 5 (1263)	*1.5 (0.3, 3.4)* *$I^2$11%* *{0 [0, 3.2]}* *5 (271)*
Visual adverse effects		10.9 (5.8, 17.5) I^2 92% {13.3 [0, 50]} 15 (1477)		2.6 (0.5, 6.2) I^2 91% {1.2 [0.6, 13.3]} 6 (1517)					4.4 (0.6, 11.6) I^2 96% {0.5 [0, 58.6]} 11 (1503)

Nonspecific adverse events (e.g., "nonserious") omitted. Adverse event rates with placebo/sham treatment are reported only for those adverse events reported by at least four studies of an active treatment. Nonspecific adverse events, and those reported by three or fewer studies, and those reported for other placebo/sham studies are summarized in Supplemental Tables 1 and 2

GI gastrointestinal

**All periurethral bulking agents combined from eight study arms: three collagen gels, two polyacrylamides (Bulkamid), one ethylene vinyl alcohol, one hyaluronic acid/dextranomer (Zuidex), one macroplastique*

†*All periurethral bulking agents combined from six study arms: two collagen gels, two polyacrylamides (Bulkamid), one hyaluronic acid/dextranomer (Zuidex), one macroplastique*

(10%; 95% CI 4, 18; 6 studies) than for tolterodine (4.6%; 95% CI 3.4, 6.0; 5 studies) or placebo (3.3%; 95% CI 2.5, 4.3; 10 studies).

Only six studies reported on AEs with bladder BTX.[50, 114, 139–142] All six reported on UTIs, with a wide range across studies (17 to 55%) and a summary estimate of 35% (95% CI 29, 43). UTIs were lower among those receiving periurethral bulking (7.5%; 95% CI 3.5, 13; 5 studies) or placebo (6.4%; 95% CI 2.7, 12; 12 studies).

The most commonly reported AE for the periurethral bulking agents was UTI in five studies (7.5%; 95% CI 3.5, 12.8)[137, 143–146] and urinary retention/voiding dysfunction in eight studies (6.9%; 95% CI 0.6, 19.5),[137, 143–149] both sets of outcomes had wide ranges across studies. However, only one of these studies, with 122 women,[137] evaluated a periurethral bulking agent currently available in the USA (macroplastique). This study found high rates of UTI (24%), headache (18%), and urinary retention/dysuria (16%). Serious AEs (erosion) were low (1.6%), as were pain (5%) and yeast infection (2.5%). All other single and combination medications were evaluated in only one or two studies each.

DISCUSSION

Although a large number of studies have evaluated AEs of interventions for urgency, stress, and mixed UI in women, the evidence regarding these outcomes is generally sparse or poor because of important limitations to the corpus of studies. Studies tend to be very inconsistent in how, and which, AEs are reported. In relatively few instances did at least four studies that compared similar interventions report common AE outcomes. Furthermore, there is extensive large statistical heterogeneity in estimates of AEs, suggesting intrinsic differences across studies either how AEs were defined, how AE data were collected, and possibly intrinsic differences across study participants. Thus, there are few definitive conclusions that can be made about the rates of AEs with the various interventions.

Low strength of evidence suggests that (first-line) behavioral therapy rarely results in AEs. AEs are more common with (second-line) pharmacologic interventions. There is high strength of evidence that anticholinergics and alpha agonists commonly cause symptomatic dry mouth, and moderate strength of evidence that alpha agonists result in a range of constitutional symptoms such as nausea, insomnia, constipation, fatigue, dizziness, and headache. For third-line interventions, there is low strength of evidence that AEs were rare with TENS and that periurethral bulking agents result in serious AEs, including erosion and need for surgical excision, in a small percentage of patients. Moderate strength of evidence suggests that the most commonly reported AEs with BTX were UTI and urinary retention (voiding dysfunction). Low strength of evidence also suggested high rates of UTI and urinary retention with periurethral bulking agents. Precise estimates of most AE rates are not available due to the wide range in event rates across studies.

