Annals of Internal Medicine | Review

Benefits and Harms of Pharmacologic Treatment for Urinary Incontinence in Women

A Systematic Review

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Background: Urinary incontinence (UI) in women adversely affects quality of life.

Purpose: To conduct a systematic literature review of drugs for urgency UI in women.

Data Sources: MEDLINE, the Cochrane Central Register of Controlled Trials, SCIRUS, and Google Scholar were searched for articles published from 1966 to November 2011.

Study Selection: Randomized, controlled trials (RCTs) reported in English.

Data Extraction: Rates of outcomes and risk of bias were extracted by using a standardized form to pool absolute risk differences and calculate the number of attributable events per 1000 patients treated, with 95% CIs.

Data Synthesis: 94 RCTs were eligible. Pooled analyses showed that among drugs for urgency UI, per 1000 treated women, continence was restored in 130 with fesoterodine (CI, 58 to 202), 85 with tolterodine (CI, 40 to 129), 114 with oxybutynin (CI, 64 to 163), 107 with solifenacin (CI, 58 to 156), and 114 with trospium (CI, 83 to 144). Rates of treatment discontinuation due to adverse effects were 31 per 1000 treated with fesoterodine (CI, 10 to 56), 63 with oxybutynin (CI, 12 to 127), 18 with trospium (CI, 4 to 33), and 13 with solifenacin (CI, 1 to 26). The studies' inconsistent definitions of reduction in UI and quality of life hampered synthesis of evidence.

Limitation: Evidence for quality-of-life improvements and comparative effectiveness with drugs was limited, and evidence for the effects of race, baseline severity of UI, and comorbid conditions on treatment success was insufficient.

Conclusion: Overall, drugs for urgency UI showed similar small benefit. Therapeutic choices should consider the harms profile. Evidence for long-term adherence and safety of treatments is lacking.

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Urinary incontinence (UI) affects many women in the United States and other countries (1). The condition adversely affects physical, psychological, and social well-being and can impose significant lifestyle restrictions (2, 3). Urinary incontinence in women is a multifactorial syndrome related to an impaired balance between sphincter activity and bladder function (4). Although clinicians seek to distinguish between the 2 types of UI (sphincter failure attributed to intra-abdominal pressure [stress UI] and involuntary loss of urine associated with urgency due to detrusor overactivity [urgency UI]) (**Supplement 1**, available at www.annals.org) (5), these distinctions are not pure or reliable (6). For older women, mixed (stress and urgency) incontinence is the most common type (1). Our review synthesizes evidence on benefits and harms with drugs for urgency UI in community-dwelling women. Treatments of pelvic organ prolapse or recurrent urinary tract infections are beyond our scope (5).

Standard treatment for women with urgency UI includes lifestyle changes and pelvic floor muscle training combined with bladder training. Several drugs have also been approved for adults who have overactive bladder with or without urgency UI (**Supplement 2**, available at www.annals.org) (7–10). No drugs have been approved for stress or mixed UI. Existing clinical, medical, and statistical reviews focus on statistically significant changes in UI frequency (4, 11–15). However, continence is the main goal of UI treatment and the outcome most closely associated with quality of life (16–18). Reviews have not emphasized continence or women's perceptions of treatment success and satisfaction (1, 19). Our review focuses on continence and quality of life as primary outcomes (20).

This study is derived from work done for an evidence report commissioned by the U.S. Agency for Healthcare Research and Quality (AHRQ). The topic of comparative effectiveness of nonsurgical treatments for female UI was nominated by the American College of Physicians to inform the development of its clinical practice guidelines.

Methods

We developed the protocol for the review and posted it online, following guidelines for systematic reviews (21, 22).

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Web-Only
Appendix
Appendix Table
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Supplements
CME quiz (preview on page I-23)
Conversion of graphics into slides

We developed an analytic framework (**Appendix Figure 1**, available at www.annals.org) that follows the clinical path of diagnosis of pure or predominant UI type, available treatments, and intermediate and patient-centered outcomes.

Our objectives were to 1) analyze the efficacy, safety, and comparative effectiveness of drugs for clinically important patient-centered outcomes, including continence and quality of life; 2) analyze long-term adherence to drug treatments; and 3) analyze which characteristics of women, including demographic characteristics, comorbid conditions, and type and severity of UI, can modify treatment effects.

Data Sources and Searches

We sought studies from MEDLINE, the Cochrane Library, SCIRUS, and Google Scholar. We also reviewed medical and statistical reviews from the U.S. Food and Drug Administration (FDA) and clinical trial registries. We searched for studies reported in English from 1966 to November 2011. We used *urinary incontinence*, *overactive urinary bladder*, *treatment outcome*, and *quality of life* as Medical Subject Headings and *fesoterodine*, *oxybutynin*, *trospium*, *solifenacin*, and *tolterodine* as key words. Exact search strategies are described in the **Appendix** (available at www.annals.org).

Study Selection

We included drugs available in the United States for overactive bladder (**Supplement 2**). We used only RCTs and published meta-analyses of individual-patient data from RCTs to assess treatment benefits and used all RCTs and observational studies to assess harms and long-term adherence and adverse effects with the drugs (23). Here we report the best evidence from RCTs and published meta-analyses of individual-patient data from RCTs that addressed continence and quality-of-life outcomes. We included RCTs that enrolled men and women if they included more than 75% women. We excluded studies of children, adolescents, or men only; UI caused by neurologic disease; and drugs not available in the United States. We assessed harms, defined as the totality of all possible adverse consequences of an intervention (24, 25). We analyzed harms regardless of how authors perceived causality.

Data Extraction and Quality Assessment

For each trial, we abstracted information on inclusion and exclusion criteria, sponsorship, and disclosed conflict of interest and number of events in the randomly assigned groups. To explore heterogeneity, we abstracted study-level variables, including inclusion of minorities, women in whom previous therapy for UI had failed, and women with mixed UI; baseline daily UI; and the presence of pelvic organ prolapse or hysterectomy.

We evaluated risk of bias using predefined criteria, including randomized treatment allocation, adequacy of allocation concealment and randomization, planned intention-to-treat analyses, and masking of treatment status (22, 24). We did not downgrade methodological quality of poorly reported studies; however, we synthesized evidence from these studies separately (26). We examined sponsorship and conflict of interest but did not downgrade quality according to this information. Rather than ranking overall risk of bias or using a global score, we incorporated individual quality criteria into synthesis of evidence (26).

We incorporated quality into the evidence synthesis by conducting meta-regression and subgroup analyses (22). We estimated applicability of the population by evaluating the selection of women in observational studies and clinical trials (27). We estimated applicability of the treatment by the length of follow-up and concomitant treatments.

We judged the strength of evidence according to the domains of risk of bias, consistency, directness, and precision for each major outcome (28). We also included dose–response association and the strength of association. Head-to-head RCTs provided direct evidence of treatment effects (28). We evaluated the strength of association, defining a priori a large effect when the absolute risk difference was more than 50%, a value that corresponds to more than 500 cases of outcomes directly attributable to drugs per 1000 treated (22).

Data Synthesis and Analysis

As recommended by guidelines (1, 19), we focused on clinically important patient-centered outcomes, including continence, clinically important improvement in UI, quality of life, adverse effects, and discontinuation due to adverse effects. Voiding frequency (or frequency in UI episodes in women with overactive bladder) was reviewed in a previously published evidence report and thus is beyond our scope (11). On the basis of published evidence, we defined clinically important improvement in UI as 50% or greater reduction in UI frequency (29). We examined clinical importance of quality-of-life score according to the threshold of minimal clinically important differences in validated scales (30–33).

We focused on self-reported adverse effects irrespective of authors' conclusions about causality, and we analyzed all unusual harmful symptoms noticed by patients (34, 35). We classified harms according to bothersomeness and adherence to treatments, the highest number of attributable events, and expected anticholinergic effects with the drugs (36). We examined adverse effects observed by investigators and measured as clinically significant laboratory or instrumental test abnormalities (37–42). We analyzed self-reported adverse effects that were judged by investigators as serious or severe. We analyzed all harmful events posted on ClinicalTrials.gov, both expected and unexpected (43–45).

We conducted a meta-analysis when clinical populations, drugs, and outcomes were deemed sufficiently similar (46, 47). For comparative effectiveness evidence, we performed a meta-analysis of direct results from head-to-head comparisons. We examined consistency in results across studies with chi-square tests and I^2 statistics (48, 49). For our meta-analyses of individual RCTs, we chose

the random-effects model that used an inverse variance weighting method (47, 50) to incorporate inevitable differences across trials in patient populations, baseline rates of outcomes, dosage, and other factors (51). We calculated pooled relative risk and absolute risk difference for efficacy outcomes. We calculated pooled double-arcsine transformation for comparing 2 proportions for adverse effects and treatment discontinuation due to adverse effect (52). We evaluated robustness of pooled estimates for adverse effects and compared meta-analysis results by using double-arcsine transformation with random-effects absolute relative risk difference and odds ratios from random effects generalized nonlinear mixed effect models (50, 52–55).

For efficacy outcomes, we used pooled absolute risk difference to calculate the number of events attributable to the treatment per 1000 treated patients (56, 57). We calculated means and 95% CIs for treatment events per 1000 treated, multiplying pooled absolute risk difference by 1000 (47, 56). For adverse effects we converted arcsine differences back to risk differences for calculation of attributable adverse events per 1000 treated.

When evaluating efficacy, we defined 50% or greater reduction in daily UI episodes as a clear, clinically important response to treatment. We gauged a large clinical magnitude of a treatment response when 500 or more cases of the outcomes (efficacy or safety) were directly attributable to drugs per 1000 treated.

Using a standard predefined algorithm, we explored heterogeneity by study-level variables, including treatment dose and duration, inclusion of women with mixed or daily UI, and inclusion of women with surgical risk factors for UI or those in whom previous therapy for urgency UI had failed (51, 58, 59).

All calculations were performed by using Meta-Analyst (Tufts Medical Center, Boston, Massachusetts) (50) and Stata, version 10.1 (StataCorp, College Station, Texas) (50, 56).

