Draft Comparative Effectiveness Review
Number XXX

Diagnosis and Comparative Effectiveness of Treatments for Urinary Incontinence in Adult Women

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the State Children's Health Insurance Program (SCHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://effectivehealthcare.ahrq.tov/referencepurpose.cfm .

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

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Structured Abstract

Objectives: To assess methods to diagnose urinary incontinence (UI) and monitor treatment effectiveness in community-dwelling adult women, and to assess clinical efficacy and comparative effectiveness of pharmacological and nonsurgical treatments for UI.

Data Sources: Major electronic bibliographic databases, the FDA reviews, trial registries, and research grant databases were searched up to December 30, 2010.

Review Methods: A systematic review of diagnostic studies and therapeutic randomized and nonrandomized studies published in English was performed to synthesize diagnostic accuracy, minimally clinically important differences in validated tools for diagnosing UI, and rates of continence and harms of examined treatments. We calculated pooled absolute risk differences to estimate the number needed to treat (NNT) to achieve continence or prevent harms with random effects models.

Results: From a total of 826 eligible references, 99 studies showed minimal diagnostic value of tests to distinguish urodynamic stress or urgency UI, and 57 studies suggested differences of importance to women in UI frequency (decrease of 70 percent or more in voiding diary) and quality of life. Pre-treatment urodynamic diagnoses were not associated with treatment outcomes. Continence was achieved in one woman with predominant urgency UI for every eight women treated with fesoterodine (NNT 8, 95 percent CI 5; 8), 12 with tolterodine (NNT=12, 95 percent CI 8; 12), nine with oxybutynin (NNT=9, 95 percent CI 6; 9), nine with solifenacin (NNT=9, 95 percent CI 6; 9), and nine with trospium (NNT=9, 95 percent CI 7; 9). Discontinuation of treatment due to adverse effects occurred in one women for every 31 treated with fesoterodine (NNT=31, 95 percent CI 21; 31), 22 with oxybutynin (NNT=22, 95 percent CI 13; 22), 59 with trospium (NNT=59, 95 percent CI 33; 59), and 83 with solifenacin (NNT=83, 95 percent CI 43; 83). Discontinuation due to adverse effects occurred more often with fesoterodine or oxybutynin than with tolterodine. Continence was achieved in one woman for every three treated with pelvic floor muscle training (NNT=3, 95 percent CI 2; 5), six with pelvic floor muscle training combined with bladder training (NNT=6, 95 percent CI 4; 16), and six with intravaginal electrical stimulations (NNT=6, 95 percent CI 4; 16). Weight loss may improve UI in obese women. Improvement in UI and quality of life were examined using different definitions that hampered synthesis of evidence. Evidence was insufficient to conclude prediction of treatment effects by age, race, baseline type and severity of UI, and comorbidities.

Conclusions: Self- reported symptoms of UI have a low diagnostic value when compared to urodynamic diagnosis of stress UI or detrusor overactivity. Assessment of quality of life, frequency, and severity of predominant stress or urgency UI has been conducted using the validated tools. Urodynamic diagnosis was not associated with differences in outcomes of nonsurgical treatments. Monitoring of treatment success includes both differences recorded on voiding diaries (>70 percent in frequency of UI episodes) and condition-specific quality of life scales. Benefits from pelvic floor muscle training combined with bladder training and electrical stimulation are greater than benefits from drugs. Drugs for predominant urgency UI had comparable effectiveness. Routine clinical practice should include monitoring of long-term safety of pharmacological treatments.

Contents

Executive Summary ES-1

Chapter 1. Introduction 1
Measuring Outcomes of UI Treatment 2

Chapter 2. Methods 7
Literature Search Strategy and Eligibility Criteria 7
Search Strategy 7
Eligibility 7
Quality Assessment and Rating the Body of Evidence 9
Grading the Evidence for Each Key Question 9
Applicability 10
Data Extraction 10
Data Synthesis 11

Chapter 3. Results 13
Question 1. What Constitutes an Adequate Diagnostic Evaluation in the Primary Care Setting on Which to Base Treatment of Urinary Incontinence (UI)? 14
Diagnostic Value of Symptoms of UI Compared to Multichannel Urodynamics 14
Diagnostic Value of Pad Tests Compared to Multichannel Urodynamics 15
Diagnostic Value of Symptoms of UI to Clinical Diagnosis 16
Diagnostic Value of Complex Clinical Algorithms 16
Comparison of Diagnostic Values of Different Tests 17
Minimal Clinically Important Differences in Diagnostic Tools to Monitor Effectiveness of the Treatments 18
Association Between Methods of Diagnosis and Patient Outcomes 19
Question 2. How Effective is the Pharmacologic Treatment of UI in Women? 38
Clinical Effectiveness of Topical Estrogen Therapy 38
Clinical Effectiveness of Duloxetine 38
Clinical Effectiveness of Oxybutynin 40
Clinical Effectiveness of Tolterodine 41
Clinical Effectiveness of Darifenacin 43
Clinical Effectiveness of Solifenacin 44
Clinical Effectiveness of Fesoterodine 45
Clinical Effectiveness of Trospium 46
Clinical Effectiveness of Propiverine 46
Clinical Effectiveness of Botulinum Toxin 47
Clinical Effectiveness of Resiniferatoxin 48
Clinical Effectiveness of Nimodipine 48
Comparative Effectiveness of Topical Estrogen on UI 57
Comparative Effectiveness of Darifenacin and Oxybutynin on UI 57
Comparative Effectiveness of Oxybutynin and Tolterodine on UI 57
Comparative Effectiveness of Propiverine and Oxybutynin on UI 58
Comparative Effectiveness of Flavoxate and Oxybutynin on UI 59

Comparative Effectiveness of Tolterodine and Propiverine on UI....59
Comparative Effectiveness of Tolterodine and Fesoterodine on UI....59
Comparative Effectiveness of Solifenacin and Tolterodine on UI....60
Comparative Effectiveness of Solifenacin and Darifenacin on UI....60
Comparative Effectiveness of Solifenacin and Oxybutynin on UI....60
Comparative Effectiveness of Solifenacin and Propiverine on UI....61
Comparative Effectiveness of Trospium and Oxybutynin on UI....61
Comparative Effectiveness of Trospium and Tolterodine on UI....61
Indirect Evidence of Comparative Effectiveness of Pharmacological Treatments on UI....62
The Role of Patient Characteristics on Patient Outcomes with Pharmacological Treatments....73
Question 3. How Effective is the Nonpharmacological Treatment of UI?....86
Clinical Effects of Bladder Training....86
Clinical Effects of Pelvic Floor Muscle Training (PFMT)....86
Clinical Effects of PFMT Combined with Bladder Training....87
Clinical Effects of PFMT with Biofeedback Using Vaginal Electromyography (EMG) Probe....87
Clinical Effects of Electrical Stimulation....88
Clinical Effects of Percutaneous Tibial Nerve Stimulation....88
Clinical Effects of Continence Services that were Implemented by Specialized Health Care Providers....89
Clinical Effects of Behavioral Modification Program....90
Clinical Effects of Magnetic Stimulation....90
Clinical Effects of Medical Devices....91
Clinical Effects of Weight Loss....91
Clinical Outcomes of Soy-Enriched Diet....92
Clinical Effects of Acupuncture....92
Clinical Effects of Bulking Agents....92
Comparative Effectiveness of Nonpharmacological Treatments....93
Comparative Effectiveness of Continence Services....93
Comparative Effectiveness of Group Versus Individual Physiotherapy Sessions....93
Comparative Effectiveness of Behavioral Weight Loss and Education....94
Comparative Effectiveness of Bladder Training....94
Comparative Effectiveness of Supervised PFMT Combined with Bladder Training and Self-Administered PFMT....94
Comparative Effectiveness of PFMT with and without Biofeedback Using Vaginal EMG Probe....95
Comparative Effectiveness of PFMT and Electrical Stimulation....95
Comparative Effectiveness of PFMT Combined with Electrical Stimulation Versus PFMT....95
Comparative Effectiveness of PFMT and Medical Devices....95
Comparative Effectiveness of Circular Muscle Exercises and PFMT....96
Comparative Effectiveness of Interventions to Increase Adherence to PFMT....96
Comparative Effectiveness of PFMT in Different Positions....96
Comparative Effectiveness of Physiotherapeutic Methods....96
Comparative Effectiveness of Medical Devices....97

Comparative Effectiveness of Bulking Agents 97
Indirect Evidence of Comparative Effectiveness of Nonpharmacological Treatments 97
Comparative Effectiveness of Nonpharmacological Treatments when Compared to Drugs or Combined Modalities 98

Chapter 4. Discussion 109
Key Findings and Recommendations 109
UI Diagnosis 110
UI Treatment 111
Future Research 112

References and Included Studies 119

List of Acronyms/Abbreviations 147

Tables

Table 1 Definitions of urinary incontinence and treatment outcomes 4
Table 2 Overall ranking of evidence 10
Table 3 Diagnostic value of the test for UI in women (pooled with random effects models and bivariate pooling) 21
Table 4 Predictive value of diagnostic tests for different types of UI in age subgroups 31
Table 5 Diagnostic tools to assess clinical importance and monitor effectiveness of treatments of UI 32
Table 6 Clinical outcomes with duloxetine treatments 49
Table 7 Clinical outcomes with pharmacological interventions compared to placebo 51
Table 8 Rates of clinical outcomes after drugs vs. placebo (significant differences only shown) 56
Table 9 Discontinuation due to adverse effects with pharmacological treatments for UI 64
Table 10 Continence with pharmacological treatments for UI 65
Table 11 Continence with 60mg once daily of trospium vs. placebo in obese and nonobese adults with overactive bladder (pooled results from RCTs using the WHO criteria for obesity) 85
Table 12 Continence with nonpharmacological treatments compared to no active treatment 101
Table 13 Severity of incontinence and quality of life with nonpharmacological treatments compared to no active treatment 102
Table 14 Comparative effectiveness of nonpharmacological treatments on continence (insufficient evidence) 103
Table 15 Continence rates compared between nonpharmacological treatments 105
Table 16 Continence with pharmacological treatments compared to nonpharmacological treatments or combined modalities 107
Table 17 Conclusions about diagnosis of UI in women 113
Table 18 Conclusions about management of UI in women 114
Table 19 Future research recommendations 117

Figures

Figure 1 Study flow 13
Figure 2 Accuracy of diagnostic methods for female UI (pooled with random effects model results) 29
Figure 3 Diagnostic odds ratio of diagnostic methods for female UI (pooled with random effects model results)....30
Figure 4 Comparative effectiveness of oxybutynin vs. tolterodine (pooled results from individual RCTs) 66
Figure 5 Continence with drugs for overactive bladder when compared to placebo (pooled results from RCTs)....67
Figure 6 Continence rates (%) with drugs vs. placebo (pooled results from RCTs) 68
Figure 7 Discontinuation of treatments due to adverse effects (%) with drugs vs. placebo (pooled results from RCTs)....69
Figure 8 Dry mouth rates (%) with drugs vs. placebo (pooled results from RCTs)....70
Figure 9 Rates (%) of the most common (>10%) adverse effects with drugs vs. placebo (pooled results from RCTs)....71
Figure 10 Treatment persistence of the drugs for UI....72
Figure 11 Clinical outcomes with duloxetine vs. placebo in age subgroups (pooled analysis of individual data from four RCTs)....76
Figure 12 Urinary continence with solifenacin when compared to placebo (pooled analysis of individual patient data from four RCTs)....77
Figure 13 Clinical outcomes with tolterodine vs. placebo in age subgroups (individual RCTs) 78
Figure 14 Clinical outcomes with duloxetine in racial subgroups of women with stress UI, DESIRE (Duloxetine Efficacy and Safety for Incontinence in Racial and Ethnic populations)....79
Figure 15 Continence with solifenacin compared to placebo in patients with mixed or pure urgency UI (pooled analyses of individual patient data)....80
Figure 16 Complete continence with tolterodine, extended release of 4 mg/day vs. placebo in groups with different baseline frequency UI episodes/week 81
Figure 17 Adverse effects of fesoterodine compared to placebo in subgroups with different baseline frequency of urgency UI (pooled analysis of four RCTs)....82
Figure 18 Continence with solifenacin vs. placebo in subgroup by response to the previous treatment with antimuscarinic medications (pooled analysis of RCT) 83
Figure 19 Patient Global Impression of Improvement rating as “better” with duloxetine when compared to placebo in subgroups with different comorbidity status (Duloxetine Urinary Incontinence Study Group)....84
Figure 20 Continence with nonpharmacological treatments for UI when compared to no active treatment (pooled results from RCTs) 106

Appendixes

Appendix A Search Strings
Appendix B List of Excluded Studies
Appendix C Technical Expert Panel Members and Affiliations
Appendix D Analytical Framework
Appendix E Abstraction Forms
Appendix F Evidence Tables

Effective Health Care

Diagnosis and Comparative Effectiveness of Treatments for Urinary Incontinence in Adult Women

Executive Summary

Effective Health Care Program

The Effective Health Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders including consumers.

The full report and this summary are available at www.effectivehealthcare.ahrq.gov. Ahrq.gov/reports/final.cfm

Background

Urinary incontinence is the involuntary loss of urine that reflects a failure to inhibit urination.[1] Urinary incontinence (UI) affects a significant number of adult women across age groups.[1] Observational studies demonstrated that about 25 percent of young women,[2] 44 to 57 percent of middle-aged and post-menopausal women,[3,4] and about 75 percent of elderly women in nursing homes[5] experience some degree of involuntary urine loss. The effects of UI can be serious, affecting women's physical, psychological, and social wellbeing, and imposing potentially significant lifestyle restrictions. UI's impact on an individual may range from slightly bothersome to debilitating.

Overall, urinary incontinence casts a broad shadow. The cost of incontinence care in the United States averaged $19.5 billion in 2004.[6] Six percent of nursing home admissions of older women are attributable to UI,[6] and by one estimate the annualized cost of women's nursing home admissions due to UI was $3 billion.[7,8]

Voluntary voiding requires a balance between sphincter activity and bladder function. Incontinence can result from a variety of circumstances. It can be caused by loss of inhibition associated with dementia.[1,9] It can result from mobility problems that make it hard to reach a toilet in a timely way.[1,9] Pelvic floor trauma after vaginal delivery, pelvic organ prolapse, or urinary tract infections can also lead to UI in women.[1,9] Assessments of women complaining of UI begin with exclusion of pelvic organ prolapse, urinary tract infection, and UI associated with poor bladder emptying,[10] conditions beyond the scope of this review. This review focuses specifically on the problems associated with sphincter function and bladder overactivity in women.

Incontinence is divided into two types: stress and urgency. Stress incontinence is associated with impaired sphincter function and results in an inability to retain urine when bladder pressure (or intra-abdominal pressure) is raised, as in coughing or sneezing.[11] Urgency incontinence is associated with the muscle in the wall of the bladder (detrusor muscle), and can be defined as involuntary loss of urine associated with the sensation of a sudden, compelling urge to void that is difficult to defer.[11] Mixed UI is the term applied when both stress and urgency UI are present. These definitions reflect the consensus definitions developed by the International Urogynecological Association (IUGA)/International Continence Society (ICS).[11]

Clinicians and researchers seek to distinguish between types of UI because attendant risk factors and recommended treatments may differ.[12-14] Stress UI is more common in younger women in association with pelvic floor trauma and uterine prolapse conditions that are often related to vaginal delivery and may require surgical treatments.[9] Urgency and mixed UI are more common in elderly women in association with overactive bladders with or without sphincter dysfunction.[1,9]

Although diagnosis of UI can be made based on patients' reports of involuntary urine leakage,[9] researchers have also proposed instrumental methods for objective diagnosis of different UI types. One method includes filling cystometry during urodynamic investigation or ultrasound examination (Table ES1). With this method, the bladder is filled with sterile water through a catheter until the first urge to urinate occurs (first sensation to void), and then to maximal bladder capacity. This test measures the amount of water a woman can hold in the bladder before involuntary urination and urine leakage occurs during a stress cough test.[11] Urodynamic evaluation may help to distinguish pure stress UI without urgency UI for women undergoing surgery for stress UI.[11] Diagnostic studies use multichannel urodynamics as a reference standard test to compare with noninvasive tests. However, no consensus exists among researchers on whether urodynamic examination represents the gold standard for UI diagnosis.[12-14] Previously published systematic reviews reported a weak association between urodynamic test results and self-reported symptoms,[15,16] but these reviews did not focus on the most appropriate methods to distinguish different types of UI in primary care clinical settings.[17-20] The role of invasive diagnostic methods in predicting better treatment outcomes for UI remains unclear.

Standard UI treatments for women include lifestyle changes, pelvic floor muscle training, and surgical treatments for stress UI.[1] In addition, several drugs have been approved for adults with overactive bladder with or without urgency UI.[1] Clinical interventions to reduce the frequency of UI episodes in women have been extensively reviewed in recent years,[10,21-51] but without emphasis on continence and women's perceptions of treatment success and satisfaction. Continence, meaning the complete alleviation of involuntary urine leakage, is the most important and most clearly and consistently defined clinical outcome of UI treatment; however, continence rarely is examined as a primary outcome in syntheses of evidence.[52]

In contrast with continence, commonly used definitions of UI improvement varied across studies, and included different degrees of change in frequency and severity of symptoms.[53] While definitions of continence are similar, improvement in UI has been judged by researchers and women very differently. Physicians have defined improvement as a decrease in the amount of lost urine during pad tests, or any statistically significant decrease in frequency of UI episodes.[53] Women have defined improvement according to reduced lifestyle restrictions or improved overall perception of bladder conditions. Measurement of treatment outcomes should be patient-centered and based on factors important to women, rather than on the results of invasive tests.[54] Thus, treatment success and failure should be evaluated according to what

women report in validated questionnaires or scales. However, meaningful differences in questionnaires or scales have not been systematically reviewed. Ultimately, discussions of UI are complicated by the wide variety of measures used to describe the problem and its treatment outcomes (Table ES1 summarizes these terms). Thus, we focus on continence as the primary outcome for this comparative effectiveness review.

Comparative effectiveness reviews attempt to provide actionable information about which treatments are the most effective.[55,56] However, published evidence of aggregate treatment effects may not be applicable for individuals with specific characteristics.[57] Individualized high-quality care for women with UI should consider evidence of treatment effects in homogeneous patient subpopulations. Yet, few existing studies examine homogeneous groups.[58] An average treatment effect in a clinically diverse population may not reflect the actual effect for a specific group.[59,60] The role of clinical predictors of treatment failure and success in patient subpopulations with UI has not been systematically evaluated. The comparative effectiveness of different UI treatments, including pharmacological therapies and their effects on patient morbidity[61] and quality of life,[62] were beyond the scope of previously published evidence-based reports.[63] In addition, previously published reports did not include pharmacological treatments for urgency UI, and did not focus on adult women.[9,23]

Comprehensive and up-to-date reviews of treatment options for women with UI are necessary in order to develop evidence-based guidelines and recommendations for patients, clinicians, and policymakers.[64-67]

This report aims to synthesize published evidence about diagnosis and management of UI in adult women. We focused on adult women in primary care settings and on nonpharmacological treatments and pharmacological agents available in the United States.

Objectives

We present a comprehensive synthesis of evidence regarding valid methods to diagnose UI in adult women and monitor treatment benefits and harms. We evaluated clinical efficacy and comparative effectiveness of pharmacological and nonsurgical treatments for UI in adult women following the principles from the Methods Guide for Comparative Effectiveness Reviews.[68,69] For this report we examined the following questions:

Key Question 1: What constitutes an adequate diagnostic evaluation for women in the primary care setting on which to base treatment of urinary incontinence (UI)?

1. What are the diagnostic values of different methods—questionnaires, checklists, scales, self-reports of UI during a clinical examination, pad tests, and ultrasound—when compared with multichannel urodynamics?
2. What are the diagnostic values of different methods—questionnaires, checklists and scales, self-reports of UI during a clinical examination, pad tests, and ultrasound—when compared with a bladder diary?
3. What are the diagnostic values of the methods listed above for different types of UI, including stress, urgency, and mixed incontinence?
4. What is the association between patient outcomes (continence, severity, and frequency of UI; quality of life) and UI diagnostic methods?

Key Question 2: How effective is the pharmacologic treatment of UI in women?

1. How do pharmacologic treatments affect continence, severity and frequency of UI, and quality of life when compared with no active treatment or to combined treatment modalities?
2. What is the comparative effectiveness of pharmacologic treatments when compared with each other or with nonpharmacologic treatments of UI?
3. What are the harms from pharmacologic treatments when compared with no active treatment?
4. What are the harms from pharmacologic treatments when compared with each other or nonpharmacologic treatments of UI?
5. Which patient characteristics, including age, type of UI, severity of UI, the baseline disease that effects UI, adherence to treatment recommendations, and comorbidities can modify the effects of the pharmacologic treatments on patient outcomes, including continence, quality of life, and harms?

Key Question 3: How effective is the nonpharmacologic treatment of UI in women?

1. How do nonpharmacologic treatments affect incontinence, UI severity and frequency, and quality of life when compared with no active treatment?
2. How do combined modalities of nonpharmacological treatments with drugs affect incontinence, UI severity and frequency, and quality of life when compared with no active treatment or with monotherapy?
3. What is the comparative effectiveness of nonpharmacologic treatments when compared with each other?
4. What are the harms from nonpharmacologic treatments when compared with no active treatment?
5. What are the harms from nonpharmacologic treatments when compared with each other?
6. Which patient characteristics including age, type of UI, severity of UI, the baseline disease that effects UI, adherence to treatment recommendations, and comorbidities can modify the effects of the nonpharmacologic treatments on patient outcomes, including continence, quality of life, and harms?

Methods

Input from stakeholders.[68-70] We developed research questions and an analytic framework (Figure ES1) after discussions with key informants and technical experts. Research questions for the systematic review were posted for public comment.

Candidates to serve as key informants, technical experts, and peer reviewers were approved by the Task Order Officer from the Agency for Healthcare Research and Quality (AHRQ) after disclosure of conflicts of interest. The protocol was developed with input from the Technical Expert Panel.

Data sources and selection. We sought studies from MEDLINE® via OVID and via PubMed®, the Cochrane Library, SCIRUS, Google Scholar, and manual searches of reference lists from systematic reviews. We repeated the literature search to identify studies published in English from 1990 until December 30, 2010.

Study Selection. Three investigators independently determined eligibility of the studies.[71] For Key Question 1 we included studies that evaluated different methods to diagnose UI in women that are applicable for primary care settings.[72]

For Key Questions 2 and 3 we included RCTs that combined men and women if they reported outcomes in women separately or included more than 75 percent women. We excluded studies of men, children, or residents of long-term care facilities. We excluded studies of surgical treatments for UI or urogenital prolapse and studies of drugs not approved by the FDA.

We analyzed harms regardless of how authors perceived the causality of treatments.[73]

Data extraction. Evaluations of the studies, data extraction, and quality control were conducted by four researchers using a standardized form.[71] We abstracted minimum data sets for diagnostic and therapeutic studies.[71] We abstracted inclusion of minorities, inclusion of women who failed prior therapy for UI, inclusion of mixed UI, baseline daily UI, and presence of urogenital prolapse or hysterectomy in women who participated in the studies.

Quality assessment. We evaluated the quality of studies[72] and classified them by design. We evaluated studies for question 1 with predefined criteria for assessing quality of the diagnostic accuracy studies.[74-79] We evaluated quality of therapeutic studies using predefined criteria to assess risk of bias that included randomization, adequacy of randomization and allocation concealment, masking of the treatment status, intention to treat principles, and justification of the sample size.[71]

Applicability of the population was estimated by evaluating the selection of women in observational studies and clinical trials.[80] We examined settings of the studies, including primary care or specialized clinics, recruitment in the clinical settings or in the community, inclusion age and type of UI, and exclusion criteria for each study.

Data synthesis and analysis. For Key Question 1 results of individual studies were summarized to analyze sensitivity, specificity, predictive values, diagnostic odds ratios, and predictive likelihood ratios for correct diagnosis of any, stress, and urgency UI. We focus on predictive likelihood ratios of UI in women examined with index tests when compared to urodynamic or clinical diagnosis.[81-84] We pooled diagnostic test data with random effects models using Meta-Analyst software.[85] In cases of heterogeneity we used bivariate pooling methods.[84,86,87]

For Key Questions 2 and 3 we calculated relative risk, absolute risk differences, number needed to treat, and the number of attributable events per 1,000 treated for binary outcomes.[88,89]

Meta-analysis was conducted when interventions and outcomes were deemed sufficiently similar.[90 85,91] We chose the random effects model to incorporate in the pooled analysis differences across trials in patient populations, baseline rates of the outcomes, dosage of drugs, and other factors.[92] We examined consistency in results across studies with Chi square tests and I square statistics.[93,94] Using a standard preplanned algorithm, we explored heterogeneity with meta-regression, subgroup, and sensitivity analysis by clinical diversity treatment dose and duration, and quality criteria of individual studies.[92,95,96] We calculated Bayesian odds ratios[85] with 95 percent credible intervals. All calculations were performed using Meta-Analyst[85] and STATA (Statistics/Data analysis, 10.1) software at 95 percent confidence limits.[85,88]

We assessed strength of evidence and judged it according to the domains of risk of bias, consistency, directness, and precision for each major outcome.[97] We defined insufficient evidence when a single study examined treatment effects or associations.

Results

We identified and retrieved 5,038 references. We included 878 references for this review (Figure ES2).

Diagnosis of UI. For Key Question 1 we identified 99 studies of 81,060 subjects that provided information on different methods for diagnosing UI.[3,98-194] Methodology of urodynamic testing as a reference standard test was very similar across the studies. Diagnostic methods to establish a clinical diagnosis of UI were described with different levels of detail and included patient history, physical and pelvic examination, urine culture, and other instrumental measures.[137,175,182]

The majority of studies demonstrated minimal or small diagnostic value of the tests to distinguish women with urodynamic stress or urgency UI (Tables ES2 and ES3). Diagnostic values were similar after random effects versus bivariate pooling methods. Quality of the studies did not contribute to statistical heterogeneity.

Measuring Treatment Success. Urodynamic evaluation that was used as a reference method in many diagnostic studies detects a presence of UI but not frequency and severity of UI episodes. Doctors, however, need information about frequency and severity of UI to start treatment and judge treatment effectiveness. Validated tools to measure UI treatment success based on meaningful changes in symptoms and quality of life for women include the Incontinence Severity Index,[195,196] Patient Global Impression of Improvement and of Severity,[197] Patient Perception of Bladder Condition,[198-200] Urogenital Distress Inventory,[136,201-203] Bladder Self-Assessment Questionnaire,[204] International Consultation on Incontinence Modular Questionnaire-SF,[205] Incontinence Impact Questionnaire,[136,201-203,206] Urinary Incontinence-Specific Quality of Life Instrument,[207-214] King's Health Questionnaire,[215-219] and Protection, Amount, Frequency, Adjustment, Body Image.[220-222]

A reduction in UI episode frequency assessed with a 3-7 day diary was the most common primary outcome in the included randomized controlled trials (RCTs). Importantly, women with daily UI perceived treatment benefit and improved quality of life only when they experienced a greater than 70 percent reduction in urinary episode frequency assessed by a voiding dairy; women considered this outcome a clinical success.[213] Smaller decreases of 20-40 percent in UI episode frequency were not clinically important when the results from a voiding diary were analyzed in association with the validated Incontinence Quality of Life (I-QOL) questionnaire (Table ES4).[213]

The few studies that analyzed differences in outcomes depending on baseline urodynamic diagnosis versus self-reported symptoms suggested no advantage with urodynamic diagnosis.[223-226] However, baseline urodynamic evaluation resulted in better benefits with surgery for stress UI.[227]

Evidence was insufficient for the association between baseline urodynamics evaluation and nonsurgical treatment outcomes. Women's perceptions of treatment success depend upon clinically important differences in voiding diaries, scales, questionnaires, and women's impressions of global improvement.

Effectiveness of pharmacological treatments. We synthesized the evidence of efficacy and comparative effectiveness of the drugs for predominantly stress UI (including topical estrogen and serotonin-noradrenalin uptake inhibitors) and drugs for overactive bladder.[10] The summary table (Table ES5) demonstrates how many studies examined each outcome, how many subjects participated in the studies, and what percentage of subjects experienced the outcomes. The last column indicates our level of confidence that the evidence reflects the true effect of the treatment and that future research is unlikely to change the estimate of effect (Table ES5). Drugs were more effective than placebo in achieving continence and improving UI, but magnitude of effect was low. Absolute risk difference in continence was less than 20 percent for all drugs.

Pharmacological treatments resulted in fewer than 200 cases of continence attributable to the drugs per 1,000 treated. Summary of evidence of effectiveness of all treatments including strength of evidence is found in Table ES4 and Appendix Table F1.

*Estrogen***.** Individual RCTs indicated greater continence and improvement in UI with vaginal estrogen formulations and worsening of UI with transdermal patches.

*Duloxetine***.** Duloxetine did not resolve stress UI when compared to placebo[166,212,224,228-249] (Table ES5). Risk of adverse effects was significantly higher with duloxetine than with placebo. Duloxetine resulted in improved UI in 75-140 women per 1,000 treated,[212,224,230,231,243,244,248] while 105 women per 1,000 treated stopped taking duloxetine because of adverse effects.

Oxybutynin. Oxybutynin increased continence and improved UI more often than placebo, but also resulted in treatment discontinuation due to adverse effects.[250-285] Oxybutynin resulted in resolved UI in 110 women per 1,000 treated, while 50 women per 1,000 discontinued oxybutynin because of adverse effects.

Tolterodine. Tolterodine increased continence and significantly improved UI more often than placebo.[29,226,286-319] Tolterodine resolved UI in 85 women per 1,000 treated, while 79 women per 1,000 treated experienced adverse effects. Discontinuation of treatment due to adverse effects did not differ between tolterodine and placebo.

Darifenacin. Darifenacin significantly improved urgency UI and several domains of quality of life more often than placebo.[320-333] Darifenacin improved UI in 112 women per 1,000 treated, while 173 women per 1,000 treated experienced adverse effects. Treatment discontinuation rates due to adverse effects did not differ between darifenacin and placebo.

Solifenacin. Solifenacin increased continence, with greater benefits with higher doses of the drug.[334-345] Treatment discontinuation due to adverse effects was more common with solifenacin than with placebo. Solifenacin resolved UI in 107 women per 1,000 treated, while 12 women per 1,000 discontinued treatment because of adverse effects.

Fesoterodine. Fesoterodine increased continence.[30,300,302,308,311,346-353] Significant improvement in UI with fesoterodine compared to placebo was dose responsive. Fesoterodine resulted in higher rates of adverse effects and discontinuation of treatment due to adverse effects than placebo. Fesoterodine resolved UI in 130 women per 1,000 treated, while 32 women per 1,000 stopped treatment due to adverse effects.

Trospium. Trospium increased continence more often than placebo.[354-364] Risk of adverse effects was greater with trospium than with placebo. Trospium resolved UI in 114 women per 1,000 treated, while 17 women per 1,000 stopped treatment due to adverse effects.

Comparative effectiveness of pharmacological treatments. Evidence of comparative effectiveness of different drugs was insufficient for the majority of comparisons. Oxybutynin and tolterodine had the same benefits, but tolterodine was safer. [29,253,256,263,289,359,365-373]

Numbers needed to treat (NNT) to achieve continence in one woman were similar across different drugs. Treatment discontinuation due to adverse effects was greater with all drugs, excluding darifenacin and tolterodine, than with placebo. NNT was highest with solifenacin (NNT=83) and lowest with oxybutynin (NNT= 22). Several retrospective observational studies analyzed long-term comparative effectiveness and safety of pharmacological treatments for UI. The evidence-based cost utility analysis reported that more than half of patients stop taking drugs for UI after 1 year of treatment. The lowest rates of treatment discontinuation were with 5 mg of solifenacin.[374]

Role of patient characteristics on outcomes. Treatment response was similar across age groups. Duloxetine was no better than a placebo in improving UI in elderly women.[240] Solifenacin increased continence more often than placebo regardless of age.[343]

Only one study examined clinical outcomes in different race groups treated with duloxetine.[228] Evidence was inconclusive about racial differences in treatment effects of duloxetine in women with stress UI.

Studies found no differences in outcomes between tolterodine[312] and solifenacin[343,344] in subjects with baseline mixed or pure urgency UI. Subjects with mixed UI may require a larger dose and longer treatment to achieve clinical benefits from solifenacin.[344,345] Overall, evidence was not sufficient to conclude differences in benefits between the types of UI.

Baseline frequency of UI did not dramatically modify the effects of the drugs on clinical outcomes.[310,343,353] Subjects with more frequent UI had slightly greater benefits with solifenacin[343] or fesoterodine[353] than with placebo.[343] In contrast, trospium was better than placebo at resolving UI only in subjects with less than 5 UI episodes/day.[375] Trospium did not resolve UI in subgroups with more than 5 episodes of UI/day (relative risk [RR] 1.2, 95 percent confidence interval [CI] 0.93; 1.56).[375]

One RCT examined the role of comorbidities.[240] Duloxetine was no better than placebo in women with depression, diabetes, and chronic lung diseases.[240] Trospium was effective in resolving UI regardless of body mass index in obese and normal weight women.[375]

Effectiveness of nonpharmacological treatments. Nonpharmacological treatments were generally better than no active treatment in achieving continence and improving UI according to 148 RCTs (Table ES5). Magnitude of effect was larger than that with pharmacological treatment. The majority of the studies included women with mixed UI. We examined the effects of the interventions on predominant stress or urgency UI when reported by the authors. A summary of the evidence of effectiveness of all treatments, including strength of evidence, is found in Table ES4.

Bladder training. Bladder training improved UI when compared to usual care.[376-378]

Pelvic floor muscle training. Pelvic floor muscle training (PFMT) increased continence rates and improvement in UI more often than usual care.[379-389] PFMT combined with bladder training increased continence and improved UI.[390-395] PFMT with biofeedback improved UI.[381,382,385,396]

Intravaginal electric stimulation. Intravaginal electrical stimulation increased continence and improved UI more often than sham stimulation.[383,397-404] Evidence was insufficient to conclude positive effects from percutaneous tibial nerve stimulation.[405,406] Magnetic stimulation improved UI, but did not increase continence more than sham stimulation.[407-411]

Specialized continence services. With regard to continence services implemented by specialized health care providers, studies indicated no consistently greater benefits for continence or improvement of UI than the benefits of usual care.[412-415] Comparison across studies was difficult because of the variety of interventions that constituted complex continence services.

Weight loss. Weight loss and exercise resulted in some improvement in obese women with UI.[416-418]

Vaginal cones. Evidence was insufficient to draw valid conclusions. Uncontrolled studies of other intravaginal and intraurethral devices demonstrated improvement in UI but also resulted in high discontinuation rates and adverse effects.

Comparative effectiveness of nonpharmacological treatments. Clinical outcomes of one nonpharmacological treatment versus another were reported in 54 RCTs. These trials rarely

examined the same active and control arms on the same outcomes, which decreased the level of evidence to low or insufficient.

No differences were seen in UI between supervised PFMT combined with bladder training and self-administered PFMT.[419-422] Continence did not differ between bladder training combined with PFMT versus bladder training alone.

Indirect comparison indicated comparable effectiveness of nonpharmacological treatments on continence. Cases of continence achieved per 1,000 treated were 299 for PFMT, 162 for electrical stimulation, and 166 for PFMT combined with bladder training. Rates of continence were comparable with different treatments: 38 percent of women became continent with PFMT, 23 percent became continent with electrical stimulation, and 21 percent became continent with PFMT combined with bladder training.

Summarizing the evidence, self-reported symptoms of UI have a low diagnostic value when compared to urodynamic diagnosis of stress UI or detrusor overactivity. Evidence was insufficient to conclude differences in outcomes after nonsurgical treatments in association with baseline urodynamic diagnosis of UI. Urodynamic examination was associated with clinical benefits only in women undergoing surgical treatments for stress UI or invasive treatments for urgency UI. Clinical history, a voiding diary to assess predominant stress or urgency UI, and cough tests serve to diagnose predominant stress or urgency UI in women in primary care settings. Validated tools of frequency, severity, and bothersomeness of UI provide information for decisions to start treatments. Women defined treatment success by a 70 percent or greater reduction in frequency of UI episodes according to voiding diaries. Differences in quality of life of importance to women, as measured by validated scales, are available to judge treatment effectiveness.

Women with predominant stress UI can achieve continence with PFMT. Women with predominant urgency UI can achieve continence performing PFMT with bladder training and/or electrical stimulation. Weight loss may improve UI in obese women. Local estrogen formulations may improve UI in postmenopausal women. Duloxetine showed an unfavorable balance between UI improvement and adverse affects. Women with predominant urgency UI who failed nonpharmacological treatments may achieve continence taking antimuscarinic drugs including trospium, solifenacin, fesoterodine, tolterodine, or oxybutynin. Drugs demonstrated comparable effectiveness, but treatment discontinuation due to adverse effects was most common with oxybutynin and least common with solifenacin. Dry mouth, constipation, and blurred vision are among the most frequent adverse effects. Evidence of long-term safety of pharmacological treatments is insufficient.

Discussion

According to our report and previous reviews: (1) Diagnosis of predominant stress or urgency UI in primary care setting can be based on clinical history, voiding diary, stress cough test, and validated scales.[15,423] (2) Multichannel urodynamics was not associated with better outcomes after nonsurgical treatments and was useful only for women who underwent invasive treatments for UI.[227] (3) Outcome assessment of treatments for female UI must address issues of importance for women: continence, 70 percent or more reduction in UI episode frequency, meaningful changes in scales measuring quality of life, and treatment satisfaction.[424] Our findings are in agreement with previously published systematic reviews of diagnosis and treatment of UI by AHRQ,[21,22] the Cochrane Collaborative Group,[23,25-28,31-35,37-50,425-428] and the International Consultation on Incontinence (ICI).[1,51]

Previous reviews of drugs for overactive bladder analyzed reduction in frequency of UI episodes and frequency of micturitions.[52,429,430] The majority of drug RCTs were designed to test differences in frequency of UI episodes. Medical and statistical reviews by the FDA also focused on reduction in frequency of UI.[264,326,327,360,361,431,432] Based on women's definition of clinical success requiring a 70 percent or greater reduction in frequency of UI episodes, we focused on clinical outcomes, including continence and quality of life. Policymakers should consider patient-centered outcomes when making regulatory decisions.

Drugs examined for UI treatment demonstrated similar efficacy. All drugs resulted in continence and improved UI without substantial differences in benefits. Clinical decisions may be made based on comparative drug safety. Long-term comparative safety was rarely available in RCTs. Routine clinical practice should integrate continuous monitoring of adverse effects of the drugs, providing a source of information about long-term comparative drug safety. For example, continuous prescription-event monitoring as a part of postmarketing surveillance provided valuable information about unfavorable long-term effects of tolterodine, which showed significantly higher risk of hallucinations than ten drugs of other therapeutic classes.[433] Postmarketing surveillance may address long-term safety of UI drugs when combined with other medications for comorbidities, while the role of concurrent treatments was not examined in RCTs. For instance, relative risks of ventricular arrhythmias (adjusted RR or sudden death 5.5, 95 percent CI 1.3; 22.3) or sudden death (adjusted RR or sudden death 21.5, 95 percent CI 5.2; 88.3) were very high among older people using medications for UI in combination with antihistamine/cytochrome inhibitors.[434] Very few studies provided evidence for individualized treatment decisions. Patient comorbidity and baseline severity of UI were associated in differences in treatment benefits. The direction and magnitude of the association differed; benefits from solifenacin and fesoterodine were greater in those with more than two or three daily episodes of UI, while trospium was not better than placebo in those with frequent baseline UI (>5 episodes/day). Which factors are associated with differences in harms remain unclear.

Adherence to UI treatments is an issue of concern. Yet very few studies addressed adherence to treatment, pharmacological or nonpharmacological. Observational economic evaluations[435-437] demonstrated greater absolute rates of treatment discontinuation due to adverse effects or treatment failure than 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.[436] Comparative effectiveness, safety, and adherence to treatments that should be incorporated into cost-effectiveness analyses[435,438-441] were beyond the scope of our review. Future research should address which factors might increase adherence to UI treatments.

All nonpharmacological treatments examined resulted in similar continence rates. However, benefits and safety of nonpharmacological treatments were considerably better than those of drug treatments. Differences in definitions of improvement in UI, quality of life, and treatment related adverse effects hampered synthesis of evidence. Valid conclusions about treatment effectiveness and harms from all studies were possible when the studies used similar definitions of the outcomes.

Our review has limitations. We restricted our review to English language studies published in journals, presented at scientific meetings, reviewed by the FDA,[442] or reported on the ClinicalTrials.gov Web site. Even after such an exhaustive review of evidence, we do not know how many funded and unregistered studies we missed in our review.

Our report has potential implications for future research. First, future research should clarify which characteristics of women, including age, race, genitourinary characteristics, and

comorbidities, are associated with benefits and lower harms of and adherence to treatments. Second, treatment success should be assessed with outcomes centered on women, including long-term continence, reduction of 70 percent or more in UI episodes, and clinically important improvement in scales of severity and quality of life. Third, all harms should be analyzed, regardless of investigator judgment about possible association with tested treatments. Fourth, nonsurgical treatments for predominant stress UI are limited to PFMT, with very few ongoing studies of bulking agents and devices. Future research should explore new treatment options for women with stress UI. The results from all studies, including 25 closed and 124 ongoing registered studies, should be made available for future reviews of evidence. A comparison of different methods of delivery of nonpharmacological interventions—internet-based, group-based, and self-management—is also a possible area of future research, with great applicability for primary care populations. Finally, the preventive effects of PFMT, bladder training, and electrical stimulation in pre-menopausal women should be addressed in future research.

Key Findings

- Self- reported symptoms of UI have a low diagnostic value when compared to urodynamic diagnosis of stress UI or detrusor overactivity. Decisions to start treatments are based on assessment of frequency, severity, and bothersomeness of UI with validated tools.
- Evidence was insufficient to conclude differences in outcomes of nonsurgical treatments in association with baseline urodynamic diagnosis of UI. Urodynamic examination was associated with clinical benefits when performed for women undergoing surgical treatments for stress UI or invasive treatments for urgency UI.
- Women defined treatment success when treatments reduced frequency of UI episodes by 70 percent or more according to voiding diaries.
- Differences of importance to women in validated scales for quality of life are available to judge treatment effectiveness.
- Nonpharmacological treatments result in significant clinical benefit with low risk of adverse effects. Women with predominant stress UI can achieve continence performing PFMT. Continence rates are similar between those who undergo PFMT with and without biofeedback.
- Women with predominant urgency UI can achieve continence performing PFMT with bladder training and/or electrical stimulation.
- Weight loss may improve UI in obese women.
- Low-dose local estrogen formulations may improve UI in postmenopausal women.
- Duloxetine has an unfavorable balance between improvement in UI and treatment discontinuation due to adverse effects.
- Women with predominant urgency UI may achieve continence taking antimuscarinic drugs including trospium, solifenacin, fesoterodine, tolterodine, or oxybutynin. Magnitude of the effect was low for all drugs (absolute risk difference <20 percent).
- Drugs demonstrated similar effectiveness, but treatment discontinuation due to adverse effects was most common with oxybutynin and least common with solifenacin.
- Dry mouth, constipation, and blurred vision were among the most frequent adverse effects. Evidence of long-term safety of pharmacological treatments is insufficient.