The choice of which treatment option is "best" for a particular woman with UI will vary depending on her symptoms, the severity of those symptoms, her history of prior treatments, treatment goals, preferences, and values regarding the types of treatments she is willing to undergo, and also the AE risks she is willing to assume. For example, some women may prefer a "simple" daily pill that can be stopped at any time, accepting the risk of dryness and constitutional complaints. Other women may prefer TENS, which has lower risk of symptoms but requires ongoing clinic visits. Yet other women may prefer BTX, which can be given infrequently but risks urinary dysfunction. Of note, among studies that have evaluated women's thoughts about what defines successful treatment, women tended to balance the potential benefits of treatment with their risks and the severity or types of adverse events that may occur. When considering medications, women thought it was important to reduce symptoms without side effects.[6] A survey of patients and clinicians found that the patients put more emphasis on limiting the risk of side effects than on improving symptoms, in contrast with physicians who put more emphasis on increasing benefits.[2]

Nevertheless, there is strong to moderate evidence that behavioral therapies, including bladder training, biofeedback, pelvic floor muscle training, and others, are most effective in achieving cure or improvement,[1] with low strength of evidence of rare AEs. Supplement Table 4 summarizes findings from this and the article regarding clinical outcomes and AEs. This information can form the basis of a guide for clinicians and their patients when considering different treatment options. Overall, the results of our review are consistent with a range of UI guidelines from six international medical organizations,[150] supporting the use of conservative treatments including behavioral therapy and physical therapy, electroacupuncture, anticholinergic medications, beta-agonists, BTX, and sacroneuromodulation.

LIMITATIONS ACROSS THE EVIDENCE BASE

The major limitation identified by this review is the relative dearth of evidence based on the non-standardized reporting and complexity of AE information reported across studies. Studies neither consistently reported AEs nor used standard terminology, limiting our ability to attain complete and unbiased estimates of AE frequency. In particular, AE rates were generally inconsistent, resulting in wide ranges of estimates and very large statistical heterogeneity across studies. The most likely reason for the heterogeneity are differing definitions and thresholds used across studies and different modes of collecting AE data (i.e., actively asking about specific AEs versus passively asking about "any" AE or only including what was reported by patients to their clinicians). Reporting on these factors was minimal.

LIMITATIONS OF THE ANALYTIC APPROACH

Despite large statistical and thus likely clinical heterogeneity across studies, we chose to conduct and report the meta-analyzed estimates to better allow indirect comparisons across interventions. Given the large heterogeneity of many AE rates, with I^2 commonly > 90%, the provided median and range of estimates across studies may be considered to be more reliable. We did not contact authors for additional data or definitions of their terminology.

RECOMMENDATIONS FOR FUTURE RESEARCH

There is a need to standardize AE reporting. If all studies had consistently and similarly reported these outcomes, our summary findings would be much more robust. Implementation and consistent use of standardized AE reporting would be immensely helpful and would improve reporting and comparisons for future systematic reviews. At a minimum, all trialists should pre-specify and report expected adverse events among outcomes to be evaluated and should incorporate methods to collect data on unexpected adverse events. All adverse events should be reported numerically (with numerators and denominators) for each intervention arm, including zero events for any expected adverse event.[151] Trialists are strongly encouraged not only to register their protocols, but also to report complete results data, including adverse events, at registries such as ClinicalTrials.gov.[152]

CONCLUSIONS

Overall information regarding possible AEs are limited due to inconsistent reporting, and the complexity of comparing the variable underlying disease severity and disparate outcomes reported. First-line behavioral interventions were found to have low risk of AEs. Second-line pharmacological interventions are associated with non-serious but bothersome AEs, such as dry mouth, nausea, and fatigue. Third-line interventions are associated with increased risk of UTIs and voiding dysfunction. As noted in the companion article,[1] most examined active intervention categories appear to be better than sham or no treatment to achieve cure or improvement. Large gaps remain in the literature regarding the comparison of individual interventions, and future studies should report subgroup analyses based on UI type and severity and prior treatment history. For clinicians, patients, and payers to make informed decisions, specifically for patient subgroups with sparse evidence, new evidence from studies comparing interventions with standardized outcomes is needed.

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Compliance with Ethical Standards:

Conflict of Interest: *The authors declare that they do not have a conflict of interest.*

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