Role of the Funding Source

The AHRQ participated in formulating the key questions and reviewed planned methods and data analyses, as well as interim and final evidence reports. It had no role in study selection, quality ratings, or interpretation or synthesis of the evidence.

Results

We identified 773 reports of therapeutic studies and present the results from 94 randomized trials of drug efficacy or comparative effectiveness (**Appendix Figure 2** and **Supplement 3**, available at www.annals.org). The same trials examined adverse effects and treatment discontinuation due to adverse effects.

Efficacy and Safety of Pharmacologic Treatments for Urgency UI

Pooled analyses of drug efficacy include the results from 72 RCTs (**Supplement 4**, available at www.annals.org). Most trials were conducted in western countries and included more than 80% women. Fewer than half of the trials included minorities, and those trials did not report outcomes among race subgroups. Most trials enrolled women with daily UI. Inclusion of mixed (urgency and stress) UI was reported in one third of RCTs, about 35% of RCTs enrolled no women with stress UI, and 36% of RCTs did not describe baseline distribution of UI types. In 42% of RCTs, enrolled women had previously been treated with drugs for UI; 13% of RCTs enrolled treatment-naive patients, and 45% did not report previous treatment status of the participants.

Most studies were double-blind, with adequate randomization (**Supplement 5**, available at www.annals.org). Previously published meta-analyses of individual-patient data reported double-blinding of treatment status in most included trials (**Supplement 6**, available at www.annals.org). We concluded that individual RCTs eligible for this review and previously published meta-analyses of individual-patient data had low risk of bias (**Appendix Figure 3**, available at www.annals.org).

Drugs were more effective than placebo in achieving continence and improving UI, with low magnitude of effect (**Table 1**). The absolute risk difference in continence was less than 20% for all drugs. Fewer than 200 cases of continence per 1000 treated were attributable to pharmacologic treatments. The effects on continence were consistent across the trials (**Appendix Table** and **Supplement 7**, available at www.annals.org). Individual risk of bias criteria and disclosure of conflict of interest were not associated with differences in the results (**Supplement 8**, available at www.annals.org). Few significant results from meta-regression could be due to chance (**Supplement 8**).

Drugs resulted in adverse effects more often than did placebo (**Appendix Table**). For adverse effects, we compared pooled estimates from different models described earlier and found similar results. We classified the harms according to bothersomeness and adherence to treatments, the most attributable events, and expected anticholinergic effects with the drugs. Dry mouth was the most common adverse effect (**Supplement 9**, available at www.annals.org). Increase in a risk for various adverse effects was consistent irrespective of inclusion of women with mixed UI, those who had surgical risk factors for UI, or those who had not improved with previous treatments (**Supplement 8**).

Evidence about efficacy and safety with different drug formulations, dose–response association, and improvement in quality of life was available for individual drugs (**Table 2** and **Supplement 10**, available at www.annals.org).

Darifenacin improved UI and several domains of quality of life more often than did placebo (**Table 1**) (60–62).

Table 1. **Patient-Centered Clinically Important Outcomes With Pharmacologic Interventions for Urgency Urinary Incontinence Compared With Placebo***

Outcome and Drug	RCTs (References)	Patients in Analyses, *n*	Rate in Active Treatment Group, %	Rate in Control Group, %	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Strength of Evidence
Continence							
Fesoterodine	2 (44, 67)	2465	61.0	48.5	1.3 (1.1 to 1.5)	0.13 (0.06 to 0.20)	Low
Oxybutynin	4 (75–79)	992	27	16	1.7 (1.3 to 2.1)	0.11 (0.06 to 0.16)	High
Solifenacin	5 (94–98)	6304	39.2	28.1	1.5 (1.4 to 1.6)	0.11 (0.06 to 0.16)	High
Tolterodine	4 (44, 67, 105, 141)	3404	53.2	43.7	1.2 (1.1 to 1.4)	0.09 (0.04 to 0.13)	High
Trospium	4 (119–122)	2677	28.3	16.6	1.7 (1.5 to 2.0)	0.11 (0.08 to 0.14)	High
Clinically important improvement in incontinence							
Darifenacin	3 (60–62)	1011	48.4	33	1.3 (1 to 1.5)	0.12 (0.06 to 0.17)	High
Fesoterodine	2 (44, 68, 69)	1896	42	32	1.3 (1.2 to 1.5)	0.10 (0.06 to 0.15)	High
Oxybutynin	9 (40, 41, 75, 77, 78, 80–86)	1244	53	32	1.5 (1.2 to 1.9)	0.17 (0.10 to 0.24)	Moderate
Solifenacin	2 (97, 99)	1507	60.2	42.0	1.5 (1.0 to 2.1)	0.18 (0.10 to 0.26)	Low
Tolterodine	7 (44, 67, 69, 70, 107–110)	6119	45	37	1.3 (1.1 to 1.4)	0.10 (0.04 to 0.15)	High
Trospium	2 (119, 123)	1176	32.4	25.4	1.1 (0.6 to 2.0)	0.08 (−0.10 to 0.25)	Low

RCT = randomized, controlled trial.
* Pooled with random-effects estimates from randomized, controlled clinical trials.

Previously published meta-analysis of individual-patient data from 3 RCTs also indicated that a greater than 90% reduction in UI episodes occurred more often with 7.5 mg and 15 mg of darifenacin than with placebo (63). Darifenacin at dosages of 7.5 mg/d (relative risk [RR], 1.47 [CI, 1.02 to 2.13]) and 15 mg (RR, 1.48 [CI, 1.04 to 2.09]) resulted in continent days (3 dry days/week) more often than did placebo (63).

Adverse effects were more common with darifenacin, 7.5 mg/d (61, 62) and 15 mg/d (61, 64), than with placebo in a dose–response fashion (**Table 1**). One RCT found no differences compared with placebo for darifenacin controlled-release (3.75, 7.5, or 15 mg once daily) or darifenacin immediate-release (5 mg 3 times daily) for short-term cognitive effects examined in elderly volunteers without clinical dementia (65).

Treatment discontinuation rates (64, 66) and discontinuation due to adverse effects did not differ between darifenacin and placebo (**Table 1**) (12, 13, 60–62, 64, 66). The Darifenacin Study Group reported a significant dose–response association (and greater rates of withdrawals due to adverse effects) with 30 mg than with 7.5 mg of darifenacin per day (61). In sensitivity analysis, darifenacin caused dry mouth more often in RCTs that restricted inclusion to women with urgency UI than in RCTs that did not specify inclusion of mixed UI (308 vs. 165 cases per 1000 treated).

Fesoterodine increased continence (44, 67) and led to clinically important improvement in UI (44, 45, 68, 69) in a dose–response fashion (70). Adverse effects were more common with fesoterodine than with placebo (44, 45, 71, 72) in a dose–response fashion; risk was significantly higher with 8 mg than with 4 mg (71, 72). Discontinuation due to adverse effects did not differ between 4 mg of fesoterodine and placebo but was significantly higher with 8 mg of fesoterodine than with placebo (44, 45, 67–69, 73, 74).

Oxybutynin increased continence rates (75–79) and reduced UI (40, 41, 75, 77, 78, 80–86) more often than did placebo, without an evident dose–response association. However, transdermal oxybutynin neither improved quality of life nor resulted in treatment satisfaction when compared with placebo (87). Change in quality of life was inconsistent within and across studies (41, 77, 88–90).

A single RCT demonstrated greater improvement in UI with higher doses of extended-release oxybutynin (15 mg vs. 5 or 10 mg) (91). Higher doses, however, resulted in greater treatment withdrawal for 15 versus 5 mg/d (91). Adverse effects were less common with once-daily, controlled-release oxybutynin than with immediate-release oxybutynin (92). A single RCT found that severe dry mouth and constipation were less common with transdermal than with oral immediate oxybutynin (93).

Solifenacin increased continence rates (94–98) and clinically important improvement in UI (97, 99), with greater benefits with higher doses. Solifenacin at a dosage of 5 mg/d improved quality of life (94, 100). The VIBRANT (VESIcare Investigation of Bother and Quality of Life in Subjects With OAB) study reported greater perceived benefit (RR, 1.78 [CI, 1.48 to 2.14]), satisfaction (RR, 1.42 [CI, 1.26 to 1.61]), and willingness to continue (RR, 1.39 [CI, 1.23 to 1.57]) with flexible 5- to 10-mg doses of solifenacin (97).

Adverse effects (96, 98, 99, 101) and adverse effects leading to discontinuation were more common with solifenacin than with placebo (94–96, 98, 99, 102–104). The association was significant but not dose-responsive.

Tolterodine increased continence rates (44, 67, 105, 106) and led to clinically important improvement in UI (44, 67, 69, 70, 107–110) more often than did placebo.