Glossary

AHRQ	Agency for Healthcare Research and Quality
CI	Confidence interval
FDA	Food and Drug Administration
ICI	International Consultation on Incontinence
ICS	International Continence Society
I-QOL	Incontinence Quality of Life
IUGA	International Urogynecological Association
NNT	Number needed to treat
PFMT	Pelvic floor muscle training
RCT	Randomized controlled trial
RR	Relative risk
SRC	Scientific Resource Center
UI	Urinary incontinence

References

Please refer to the reference list in the full report for documentation of statements contained in the Executive Summary.

Table ES1. Definitions of urinary incontinence and treatment outcomes[11]

Outcomes	Definition
Symptoms of urinary incontinence[443]	Complaint of involuntary loss of urine.
Signs of urinary incontinence	Observation of involuntary loss of urine on examination; may be urethral or extraurethral
Transient urinary incontinence[444,445]	Potentially reversible incontinence resulting from conditions that may resolve if the underlying cause is managed: delirium/confusional state; urinary tract infection (symptomatic); atrophic urethritis/vaginitis; use of pharmaceuticals; psychological conditions, especially depression; excessive urine output related to another medical condition (e.g., congestive heart failure, hyperglycemia); restricted mobility; stool impaction
Established urinary incontinence[444,445]	Urinary incontinence that is attributed to bladder or urethral dysfunction, such as: detrusor overactivity; detrusor underactivity; urethral obstruction; urethral incompetence
Stress urinary incontinence	Complaint of involuntary loss of urine on effort or physical exertion (or on sneezing or coughing
Pure (urodynamic) stress UI	The finding of involuntary leakage during filling cystometry, associated with increased intra-abdominal pressure (stress test), in the absence of a detrusor contraction
Urgency UI[11]	Complaint of involuntary loss of urine associated with urgency
Pure (urodynamic) detrusor overactivity	Observation of involuntary leakage from the urethra synchronous with the sensation of a sudden, compelling desire to void that is difficult to defer, involuntary detrusor muscle contractions occur during filling cystometry
UI associated with poor bladder emptying[446]	Urinary incontinence associated with: bladder over distention; a contractile detrusor; hypotonic or underactive detrusor, occurring secondarily to drugs, fecal impaction, diabetes, lower spinal cord injury, or disruption of the motor innervations of the detrusor muscle
Mixed urinary incontinence[443]	Complaint of involuntary loss of urine associated with urgency and also with effort or physical exertion or on sneezing or coughing
Predominant stress UI	Mixed urinary incontinence with predominant, more frequent symptoms of stress UI
Predominant urgency UI	Mixed urinary incontinence with predominant, more frequent symptoms of urgency UI
Postural incontinence	Complaint of involuntary loss of urine associated with change of body position, for example, rising from a seated or lying position
Continuous incontinence	Complaint of continuous involuntary loss of urine
Coital incontinence	Complaint of involuntary loss of urine with coitus. This symptom might be further divided into that occurring with penetration or intromission and that occurring at orgasm
Insensible (urinary incontinence)	Complaint of urinary incontinence where the woman has been unaware of how it occurred
Nocturnal enuresis	Complaint of involuntary urine loss which occurs during sleep
Acute incontinence[447]	Sudden onset of symptoms related to an illness, treatment, or medication
Chronic incontinence	Persistent urinary incontinence, including disorders of storage (stress and urgency) and of emptying (overflow) and functional and mixed incontinence
Severity of incontinence	Measured as incontinent episodes/unit time; pad changes/unit time; pad weight/unit time; number of micturitions/unit time; urine loss on a pad test; also indicated by urodynamically diagnosed detrusor overactivity; urodynamic stress incontinence
Outcomes to examine treatment effectiveness	
Continence	Absence of any involuntary leakage of urine Author's reports of cure, absence of incontinent episodes in bladder diaries, negative pad stress, or no abnormalities noted on urodynamics

Table ES1. Definitions of urinary incontinence and treatment outcomes{Haylen, 2010 #4534} (continued)

Outcomes	Definition
Resolved stress urinary incontinence	No involuntary urine leakage on physical exertion or effort or with sneezing or coughing
Resolved urgency urinary incontinence	No involuntary leakage accompanied by or immediately proceeded by urgency
Resolved mixed urinary incontinence	No involuntary leakage associated with urgency and also with exertion, effort, sneezing, or coughing
Improvement in incontinence	Reduction frequency and severity of incontinence episodes by >50% Reduction in pad stress test by >50% Reduction in restrictions of daily activities due to incontinence Women's perception of improvement in their bladder condition
Treatment failure	Progression of incontinence: Increase in frequency and severity of incontinence episodes Increase in restrictions of daily activities because of incontinence Continence not achieved No reduction in the frequency and severity of incontinent episodes
Discontinuation of treatment	Subject refusal to continue treatment
Discontinuation of treatment due to adverse effect	Subject refusal to continue treatment due to adverse effects or physician decision to withdraw treatment due to adverse effects
Discontinuation of treatment due to treatment failure	Subject refusal to continue treatment due to lack of efficacy
Quality of life	Subject's reports about emotional, physical, and social wellbeing
Adverse effects	Any harmful and undesired effect in treated subjects

Figure ES1. Diagnosis and comparative effectiveness of treatments for UI in adult women

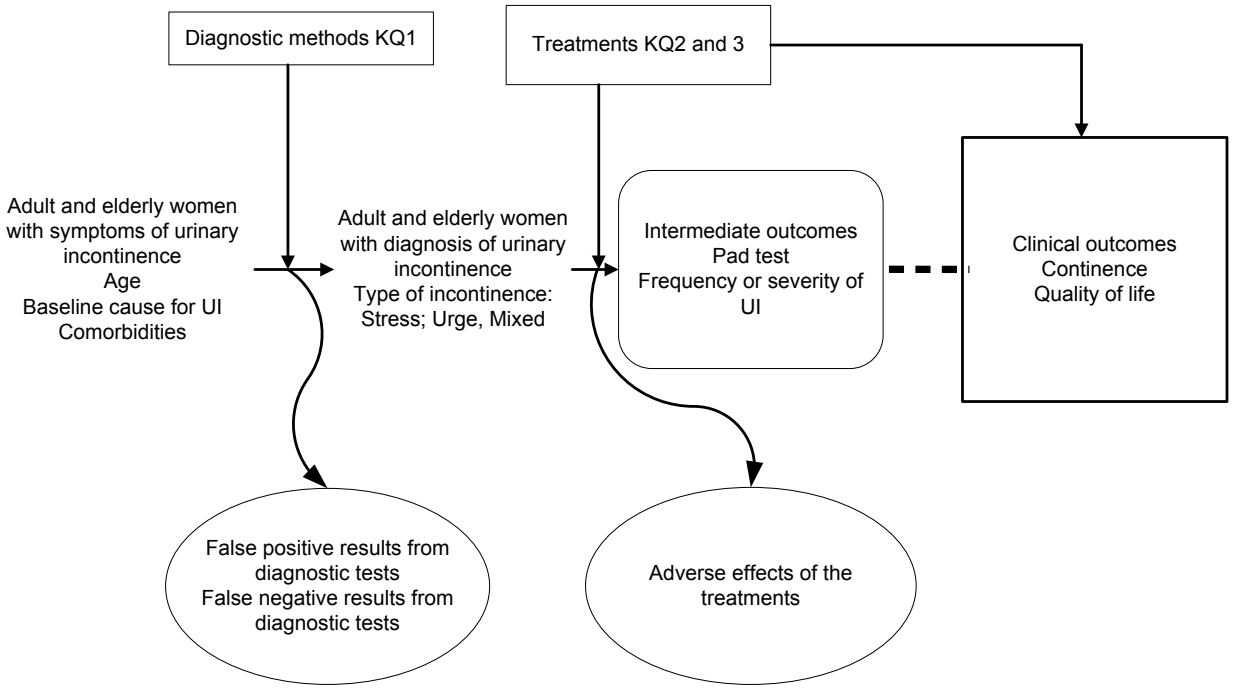


Figure ES2. Study flow

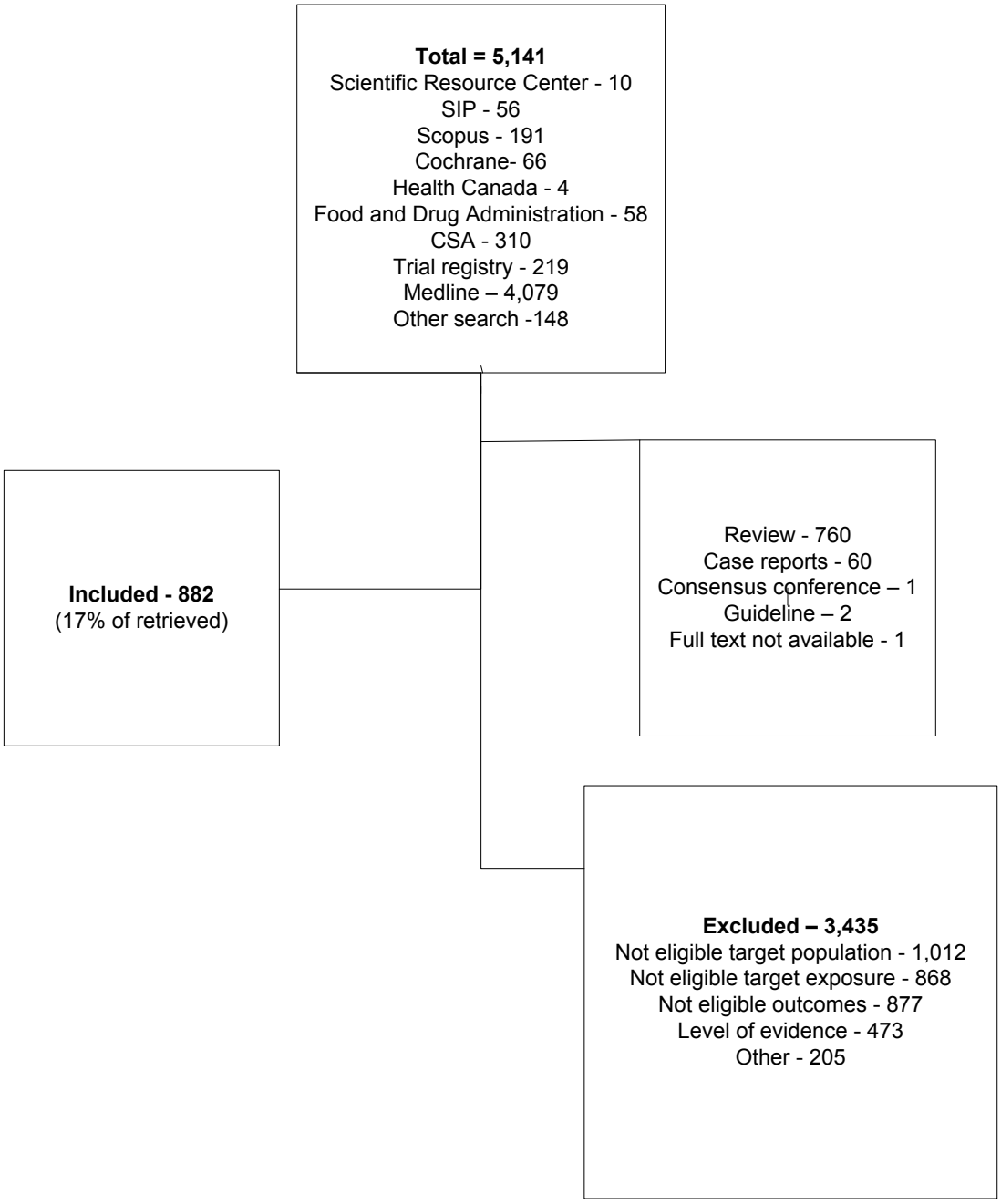


Table ES2. Diagnostic value of the test for UI in women (pooled with random effects models and bivariate pooling)

Type of Incontinence	Method Index/Standard	Number of Studies and References Number of Subjects	Sensitivity/ Bivariate Pooling	Specificity/ Bivariate Pooling	Positive Likelihood Ratio†	Negative Likelihood Ratio†	Positive Predictive Value	Negative Predictive Value
Urodynamic stress UI	Symptoms of stress UI/UD	27[100,101,103,105,107,109,112,114,115,118,119,121,125,129,133,142,143,153,160,162,167,169,189,448-451] 5,780	0.93^ (0.90, 0.95) 0.94 (0.91, 0.96)	0.41^ (0.34, 0.49) 0.41 (0.31, 0.51)	1.54 (1.40, 1.7)	0.20 (0.14, 0.27)	0.74 (0.68, 0.80)	0.74 (0.67, 0.81)
Detrusor overactivity	Symptoms of urgency UI/UD	23[100,103,107,112,114,115,118,119,121,125,128,129,131,133,142,143,153,160,162,167,189,448,449] 5,485	0.82^ (0.76, 0.87) 0.82 (0.75, 0.88)	0.51^ (0.44, 0.59) 0.52 (0.40, 0.65)	1.54 (1.38, 1.73)	0.39 (0.30, 0.50)	0.56 (0.48, 0.63)	0.80 (0.73, 0.86)
Detrusor overactivity	Symptoms of urgency/UD	9[114,118,121,125,129,131,133,143,163] 6,418	0.84^ (0.59, 0.95) 0.82 (0.70, 0.92)	0.39^ (0.17, 0.67) 0.39 (0.24, 0.55)	1.36 (1.18, 1.58)	0.47 (0.33, 0.67)	0.48 (0.39, 0.57)	0.75 (0.67, 0.81)
Detrusor overactivity*	Symptoms of urgency UI/UD	17[103,107,112,115,118,119,121,123-125,129,133,142,143,160,167,189] 3,924	0.84^ (0.78; 0.89) 0.84 (0.79, 0.90)	0.43^ (0.36; 0.50) 0.44 (0.34, 0.54)	1.48 (1.31; 1.66)	0.40 (0.29; 0.54)	0.33 (0.26; 0.41)	0.89 (0.83; 0.93)
Detrusor overactivity*	Symptoms of urgency /UD	6[118,121,125,129,133,143] 1,598	0.86 (0.83; 0.89) 0.86 (0.80, 0.90)	0.31^ (0.24; 0.39) 0.31 (0.20, 0.45)	1.21 (1.11; 1.32)	0.523 (0.41; 0.67)	0.27 (0.17; 0.40)	0.86 (0.76;0.93)
Mixed UI	Symptoms of stress and urgency UI/UD	11[103,107,111,112,115,119,142,160,162,167,189] 2,767	0.73^ (0.61, 0.82) 0.72 (0.58, 0.83)	0.53^ (0.40, 0.66) 0.53 (0.34, 0.72)	1.45 (1.27, 1.67)	0.61 (0.52, 0.71)	0.26 (0.20, 0.34)	0.89 (0.85, 0.92)
Urodynamic stress UI	Pad test/UD	3[139,187,191] 574	0.84 (0.76, 0.90) 0.83 (0.75, 0.91)	0.77 (0.72, 0.82) 0.77 (0.17, 0.97)	3.62 (2.88, 4.57)	0.22 (0.15, 0.32)	0.82 (0.77, 0.86)	0.78 (0.73, 0.83)
Detrusor overactivity	Pad test/UD	2[187,191] 469	0.72^ (0.30, 0.94)	0.56^ (0.38, 0.72)	1.56 (0.62, 3.90)	0.47 (0.10, 2.33)	0.32 (0.04, 0.83)	0.88 (0.83, 0.91)
Urodynamic stress UI	Symptoms of stress UI/clinical diagnosis	5[130,137,175,182,452] 947	0.88^ (0.68, 0.96) 0.86 (0.70, 0.96)	0.67^ (0.54, 0.78) 0.67 (0.51, 0.81)	2.35 (1.97, 2.81)	0.19 0.09, 0.41)	0.80 (0.66, 0.89)	0.75 (0.58, 0.87)

Table ES2. Diagnostic value of the test for UI in women (pooled with random effects models and bivariate pooling) (continued)

Type of Incontinence	Method Index/Standard	Number of Studies and References Number of Subjects	Sensitivity/ Bivariate Pooling	Specificity/ Bivariate Pooling	Positive Likelihood Ratio†	Negative Likelihood Ratio†	Positive Predictive Value	Negative Predictive Value
Detrusor overactivity	Symptoms of urgency UI/clinical diagnosis	4[130,137,175,182] 735	0.82^ (0.73, 0.89) 0.82 (0.73, 0.90)	0.67^ (0.53, 0.79) 0.67 (0.45, 0.86)	2.52 (1.81, 3.50)	0.26 (0.18, 0.38)	0.72 (0.48, 0.88)	0.79 (0.54, 0.92)
Mixed UI	Symptoms of stress and urgency UI/clinical diagnosis	3[137,175,182] 654	0.65^ (0.36, 0.86) 0.64 (0.38, 0.85)	0.54^ (0.21, 0.84) 0.52 (0.06, 0.94)	1.57 (0.68, 3.59)	0.74 (0.28, 1.95)	0.36 (0.27, 0.47)	0.80 (0.43, 0.96)
Urodynamic stress UI	Q-tip test/UD	3[120,453,454] 267	0.62 (0.53, 0.70) 0.62 (0.49, 0.74)	0.60^ (0.40, 0.78) 0.58 (0.00, 1.00)	1.70 (0.89, 3.23)	0.60 0.31, 1.17)	0.58 0.26, 0.85)	0.67 (0.34, 0.89)

Symptoms of stress UI, urgency, or urgency UI have minimal or small diagnostic value to identify women with pure urodynamic stress UI or detrusor overactivity.

* pure type
** not pooled because of poor reporting quality
\# 68% women and 32% men, the golden standard was not clearly defined
† Clinical interpretations of likelihood ratios[455]
^ significant heterogeneity

Likelihood Ratio	Interpretation
>10	Large and often conclusive increase in the likelihood of disease
5 - 10	Moderate increase in the likelihood of disease
2 - 5	Small increase in the likelihood of disease
1 - 2	Minimal increase in the likelihood of disease
1	No change in the likelihood of disease

Table ES3. Conclusions about diagnosis of UI in women

Conclusions	Level of Evidence
Diagnosis of UI	
Symptoms of stress UI, urgency, or urgency UI have minimal or small diagnostic value to identify women with urodynamic stress UI or detrusor overactivity.	High
Complex clinical algorithms demonstrated better diagnostic performance. Individual studies suggested a good diagnostic value of the epidemiology of prolapse and incontinence questionnaires.	Moderate
Women in primary care settings have been diagnosed with UI after obtaining clinical history, a voiding diary to assess predominant stress or urgency UI and cough stress or pad tests, and after excluding urogenital prolapse and urinary tract infections.	High
Decisions to start treatments have been based on assessment of frequency, severity, and bothersomeness of UI with validated tools.	High
Urodynamic examination was not associated with better outcomes after nonsurgical treatments for UI.	Moderate
Urodynamic examination was associated with treatment outcomes in women undergoing surgical treatments for stress UI.	
Monitoring treatment success can address differences in the voiding diary (>70 percent in frequency of UI episodes) and scales measuring quality of life that are important for women, and women's impressions of global improvement and treatment satisfaction. A variety of the validated tools are available to monitor quality of life in women with UI and with different UI types. Several tools that can define clinically important differences in scores can be used to assess treatment success in clinical settings	High

Table ES4. Conclusions about management of UI in women

Conclusions	Level of Evidence
Drug treatment for predominant stress UI	
Duloxetine was worse than placebo resolving stress UI	Low
Duloxetine improved stress UI in women.	High
Risk of adverse effects was significantly higher with duloxetine compared to placebo. Women stopped taking the drug because of nausea, somnolence, insomnia, dizziness, headache, fatigue, diarrhea, and constipation.	High
Drug treatment for predominant urgency UI	
Oxybutynin compared to placebo increased continence and improved UI.	High
Oxybutynin compared to placebo increased treatment discontinuation due to adverse effects. Dry mouth was the most common adverse effect.	High
Immediate release oxybutynin when compared to controlled release oral or transdermal oxybutynin resulted in greater rates of adverse effects and dry mouth.	Low
Higher vs. lower doses of oxybutynin resulted in greater improvement in UI, the same rates of dry mouth, but in greater treatment withdrawal.	Low
Tolterodine increased continence and improved UI when tolterodine treatments when compared to placebo.	High
Tolterodine improved quality of life in women with urgency UI.	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 due to adverse effects did not differ with tolterodine compared to placebo.	High
Darifenacin, 7.5 and 15 mg, improved urgency UI and several domains of quality of life when compared to placebo.	High
Adverse effects were more common with darifenacin than placebo. Among examined adverse effects, darifenacin increased rates of constipation, dry mouth, dyspepsia, and headache.	Moderate
Larger dose, 30 mg of darifenacin/day, did not result in better benefits but caused greater rates of adverse effects.	High
Treatment discontinuation rates because of adverse effects were the same with darifenacin vs. placebo.	High
Solifenacin increased continence with greater benefits with the larger dose of the drug in women with urgency and mixed UI.	High
Solifenacin increased risk of dry mouth, constipation, and blurred vision, 10 mg of solifenacin increased the risk of severe dry mouth and constipation.	High
Treatment discontinuation because of adverse effects was more common with solifenacin compared to placebo.	High
Fesoterodine increased continence when compared to placebo.	Low
Fesoterodine improved urgency UI with fesoterodine compared to placebo, with a better response with 8 mg versus 4 mg.	High
Fesoterodine improved quality of life in women with urgency UI.	Low
Fesoterodine treatment resulted in higher rates of adverse effects and discontinuation of the treatments because of adverse effects compared to placebo. Adverse effects were more common with 8 mg compared to 4 mg of fesoterodine.	High
Trospium increased continence when compared to placebo.	High
Women experienced dry mouth, dry eye, dry skin, and constipation more often with the drug than with placebo.	Moderate
Adverse effects resulted in treatment discontinuation more often than placebo.	High
Fesoterodine resulted in greater rates of continence when compared to tolterodine.	Low
Fesoterodine resulted in greater rates of improved UI when compared to tolterodine.	High
Fesoterodine resulted in greater treatment discontinuation due to adverse effects when compared to tolterodine.	Moderate
Oxybutynin resulted in greater treatment discontinuation due to adverse effects when compared to tolterodine.	High
Improvement in UI did not differ with oxybutynin when compared to tolterodine	Moderate
Adherence to drug treatments is low, more than 50% of women stopped treatments within one year.	Moderate
Role of characteristics in women in association with treatment effects	
Age did not modify the effects from the tested drugs on examined clinical outcomes.	Moderate
Duloxetine was no better than a placebo in improving UI in elderly women.	High
Solifenacin increased continence when compared to placebo, irrespective to age.	High

Table ES4. Conclusions about management of UI in women (continued)

Conclusions	Level of Evidence
Baseline frequency of UI did not dramatically modify the effects of the drugs on clinical outcomes. Subjects with more frequent UI had slightly greater benefits when compared to placebo.	Low
Solifenacin was effective irrespective of the response to previous treatments, even though poor responders did not benefit from increasing the dose of the drug.	High
Nonpharmacological treatments	
Bladder training compared to usual care improved UI	Low
Pelvic floor muscle training increased continence and improved UI when compared to no active treatment.	High
PFMT also improved several domains of quality of life in women with UI.	Low
PFMT combined with bladder training increased continence and improved UI.	High
PFMT combined with bladder training reduced severity of UI	Low
PFMT with biofeedback when compared to usual care increased continence.	Low
PFMT with biofeedback when compared to usual care improved UI.	High
Electrical stimulation when compared to sham stimulation increased continence and improved UI.	High
Electrical stimulation when compared to sham stimulation improved quality of life.	Moderate
Continence services that were implemented by specialized health care providers increased continence and improved UI when compared to usual care.	Low
Magnetic stimulation improved UI but did not increase urinary continence when compared to sham stimulation.	Moderate
Evidence of improved quality of life.	Low
Uncontrolled studies of other intravaginal and intraurethral devices demonstrated improvement in UI but also high discontinuation rates and evident harms.	Low
Weight loss and exercise improved UI in obese women.	Moderate
Acupuncture improved quality of life after active acupuncture.	Low
Continence did not differ	
PFMT + bladder training when compared to bladder training	High
PFMT + biofeedback when compared to PFMT	High
Supervised PFMT when compared to PFMT	High
PFMT when compared to electrical stimulation	Moderate
Insufficient Evidence	
Drug treatment for predominantly stress UI	
Individual RCT demonstrated greater continence and improvement in UI with vaginal estrogen formulations and worsening of UI with transdermal patches.	Insufficient
Individual studies reported that duloxetine improved urgency UI.	Insufficient
Drug treatment for predominantly urgency UI	
Individual studies reported inconsistent improvement in quality of life with oxybutynin.	Insufficient
Solifenacin improved quality of life.	Insufficient
Trospium improved quality of life in individual RCTs.	Insufficient
Continence, improvement in UI, and adverse effects did not differ with other drugs when compared to each other.	Insufficient
Racial differences in treatment effects of duloxetine in women with stress UI.	Insufficient
Clinical outcomes with tolterodine and solifenacin did not differ in subjects with baseline mixed or pure urgency UI.	Insufficient
Subjects with mixed UI may require a larger dose and longer treatment duration to achieve clinical benefits from solifenacin.	Insufficient
One study reported that darifenacin was effective in those who failed previous treatment.	Insufficient
Tolterodine was not better than placebo in achieving clinical benefits among poor responders to the previous muscarinic antagonists in one RCT.	Insufficient
Duloxetine was no better than placebo improving stress UI in women with comorbidities.	Insufficient
Nonpharmacological treatments	
Bladder training compared to usual care improved quality of life in women with UI	Insufficient
PFMT combined with bladder training improved quality of life in women with UI.	Insufficient
PFMT with biofeedback when compared to usual care improved quality of life in women with UI.	Insufficient
PFMT performed under the supervision of physical therapists or nonmedical instructors may improve continence or quality of life in women with UI.	Insufficient
Continence services that were implemented by specialized health care providers improved quality of life.	Insufficient
Vaginal cones improved UI.	Insufficient
Weight loss and exercise improved quality of life.	Insufficient
Acupuncture improved UI.	Insufficient

Table ES4. Conclusions about management of UI in women (continued)

Conclusions	Level of Evidence
Continence and improvement in UI did not differ with nonpharmacological treatment when compared to each other or combined with drug modalities.	Insufficient
Adverse effects were higher with pharmacological treatments when compared to nonpharmacological in individual head-to-head RCTs.	Insufficient

Table ES5. Clinical outcomes with treatments for UI (direct evidence from pooled with random effects models RCTs)

Treatments	Outcomes	Studies	Patients	Rate, % Active/ Control	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat (95% CI)	Attributable Events (95% CI)	Effect in Relative/ Absolute Scale	Evidence
Pharmacological treatments										
Duloxetine vs. placebo	Continence	2	736	38/40	0.92 (0.86; 0.99)	-0.03 (-0.12; 0.06)			↓/NS	Low
Duloxetine vs. placebo	Improved UI	4	1,138	37/29	1.68 (0.94; 3.00)	0.08 (0.01; 0.14)	13 (7; 143)	75 (7; 142)	NS/↑	High
Duloxetine vs. placebo	Discontinuation due to adverse effects	9	3,252	16/3	4.4 (3.24; 5.86)	0.13 (0.06; 0.19)	8 (5; 16)	129 (64; 193)	↑	High
Darifenacin vs. placebo	Improved UI	3	2,677	53/38	1.3 (1.2; 1.4)	0.11 (0.08; 0.15)	9 (7; 9)	112 (78; 147)	↑	High
Darifenacin vs. placebo	Discontinuation due to adverse effects	7	3,138	5/3	1.2 (0.8; 1.8)	0.00 (-0.01; 0.02)			NS	High
Darifenacin vs. placebo	Discontinuation due to failure	4	1,280	1/2	0.6 (0.2; 1.7)	-0.01 (-0.02; 0.01)			NS	Moderate
Fesoterodine vs. placebo	Continence	2	2,465	61/48	1.3 (1.1; 1.5)	0.13 (0.06; 0.20)	8 (5; 8)	130 (58; 202)	↑	Low
Fesoterodine vs. placebo	Improved UI	4	3,801	33/26	1.3 (1.2; 1.5)	0.08 (0.05; 0.10)	13 (10; 13)	75 (48; 102)	↑	High
Fesoterodine vs. placebo	Adverse effects	4	4,145	51/38	1.4 (1.2; 1.6)	0.15 (0.11; 0.19)	7 (5; 7)	153 (112; 194)	↑	High
Fesoterodine vs. placebo	Discontinuation due to adverse effects	6	6,338	6/3	2.1 (1.5; 2.9)	0.03 (0.02; 0.05)	31 (21; 31)	32 (16; 48)	↑	High
Fesoterodine vs. placebo	Discontinuation due to failure	4	3,801	2/3r	0.6 (0.3; 1.4)	-0.01 (-0.03; 0.01)			NS	Moderate
Oxybutynin vs. placebo	Continence	5	1,124	25/15	1.7 (1.3; 2.1)	0.11 (0.07; 0.16)	9 (6; 9)	112 (66; 158)	↑	High
Oxybutynin vs. placebo	Improved UI	12	1,627	47/32	1.4 (1.0; 1.8)	0.12 (0.03; 0.22)	8 (5; 8)	122 (27; 217)	↑	Moderate
Oxybutynin vs. placebo	Discontinuation due to adverse effects	6	1,662	11/5	1.7 (1.2; 2.5)	0.05 (0.01; 0.08)	22 (13; 22)	46 (11; 80)	↑	High
Propiverine vs. placebo	Continence	2	691	53/37	1.4 (1.2; 1.7)	0.16 (0.09; 0.24)	6 (4; 6)	163 (86; 239)	↑	Low

Table ES5. Clinical outcomes with treatments for UI (direct evidence from pooled with random effects models RCTs) (continued)

Treatments	Outcomes	Studies	Patients	Rate, % Active/ Control	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat (95% CI)	Attributable Events (95% CI)	Effect in Relative/ Absolute Scale	Evidence
Propiverine vs. placebo	Improved UI	3	985	55/35	1.6 (1.3; 2.0)	0.19 (0.13; 0.25)	5 (4; 5)	192 (132; 252)	↑	Moderate
Propiverine vs. placebo	Discontinuation due to adverse effects	2	1,401	5/2	2.6 (1.4; 5.00)	0.03 (0.01; 0.04)	36 (23; 36)	28 (12; 43)	↑	Low
Solifenacin vs. placebo	Continence	5	6,304	39/28	1.5 (1.4; 1.6)	0.11 (0.06; 0.16)	9 (6; 9)	107 (58; 156)	↑	High
Solifenacin vs. placebo	Improved UI	2	1,507	60/42	1.5 (1.0; 2.1)	0.18 (0.10; 0.26)	6 (4; 6)	180 (97; 263)	↑	Low
Solifenacin vs. placebo	Adverse effects	4	2,452	49/33	1.7 (1.3; 2.2)	0.17 (0.10; 0.23)	6 (4; 6)	165 (99; 231)	↑	High
Solifenacin vs. placebo	Discontinuation due to adverse effects	8	9,819	6/4	1.4 (1.1; 1.7)	0.01 (0.00; 0.02)	83 (43; 83)	12 (1; 23)	↑	High
Solifenacin vs. placebo	Discontinuation due to failure	4	2,812	2/1	1.0 (0.5; 1.8)	0.00 (-0.01; 0.01)			NS	Moderate
Tolterodine vs. placebo	Continence	4	3,404	53/44	1.2 (1.1; 1.4)	0.09 (0.04; 0.13)	12 (8; 12)	85 (40; 129)	↑	High
Tolterodine vs. placebo	Improved UI	8	6,783	45/36	1.3 (1.2; 1.5)	0.11 (0.06; 0.16)	9 (6; 9)	108 (55; 161)	↑	High
Tolterodine vs. placebo	Adverse effects	12	4,162	45/38	1.2 (1.1; 1.3)	0.08 (0.05; 0.11)	13 (9; 13)	79 (47; 112)	↑	High
Tolterodine vs. placebo	Discontinuation due to adverse effects	13	7,801	4/3	1.1 (0.8; 1.6)	0.01 (-0.00; 0.02)			NS	High
Tolterodine vs. placebo	Discontinuation due to failure	5	4,049	1/2r	0.5 (0.2; 0.9)	-0.01 (-0.02; 0.00)			NS	High
Trospium vs. placebo	Continence	4	2,677	28/17	1.7 (1.5; 2.0)	0.11 (0.08; 0.14)	9 (7; 9)	114 (83; 144)	↑	High
Trospium vs. placebo	Improved UI	2	1,176	32/25	1.1 (0.6; 2.0)	0.08 (-0.10; 0.25)			NS	Low
Trospium vs. placebo	Adverse effects	5	2,967	41/29	1.4 (1.2; 1.7)	0.09 (0.03; 0.16)	11 (6; 11)	94 (27; 160)	↑	Moderate
Trospium vs. placebo	Discontinuation due to adverse effects	6	3,936	6/4	1.5 (1.1; 1.9)	0.02 (0.00; 0.03)	59 (33; 59)	17 (4; 30)	↑	High
Fesoterodine vs. tolterodine	Continence	2	3,312	61/56	1.10 (1.04; 1.16)	0.06 (0.02; 0.09)	18 (11; 48)	55 (21; 88)	↑	Low

Table ES5. Clinical outcomes with treatments for UI (direct evidence from pooled with random effects models RCTs) (continued)

Treatments	Outcomes	Studies	Patients	Rate, % Active/ Control	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat (95% CI)	Attributable Events (95% CI)	Effect in Relative/ Absolute Scale	Evidence
Fesoterodine vs. tolterodine	Improved UI	4	6,015	43/36	1.08 (0.99; 1.17)	0.03 (0.002; 0.06)	31 (16;500)		NS/↑	High
Fesoterodine vs. tolterodine	Discontinuation due to adverse effects	4	5,815	5/4	1.54 (1.21; 1.97)	0.02 (0.01; 0.03)	56 (36; 143)	18 (7; 28)	↑	Moderate
Oxybutynin vs. tolterodine	Improved UI	3	947	50/45	1.11 (0.94; 1.31)	0.05 (-0.03; 0.13)			NS	Moderate
Oxybutynin vs. tolterodine	Discontinuation due to adverse effects	10	4,639	10/6	1.64 (1.15; 2.33)	0.06 (0.02; 0.10)	18 (11; 67)	55 (15; 95)	↑	High
Solifenacin vs. tolterodine	Discontinuation due to adverse effects	4	3,932	3/2	1.28 (0.86; 1.91)	0.01 (-0.01; 0.02)			NS	Moderate
Trospium vs. oxybutynin	Discontinuation due to adverse effects	2	2,015	6/5	0.98 (0.39; 2.46)	0.003 (-0.03; 0.04)			NS	Low
Nonpharmacological treatments										
Bladder training vs. no active treatment	Improved UI	2	283	61.4/19.2	3.22 (2.25; 4.60)	0.43 (0.28; 0.59)	2 (2; 4)	430 (275; 585)	↑	Low
Continence service vs. no active treatment	Continence	3	3,939	29/20	1.6 (1.1; 2.3)	0.30 (-0.01; 0.60)			↑/NS	Moderate
Continence service vs. no active treatment	Improved UI	2	4,038	62.6/53.5	1.33 (1.06; 1.68)	0.20 (-0.01; 0.41)			↑/NS	Low
Electrical stimulation vs. no active treatment	Continence	9	420	23/8	2.9 (1.6; 5.2)	0.16 (0.06; 0.26)	6 (4; 16)	162 (64; 259)	↑	High
Electrical stimulation vs. no active treatment	Improved UI	8	582	31.7/15.1	2.01 (1.28; 3.15)	0.16 (0.08; 0.23)	6 (4; 12)	156 (84; 228)	↑	High

Table ES5. Clinical outcomes with treatments for UI (direct evidence from pooled with random effects models RCTs) (continued)

Treatments	Outcomes	Studies	Patients	Rate, % Active/ Control	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat (95% CI)	Attributable Events (95% CI)	Effect in Relative/ Absolute Scale	Evidence
Magnetic stimulation vs. no active treatment	Improved UI	3	153	46.8/21.2	2.30 (1.43; 3.71)	0.27 (0.11; 0.42)	4 (2; 9)	265 (112; 417)	↑	Moderate
Magnetic stimulation vs. no active treatment	Continence	3	171	30.7/17.8	1.22 (0.78; 1.88)	0.09 (-0.01; 0.18)			NS	Moderate
Percutaneous electrical stimulation vs. no active treatment	Improved UI	2	370	37.3/21.9	1.70 (1.22; 2.36)	0.15 (0.06; 0.24)	7 (4; 16)	152 (61; 244)	↑	Low
PFMT vs. no active treatment	Continence	10	959	38/12	3.8 (2.1; 6.8)	0.30 (0.19; 0.41)	3 (2; 5)	299 (188; 410)	↑	High
PFMT vs. no active treatment	Improved UI	6	510	56.9/14.7	5.44 (1.57; 18.83)	0.41 (0.17; 0.65)	2 (2; 6)	412 (174; 649)	↑	High
PFMT with bladder training vs. no active treatment	Continence	5	1,369	21/12	3.8 (1.5; 9.3)	0.17 (0.06; 0.27)	6 (4; 16)	166 (63; 268)	↑	High
PFMT with bladder training vs. no active treatment	Improved UI	4	1,171	53.3/22.5	4.13 (1.58; 10.78)	0.39 (0.17; 0.60)	3 (2; 6)	387 (171; 603)	↑	High
PFMT with biofeedback vs. no active treatment	Continence	2	185	42/2	11.2 (2.2; 56.4)	0.49 (-0.10; 1.08)			↑/NS	Low
PFMT with biofeedback vs. no active treatment	Improved UI	4	383	60.1/18.6	3.93 (1.00; 15.49)	0.39 (0.17; 0.61)	3 (2; 6)	390 (170;610)	↑	High

Table ES5. Clinical outcomes with treatments for UI (direct evidence from pooled with random effects models RCTs) (continued)

Treatments	Outcomes	Studies	Patients	Rate, % Active/ Control	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat (95% CI)	Attributable Events (95% CI)	Effect in Relative/ Absolute Scale	Evidence
Weight Loss vs. no active treatment	Improved UI	2	386	42.8/20.8	2.17 (1.26; 3.76)	0.27 (0.06; 0.50)	4 (2; 18)	273 (57; 490)	↑	Moderate
PFMT + bladder training vs. bladder training	Continence	3	406	22/19	1.17 (0.60; 2.28)	0.03 (-0.10; 0.16)			NS	High
PFMT vs. electrical stimulation	Continence	3	99	24/29	0.85 (0.45; 1.61)	-0.04 (-0.20; 0.11)			NS	Moderate
PFMT vs. electrical stimulation	Improved UI	4	136	31/45	0.97 (0.62; 1.51)	-0.01 (-0.17; 0.16)			NS	Moderate
PFMT vs. vaginal cone	Continence	3	320	22/27	0.78 (0.58; 1.06)	-0.11 (-0.26; 0.04)			NS	Moderate
PFMT vs. vaginal cone	Improved UI	4	440	41/41	1.02 (0.91; 1.14)	0.01 (-0.08; 0.09)			NS	Moderate
PFMT with biofeedback vs. PFMT	Continence	6	542	30/25	1.27 (0.88; 1.85)	0.08 (-0.03; 0.19)			NS	High
Supervised PFMT vs. self PFMT	Continence	4	300	35/22	1.92 (0.87; 4.23)	0.20 (-0.03; 0.43)			NS	High
Supervised PFMT vs. self-PFMT	Improved UI	4	283	50/33	1.51 (0.85; 2.67)	0.14 (-0.05; 0.32)			NS	Moderate

PFMT=Pelvic floor muscle training; ↑= effect of active drug is greater than control ; ↓= effect of active drug is lower than control; NS- not significant;

Chapter 1. Introduction

Urinary incontinence (UI) is the involuntary loss of urine that reflects a failure to inhibit urination.[1] UI affects a significant number of women in the United States and other countries.[10] Almost one-third of elderly women, 25 percent of middle aged women, and 19 percent of women 19-44 years old reported ever having UI.[3,4,9,108,150,155,391,423,456-565] Women with UI experience effects on their physical, psychological, and social wellbeing, including potentially significant lifestyle restrictions. Effects may range from slightly bothersome to debilitating.

Overall, urinary incontinence casts a broad shadow. The cost of UI care in the United States averaged $19.5 billion in 2004.[6]Six percent of nursing home admissions of older women are attributable to UI[6] and, by one estimate, the annualized cost of nursing home admissions of elderly women due to UI was $3 billion.[7,8]

Voluntary voiding requires a balance between sphincter activity and bladder function. Incontinence can result from a variety of circumstances, and its etiology may be physiological, situational, or both. For example, nursing home residents may be rendered incontinent because they cannot get to the bathroom in a timely way,[1,9] but they may also suffer from an underlying bladder or sphincter problem that creates UI. Loss of inhibition associated with dementia can also cause UI.[1,9] Pelvic floor trauma after vaginal delivery, pelvic organ prolapse, and urinary tract infections are also associated with UI in women.[1,9] The initial assessment of women complaining of UI starts with exclusion of urinary tract infection, pelvic organ prolapse, and UI associated with poor bladder emptying,[10] conditions beyond the scope of this review. This review focuses specifically on the problems associated with sphincter function and bladder overactivity in women.

Variation in baseline mechanisms of UI result in different types of incontinence: stress and urgency. Stress incontinence is associated with sphincter function, and results in an inability to retain urine when bladder pressure (or intra-abdominal pressure) is raised, as in coughing or sneezing.[11] Urgency incontinence is associated with the muscle in the wall of the bladder (detrusor muscle) and can be defined as involuntary loss of urine associated with the sensation of a sudden, compelling urge to void that is difficult to defer.[11] Mixed UI is the term applied when both stress and urgency UI are present. These definitions reflect the consensus definitions developed by the International Urogynecological Association (IUGA)/International Continence Society (ICS).[11] Stress incontinence was the most prevalent type in women 19-44 years of age (31 percent),[471,479,493,500,506,509,512,518,522,523,531,546,549,562] and in those 45-64 years of age (33 percent).[3,155,459,465,471,475,484,487-489,491,493,499,500,502,504,509,518,522,527,531-533,538,540,543,545,547,551-553,555,558,562,566] The prevalence of urgency UI gradually increased from 13 percent in younger women[471,479,493,500,506,509,512,515,518,522,531,546,549,562] to 17 percent in women 45-64 years of age,[155,459,465,471,475,484,487-489,491,493,499,500,502] and to 25 percent in women older than 65 years.[470,473,475,477,478,481,485,486,488,493,499,500,505,518,520,522,524,531,534,535,539,541,544,549,559,560,562,567] Older women suffer from both types, or so-called mixed UI; 33 percent of older women[473,478,481,485,486,488,493,500,505,518,520,522,524,535,544,559,560,562,567] reported mixed UI.[485,488,493]

Clinicians and researchers seek to distinguish between types of UI because attendant risk factors and recommended treatments may differ.[12-14] Stress UI is associated with pelvic floor trauma and uterine prolapse, conditions associated with vaginal delivery that often require surgical treatments.[9] Urgency and mixed UI are associated with overactive bladder with or without sphincter dysfunction and may benefit from nonsurgical treatments, including pharmacological and nonpharmacological options.[1,9]

Although diagnosis of UI can be made based on patients' reports of involuntary urine leakage,[9] researchers have also proposed instrumental methods for objective diagnosis of different types of UI. One method includes filling cystometry during urodynamic investigation or ultrasound examination (Table 1). With this method, the bladder is filled with sterile water through a catheter until the first urge to urinate occurs (first sensation to void), and then to maximal bladder capacity. The test measures the amount of water a woman can hold in the bladder before involuntary urination and urine leakage occurs during a stress cough test.[11] Urodynamic evaluation may help to distinguish pure stress UI without urgency UI for women undergoing surgery for stress UI.[11] Diagnostic studies use multichannel urodynamics as a reference standard test to compare with noninvasive tests. However, no consensus exists among researchers on whether urodynamic examination represents the gold standard for UI diagnosis.[12-14] Previously published systematic reviews reported a weak association between urodynamic results and self-reported symptoms;[15,16] however, previous reviews did not focus on the most appropriate methods to distinguish different types of UI in primary care clinical settings.[17-20] The role of invasive diagnostic methods in predicting better treatment outcomes for UI remains unclear.