Table 2. **Conclusions About Pharmacologic Management of Urgency Urinary Incontinence in Women***

Variable	Conclusions	Strength of Evidence
Efficacy and safety		
Darifenacin	At 7.5 and 15 mg, improved urgency UI and several domains of quality of life when compared with placebo	High
	Caused adverse effects more often than did placebo; among examined adverse effects, darifenacin increased rates of constipation, dry mouth, dyspepsia, and headache	Moderate
	Higher dosage (30 mg/d) did not result in better benefits but caused greater rates of adverse effects	High
	Treatment discontinuation rates due to adverse effects were the same with darifenacin and placebo	High
Fesoterodine	Increased continence rate when compared with placebo	Low
	Improved urgency UI and better response with 8 mg vs. 4 mg	High
	Improved quality of life	Low
	Resulted in higher rates of adverse effects and discontinuation of the treatments due to adverse effects; adverse effects were more common with 8 mg than 4 mg	High
Oxybutynin	Increased continence rates and improved UI	High
	Increased treatment discontinuation due to adverse effects; dry mouth was the most common adverse effect	High
	Immediate-release oxybutynin resulted in greater rates of adverse effects and dry mouth compared with controlled-release oral or transdermal oxybutynin	Low
	Higher vs. lower doses resulted in greater improvement in UI, the same rates of dry mouth, and greater rates of treatment withdrawal	Low
Solifenacin	Increased continence rates and greater benefits with the higher dose in women with urgency and mixed UI	High
	Increased risk for dry mouth, constipation, and blurred vision; 10 mg increased the risk for severe dry mouth and constipation	High
	Resulted in treatment discontinuation due to adverse effects more often than did placebo	High
Tolterodine	Increased continence rates and improved UI	High
	Improved quality of life	Low
	Adverse effects, including autonomic nervous system disorders, abdominal pain, dry mouth, dyspepsia, and fatigue, were significantly more common in women taking tolterodine	High
	Discontinuation of the treatment and stopping the treatment because of adverse effects did not differ compared with placebo	High
Trospium	Increased continence rates	High
	Dry mouth, dry eye, dry skin, and constipation occurred more often than with placebo	Moderate
	Adverse effects resulted in treatment discontinuation more often than did placebo	High
Comparative effectiveness and safety		
Fesoterodine vs. tolterodine	Greater rates of continence	Low
	Greater rates of reduced UI	High
	Greater rate of treatment discontinuation due to adverse effects	Moderate
Oxybutynin vs. tolterodine	Greater rate of treatment discontinuation due to adverse effects	High
	No difference in improvement in UI rates	Moderate
	Low adherence to drug treatment; >50% of women stopped treatments within 1 y	Moderate
Role of women's characteristics associated with treatment effects		
Age	Did not modify effects from tested drugs on examined clinical outcomes	Moderate
	Solifenacin increased continence rate when compared with placebo, regardless of age	High
	Oxybutynin, trospium, and darifenacin improved UI in older women	High
Baseline frequency of UI	Did not dramatically modify the effects of the drugs on clinical outcomes; patients with more frequent UI had slightly greater benefits than placebo recipients	Low
	Solifenacin was effective regardless of the response to previous treatments, even though poor responders did not benefit from increasing the drug dose	High
Concomitant medications	Trospium reduced number of urgency UI episodes regardless of therapy with concomitant drugs; adverse effects were more common in patients taking ≥7 concomitant medications	Moderate
Obesity	Trospium was more effective than placebo in achieving continence in obese and nonobese adults	High
Evidence from individual RCTs	Individual studies reported inconsistent improvement in quality of life with oxybutynin	Insufficient
	Solifenacin improved quality of life	Insufficient
	Trospium improved quality of life	Insufficient
	Clinical outcomes with tolterodine and solifenacin did not differ in patients with baseline mixed or pure urgency UI	Insufficient
	Patients with mixed UI may require a larger dose and longer treatment to achieve clinical benefits from solifenacin	Insufficient
	Darifenacin was effective in those in whom previous treatment had failed	Insufficient
	Tolterodine was not better than placebo in achieving clinical benefits among poor responders to the previous muscarinic antagonists	Insufficient

UI = urinary incontinence; RCT = randomized, controlled trial.
* Direct evidence from randomized, controlled clinical trials.

Table 3. **Continence With Pharmacologic Treatments for Urgency Urinary Incontinence***

Active Drug	Control Drug	RCTs (References), *n*	Patients in Analyses, *n*	Rate in Active Treatment Group, %	Rate in Control Group, %	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Strength of Evidence
Fesoterodine, 4–8 mg/d	Tolterodine, 4–8 mg/d	2 (44, 67)	3312	61.0	55.5	1.10 (1.04–1.16)	0.06 (0.02–0.09)	Low
Trospium, 20 mg twice daily	Oxybutynin, 5 mg twice daily	1 (37)	357	22.5	12.2	1.84 (1.01–3.34)	0.1 (0.02–0.19)	Insufficient
Oxybutynin, 10 mg/d	Tolterodine, 4 mg/d	1 (129)	790	23.0	16.8	1.37 (1.03–1.82)	0.06 (0.01–0.12)	Insufficient
Solifenacin, 5–10 mg/d	Tolterodine, 4 mg/d	1 (168)	1177	59.0	49.0	1.20 (1.08–1.34)	0.1 (0.04–0.16)	Insufficient

RCT = randomized, controlled trial.
* Head-to-head randomized, controlled clinical trials.

Adverse effects were more common with tolterodine than with placebo (44, 71, 82, 101, 105, 106, 111–116). However, treatment discontinuation due to bothersome adverse effects did not differ between formulations and doses of tolterodine and placebo (44, 67, 69, 71, 82, 102, 109, 111, 113–115, 117, 118).

Trospium increased continence rates (119–122) and led to clinically important improvement in UI (119, 123) more often than did placebo. Trospium increased rates of a complete response, defined as continence and normal voiding (124). Adverse effects (116, 120–122, 125) and treatment discontinuation due to adverse effects were higher with trospium than with placebo (14, 15, 119, 120, 122, 125).

Comparative Effectiveness and Safety of Pharmacologic Treatments for Urgency UI

Twenty-one reports of head-to-head RCTs comparing drugs for urgency UI suggested similar effectiveness but different safety (**Supplement 11**, available at www.annals.org). Most RCTs had low risk of bias; they were double-blind, with adequate randomization (**Supplement 5**).

Among individual drug comparisons, fesoterodine was more effective than tolterodine in achieving continence (**Table 3**) and improving UI (44, 67). Discontinuation due to adverse effects occurred more often with fesoterodine (44, 67, 69, 71) or oxybutynin (35, 41, 82, 113, 126–131) than with tolterodine (**Table 4**). Individual RCTs demonstrated that trospium was more effective than oxybutynin and solifenacin was more effective than tolterodine. Randomized, controlled trials demonstrated a significant increase in adverse effects with the highest dose of solifenacin (20 mg once daily) when compared with tolterodine, with no difference at a lower dose of solifenacin (101, 132). Rates of treatment discontinuation due to adverse effects did not differ between the 2 drugs (102, 132–134).

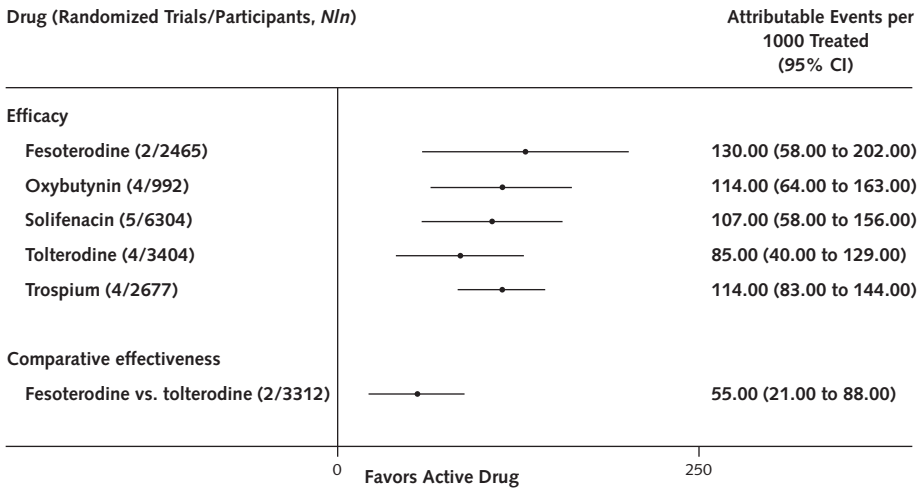
Qualitative comparisons of relative effects from placebo-controlled trials indicated no substantial differences between drugs in resolving or reducing UI (**Figure 1**) but demonstrated different treatment discontinuation rates due to adverse effects (**Figure 2**). Dry mouth was the most common adverse effect and occurred most often with oxybutynin.

Table 4. **Discontinuation due to Adverse Effects With Pharmacologic Treatments for Urgency Urinary Incontinence***

Active Drug	Control Drug	RCTs (References)	Patients in Analyses, *n*	Rate in Active Treatment Group, %	Rate in Control Group, %	Absolute Risk Difference (95% CI)	Attributable Events per 1000 Treated (95% CI)	Strength of Evidence
Darifenacin, 7.5 mg/d	Oxybutynin, 7.5 mg/d	1 (169)	16	0	12.5	−0.13 (−0.41 to 0.16)		Insufficient
Darifenacin, 7.5 to 15 mg/d	Oxybutynin, 15 mg/d	2 (161, 169)	62	3.2	12.9	−0.065 (−0.35 to 0.223)	Not significant	Low
Darifenacin controlled-release, 30 mg/d	Oxybutynin IR, 15 mg/d	2 (161, 169)	63	6.25	19.4	−0.13 (−0.19 to 0.04)	Not significant	Low
Solifenacin	Darifenacin	1 (170)	77	20	21.6	−0.02 (−0.20 to 0.17)		Insufficient
Fesoterodine	Tolterodine	4 (44, 67, 69, 71)	4440	5.4	3.5	0.02 (0.00 to 0.03)	17 (5 to 31)	Moderate
Oxybutynin	Tolterodine	6 (35, 41, 82, 113, 126–131)	2323	13	6	0.07 (0.01 to 0.15)	72 (7 to 154)	High
Solifenacin	Tolterodine	3 (102, 132–134)	2755	4	3	0.01 (0.00 to 0.03)		Moderate
Trospium	Oxybutynin	2 (37, 171)	2015	5	7	0.00 (−0.03 to 0.05)		Low
Trospium, 20 mg twice daily	Oxybutynin, 5 mg twice daily	1 (37)	357	3.7	6.7	−0.029 (−0.086 to 0.027)		Insufficient
Solifenacin	Oxybutynin IR	1 (172)	132	10.3	10.9	−0.006 (−0.112 to 0.099)		Insufficient

IR = immediate release; RCT = randomized, controlled trial.
* Head-to-head randomized, controlled clinical trials.

Figure 1. **Continence with drugs for urgency urinary incontinence (pooled with random effects from randomized, controlled trials).**



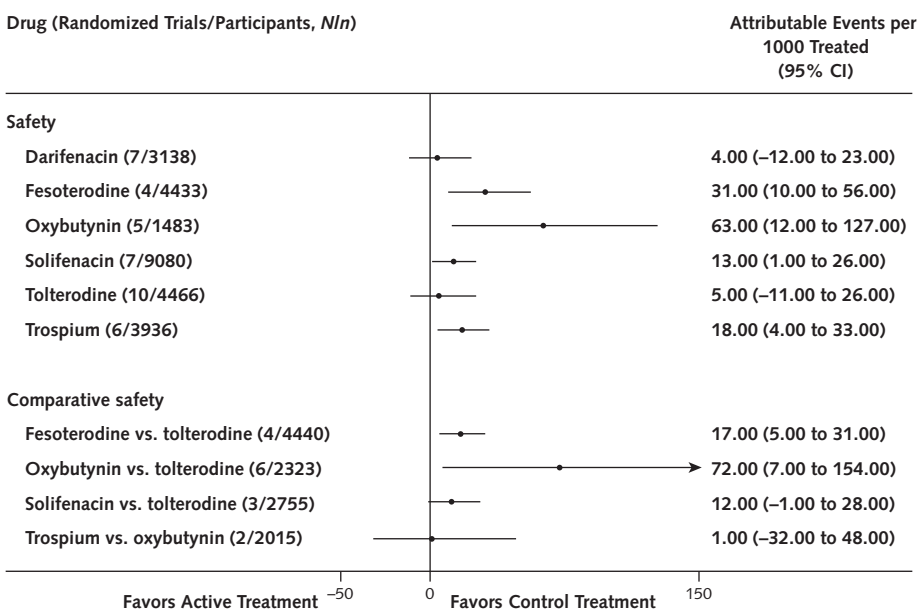
Role of Patient Characteristics

Few RCTs examined how patient characteristics might modify drug effects, and none provided strong evidence for individualized treatment decisions.

Age

Several studies aimed to test treatment effects in older populations and found that oxybutynin, trospium, and darifenacin improved UI in older women. Oxybutynin in frail community-dwelling older people reduced frequency of UI; withdrawal rates did not differ compared with placebo (81). Two RCTs and 1 previously published meta-analysis of individual-patient data from 3 RCTs examined darifenacin in older populations (62, 65, 135). Darifenacin resulted in improvement in UI when compared with placebo in older women (62). Cognitive function did not differ between 2-week darifenacin and placebo treatment (65). Trospium improved UI and quality of life in older patients with overactive bladder (136). A single RCT reported that tolterodine extended-release reduced urgency UI more than did placebo in older but not younger patients (137).

Figure 2. **Treatment discontinuation due to adverse effects from drugs for urgency urinary incontinence (pooled results from randomized, controlled trials by using rate arcsine transformation).**



Baseline Type of UI

Clinical outcomes of tolterodine (138) and solifenacin (95, 139) did not differ between individuals with baseline mixed versus pure urgency UI. Individuals with mixed UI may require a larger dose and longer treatment to achieve clinical benefits from solifenacin than those with urgency UI only (94). We conducted subgroup analyses by enrolling women with mixed UI and found no consistent differences in effects.

We found no evidence that outcomes of drug treatments were better predicted by urodynamic diagnosis of pure detrusor overactivity. One multicenter RCT examined clinical outcomes with fesoterodine in subgroups according to urodynamic findings of detrusor overactivity (140). Treatment response, discontinuation rate, and adverse effects did not differ between individuals with versus those without a urodynamic diagnosis of detrusor overactivity (140, 141). One RCT that compared clinical outcomes with tolterodine extended-release versus placebo also demonstrated no difference in treatment effects in women with and those without urodynamic detrusor overactivity (106).

Baseline Frequency of UI

Baseline UI frequency demonstrated no significant consistent association with clinical outcomes of drug treatment (95, 142, 143). Solifenacin increased continence rates regardless of baseline frequency (95).

Individuals with more frequent UI had slightly greater benefit from some drugs than from placebo. Tolterodine extended-release increased continence rates compared with placebo (143), with a larger relative benefit for those who had more frequent baseline UI (143). In a previously published meta-analysis of individual-patient data from 2 RCTs, fesoterodine was more effective in patients with more than 2 urgency UI episodes per day (142). Adverse effects leading to discontinuation were more common in patients with 2 to 4 episodes of urgency UI per day (142). In contrast, trospium was better than placebo at resolving UI only in patients with fewer than 5 UI episodes per day (144). Trospium did not resolve UI in subgroups with more than 5 episodes of UI per day (144).

Previous Treatment Status

Many studies reported previous treatment status, but very few reported clinical outcomes in subgroups by the response to previous treatments. In a previously published meta-analysis of individual-patient data from 4 RCTs, solifenacin increased continence rates when compared with placebo, regardless of the response to previous treatments (95). Those who had not responded to previous treatment experienced a greater relative benefit than those who had responded, but the former group did not benefit from increasing the dose (95).

In a post hoc analysis of the OPERA (Overactive bladder: Performance of Extended Release Agents) trial, oxybutynin demonstrated greater rates of continence than did tolterodine in patients treated previously with antimuscarinic drugs, but the 2 drugs did not differ in treatment of naive patients (145).

In 1 RCT, tolterodine was no better than placebo among those who responded poorly to muscarinic antagonists (114).

Concomitant Treatments

Trospium reduced the number of urgency UI episodes, irrespective of concomitant medications. Adverse effects were more common in patients taking 7 or more concomitant medications (146).

Obesity

According to a published meta-analysis of individual-patient data from RCTs, baseline obesity did not modify the effect of trospium (147). Trospium was equally more effective than placebo in achieving continence irrespective of baseline obesity (147).

DISCUSSION

Overall, our findings demonstrated strong evidence that rates of continence and clinically important improvement in UI were greater with drugs than with placebo, but drugs also resulted in treatment discontinuation due to bothersome adverse effects. Our results are consistent with those of previously published systematic reviews of UI treatment (4, 7, 11). In addition, on the basis of women's definitions of clinical success, we focused on patient-centered outcomes, including continence, clinically important reduction in UI, and adverse effects that provide critical decision-making information to patients and clinicians (148). The drugs examined in well-designed RCTs were better than placebo and had similar effectiveness. However, more women discontinued treatment with some drugs because of bothersome side effects.

Drug safety is an important clinical issue. In contrast to RCTs, continuous monitoring of drug-related adverse effects in routine clinical practice has provided valuable information about long-term safety. For example, continuous prescription-event monitoring as a part of postmarketing surveillance revealed that tolterodine was strongly associated with a significant risk for hallucinations at long-term follow-up (149). Further, RCTs have not examined concurrent treatments for comorbid conditions; thus, postmarketing surveillance may also address long-term safety of UI drugs combined with other medications. For instance, RRs for ventricular arrhythmias (5.5 [CI, 1.3 to 22.3]) or sudden death (21.5 [CI, 5.2 to 88.3]) were high among older people using UI drugs in combination with antihistamine or cytochrome inhibitors (150).

Adherence to UI treatments is an unaddressed problem. Individual RCTs lasted 2 to 3 months and did not analyze long-term adherence. The evidence-based cost–

utility analysis reported that more than half of patients stop taking drugs for UI after 1 year of treatment (151). The lowest rates of treatment discontinuation were with 5 mg of solifenacin (151). Observational economic evaluations (152–154) demonstrated greater absolute rates of treatment discontinuation due to adverse effects or treatment failure than did RCTs. Among possible explanatory factors, polypharmacy or previous use of the drugs for urinary tract infections was associated with adherence to the drugs for overactive bladder in California Medicaid program beneficiaries (153). Cost-effectiveness analyses (152, 155–158) that should incorporate comparative effectiveness, safety, and adherence to treatments were beyond our scope. Future research should address which factors might increase adherence to UI treatments.

Critical assessment of the strength of the available evidence suggested low risk of bias in most double-blind trials. We relied on direct evidence from head-to-head RCTs that provided consistent estimates of treatment benefits and harms. We also analyzed previously published meta-analyses of individual-patient data that provided valid estimation of dose–response effects with drugs. Risk of bias assessment was complicated by the fact that many authors of individual RCTs and previously published meta-analyses of individual-patient data did not provide sufficient details about allocation concealment methods, multiple publications of the same trials, or planned measurements of clinically important changes in quality-of-life scores. In addition, authors inconsistently reported characteristics of patients, including baseline predominant UI type, severity, and frequency; comorbid conditions; and concomitant treatments. They also did not analyze treatment benefits and harms within subgroups, such as age, sex, race, or response to previous treatments. On the basis of available information, we found no significant effect of risk of bias on drug benefits or safety. We found it difficult to evaluate financial conflict of interest and industry sponsor participation in data analyses and interpretation because studies inconsistently reported necessary details. For example, sometimes the same authors disclosed no or different relationships with industry in multiple publications within the same period.

Average treatment effects in a clinically diverse population may not reflect the actual effects for a specific subgroup (159). Yet, very few studies provided evidence for individualized treatment decisions with clear descriptions of planned stratified randomization and subgroup analyses. Differences in definitions and measurements of quality of life precluded quantitative analyses and hampered synthesis of evidence.

Among limitations of our work, we acknowledge possible reporting bias. We restricted our review to studies reported in English and published in journals, presented at scientific meetings, reviewed by the FDA (160), or reported on the ClinicalTrials.gov Web site. Even after such an exhaustive review of evidence, we do not know how many funded but unregistered studies we may have missed. Published articles and FDA reviews rarely provided unique trial registration numbers from ClinicalTrials.gov. On the basis of the available data, we concluded that there were multiple reports of the same data, and we did not contact the authors for further clarifications. We suspected selective harms reporting because published articles reported common and expected adverse effects. In contrast, few RCTs that posted the results in ClinicalTrials.gov reported all harms irrespective of rate or assumed association with active drugs. We did not contact the authors to request unreported benefits and harms. In cases of unclear allocation concealment, we did not contact the authors for additional details about methodological quality.