Measuring Outcomes of UI Treatment

The variations in definitions of UI complicate assessing the success of treatment. Standard UI treatment for women includes lifestyle changes, pelvic floor muscle training (PFMT), and surgical treatments for stress UI.[1] In addition, several drugs have been approved for adults with overactive bladder with or without urgency UI.[1] Clinical interventions to reduce the frequency of UI episodes in women have been extensively reviewed in recent years,[10,21-51] but the reviews have not emphasized outcomes of continence or women's perceptions of treatment success and satisfaction. Although continence, meaning the complete alleviation of involuntary urine leakage, is the most important and most consistently defined clinical outcome of UI treatment, continence is rarely examined as a primary outcome in syntheses of evidence.[52] The FDA clinical reviews defined treatment success as a significant reduction in daily UI episodes.[52,264,568] An average effect was a significant reduction by two UI episodes per day.[52] Clinical importance of this reduction was not clear. Women with severe UI may not even notice this reduction, let alone judge it as a treatment success. Other studies and reviews defined treatment success differently. In contrast with continence, commonly used definitions of UI improvement varied across studies, and included different degrees of change in frequency and severity of symptoms.[53] In addition to varied definitions across studies, improvement in UI has been judged by researchers and women very differently. Physicians have defined improvement as a decrease in the amount of lost urine during pad tests, or any statistically significant decrease in frequency of UI episodes.[53] Women have defined improvement according to reduced restrictions in lifestyle or improved overall perception of bladder conditions. Measurement of treatment outcomes should be patient-centered and based on factors important to women rather than on the results of invasive tests.[54] Thus, treatment success and failure should be evaluated according to what women report in validated questionnaires or scales. However, meaningful differences in questionnaires or scales have not been systematically reviewed. Ultimately, discussions of UI are complicated by the wide variety of measures used to describe the problem and its treatment outcomes. We focus on continence as the primary outcome for this comparative effectiveness review.

Individualized high-quality care for women with UI should be based on evidence of treatment effects in homogeneous patient subpopulations. However, few existing studies examine homogeneous groups.[58] An average treatment effect in a clinically diverse population may not reflect the actual effect for a specific group.[59,60] The role of clinical predictors of treatment failure and success in patient subpopulations with UI has not been systematically evaluated.

Clinical interventions to reduce the progression of UI have been extensively reviewed during recent years by the Agency for Healthcare Research and Quality (AHRQ),[21,22] the Cochrane Collaborative Group,[23-31,33-50,569] the International Consultation on Incontinence (ICI),[10,51] and the National Institute for Health and Clinical Excellence.[570] However, the comparative effectiveness of different UI treatments, including pharmacological therapies and their effects on patient morbidity[61] and quality of life,[62] were beyond the scope of previously published evidence-based reports.[63] In addition, previously published reports did not include pharmacological treatments for urgency UI.[9,23]

Pharmacological agents to treat urgency UI act as muscarinic antagonists.[571-573] The drugs bind to muscarinic receptors but do not activate them, thereby blocking the actions of the endogenous neurostimulator of urinary bladder tone, acetylcholine. Such blocking leads to less frequent urination and thus potential improvement in UI. However, antimuscarinic drugs also block many other effects of acetylcholine, including secretions of the respiratory tract, gastrointestinal system, and salivary glands, and actions on the central nervous system, the iris and ciliary muscle of the eye, heart, and blood vessels. Such blocking leads to adverse effects, including dry mouth, dry eye, constipation, confusion, headache, blurred vision, and others.[571,574-576] Previously published advocacy reviews did not focus on comparative safety of these drugs in adult women.[577-584] Moreover, a large number of recently published studies have not yet been synthesized into clinical recommendations for physicians.

Comprehensive and up-to-date reviews of treatment options for women with UI are necessary in order to develop evidence-based guidelines and recommendations for patients, clinicians, and policymakers.[64-67]

This report synthesizes published evidence about diagnosis and management of UI in adult women. We focused on adult women in primary care settings and on pharmacological agents available in the United States.

Table 1. Definitions of urinary incontinence and treatment outcomes[11]

Outcome	Definition
Symptoms of urinary incontinence[443]	Complaint of involuntary loss of urine.
Signs of urinary incontinence	Observation of involuntary loss of urine on examination; may be urethral or extraurethral
Transient urinary incontinence[444,445]	Potentially reversible incontinence resulting from conditions that may resolve if the underlying cause is managed: delirium/confusional state; urinary tract infection (symptomatic); atrophic urethritis/vaginitis; use of pharmaceuticals; psychological conditions, especially depression; excessive urine output related to another medical condition (e.g., congestive heart failure, hyperglycemia); restricted mobility; stool impaction
Established urinary incontinence[444,445]	Urinary incontinence that is attributed to bladder or urethral dysfunction, such as: detrusor overactivity; detrusor underactivity; urethral obstruction; urethral incompetence
Stress urinary incontinence	Complaint of involuntary loss of urine on effort or physical exertion (or on sneezing or coughing
Pure (urodynamic) stress UI	The finding of involuntary leakage during filling cystometry, associated with increased intra-abdominal pressure (stress test), in the absence of a detrusor contraction
Urgency UI[11]	Complaint of involuntary loss of urine associated with urgency
Pure (urodynamic) detrusor overactivity	Observation of involuntary leakage from the urethra synchronous with the sensation of a sudden, compelling desire to void that is difficult to defer, involuntary detrusor muscle contractions occur during filling cystometry
UI associated with poor bladder emptying[446]	Urinary incontinence associated with: bladder over distention; a contractile detrusor; hypotonic or underactive detrusor, occurring secondarily to drugs, fecal impaction, diabetes, lower spinal cord injury, or disruption of the motor innervations of the detrusor muscle
Mixed urinary incontinence[443]	Complaint of involuntary loss of urine associated with urgency and also with effort or physical exertion or on sneezing or coughing
Predominant stress UI	Mixed urinary incontinence with predominant, more frequent symptoms of stress UI
Predominant urgency UI	Mixed urinary incontinence with predominant, more frequent symptoms of urgency UI
Postural incontinence	Complaint of involuntary loss of urine associated with change of body position, for example, rising from a seated or lying position
Continuous incontinence	Complaint of continuous involuntary loss of urine
Coital incontinence	Complaint of involuntary loss of urine with coitus. This symptom might be further divided into that occurring with penetration or intromission and that occurring at orgasm
Insensible (urinary incontinence)	Complaint of urinary incontinence where the woman has been unaware of how it occurred
Nocturnal enuresis	Complaint of involuntary urine loss which occurs during sleep
Acute incontinence[447]	Sudden onset of symptoms related to an illness, treatment, or medication
Chronic incontinence	Persistent urinary incontinence, including disorders of storage (stress and urgency) and of emptying (overflow) and functional and mixed incontinence
Severity of incontinence	Measured as incontinent episodes/unit time; pad changes/unit time; pad weight/unit time; number of micturitions/unit time; urine loss on a pad test; also indicated by urodynamically diagnosed detrusor overactivity; urodynamic stress incontinence
Outcomes to examine treatment effectiveness	
Continence	Absence of any involuntary leakage of urine Author's reports of cure, absence of incontinent episodes in bladder diaries, negative pad stress, or no abnormalities noted on urodynamics

Table 1. Definitions of urinary incontinence and treatment outcomes[11] (continued)

Outcome	Definition
Resolved stress urinary incontinence	No involuntary urine leakage on physical exertion or effort or with sneezing or coughing
Resolved urgency urinary incontinence	No involuntary leakage accompanied by or immediately proceeded by urgency
Resolved mixed urinary incontinence	No involuntary leakage associated with urgency and also with exertion, effort, sneezing, or coughing
Improvement in incontinence	Reduction frequency and severity of incontinence episodes by >50% Reduction in pad stress test by >50% Reduction in restrictions of daily activities due to incontinence Women's perception of improvement in their bladder condition
Treatment failure	Progression of incontinence: Increase in frequency and severity of incontinence episodes Increase in restrictions of daily activities because of incontinence Continence not achieved No reduction in the frequency and severity of incontinent episodes
Discontinuation of treatment	Subject refusal to continue treatment
Discontinuation of treatment due to adverse effect	Subject refusal to continue treatment due to adverse effects or physician decision to withdraw treatment due to adverse effects
Discontinuation of treatment due to treatment failure	Subject refusal to continue treatment due to lack of efficacy
Quality of life	Subject's reports about emotional, physical, and social wellbeing
Adverse effects	Any harmful and undesired effect in treated subjects

Chapter 2. Methods

Literature Search Strategy and Eligibility Criteria

Search Strategy

We sought studies from a wide variety of sources, including MEDLINE® via OVID and via PubMed®, the Cochrane Library, SCIRUS, Google Scholar, and manual searches of reference lists from systematic reviews, the proceedings of the International Continence Society (ICS), and systematic reviews by the ICI. We also reviewed grey literature packets from the Scientific Resource Center (SRC). This search included regulatory documents and conducted clinical trials. The regulatory documents included medical and statistical reviews from the U.S. FDA, Health Canada - Drug Monographs, and Authorized Medicines for the European Union - Scientific Discussions. We searched the website www.clinicaltrials.gov on May 20, 2010, to find closed studies of urinary incontinence or overactive bladder. In addition, the following clinical trial registries were searched for completed trials related to the key questions: Current Controlled Trials (United Kingdom), Clinical Study Results (Pharmaceutical Research and Manufacturers of America [PhRMA]), and World Health Organization (WHO) Clinical Trials (International). Scopus and Physical Education Index (CSA) was searched for conference papers and abstracts related to UI. We identified ongoing studies in ClinicalTrials.gov and the National Institutes of Health (NIH) Research Portfolio Online Reported Tools (report) http://report.nih.gov/index.aspx websites.

The search strategies for the three research questions are described in Appendix A. Exact search strategies were developed through consultation with qualified librarians and guided by the SRC. We developed an a priori search strategy based on relevant medical subject headings (MeSH) terms, text words, and weighted word frequency algorithms to identify related articles. We documented each recommended, included, and excluded study in the master library. We repeated the literature search to identify studies published in English from 1990 until December 30, 2010.

Excluded references are shown in Appendix B. The protocol was developed with input from the Technical Expert Panel (TEP), whose members are identified in Appendix C.

Eligibility

Three investigators independently determined eligibility of the studies according to recommendations from the Cochrane Manual for systematic Reviews.[71] The algorithm to define study eligibility was developed for each research question (Appendix D). We followed the Comparative Effectiveness Manual to select evidence from controlled trials and observational studies.[585] We defined the target population, eligible independent and dependent variables, outcomes, time, and setting following the PICOTS framework (Appendix D). We reviewed abstracts to exclude news, reviews, letters, comments, and case reports. Then we confirmed eligible target populations of adult women residing in the community.

Inclusion criteria:

- Studies published in English after 1989.
- Studies that examined eligible interventions of drug therapies or nonsurgical treatments for women with UI.
- Studies that examined eligible outcomes of UI (total, mixed, stress, urgency), quality of life in women with UI, and harms of the treatments.

We included all RCTs, pooled individual patient data from RCTs, nonrandomized multicenter clinical trials, and observational studies that used strategies to reduce bias (adjustment, stratification, matching, or propensity scores).

For Key Question 1 we included studies that evaluated different diagnostic methods for UI in women that are applicable for primary care settings. We applied criteria for assessing whether a body of study data was sufficient to answer the question of diagnostic methods.[72] We included any observational studies that reported sensitivity and specificity of diagnostic methods for different types of female UI.

For Key Questions 2 and 3 we defined efficacy and effectiveness trials following criteria from the CER manual.[72] We compared the results from observational studies and RCTs on positive clinical outcomes and harms.[72] We included randomized controlled trials (RCTs) that combined men and women if they reported outcomes in women separately or included more than 75 percent women. We examined unpublished RCTs from the medical and statistical reviews that were conducted by the FDA. We reviewed nonrandomized studies if they reported clinical outcomes after nonsurgical treatments that were not available in published RCTs.

Exclusion criteria:

- Studies that did not test the associative hypotheses and did not provide adequate information on tested hypotheses (e.g., least square means, relative risk).
- Case series with fewer than 100 subjects.
- Case series that reported short-term (less than 4 weeks) crude rates of the outcomes and/or did not use strategies to reduce bias.
- Secondary data analysis, nonsystematic reviews, letters, or comments.
- Studies of children, adolescents, or men.
- Studies of surgical treatments for urinary incontinence or urogenital prolapse.
- Studies of drugs not available in the United States; studies with no clinical outcomes relevant to urinary incontinence.
- Studies that reported absolute values of the diagnostic tests in incontinent women.
- Studies that did not report true and false positive and negative cases of diagnostic tests.

To assess harms of the treatments we followed the recommendations from the CER manual[72,73] and reviewed published and unpublished evidence of the adverse effects of eligible drugs and nonsurgical treatments for female urinary incontinence including:

- Randomized controlled trials.
- Unpublished supplemental trials data from the website http://www.clinicalstudyresults.org.
- Observational cohort and case control studies.
- Observational studies based on patient registries or large databases.
- Case reports and post-marketing surveillance.

We defined harms as the totality of all possible adverse consequences of an intervention.[73] We analyzed harms regardless of how authors perceived the causality of treatments.

We did not contact the investigators of the primary studies.

Quality Assessment and Rating the Body of Evidence

We rated the quality of studies according to recommendations from the Methods Guide for Comparative Effectiveness Review.[72] We classified the studies by design to distinguish randomized and nonrandomized controlled clinical trials from observational studies. We evaluated reporting and methodological quality of the studies for Key Question 1 with predefined criteria for assessing quality of diagnostic accuracy studies.[74-79] We evaluated quality of therapeutic studies using predefined criteria that included randomization, adequacy of randomization and allocation concealment, masking of the treatment status, intention to treat principles, and justification of the sample size.[71]

We defined well designed RCTs with adequate allocation concealment, intention to treat principles in analysis, and appropriate measurements of clinically important outcomes as studies with low risk of bias.

We defined studies as having medium risk of bias if they were susceptible to some bias, but it was not sufficient to invalidate the results (e.g., open label RCTs, RCTs with unclear allocation concealment, short-term of followup, unjustified sample size, or cross-over RCTs) without assessment of carryover effect.

We defined studies as having high risk of bias if they had significant flaws that imply biases of various types that may invalidate the results, including nonrandom treatment allocation, no strategies to reduce bias, or ignoring randomization in analysis.

Grading the Evidence for Each Key Question

We assessed study quality and strength of evidence following the guidelines in the CER Manual.[97] We judged the strength of evidence according to the domains of risk of bias, consistency, directness, and precision for each major outcome.[72] When appropriate, we also included dose response association, presence of confounders that would diminish an observed effect, and strength of association. We defined high level of evidence on the basis of consistent findings from RCTs that reflected true effects of the treatments; these are findings for which future research would be very unlikely to change the estimate of effect. We assigned a moderate level of evidence when several small RCTs reported consistent treatment effects or large observational studies reported consistent associations. We assigned a low level of evidence to data from small RCTs or from RCTs with serious flaws in design/analysis, and from post hoc subgroup analysis; these are findings for which further research is likely to change the estimate. We defined insufficient evidence when a single study examined treatment effects or associations. We graded the quality of evidence for primary outcomes across studies as illustrated in Table 2.

Table 2. Overall ranking of evidence

Grade	Definition
High	**High confidence that the evidence reflects the true effect.** Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	**Moderate confidence that the evidence reflects the true effect.** Further research may change our confidence in the estimate of effect and may change the estimate.
Low	**Low confidence that the evidence reflects the true effect.** Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit a conclusion.

Applicability

Applicability of the population was estimated by evaluating the female population from which samples have been selected in observational studies and clinical trials.[80] We examined settings of the studies including primary care or specialized clinics, recruitment in clinical settings or in the community, inclusion age and type of UI, and exclusion criteria for each study. The studies that recruited women from the population had better applicability.

We assumed the presence of publication bias and did not use statistical tests for bias defined as the tendency to publish positive results.[586-589] We used several strategies to reduce bias, including a comprehensive literature search of published and unpublished evidence in several databases, reference lists of systematic reviews, proceedings of scientific meetings, contacts with experts for additional references, and agreement on the eligibility status by several investigators.

Data Extraction

Evaluations of the studies and data extraction were performed manually and independently by four researchers. The data abstraction forms are shown in Appendix E. We did multiple quality controls of all data from RCTs and in a 30 percent random sample of observational studies. Errors in data extractions were assessed by a comparison with the established ranges for each variable and the data charts with the original articles. Any discrepancies were detected and discussed. We abstracted the number of positive (true and false) and negative (true and false) after index diagnostic tests when compared to multichannel urodynamics or diary. We abstracted descriptive information about populations, interventions, controls, outcomes, settings, and time to measure outcomes in relation to the randomization or beginning of the treatment. We abstracted the number randomized into active and control treatments, doses of the drugs, events or rates, or means and standard deviations after active and control treatments. We abstracted sponsorship of the studies, sponsor participation in design and data analysis and presentation, and conflict of interest by the authors of the studies. We abstracted inclusion of minorities in the studies, inclusion of women who failed prior therapy for UI, inclusion of mixed UI, baseline daily UI, and presence of urogenital prolapse or hysterectomy in women who participated in the studies. Adjustments for age, race, comorbidities, socioeconomic status, previous treatments, and baseline severity of UI were extracted from observational studies.

Data Synthesis

For Key Question 1 results of individual studies were summarized in evidence tables to analyze sensitivity, specificity, predictive values, diagnostic odds ratios, and predictive likelihood ratios for correct diagnosis of any, stress, and urgency UI. We focus on predictive likelihood ratios of UI in women examined with index tests when compared to urodynamic or clinical diagnosis.[81-84] Tabulation was performed for each article regarding symptoms or results of diagnostic tests and the diagnosis of stress incontinence or detrusor overactivity, using either urodynamic testing or clinical final diagnosis separately as the criterion standard. Specifically, the diagnostic value of history of three symptoms was evaluated: symptoms of stress incontinence for stress UI and symptoms of urgency incontinence and urgency for detrusor overactivity. We pooled diagnostic test data with random effects models using Meta-Analyst software.[85] In cases of heterogeneity we used bivariate pooling methods.[84,86,87]

Urodynamic evaluation detects a presence of UI but not severity and frequency of UI. However, doctors need information about frequency and severity of UI to make treatment decisions and evaluate treatment effectiveness. To address the diagnostic methods of frequency and severity of UI we synthesized content and applicability of checklists and scales to assess symptom frequency and bothersomeness, quality of life, and women's satisfaction with treatments. We evaluated validation, reliability, and the proposed minimal important differences in total scores when this information was available.

For Key Questions 2 and 3 we calculated relative risk, absolute risk differences, number needed to treat (NNT), and the number of attributable events per 1,000 treated for binary outcomes. We used the number of randomized subjects forcing intention to treat principles independent of the primary studies analyses. We calculated mean differences from the reported means and standard deviations among randomized to active and control treatments. We used Meta-Analyst[85] and STATA (Statistics/Data analysis, 10.1) software to calculate individual study estimates with a 95 percent confidence interval (CI).

We used the definitions of signs and symptoms of UI promoted by the IUGA/ICS (Appendix D), including mixed, stress, and urgency UI.[11] We defined continence when the authors reported cure, absence of incontinent episodes in bladder diaries, or negative pad or stress tests (Table 1). We defined improvement in UI when the authors reported reduction by more than 50 percent in frequency of UI in diaries or patient-reported significant improvement in UI. We defined failure when frequency of UI did not change or became worse in diaries or according to patient reported worsening of UI. We relied on patient outcomes rather than continuous measures of UI episodes or urine loss.[54] We analyzed discontinuation rates independent of investigator judgments about association with tested drugs. We analyzed adverse effects as reported by the authors.

Pooling criteria included the same operational definitions of incontinence outcomes, the same clinical interventions, and the time of the assessment of the outcomes.[90] Meta-analysis was used to assess the consistency of the association between treatments and incontinence outcomes with random effects models using an inverse variance weighting method.[85,91] We chose the random effects model to incorporate in the pooled analysis differences across trials in patient populations, baseline rates of the outcomes, dosage of drugs, and other factors.[92] For pooled relative risks (RR) and absolute risk difference (ARD) we excluded trials with no events in both groups and added a correction coefficient of 0.5 in the trials with no events only in one group.[92] We used pooled ARD to calculate the number needed to treat and the number of attributable to the treatment events per 1,000 treated patients.[88,89] We calculated means and 95 percent CI for

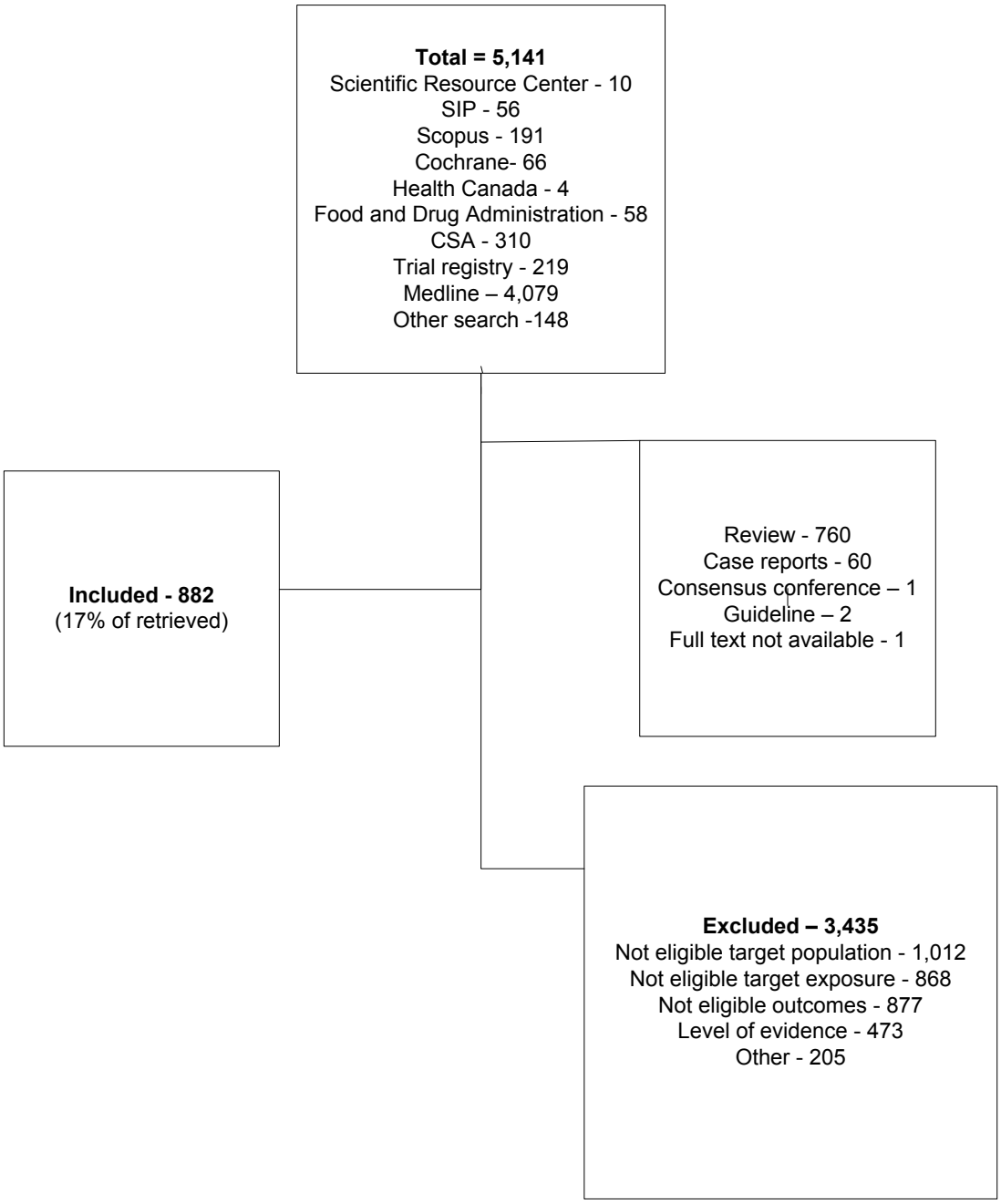
the number needed to treat as reciprocal to pooled ARD when ARD was significant.[590] We calculated means and 95 percent CI for treatment events per 1,000 treated, multiplying pooled absolute risk difference by 1,000.[85,88,89,91,590]

We examined consistency in results across the studies with Chi square tests and I square statistics.[93,94] We explored heterogeneity with meta-regression, subgroup, and sensitivity analysis and reported the results from random effects models only.[92] Using standard preplanned algorithm, we explored heterogeneity by clinical diversity, comprised of the proportion of women, proportion of minority population, age of women, severity of UI, failure after prior treatments, concomitant treatments, inclusion of women with urogenital prolapse and inclusion of women with mixed UI.[92] We explored heterogeneity by dose (when applicable), by duration of the treatments, and by control rate of the outcomes. We explored heterogeneity by quality criteria of individual studies and by the disclosed conflict of interest.[92] We explored heterogeneity with individual quality criteria rather than the global quality score.[95,96] We calculated pooled relative risk, absolute risk difference with 95 percent CI, and Bayesian odds ratios with 95 percent credible intervals using STATA 10.1 and Meta-Analyst software.[85,88] We analyzed the probability that active treatments increased the chances of continence, improvements of UI, or adverse effects with the Bayesian approach using noninformative prior probability of the events.[85] The analytic framework and algorithms for the meta-analysis are shown in Appendix D.

Chapter 3. Results

We identified and retrieved 5,038 references (Figure 1). We excluded 3,391 references. (Appendix B). We included 878 references for this review. Eligible references presented the results from individual studies, several publications of the same study, pooled analyses of the aggregate data, pooled analyses of the individual patient data, or statistical analyses of several studies. As an example of the latter, the FDA medical and statistical reviews contained 43 eligible studies (5 percent of all included) (Appendix Table F2).

Figure 1. Study flow



Question 1. What Constitutes an Adequate Diagnostic Evaluation in the Primary Care Setting on Which to Base Treatment of Urinary Incontinence (UI)?

Reporting quality of the studies precluded definitive conclusions about methodological quality (Appendix Table F3).[74,84] We did not identify the studies that reported sensitivity or specificity of different methods when compared to bladder diaries.

We identified 99 studies that provided diagnostic values of different methods for UI (Appendix Table F4).[3,98-194]

The studies included a total of 81,060 women. The sample size of individual studies varied from the largest study of 42,724 Australian women[150] to the small studies of fewer than 100 women[98,101,102,110,113,116,117,123,125,127,144,147,156,157,161,167,184-186,194] (Appendix Figure F1).

We summarized diagnostic values of diagnostic methods to differentiate stress, urgency, and mixed UI when compared to multichannel urodynamics or to clinical diagnosis. Methodology of urodynamic testing was very similar across the studies. Diagnostic methods to establish a clinical diagnosis of UI were described with different levels of detail and included history, physical examination, pelvic examination, urine culture, Q-tip test, diary, cytometry,[130] cough stress test, 48-hour home pad test,[175] evaluation of sacral nerves 2 to 4 (deep tendon reflexes, anal wink, perineal sensation, and bulbocavernosus reflex), and measurement of postvoid residual volume (by catheter or ultrasonography).

Diagnostic Value of Symptoms of UI Compared to Multichannel Urodynamics

Diagnostic value of the symptoms of stress UI to distinguish urodynamic stress UI was low. The diagnostic value of symptoms of stress incontinence compared to multichannel urodynamics for stress UI was examined in 27 studies of 5,780 (Appendix Table F5) patients.[100,101,103,105,107,109,112,114,115,118,119,121,125,129,133,142,143,153,160,162,167,169,189,448-451] Sensitivity was more than 70 percent, while specificity varied from 10-13 percent[125,189,448] to 79-88 percent.[109,153]

Pooled sensitivity was 93 percent (95 percent CI 90; 95 percent) (Appendix Figure F2). The test was not specific with pooled specificity of 41 percent (95 percent CI 34; .49 percent) (Appendix Figure F3). Positive predictive likelihood was small at 1.5 (95 percent CI 1.4; 1.7) (Appendix Table F6).

Diagnostic value of urgency symptoms of UI to distinguish urodynamic detrusor overactivity was low. The diagnostic value of the symptoms of urgency UI compared to multichannel urodynamics to distinguish detrusor overactivity was examined in 23 studies of 5,485 patients (Appendix Table F7)[100,103,107,112,114,115,118,119,121,125,128,129,131,133,142,143,153,160,162,167,189,448,449] for detrusor overactivity). Sensitivity varied across the individual studies from 14 percent[448] to more than 90 percent.[100,128,131,133,160,167] Specificity varied across the individual studies from 21 percent[119] to more than 90 percent.[115,448] Pooled sensitivity was 82 percent (95 percent CI 76; 87 percent) (Appendix Figure F4) for any detrusor overactivity) while pooled specificity was as low as 51 percent (95 percent CI 44; 59 percent) (Appendix Figure F5)**.** The positive predictive likelihood ratio was small at 1.5 (95 percent CI 1.4; 1.7).

Urgency symptoms of UI had a low diagnostic value to distinguish pure detrusor overactivity. The diagnostic value of the symptoms of urgency UI compared to multichannel

urodynamics to distinguish pure detrusor overactivity was examined in 17 studies of 3,924 subjects[103,107,112,115,118,119,121,123-125,129,133,142,143,160,167,189] (Appendix Table F8) Pooled sensitivity was 84 percent (95 percent CI 78; 89 percent) (Appendix Figure F6). Pooled specificity was as small as 43 percent (95 percent CI 36; 50 percent) (Appendix Figure F7). The positive predictive likelihood ratio was small at 1.5 (95 percent CI 1.3; 1.7) (Appendix Table F9).

Urgency symptoms alone, with or without UI, had a minimal diagnostic value in distinguishing detrusor overactivity in women. The diagnostic value of urgency symptoms with or without UI compared to multichannel urodynamics to distinguish detrusor overactivity was examined in nine studies of 6,418 patients[114,118,121,125,129,131,133,143,163] (Appendix Table F10). Pooled sensitivity was 84 percent (95 percent CI 59; 95 percent) (Appendix Figure F8). Pooled specificity was as low as 39 percent (95 percent CI 17; 67 percent) with substantial heterogeneity across the studies (Appendix Figure F9). The positive likelihood ratio (LR) was also low at 1.36 (95 percent CI 1.2; 1.6) (Appendix Table F11).

Urgency symptoms had minimal diagnostic value to distinguish pure detrusor overactivity in women. The diagnostic value of urgency symptoms with or without UI compared to multichannel urodynamics to distinguish pure detrusor overactivity was examined in six studies of 1,625 subjects[118,121,125,129,133,143] (Appendix Table F12). Pooled sensitivity was 86 percent (95 percent CI 83; 89 percent) (Appendix Figure F10). Pooled specificity was as low as 31 percent (95 percent CI 24; 39 percent) (Appendix Figure F11). The positive likelihood ratio was also low at 1.21 (95 percent CI 1.1; 1.3) (Appendix Table F13).

Mixed symptoms had minimal diagnostic value for urodynamic criteria of mixed UI. The diagnostic value of mixed UI symptoms compared to multichannel urodynamics for mixed UI was examined in 11 studies of 2,767 subjects[103,107,111,112,115,119,142,160,162,167,189] (Appendix Table F14). Pooled sensitivity was 73 percent (95 percent CI 61; 82 percent) (Appendix Figure F12). Pooled specificity was as low as 53 percent (95 percent CI 40; 66 percent) (Appendix Figure F13). Positive likelihood ratio was also low at 1.5 (95 percent CI 1.3; 1.7) (Appendix Table F15). Sensitivity and specificity differed across individual studies. Quality of the studies was not associated with differences in sensitivity or specificity. The results were similar after pooling with random effects models that incorporated heterogeneity across the studies in pooled estimates and bivariate pooling as recommended in cases of detected heterogeneity (Table 3).

Diagnostic Values of Pad Tests Compared to Multichannel Urodynamics

Pad tests had a minimal diagnostic value in detecting urodynamic detrusor overactivity. The diagnostic value of a 1-hour pad test compared to multichannel urodynamics for stress UI was examined in three studies of 574 women[119,187,191] (Appendix Table F16). Pooled sensitivity was 84 percent (95 percent CI 76; 90 percent) (Appendix Figure F14). Pooled specificity was 77 percent (95 percent CI 72; 82 percent) (Appendix Figure F15). The positive likelihood ratio was below 5 (3.6, 95 percent CI 2.9; 4.6), pointing out a small increase in the likelihood of urodynamic stress UI in women with positive pad test (Appendix Table F17).

The diagnostic value of a 1-hour pad test compared to multichannel urodynamics for detrusor overactivity was examined in two studies of 469 subjects. Sensitivity varied in studies with pooled estimates of 72 percent (95 percent CI 30; 94 percent)[187,191] (Appendix Figure F16). Pooled specificity was as low as 56 percent (95 percent CI 38; 72 percent) (Appendix Figure F17). The positive likelihood ratio was as small as 1.7 (95 percent CI 0.6; 3.9) (Appendix Table F18).

Diagnostic Value of Symptoms of UI to Clinical Diagnosis

Clinical diagnosis of UI was based on history, physical examination, pelvic examination, urine culture, Q-tip test, diary, cytometry,[130] cough stress test, 48-hour home pad test,[175] and measurement of postvoid residual volume (by catheter or ultrasonography).[137,182]

Women with urgency symptoms had a small likelihood of a clinical diagnosis of detrusor overactivity. The diagnostic value of urgency UI symptoms compared to clinical diagnosis for any detrusor overactivity was examined in four studies of 735 subjects [130,137,175,182] (Appendix Table F19). Pooled sensitivity was 82 percent (95 percent CI 73; 89 percent) (Appendix Figure F18). Pooled specificity was 67 percent (95 percent CI 53; 79 percent) (Appendix Figure F19). The positive likelihood ratio was above 2 (2.5, 95 percent CI 1.8; 3.5) (Appendix Table F20).

Women with symptoms of stress UI had a minimal likelihood of a clinical diagnosis of stress UI. The diagnostic value of symptoms of stress UI compared to a clinical diagnosis of stress UI was examined in five studies of 947 subjects[130,137,175,182,452] (Appendix Table F19). Pooled sensitivity was 88 percent (95 percent CI 68; 96 percent) (Appendix Figure F20). Pooled specificity was 67 percent (95 percent CI 54; 78 percent) (Appendix Figure F21). The positive likelihood ratio was above 2 (2.4, 95 percent CI 2.0; 2.8) (Appendix Table F21). The diagnostic value of symptoms of mixed UI compared to clinical diagnosis of mixed UI was examined in three studies of 654 subjects. Pooled sensitivity was 65 percent (95 percent CI 36; 86 percent) (Appendix Figure F22). Pooled specificity was 54 percent (95 percent CI 21; 84 percent) (Appendix Figure F23). The positive likelihood ratio was as small as 1.6 (95 percent CI 0.7; 3.6) (Appendix Table F22).

Women with urgency symptoms had a minimal likelihood of having a clinical diagnosis of pure detrusor overactivity. The diagnostic value of urgency UI symptoms compared to clinical diagnosis for pure detrusor overactivity was examined in two studies of 551 women (Appendix Table F23). Pooled sensitivity was 70 percent (95 percent CI 43; 88 percent) (Appendix Figure F24). Pooled speicificty was 55 percent (95 percent CI 28; 79 percent) (Appendix Figure F25). The positive likelihood ratio was as small as 1.6 (95 percent CI 0.6; 4.2) (Appendix Table F24).

Individual studies reported diagnostic values of the tests that did not meet pooling criteria (Table 3). One study of 488 women analyzed diagnostic value of the symptoms reported in mailed questionnaires compared to multichannel urodynamics.[174] Questionnaires had a minimal diagnostic value for stress (positive likelihood ratio=1.8) and urgency (positive likelihood ratio=1.8) UI.

Diagnostic Value of Complex Clinical Algorithms

The diagnostic values of complex clinical algorithms were high and varied depending on components of algorithms and reference methods to diagnose UI.

Diagnostic value of a clinical algorithm versus urodynamics. Diagnostic value of complex clinical algorithms for UI was high when compared to urodynamic evaluation. Two studies examined diagnostic value of algorithms for stress UI. One study of 1,455 women examined diagnostic value of a clinical algorithm versus urodynamics. Included subjects had predominant symptoms of stress UI with more than four episodes of UI per week, normal diurnal and nocturnal frequency, a bladder capacity of 400 ml or greater, and a positive cough stress (sign of

stress UI) and stress pad test.[170] The authors reported positive predictive values of 90.2 percent for urodynamic stress UI and 76.9 percent for pure urodynamic stress UI.[170] Diagnostic accuracy was the same across age categories and among those with previous surgery for stress UI.[170] The authors did not report positive predictive likelihood of the clinical algorithm. Another study of 652 women examined the diagnostic value of a clinical algorithm that required the presence of a predominant complaint of stress UI, positive cough stress test results, postvoid residual urine volume of no more than 50 ml, and a functional bladder capacity of at least 400 ml as determined by a completed 24-hour frequency volume chart.[144] This study also used urodynamics as a reference standard test. The algorithm had a positive predictive value of 95 percent when compared to multichannel urodynamics to diagnose stress UI.[144]

One study examined diagnostic value of algorithms for urgency UI. The diagnosis of pure detrusor overactivity was accurate when compared to urodynamics in scoring frequency, urgency, nocturia, and self-reported urgency UI.[192,193] The algorithm demonstrated good diagnostic value with a positive predictive likelihood ratio of 12.6 and a diagnostic odds ratio of 27.3. The same study proposed scoring of urodynamic stress UI based on self-reported frequency of incontinent episodes and the amount of protection.[192,193] The diagnostic value of such composite score was moderate with a positive predictive likelihood ratio of 3.8 and a diagnostic odds ratio of 11.

Diagnostic value of clinical algorithms based on the epidemiology of a pelvic organ prolapse and incontinence questionnaire when compared to clinical diagnosis. The diagnostic value of clinical algorithms based on the epidemiology of a pelvic organ prolapse and incontinence questionnaire when compared to clinical diagnosis was tested in one study of 110 women.[178] The questionnaire had a moderate likelihood of identifying women with detrusor overactivity (positive likelihood ratio=7.7) and a large likelihood of identifying women with stress UI (positive likelihood ratio=19).[178] One study demonstrated moderate diagnostic value of the Three Incontinence Questions Questionnaire (3IQ) when compared to clinical diagnosis in 301 women to detect those with stress or urgency UI.[182]

Diagnostic values of individual tests when compared to urodynamics. In individual studies, other examined tests using urodynamics as a reference standard, including the Q-tip test,[120,453] UDI-6,[160,591] questionnaire for urinary incontinence diagnosis (QUID) stress score,[592] or Bristol Female Lower Urinary Tract Symptoms Questionnaire,[169] demonstrated minimal diagnostic value for UI with positive predictive likelihood ratios less than 2 (Table 3). The studies of the Gaudenz questionnaire reported different results depending on the country where the study was conducted.[134,153]

Diagnostic values of ultrasound versus urodynamics as a reference standard. The diagnostic values of ultrasound using urodynamics as a reference standard were examined in five studies of 540 women.[454,593-596] Perineal ultrasound had a small diagnostic value with a positive predictive likelihood ratio of 3 for urodynamic stress UI.[593] Vaginal ultrasound had a moderate diagnostic value with a positive predictive likelihood ratio of 5.3 for urodynamic stress UI.[596] Transrectal ultrasound that detected a decreased angle of UV junction demonstrated a large and conclusive increase in the likelihood of urodynamic stress UI.[454,595]

Comparison of Diagnostic Values of Different Tests

The majority of studies demonstrated minimal or small diagnostic value of the tests to identify women with different types of urodynamic UI as well as a clinical diagnosis of UI.

Complex clinical algorithms demonstrated better diagnostic performance. Individual studies suggested a good diagnostic value of the epidemiology of prolapse and incontinence questionnaires. Post-test probability of mixed or urgency UI increased in aging women.[597]

We compared the accuracy of diagnostic tests for different types of UI across studies (Table 3). Urodynamic stress UI was accurately diagnosed in 80 percent of women using 1-hour pad test and in 75 percent of women using self-reported symptoms of stress UI (Figure 2). Urge symptoms accurately diagnosed urodynamic urgency UI in 69 percent of women. Pad tests accurately diagnosed urodynamic urgency UI in 61 percent of women. Accuracy of the symptoms of mixed UI to diagnose urodynamic stress UI combined with detrusor overactivity was low (56 percent). Clinical diagnosis of stress UI was accurately detected with self-reported symptoms of stress UI in 80 percent of women. Clinical diagnosis of detrusor overactivity was accurately detected with self-reported symptoms of urgency UI in 73 percent. The pooled diagnostic odds ratio demonstrated the same pattern with the best discriminatory performance of symptoms of stress UI and pad test when compared to urodynamic diagnosis of stress UI (Figure 3). The diagnostic odds ratio was the more than 10 for the symptoms for stress and urgency UI when compared to a clinical diagnosis.

We also compared predictive values of diagnostic tests for different type of UI across the studies (Table 4). Positive predictive values were less than 50 percent for most comparisons while negative predictive values were larger than 90 percent. Positive predictive value of the symptoms of mixed UI and urgency UI increased with age. The majority of women without symptoms of UI did not have clinical diagnosis of UI.

Minimal Clinically Important Differences in Diagnostic Tools to Monitor Effectiveness of the Treatments

Women considered a reduction of 70 percent or more in UI episode frequency a clinical success.[213] However, clinical trials and the FDA reviews did not define women centered outcomes as primary outcomes.

Clinically important differences have been determined for several questionnaires and scales. Among validated diagnostic questionnaires, The Leicester Urinary Symptom Questionnaire (LUSQ)[598] and Medical, Epidemiological, and Social Aspects of Aging Questionnaire (MESA)[599] provided information about presence and severity of UI in categorical terms. Other tools suggested scoring of the symptoms of any UI[175,600] or urgency UI.[180] The overall score varied for different tools (Table 5). The Bladder Self-Assessment Questionnaire and Bladder Control Self-Assessment Questionnaires defined minimal important differences in scores that can be used to detect treatment success in clinical settings.[204]

A variety of validated tools are available to monitor quality of life in women with UI and with different UI types. Several tools that define clinically important differences in scores can be used to assess treatment success in clinical settings.

Patient satisfaction can be assessed with several validated tools, including the Overactive Bladder Symptom Score,[601] the Benefit, Satisfaction with Treatment, and Willingness,[602] the Estimated Percent Improvement,[603] or the Global Perception of Improvement[603] (Table 5). Some tools focused on satisfaction with treatments in women with urgency UI,[601,602,604] while other tools were proposed for any UI type. These instruments are brief and do not require much time to complete. Clinical importance of different responses is self-explanatory. Patient satisfaction measures define treatment success but do not provide many details to explain treatment failure.

We analyzed validity and reliability of the tools and sought literature to find definitions of the minimal important differences in continuous measures of severity of UI, bothersomeness, or quality of life (Table 5). We evaluated the scales and questionnaires recommended by the ICI for diagnosis, monitoring of treatment, and assessment of quality of life in women with UI.[605]

Effectiveness of treatments in randomized controlled clinical trials was assessed with 3-7 day diaries. A reduction in UI episode frequency was the most common primary outcome RCTs were designed to examine.[224,257,263,264,278,287,293,301,303,308,320,326,327,346,349,357,362,606-611] Medical and statistical reviews conducted by the FDA focused on the same primary outcomes that RCTs were designed to examine—absolute changes in UI episode frequency.[264,326,327,360,361,431,432] Some RCTs further categorized treatment success as any reduction in UI episode frequency or reduction by 50, 75, or 90 percent in UI episode frequency.

One pooled analysis of individual data of 1,913 women with predominant stress UI who participated in four RCTs examined what reduction in UI episode frequency was important for the patients.[213] The authors examined the relationship between relative reduction in UI episode frequency and improvement meaningful for women in the Incontinence Quality of Life questionnaire.[213] The study concluded that women noticed improvement in quality of life when UI episode frequency was reduced by more than 70 percent.[213] Small changes of 20-40 percent in incontinence episode frequency were not important to women when the results from a voiding diary were analyzed in association with the validated Incontinence Quality of Life (I-QOL) questionnaire. No studies examined clinically important reduction in UI episode frequency for women with predominant urgency UI.

All tools to assess symptom bother have been validated. Tools that distinguish symptom bother for stress UI include Patient Global Impression of Improvement PGI-I,[197] PGI-S Patient Global Impression of Improvement and Severity,[197] or Symptom Severity Index and Symptom Impact Index for stress UI in women.[612] The Primary OAB Symptom Questionnaire provided four scales to assess symptom bother for urgency UI.[200] Other tools evaluated symptom bother for any type of UI (Table 5). The Incontinence Severity Index,[195,196] Patient Global Impression of Improvement and of Severity,[197] Urogenital Distress Inventory,[136,201,202] and Patient Perception of Bladder Condition[198-200] developed definitions of minimal important differences in any UI that can be used to define treatment success in clinical settings. The Urogenital Distress Inventory stress subscale also can distinguish minimal important differences in stress UI.[201] Women reported improvement in UI when the incontinence episode frequency was reduced by 63 or more percent.[197]

Several tools have been validated to assess quality of life in women with UI (Table 5). All tools provided scoring for different domains of quality of life and overall total scores that varied by direction and magnitude across the scales. Comparing efficacy of the tools was difficult because of such variability in content and psychometric properties. Few tools addressed quality of life depending on the type of incontinence.

Association Between Methods of Diagnosis and Patient Outcomes

We found no evidence that outcomes of conservative treatments differ depending on urodynamic diagnosis. Mixed UI (the most prevalent type of UI in aging women), predominant stress, or predominant urgency UI can be assessed with validated tools that evaluate symptom frequency. An accurate diagnosis of pure stress or pure detrusor overactivity is possible using complex clinical algorithms with multichannel cystometry.

Women who failed conservative treatments and/or decided to have surgery for stress UI may need a multichannel urodynamic evaluation. In all cases, a diagnostic algorithm assumes adequate assessment of baseline conditions that may result in UI, including pelvic organ prolapse, urinary tract infection, or pelvic floor trauma.

A few studies tested the effect of baseline urodynamic examination in association with treatment outcomes. The studies that examined treatment outcomes among women with and without baseline urodynamics did not demonstrate significant differences in outcomes depending on baseline urodynamic findings. One extension of RCTs of conservative treatment concluded that continence (RR 1.24, 95 percent CI 0.30; 5.23), improvement in UI (RR 0.85, 95 percent CI 0.55; 1.31), or treatment failure with worsening of UI (RR 1.24, 95 percent CI 0.47; 3.29) did not differ between women who did or did not have a baseline urodynamic evaluation.[223] The second RCT randomized women to conservative treatments depending on baseline urodynamics or clinical symptoms.[613] Treatments included fluid management, physiotherapy, and drugs, depending on urodynamic or clinical diagnosis. Quality of life measured with King's Health Questionnaire and frequency of UI episodes measured with voiding diary did not differ between randomized groups.[613] The authors concluded that baseline urodynamic diagnosis was not associated with better outcomes.

Drug studies showed that in women with severe stress UI, duloxetine versus placebo decreased the frequency of UI episodes independent of baseline urodynamic findings.[224] Women with intrinsic sphincter deficiency experienced more than a 50 percent decrease in daily UI (RR 6.15, 95 percent CI 1.54; 24.54), as did women without intrinsic sphincter deficiency (RR 4.20, 95 percent CI 1.81; 9.76). The RCT, however, was not designed to detect differences in duloxetine effect by using a baseline urodynamic evaluation. One multicenter RCT examined clinical outcomes with fesoterodine in subgroups by urodynamic findings of detrusor overactivity.[225] Treatment response, discontinuation rate, and adverse effects did not differ between individuals with versus without urodynamic diagnosis of detrusor overactivity (Appendix Table F25).[225] One RCT that compared clinical outcomes with tolterodine-ER versus placebo also did not demonstrate differences in treatment effects in women with and without urodynamic detrusor overactivity.[226] Baseline urodynamic examination did not predict treatment outcomes. Case series also found no differences in treatment response with oxybutynin between those with versus without urodynamically verified symptoms [614] (Appendix Table F26).

The studies generally showed that urodynamic findings did not predict response to conservative treatments. In contrast, one large analysis of 6,276 women with UI from the United Kingdom suggested that urodynamic evaluation is essential to predict outcomes, but only after surgery for UI.[227] The authors examined the accuracy of the history of pure stress UI in predicting only urodynamic stress UI compared to the NICE guidance and found very low sensitivity of 11 percent and good specificity of 98 percent (NICE, 83 percent; 95 percent CI 49; 92 percent). The study suggested that a multichannel urodynamic evaluation is indicated in women who decided to have surgery for stress UI.[227] A recent study also concluded that all women who undergo surgery for stress UI should have multichannel urodynamic evaluation.[615]

Table 3. Diagnostic value of the test for UI in women (pooled with random effects models and bivariate pooling)

Type of Incontinence	Method Index/Standard	Number of Studies and References Number of Subjects	Sensitivity/ Bivariate Pooling	Specificity/ Bivariate Pooling	Positive Likelihood Ratio†	Negative Likelihood Ratio†	Positive Predictive Value	Negative Predictive Value
Urodynamic stress UI	Symptoms of stress UI/UD	27[100,101,103,105,107,109,112,114,115,118,119,121,125,129,133,142,143,153,160,162,167,169,189,448-451] 5,780	0.93^ (0.90, 0.95) 0.94 (0.91, 0.96)	0.41^ (0.34, 0.49) 0.41 (0.31, 0.51)	1.54 (1.40, 1.7)	0.20 (0.14, 0.27)	0.74 (0.68, 0.80)	0.74 (0.67, 0.81)
Detrusor overactivity	Symptoms of urgency UI/UD	23[100,103,107,112,114,115,118,119,121,125,128,129,131,133,142,143,153,160,162,167,189,448,449] 5,485	0.82^ (0.76, 0.87) 0.82 (0.75, 0.88)	0.51^ (0.44, 0.59) 0.52 (0.40, 0.65)	1.54 (1.38, 1.73)	0.39 (0.30, 0.50)	0.56 (0.48, 0.63)	0.80 (0.73, 0.86)
Detrusor overactivity	Symptoms of urgency/UD	9[114,118,121,125,129,131,133,143,163] 6,418	0.84^ (0.59, 0.95) 0.82 (0.70, 0.92)	0.39^ (0.17, 0.67) 0.39 (0.24, 0.55)	1.36 (1.18, 1.58)	0.47 (0.33, 0.67)	0.48 (0.39, 0.57)	0.75 (0.67, 0.81)
Detrusor overactivity*	Symptoms of urgency UI/UD	17[103,107,112,115,118,119,121,123-125,129,133,142,143,160,167,189] 3,924	0.84^ (0.78; 0.89) 0.84 (0.79, 0.90)	0.43^ (0.36; 0.50) 0.44 (0.34, 0.54)	1.48 (1.31; 1.66)	0.40 (0.29; 0.54)	0.33 (0.26; 0.41)	0.89 (0.83; 0.93)
Detrusor overactivity*	Symptoms of urgency /UD	6[118,121,125,129,133,143] 1,598	0.86 (0.83; 0.89) 0.86 (0.80, 0.90)	0.31^ (0.24; 0.39) 0.31 (0.20, 0.45)	1.21 (1.11; 1.32)	0.523 (0.41; 0.67)	0.27 (0.17; 0.40)	0.86 (0.76;0.93)
Mixed UI	Symptoms of stress and urgency UI/UD	11[103,107,111,112,115,119,142,160,162,167,189] 2,767	0.73^ (0.61, 0.82) 0.72 (0.58, 0.83)	0.53^ (0.40, 0.66) 0.53 (0.34, 0.72)	1.45 (1.27, 1.67)	0.61 (0.52, 0.71)	0.26 (0.20, 0.34)	0.89 (0.85, 0.92)
Urodynamic stress UI	Pad test/UD	3[139,187,191] 574	0.84 (0.76, 0.90) 0.83 (0.75, 0.91)	0.77 (0.72, 0.82) 0.77 (0.17, 0.97)	3.62 (2.88, 4.57)	0.22 (0.15, 0.32)	0.82 (0.77, 0.86)	0.78 (0.73, 0.83)
Detrusor overactivity	Pad test/UD	2[187,191] 469	0.72^ (0.30, 0.94)	0.56^ (0.38, 0.72)	1.56 (0.62, 3.90)	0.47 (0.10, 2.33)	0.32 (0.04, 0.83)	0.88 (0.83, 0.91)
Urodynamic stress UI	Symptoms of stress UI/clinical diagnosis	5[130,137,175,182,452] 947	0.88^ (0.68, 0.96) 0.86 (0.70, 0.96)	0.67^ (0.54, 0.78) 0.67 (0.51, 0.81)	2.35 (1.97, 2.81)	0.19 0.09, 0.41)	0.80 (0.66, 0.89)	0.75 (0.58, 0.87)

Table 3. Diagnostic value of the test for UI in women (pooled with random effects models and bivariate pooling) (continued)

Type of Incontinence	Method Index/Standard	Number of Studies and References Number of Subjects	Sensitivity/ Bivariate Pooling	Specificity/ Bivariate Pooling	Positive Likelihood Ratio†	Negative Likelihood Ratio†	Positive Predictive Value	Negative Predictive Value
Detrusor overactivity	Symptoms of urgency UI/clinical diagnosis	4[130,137,175,182] 735	0.82^ (0.73, 0.89) 0.82 (0.73, 0.90)	0.67^ (0.53, 0.79) 0.67 (0.45, 0.86)	2.52 (1.81, 3.50)	0.26 (0.18, 0.38)	0.72 (0.48, 0.88)	0.79 (0.54, 0.92)
Mixed UI	Symptoms of stress and urgency UI/clinical diagnosis	3[137,175,182] 654	0.65^ (0.36, 0.86) 0.64 (0.38, 0.85)	0.54^ (0.21, 0.84) 0.52 (0.06, 0.94)	1.57 (0.68, 3.59)	0.74 (0.28, 1.95)	0.36 (0.27, 0.47)	0.80 (0.43, 0.96)
Urodynamic stress UI	Logistic regression model/UD	1[174] 488	0.77	0.56	1.76	0.41	0.68	0.65
Detrusor overactivity	Logistic regression model/UD	1[174] 388	0.63	0.65	1.81	0.57	0.63	0.67
Urodynamic stress UI	Clinical algorithm/UD	1[170] 173					0.90 (0.85, 0.94)	
Urodynamic stress UI	Clinical algorithm /UD	1[144] 74					0.97	
Urodynamic stress UI	Clinical algorithm based on EPIQ/Clinical diagnosis	1[178] 110	0.80	0.92	10.00	0.22	0.88	0.87
Detrusor overactivity	Clinical algorithm based on EPIQ/Clinical diagnosis	1[178] 110	0.77	0.90	7.70	0.26	0.77	0.90
Detrusor overactivity	Clinical algorithm based on OAB-V8/Clinical diagnosis	1[180] 1,260	0.98	0.83	5.66	0.02	0.44	1.00
Urodynamic stress UI	Q-tip test/UD	3[120,453,454] 267	0.62 (0.53, 0.70) 0.62 (0.49, 0.74)	0.60^ (0.40, 0.78) 0.58 (0.00, 1.00)	1.70 (0.89, 3.23)	0.60 0.31, 1.17)	0.58 0.26, 0.85)	0.67 (0.34, 0.89)
Detrusor overactivity	Q-tip test/UD	1[120] 100	0.40	0.40	0.66	1.50	0.33	0.47

Table 3. Diagnostic value of the test for UI in women (pooled with random effects models and bivariate pooling) (continued)

Type of Incontinence	Method Index/Standard	Number of Studies and References Number of Subjects	Sensitivity/ Bivariate Pooling	Specificity/ Bivariate Pooling	Positive Likelihood Ratio†	Negative Likelihood Ratio†	Positive Predictive Value	Negative Predictive Value
Urodynamic stress UI	UDI-6 question 3 score ≥2/UD**	1[149] 128	0.85	0.63	2.32	0.24		
Urodynamic stress UI	UDI-6 question 3 score ≥2/UD**	1[160] 202	0.88	0.55	1.97	0.21	0.86	0.60
Urodynamic stress UI	DIS	1[120] 250	0.60	0.77	2.61	0.52	0.82	0.52
Detrusor overactivity	UDI-6 question 1 score ≥2/UD	1[149] 128	0.83	0.50	1.67	0.33		
Detrusor overactivity	UDI-6 question 2 score ≥2/UD	1[149] 128	0.75	0.33	1.11	0.77		
Detrusor overactivity	UDI-6 question 1 and 2 score ≥2/UD	1[149] 128	0.69	0.64	1.90	0.49		
Urodynamic stress UI	QUID stress score ≥4/Clinical diagnosis	1[175] 117	0.85	0.71	2.93	0.21	0.90	0.61
Detrusor overactivity	QUID urge score ≥6/Clinical diagnosis	1[175] 117	0.79	0.79	3.76	0.27	0.95	0.43
Detrusor overactivity	BIDI from diary/UD	1[592] 217	0.88	0.83	5.12	0.14	0.41	0.98
Detrusor overactivity	Logistic regression model/UD	1[193] 200	0.81	0.72	2.89	0.26	0.74	0.79
Detrusor overactivity*	Logistic regression model/UD	1[192] 207	0.56	0.96	12.56	0.46	0.80	0.87
Urodynamic stress UI	Gaudenz-Incontinence-questionnaire predominant urgency UI symptoms/UD	1[134] 1,938	0.56	0.45	1.01	0.99	0.88	0.18

Table 3. Diagnostic value of the test for UI in women (pooled with random effects models and bivariate pooling) (continued)

Type of Incontinence	Method Index/Standard	Number of Studies and References Number of Subjects	Sensitivity/ Bivariate Pooling	Specificity/ Bivariate Pooling	Positive Likelihood Ratio†	Negative Likelihood Ratio†	Positive Predictive Value	Negative Predictive Value
Detrusor overactivity	Gaudenz-Incontinence-questionnaire predominant stress UI symptoms/UD	1[134] 1,938	0.62	0.56	1.40	0.69	0.03	0.99
Urodynamic stress UI*	Logistic regression/UD	1[192] 207	0.95	0.43	1.66	0.13	0.48	0.93
Urodynamic stress UI	Logistic regression/UD	1[193] 200	0.72	0.81	3.79	0.35	0.79	0.74
Urodynamic stress UI*	Clinical algorithm based on I-QOL/UD	1[166] 86					0.76	
Urodynamic stress UI	Clinical algorithm based on I-QOL/UD	1[166] 86					0.92	
Urodynamic stress UI*	Clinical algorithm/UD	1[170] 173					0.77 (0.7, 0.83)	
Urodynamic stress UI	Clinical algorithm/clinical diagnosis	1[170] 173					0.98 (0.95, 1.00)	
Urodynamic stress UI*	Clinical algorithm/clinical diagnosis	1[170] 173					0.85 (0.79, 0.90)	
Urodynamic stress UI*	Clinical algorithm/UD	1[144] 74					0.82	
Urodynamic stress UI*	Clinical algorithm retrospective/UD	1[146] 57	0.90	1.00		0.10	1.00	0.82
Urodynamic stress UI*	Clinical algorithm prospective/UD	1[146] 19	0.62	1.00		0.38	1.00	0.55
Urodynamic stress UI*	Clinical algorithm combining retrospective and prospective/UD	1[146] 76	0.83	1.00		0.17	1.00	0.73

Table 3. Diagnostic value of the test for UI in women (pooled with random effects models and bivariate pooling) (continued)

Type of Incontinence	Method Index/Standard	Number of Studies and References Number of Subjects	Sensitivity/ Bivariate Pooling	Specificity/ Bivariate Pooling	Positive Likelihood Ratio†	Negative Likelihood Ratio†	Positive Predictive Value	Negative Predictive Value
Urodynamic stress UI*	Q-tip test/UD	1[120] 100	0.38	0.44	0.67	1.42	0.22	0.63
Detrusor overactivity*	Q-tip test/UD	1[120] 100	0.63	0.56	1.45	0.65	0.47	0.71
Urodynamic stress UI	Self reported questionnaire/UD	1[109] 161	0.68	0.79	3.23	0.40	0.82	0.63
Detrusor overactivity	Self reported questionnaire/UD	1[109] 166	0.67	0.66	1.94	0.51	0.13	0.96
Detrusor overactivity	Bristol Female Lower Urinary Tract Symptoms Questionnaire, interview/UD	1[169] 72	0.85	0.16	1.01	0.94		
Detrusor overactivity	Bristol Female Lower Urinary Tract Symptoms Questionnaire, interview/UD	1[169] 72	0.81	0.12	0.92	1.58		
Urodynamic stress UI	Bristol Female Lower Urinary Tract Symptoms Questionnaire, interview/UD	1[169] 72	0.89	0.30	1.27	0.37		
Urodynamic stress UI	Bristol Female Lower Urinary Tract Symptoms Questionnaire, interview/UD	1[169] 72	0.88	0.29	1.24	0.41		
Urodynamic stress UI	Discriminant score/UD	1[104] 252	0.78	0.84	4.97	0.26	0.81	0.81

Table 3. Diagnostic value of the test for UI in women (pooled with random effects models and bivariate pooling) (continued)

Type of Incontinence	Method Index/Standard	Number of Studies and References Number of Subjects	Sensitivity/ Bivariate Pooling	Specificity/ Bivariate Pooling	Positive Likelihood Ratio†	Negative Likelihood Ratio†	Positive Predictive Value	Negative Predictive Value
Urodynamic stress UI*	Gaudenz-Incontinence-questionnaire score predominant stress UI symptoms/UD	1[153] 198	0.83	0.92	10.12	0.18	0.95	0.76
Urodynamic stress UI*	3IQ predominant stress UI symptoms/clinical diagnosis	1[182] 301	0.77	0.79	3.63	0.29	0.74	0.82
Urodynamic stress UI*	Clinical algorithm of predominant stress UI symptoms based on UITN/UD	1[183] 655	0.91					
Detrusor overactivity*	3IQ predominant stress UI symptoms/ clinical diagnosis	1[153] 301	0.57	0.87	4.52	0.49	0.75	0.76
Urodynamic stress UI	3IQ predominant stress UI symptoms/clinical diagnosis	1[153] 301	0.68	0.85	4.57	0.37	0.86	0.66
Detrusor overactivity	3IQ predominant stress UI symptoms/ clinical diagnosis	1[153] 301	0.48	0.91	5.22	0.57	0.86	0.60
Detrusor overactivity*	Gaudenz-Incontinence-questionnaire score predominant urgency UI symptoms/UD	1[153] 198	0.86	0.96	24.28	0.14	0.81	0.98

Table 3. Diagnostic value of the test for UI in women (pooled with random effects models and bivariate pooling) (continued)

Type of Incontinence	Method Index/Standard	Number of Studies and References Number of Subjects	Sensitivity/ Bivariate Pooling	Specificity/ Bivariate Pooling	Positive Likelihood Ratio†	Negative Likelihood Ratio†	Positive Predictive Value	Negative Predictive Value
Mixed UI	Gaudenz-Incontinence-questionnaire score mixed UI symptoms/UD	1[153] 198	0.61	0.87	4.56	0.45	0.54	0.89
Urodynamic stress UI	Gaudenz-Incontinence-questionnaire score predominant stress UI symptoms/UD	1[153] 198	0.98	0.55	2.18	0.03	0.79	0.95
Detrusor overactivity	Gaudenz-Incontinence-questionnaire score predominant urgency UI symptoms/UD	1[153] 198	0.90	0.70	2.97	0.15	0.34	0.98
Urodynamic stress UI	Symptoms, Q-tip, and cough test/UD	1[616] 87	0.94	0.84	5.85	0.08	0.94	0.84
Detrusor overactivity	Symptoms, Q-tip, and cough test/UD	1[616] 87	0.78	0.87	5.98	0.25	0.84	0.82
Urodynamic stress UI*	Symptoms, Q-tip, and cough test/UD	1[616] 87	0.92	0.45	1.67	0.18	0.56	0.88
Detrusor overactivity*	Symptoms, Q-tip, and cough test/UD	1[616] 87	0.88	0.67	2.69	0.18	0.39	0.96
Mixed UI	Symptoms, Q-tip, and cough test/UD	1[616] 87	0.67	0.89	6.00	0.38	0.70	0.88
Urodynamic stress UI	Ultrasound (perineal, BND)/UD	1[593] 102	0.73	0.77	3.16	0.35	0.64	0.83
Urodynamic stress UI	Ultrasound (perineal, BND)/UD	1[594] 38	0.72					

Table 3. Diagnostic value of the test for UI in women (pooled with random effects models and bivariate pooling) (continued)

Type of Incontinence	Method Index/Standard	Number of Studies and References Number of Subjects	Sensitivity/ Bivariate Pooling	Specificity/ Bivariate Pooling	Positive Likelihood Ratio†	Negative Likelihood Ratio†	Positive Predictive Value	Negative Predictive Value
Urodynamic stress UI	Ultrasound (transrectal, drop of UV junction)/UD	1[454] 91	0.86	0.96	20.30	0.14	0.95	0.88
Urodynamic stress UI	Ultrasound (transrectal, drop of UV junction)/UD	1[595] 85	0.94	0.87	7.10	0.07	0.81	0.96
Urodynamic stress UI	Ultrasound (vaginal, opening of bladder neck/proximal urethral with leakage during cough)/UD	1[596] 124	0.96	0.82	5.33	0.05		
Detrusor overactivity	Symptoms and pad test/UD#	1[617] 100	0.88					

* pure type
** not pooled because of poor reporting quality
\# 68% women and 32% men, the golden standard was not clearly defined
† Clinical interpretations of likelihood ratios[455]
^ significant heterogeneity

Likelihood Ratio	Interpretation
>10	Large and often conclusive increase in the likelihood of disease
5 - 10	Moderate increase in the likelihood of disease
2 - 5	Small increase in the likelihood of disease
1 - 2	Minimal increase in the likelihood of disease
1	No change in the likelihood of disease

Figure 2. Accuracy of diagnostic methods for female UI (pooled with random effects model results)

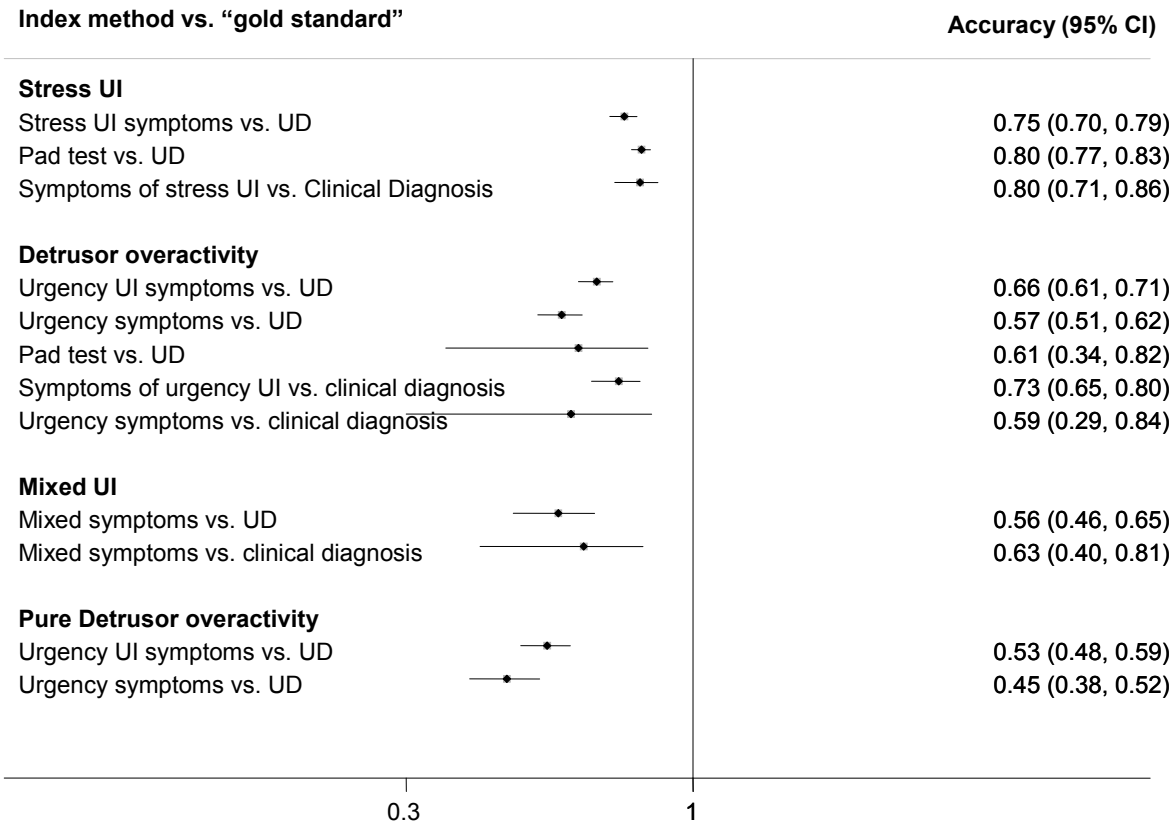


Figure 3. Diagnostic odds ratio of diagnostic methods for female UI (pooled with random effects model results)

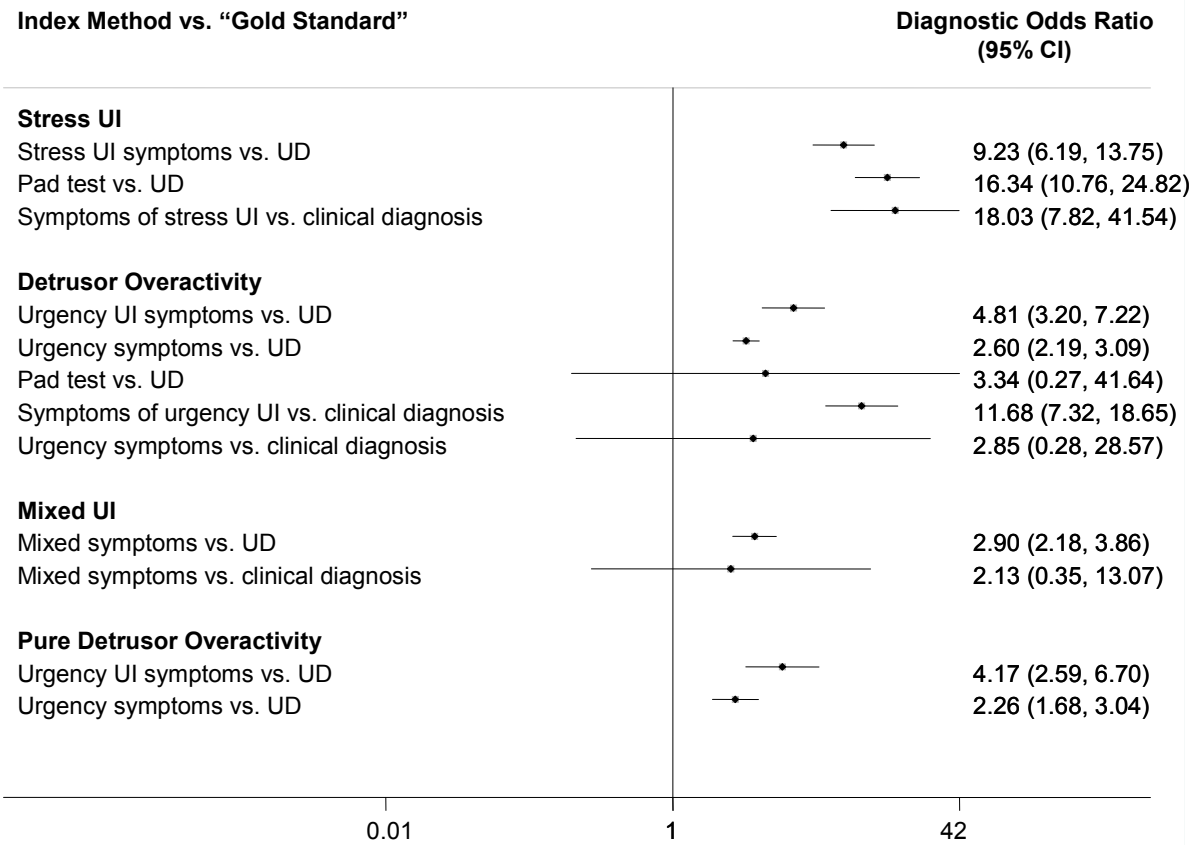


Table 4. Predictive value of diagnostic tests for different types of UI in age subgroups

Age Groups	Prevalence of UI,%	Symptoms of Mixed UI Compared to Clinical Diagnosis for Mixed UI		Symptoms of Mixed UI Compared to Urodynamic Diagnosis of Stress UI and Diagnostic Odds Ratio	
	Mixed UI	PPV+, %	PPV-, %	PPV+, %	PPV-, %
19-44	21.6	28.0	84.8	30.0	87.7
45-64	20.2	26.4	85.9	28.3	88.6
65+	33.4	41.4	75.5	43.7	79.7
80+	32.8	40.8	76.0	43.1	80.1
		Symptoms of Stress Incontinence Compared to Clinical Diagnosis for Stress UI		**Symptoms of Stress Incontinence Compared to Urodynamic Stress UI**	
	Stress UI	PPV+, %	PPV-, %	PPV+, %	PPV-, %
19-44	30.6	50.3	94.5	40.9	93.0
45-64	33.4	53.6	93.7	44.2	92.1
65+	28.6	47.9	94.9	38.7	93.6
80+	25.1	43.5	95.7	34.6	94.6
		Symptoms of Urgency UI Compared to Clinical Diagnosis for Detrusor Overactivity		**Symptoms of Urgency UI Compared to Urodynamic Diagnosis of Detrusor Overactivity**	
	Urgency UI	PPV+, %	PPV-, %	PPV+, %	PPV-, %
19-44	13.2	27.5	96.1	20.3	94.9
45-64	17.4	34.3	94.7	26.0	93.1
65+	25.4	45.8	91.6	36.3	89.3
80+	24.7	45.0	91.9	35.5	89.6

Table 5. Diagnostic tools to assess clinical importance and monitor effectiveness of treatments of UI

Tools*	References (all that mentioned)	Conditions	Domain	Minimal Important Differences	Worst to Best	Validity/ Reliability
Symptom Bother						
ISI	Sandvik, 1993[195] Sandvik, 2000[196]	Any/not specified	Frequency Severity	1993 version 6-8 as severe UI (pad test mean 56-63g/24 hours) 3-4 as moderate UI (pad test 17g/24 hours) 2000 version 8-9 as severe UI(pad test mean 52g/24 hours) 12 as very severe UI (pad test mean 122g/24 hrs)	1993 version 8 to 1 2000 version 12 to 1	Yes/No
PGI-I	Yalcin, 2003[197]	Stress UI	1 item for improvement	Change incontinence episode frequency -92% in very much better group -63% in much better group	7 to 1 for improvement	Yes/No
PGI-S	Yalcin, 2003[197]	Stress UI	1 item for severity	Mean incontinence episode frequency 32.8 per week for severe cases	4 to 1 for severity	Yes/No
POSQ	Matza, 2005[200]	Urgency UI or OAB	4 bother scales for OAB symptoms 1 item to indicate the most bother symptom	Not available	5 to 1 for first 4 items	Yes/Yes
PPBC	Coyne, 2005[198] Capo, 2008[199] Matza, 2005[200]	Any/not specified	Single-Item Global Measure	Incontinence episodes/7days diary 7.4 in many severe cases 3.3 in very severe cases 2.0 in moderate severe cases	6 to 1	Yes/Yes
SSI/SII	Black, 1996[612]	Stress UI	Severity Incontinence impact	Not available	20 to 0 for SSI 16 to 0 for SII	Yes/Yes
SUIQQ	Kulseng-Hanssen, 2003[168]	Stress UI or Urgency UI (OAB)	Total QoL	Not available	12 to 0 for the stress incontinence index 8 to 0 for the urgency incontinence index 16 to 0 for the QoL index	Yes/Yes
UDI	Uebersax,1995[201] Shumaker, 1994[136] Barber,2009[202] Dyer, 2010[203]	Stress UI or Urgency UI (OAB)	Symptom: irritative, stress, obstructive	-6.4 to -22.4 -35 to -43 (anchor-based) or -10 to -25 (distribution-based) for UUI -4.6 to -16.5 for UDI-stress subscale	100 to 0 for each subscale	Yes/Yes
UDI-6	Uebersax, 1995[201]	Any/not specified	Symptom: irritative, stress, obstructive	Not available	18 to 0	Yes/Yes
Screening						
3IQ	Brown, 2006[182]	Any/not specified	3 questions to classify UUI and SUI	Not available	Categorical variables	No/No

Table 5. Diagnostic tools to assess clinical importance and monitor effectiveness of treatments of UI (continued)

Tools*	References (all that mentioned)	Conditions	Domain	Minimal Important Differences	Worst to Best	Validity/ Reliability
B-SAQ	Basra, 2007[204]	Any/not specified	Symptoms Bother	Symptom score 7-9: significant problem Symptom score 10-12: very significant problem Bother score 7-9: significant problem Bother score 10-12: major problem	12 to 0	Yes/Yes
ISQ	Gunthorpe, 20002[156]	Any/not specified	Five items for predicting UI Three items for concerns	Not available	Algorism for predicting UI 12 to 3 for concerns of UI	Yes/Yes
LUSQ	Shaw, 2002[598]	Any/not specified	Presence of incontinence Severity Urgency Frequency Nocturia	Not available	Categorical variables	Yes/Yes
MESA	Diokno, 1986[599]	Any/not specified	General medical Urological: severity (frequency and quantity) and nature (stress, urge, or mixed) Social Mental health	Not available	Categorical variables	Yes/Yes
OAB-V8	Yalcin, 2003[197]	Urgency UI or OAB	8 items for screening	Not available	40 to 0	Yes/No
QUID	Bradley, 2005[175]	Any/not specified	Stress score Urge score	Not available	15 to 0 for each score	Yes/Yes
USP	Haab, 2008[600]	Any/not specified	Stress urinary incontinence Overactive bladder Low stream	Not available	9 to 0 for SUI 21 to 0 for OAB 9 to 0 for low stream	Yes/Yes
Quality of Life						
BFLUTS-SF	Jackson, 1996[141] Brookes, 2004[618] Reid, 2007[619]	Any/not specified	Symptom Severity Bothersome Sexual function Total QoI	Not available	20 to 0 for the incontinence score 12 to 0 for the voiding score 15 to 0 for the filling score 6 to 0 for the sexual function score 18 to 0 for the QoI score	Yes/Yes

Table 5. Diagnostic tools to assess clinical importance and monitor effectiveness of treatments of UI (continued)

Tools*	References (all that mentioned)	Conditions	Domain	Minimal Important Differences	Worst to Best	Validity/ Reliability
CONTLIFE	Amarenco, 2003[164]	Any/not specified	Global health and quality of life Daily Activities Emotions Sexual function Effort Activities Self-Image Well-Being	-7 to -20 (graph only), depending on the domain, in improved population defined by decrease of at least 50% in the number of urinary leaks under treatment	0 to 100	Yes/Yes
EPIQ	Lukacz, 2005[178]	Any/not specified	QoI Defecatory dysfunction Pelvic organ prolapse Stress urinary incontinence Overactive bladder Pain and difficult voiding Anal incontinence	Not available	Not available	Yes/Yes
IBS	Abdel-Fattah, 2007[620]	Any/not specified	Simple visual analogue scale	Not available	100 to 0	No/No
ICIQ	Avery, 2004[621]	Any/not specified	Frequency Severity Bothersome Social limitation Sexual function Interference with everyday life Total QoI	Not available	21 to 0	Yes/Yes
ICIQ-SF	Klovning, 2009[205]	Any/not specified	Frequency Severity Total QoI	With QoI Mean 16.3 for very severe UI (defined by 2000 ISI) 12.3 for severe UI Without QoI 9.4 for very severe UI 6.8 for severe UI	21 to 0 with QoI 11 to 0 without QoI	Yes/Yes
ICS	Stothers, 2004[622]	Any/not specified	Global health and quality of life Social interaction Sexual function Financial impact Satisfaction Personal strain	Not available	45 to 0	Yes/Yes

Table 5. Diagnostic tools to assess clinical importance and monitor effectiveness of treatments of UI (continued)

Tools*	References (all that mentioned)	Conditions	Domain	Minimal Important Differences	Worst to Best	Validity/ Reliability
IHI	Rai, 1994[623]	Urgency UI or OAB	Health/function Emotion	Not available	68 to 0	Yes/No
IIQ	Shumaker,1994[136] Uebersax, 1995[201] Hagen, 2002[206] Barber, 2009[202] Dyer, 2010[203]	Any/not specified	Travel Physical activity Social Emotional Total QoI	-6.5 to -17.0 -18 to -50 for UUI	100 to 0 for each domain	Yes/Yes
IIQ-7	Uebersax, 1995[201]	Any/not specified	Travel Physical activity Social Emotional Total QoI	Not available	21 to 0	Yes/No
IOQ	Bjelic-Radisic, 2007[624]	Stress UI	Symptom Complication Satisfaction QoI	Not available	2100 to 0	Yes/Yes
I-QOL	Patrick,1999[207] Bushnell, 2005[208] Wagner, 1996[209] Oh, 2007[210] Schurch, 2007[211] Yalcin, 2006[212] Yalcin, 2010[213] Hollingworth, 2010[214]	Any/not specified Neurogenic UI	Avoidance and Limiting behavior Psychological impact Social embarrassment Total QoI	2 to 5 for UI 6.3 for the within-group MCID: Patients appear to recognize important clinical value at reductions of 70% or more incontinence episode frequency 2.5 for the between-group MCID 4 to 11 for neurogenic UI A ≥10-point increase was associated with a 0.05 SF- 6D increase in patients with neurogenic UI	0 to 100	Yes/Yes
KHQ	Kelleher, 1997[215] Reese, 2003[216] Sand, 2007[217] Kelleher, 2004[218] Mostafa, 2010[219]	Any/not specified Urgency UI or OAB	Severity Incontinence impact Role limitation Physical limitation Social limitation Personal relationship Emotions Sleep and energy General health	-3 to -4 for general health and severity domains -5 to -6 for other domains "Very Much improved or Much improved" in PGI-I corresponds to a mean change in KHQ of 46 & 35 points (Range 17 – 60 points) with clear demarcation from those reporting "no change and/or worse condition" (mean 2 & -21; Range -25 – 10).	100 to 0 for each domain	Yes/Yes
LIS	Shaw, 2 004[625]	Any/not specified	Impact on activities Impact on feelings	Not available	22 to 0 for activities 20 to 10 on feelings	Yes/Yes
OAB-q	Coyne, 2002[626] Coyne, 2006[627]	Urgency UI or OAB	Bothersome Social interaction Sleep and energy Concern/worry Coping Total QoI	10	0 to 100 for bother score 100 to 0 for QoI	Yes/Yes

Table 5. Diagnostic tools to assess clinical importance and monitor effectiveness of treatments of UI (continued)

Tools*	References (all that mentioned)	Conditions	Domain	Minimal Important Differences	Worst to Best	Validity/ Reliability
PISQ	Rogers, 2001[628]	Any/not specified	Behavioral/emotive Physical activity Partner-related Total score	Not available	0 to 125	Yes/Yes
PRAFAB	Hendriks, 2007[220] Hendriks, 2008[221] Hendriks, 2008[222]	Any/not specified	Protection Amount Frequency Adjustment Body image	>14 points for severe UI (>2 g/hour urine loss)	20 to 5. 4 points/ item (1–4) with a total PRAFAB-Q score of 20 points	Yes/Yes
UISS	Stach-Lempinen, 2001[161]	Any/not specified	Elimination Usual activities Sexual function Depression Distress Total QoI	>11.02 points for severe UI (>30 g/24 hour urine loss)	30 to 0	Yes/Yes
UQ	Matza, 2005[200]	Stress UI or Urgency UI (OAB)	15 Likert-scale items nocturia Fear of incontinence Time to control urge Impact on daily activities 4 visual analog scales Urinary urgency's severity Intensity Impact Discomfort	Not available	1 (or 5) to 5 (or 1) for Likert-scale 10 to 1 for visual analog scales	Yes/Yes
YIPS	Lee, 1995[629]	Any/not specified	Eight-item seven-point rating scales a unidimensional measure Three single-item measures of self-perceptions of change in continence status, health status, amount of leakage	Not available	0 to 7 for eight rating scales Categorical variables for three single-item measures	Yes/Yes
Patient Satisfaction						
OAB-SS	Blaivas, 2007[601]	Urgency UI or OAB	5 items for urgency 2 items for frequency	Not available	5 points Likert scales	Yes/Yes

Table 5. Diagnostic tools to assess clinical importance and monitor effectiveness of treatments of UI (continued)

Tools*	References (all that mentioned)	Conditions	Domain	Minimal Important Differences	Worst to Best	Validity/ Reliability
BSW	Pleil, 2005[602]	Urgency UI or OAB	Benefit Satisfaction Willingness to continue	-2.21 mean number of incontinence episodes per 24 hours for much benefit population	Categorized for each domain	Yes/No
EPI	Burgio, 2006[603]	Any/not specified	One item for estimated percent improvement	Not available	0 to 100	Yes/No
GPI	Burgio, 2006[603]	Any/not specified	One item for global perception of improvement	Not available	5 categories	Yes/No
PSQ	Burgio, 2006[603]	Any/not specified	One item for patient satisfaction	A 70% improvement in the frequency of incontinence episodes on bladder diary as a critical threshold	3 categories	Yes/No
TBS	Colman, 2008[604]	Urgency UI or OAB	One item for patient-reported benefits	UUI episodes/24 hours +1.31 in "4" group -0.52 in "3" group -1.62 in "2" group -2.38 in "1" group	4 to 1	Yes/Yes

* **3IQ:** Three Incontinence Questions Questionnaire; **BFLUTS:** Bristol Female Lower Urinary Tract Symptoms Questionnaire; **B-SAQ:** Bladder Self-Assessment Questionnaire or Bladder Control Self-Assessment Questionnaire (BCSQ); **BSW:** Benefit, Satisfaction with treatment, and Willingness; **Contilife:** Quality of Life Assessment Questionnaire Concerning Urinary Incontinence; **EPI:** Estimated Percent Improvement; **EPIQ:** Epidemiology of Prolapse and Incontinence Questionnaire; **GPI:** Global Perception of Improvement; **IBS:** Incontinence Bothersome Scale; **ICIQ:** International Consultation on Incontinence Modular Questionnaire; **ICS:** Incontinence Classification System; **IHI:** Urinary Incontinence Handicap Inventory; **IIQ:** Incontinence Impact Questionnaire; **IIQ-7:** Incontinence Impact Questionnaire - short form; **IOQ:** Incontinence Outcome Questionnaire; **I-QOL:** Urinary Incontinence- Specific Quality of Life Instrument; **ISI:** Incontinence Severity Index; **ISQ:** Incontinence Screening Questionnaire; **KHQ:** King's Health Questionnaire; **LIS:** Leicester Impact Scale; **LUSQ:** The Leicester Urinary Symptom Questionnaire; **MESA:** Medical, Epidemiological, and Social Aspects of Aging Questionnaire; **OAB-q:** Overactive Bladder Questionnaire; **OAB-S:** Overactive Bladder Satisfaction Questionnaire; **OAB-SS:** Overactive Bladder Symptom Score; **OAB-V8:** OAB Awareness Tool; **PGI-I and PGI-S:** Patient Global Impression of Improvement and of Severity; **PISQ:** Pelvic Organ Prolapse–Urinary Incontinence Sexual Function Questionnaire; **POSQ:** Primary OAB Symptom Questionnaire; **PPBC:** Patient Perception of Bladder Condition; **PRAFAB:** Protection, Amount, Frequency, Adjustment, Body image; **PSQ:** Patient Satisfaction Question; **PUF:** patient symptom scale (Pelvic Pain, Urgency, and Frequency; **QUID:** Questionnaire for Urinary Incontinence Diagnosis; **SF:** Short Form**; SSI and SII:** Symptom Severity Index and Symptom Impact Index for stress incontinence in women; **SUIQQ:** Stress and Urge Incontinence and Quality of Life Questionnaire; **TBS:** Treatment Benefit Scale; **UDI:** Urogenital Distress Inventory; **UDI-6:** Urogenital Distress Inventory-6; **UISS:** Urinary Incontinence Severity Score; **UI:** Urinary Incontinence Score; **UQ:** Urgency Questionnaire; **USP:** Urinary Symptom Profile; **YIPS:** York Incontinence perceptions scale.