We identified gaps and biases in available evidence that suggest directions for future research. Such research should clarify which characteristics of women, including age, race, genitourinary characteristics, and comorbid conditions, are associated with greater treatment benefits and adherence and fewer adverse events. Such studies should be designed to assess long-term treatment success with primary outcomes centered on women, including long-term continence, reduction of 50% to 70% or more in UI episodes, and clinically important improvement in scales of UI severity and quality of life. Future research should examine safety of drugs among older women, women with comorbid conditions, concomitant medications, and failure of previous treatments. All harms should be analyzed, regardless of investigator judgment about possible association with tested treatments. Future research should also address which factors might increase adherence to UI treatments. Investigators should register all trials in ClinicalTrials.gov and provide sufficient details about planned assessments of benefits and harms. Protocols and publications should provide sufficient details about masking treatment status and outcome assessment, as well as methods for allocation concealment.

Our review has implications for clinical practice. Because all drugs for urgency UI have similar effectiveness, therapeutic choices should consider the harms profile, and women should be informed about all possible adverse effects. Benefits from drugs are small, with fewer than 200 cases of continence attributable per 1000 treated (absolute risk difference with placebo <20%). Adherence rates for prescription drugs are low; discontinuation due to bothersome side effects is common. Women with urgency UI whose previous treatments failed may benefit from solifenacin; however, they would not benefit from increasing the dose of the drug. Oxybutynin, trospium, and darifenacin reduced UI in older women. Trospium reduced the number of urgency UI episodes irrespective of concomitant medications. Adverse effects were more common in women taking 7 or more concomitant medications. Given the lack of strong evidence about long-term benefits of and adherence to drugs, these should be closely monitored and routinely analyzed in clinical settings.

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Appendix: Search Strings

The numbers of results are given in parentheses.

14 April 2009

Search ("Urinary Incontinence/radiotherapy"[Mesh] OR "Urinary Incontinence/rehabilitation"[Mesh] OR "Urinary Incontinence/surgery"[Mesh] OR "Urinary Incontinence/therapy"[Mesh]) Limits: Humans, Randomized Controlled Trial, English (612).

Search ("Urinary Incontinence/radiotherapy"[Mesh] OR "Urinary Incontinence/rehabilitation"[Mesh] OR "Urinary Incontinence/surgery"[Mesh] OR "Urinary Incontinence/therapy"[Mesh]) Limits: Humans, Journal Article, English (9182).

Search "Epidemiologic Studies"[Mesh] AND #4 Limits: Humans, Journal Article, English (2367).

Search "Epidemiologic Studies"[Mesh] Limits: Humans, Journal Article, English (901 758).

Search ("Urinary Incontinence/radiotherapy"[Mesh] OR "Urinary Incontinence/rehabilitation"[Mesh] OR "Urinary Incontinence/surgery"[Mesh] OR "Urinary Incontinence/therapy"[Mesh]) (13 222).

16 April 2009

Ovid MEDLINE, 1950 to Week 1 of April 2009

1 exp Urinary Incontinence/di [Diagnosis] (2523).
2 limit 1 to (english language and humans and (guideline or practice guideline)) (13).
3 exp Clinical Protocols/ (91 702).
4 1 and 3 (18).
5 exp Decision Trees/ (6776).
6 1 and 5 (19).
7 6 or 4 (34).
8 limit 7 to (English language and humans) (25).
9 2 or 8 (37).

Ovid MEDLINE, 1950 to Week 2 of April 2009

1 exp urinary incontinence/dh, th, su, rt (9205).
2 exp urinary incontinence/dt (1539).
3 1 not 2 (8998).
4 (non pharmacologic or nonpharmacologc).mp. (2448).
5 1 and 4 (8).
6 exp treatment outcome/ (383 394).
7 exp epidemiologic studies/ (1 103 515).
8 3 or 5 (9001).
9 6 and 7 and 8 (939).
10 exp quality of life/ (73 696).
11 7 and 8 and 10 (230).
12 9 or 11 (1032).
13 limit 12 to (English language and humans) (908).
14 limit 13 to journal article (893).

Ovid MEDLINE, 1950 to Week 2 of April 2009

1 exp urinary incontinence/dt (1539).
2 exp treatment outcome/ (383 394).
3 exp quality of life/ (7696).
4 3 or 2 (444 907).
5 4 and 1 (365).
6 exp epidemiologic studies/ (1 103 515).
7 6 and 5 (96).
8 limit 7 to (English language and humans) (85).
9 limit 8 to journal article (84).
Question 4.

Ovid MEDLINE, 1950 to Week 2 of April 2009

1 exp Urinary Incontinence/dh, nu, th, su, rt, dt, rh [Diet Therapy, Nursing, Therapy, Surgery, Radiotherapy, Drug Therapy, Rehabilitation] (12 453).
2 exp Office Visits/ or exp Medical Office Buildings/ (4554).
3 exp Hospitals/ (161 857).
4 exp Nursing Homes/ (26 676).
5 4 or 3 or 2 (191 276).
6 1 and 5 (314).
7 exp epidemiologic studies/ (1 103 515).
8 6 and 7 (52).
9 limit 8 to (English language and humans) (48).

Ovid MEDLINE, 1950 to Week 2 of April 2009

1 exp urinary incontinence/ (20 881).
2 exp primary health care/ (55 252).
3 1 and 2 (124).
4 exp epidemiologic studies/ (1 103 515).
5 4 and 3 (16).
6 exp physician-patient relations/ (48 990).
7 6 and 4 and 1 (12).
8 7 or 5 (26).
9 limit 8 to English language (23).
10 limit 9 to journal article (22).

Ovid MEDLINE, 1950 to Week 2 of April 2009

1 exp Urinary Incontinence/di [Diagnosis] (2529).
2 exp Diagnosis, Differential/ (316 330).
3 1 and 2 (190).
4 limit 3 to (English language and humans) (115).

Ovid MEDLINE, 1950 to Week 2 April 2009

1 exp Urinary Incontinence/th, su, dt, rh [Therapy, Surgery, Drug Therapy, Rehabilitation] (11 383).
2 exp Treatment Outcome/ (383 394).
3 1 and 2 (2157).
4 exp Evidence-Based Practice/ or exp Evidence-Based Medicine/ or evidence.mp. (756 148).
5 4 and 3 (146).
6 limit 3 to "therapy (optimized)" (399).
7 6 or 5 (502).
8 limit 7 to (English language and humans) (463).

9 exp epidemiological studies/ (1 103 515).
10 8 and 9 (180).
11 limit 10 to journal article (177).

26 May 2009

Search #6 or #7 Limits: Humans, Randomized Controlled Trial, English (46).

Search #6 or #7 Limits: Humans, English (758).

Search #9 and #1 and #3 Limits: Humans, Randomized Controlled Trial, English (402).

Search #9 and #1 and #3 Limits: Humans, English (5442).

Search clinic or office or hospital or nursing home or longterm care, Limits: Humans, English (1 645 316).

Search "health services research"[MeSH Terms] and urine incontinence Limits: Humans, English (214).

Search #4 or #5 Limits: Humans, English (588).

Search "Physician's Practice Patterns"[MeSH Terms] and urine incontinence Limits: Humans, English (64).

Search #1 and #2 and #3 (539).

Search treatment or outcome (3 837 858).

Search primary care or specialized care or urologist or urogynecologist (118 680).

Search urine incontinence (18 607).

Search urine incontinence and professional practice Limits: Humans, English (228).

Stem cell AND "urinary incontinence" Limits: Humans, Journal Article, English (42).

Estrogen AND "urinary incontinence" Limits: Humans, Journal Article, English (368).

Adrenergic Uptake Inhibitors AND "urinary incontinence" Limits: Humans, Journal Article, English (162).

Imipramine hydrochloride AND "urinary incontinence" Limits: Humans, Journal Article, English (76).

Tricyclic antidepressant AND "urinary incontinence" Limits: Humans, Journal Article, English (81).

Botulinum toxin AND "urinary incontinence" Limits: Humans, Journal Article, English (109).

Alpha-blockers AND "Urinary Incontinence" Limits: Humans, Journal Article, English (101).

Solifenacin AND "Urinary Incontinence" Limits: Humans, Journal Article, English (48).

Vesicare AND "Urinary Incontinence" Limits: Humans, Journal Article, English (4).

Enablex AND "Urinary Incontinence" Limits: Humans, Journal Article, English (54).

Sanctura AND "Urinary Incontinence" Limits: Humans, Journal Article, English (3).

Ditropan AND "Urinary Incontinence" Limits: Humans, Journal Article, English (286).

Detrol AND "Urinary Incontinence" Limits: Humans, Journal Article, English (198).

"Urinary Incontinence" Limits: Humans, Randomized Controlled Trial, English (789).

("Urinary Incontinence/radiotherapy"[Mesh] OR "Urinary Incontinence/rehabilitation"[Mesh] OR "Urinary Incontinence/surgery"[Mesh] OR "Urinary Incontinence/therapy"[Mesh]) Limits: Humans, Randomized Controlled Trial, English (621).

("Urinary Incontinence/radiotherapy"[Mesh] OR "Urinary Incontinence/rehabilitation"[Mesh] OR "Urinary Incontinence/surgery"[Mesh] OR "Urinary Incontinence/therapy"[Mesh]) (13 302).

"Caregivers"[Mesh] AND "Urinary Incontinence" Limits: Humans, Journal Article, English (40).

"Physician-Patient Relations" [Mesh] AND "Urinary incontinence" (48).

"Delivery of Health Care"[Mesh] AND "Urinary incontinence" Limits: Humans, Journal Article, English (1438).

"Health services re"[MeSH] AND "Urinary incontinence" Limits: Humans, Journal Article, English (186).

"Physician's Practice Patterns"[MeSH] AND "Urinary incontinence" Limits: Humans, Journal Article, English (57).

"Quality of life" AND "Urinary incontinence" Limits: Humans, Journal Article, English (1689).

"Urinary Incontinence/diagnosis"[Mesh] Limits: Humans, Randomized Controlled Trial, English (83).