Question 2: How Effective is the Pharmacologic Treatment of UI in Women?

We synthesized evidence of efficacy and comparative effectiveness of the drugs for stress UI, including topical estrogen and serotonin-noradrenalin uptake inhibitors and drugs used in the treatment of overactive bladder.[10] We integrated information about inclusion, exclusion criteria, sponsorship, conflict of interest (Appendix Table F27) and quality of the studies (Appendix Table F28) in synthesis of evidence. We report here study characteristics that could influence the treatment effects of drugs for UI.

Clinical Effectiveness of Topical Estrogen Therapy

Evidence from individual RCTs indicated greater continence and improvement in UI with vaginal estrogen formulations and worsening of UI with transdermal patches (Table F29). Evidence was insufficient to draw conclusions about clinical efficacy of different topical estrogen treatments for UI.

Four RCTs of 640 women examined the effects of topical estrogen formulations compared to placebo on UI (Appendix Table F27). The studies enrolled postmenopausal women with urodynamic stress,[630,631] clinical symptoms of any UI,[632] or with urge syndrome.[633] Estrogen was administered in vaginal tablets, gel,[630] subcutaneous implants,[633] intravaginal ovules,[631] or transdermal patches.[632] The length of treatment varied from 6 months[630,631,633] to 2 years.[632] Three studies aimed to treat UI.[630,631,633] One study examined very low dose transdermal estrogen formulation proposed for prevention of osteoporosis in postmenopausal women..[632]

Continence. Two RCTs examined urinary continence [630,633] (Appendix Table F30). Vaginal estrogen tablets increased continence more often than placebo (RR 20.68, 95 percent CI 1.23; 346.46).[630] The authors needed to treat five women with estrogen tablets to achieve continence in one woman (number needed to treat [NNT] 5, 95 percent CI 3; 12).[630] In contrast, 25 mg 17 beta-estradiol implant did not resolve stress or urgency UI compared to placebo.[633]

Improvement in UI. Improvement in UI was significantly greater than placebo with vaginal estrogen tablets [630] and vaginal ovules.[631] (Appendix Table F31). Women complained of stress UI less frequently with intravaginal estrogen formulations than with placebo.[631] Unchanged incontinence was less frequent with intravaginal estrogen than with placebo.[630] In contrast, transdermal patches with very low doses of estrogen worsened any UI and stress UI at 2 years[632] (Appendix Table F32). Adjusted for clinical site odds ratios of worsened UI demonstrated increases in odds of stress UI at 4 months (OR 2.05, 95 percent CI 1.09; 3.85) but not 4 years.

Clinical Effectiveness of Duloxetine

A high level of evidence indicated significant improvement in stress UI with duloxetine, while a low level of evidence suggested that duloxetine did not resolve stress UI when compared to placebo. A low level of evidence suggested improvement in quality of life in women with UI. Evidence was insufficient to conclude benefits of duloxetine in women with urgency UI. Risk of adverse effects was significantly higher with duloxetine than with placebo. Duloxetine resulted in improved UI in 75-140 women per 1,000 treated, [212,224,230,231,243,244,248] while 105 women per 1,000 treated stopped taking duloxetine because of adverse effects.

The 24 publications that reported clinical outcomes with duloxetine,[166,212,224,228-249] included six primary RCTs of 4,292 women,[224,243-246,248] collaborative publications from the DESIRE Study group (3,983 subjects),[228] Duloxetine Dose Escalation Study Group (516 subjects),[229] Duloxetine OAB Study Group (306 subjects),[230] Duloxetine Urinary Incontinence Study Group (2,741 patients),[166,231-234] Duloxetine/Pelvic Floor Muscle Training Clinical Trial Group (201 subjects), pooled analyses of individual patient data (52,891 subjects),[212,238-242,249] safety evaluation using pooled analysis of 42 placebo-controlled clinical trials of 8,504 patients[247] (Appendix Table F27), and nonrandomized prospective observational studies[236,237] (Appendix Table F33).

Continence. Two studies of 736 women demonstrated greater continence with placebo than with duloxetine (pooled RR 0.92, 95 percent CI 0.86; 0.99)[231,232] (Appendix Table F34). One publication from the Duloxetine Urinary Incontinence Study Group did not find significant dose response increase in continence with 40 mg of the drug versus 20 mg/day[232] (Appendix Table F35).

Improvement in UI. Women experienced more than a 50 percent reduction in frequency of UI episodes with duloxetine[212,224,231,243,248] (Appendix Table F36). More women perceived an improvement in UI as either much better or better with duloxetine than with placebo[224,230,231,244] (Appendix Table F36). Seven women had to take duloxetine to achieve a 50 percent reduction in UI episodes in one woman (Table 6). Thirteen women (NNT 13, 95 percent CI 7; 143) needed to be treated so one woman would perceive an improvement as either much better or better. Improvement in UI was greater with 40 mg/day compared to 20 mg/day[232] (Appendix Table F37). Treatment failure did not differ between duloxetine and placebo[224,230,244,246] (Appendix Table F38).

Adverse effects. Adverse effects with duloxetine versus placebo were examined in 15 studies of 26,703 subjects.[224,229-235,239,243-246,248,249] Results demonstrated the importance of definitions and measurements of harms. Studies of any adverse effects or treatment-related adverse effects (as judged by investigators) reported less relative harm from the drug than studies of individual adverse effects. For example, the relative increase in treatment-related adverse effects (as judged by investigators) was 36 percent (pooled RR 1.36, 95 percent CI 1.28; 1.44)[224,230,231,233,234,243-245,248] (Appendix Table F39). At the same time, the relative increase in several harms was much larger. For instance, relative increase in somnolence was 761 percent (pooled RR 8.61, 95 percent CI 4.58; 16.20).[224,229-231,233-235,239,243-246,248] Nausea (NNT 5, 95 percent CI 4; 7),[224,231,232,234,235,239,245] dry mouth (NNT 9, 95 percent CI 7; 11),[224,229-235,239,243-246,248] and fatigue (NNT 13, 95 percent CI 10; 19)[224,230-234,239,243-246,248] were among the most common adverse effects of duloxetine when compared to placebo (Appendix Table F40).

The studies did not show consistent dose response associations between duloxetine and adverse effects (Appendix Table F41). The Duloxetine Dose Escalation study reported lower risks of adverse effects at a starting dose of 20 mg with a slow dose escalation to 80 mg/day.[229] Large pooled analysis that examined cardiovascular adverse effects of duloxetine[247] demonstrated electrocardiographic abnormalities that were statistically but not clinically significant.

Women stopped taking duloxetine because of adverse effects more often than because of placebo (Appendix Table F42). The relative increase in discontinuation of duloxetine treatment for any adverse effects was 340 percent (pooled RR 4.4, 95 percent CI 3.24; 5.86).[224,229,231-234,236,243,244,246] Discontinuation rates differed across the studies. We explored heterogeneity by women's age, prior treatments, and concurrent medications for UI, and baseline type and severity

of UI (Appendix Table F43), and did not find significant association with the outcome (Appendix Table F44). We explored heterogeneity by study quality (Appendix Table F45) and did not find significant association with the outcome (Appendix Table F44).

Among individual adverse effects leading to treatment discontinuation, every tenth woman stopped taking duloxetine because of effects such as nausea,[229,231-235,239,243,246] somnolence,[232,233,235,239,243,246] insomnia ,[229,231,233-235,239,243] dizziness,[229,231-235,239,243] headache,[229,232,246] fatigue,[229,233,239,246] diarrhea,[239,246] and constipation,[235,239] which were the most common adverse effects leading to treatment discontinuation (Appendix Table F40).

Clinical Effectiveness of Oxybutynin

A high level of evidence indicated that oxybutynin increased continence and improved UI more often than placebo but also resulted in treatment discontinuation due to adverse effects (see Table ES2 in the Executive Summary). Dry mouth was the most common adverse effect. Oxybutynin resulted in resolved UI in 110 women per 1,000 treated while 50 women per 1,000 treated stopped taking oxybutynin because of adverse effects. Evidence was insufficient to conclude improved quality of life with oxybutynin. A low level of evidence indicated greater rates of adverse effects and dry mouth with immediate release oxybutynin than with controlled release oral or transdermal oxybutynin. A low level of evidence indicated that larger versus lower doses of extended oxybutynin resulted in greater improvement in UI and the same rates of dry mouth, but greater treatment withdrawal.

We identified 15 publications of individual RCTs,[250-264] one RCT of intravesicular injection of oxybutynin in 52 women,[265] one post hoc analysis of RCTs,[266] and ten RCTs that compared different doses and formulations of oxybutynin[267-276] (Appendix Table F27). We also reviewed a noncontrolled Ditropan XL study of 256 women,[277] a Multicentre Assessment of Transdermal Therapy in Overactive Bladder With Oxybutynin (MATRIX) study of 2,888 women, pooled analysis of dosing studies,[278-280] and five observational studies of harms and discontinuation rates of oxybutynin therapy[281-285] (Appendix Table F33).

Continence. Urinary continence was greater with oxybutynin than with placebo[254,259,262,634,635] (Appendix Table F46). Pooled results were consistent with nonsignificant heterogeneity across the studies despite differences in populations and doses of the drug. The pooled results, however, were sensitive to one multicenter study at 76 clinics in the United States that demonstrated significant increase in resolved UI with oxybutynin.[259] The drug needed to be given to nine women to achieve continence in one woman (Table 7).

Improvement in UI. Oxybutynin improved UI more often than placebo[251,261-263,266,369,370,396,634-637] (Appendix Table F46). The drug needed to be given to eight women to improve UI in one woman (Table 7). Magnitude of the effect varied across the studies with significant heterogeneity in pooled estimates. Dose of the drug did not explain heterogeneity (p value for meta-regression >0.5). Differences in definitions of improved UI may contribute to heterogeneity. The studies that defined improvement as a reduction of 75 percent in UI episodes[261,634] reported similar relative risk and absolute risk difference. In contrast, the studies that did not quantify improvement in UI tended to demonstrated very large benefits from oxybutynin compared to placebo (Appendix Table F46).

We explored heterogeneity by women, treatment, and study characteristics and did not find significant association with the outcomes (Appendix Table F47).

Change in quality of life was inconsistent within the studies and across the studies[252,255,370,634,638] (Appendix Tables F48 and F49).

Treatment failure with unchanged or worsened UI was less common with oxybutynin than with placebo[261,369,634,636,637] (Appendix Table F46).[369,634,636,637]

Adverse effects. Discontinuation of treatments did not differ between oxybutynin and placebo[251,259,634,636,639] (Appendix Table F46). However, discontinuation of treatment due to adverse effects was greater with active drugs than with placebo (Appendix Table F46).[29,258,259,369,370,639] Among every 22 treated, one woman stopped taking the drug because of adverse effects. Interestingly, the relative increase in total adverse effects[256,369,636] or serious adverse effects[256,259,369] was not different from placebo (Appendix Table F46). The differences across the studies in definitions and methods to assess harms may contribute to discrepancies.

Dry mouth was the most common adverse effect[250,251,255,259,262,263,369,370,634,639] (Appendix Table F46). Oxybutynin given to three women caused dry mouth in one woman (NNT 3, 95 percent CI 2; 3) (Table 7).

Several studies compared formulations and doses of oxybutynin (Appendix Table F50). The Uromax Study demonstrated greater improvement in UI with larger doses of extended oxybutynin (15 mg versus 5 or 10 mg).[275] The larger doses, however, resulted in greater treatment withdrawal for 5 versus 15 mg/day.[275] The Transdermal Oxybutynin Study found that severe dry mouth and constipation were less common with transdermal when than with oral immediate oxybutynin.[271] Adverse effects were less common with once-daily, controlled-release formulation oxybutynin than with immediate-release oxybutynin.[640] Dry mouth was less common with transdermal versus oral immediate release oxybutynin,[271] with controlled versus immediate release oxybutynin,[267] and with lower versus larger doses of controlled release oxybutynin.[275]

Clinical Effectiveness of Tolterodine

A high level of evidence indicated increased continence and significant improvement in UI with tolterodine treatments than with placebo in women with UI (see Table ES2 in the Executive Summary). A low level of evidence indicated improvement in quality of life with tolterodine treatment. Adverse effects including autonomic nervous system disorders, abdominal pain, dry mouth, dyspepsia, and fatigue were significantly more common in women with tolterodine than with placebo. Tolterodine resulted in resolved UI in 85 women per 1,000 treated, while 79 women per 1,000 treated experienced various adverse effects. Discontinuation of the treatment and stopping treatment due to adverse effects did not differ between tolterodine and placebo.

We identified 24 RCTs that examined clinical outcomes with tolterodine versus placebo,[226,286-304,306-308,641] publications of secondary data analyses,[29,309-311] multicenter nonrandomized clinical trials,[312] including the IMPACT study (Appendix Table F27)[313-315] and several noncontrolled observational studies of harms with tolterodine treatments (Appendix Table 33).[316-319]

Continence. Urinary continence was achieved more often with tolterodine than with placebo in pooled analysis (pooled RR 1.2, 95 percent CI 1.1; 1.4)[226,301,308,349] (Appendix Table F46). The drug had to be given to 12 women to achieve continence in one woman (NNT 12, 95 percent CI 8; 12) (Table 7).

Improvement in UI. Tolterodine improved UI more often than placebo[30,294,296,302,306,308,349,641] (Appendix Table F46). The drug needed to be given to nine

women to achieve improvement in UI in one woman (Table 7). Magnitude of the association differed across the studies, probably because of different definitions of improvement. Women's characteristics, treatment dose and duration, and study quality were not associated with the outcome (Appendix Table F47).

Secondary data analyses demonstrated that 4mg/day of tolterodine, but not 2 mg/day, improved subjects' perceptions of their bladder condition (Appendix Table F51).[29,30,296] Women evaluated treatment success as "much better" more often with 4 mg/day of tolterodine than with placebo[296] (Appendix Table F51). One pooled analysis reported a greater decrease in the urgency perception scale score with 4 mg of tolterodine daily than with placebo.[296] An evidence-based report about treatment of overactive bladder in women showed a significant decrease in frequency of UI episodes with immediate release (weighted mean difference 1.45, 95 percent CI 1.24; 1.66) and with controlled release tolterodine (weighted mean difference 1.75, 95 percent CI 1.65; 1.85).[52] One nonrandomized study reported that 79 percent of subjects experience improvement in UI after 12 weeks of tolterodine.[313-315]

Adverse effects. Adverse effects were more common with tolterodine than with placebo[226,263,288,289,292,297,300,301,303,307,308,337] (Appendix Table F46). Active drugs needed to be given to 13 subjects in order cause adverse effects in one woman (Table 7). Half of the women experienced adverse effects with 4 mg/day of tolterodine in the IMPACT noncontrolled study.[313-315] According to pooled analysis of the aggregate data[286,289-291,308] and one pooled analysis of individual patient data, women did not have serious adverse effects more often with tolterodine than with placebo.[29] The same pooled analysis, however, reported that dose reduction in the case of intolerance was more common with 2 mg twice/day of tolterodine than with placebo[29] (Appendix Table F51). The rates of all[288,292] or serious adverse effects with different doses and formulations of tolterodine did not differ[290,291] (Appendix Table F52).

Among individual adverse effects, tolterodine significantly increased rates of autonomic nervous system disorders,[286,288,289] constipation,[288,290-292,295,297,298,303,337,338 300-302,308,349,641] dyspepsia,[226,263,290,291,295,297,308] and fatigue[300,308,641] (Table 8).Tolterodine also increased rates of abdominal pain.[290-292,295,297,308] Pooled analysis of individual patient data demonstrated greater rates of abdominal pain,[296] autonomic nervous system disorder,[29] fatigue,[30,311] and dry mouth[30,296,311] (Appendix Table F51). Autonomic nervous system disorder was less common with 1 mg twice daily versus 2 mg daily.[29,286] Differences in adverse effects of different doses and formulations of tolterodine were not consistent across the individual studies and pooled data from individual patients (Appendix Table F52). Tolterodine caused dry mouth in one woman among eight treated according to a pooled analysis of 14 studies (Table 7).[226,263,290,292,300-303,307,308,337,338,349,641] Increases in the rates of dry mouth were not greater with higher doses of tolterodine (p value for meta regression >0.5).

Treatment discontinuation rates[289,290,294,298,300,302,304,308,337,338] and treatment discontinuation due to adverse effects did not differ between tolterodine and placebo[263,289,291,292,297,298,300,302,303,308,338,349,641] (Table 7). Pooled analyses also demonstrated no differences in discontinuation rates between 2 mg of tolterodine twice daily[29] and 4 mg of tolterodine once daily[311] (Appendix Table F51). One pooled analysis reported that treatment discontinuation was lower with 1 mg twice daily than with 2 mg daily of tolterodine (Appendix Table F52). Treatment discontinuation due to adverse effects did not differ in individual RCTs[292] and in pooled analyses of the studies that examined 2 mg of tolterodine twice daily[289,291,292] or 4 mg daily[297,298,300] (Appendix Table F53).

Clinical Effectiveness of Darifenacin

A high level of evidence indicated significant improvement in urgency UI episodes and several domains of quality of life with 7.5 and 15 mg of darifenacin compared to placebo. Adverse effects were more common with darifenacin than with placebo. Darifenacin increased rates of constipation, dry mouth, dyspepsia, and headache. Darifenacin improved UI in 112 women per 1,000 treated while 173 women per 1,000 treated experienced various adverse effects. Evidence was insufficient to conclude better benefits with 30 mg of darifenacin/day. The largest dose, however, resulted in greater rates of adverse effects. Treatment discontinuation rates due to adverse effects were the same between darifenacin and placebo.

Seven RCTs reported clinical outcomes of darifenacin versus placebo[320-325 326,327] and several publications of secondary data analyses[328-333] (Appendix Tables F27 and F28).

Continence. Urinary continence outcomes were not examined with darifenacin treatment. One pooled analysis demonstrated that women did not experience continence for more than 7 consecutive days more often with 15 mg of darifenacin than with placebo[330] (Appendix Table F54). The rates of more than 3 dry days/week were greater than placebo with 7.5 mg of darifenacin (RR 1.47, 95 percent CI 1.02; 2.13) and with 15 mg of darifenacin (RR 1.48, 95 percent CI 1.04; 2.09).[330] The drug had to be given to 17 women to achieve 3 dry days/week in one woman.[330]

Improvement in UI. Darifenacin improved UI more often than placebo[322,323,325] (Appendix Table F46). Darifenacin needed to be given to nine women in order to improve UI in one woman (Table 7). Pooled individual patient data from three RCTs also indicated a significant reduction of more than 90 percent in UI episodes more often with 7.5 mg and 15 mg of darifenacin than with placebo[330] (Appendix Table F54). Women experienced reductions of more than 50 percent [322,323,325] or more than 70 percent [323,325] in UI episodes more often with darifenacin than with placebo.

Adverse effects. Adverse effects were more common with 7.5[323,325] and 15 mg/day of darifenacin than with placebo.[323,324] Adverse effects were experienced by one woman among every six treated with darifenacin[323-325] (Table 7). The Darifenacin Study found a significant dose response association with a greater rate of adverse effects with larger doses of darifenacin (Appendix Tables F55 and F56). The rates of serious adverse effects did not differ between darifenacin and placebo.[323,324]

Rates of individual adverse effects did not demonstrate a consistent dose response association with darifenacin (Appendix Table F56). Among individual adverse effects, darifenacin increased rates of constipation.[321,323-325,333] The association was not dose responsive because constipation with 15 mg/day did not differ from placebo.[321,323,324,333] Dry mouth was more common with darifenacin than with placebo.[321,323-325,333] Much less expected was the fact that rates of dry mouth did not differ from placebo, even with larger doses of darifenacin of 15 mg[321,323,324,333] or 30 mg/day.[323,333] Dyspepsia was more common with darifenacin than with placebo[321,323,324,333] (Table 8).

One RCT examined short-term effects of darifenacin controlled release (3.75, 7.5, or 15 mg once daily), darifenacin immediate-release (5 mg three times daily), or placebo on cognitive function in elderly volunteers without clinical dementia.[321] The authors did not find statistically significant differences, except increased memory scanning speed, with 7.5 and 15 mg of darifenacin.[321]

Treatment discontinuation rates[324,333] and discontinuation because of adverse effects did not differ between darifenacin and placebo[322-327,333] (Table 7). The Darifenacin Study Group reported a significant dose response association with greater rates of withdrawals due to adverse effects with 30 mg than with 7.5 mg of darifenacin/day[323] (Appendix Table F56).

Clinical Effectiveness of Solifenacin

A high level of evidence suggested that solifenacin increased continence with greater benefits with the larger dose of the drug in women with urgency and mixed UI. Evidence was insufficient that solifenacin improved quality of life. A high level of evidence suggested greater risk of dry mouth, constipation, and blurred vision with the drug. A high level of evidence suggested that 10 mg of solifenacin increased the risk of severe dry mouth and constipation. Treatment discontinuation due to adverse effects was more common with solifenacin than with placebo. Solifenacin resolved UI in 107 women per 1,000 treated, while 12 women per 1,000 treated stopped taking the drug because of adverse effects.

We identified nine publications of individual RCTs[334-342] and pooled analysis of individual patient data from four RCTs[343-345] that examined clinical outcomes with solifenacin compared to placebo (Appendix Table F27). We also reviewed the results from the nonrandomized VOLT flexible-dosing trial (VESIcare Open-Label Trial) that examined quality of life in subjects with OAB and urgency UI at 207 centers in the United States.[642,643]

Continence. Solifenacin resolved UI more often than placebo (pooled RR 1.5, 95 percent CI 1.4; 1.6)[336,340,342,343,345] (Appendix Table F46). Solifenacin needed to be given to nine women to achieve continence in one woman (Table 7). The effect was consistent across the studies. Complete urinary continence was greater with 10 mg of solifenacin than with placebo in two pooled analyses of individual patient data with a relative increase of 43 percent[345] to 53 percent[343] (Appendix Table F57). One pooled analysis of four RCTs demonstrated significant dose response increase in continence with better effect with 10 versus 5 mg of solifenacin in women with mixed UI[345] (Appendix Table F58). Another pooled analysis, however, did not find better continence rates with the larger dose of the drug in women with urgency UI.[343]

Improvement in UI. Solifenacin improved UI more often than placebo[336,341] (Table 7). The drug needed to be given to six women to achieve improvement in one woman.[336,341]

Solifenacin in a dose of 5 mg/day improved all examined domains of quality of life measured with King's Health Questionnaire in one RCT.[345] The largest improvement was in role limitations (mean difference -10.92, 95 percent CI -11.25; -10.59), coping/severity measures (mean difference -8.21, 95 percent CI -8.48; -7.94), emotions (mean difference -7.84, 95 percent CI -8.18; -7.51), and physical limitations (mean difference -7.54, 95 percent CI -7.88; -7.21). The VOLT study found that 80.4 percent of the subjects reported improvement in their Patient Perception of Bladder Condition.[643] The VESIcare Investigation of Bother and Quality of Life in Subjects With OAB VIBRANT study reported greater perceived benefit (RR 1.78, 95 percent CI 1.48; 2.14), satisfaction (RR 1.42, 95 percent CI 1.26; 1.61), and willingness to continue (RR 1.39, 95 percent CI 1.23; 1.57) with flexible 5-10 mg doses of solifenacin[336] (Appendix Table F59).

Adverse effects. Adverse effects were more common with solifenacin than with placebo[337,340-342] (Table 7). The association was significant but not dose responsive (p value for meta-regression >0.5). Among individual adverse effects, dry mouth was the most common with both doses of solifenacin.[336,337,339-341,343,345,644] Pooled analysis of individual patient data reported significant positive dose response association between dry mouth and the larger dose of the

drug[343,345] (Appendix Table F58). The larger dose of the drug caused blurred vision and mild blurred vision more often than placebo (Appendix Table F57).[343,345] Constipation and severe constipation were more common with 10 mg of solifenacin than with placebo.[343,345]

Adverse effects leading to discontinuation were more common with solifenacin than with placebo (Table 7).[338-343,345,644] Every 83rd woman discontinued the treatment with solifenacin because of adverse effects. Much less expected was the fact that two pooled analyses demonstrated no difference in treatment discontinuation with 5 or 10 mg of solifenacin than with placebo[343,345] (Appendix Table F57). One pooled analysis of individual patient data of four RCTs reported that women with mixed UI stopped treatment because of adverse effects more often with 10 mg of solifenacin than with 5 mg of the drug[345] (Appendix Table F58).

Clinical Effectiveness of Fesoterodine

A low level of evidence indicated a significant increase in continence with fesoterodine. A high level of evidence indicated a significant improvement in urgency UI with fesoterodine compared to placebo, with a better response with 8 mg versus 4 mg. Evidence was low that fesoterodine improved quality of life in women with urgency UI. Fesoterodine treatment resulted in higher rates of adverse effects and related discontinuation of treatment than placebo. Adverse effects were more common with 8 mg than with 4 mg of fesoterodine. Women experienced dry mouth and severe dry mouth with fesoterodine more often than with placebo, with a greater risk with the larger dose of the drug. Fesoterodine resolved UI in 130 women per 1,000 treated, while 32 women per 1,000 treated stopped taking the drug because of adverse effects.

Nine RCTs[300,302,308,346-351] and four publications of secondary data analyses[30,311,352,353] reported clinical outcomes with fesoterodine compared to placebo (Appendix Table F27). All RCTs were double blinded (Appendix Table F28).

Continence. Continence was greater with fesoterodine than with placebo in two unpublished RCTs[308,349] (Appendix Table F46).

Improvement in UI. Fesoterodine improved UI more often than placebo.[302,308,347,350]The drug needed to be given to 13 women to achieve improvement in UI in one woman (Table 7). One pooled analysis with data from two RCTs of individual women found that the proportion of women indicating that their condition greatly improved or improved was significantly larger with 4 or 8 mg of fesoterodine than with placebo[30] (Appendix Table F60). Treatment response was significantly better with the higher dose of the drug[30] (Appendix Table F61). An evidence-based report about treatment of overactive bladder in women found a significant reduction in daily UI episodes with fesoterodine (weighted mean difference 2.03, 95 percent CI 1.74; 2.31).[52]

Adverse effects. Adverse effects were more common with fesoterodine than with placebo (Appendix Table F46).[300,308,350,351] One pooled analysis of two RCTs also demonstrated increased rates of adverse effects with fesoterodine than with placebo, showing that the drug given to six to ten women results in adverse effects in one woman.[353] The risk of adverse effects was dose responsive with significantly higher rates with 8 mg than with 4 mg of the drug (Appendix Table F61).[300,351] Dry mouth was the most common adverse effect with fesoterodine [300,302,308,346,347,349-351] (Appendix Table F46). An increased risk of dry mouth was dose responsive with greater rates with 8 mg than with 4 mg of the drug[300,351,352] (Appendix Table F61).

Among other adverse effects, individual RCTs (Appendix Table F46), pooled analyses of aggregate (Table 7), and pooled analyses of individual patient data (Appendix Table F60),[30,311,352] found higher rates of constipation with fesoterodine than with

placebo.[300,302,308,346,347,349-351] Increased risk of urinary tract infection was small but significant with fesoterodine versus placebo in one RCT[302] while pooled analysis of individual patient data did not show statistically significant differences in the rates of urinary tract infection between 4 or 8 mg of darifenacin and placebo[353] (Appendix Table F62).

Discontinuation due to adverse effects was more common with fesoterodine than with placebo[302,308,346,347,349,350] (Appendix Table F46). The drug given to 31 women resulted in discontinuation of treatment due to adverse effects in one woman (Table 7). One pooled analysis of individual patient data from two RCTs[352] examined withdrawal rates due to adverse effects with fesoterodine and placebo (Appendix Table F60). Discontinuation rates due to adverse effects did not differ between 4 mg of fesoterodine and placebo, but were significantly higher with 8 mg of darifenacin than with placebo.[352]

Clinical Effectiveness of Trospium

A high level of evidence indicated increased continence with trospium compared to placebo. There was insufficient evidence that trospium improved quality of life. Women experienced dry mouth, dry eye, dry skin, and constipation more often with the drug than with placebo. Adverse effects resulted in treatment discontinuation with the drug more often than with placebo. Trospium resolved UI in 114 women per 1,000 treated, while 17 women per 1,000 treated stopped taking the drug because of adverse effects.

Eight publications of RCTs,[354-358,360-362] two publications of the Trospium Study Group,[363,364] and one pooled analysis of individual patient data from two RCTs[358] examined the effects of trospium on clinical outcomes compared to placebo (Appendix Table F27).

Continence. Trospium increased continence more often than placebo [357,358,363,364] (Appendix Table F46). The drug needed to be given to nine women to achieve continence in one woman (Table 7).

Improvement in UI. Trospium improved UI more often than placebo.[354,363] The Trospium Study Group demonstrated a significant improvement in UI, defined as a greater than 50 percent decrease in the number of incontinent episodes per 24 hours.[363] An evidence-based report about treatments for overactive bladder in women demonstrated a significant reduction in urgency UI by 2.45 episodes per day (mean difference 2.45, 95 percent CI 2.19; 2.7).[52]

Adverse effects. Adverse effects were more common with trospium than with placebo[307,355,357,358,364] (Appendix Table F46). The drug had to be given to 11 women to observe an adverse effect in one woman (Table 7). Constipation rates were greater with trospium than with placebo.[355,357,358,363,364]

Women using trospium experienced dry eye,[358,364] dry mouth,[307,355,357,358,363,364] and dry skin[358,364] more often than those using a placebo. The most common adverse effect was dry mouth, experienced by one woman of every nine treated (Table 7). Discontinuation rates due to adverse effects were also higher with trospium than with placebo[355,358,360,361,363,364] (Table 7).

Clinical Effectiveness of Propiverine

A low level of evidence indicated that propiverine resolved UI. A moderate level of evidence indicated that propiverine improved urgency UI and increased the risk of adverse effects, including abnormal vision, constipation, and dry mouth in a dose responsive manner. Propiverine

resolved UI in 163 women per 1,000 treated, while 28 women per 1,000 treated stopped taking the drug because of adverse effects.

Five RCTs examined clinical outcomes of propiverine compared to placebo or to different doses of the drug[609,644-647] (Appendix Tables F27 and F28).

Continence. Propiverine increased continence more often than placebo[609,645] (Appendix Table F46). The drug had to be given to five women to achieve continence in one woman (Table 7). One study concluded higher rates of continence with immediate release propiverine than extended release (RR 1.3, 95 percent CI 1.1; 1.6).[609]

Improvement in UI. Propiverine improved UI more often than placebo[609,645,647] (Appendix Table F46). The drug was effective in resolving symptoms of urgency but not UI in older women with mixed UI (Appendix Table F63).[645] One study compared immediate versus extended release of propiverine and concluded opposite association depending on the definition of improvement.[609] Investigators rated better overall efficacy with extended release of the drug. In contrast, patients reported better overall efficacy with immediate release of the drug.[609]

Adverse effects. Propiverine caused adverse effects more often than placebo[609,646,647] (Appendix Table F46). Propiverine caused adverse effects in one woman of every six treated (Table 7). Rates of adverse effects were relatively higher with 20 mg of propiverine and 45 mg/day of propiverine than with placebo.[646] Treatment discontinuation due to adverse effects was more common with propiverine than with placebo [609,644] (Appendix Table F46).

Clinical Effectiveness of Botulinum Toxin

A high level of evidence suggested a reduction in UI episodes due to treatment with botulinum toxin, with an increased risk of elevated post-void residual in patients with severe urgency UI refractory to antimuscarinic drugs.

Four RCTs of 185 subjects reported clinical outcomes after intravesicular injection of botulinum toxin (Appendix Table F27).[607,648-650] There was one systematic review of the literature about the efficacy and safety of botulinum toxin in the management of OAB.[651]

Continence. Two RCTs demonstrated that botulinum injections resolved urgency UI. A single published RCT randomized 313 adults with idiopathic OAB and daily urgency UI to placebo or different doses of botulinum toxin.[652] The outcomes were compared after intradetrusor injections of 50, 100, 150, 200, or 300 U of botulinum toxin or placebo.[652] Continence rates were greater with the active drug (29.8 to 57.1 percent) than with placebo (15.9 percent, P <0.5) in a dose responsive fashion.[652] One unpublished RCT[607] demonstrated a significant increase in continence after a 100U-300U single injection of botulinum toxin.

Improvement in UI. One RCT reported greater rates of significant improvement in UI (>75 percent decrease in daily UI episodes) with botulinum toxin than with placebo[649] (Appendix Table F64). Recently published RCTs examined different doses of the drug and demonstrated minimal additional or clinically relevant improvement in symptoms with doses higher than 150U.[652] One RCT reported improvement in several domains in King's Health Questionnaire on quality of life after botulinum toxin compared to placebo[648] (Appendix Table F65). The differences were small but statistically significant for UI impact, severity measure, and sleep-energy disturbances.[648]

A systematic review demonstrated a significant reduction in daily UI episodes by 3.88 episodes per day (95 percent C.I. -6.15, -1.62) after botulinum.[651] Botulinum toxin, however, increased the risk of elevated post-void residual (pooled RR 8.55, 95 percent CI 3.2; 22.71).

Published RCTs found that the drug caused treatment-related adverse effects in 40 percent, and PVR (post-void residual) related catheterization in 20 percent of patients.[652] The rates of urinary tract infection increased in a dose responsive manner from 37 percent with 100U to 47.2 percent with 300U.[652] The rates of urinary retention also increased in a dose responsive manner from 19 percent with 100U to 25 percent in 300U.[652] Treatment failure with unchanged or increased UI was less common with botulinum than with placebo (RR 0.29, 95 percent CI 0.14; 0.63).[649]

Clinical Effectiveness of Resiniferatoxin

There was insufficient evidence on the benefits and harms of resiniferatoxin versus placebo in women with urgency UI.

A single RCT enrolled 58 women with idiopathic detrusor overactivity and urgency incontinence to examine clinical outcomes of resiniferatoxin versus placebo (Appendix Table F27).[653] The study did not demonstrate benefits of resiniferatoxin versus placebo (Appendix Table F66).[653] The rates of the expected adverse effects, including hypogastric pain, dysuria, and minor hematuria, did not differ between resiniferatoxin and placebo.[653]

Clinical Effectiveness of Nimodipine

There was insufficient evidence on the benefits or harms with nimodipine compared to placebo in elderly women with predominant urgency UI.

A single RCT enrolled 86 elderly adult women with urodynamic urgency UI and without clinically important stress UI to examine outcomes after 3 weeks of 30 mg nimodipine twice daily or placebo (Appendix Table F27).[654] Nimodipine reduced incontinent episodes but did not improve IIQ scores and American Urological Association (AUA) symptom scores (Appendix Table F67). Treatment discontinuation did not differ between nimodipine and placebo.[654]

Table 6. Clinical outcomes with duloxetine treatments

Reference Number of Studies	Number of Subjects	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat (95% CI)	Attributable Events/1000 Treated (95% CI)	Bayesian Odds Ratio Median (2.5; 97.5%)	Evidence
Continence 2 studies[231,232]	736	0.92 (0.86; 0.99)	-0.03 (-0.12; 0.06)			0.67 (0.23; 1.88)	Low
Improvement in PGI rating: very much or much better 4 studies[224,230,231,244]	1,138	1.68 (0.94; 3.00)	0.08 (0.01; 0.14)	13 (7; 143)	75 (7; 142)	1.99 (1.10; 4.19)	High
Improvement in UI: >50% reduction in UI episodes 5 studies[212,224,231,243,248]	4,304	1.5 (1.3; 1.7)	0.14 (0.08; 0.21)	7 (5; 13)	140 (80; 210)	1.9 (1.4; 2.9)	High
Deterioration in PGI-I rating scale: very much worse 4 studies[224,230,244,246]	1,268	0.74 (0.54; 1.02)	0.00 (-0.02; 0.02)			0.68 (0.20; 2.82)	Moderate
Deterioration in PGI-I rating scale: much worse 3 studies[230,244,246]	1,159	1.19 (0.29; 4.90)	0.00 (-0.01; 0.01)			1.18 (0.27; 5.44)	Moderate
No improvement in PGI-I rating scale: no change 3 studies[230,244,246]	1,159	0.78 (0.65; 0.94)	-0.07 (-0.12; -0.02)			0.71 (0.44; 1.17)	Low
Deterioration in PGI-I rating scale: a little worse 3 studies[230,244,246]	1,160	0.58 (0.32; 1.05)	-0.03 (-0.06; 0.01)			0.51 (0.23; 1.11)	Low
Adverse Effects that Resulted in Discontinuation of the Treatment							
Anxiety 2 studies[231,239]	2,371	10.92 (1.41; 84.60)	0.01 (0.00; 0.02)		8 (0; 16)		Low
Asthenia 4 studies[229,235,243,246]	1,166	3.71 (0.79; 17.52)	0.01 (0.00; 0.02)				Low
Constipation 2 studies[235,239]	2,114	1.29 (0.15; 11.00)	0.00 (0.00; 0.01)	0 (0; 0)	0 (0; 0)	1.42 (0.12; 14.77)	Low
Dizziness 8 studies[229,231-235,239,243]	4,404	5.49 (2.56; 11.74)	0.02 (0.01; 0.02)	59 (43; 91)	17 (11; 23)	8.25 (3.59; 24.02)	High
Fatigue 4 studies[229,233,239,246]	3,440	4.02 (0.91; 17.71)	0.01 (0.00; 0.02)	91 (45; 1000)	11 (1; 2)	5.04 (1.63; 16.90)	High
Insomnia 7 studies[229,231,233-235,239,243]	4,126	5.70 (2.46; 13.19)	0.02 0.01; 0.02)	67 (48; 111)	15 9; 21)	8.53 (3.37; 25.41)	High
Nausea 9 studies[229,231-235,239,243,246]	4,992	11.27 (5.69; 22.30)	0.04 (0.03; 0.05)	25 (20; 32)	40 (31; 50)	20.92 (9.26; 60.26)	High
Somnolence 6 studies[232,233,235,239,243,246]	3,784	6.68 (2.34; 19.08)	0.01 (0.01; 0.02)	91 (59; 167)	11 (6; 17)	15.73 (4.14; 148.80)	High

Table 6. Clinical outcomes with duloxetine treatments (continued)

Reference Number of Studies	Number of Subjects	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat (95% CI)	Attributable Events/1000 Treated (95% CI)	Bayesian Odds Ratio Median (2.5; 97.5%)	Evidence
Diarrhea 2 studies [239,246]	2,501	2.42 (0.47; 12.54)	0.00 (0.00; 0.01)			2.91 (0.45; 29.21)	Low
Headache 3 studies [229,232,246]	1,122	4.31 (0.93; 20.02)	0.01 (0.00; 0.03)	71 (40; 500)	14 (2; 25)	11.67 (1.71; 263.20)	Moderate

Table 7. Clinical outcomes with pharmacological interventions compared to placebo