"Urinary Incontinence/diagnosis"[Mesh] Limits: Humans, Journal Article, English (2328).

"Epidemiologic Studies"[Mesh] AND "Urinary Incontinence/diagnosis"[Mesh] Limits: Humans, Randomized Controlled Trial, Controlled Clinical Trial, Multicenter Study, Validation Studies, English (66).

"Urinary Incontinence" AND urologist Limits: Humans, Journal Article, English (78).

"Urinary Incontinence" AND urogynecologist Limits: Humans, Journal Article, English (7).

"Urinary Incontinence" AND gynecologist Limits: Humans, Journal Article, English (29).

26 June 2009

Search (Urinary incontinence) AND systematic[sb] (581).

20 July 2009

Cochrane RCT database:

Urinary incontinence and Women (457).

Urinary incontinence NOT surgery (138).

Updated Search 10 November 2009

Search (("Urinary incontinence"[Text Word]) AND ("2009/04/01"[Publication Date]: "3000"[Publication Date])) AND (Urinary incontinence) Limits: Randomized Controlled Trial English (33).

25 March 2010

Search tolterodine Limits: Randomized Controlled Trial ("2009/04/01"[Publication Date]: "3000"[Publication Date])) AND (Urinary incontinence) Limits: Randomized Controlled Trial, English (134).

Search fesoterodine (48).

Search Solifenacin (194).

30 March 2011

"urinary incontinence" OR "overactive bladder" OR fesoterodine OR oxybutynin OR trospium OR solifenacin OR tol-

terodine Limits: Female, Randomized Controlled Trial, English, All Adult: 19+ years (865).

Gray Literature Search Using Key Words "Urinary Incontinence" on 27 July 2010

Regulatory Information: Food and Drug Administration, Health Canada, Authorized Medicines for European Union.

Clinical Trial Registries: ClinicalTrials.gov (120), Search for UI among all close studies (additional 100 records), Australian New Zealand Clinical Trials Registry (1), Clinical study results (4), World Health Organization clinical trials (18), Clinical Trials Registry—India (1), Japanese Registry of Clinical Trials (4), Netherlands Trial Register (6).

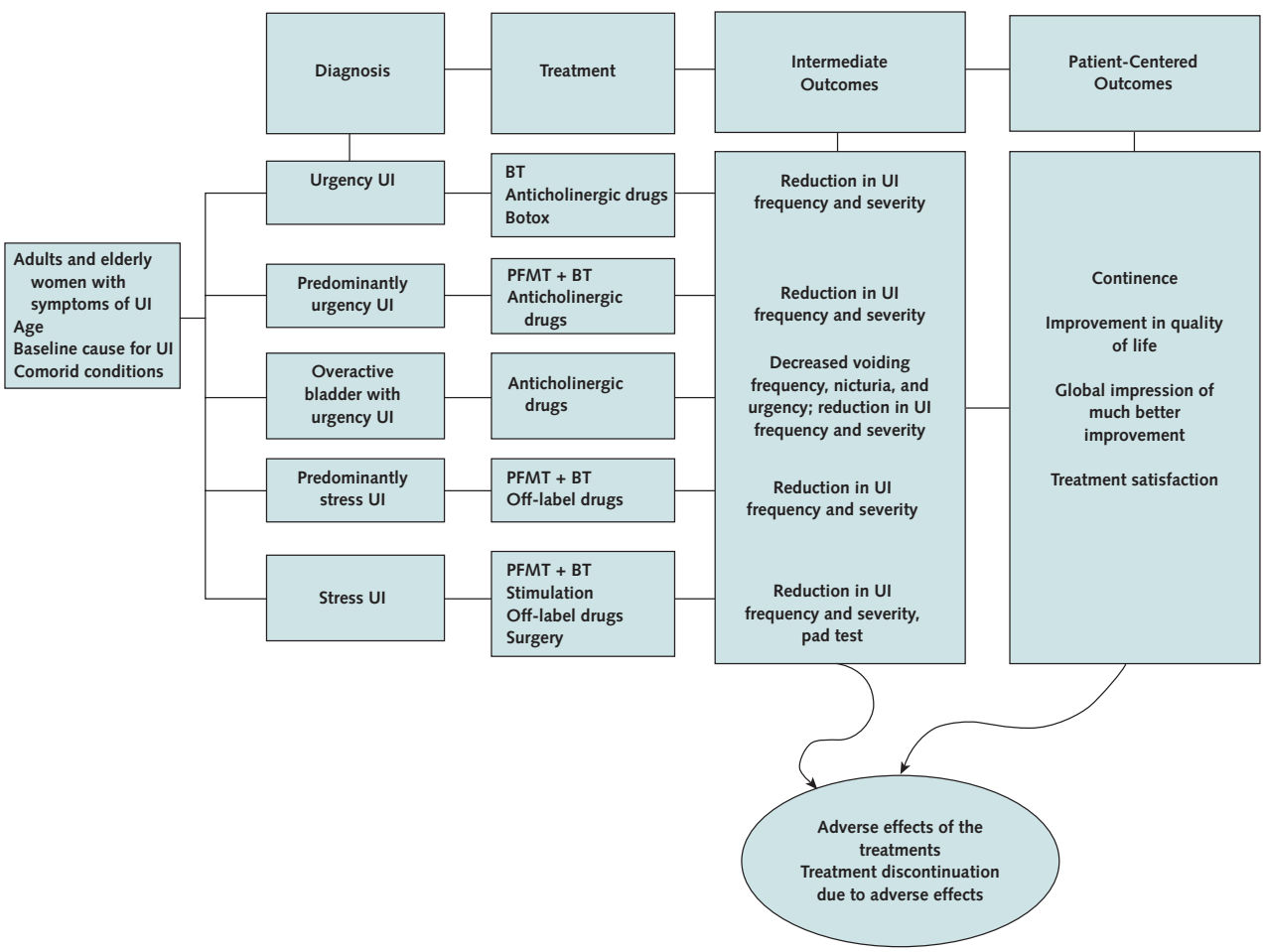
Abstracts and conference papers: Conference Papers Index (318), Scopus (243), International Continence Society and the International Urogynecological Association 2010 meeting.

Grants and federally funded research: NIH RePORTER, a searchable database of federally funded biomedical research projects conducted at universities, hospitals, and other research institutions (487).

November 2011: Updated Searches

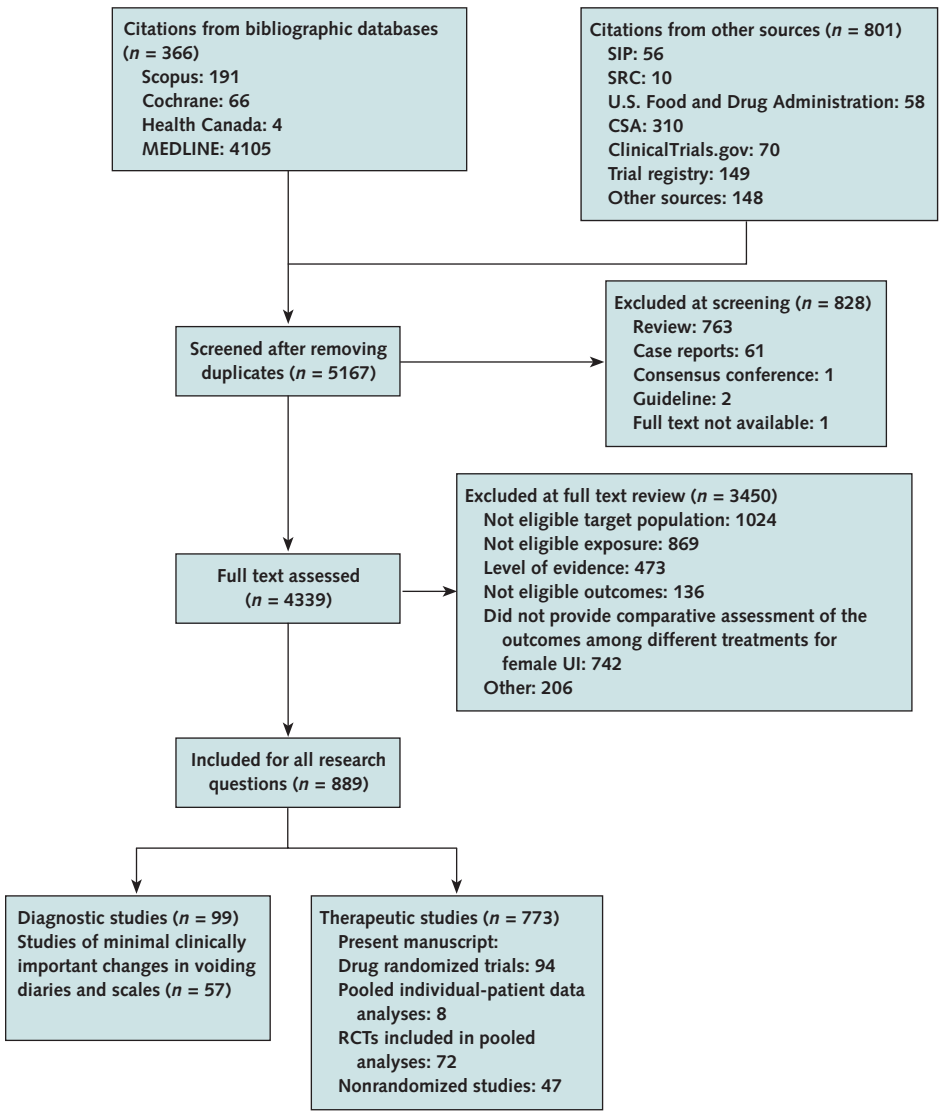
"Urinary incontinence" OR "overactive bladder" OR fesoterodine OR oxybutynin OR trospium OR solifenacin OR tolterodine Limits: Humans, Randomized Controlled Trial, English, published in the last 3 years (267).