Drug	Outcome	Studies	Patients	Rate Active/Control	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat (95% CI)	Bayesian Odds Ratio Median (2.5; 97.5%)	Evidence
Darifenacin	Improvement in UI	3[322,323,325]	2,677	52.9/37.8	1.3 (1.2; 1.4)	0.11 (0.08; 0.15)	9 (7; 9)	1.8 (1.4; 2.2)	High
Darifenacin	Adverse effects	3[323-325]	399	37.2/18.0	1.5 (1.2; 1.8)	0.17 (0.12; 0.23)	6 (4; 6)	2.2 (1.3; 3.6)	Moderate
Darifenacin	Serious adverse effects	2[323,324]	655	1.2/2.1	0.6 (0.2; 2.1)	-0.01 (-0.03; 0.01)		0.6 (0.1; 2.6)	Low
Darifenacin	Discontinuation	2[324,333]	656	12.4/12.6	0.9 (0.6; 1.3)	-0.02 (-0.07; 0.04)		0.9 (0.4; 2.1)	Low
Darifenacin	Discontinuation Adverse effects	7[322-327,333]	3,138	4.6/3.3	1.2 (0.8; 1.8)	0.00 (-0.01; 0.02)		1.2 (0.7; 2.0)	High
Darifenacin	Discontinuation Treatment failure	4[323,324,326,327]	1,280	1.0/1.7	0.6 (0.2; 1.7)	-0.01 (-0.02; 0.01)		0.6 (0.2; 1.7)	Moderate
Darifenacin	Dry mouth	5[321,323-325,333]	2,382	22.0/5.6	3.6 (2.2; 5.8)	0.17 (0.07; 0.26)	6 (4; 6)	4.1 (2.1; 8.1)	High
Darifenacin	dyspepsia	4[321,323,324,333]	1,772	4.4/1.3	3.1 (1.4; 7.0)	0.03 (0.01; 0.05)	33 (19; 33)	3.6 (1.7; 7.9)	High
Darifenacin	Headache	3[321,323,324]	1,155	4.1/1.1	3.6 (1.6; 8.3)	0.03 (0.01; 0.05)	37 (22; 37)	4.2 (1.6; 12.3)	Moderate
Darifenacin	Nausea	2[321,324]	573	1.3/0.7	1.4 (0.3; 6.3)	0.00 (-0.01; 0.02)		1.4 (0.2; 9.9)	Low
Darifenacin	Urinary tract infection	2[323,324]	655	2.9/2.3	1.2 (0.5; 3.0)	0.00 (-0.02; 0.03)		1.2 (0.3; 4.1)	Low
Darifenacin	Constipation	5[321,323-325,333]	2,239	14.6/5.7	2.3 (1.4; 3.6)	0.08 (0.03; 0.14)	12 (7; 12)	2.6 (1.4; 4.4)	High
Fesoterodine	Continence	2[308,349]	2,465	61.0/48.5	1.3 (1.1; 1.5)	0.13 (0.06; 0.20)	8 (5; 8)	1.7 (0.9; 3.3)	Low
Fesoterodine	Improvement in UI	4[302,308,347,350]	3,801	32.9/26.4	1.3 (1.2; 1.5)	0.08 (0.05; 0.10)	13 (10; 13)	1.5 (1.1; 2.1)	High
Fesoterodine	Treatment failure	4[302,308,347,350]	3,801	4.9/8.3	0.5 (0.4; 0.7)	-0.04 (-0.05; -0.02)	-26 (-43; -26)	0.5 (0.3; 0.8)	High
Fesoterodine	Adverse effects	4[300,308,350,351]	4145	51.4/37.8	1.4 (1.2; 1.6)	0.15 (0.11; 0.19)	7 (5; 7)	1.9 (1.5; 2.5)	High
Fesoterodine	Serious adverse effects	2[308,350]	1905	1.8/1.9	0.8 (0.4; 1.7)	0.00 (-0.02; 0.01)		0.9 (0.3; 2.3)	Low
Fesoterodine	Discontinuation	6[300,302,308,347,350,351]	6,041	11.6/11.2	1.2 (1.0; 1.3)	0.01 (-0.01; 0.02)		1.2 (0.9; 1.5)	Moderate
Fesoterodine	Discontinuation Adverse effects	6[302,308,346,347,349,350]	6,338	6.4/3.3	2.1 (1.5; 2.9)	0.03 (0.02; 0.05)	31 (21; 31)	2.1 (1.5; 3.0)	High
Fesoterodine	Discontinuation Treatment failure	4[302,308,347,350]	3,801	1.6/2.7	0.6 (0.3; 1.4)	-0.01 (-0.03; 0.01)		0.6 (0.3; 1.1)	Moderate
Fesoterodine	Abdominal pain	2[308,346]	1,747	3.7/2.7	1.9 (1.1; 3.2)	0.02 (-0.01; 0.05)		1.9 (0.8; 4.0)	Low
Fesoterodine	Abnormal vision	1[346]	1,094	0.3/1.0	0.5 (0.1; 2.0)	-0.01 (-0.02; 0.00)		0.2 (0.0; 1.4)	Insufficient
Fesoterodine	Back pain	2[308,346]	2,116	2.1/3.0	0.8 (0.5; 1.4)	-0.01 (-0.02; 0.01)		0.8 (0.4; 1.7)	Low
Fesoterodine	Constipation	8[300,302,308,346,347,349-351]	8,578	10.6/3.2	2.3 (1.5; 3.5)	0.05 (0.01; 0.09)	21 (12; 21)	2.3 (1.4; 3.6)	High

Table 7. Clinical outcomes with pharmacological interventions compared to placebo (continued)

Drug	Outcome	Studies	Patients	Rate Active/Control	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat (95% CI)	Bayesian Odds Ratio Median (2.5; 97.5%)	Evidence
Fesoterodine	Cough	3[308,346,350]	2,999	1.8/1.9	1.2 (0.5; 2.8)	0.00 (-0.01; 0.02)		1.1 (0.6; 2.2)	Moderate
Fesoterodine	Diarrhea	3[302,308,350]	2,918	2.1/2.4	1.0 (0.4; 2.6)	0.00 (-0.02; 0.02)		0.9 (0.4; 2.2)	Low
Fesoterodine	Dizziness	2[308,346]	3,138	1.2/0.9	1.0 (0.5; 1.9)	0.00 (-0.01; 0.01)		0.9 (0.4; 2.0)	Low
Fesoterodine	Dry eye	5[300,308,347,350,351]	5,028	2.4/0.9	2.4 (1.1; 5.2)	0.02 (0.01; 0.03)	63 (37; 63)	2.7 (1.5; 5.3)	High
Fesoterodine	Dry mouth	8[300,302,308,346,347,349-351]	8,579	27.3/7.0	3.8 (3.3; 4.4)	0.20 (0.17; 0.23)	5 (4; 5)	5.0 (4.0; 6.1)	High
Fesoterodine	Fatigue	2[308,350]	1,905	2.0/0.3	6.7 (1.8; 25.0)	0.02 (0.01; 0.03)	56 (37; 56)	10.3 (2.2; 88.5)	Low
Fesoterodine	Headache	7[300,302,308,346,347,350,351]	7,135	6.1/5.6	1.1 (0.9; 1.4)	0.01 (0.00; 0.02)	111 (48; 111)	1.2 (0.9; 1.5)	High
Fesoterodine	Influenza-like symptoms	1[346]	1,094	5.7/8.0	0.7 (0.4; 1.2)	-0.03 (-0.06; 0.00)			Insufficient
Fesoterodine	Nasopharyngitis	4[300,308,350,351]	4,145	2.5/3.3	0.8 (0.6; 1.2)	-0.01 (-0.02; 0.00)		0.8 (0.5; 1.2)	Moderate
Fesoterodine	Nausea	5[300,308,346,350,351]	5,239	2.0/3.1	0.7 (0.5; 1.0)	-0.01 (-0.02; 0.00)		0.6 (0.4; 1.0)	High
Fesoterodine	Upper respiratory tract infection	2[308,350]	1,905	2.0/3.5	0.6 (0.2; 2.0)	-0.01 (-0.02; 0.00)		0.6 (0.1; 1.9)	Low
Fesoterodine	Urinary tract infection	3[302,308,350]	2,918	2.1/1.4	1.9 (0.5; 6.5)	0.01 (-0.01; 0.02)		1.6 (0.7; 3.8)	Low
Oxybutynin	Continence	5[254,259,262,634,635]	1,124	26.3/15.5	1.7 (1.3; 2.1)	0.11 (0.07; 0.16)	9 (6; 9)	2.0 (1.3; 3.4)	High
Oxybutynin	Improvement in UI	12[251,261-263,266,369,370,396,634-637]	1,627	47.1/31.9	1.4 (1.0; 1.8)	0.12 (0.03; 0.22)	8 (5; 8)	1.8 (1.1; 3.0)	Moderate
Oxybutynin	Treatment failure	5[261,369,634,636,637]	874	12.2/22.9	0.6 (0.5; 0.8)	-0.10 (-0.17; -0.02)		0.4 (0.2; 0.7)	Moderate
Oxybutynin	Adverse effects	3[256,369,636]	821	27.7/15.2	1.5 (0.6; 3.6)	0.10 (-0.05; 0.26)		2.0 (0.6; 6.2)	Moderate
Oxybutynin	Serious adverse effects	3[256,259,369]	1,393	3.7/2.0	1.3 (0.2; 8.7)	0.02 (-0.04; 0.07)		1.5 (0.3; 6.4)	Moderate
Oxybutynin	Discontinuation	5[251,259,634,636,639]	1,233	12.8/12.0	1.1 (0.8; 1.5)	0.01 (-0.03; 0.04)		1.2 (0.7; 2.2)	Moderate
Oxybutynin	Discontinuation adverse effects	6[259,261,263,369,370,639]	1,662	11.3/5.1	1.7 (1.2; 2.5)	0.05 (0.01; 0.08)	22 (13; 22)	2.1 (1.2; 3.5)	High
Oxybutynin	Blurred vision	5[250,251,369,634,639]	663	10.4/9.1	1.7 (0.8; 4.0)	0.05 (0.00; 0.10)	20 (10; 20)		Moderate
Oxybutynin	Constipation	7[250,255,259,262,369,634,639]	1,743	7.3/5.5	1.2 (0.9; 1.7)	0.01 (-0.02; 0.04)		1.4 (0.8; 2.6)	Moderate
Oxybutynin	Dizziness	5[255,259,262,369,639]	1,541	2.3/1.7	1.3 (0.6; 2.7)	0.01 (0.00; 0.02)			Moderate
Oxybutynin	Dry mouth	10[250,251,255,259,262,263,369,370,634,639]	2,417	36.4/14.1	2.6 (1.7; 3.9)	0.35 (0.19; 0.51)	3 (2; 3)	8.2 (3.8; 18.0)	High
Oxybutynin	Dry skin	3[250,251,369]	493	10.0/10.4	2.2 (0.4; 11.1)	0.09 (-0.13; 0.31)			Low
Oxybutynin	Dyspepsia	3[253,263,369]	613	12.1/3.3	3.2 (1.5; 6.8)	0.08 (0.00; 0.15)	13 (7; 13)	3.9 (1.2; 12.2)	Moderate
Oxybutynin	Dysuria	2[255,259]	1,046	0.8/0.2	2.6 (0.3; 19.5)	0.01 (-0.01; 0.03)		5.8 (0.5; 254.9)	Low
Oxybutynin	Headache	3[253,259,369]	1,299	4.1/4.5	0.9 (0.5; 1.5)	-0.01 (-0.03; 0.01)		0.9 (0.4; 2.2)	Moderate
Oxybutynin	Nausea	7[250,253,255,259,262,263,636]	1,743	3.9/3.0	0.9 (0.5; 1.7)	0.00 (-0.03; 0.03)		1.0 (0.4; 2.4)	High

Table 7. Clinical outcomes with pharmacological interventions compared to placebo (continued)

Drug	Outcome	Studies	Patients	Rate Active/Control	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat (95% CI)	Bayesian Odds Ratio Median (2.5; 97.5%)	Evidence
Oxybutynin	Retention	3[259,369,634]	1,287	3.2/0.5	3.9 (0.7; 20.2)	0.04 (-0.01; 0.09)		6.1 (0.2; 57.0)	Moderate
Oxybutynin	Somnolence	3[255,259,369]	1,412	0.9/0.8	0.9 (0.3; 2.6)	0.00 (0.00; 0.01)			Low
Oxybutynin	Vision disorder	3[255,261,636]	589	8.1/4.7	1.2 (0.6; 2.3)	0.00 (-0.03; 0.02)		1.1 (0.2; 3.4)	Low
Oxybutynin	Vomiting	2[253,636]	361	2.3/1.4	1.2 (0.3; 5.3)	0.01 (-0.03; 0.05)		2.0 (0.3; 19.0)	Low
Propiverine	Continence	2[609,645]	691	53.4/36.7	1.4 (1.2; 1.7)	0.16 (0.09; 0.24)	6 (4; 6)	2.0 (0.9; 4.2)	Low
Propiverine	Improvement in UI	3[609,645,647]	985	54.9/34.5	1.6 (1.3; 2.0)	0.19 (0.13; 0.25)	5 (4; 5)	2.4 (1.4; 4.2)	Moderate
Propiverine	Treatment failure	2[609,645]	720	11.6/46.7	0.4 (0.2; 0.8)	-0.23 (-0.44; -0.02)	-4 (-67; -4)	0.3 (0.1; 0.8)	Low
Propiverine	Adverse effects	3[609,646,647]	981	32.9/18.9	1.7 (1.4; 2.2)	0.16 (0.07; 0.25)	6 (4; 6)	2.7 (1.5; 5.1)	Moderate
Propiverine	Discontinuation	2[609,644]	1,401	7.4/7.4	1.1 (0.7; 1.6)	0.01 (-0.02; 0.03)		1.1 (0.5; 2.3)	Moderate
Propiverine	Discontinuation adverse effects	2[609,644]	1,401	4.7/2.0	2.6 (1.4; 5.0)	0.03 (0.01; 0.04)	36 (23; 36)	2.7 (1.0; 7.8)	Low
Propiverine	Blurred vision	2[609,644]	1,401	4.2/1.5	3.2 (0.7; 13.9)	0.03 (0.01; 0.05)	34 (19; 34)	3.1 (1.1; 9.4)	Low
Propiverine	Constipation	4[609,644,646,647]	1,789	7.5/2.4	3.2 (1.9; 5.2)	0.06 (0.02; 0.10)	16 (10; 16)	4.5 (2.1; 11.7)	High
Propiverine	Dizziness	2[609,647]	857	1.2/1.0	0.9 (0.1; 11.0)	0.00 (-0.03; 0.03)		1.2 (0.2; 7.0)	Low
Propiverine	Dry mouth	4[609,644,646,647]	1836	22.6/6.2	3.7 (2.7; 5.0)	0.16 (0.08; 0.24)	6 (4; 6)	4.6 (2.7; 8.0)	High
Propiverine	Headache	3[609,646,647]	989	1.7/0.9	1.5 (0.4; 5.4)	0.01 (-0.02; 0.03)		2.3 (0.6; 12.3)	Moderate
Solifenacin	Continence	5[336,340,342,343,345]	6,304	39.2/28.1	1.5 (1.4; 1.6)	0.11 (0.06; 0.16)	9 (6; 9)	1.7 (1.3; 2.1)	High
Solifenacin	Improvement in UI	2[336,341]	1,507	60.2/42.0	1.5 (1.0; 2.1)	0.18 (0.10; 0.26)	6 (4; 6)	2.2 (1.1; 4.3)	Low
Solifenacin	Treatment failure	4[336,338,339,341]	2,918	27.7/30.1	0.6 (0.5; 0.7)	-0.14 (-0.27; -0.01)			Moderate
Solifenacin	Adverse effects	4[337,340-342]	2,452	49.2/32.6	1.7 (1.3; 2.2)	0.17 (0.10; 0.23)	6 (4; 6)	2.2 (1.5; 3.2)	High
Solifenacin	Discontinuation	6[337-339,341,342,644]	4,431	9.1/10.4	0.9 (0.7; 1.1)	-0.02 (-0.03; 0.00)		0.8 (0.6; 1.1)	High
Solifenacin	Discontinuation Adverse effects	8[338-343,345,644]	9,819	5.5/4.2	1.4 (1.1; 1.7)	0.01 (0.00; 0.02)	83 (43; 83)	1.3 (1.0; 1.7)	High
Solifenacin	Discontinuation Treatment failure	4[338,339,341,342]	2,812	1.5/1.3	1.0 (0.5; 1.8)	0.00 (-0.01; 0.01)		1.0 (0.4; 2.2)	Moderate
Solifenacin	Blurred vision	10[336-343,345,644]	13,661	3.5/1.7	2.1 (1.7; 2.6)	0.02 (0.01; 0.02)	67 (43; 67)	2.1 (1.5; 2.8)	High
Solifenacin	Dry mouth	8[336,337,339-341,343,345,644]	11,828	21.6/4.8	4.1 (3.1; 5.4)	0.16 (0.12; 0.21)	6 (5; 6)	5.0 (3.7; 6.8)	High
Solifenacin	Dyspepsia	3[336,337,342]	1,663	3.4/0.4	5.6 (2.2; 14.5)	0.03 (0.01; 0.05)	36 (20; 36)	11.4 (3.3; 53.4)	Moderate
Solifenacin	Fatigue	3[336,340,341]	2,246	2.3/0.9	2.6 (1.2; 5.3)	0.01 (0.00; 0.02)	83 (45; 83)	2.6 (1.1; 6.7)	Moderate
Solifenacin	Headache	5[336,337,340-342]	3,220	3.7/4.4	0.9 (0.6; 1.2)	-0.01 (-0.02; 0.01)		0.8 (0.5; 1.3)	Moderate
Solifenacin	Nausea	2[336,342]	1,440	3.2/2.7	1.2 (0.6; 2.3)	0.00 (-0.02; 0.02)		1.1 (0.3; 3.1)	Low

Table 7. Clinical outcomes with pharmacological interventions compared to placebo (continued)

Drug	Outcome	Studies	Patients	Rate Active/Control	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat (95% CI)	Bayesian Odds Ratio Median (2.5; 97.5%)	Evidence
Solifenacin	Urinary retention	2[337,342]	747	2.4/0.8	2.6 (0.8; 8.9)	0.01 (0.00; 0.03)		3.6 (0.8; 23.4)	Low
Solifenacin	Constipation	9[336,337,339-343,345,644]	12,504	11.0/3.7	2.8 (2.1; 3.7)	0.07 (0.05; 0.09)	15 (11; 15)	3.0 (2.2; 3.9)	High
Solifenacin	Dizziness	3[340-342]	2,150	3.1/2.1	1.5 (0.9; 2.5)	0.01 (0.00; 0.02)		1.5 (0.7; 3.1)	Moderate
Tolterodine	Continence	4[226,301,308,349]	3,404	53.2/43.7	1.2 (1.1; 1.4)	0.09 (0.04; 0.13)	12 (8; 12)	1.5 (1.0; 2.1)	High
Tolterodine	Improvement in UI	8[30,294,296,306,641 302,308,349]	6,783	44.7/35.7	1.3 (1.2; 1.5)	0.11 (0.06; 0.16)	9 (6; 9)	1.6 (1.3; 2.1)	High
Tolterodine	Treatment failure	7[294,296,301,302,306,308,641]	5,275	9.0/15.4	0.7 (0.5; 0.9)	-0.05 (-0.09; -0.01)		0.6 (0.4; 0.9)	High
Tolterodine	Adverse effects	12[226,263,288,289,292,297,30 0,301,303,307,308,337]	4,162	44.7/38.1	1.2 (1.1; 1.3)	0.08 (0.05; 0.11)	13 (9; 13)	1.5 (1.2; 1.8)	High
Tolterodine	Serious adverse effects	5[286,289-291,308]	3,550	1.8/3.1	0.6 (0.4; 0.9)	-0.01 (-0.02; 0.00)		0.6 (0.3; 1.1)	Moderate
Tolterodine	Discontinuation	10[289,290,294,298,300,302,30 4,308,337,338]	6,399	6.5/7.8	0.9 (0.8; 1.1)	-0.01 (-0.02; 0.00)		0.9 (0.7; 1.2)	High
Tolterodine	Discontinuation Adverse effects	13[263,289,291,292,297,298,30 0,302,303,308,338,349,641]	7,801	3.9/3.2	1.1 (0.8; 1.6)	0.01 (0.00; 0.02)		1.2 (0.9; 1.7)	High
Tolterodine	Discontinuation treatment failure	5[297,302,308,338,641]	4,049	0.7/1.6	0.5 (0.2; 0.9)	-0.01 (-0.02; 0.00)		0.4 (0.2; 0.9)	High
Tolterodine	Autonomic nervous system disorders	3[286,288,289]	831	27.2/15.5	1.8 (1.3; 2.4)	0.11 (0.03; 0.19)	9 (5; 9)	2.0 (1.1; 3.5)	Moderate
Tolterodine	Blurred vision	2[337,338]	608	1.3/3.0	0.5 (0.2; 1.5)	-0.01 (-0.04; 0.01)		0.4 (0.1; 1.7)	Low
Tolterodine	Constipation	15[288,290-292,295,297,298,300-303,308,337,338,349,641]	11,273	3.7/2.8	1.4 (1.2; 1.8)	0.01 (0.00; 0.02)	111 (67; 111)	1.4 (1.1; 1.9)	High
Tolterodine	Diarrhea	6[290,291,295,297,302,308]	5,910	2.3/1.9	1.3 (0.9; 1.9)	0.01 (0.00; 0.01)		1.3 (0.8; 2.0)	High
Tolterodine	Dizziness	7[290,291,295,297,300,308,641]	6,084	1.6/1.5	1.1 (0.7; 1.7)	0.00 (0.00; 0.01)		1.1 (0.7; 1.8)	High
Tolterodine	Dry mouth	14[226,263,290,292,300-303,307,308,337,338,349,641]	7,637	18.4/6.7	2.6 (2.2; 3.2)	0.13 (0.10; 0.15)	8 (6; 8)	3.4 (2.7; 4.5)	High
Tolterodine	Dry skin	2[290,295]	1,842	0.4/0.2	2.0 (0.4; 10.8)	0.00 (0.00; 0.01)		2.2 (0.3; 20.6)	Low
Tolterodine	Dyspepsia	7[226,263,290,291,295,297,308]	5,374	2.8/1.5	1.8 (1.2; 2.8)	0.01 (0.00; 0.02)	71 (43; 71)	2.1 (1.3; 3.6)	High
Tolterodine	Fatigue	4[290,300,308,641]	3,234	1.9/0.7	2.5 (1.2; 5.2)	0.01 (0.00; 0.02)	83 (45; 83)	3.1 (1.3; 7.8)	High
Tolterodine	Flatulence	2[290,295]	1,842	1.9/1.6	1.2 (0.6; 2.4)	0.00 (-0.01; 0.02)		1.2 (0.4; 3.2)	Low
Tolterodine	General body disorders	2[288,289]	308	22.3/18.6	1.2 (0.7; 2.1)	0.02 (-0.10; 0.15)		1.1 (0.3; 3.5)	Low

Table 7. Clinical outcomes with pharmacological interventions compared to placebo (continued)

Drug	Outcome	Studies	Patients	Rate Active/Control	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat (95% CI)	Bayesian Odds Ratio Median (2.5; 97.5%)	Evidence
Tolterodine	Headache	14[226,288,290-292,295,297,298,300-302,308,337,641]	9,474	4.4/3.5	1.3 (1.0; 1.6)	0.01 (0.00; 0.02)	91 (53; 91)	1.3 (1.0; 1.7)	High
Tolterodine	Insomnia	3[290,295,301]	2,255	1.7/1.6	1.0 (0.4; 2.5)	0.00 (-0.01; 0.02)		1.1 (0.5; 2.7)	Moderate
Tolterodine	Nasopharyngitis	6[30,300,301,308,311,641]	3,862	2.8/2.9	1.0 (0.7; 1.5)	0.00 (-0.01; 0.01)		1.0 (0.6; 1.6)	High
Tolterodine	Nausea	7[263,290,291,295,297,300,308]	5,642	1.6/2.0	0.8 (0.5; 1.1)	0.00 (-0.01; 0.01)		0.8 (0.5; 1.3)	High
Tolterodine	Somnolence	3[290,295,297]	2,696	1.8/1.6	1.4 (0.7; 2.5)	0.00 (-0.01; 0.01)		1.1 (0.3; 2.9)	Low
Tolterodine	Urinary tract infection	7[288,290,295,297,301,302,308]	6,319	2.2/2.7	1.0 (0.6; 1.5)	0.00 (-0.01; 0.01)		0.9 (0.6; 1.5)	High
Tolterodine	Xerophthalmia	2[290,295]	1,842	3.6/2.0	1.8 (1.0; 3.2)	0.02 (0.00; 0.03)	63 (32; 63)	1.9 (0.8; 4.6)	Low
Tolterodine	Abdominal pain	6[290-292,295,297,308]	5,194	2.8/1.7	1.7 (1.2; 2.5)	0.01 (0.00; 0.02)	91 (50; 91)	1.8 (1.1; 2.9)	High
Tolterodine	Abnormal vision	3[290,295,303]	1,968	1.4/0.8	1.5 (0.6; 3.7)	0.01 (0.00; 0.01)		1.7 (0.6; 5.3)	Moderate
Trospium	Continence	4[357,358,363,364]	2,677	28.3/16.6	1.7 (1.5; 2.0)	0.11 (0.08; 0.14)	9 (7; 9)	2.0 (1.4; 2.9)	High
Trospium	Improvement in UI	2[354,363]	1,176	32.4/25.4	1.1 (0.6; 2.0)	0.08 (-0.10; 0.25)	13 (4; 13)	1.4 (0.4; 3.8)	Low
Trospium	Adverse effects	5[307,355,357,358,364]	2,967	40.5/28.7	1.4 (1.2; 1.7)	0.09 (0.03; 0.16)	11 (6; 11)		Moderate
Trospium	Discontinuation	2[360,361]	1,165	12.5/11.2	1.1 (0.8; 1.5)	0.01 (-0.02; 0.05)	77 (20; 77)	1.1 (0.6; 2.3)	Low
Trospium	Discontinuation adverse effects	6[355,358,360,361,363,364]	3,936	5.8/3.9	1.5 (1.1; 1.9)	0.02 (0.00; 0.03)	59 (33; 59)	1.5 (1.0; 2.2)	High
Trospium	Abdominal distention	2[358,364]	989	1.0/0.3	3.1 (0.8; 11.4)	0.01 (0.00; 0.02)		3.4 (0.8; 19.1)	Low
Trospium	Abdominal pain	3[358,363,364]	2,113	1.7/0.7	2.6 (1.1; 6.2)	0.01 (0.00; 0.02)	111 (56; 111)	2.7 (1.0; 8.1)	Moderate
Trospium	CNS	2[354,357]	1,217	3.9/3.8	1.0 (0.6; 1.8)	0.00 (-0.02; 0.02)		1.0 (0.4; 2.6)	
Trospium	Constipation	5[355,357,358,363,364]	3,335	9.3/2.6	3.7 (2.1; 6.6)	0.07 (0.05; 0.08)	15 (12; 15)	3.9 (2.5; 6.3)	High
Trospium	Diarrhea	2[355,363]	1,181	2.5/4.6	0.6 (0.3; 1.0)	-0.02 (-0.04; 0.00)		0.5 (0.2; 1.4)	Low
Trospium	Dry eye	2[358,364]	1,590	1.7/0.2	6.3 (1.4; 28.4)	0.01 (0.00; 0.02)	71 (43; 71)	8.0 (1.7; 59.3)	Low
Trospium	Dry mouth	6[307,355,357,358,363,364]	3,490	15.1/4.5	3.3 (2.6; 4.2)	0.11 (0.07; 0.15)	9 (7; 9)	3.9 (2.6; 5.8)	High
Trospium	Dry skin	2[358,364]	1,590	1.0/0.1	5.8 (1.0; 32.9)	0.01 (0.00; 0.02)	111 (59; 111)	12.3 (1.6; 420.5)	Low
Trospium	Dyspepsia	2[358,364]	1,590	1.5/0.9	1.8 (0.7; 4.5)	0.01 (0.00; 0.02)		1.8 (0.6; 6.4)	Low
Trospium	Headache	4[355,358,363,364]	2,771	3.3/3.5	0.9 (0.5; 1.5)	-0.01 (-0.02; 0.01)		0.9 (0.4; 1.7)	High
Trospium	Nausea	2[358,364]	1,590	1.3/0.4	3.0 (0.7; 13.8)	0.01 (0.00; 0.02)	111 (56; 111)	3.7 (0.8; 20.0)	Low
Trospium	Urinary tract infection	3[355,358,364]	2,248	2.6/1.3	2.0 (1.1; 3.6)	0.01 (0.00; 0.02)	100 (50; 100)	2.0 (0.9; 4.6)	Moderate

Table 8. Rates of clinical outcomes after drugs vs. placebo (significant differences only)

Outcome	Drug	Studies	Patients	Rate with Drug,%	Rate with Placebo, %	Number Needed to Treat	Attributable Events/ 1,000 Treated
Abdominal pain	Tolterodine	6	5,194	2.8	1.7	91	11
Abdominal pain	Trospium	3	2,113	1.7	0.7	111	9
Autonomic nervous system disorders	Tolterodine	3	831	27.2	15.5	9	110
Blurred vision	Oxybutynin	5	663	10.4	9.1	20	50
Blurred vision	Propiverine	2	1,401	4.2	1.5	34	29
Blurred vision	Solifenacin	10	13,661	3.5	1.7	67	15
Constipation	Darifenacin	5	2,239	14.6	5.7	12	84
Constipation	Solifenacin	9	12,504	11.0	3.7	15	66
Constipation	Fesoterodine	8	8,578	10.6	3.2	21	47
Constipation	Trospium	5	3,335	9.3	2.6	15	68
Constipation	Propiverine	4	1,789	7.5	2.4	16	63
Constipation	Tolterodine	15	11,273	3.7	2.8	111	9
Dry eye	Fesoterodine	5	5,028	2.4	0.9	63	16
Dry eye	Trospium	2	1,590	1.7	0.2	71	14
Dry eye	Tolterodine	2	1,842	3.6	2.0	63	16
Dry mouth	Oxybutynin	10	2,417	36.4	14.1	3	347
Dry mouth	Fesoterodine	8	8,579	27.3	7.0	5	200
Dry mouth	Propiverine	4	1,836	22.6	6.2	6	161
Dry mouth	Darifenacin	5	2,382	22.0	5.6	6	165
Dry mouth	Solifenacin	8	11,828	21.6	4.8	6	161
Dry mouth	Tolterodine	14	7,637	18.4	6.7	8	127
Dry mouth	Trospium	6	3,490	15.1	4.5	9	109
Dry skin	Trospium	2	1,590	1.0	0.1	111	9
Dyspepsia	Oxybutynin	3	613	12.1	3.3	13	76
Dyspepsia	Darifenacin	4	1,772	4.4	1.3	33	30
Dyspepsia	Solifenacin	3	1,663	3.4	0.4	36	28
Dyspepsia	Tolterodine	7	5,374	2.8	1.5	71	14
Fatigue	Solifenacin	3	2,246	2.3	0.9	83	12
Fatigue	Tolterodine	4	3,234	1.9	0.7	83	12
Fatigue	Fesoterodine	2	1,905	2.0	0.3	56	18
Headache	Tolterodine	14	9,474	4.4	3.5	91	11
Headache	Darifenacin	3	1,155	4.1	1.1	37	27
Nausea	Trospium	2	1,590	1.3	0.4	111	9
Retention	Oxybutynin	3	1,287	3.2	0.5	26	38
Urinary retention	Solifenacin	2	747	2.4	0.8	77	13
Urinary tract infection	Trospium	3	2,248	2.6	1.3	100	10

Comparative Effectiveness of Topical Estrogen on UI

Evidence was insufficient to determine whether an estrogen releasing intravaginal ring was more effective in resolving and improving UI than a pessary, or to determine whether an intravaginal tablet was more effective than intravaginal estrogen cream (Appendix Table F68).

Two RCTs of 291 women compared different estrogen formulations (Appendix Table F27).[655,656] The studies enrolled postmenopausal women with lower urinary tract symptoms including UI.[655,656] The first study compared an intravaginal tablet with intravaginal conjugated estrogen cream administered for 8 weeks.[655] The second study compared an estrogen releasing ring with an estrogen pessary administered for 24 weeks.[656] Urinary continence rates did not differ between the intravaginal tablet and the intravaginal cream[655] (Appendix Table F69). Women treated with an estrogen releasing ring did not experience urgency UI more often than those treated with a pessary.[656] The rates of resolved stress UI did not differ between estrogen rings and pessaries.[656] Women were satisfied with the estrogen ring more often than with the estrogen pessary.[656]

Comparative Effectiveness of Darifenacin and Oxybutynin on UI

Evidence was insufficient to conclude comparative effectiveness between darifenacin and oxybutynin on continence or improved UI. A low level of evidence indicated lower rates of total adverse effects and dry mouth with darifenacin with no differences in adverse effects leading to treatment discontinuation.

Two RCTs[639,657] compared clinical outcomes of oxybutynin and darifenacin.

Continence. The studies did not examine continence outcomes of oxybutynin compared to darifenacin.

Improvement in UI. The studies found no differences in improvement of UI between the two drugs. Both drugs significantly reduced incontinence episodes compared to placebo with no differences between drugs.[639]

Adverse effects. Darifenacin was safer than oxybutynin. Total rates of adverse effects were lower with darifenacin than with oxybutynin[657] (Appendix Table F70). Rates of dry mouth were lower with darifenacin than oxybutynin.[639] Severe dry mouth was less common with 7.5 mg/day of darifenacin than with 7.5mg/day of oxybutynin, and lower with 15 mg/day of darifenacin than with 15 mg/day of oxybutynin[657] (Appendix Table F71). Only one adverse effect, constipation, was more common with 30 mg of darifenacin than with 15mg of oxybutynin[657] (Appendix Table F72). Discontinuations from the study due to treatment-related adverse effects were lower with darifenacin than with oxybutynin in one RCT[639] (Appendix Table F73). Pooled analysis of two RCTs did not find significant differences between the two drugs in adverse effects leading to treatment discontinuation (Table 9).

Comparative Effectiveness of Oxybutynin and Tolterodine on UI

Evidence was insufficient to draw conclusions about comparative effectiveness between oxybutynin and tolterodine on continence. A moderate level of evidence indicated no difference between the drugs for UI improvement. A high level of evidence indicated more frequent treatment discontinuation due to adverse effects with oxybutynin than with tolterodine. Women

experienced dry mouth and several other adverse effects more often with oxybutynin than with tolterodine. Thus, the drugs offered equal benefits but tolterodine resulted in fewer harms.

We identified 15 publications that compared clinical outcomes of oxybutynin and tolterodine,[29,253,256,263,289,359,365-373] including secondary data analyses,[29,372,373] OBJECT Study group,[365] OPERA Study group,[368] Transdermal Oxybutynin Study Group,[256] and Japanese and Korean Tolterodine Study Group[369] (Appendix Table F27).

Continence. Urinary continence was reported in the OPERA (Overactive bladder: Performance of Extended Release Agents) trial of 790 women.[368] Ten mg/day of oxybutynin, compared to 4mg/day of tolterodine, resulted in greater rates of continence[368] (Appendix Table F74). Drugs had to be given to 16 women to achieve continence in one woman. (Table 10).

Improvement in UI. There was no difference between the two drugs[263,366,369] (Figure 4). Treatment-related rates of improved bladder condition did not differ between the two drugs in a pooled analysis of individual patient data from four RCTs[29] (Appendix Table F75).

Adverse effects. Tolterodine demonstrated better safety than oxybutynin in several individual RCTs and secondary data analyses (Appendix Table F70). Total adverse effects did not differ between the drugs according to the pooled aggregate data from the published studies.[289,366,367] However, one pooled analysis of four RCTs demonstrated higher rates of moderate and severe adverse effects with 10 mg/day of oxybutynin compared to extended release, 4 mg/day tolterodine[373] (Appendix Table F75). Even though another pooled analysis of four RCTs found no differences in serious adverse effects between oxybutynin and tolterodine, dose reduction rates due to intolerance were more common with oxybutynin than with tolterodine.[29]

Among individual adverse effects, dry mouth was more common with oxybutynin than with tolterodine[289,365,366,368-371] (Figure 4). Severe dry mouth was also more common with 5 mg/day of oxybutynin than with 2mg/day or 1mg/day of tolterodine.[29] In addition to dry mouth, women experienced asthenia,[373] autonomic nervous system disorder,[29] gastrointestinal disorders,[29] dyspepsia,[29] nausea,[373] pain,[373] palpitations,[29] rhinitis,[373] and urinary tract infections[373] more often with oxybutynin than with tolterodine.

Women stopped taking oxybutynin more often that tolterodine because of adverse effects (Figure 4).[256,289,365,366,368-371] During the studies, 10 percent of women stopped taking oxybutynin and 5.6 percent of women stopped taking tolterodine because of adverse effects [29,263,289,365,366,368,370-373] (Table 9).

Comparative Effectiveness of Propiverine and Oxybutynin on UI

Evidence was insufficient to draw conclusions about comparative effectiveness and safety of propiverine and oxybutynin.

One RCT compared clinical outcomes of propiverine and oxybutynin.[636]

Improvement in UI and subject satisfaction did not differ between the two drugs (Appendix Table F76). Total adverse effects did not differ between the two drugs (Appendix Table F70). Fewer subjects experienced severe dry mouth with propiverine than with oxybutynin.[636] No studies compared rates of treatment discontinuation due to adverse effects between the two drugs.

Comparative Effectiveness of Flavoxate and Oxybutynin on UI

Evidence was insufficient to draw conclusions about comparative effectiveness and safety of flavoxate and oxybutynin.

A single RCT of 100 subjects compared clinical outcomes of 1,200 mg/day of flavoxate hydrochloride and 15mg/day of oxybutynin.[658] Urinary continence did not differ between the two drugs[658] (Appendix Table F74). Improvement in UI did not differ between the two drugs[658] (Appendix Table F76). Neither treatment failure with worsening of UI nor total number of adverse effects differed between the two drugs.[658] Rates of dry mouth and dry eyes were significantly lower with flavoxate than with oxybutynin. Nausea was also significantly less common with flavoxate than with oxybutynin.[658]

Comparative Effectiveness of Tolterodine and Propiverine on UI

Evidence was insufficient to draw conclusions about comparative effectiveness and safety of propiverine and tolterodine.

We identified one RCT of 202 patients treated with 15 mg of propiverine twice daily or 2 mg of tolterodine twice daily.[659] No studies compared continence and improvement in UI with the two drugs.[659] Improvement in urodynamic criteria of detrusor overactivity did not differ between the two drugs.[659] Both drugs improved quality of life scores without significant differences between them. The rates of total adverse effects did not differ between the two drugs (Appendix Table F70).

Comparative Effectiveness of Tolterodine and Fesoterodine on UI

A low level of evidence indicated greater continence rates with fesoterodine than with tolterodine. A high level of evidence indicated greater rates of improvement in UI with fesoterodine than with tolterodine. A moderate level of evidence indicated higher rates of adverse effects that led to treatment discontinuation with fesoterodine than with tolterodine.

Six publications of RCTs compared clinical outcomes of fesoterodine and tolterodine.[30,300,302,308,311,349]

Continence. Urinary continence was more often achieved with fesoterodine than with tolterodine[308,349] (Table 10).

Improvement in UI. Rates of improvement in UI were greater with fesoterodine[30,302,308,349] (Table 10). Pooled analysis of data of individual women from two RCTs that included 1,548 women analyzed self-rated substantial benefits from the treatments.[30] The rates of this outcome did not differ between fesoterodine and tolterodine (Appendix Table F74).

Quality of life did not differ between fesoterodine (4 or 8 mg) and tolterodine extended release in pooled analysis of individual subject data from two RCTs.[660]

Adverse effects. Rates of total adverse effects did not differ between 4 mg of tolterodine and 4 mg of fesoterodine, but were less with tolterodine than with 8 mg of fesoterodine.[300] The rates of dry mouth were less with tolterodine than with 4 mg of fesoterodine. Pooled analysis of data of individual women from two RCTs found that dry mouth was less common in women with treatment with tolterodine than with 8 mg/day of fesoterodine, with no significant differences when compared to 4 mg of fesoterodine.[30] Urinary tract infection was also less common in

women treated with tolterodine than with 8 mg/day of fesoterodine with no significant differences when compared to 4 mg or fesoterodine.[30]

Adverse effects resulting in treatment discontinuation were more common with fesoterodine than with tolterodine[300,302,308,349] (Table 9).

Comparative Effectiveness of Solifenacin and Tolterodine on UI

Evidence was insufficient to compare effectiveness of solifenacin and tolterodine. A moderate level of evidence indicated that adverse effects leading to treatment discontinuation did not differ between the two drugs.

Six publications of RCTs compared clinical outcomes of solifenacin and tolterodine,[337,338,568,661-663] including the Solifenacin and Tolterodine as an Active comparator in a Randomized STAR study group that compared clinical outcomes of 5 or 10 mg of solifenacin and 4 mg of extended release tolterodine.[661,662] The studies examined different doses of the drugs on a variety of outcomes that hampered synthesis of evidence.

Continence. Urinary continence was greater with solifenacin than with tolterodine.[661] (Table 10).

Improvement in UI. Solifenacin resulted in greater rates of improvement than tolterodine [661] (Appendix Table F78). Both drugs improved quality of life without evidence of differences between them.

Adverse effects. Total rates of adverse effects did not differ between solifenacin and tolterodine[337,568] (Appendix Table F70). However, one published RCT demonstrated a significant increase in adverse effects with the highest dose of solifenacin (20mg once daily) when compared to tolterodine. A lower dose of solifenacin resulted in the same rates of adverse effects as tolterodine in one published[337] and one unpublished RCT.[568] Dry mouth and constipation were more common in women treated with solifenacin than with tolterodine.[662] Blurred vision was less common with solifenacin than with tolterodine [662] (Appendix Table F79).

Treatment discontinuation rates because of adverse effects did not differ between the two drugs.[338,568,662,663]

Comparative Effectiveness of Solifenacin and Darifenacin on UI

Evidence was insufficient to conclude comparative effectiveness and safety of solifenacin and darifenacin.

One unpublished RCT, the Solidair study, compared solifenacin and darifenacin.[664]

No studies compared continence and improvement in UI with solifenacin and darifenacin.

The Solidair study found that women taking solifenacin had to increase the dose of the drug more often than women taking darifenacin.[664] The Solidair study found that the rates of treatment discontinuation due to adverse effects did not differ between solifenacin and darifenacin.

Comparative Effectiveness of Solifenacin and Oxybutynin on UI

Evidence was insufficient to conclude comparative effectiveness and safety of solifenacin oxybutynin.

A single RCT, the VECTOR trial, compared 5 mg solifenacin once daily versus 5 mg oxybutynin immediate release three times daily.[665] Both drugs caused improvement in the Patient

Perception of Bladder Condition scale and Overactive Bladder Questionnaire without evident differences between them.

The rates of adverse effects were lower with solifenacin than with oxybutynin.[665] Dry mouth was less common with solifenacin than with oxybutynin.[665] Rates of dry mouth leading to treatment discontinuation were lower with solifenacin than with oxybutynin.[665] Rates of other adverse effects resulting in treatment discontinuation did not differ between the two drugs.[665]

Comparative Effectiveness of Solifenacin and Propiverine on UI

Evidence was insufficient to conclude comparative effectiveness and safety of solifenacin and propiverine.

A single RCT compared clinical outcomes of solifenacin and propiverine.[644]

This study reported a significant reduction in UI episodes with both drugs, without significant differences between them.[644]

The highest dose of solifenacin, 10mg daily, caused greater rates of constipation and dry mouth than propiverine.[644] The rates of dry mouth did not differ between 5mg/day of solifenacin and propiverine.[644] Adverse effects leading to treatment discontinuation did not differ between the two drugs.

Comparative Effectiveness of Trospium and Oxybutynin on UI

Evidence was insufficient to draw valid conclusions about comparative effectiveness between trospium and oxybutynin. Individual studies found lower rates of dry mouth with trospium than with oxybutynin. A low level of evidence indicated no differences in treatment discontinuation due to adverse effects between the two drugs.

Two RCTs compared clinical outcomes of oxybutynin and trospium chloride.[606,666]

Continence. Urinary continence was achieved more often with trospium than with oxybutynin[666] (Appendix Table F74).

Improvement in UI. One RCT compared improvement in UI with oxybutynin and trospium and did not find significant differences[606] (Appendix Table F76). Dose escalation of either trospium or oxybutynin reduced frequency of urge UI without statistically significant differences between two drugs.[667]

Adverse effects. Trospium was better tolerated with fewer adverse effects than oxybutynin[666] (Appendix Table F70). Dry mouth was less common with trospium than with oxybutynin[666] (Appendix Table F71). With dose escalation, worsening of dry mouth was lower in the trospium groups than in the oxybutynin groups.[667] Treatment discontinuation due to adverse effects did not differ between the two drugs[606,666] (Table 9).

Comparative Effectiveness of Trospium and Tolterodine on UI

Evidence was insufficient to draw valid conclusions about comparative effectiveness and safety of trospium and tolterodine.

A single unpublished study compared clinical outcomes of trospium and tolterodine.[307]

The rates of total adverse effects and dry mouth were the same with trospium and tolterodine.[307]

Indirect Evidence of Comparative Effectiveness of Pharmacological Treatments on UI

Indirect evidence did not indicate substantial differences in resolving or improving UI with different drugs. Differences in discontinuation due to adverse effects, including dry mouth, were more evident than differences in benefits. However, head-to-head comparisons were rarely available in more than one study, and the studies used different definitions of treatment success and different tools to measure quality of life.

We compared relative benefits and harms of drugs compared to placebo. Such indirect evidence from all RCTs that examined clinical outcomes of active drugs versus placebo indicated that trospium was the most effective to resolve UI (Figure 5), but the differences across the drugs were not significant. Absolute rates of continence were the highest with solifenacin and fesoterodine (Figure 6). Indirect statistical comparisons were difficult because of substantial variability in continence rates with placebo. For instance, women became continent with placebo in RCTs of fesoterodine (48 percent), oxybutynin (15 percent), solifenacin (28 percent), tolterodine (44 percent), and trospium (17 percent).

We analyzed which factors may contribute to such differences in continence with placebo. The studies that did not report whether they included cases of mixed incontinence had lower rates of continence with placebo (18 percent) than studies that excluded women with stress UI (30 percent). The studies that included women with severe daily UI reported higher rates of continence with placebo (28 percent) than the studies that omitted baseline daily frequency of UI (15 percent).

From quality criteria of the studies, masking of treatment would be the most obvious candidate to explain continence with placebo. All drug studies that examined continence, however, were double blinded. From other quality criteria, the studies that reported justification of the sample size had higher continence with placebo (28 percent) than the studies that did not justify sample size (17 percent). Considering substantial variability in continence rates with drugs and placebo but comparable relative effectiveness of the drugs, comparative safety of the drugs may influence decisions on which drug offers a better balance between benefits and harms.

Treatment discontinuation due to adverse effects was greater with all drugs excluding darifenacin and tolterodine, than with placebo. The number needed to treated was the highest with solifenacin (NNT=83) and the lowest with oxybutynin (NNT=22). The absolute rates of adverse effects leading to treatment discontinuation were the highest with oxybutynin (11.3 percent) and were comparable between other drugs (Figure 7). Dry mouth was the most common adverse effect (Figure 8). The rates of dry mouth were the highest with oxybutynin. Among other adverse effects, constipation and blurred vision were the most common (Figure 9).

Indirect comparisons indicated comparable effectiveness of the drugs on continence. Oxybutynin had higher rates of dry mouth and treatment discontinuation due to adverse effects than other drugs.

Several retrospective observational studies analyzed comparative effectiveness and safety of pharmacological treatments for UI. The evidence-based cost utility analysis reported that more than half of patients stop taking drugs for UI after 1 year of treatment (Figure 10).[374] The lowest rates of treatment discontinuation were with 5 mg of solifenacin.[374] The authors estimated quality adjusted life years using treatment response rates and discontinuation rates for all drugs, and demonstrated the largest gain in quality adjusted life years per 1,000 treated with solifenacin

(Figure 11). Trospium, which demonstrated the highest continence rates, was not included in this analysis (Appendix Figure F26).

Table 9. Discontinuation due to adverse effects with pharmacological treatments for UI

Active	Dose	Control	Dose	Studies	Patients	Rate in Active Group	Rate in Control Group	Relative Risk (95% CI)	Absolute Risk Difference (95%CI)	Number Needed to Treat (95% CI)	Evidence
Darifenacin	7.5	Oxybutynin	7.5	1[657]	16	0	12.5	0.33 (0.02; 7.14)	-0.13 (-0.41; .16)		Insufficient
Darifenacin	7.5-15	Oxybutynin	15	2[639,657]	62	3.2	12.9	0.54 (0.02; 13.7)	-0.065 (-0.353; 0.223)		Low
Darifenacin control release	30	Oxybutynin-immediate release	15	2[639,657]	63	6.25	19.4	0.32 (0.07; 1.55)	-0.131 (-0.292; 0.031)		Low
Solifenacin	Not reported	Darifenacin control release	Not reported	1[664]	77	20	21.6	0.93 (0.39; 2.21)	-0.02 (-0.20; .17)		Insufficient
Fesoterodine fumarate		Tolterodine		4[300,302,308,349]	5,815	5.4	3.5	1.54 (1.21; 1.97)	0.018 (0.007; 0.028)	56 (36; 143)	Moderate
Oxybutynin		Tolterodine tartrate		10[29,263,289,365,366,368,370-373]	4,639	10.0	5.6	1.64 (1.15; 2.33)	0.055 (0.015; 0.095)	18 (11; 67)	High
Solifenacin		Tolterodine		4[338,568,662,663]	3,932	2.9	2.2	1.28 (0.86; 1.91)	0.005 (-0.006; 0.015)		Moderate
Trospium Chloride		Oxybutynin Hydrochloride		2[606,666]	2,015	5.9	5.4	0.98 (0.39; 2.46)	0.003 (-0.031; 0.037)		Low
Trospium chloride	20mg twice daily	Oxybutynin	5mg twice daily	1[666]	357	3.7	6.7	0.56 (0.21; 1.50)	-0.029 (-0.086; 0.027)		Insufficient
Trospium chloride	20mg twice daily	Oxybutynin	5mg twice daily	1[666]	357	1.5	3.3	0.45 (0.10; 1.97)	-0.018 (-0.058; 0.021)		Insufficient
Solifenacin	5mg daily	Propiverine	20mg daily	1[644]	802	5.0	6.5	0.77 (0.44; 1.36)	-0.015 (-0.047; 0.017)		Insufficient
Solifenacin	10mg daily	Propiverine	20mg daily	1[644]	787	6.8	6.5	1.04 (0.62; 1.77)	0.003 (-0.032; 0.038)		Insufficient
Solifenacin	5mg once daily	Oxybutynin IR	5mg 3 times daily	1[665]	132	10.3	10.9	0.94 (0.35; 2.53)	-0.006 (-0.112; 0.099)		Insufficient

Table 10. Continence with pharmacological treatments for UI

Active	Dose	Control	Dose	Studies	Patients	Rate in Active Group	Rate in Control Group	Relative Risk (95% CI)	Absolute Risk Difference (95%CI)	Number Needed to Treat (95% CI)	Evidence
Fesoterodine		Tolterodine		2[308,349]	3,312	61.0	55.5	1.10 (1.04; 1.16)	0.055 (0.021; 0.088)	18 (11; 48)	Low
Trospium chloride	20mg twice daily	Oxybutynin	5mg twice daily	1[666]	357	22.5	12.2	1.84 (1.01; 3.34)	0.102 (0.018; 0.187)	10 (5; 55)	Insufficient
Oxybutynin	10mg/d	Tolterodine	4mg/d	1[368]	790	23.0	16.8	1.37 (1.03; 1.82)	0.062 (0.007; 0.118)	16 (8; 149)	Insufficient
Solifenacin succinate	5-10 mg once daily	Tolterodine	4mg once daily	1[661]	1,177	59.0	49.0	1.20 (1.08; 1.34)	0.099 (0.042; 0.156)	10 (6; 24)	Insufficient
Flavoxate hydrochloride	1,200	Oxybutynin	5mg t.i.d.	1[658]		28.0	42.0	0.67 (0.38; 1.16)	-0.140 (-0.325; 0.045)		Insufficient

Figure 4. Comparative effectiveness of oxybutynin vs. tolterodine (pooled results from individual RCTs)[29,256,263,289,365-373]

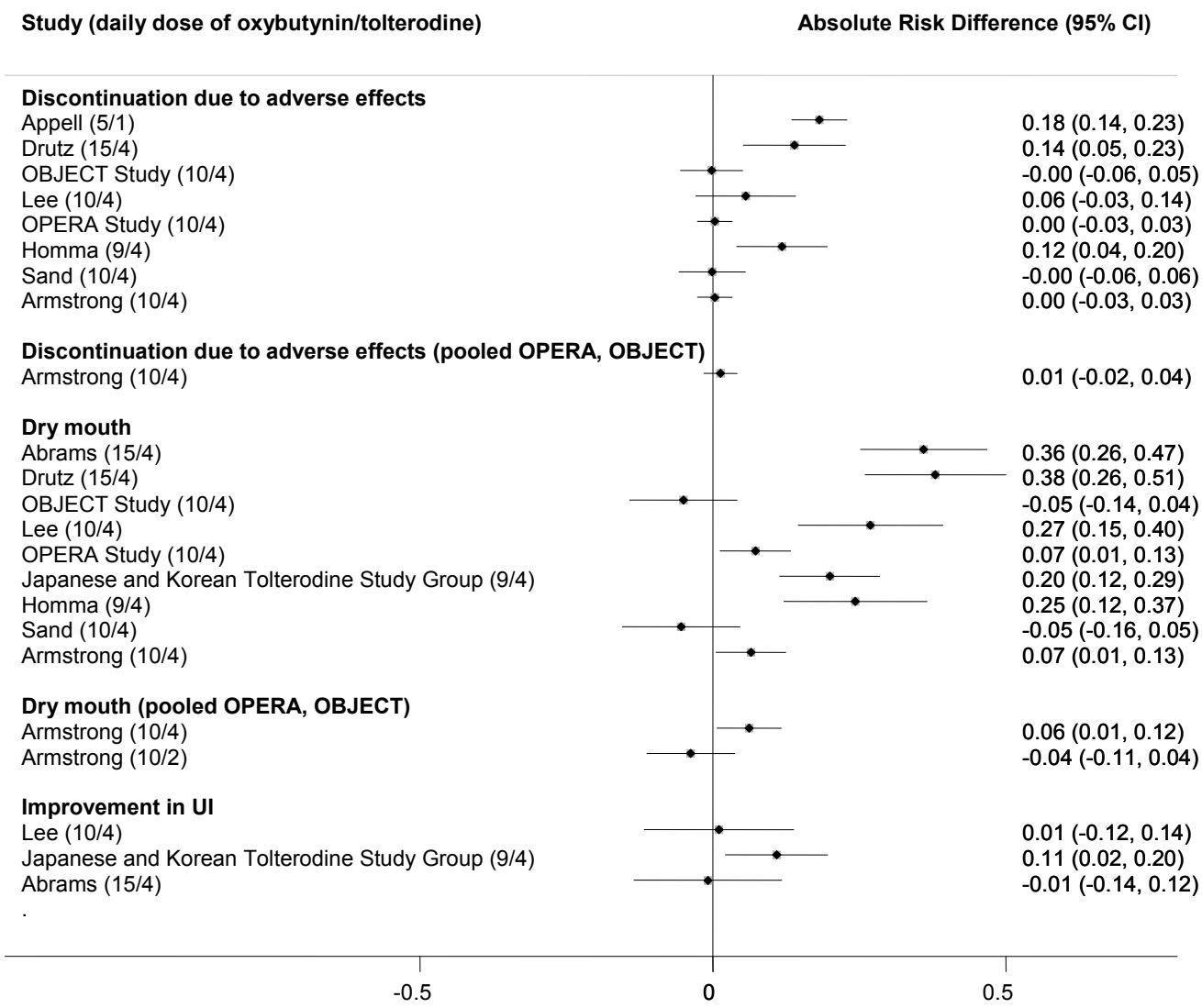


Figure 5. Continence with drugs for overactive bladder when compared to placebo (pooled results from RCTs)

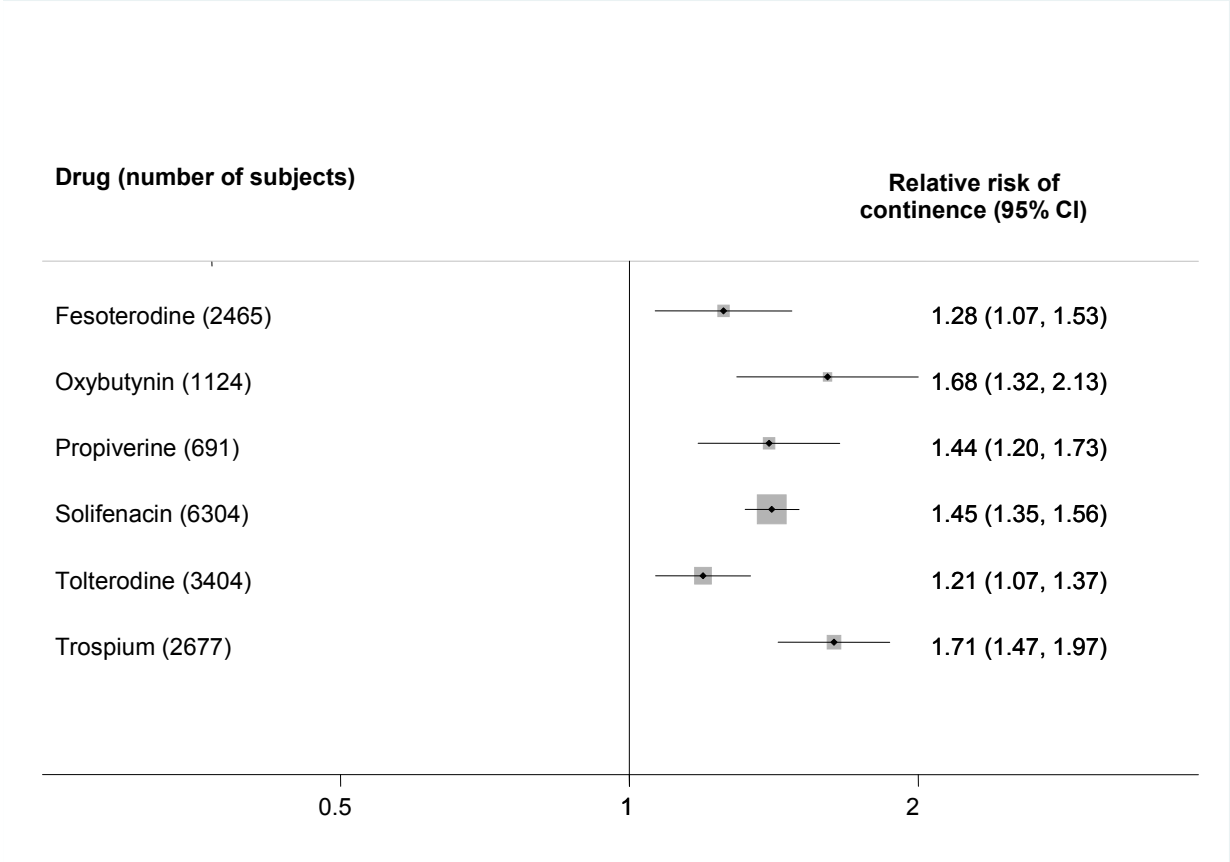
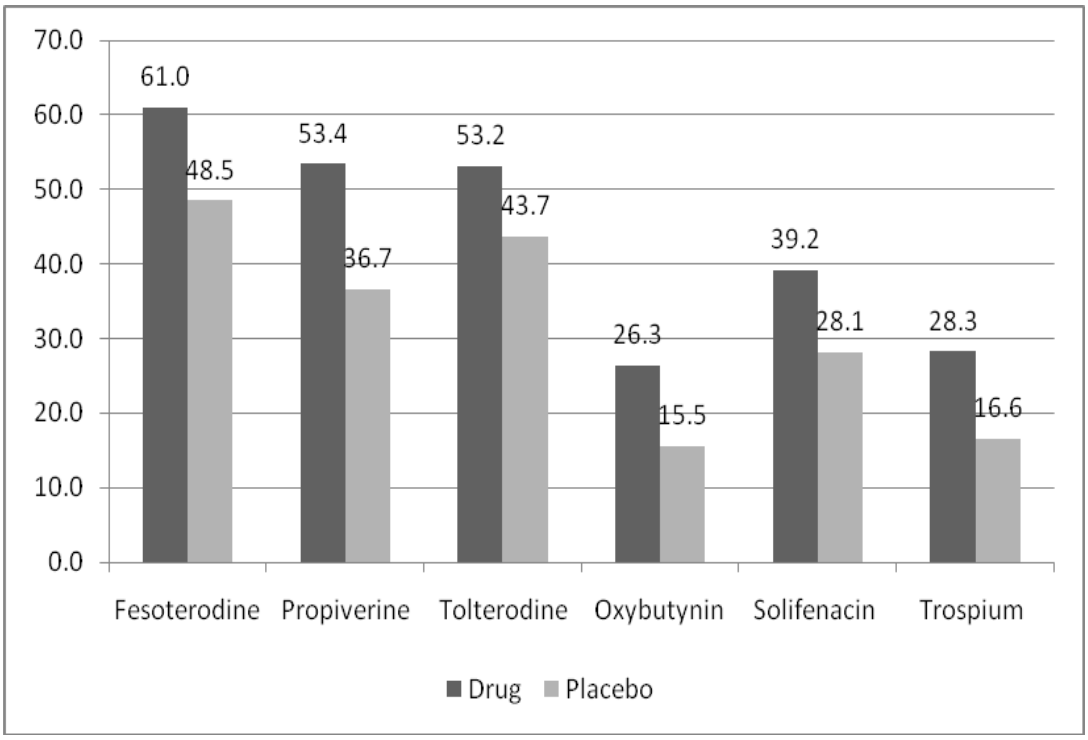
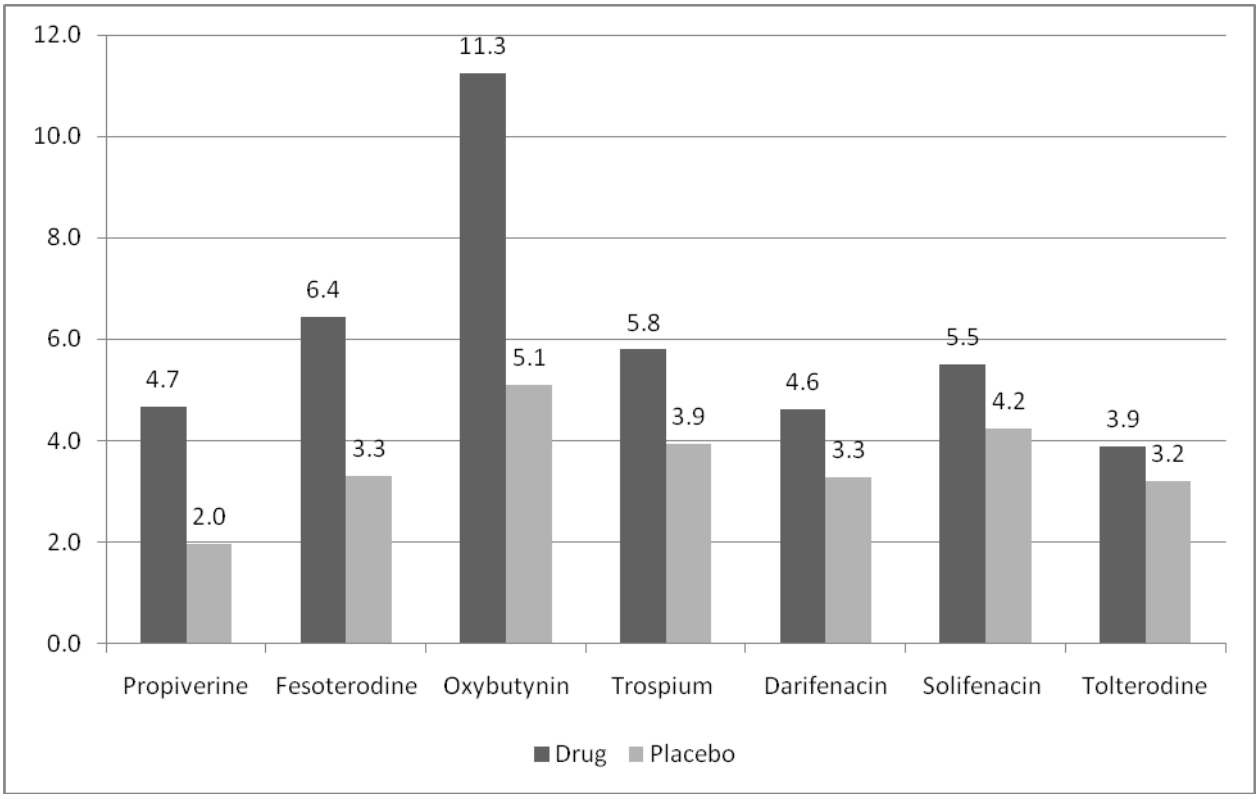


Figure 6. Continence rates (%) with drugs vs. placebo (pooled results from RCTs)



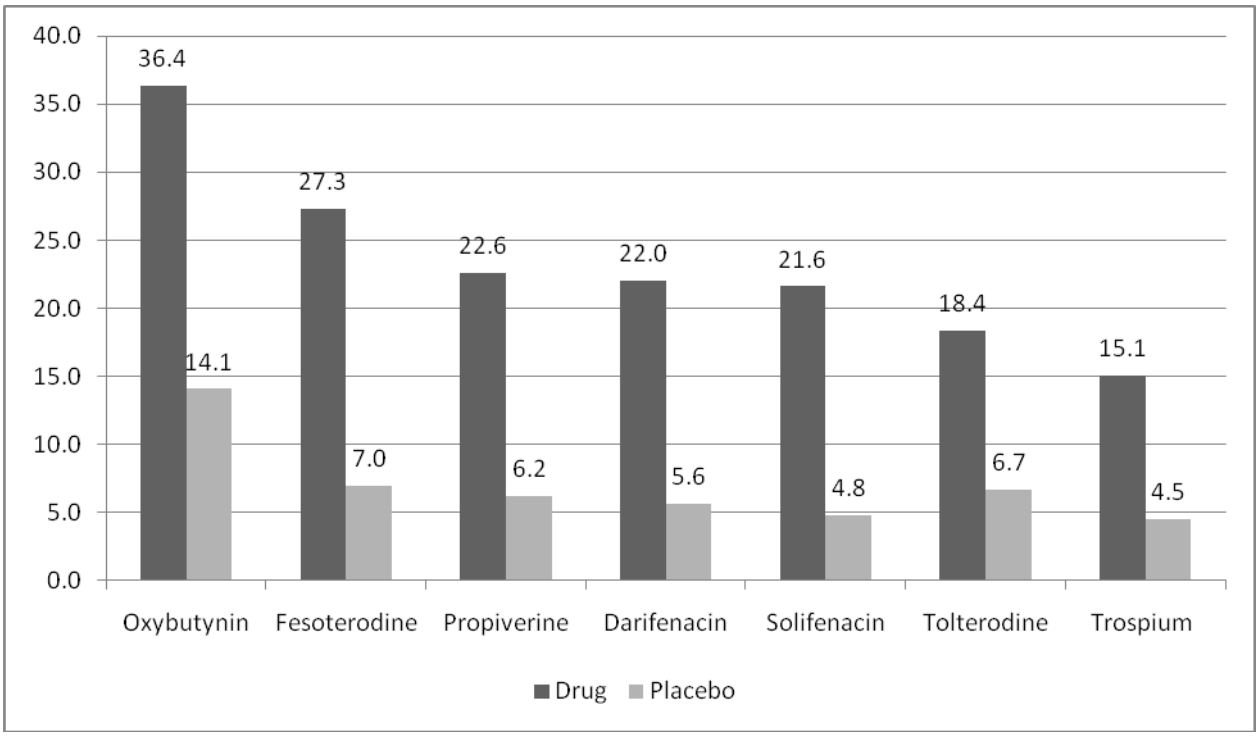
Vertical axis - percentage of continent with treatments
Horizontal axis - treatments with drug or placebo

Figure 7. Discontinuation of treatments due to adverse effects (%) with drugs vs. placebo (pooled results from RCTs)



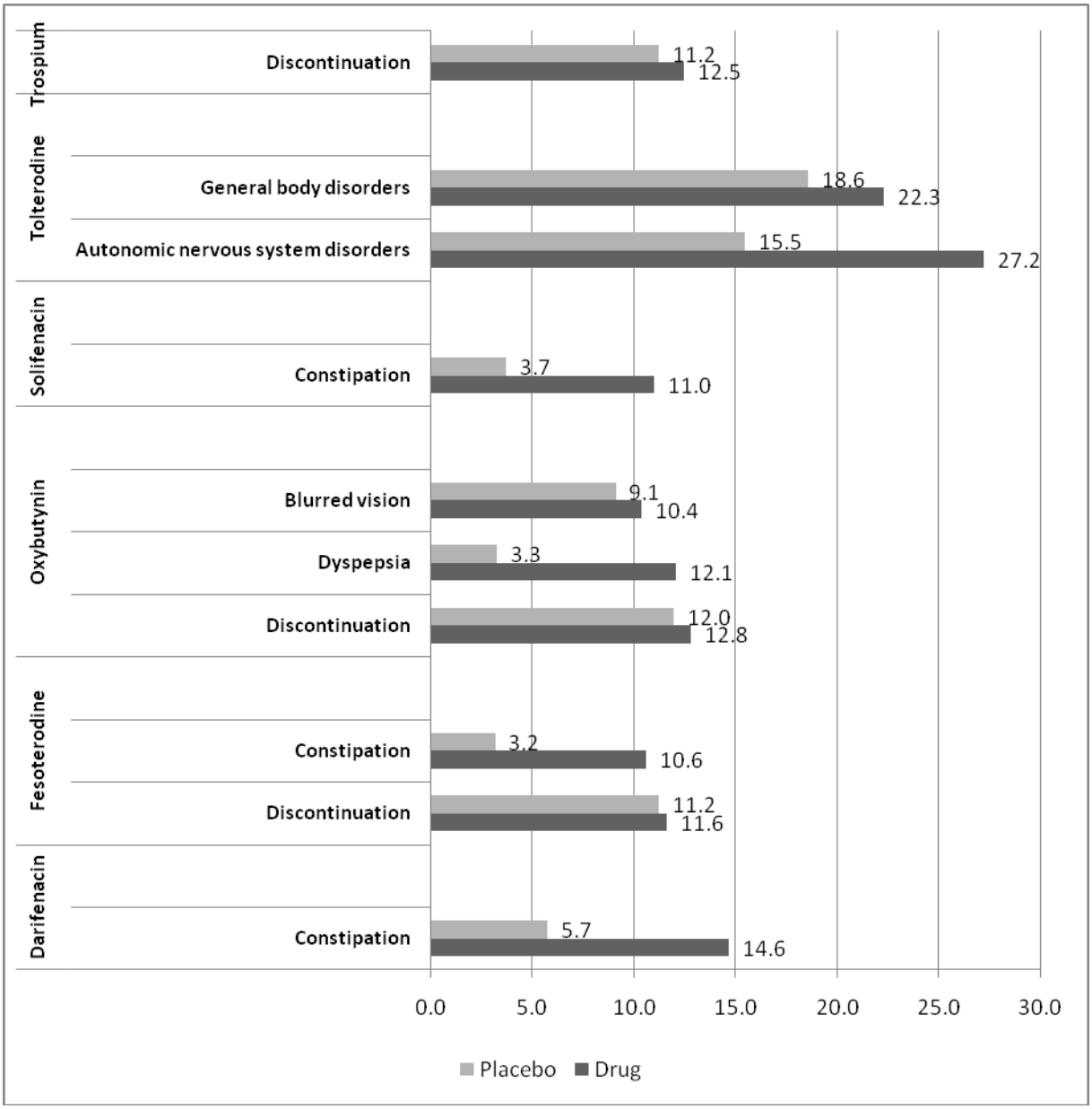
Vertical axis - percentage of those who discontinued treatments due to adverse effects
Horizontal axis - treatments with drug or placebo

Figure 8. Dry mouth rates (%) with drugs vs. placebo (pooled results from RCTs)



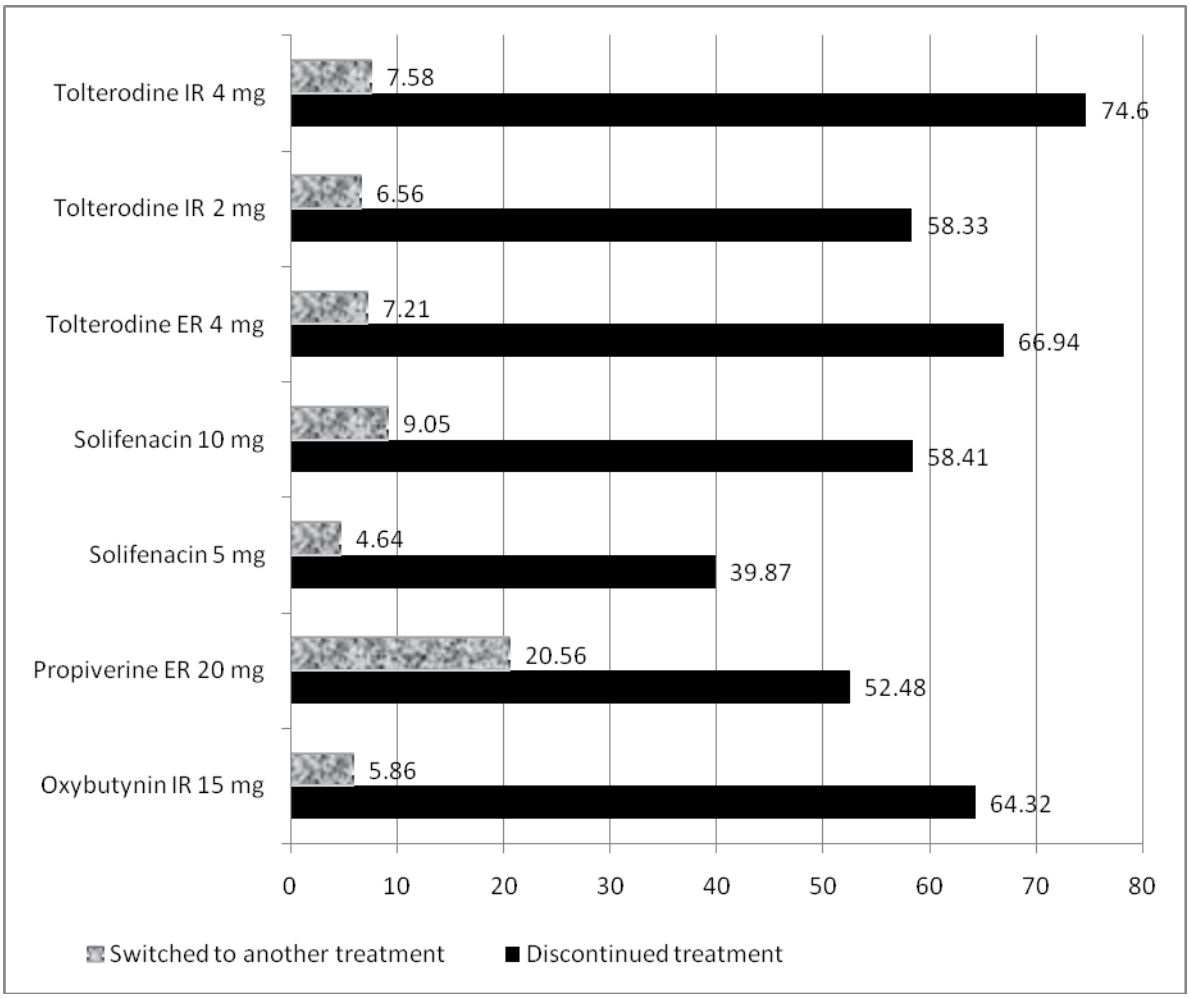
Vertical axis - percentage of subjects with dry mouth with treatment
Horizontal axis - treatments with drug or placebo

Figure 9. Rates (%) of the most common (>10%) adverse effects with drugs vs. placebo (pooled results from RCTs)



Horisontal axis - percentage of subjects with adverse effects

Figure 10. Treatment persistence of the drugs for UI[374]



The Role of Patient Characteristics on Patient Outcomes with Pharmacological Treatments

Age. The rates of clinical outcomes were similar in age subgroups**.** Clinical outcomes in age subgroups were reported in four studies involving duloxetine,[240] solifenacin,[343] tolterodine,[293] and oxybutynin.[240,293,343,371] Active and control treatments, outcomes, and definitions of age subgroups varied across the studies. We describe clinical outcomes in age subgroups treated with the drugs from individual studies and pooled analyses of individual subject data.

In 1,913 women ages 22-83 years with predominant stress UI, duloxetine compared to placebo did not improve UI in elderly women (Figure 11).[240]

In contrast, younger women reported improvement in UI more often with duloxetine than with placebo.[240] Duloxetine prevented worsening of UI in older women, but was not better than placebo in women younger than 50 years of age.[240]

Solifenacin increased continence more often than placebo in all age groups (Figure 12).[343]

The drug tended to benefit older women more than younger women. For instance, the relative increase in continence with 5 mg was 38 percent in younger and 69 percent in older individuals.[343] The same tendency was observed with 10 mg of solifenacin, with a relative increase in continence of 49 percent in younger people and of 63 percent in older people.[343] This tendency was not statistically significant.

Tolterodine extended release, when compared to placebo in 1,015 individuals with urgency UI, improved UI more than placebo in older but not younger subjects.[293] (Figure 13).

Oxybutynin reduced the number of urgency and total UI episodes more often than tolterodine in women younger than 64 years with urgency or mixed UI in one RCT.[371] The rates of adverse effects did not differ between age groups.

Several studies did not directly compare the outcomes among treatment groups but aimed to test treatment effects in elderly populations. The treatment effects in such studies did not substantially differ from other studies with younger populations. Oxybutynin in frail community dwelling older people reduced frequency and produced subjective benefits without differences in withdrawal compared to placebo.[251] Darifenacin was examined in elderly populations in two RCTs[321,325] and one pooled analysis of three RCTs.[331] Darifenacin resulted in improvement in UI when compared to placebo in the elderly.[325] The drug needed to be given to eight elderly patients to achieve more than a 50 percent reduction in UI episodes in one person. Cognitive function did not differ between short-term 2 week treatment with darifenacin and placebo.[321] Dry mouth, constipation, and dyspepsia were the most common adverse effects in the elderly. Evidence suggested that age did not modify the effects of the tested drugs on examined clinical outcomes.

A high level of evidence suggested that duloxetine was no better than a placebo in improving UI in elderly women. A high level of evidence suggested that solifenacin increased continence more often than placebo, regardless of age.

Race. Evidence was inconclusive about racial differences in treatment effects of duloxetine in women with stress UI. Only one study, DESIRE (Duloxetine Efficacy and Safety for Incontinence in Racial and Ethnic Populations) examined clinical outcomes in different race groups.[228] Women with stress UI were treated with 80 mg of duloxetine per day. Weekly UI episodes were reduced compared to baseline in all race groups, by 65.7 percent in African Americans, by 73.0 percent in Hispanics, and by 75.0 percent in Caucasian women. Clinical outcomes rarely differed between racial subgroups (Figure 14).[228] African American women reported improvement in UI more often than Caucasian women. Hispanic women experienced a

reduction in UI by more than 50 percent less often than Caucasian women. Several adverse effects, including dizziness, headache, and somnolence, were less common among African American women and more common among Hispanic women than among Caucasian women. The biological plausibility of such differences is not clear.

Baseline type of UI. Evidence was not sufficient for individualized prediction of benefits by the urodynamic type of UI.

The studies of antimuscarinic drugs enrolled subjects with overactive bladder and predominant urgency UI. The studies of duloxetine enrolled subjects with predominant stress UI. Few studies compared the outcomes in subgroups with the predominant type of UI. One RCT of tolterodine compared continence rates, reduction in UI episodes, and pad utilization in subjects with predominant urgency and pure urgency UI and concluded the same treatment benefits in all subjects regardless of the type of UI.[312] Two pooled analyses of individual patient data compared clinical outcomes between 5 or 10 mg of solifenacin and placebo.[343,344]

Both doses of solifenacin increased continence compared to placebo. Solifenacin increased continence in subjects with pure urgency and mixed UI. The effect size did not differ between subgroups with different types of UI (Figure 15). The relative increase in continence rates was greater with 5 mg of solifenacin in patients with pure urgency UI than those with mixed UI. One pooled analysis demonstrated that 5 mg of solifenacin was not better than placebo in achieving continence in subjects with mixed UI.[344] Individuals with mixed UI required longer treatment duration to achieve greater benefits from solifenacin. At the end of 40 weeks of treatment, 52 percent of the people with mixed UI reported regaining continence, and 34 percent reported resolution of symptomatic urgency on uncontrolled extension in one RCT.[345]

Clinical outcomes of tolterodine and solifenacin did not differ in individuals with baseline mixed or pure urgency UI. Individuals with mixed UI may require a larger dose and longer treatment duration to achieve clinical benefits from solifenacin.

Baseline frequency of UI. Baseline frequency of UI did not demonstrate a significant or consistent association with clinical outcomes of any drug. Individuals with more frequent UI had slightly greater benefits from drugs than from placebo. Variability in definitions of baseline severity and clinical outcomes lowered the level of evidence.

Three secondary data analyses of drug trials examined clinical outcomes among subgroups with different baseline frequency of UI.[310,343,353] The results indicated that baseline frequency of UI tended to modify the treatment effects of the drugs; however, statistical significance of such modifications was not consistent across the definitions of baseline severity, drugs, and treatment outcomes.

Several drugs resulted in greater benefits for the patients with more frequent baseline UI. Tolterodine extended-release increased continence rates compared to placebo in a post hoc analysis of an RCT in patients with symptoms of urinary frequency and pure urgency UI. Urinary continence rates varied by diary-recorded duration and frequency of UI at baseline (Figure 16).[310] Individuals with more frequent baseline UI had a larger relative benefit with the drug than with placebo. Five or 10 mg of solifenacin per day increased the rates of continence regardless of baseline frequency of UI in a pooled analysis of 1,873 people with OAB.[343] Those with more than three episodes of urgency UI per day at baseline experienced a slightly larger relative benefit than those with less frequent UI.[343] Patients with more than two urgency UI episodes per day experienced a greater reduction in the number of urgency UI episodes with 8 mg of fesoterodine in a pooled analysis of two RCTs.[353] In contrast, trospium was better than placebo at resolving UI only in subjects with fewer than five UI episodes/day.[375] Trospium did not resolve UI in subgroups with more than 5 episodes of UI /day.[375]

Adverse effects leading to discontinuation were more common with 8 mg in patients with two to four episodes of urgency UI per day (Figure 17).[353]

Prior treatment status. Solifenacin was effective regardless of the response to previous treatments, even though poor responders did not benefit from increasing the dose of the drug (high level of evidence). One study reported that darifenacin was effective in those who failed previous treatment (evidence insufficient). Tolterodine was not better than placebo in achieving clinical benefits among poor responders to the previous muscarinic antagonists in one RCT (evidence insufficient).

Many studies reported prior treatment status, but very few reported clinical outcomes in subgroups by the response to previous treatments. Solifenacin increased continence when compared to placebo, regardless of the response to previous treatments in a pooled analysis of four RCTs (Figure 18).[343] Previous nonresponders experienced a greater relative benefit than those who responded to previous treatments.[343] Patients who did not respond to previous treatments did not benefit from increasing the dose of solifenacin.[343] Post hoc analysis of the OPERA trial demonstrated greater rates of continence with oxybutynin than with tolterodine in patients with prior treatments with antimuscarinic drugs, but no difference was demonstrated between the two drugs in treatment of naïve patients.[668] Tolterodine was not better than placebo among poor responders to the previous muscarinic antagonists in one RCT.[292]

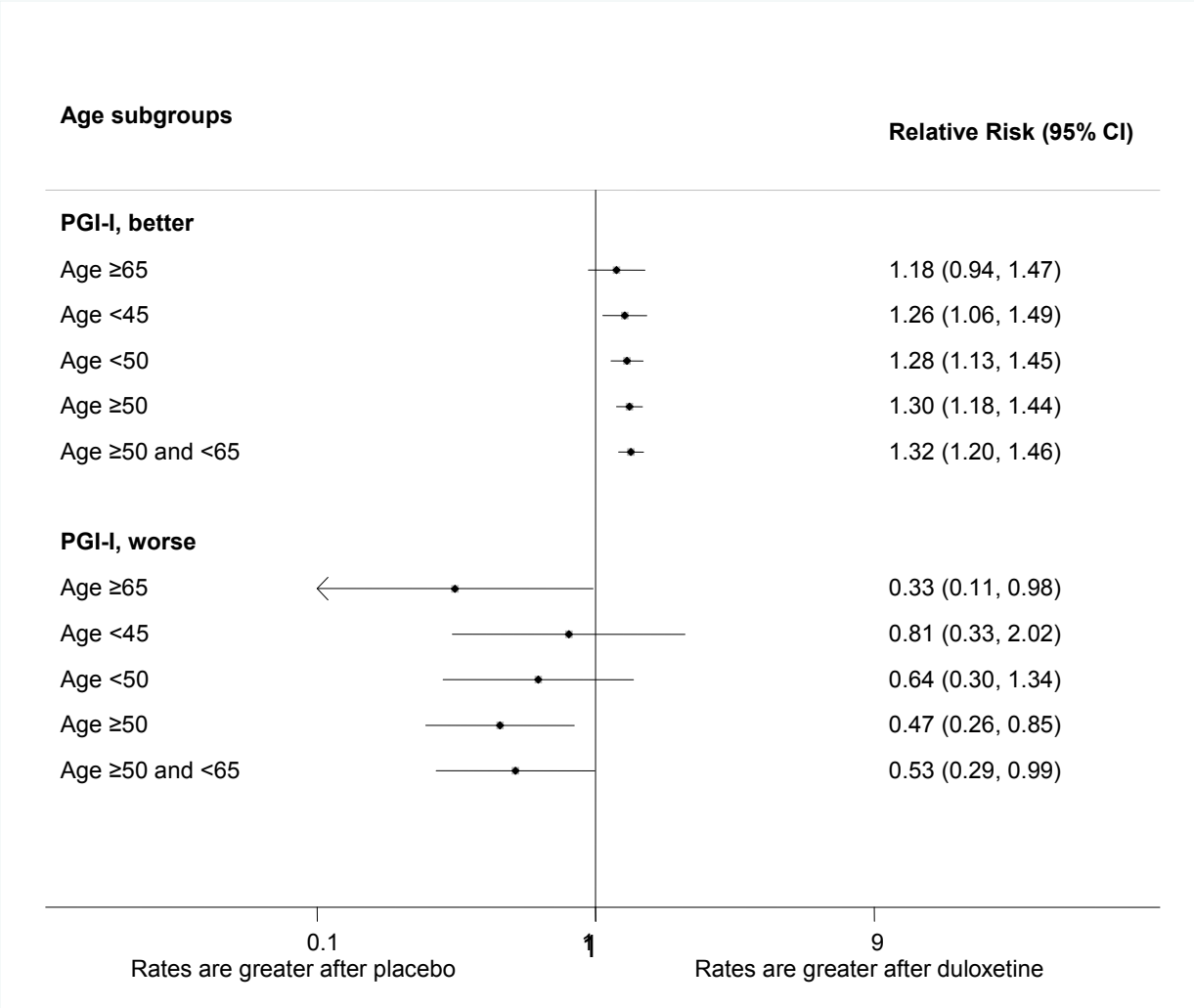
Darifenacin improved clinical outcomes in OAB patients who expressed dissatisfaction with prior extended-release (ER) oxybutynin or tolterodine therapy in one nonrandomized study.[329] Darifenacin improved the Patient's Perception of Bladder Condition regardless of previous treatments by 108 percent (OR 2.08, 95 percent CI 1.48, 2.92) in oxybutynin treated patients and by 77 percent (OR 1.77, 95 percent CI 1.29, 2.43) in tolterodine treated patients.[329]

Comorbidities. Duloxetine was no better than placebo in women with stress UI and comorbidities (insufficient evidence from one RCT).

One RCT examined clinical outcomes with duloxetine compared to placebo in women with comorbidities (Figure 19).[240] Duloxetine was not better than placebo in women with depression, diabetes, and chronic lung diseases, and it was not better than placebo in preventing worsening of UI in underweight women and women with depression, diabetes, and chronic lung diseases.[240]

Obesity. Baseline obesity did not modify the effect of trospium in pooled analysis of individual patient data from RCTs (Table 11).[669] Trospium was more effective than placebo in achieving continence in obese and nonobese adults.[669] The magnitude of the benefit was similarly low in subgroups with different baseline BMI. Trospium resolved urgency UI in 140 per 1,000 treated adults with normal weight or obesity.