Appendix Figure 1. **Analytic framework.**



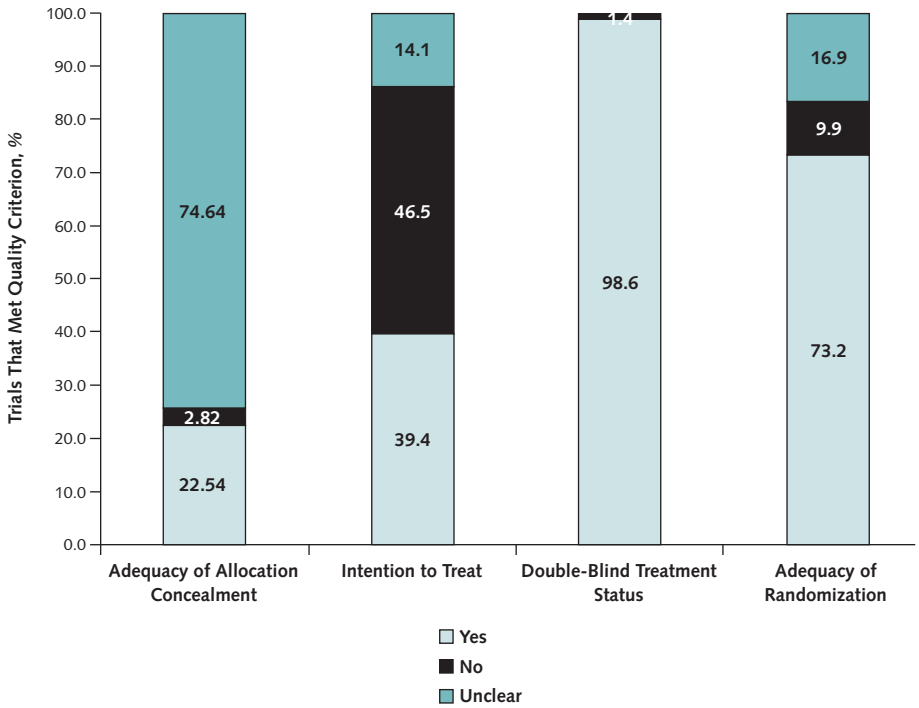
BT = bladder training; PFMT = pelvic floor muscle training; UI = urinary incontinence.

Appendix Figure 2. **Summary of evidence search and selection.**



CSA = bibliographical database, formerly Cambridge Scientific Abstracts; RCT = randomized, controlled trail; SIP = Scientific Information Package; SRC = Scientific Resource Center; UI = urinary incontinence.

Appendix Figure 3. **Risk of bias criteria in randomized, controlled trials.**



Appendix Table. **Adverse Effects and Treatment Discontinuation due to Bothersome Adverse Effects With Pharmacologic Interventions for Urgency Urinary Incontinence Compared With Placebo***

Outcome	RCTs (References)	Patients in Analyses, *n*	Rate in Active Treatment Group, %	Rate in Control Group, %	Risk Difference (95% CI)†	Attributable Events per 1000 Treated	Bayesian Odds Ratio Median (2.5% to 97.5% Percentile Range)	Strength of Evidence
Darifenacin								
Serious adverse effects	2 (61, 64)	655	1.2	2.1	−0.01 (−0.02 to 0.01)		0.6 (0.1 to 2.6)	Low
Discontinuation: adverse effects	7 (12, 13, 60–62, 64, 66)	3138	4.6	3.3	0.00 (−0.01 to 0.02)		1.2 (0.7 to 2.0)	High
Discontinuation: treatment failure	4 (12, 13, 61, 64)	1280	1.0	1.7	−0.01 (−0.01 to 0.01)		0.6 (0.2 to 1.7)	Moderate
Dry mouth	5 (61, 62, 64–66)	2382	22.0	5.6	0.16 (0.07 to 0.27)	158 (65 to 269)	4.1 (2.1 to 8.1)	High
Dyspepsia	4 (61, 64–66)	1772	4.4	1.3	0.03 (0.01 to 0.06)	31 (7 to 62)	3.6 (1.7 to 7.9)	High
Headache	3 (61, 64, 65)	1155	4.1	1.1	0.03 (0.01 to 0.06)	34 (13 to 61)	4.2 (1.6 to 12.3)	Moderate
Nausea	2 (64, 65)	573	1.3	0.7	0.00 (−0.01 to 0.03)		1.4 (0.2 to 9.9)	Low
Urinary tract infection	2 (61, 64)	655	2.9	2.3	0.01 (−0.01 to 0.04)		1.2 (0.3 to 4.1)	Low
Constipation	5 (61, 62, 64–66)	2239	14.6	5.7	0.08 (0.02 to 0.15)	80 (24 to 148)	2.6 (1.4 to 4.4)	High
Fesoterodine								
Treatment failure	2 (44, 45, 68, 69)	1896	4	8	−0.04 (−0.06 to −0.02)	−43 (−59 to −24)	0.4 (0.2 to 1.0)	High
Serious adverse effects	2 (44, 45)	1905	1.8	1.9	0.00 (−0.01 to 0.01)		0.9 (0.3 to 2.3)	Low
Discontinuation: adverse effects	4 (44, 45, 67–69, 73)	4433	6	3	0.03 (0.01 to 0.06)	31 (10 to 56)	2.0 (1.2 to 3.2)	High
Discontinuation: treatment failure	2 (44, 45, 68, 69)	1896	2	3	−0.01 (−0.03 to 0.02)		0.6 (0.2 to 1.7)	Moderate
Abdominal pain	2 (44, 73)	1747	3.7	2.7	0.02 (0.00 to 0.04)		1.9 (0.8 to 4.0)	Low
Abnormal vision	1 (73)	1094	0.3	1.0	−0.01 (−0.01 to 0.00)		0.2 (0.0 to 1.4)	Insufficient
Back pain	2 (44, 73)	2116	2.1	3.0	−0.01 (−0.02 to 0.01)		0.8 (0.4 to 1.7)	Low
Constipation	7 (44, 45, 67–69, 71–73)	7695	11	3	0.04 (0.00 to 0.10)	41 (1 to 97)	2.4 (1.4 to 3.9)	High
Cough	3 (44, 45, 73)	2999	1.8	1.9	0.00 (−0.01 to 0.02)		1.1 (0.6 to 2.2)	Moderate
Diarrhea	2 (44, 45, 69)	1896	2	3	0.00 (−0.03 to 0.03)		0.8 (0.3 to 2.1)	Low
Dizziness	2 (44, 73)	3138	1.2	0.9	0.00 (−0.01 to 0.01)		0.9 (0.4 to 2.0)	Low
Dry eye	4 (44, 45, 68, 71, 72)	4145	2	1	0.03 (0.01 to 0.06)	28 (6 to 60)	3.4 (1.6 to 8)	High
Dry mouth	5 (44, 45, 67–69, 71–73)	6674	27	7	0.20 (0.16 to 0.24)	199 (161 to 239)	4.9 (3.8 to 6.3)	High
Fatigue	2 (44, 45)	1905	2.0	0.3	0.02 (0.01 to 0.04)	24 (11 to 41)	10.3 (2.2 to 88.5)	Low
Headache	5 (44, 45, 68, 69, 71–73)	5230	7	6	0.00 (−0.01 to 0.02)		1.1 (0.8 to 1.4)	High
Influenza-like symptoms	1 (73)	1094	5.7	8.0	−0.03 (−0.05 to 0.01)			Insufficient
Nasopharyngitis	4 (44, 45, 71, 72)	4145	2.5	3.3	−0.01 (−0.02 to 0.00)		0.8 (0.5 to 1.2)	Moderate
Nausea	5 (44, 45, 71–73)	5239	2.0	3.1	−0.01 (−0.02 to 0.00)		0.6 (0.4 to 1.0)	High
Upper respiratory tract infection	2 (44, 45)	1905	2.0	3.5	−0.01 (−0.02 to 0.01)		0.6 (0.1 to 1.9)	Low
Urinary tract infection	2 (44, 45, 69)	1896	2	2	0.01 (−0.01 to 0.05)		1.2 (0.4 to 3.7)	Low
Oxybutynin								
Treatment failure	5 (40, 77, 80, 83, 86)	874	12.2	22.9	−0.11 (−0.16 to −0.05)	−110 (−161 to −46)	0.4 (0.2 to 0.7)	Moderate
Serious adverse effects	3 (40, 76, 111)	1393	3.7	2.0	0.02 (−0.02 to 0.15)		1.5 (0.3 to 6.4)	Moderate
Discontinuation: adverse effects	5 (40, 41, 76, 80, 82, 161)	1483	10	5	0.06 (0.01 to 0.13)	63 (12 to 127)	2.0 (1.1 to 3.8)	High
Blurred vision	5 (40, 77, 81, 161, 162)	663	10.4	9.1	0.10 (0.02 to 0.19)	98 (22 to 187)		Moderate
Constipation	7 (40, 75–77, 89, 161, 162)	1743	7.3	5.5	0.03 (−0.01 to 0.09)		1.4 (0.8 to 2.6)	Moderate
Dizziness	5 (40, 75, 76, 89, 161)	1541	2.3	1.7	0.01 (0.00 to 0.03)			Moderate
Dry mouth	9 (40, 41, 75–77, 81, 82, 89, 161, 162)	2238	34	15	0.35 (0.16 to 0.54)	347 (158 to 536)	7.2 (3.2 to 16.5)	High
Dry skin	3 (40, 81, 162)	493	10.0	10.4	0.09 (−0.07 to 0.35)			Low

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Appendix Table—Continued

Outcome	RCTs (References)	Patients in Analyses, *n*	Rate in Active Treatment Group, %	Rate in Control Group, %	Risk Difference (95% CI)†	Attributable Events per 1000 Treated	Bayesian Odds Ratio Median (2.5% to 97.5% Percentile Range)	Strength of Evidence
Dyspepsia	3 (40, 82, 163)	613	12.1	3.3	0.08 (0.03 to 0.16)	85 (27 to 158)	3.9 (1.2 to 12.2)	Moderate
Dysuria	2 (76, 89)	1046	0.8	0.2	0.01 (0.00 to 0.07)		5.8 (0.5 to 254.9)	Low
Headache	3 (40, 76, 163)	1299	4.1	4.5	−0.01 (−0.03 to 0.01)		0.9 (0.4 to 2.2)	Moderate
Nausea	7 (75, 76, 82, 83, 89, 162, 163)	1743	3.9	3.0	0.00 (−0.02 to 0.05)		1.0 (0.4 to 2.4)	High
Urine retention	3 (40, 76, 77)	1287	3.2	0.5	0.04 (−0.01 to 0.16)		6.1 (0.2 to 57.0)	Moderate
Somnolence	3 (40, 76, 89)	1412	0.9	0.8	0.00 (−0.01 to 0.02)			Low
Vision disorder	3 (80, 83, 89)	589	8.1	4.7	0.00 (−0.04 to 0.09)		1.1 (0.2 to 3.4)	Low
Vomiting	2 (83, 163)	361	2.3	1.4	0.03 (−0.01 to 0.14)		2.0 (0.3 to 19.0)	Low
Solifenacin								
Treatment failure	4 (97, 99, 102, 104)	2918	27.7	30.1	−0.14 (−0.22 to −0.06)	−143 (−217 to −60)		Moderate
Discontinuation: adverse effects	7 (94–96, 98, 99, 102–104)	9080	5	4	0.01 (0.00 to 0.03)	13 (1 to 26)	1.3 (1.0 to 1.7)	High
Discontinuation: treatment failure	4 (98, 99, 102, 104)	2812	1.5	1.3	0.00 (−0.01 to 0.01)		1.0 (0.4 to 2.2)	Moderate
Blurred vision	9 (94–99, 101–104)	12 922	4	2	0.02 (0.01 to 0.03)	17 (10 to 26)	2 (1.4 to 2.7)	High
Dry mouth	7 (94–97, 99, 101, 103, 104)	11 089	21	5	0.17 (0.12 to 0.23)	175 (122 to 232)	5.2 (3.7 to 7.2)	High
Dyspepsia	3 (97, 98, 101)	1663	3.4	0.4	0.04 (0.02 to 0.06)	37 (16 to 64)	11.4 (3.3 to 53.4)	Moderate
Fatigue	2 (96, 97, 99)	1507	2	1	0.01 (0.00 to 0.03)	12 (0 to 28)	2.6 (0.8 to 9.4)	Low
Headache	4 (96–99, 101)	2481	3	4	−0.01 (−0.02 to 0.01)		0.8 (0.4 to 1.4)	Moderate
Nausea	2 (97, 98)	1440	3.2	2.7	0.00 (−0.01 to 0.03)		1.1 (0.3 to 3.1)	Low
Urine retention	2 (98, 101)	747	2.4	0.8	0.03 (−0.01 to 0.12)		3.6 (0.8 to 23.4)	Low
Constipation	8 (94–99, 101, 103, 104)	11 765	11	3	0.07 (0.05 to 0.10)	73 (49 to 99)	3.1 (2.3 to 4.2)	High
Dizziness	2 (96, 98, 99)	1411	3	2	0.01 (−0.01 to 0.03)		1.5 (0.6 to 3.8)	Low
Tolterodine								
Treatment failure	6 (44, 69, 105, 107–110)	4260	9	16	−0.05 (−0.10 to 0.01)		0.6 (0.4 to 1.0)	High
Serious adverse effects	5 (44, 113, 117, 164, 165)	3550	1.8	3.1	−0.01 (−0.02 to 0.00)		0.6 (0.3 to 1.1)	Moderate
Discontinuation: adverse effects	10 (44, 67, 69, 71, 82, 102, 109, 111, 113–115, 117, 118)	4466	4	3	0.01 (−0.01 to 0.03)		1.1 (0.8 to 1.7)	High
Discontinuation: treatment failure	5 (44, 69, 102, 109, 115)	4049	0.7	1.6	−0.01 (−0.01 to 0.00)		0.4 (0.2 to 0.9)	High
Autonomic nervous system disorders	3 (112, 113, 164)	831	27.2	15.5	0.12 (0.05 to 0.20)	117 (46 to 195)	2.0 (1.1 to 3.5)	Moderate
Blurred vision	2 (101, 102)	608	1.3	3.0	−0.03 (−0.02 to 0.03)		0.4 (0.1 to 1.7)	Low
Constipation	14 (44, 67, 69, 71, 101, 102, 105, 109, 111, 112, 114, 115, 117, 118, 165, 166)	9592	4	3	0.01 (0.00 to 0.02)	12 (3 to 22)	1.4 (1.1 to 1.9)	High
Diarrhea	4 (44, 69, 115, 117, 165, 166)	4056	2	2	0.01 (0.00 to 0.02)		1.2 (0.7 to 2.2)	High
Dizziness	6 (44, 71, 109, 115, 117, 165, 166)	5257	2	2	0.00 (0.00 to 0.01)		1.0 (0.6 to 1.7)	High
Dry mouth	14 (44, 67, 69, 71, 82, 101, 102, 105, 106, 109, 111, 114, 116, 165)	7637	18.4	6.7	0.14 (0.10 to 0.18)	139 (104 to 175)	3.4 (2.7 to 4.5)	High
Dyspepsia	6 (44, 82, 106, 115, 117, 165, 166)	3525	3	2	0.02 (0.00 to 0.05)	22 (1 to 53)	2.1 (1.1 to 4.4)	High

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Appendix Table—Continued

Outcome	RCTs (References)	Patients in Analyses, *n*	Rate in Active Treatment Group, %	Rate in Control Group, %	Risk Difference (95% CI)†	Attributable Events per 1000 Treated	Bayesian Odds Ratio Median (2.5% to 97.5% Percentile Range)	Strength of Evidence
Fatigue	4 (44, 71, 109, 165)	3234	1.9	0.7	0.02 (0.01 to 0.03)	17 (7 to 29)	3.1 (1.3 to 7.8)	High
General body disorders	2 (112, 113)	308	22.3	18.6	0.03 (−0.09 to 0.18)		1.1 (0.3 to 3.5)	Low
Headache	11 (44, 69, 71, 101, 105, 106, 109, 112, 114, 115, 117, 118, 165, 166)	6766	4	4	0.01 (0.00 to 0.03)		1.3 (1.0 to 1.8)	High
Insomnia	2 (105, 165, 166)	1428	1.7	1.3	0.02 (−0.01 to 0.10)		1.5 (0.5 to 5.8)	Moderate
Nasopharyngitis	5 (44, 70, 71, 105, 109, 167)	2835	3	3	0.00 (−0.01 to 0.02)		1.1 (0.7 to 1.9)	High
Nausea	7 (44, 71, 82, 115, 117, 165, 166)	5642	1.6	2.0	0.00 (−0.01 to 0.01)		0.8 (0.5 to 1.3)	High
Somnolence	2 (115, 165, 166)	1869	1	1	0.00 (−0.01 to 0.02)		0.9 (0.1 to 3.7)	Low
Urinary tract infection	5 (44, 69, 105, 112, 115, 165, 166)	4465	2	3	0.00 (−0.01 to 0.01)		0.9 (0.6 to 1.5)	High
Abdominal pain	5 (44, 114, 115, 117, 165, 166)	4637	3	2	0.01 (0.00 to 0.02)	9 (1 to 20)	1.6 (0.9 to 2.8)	High
Abnormal vision	2 (111, 165, 166)	1141	2	1	0.00 (−0.01 to 0.02)		1.4 (0.4 to 5.5)	Moderate
Trospium								
Discontinuation: adverse effects	6 (14, 15, 119, 120, 122, 125)	3936	5.8	3.9	0.02 (0.00 to 0.03)	18 (4 to 33)	1.5 (1.0 to 2.2)	High
Abdominal distention	2 (120, 122)	989	1.0	0.3	0.01 (0.00 to 0.02)	8 (0 to 21)	3.4 (0.8 to 19.1)	Low
Abdominal pain	3 (119, 120, 122)	2113	1.7	0.7	0.01 (0.00 to 0.02)	10 (1 to 23)	2.7 (1.0 to 8.1)	Moderate
Central nervous system disorders	2 (121, 123)	1217	3.9	3.8	0.00 (−0.02 to 0.03)		1.0 (0.4 to 2.6)	
Constipation	5 (119–122, 125)	3335	9.3	2.6	0.07 (0.05 to 0.09)	70 (47 to 95)	3.9 (2.5 to 6.3)	High
Diarrhea	2 (119, 125)	1181	2.5	4.6	−0.02 (−0.04 to 0.00)		0.5 (0.2 to 1.4)	Low
Dry eye	2 (120, 122)	1590	1.7	0.2	0.01 (0.00 to 0.03)	14 (4 to 29)	8.0 (1.7 to 59.3)	Low
Dry mouth	6 (116, 119–122, 125)	3490	15.1	4.5	0.11 (0.07 to 0.14)	106 (75 to 140)	3.9 (2.6 to 5.8)	High
Dry skin	2 (120, 122)	1590	1.0	0.1	0.01 (0.00 to 0.02)	11 (2 to 24)	12.3 (1.6 to 420.5)	Low
Dyspepsia	2 (120, 122)	1590	1.5	0.9	0.00 (−0.01 to 0.02)		1.8 (0.6 to 6.4)	Low
Headache	4 (119, 120, 122, 125)	2771	3.3	3.5	−0.01 (−0.02 to 0.01)		0.9 (0.4 to 1.7)	High
Nausea	2 (120, 122)	1590	1.3	0.4	0.01 (0.00 to 0.02)		3.7 (0.8 to 20.0)	Low
Urinary tract infection	3 (120, 122, 125)	2248	2.6	1.3	0.01 (0.00 to 0.03)		2.0 (0.9 to 4.6)	Moderate

RCT = randomized, controlled trial.
* Pooled estimates from randomized, controlled clinical trials.
† We calculated pooled double-arcsine transformation for comparing 2 proportions and converted arcsine differences back to risk differences.