Figure 11. Clinical outcomes with duloxetine vs. placebo in age subgroups (pooled analysis of individual data on women from four RCTs)[240]



PGI-I -Patient Global Impression of Improvement

Figure 12. Urinary continence with solifenacin when compared to placebo (pooled analysis of individual patient data from four RCTs)[343]

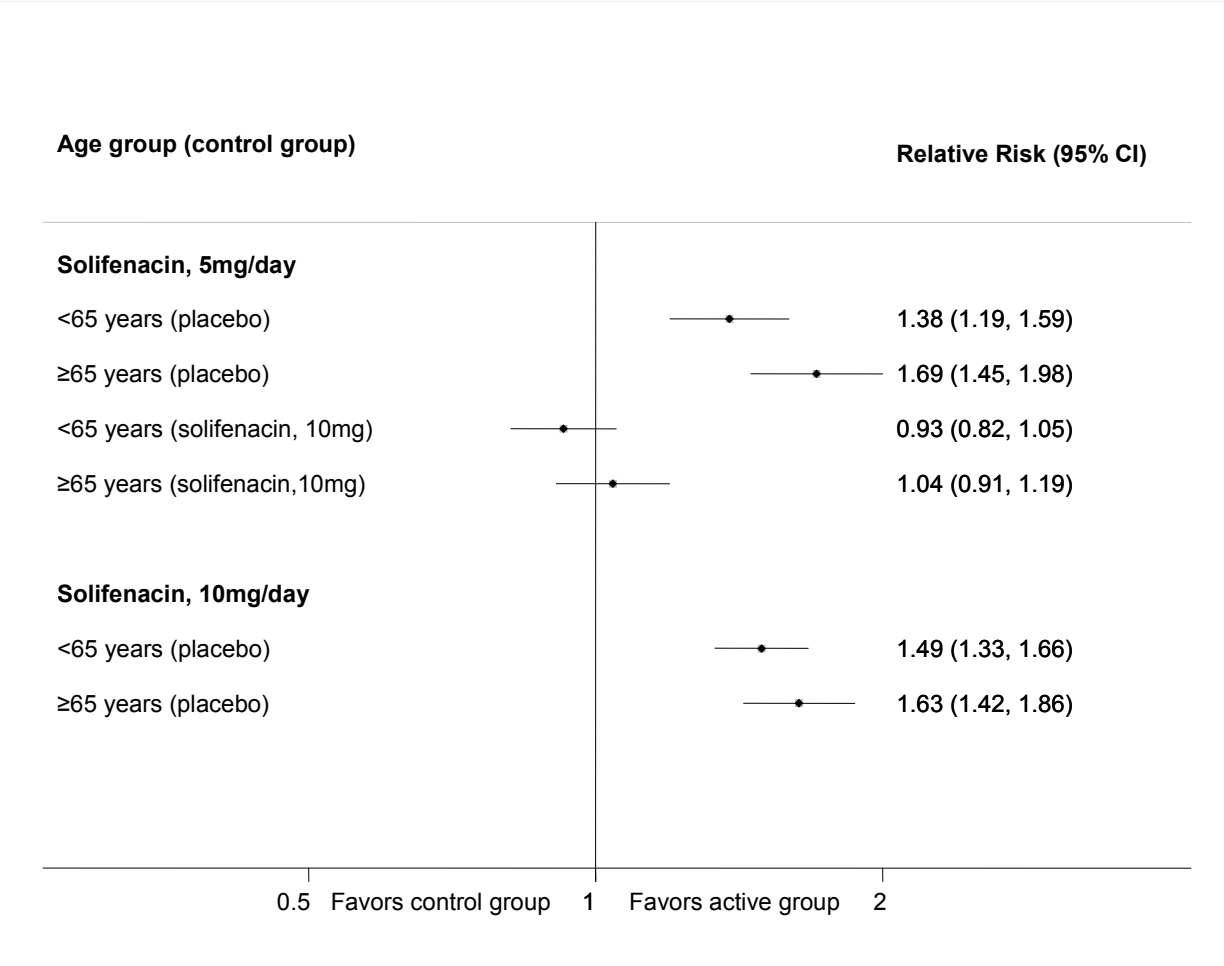


Figure 13. Clinical outcomes with tolterodine vs. placebo in age subgroups (individual RCTs)[293]

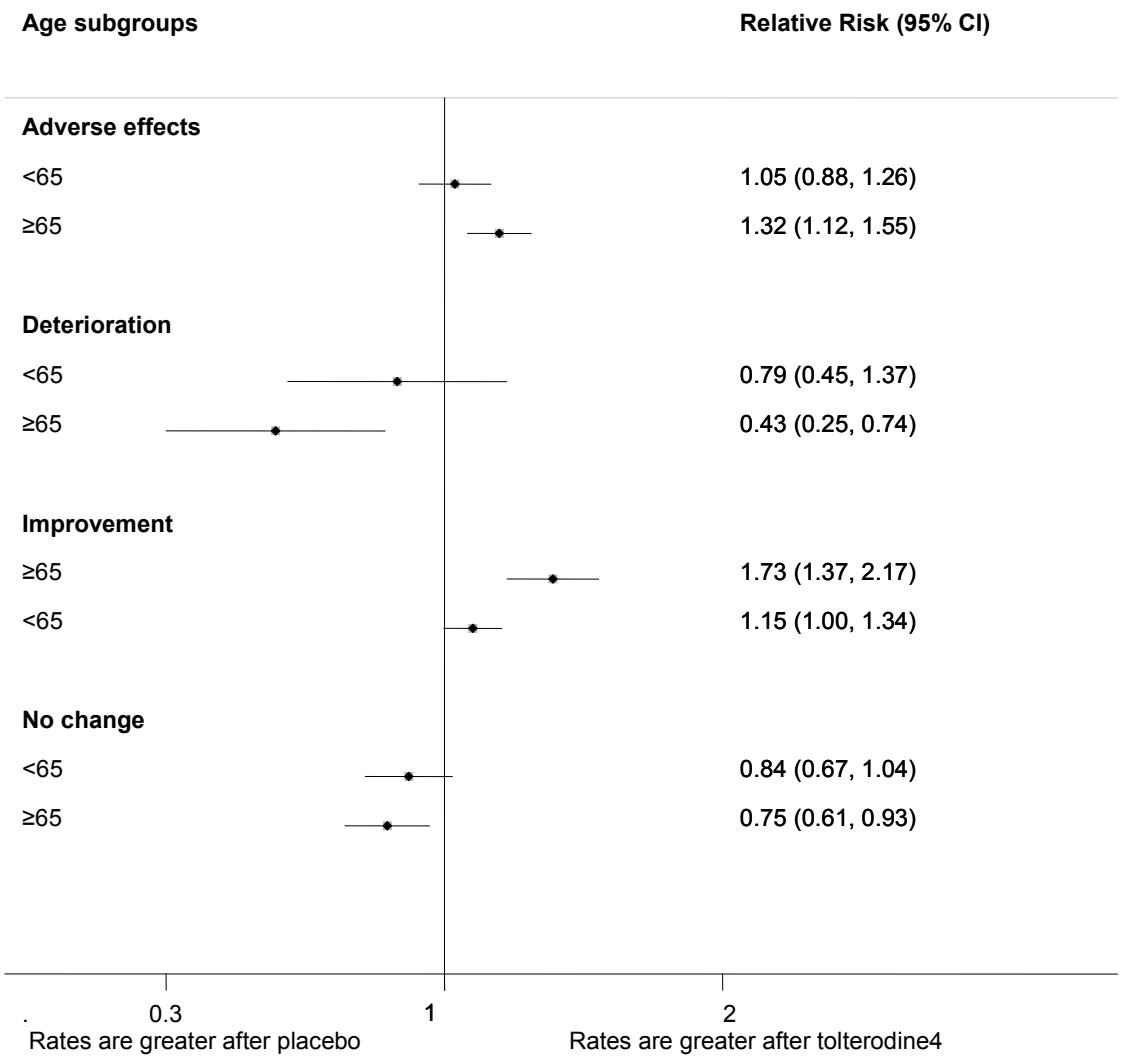


Figure 14. Clinical outcomes with duloxetine in racial subgroups of women with stress UI, DESIRE (Duloxetine Efficacy and Safety for Incontinence in Racial and Ethnic populations)[228]

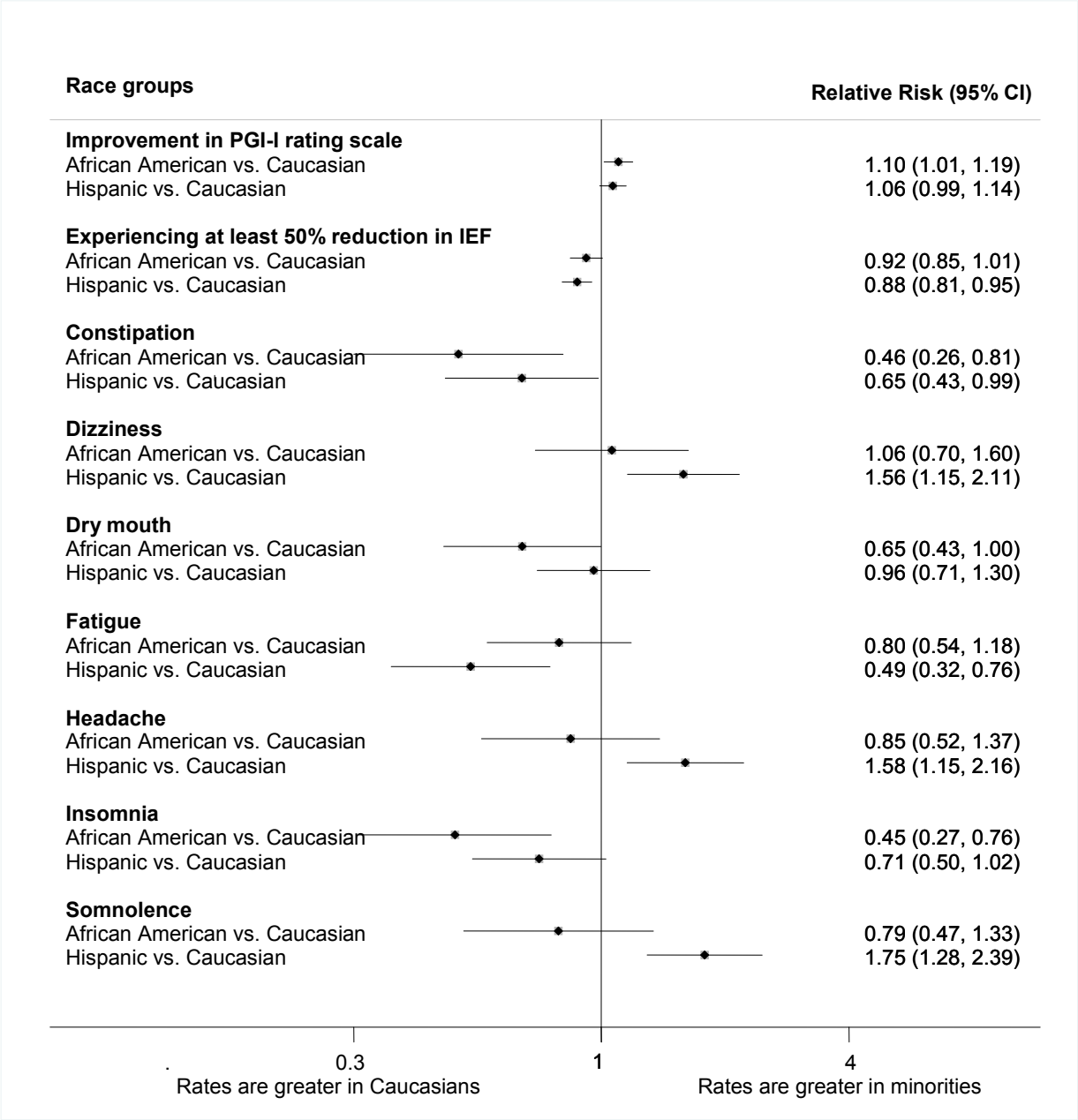


Figure 15. Continence with solifenacin compared to placebo in patients with mixed or pure urgency UI (pooled analyses of individual patient data)[343,344]

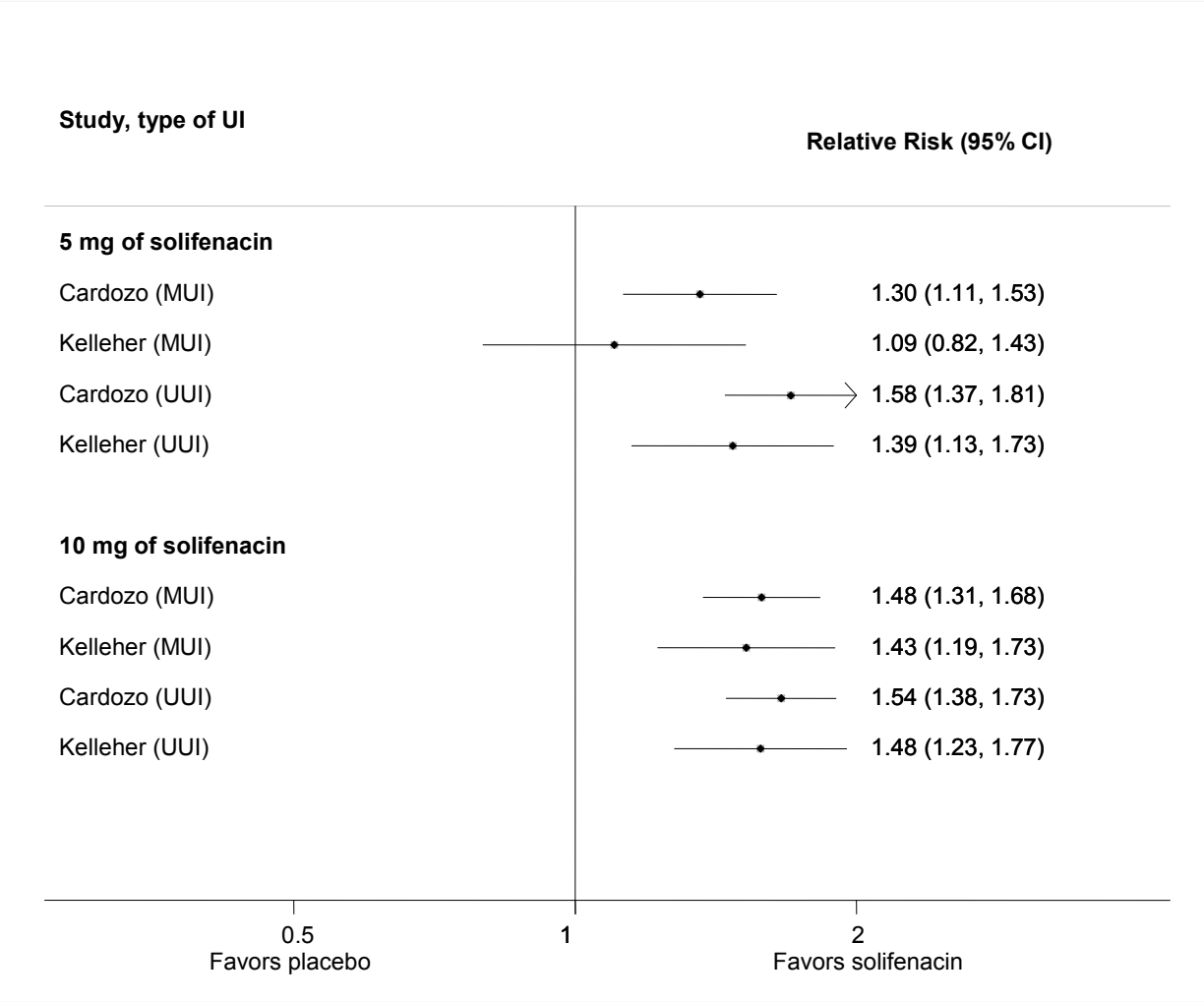


Figure 16. Complete continence with tolterodine, extended release of 4 mg/day vs. placebo in groups with different baseline frequency UI episodes/week[310]

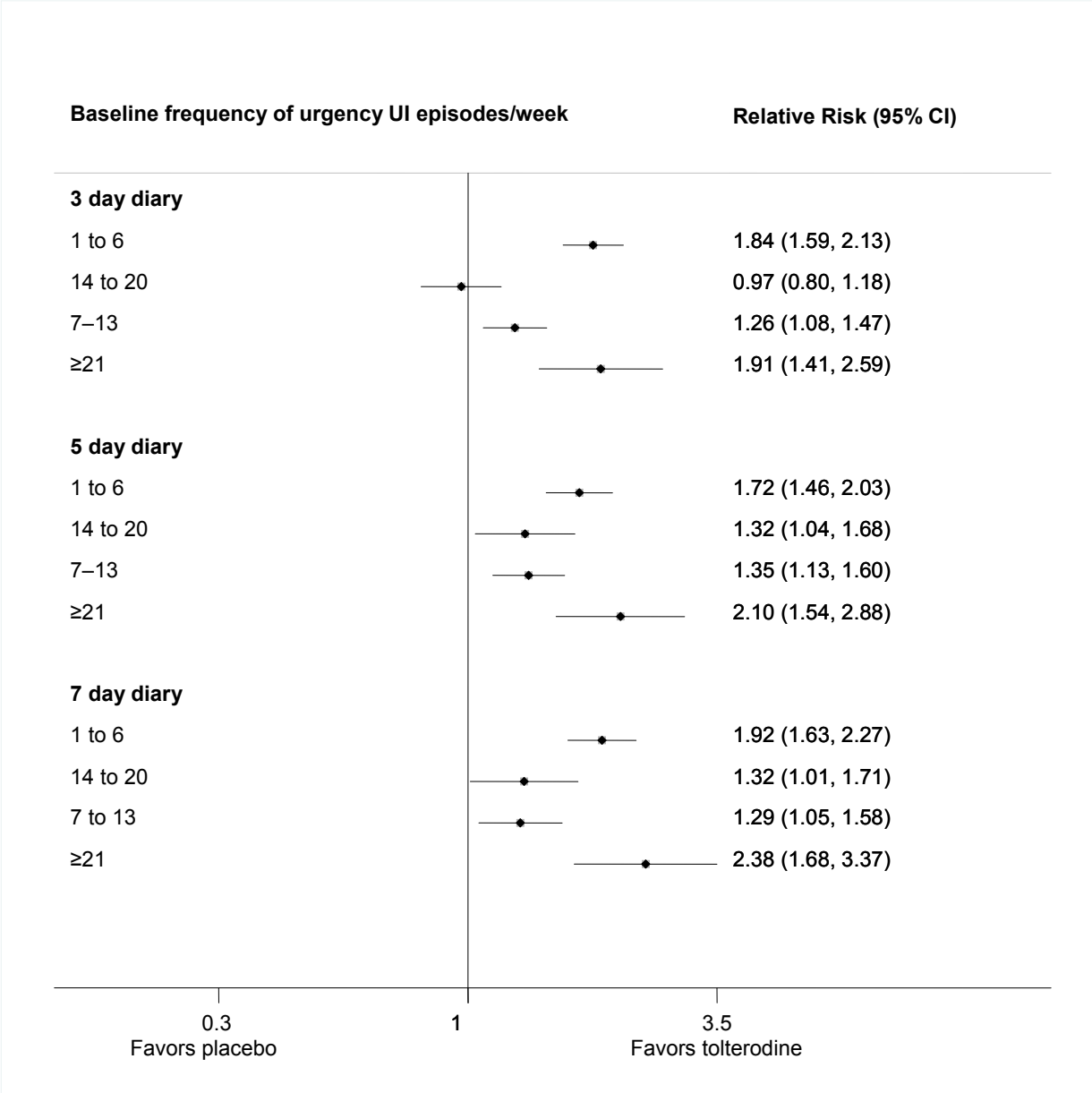


Figure 17. Adverse effects of fesoterodine compared to placebo in subgroups with different baseline frequency of urgency UI (pooled analysis of four RCTs)[353]

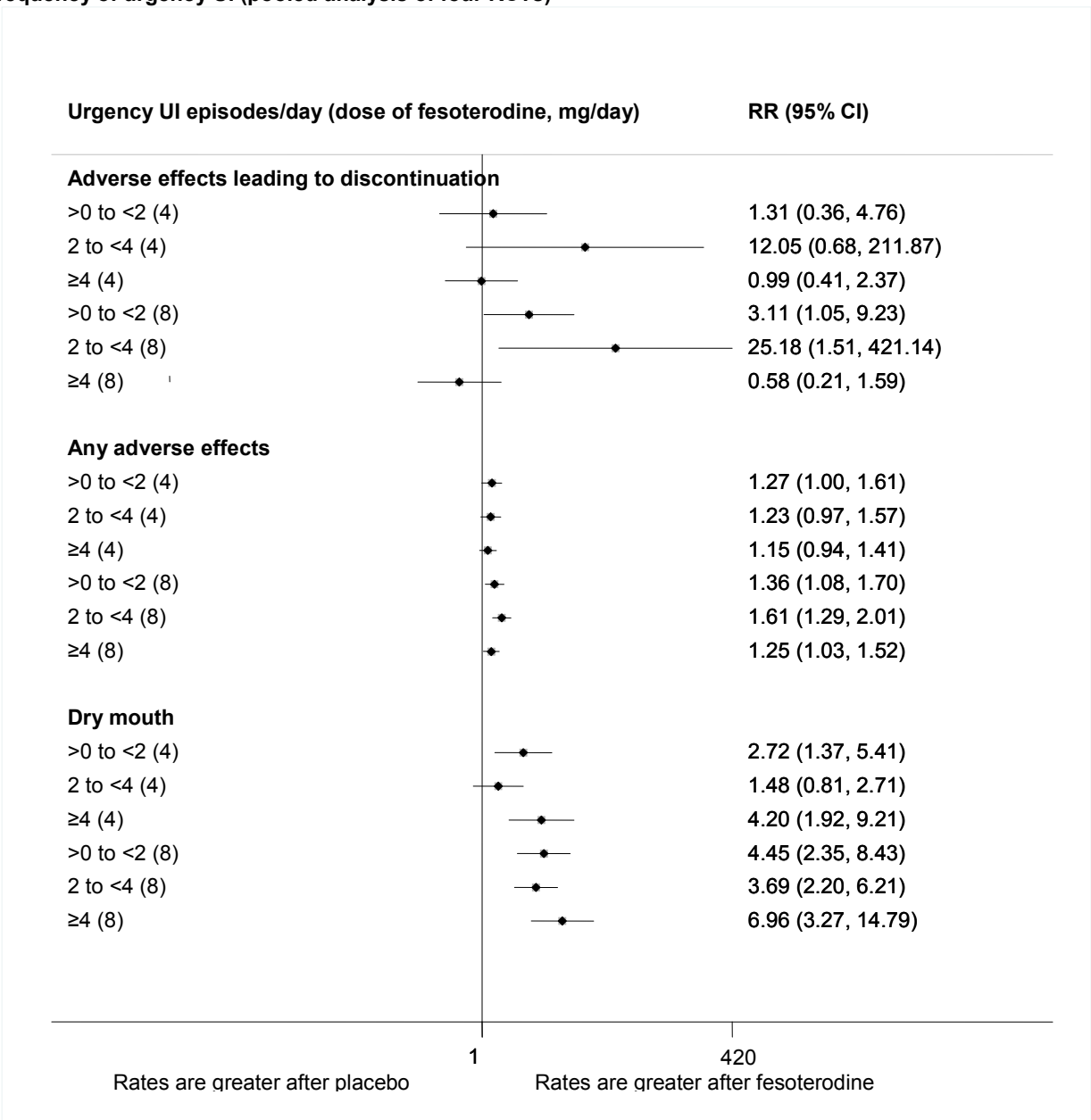


Figure 18. Continence with solifenacin vs. placebo in subgroup by response to the previous treatment with antimuscarinic medications (pooled analysis of RCT)[343]

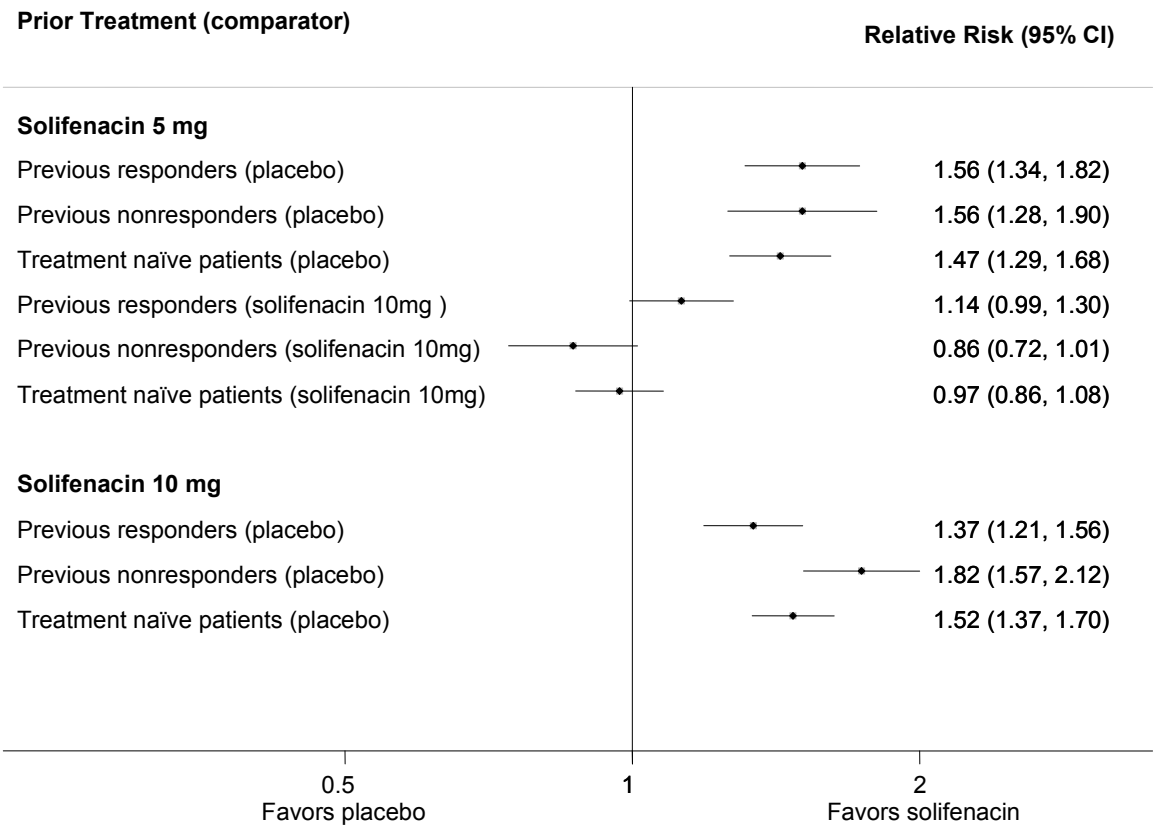


Figure 19. Patient Global Impression of Improvement rating as "better" with duloxetine when compared to placebo in subgroups with different comorbidity status (Duloxetine Urinary Incontinence Study Group)[240]

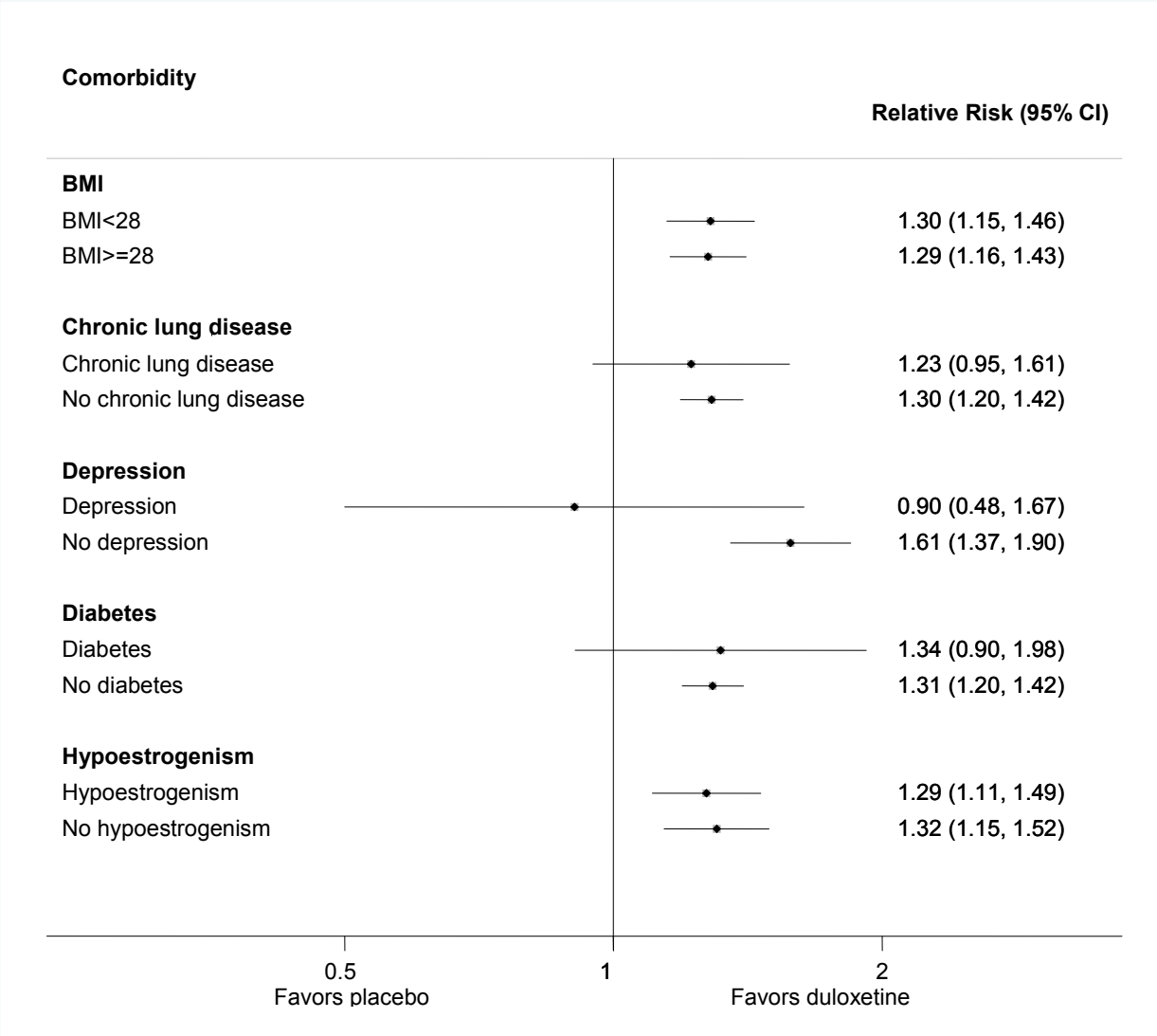


Table 11. Continence with 60mg once daily of trospium vs. placebo in obese and nonobese adults with overactive bladder (pooled results from RCTs using the WHO criteria for obesity)[669]

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Baseline Body Mass Index	Drug Events/ Randomized	Placebo Events/ Randomized	Rate (%) in Active/ Control	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat (95% CI)	Attributable Events Per 1,000 Treated (95% CI)
BMI <30kg/m^2	214/578	133/578	37/23	1.6 (1.3; 1.9)	0.14 (0.09; 0.19)	7 (5; 11)	140 (88; 192)
BMI <35kg/m^2	202/578	133/578	35/23	1.5 (1.3; 1.8)	0.12 (0.07; 0.17)	8 (6; 15)	119 (68; 171)
BMI >30kg/m^2	191/578	127/578	33/22	1.5 (1.2; 1.8)	0.11 (0.06; 0.16)	9 (6; 17)	111 (60; 162)
BMI >35kg/m^2	202/578	121/578	35/21	1.7 (1.4; 2.0)	0.14 (0.09; 0.19)	7 (5; 11)	140 (89; 191)

Question 3. How Effective is the Nonpharmacological Treatment of UI?

One hundred forty eight RCTs tested nonsurgical nonpharmacological treatments for UI (Appendix Table F80). A small proportion of RCTs reported sponsorship and conflict of interest (Appendix Table F81). Sample size was justified in 63 RCTs (43 percent) (Appendix Table F82). Quality of the studies, including intention to treat principle and adequacy of allocation concealment, did not demonstrate significant modification of the association between treatments and patient outcomes (Appendix Table F83). In addition, we reviewed five RCTs that examined eligible treatments for female UI but did not report the rates of clinical outcomes that can be reproduced and synthesized (Appendix Table F84). We also reviewed the results from 45 nonrandomized studies that reported crude rates of outcomes with medical devices that have never been tested in RCTs (Appendix Table F26). Here, we review clinical effects of nonpharmacological treatments compared to regular care or no active treatment. The majority of the trials included women with mixed UI. We examined the effects of predominantly stress or urgency UI when reported by the authors.

Clinical Effects of Bladder Training

A low level of evidence indicated an improvement in UI with bladder training compared to usual care. Evidence of benefits from bladder training was not sufficient for urinary continence.

Two RCTs examined bladder training compared to no active treatment.[376,377]

Continence. Urinary continence was reported in one RCT that found a borderline significant increase in continence rates with bladder training compared to usual care[376] (Appendix Table F85).

Improvement in UI. Bladder training improved UI (Appendix Table F85).[376,377] Bladder training needed to be provided to two women to achieve an improvement in UI in one woman[376,377] (Appendix Table F86). The studies did not examine quality of life with bladder training.

Clinical Effects of Pelvic Floor Muscle Training (PFMT)

A high level of evidence indicated significant benefits from PFMT for women with UI. Compared to regular care, PFMT increased urinary continence rates and improvement in UI. Benefits were consistent across different regimens of training and definitions of improvement in UI.

Eleven studies[379-389] examined PFMT compared to regular care or no active treatment.

Continence. Despite differences in exercise regimens, the majority of the studies reported significant increases in urinary continence rates with PFMT compared to no active treatment (Appendix Table F87).[379,380,382,383,385-389] The studies that included women with pure stress UI reported greater benefits from PFMT.[379,383,385]

Improvement in UI. The majority of the studies also demonstrated a significant benefit from PFMT on improvement of UI (Appendix Table F87).[380-382,385,388,389] Women reported improvement in UI with PFMT more often than with regular care.[380-382,385,388,389] PFMT improved UI in one woman of two treated.

Clinical Effects of PFMT Combined with Bladder Training

A high level of evidence indicated significant benefits from PFMT combined with bladder training on urinary continence and improvement in UI. The evidence was low that this treatment reduced severity of UI and insufficient that it can improve quality of life in women with UI.

Six publications of five RCTs examined PFMT combined with bladder training.[390-395]

Continence. Urinary continence was significantly more common in women with PFMT combined with bladder training than with no active treatment (Appendix Table F88).[390-392,394,395] One study reported very large significant increases in continence.[395] Sensitivity analysis, excluding that study, demonstrated smaller but still highly significant increases in continence with PFMT combined with bladder training.[390,392 391,394] PFMT combined with bladder training needed to be administered to six women to achieve continence in one woman (Table 12).

Improvement in UI. PFMT combined with bladder training resulted in a significant improvement in UI in all studies that examined this outcome (Appendix Table F86).[390-392,394] PFMT combined with bladder training had to be administered in three women to improve UI in one woman.

PFMT combined with bladder training reduced severity of UI (Appendix Table F89).[390,395,670] One study found that self-reported severe UI was reduced by 82 percent.[390] Another study demonstrated that self-reported bothersome UI was reduced by 31 percent.[670] Use of absorbent pads for UI was reduced by 29 percent in one study.[670] One study found a significant reduction in stress and urgency UI, but not in mixed UI[395] (Appendix Table F90). Quality of life was examined in one study that reported significant changes in IIQ score after treatment and 6 months at followup[395] (Appendix Table F91). The evidence was insufficient to determine improvement in quality of life with PFMT combined with bladder training (Table 13).

Clinical Effects of PFMT with Biofeedback Using Vaginal Electromyography (EMG) Probe

A low level of evidence indicated increased urinary continence with PFMT with biofeedback when compared to usual care. Evidence was high that this treatment improved UI.

Four RCTs examined PFMT with biofeedback using a vaginal EMG probe.[381,382,385,396]

The studies included women over 55 years of age with urodynamic UI[381,382,385,396] (Appendix Table F80).

Continence. PFMT with biofeedback increased urinary continence in both RCTs that reported this outcome[382,385] (Appendix Table F92). Overall, continence rates were significantly greater with active treatment than with usual care.[382,385] Pooled absolute risk difference was not significant, however.[382,385]

Improvement in UI. PFMT with biofeedback improved UI.[381,382,385,396] On average, three women needed to be treated to achieve UI improvement in one woman (Table 10). The study of weekly sessions of PFMT reported larger improvement in UI.[381,382] Impact from UI was reported in one study that found a small significant improvement on the Social Activity Index[385] (Appendix Table F93).

One study examined the effects of PFMT supervised weekly by skilled physical therapists in women with pure urodynamic stress UI[383] (Appendix Table F94). The study reported a large and significant increase in continence (RR 13.24, 95 percent CI 1.83; 95.63).[383] The treatment had to

be provided to three women to achieve continence in one woman. The same study reported a small but significant improvement in the Leakage Index and in the Social Activity Index (Appendix Table F95).

One noncontrolled study examined the effects of pelvic fitness and education classes taught by a lay instructor to women with urgency UI.[671] The training improved quality of life and sexual function measured with Urogenital Distress Inventory-Short Form (UDI-SF) scores. Achievement of self-selected goals was reported by 71 percent at 11 weeks and by 67 percent at 1 year of followup. Evidence was insufficient to draw valid conclusions that PFMT performed under the supervision of physical therapists or nonmedical instructors may improve continence or quality of life in women with UI.

Clinical Effects of Electrical Stimulation

A high level of evidence suggests increased continence and improvement in UI with electrical stimulation.

Nine studies examined intravaginal electrical stimulation.[383,397-404] The studies included women with predominant urgency UI,[401,403] clinical[399,400] or urodynamic stress UI,[383,397] or urodynamic mixed UI[398] (Appendix Table F80). Few studies excluded women with detrusor overactivity.[397,399] Electrical stimulation was described with different levels of detail and had variable stimulation parameters, depending on the UI type being treated, including the use of 4 Hz,[403] 10 Hz,[401] 20 Hz,[398] or 50 Hz[383,399,400] frequency for 4,[383,401] 7-8,[398,403] 12,[399] or 15 weeks.[397]

Continence. Electrical stimulation increased continence rates more often than sham stimulation (Appendix Table F96).[383,388,397,399-401,404] The benefit was consistent across the studies, despite differences in women and treatment characteristics. One RCT reported significantly higher rates of continence with electrical stimulation.[404] Electrical stimulation needed to be administered in nine women to achieve continence in one woman (Table 12).

Improvement in UI. Electrical stimulation improved UI in pooled analysis of RCTs[383,388,397-401,403] (Appendix Table F86). Benefit was consistent across the studies, despite differences in women and treatment characteristics (heterogeneity was not significant). Electrical stimulation needed to be administered in six women to improve UI in one woman (Appendix Table F86).

Improvement in UI was also demonstrated in a large prospective cohort study of 3,198 women treated with home managed vaginal/anal stimulators (20–50 Hz) for at least 3 months before evaluation of the effect[672] (Appendix Table F26). Women experienced daily urine loss, substantial urine loss, and severe UI less often with treatment when compared to baseline.[672]

Electrical stimulation did not reduce prevalence of detrusor overactivity or urgency UI in the few studies that reported this outcome[398,403,673] (Appendix Table F97). One RCT found that discontinuation of the treatment did not differ between active and sham stimulation[402] (Appendix Table F90). A cohort study found that 12 percent of women stopped using electrical stimulation at home at 2 years of followup.[672]

Clinical Effects of Percutaneous Tibial Nerve Stimulation

Evidence was insufficient to conclude positive effects from percutaneous tibial nerve stimulation on continence or improved UI in adults with overactive bladder.

Two RCTs examined clinical effects of precutaneous tibial nerve stimulation,[405,406] including the Study of Urgent PC versus Sham Effectiveness in Treatment of Overactive Bladder

Symptoms (SUmiT) trial[405] and one unpublished study[406] (Appendix Table F98). The studies treated adults with overactive bladder with either active stimulation with a current level of 0.5 to 9 mA at 20 Hz or sham stimulation.

Continence. No studies examined continence after percutaneous tibial nerve stimulation in adults with UI.

Improvement in UI. Percutaneous tibial nerve stimulation improved UI.[405,406] Seven women need to be treated with percutaneous tibial nerve stimulation to achieve improvement in one woman (Appendix Table F86).

Adverse effects. Patients experienced ankle bruising (1 of 110, 0.9 percent), discomfort at the needle site (2 of 110, 1.8 percent), bleeding at the needle site (3 of 110, 2.7 percent), and tingling in the leg (1 of 110, 0.9 percent) without statistical significance when compared to sham stimulation.

Clinical Effects of Continence Services that were Implemented by Specialized Health Care Providers

A low level of evidence indicated no consistent benefits from continence services that were implemented by specialized health care providers on continence and improvement of UI in women when compared to usual care. Promising results on improved quality of care need further confirmation. Comparison across the studies was difficult because of the variety of interventions that constituted complex continence services.

Clinical outcomes were reported in four RCTs that compared continence services with usual care[412-415] (Appendix Table F80). Continence services were described with different levels of detail and usually included advice on diet and fluids, bladder training, pelvic floor muscle education and awareness, lifestyle advice,[412] use of an audiovisual program, calendar, counseling, voiding schedule recommendations, and assessing self-care methods.[413] The services were implemented by continence nurse advisors[414,415] and consulting urogynecologists.[414] The studies included subjects with any UI.

Continence. Continence was reported in three studies[412-414] (Appendix Table F99). The Continence Efficacy Intervention Program increased the rate of continence when compared to conventional care by 556 percent.[413] The investigators had to treat one woman to achieve one additional case of continence.[413] Among every 1,000 women treated with the program, 743 cases of continence would be attributable to the Continence Efficacy Intervention Program.[413] The largest RCT of 2,248 women reported smaller benefits from continence service than with usual care, with 90 additional cases of continence attributable to active treatment per 1,000 treated.[412] Pooled analysis of three studies found a significant relative increase of 58 percent with continence services but no significant differences in absolute rates of continence.[412-414]

Improvement in incontinence. Improvement was not consistent across the studies[412,415] (Appendix Table F100). Pooled analysis of two studies[412,415] found significant improvement in UI (33 percent) but no significant differences in absolute rates of improved incontinence.

Continence services improved quality of life in women with UI[412,674] (Appendix Table F101). With services by the continence nurse and multidisciplinary team, comprised of a general practitioner, urologist, and physiotherapist, women did not experience pain or discomfort at 1 year of followup (RR 3.88, 95 percent CI 1.57; 9.58), did not have a UI related problem with usual activities (RR 3.74, 95 percent CI 1.66; 8.44), and did not complain about anxiety/depression more often than with usual care.[674] Two to four women should be treated with

a multidisciplinary team to achieve improved quality of life in one woman.[674] Another study found a 21 percent relative increase in the proportion of women who were satisfied with their level of current urinary symptoms for the rest of their lives with continence services compared to usual care (RR 1.21, 95 percent CI 1.12; 1.30).[412] Such services should be provided to nine women to achieve improved quality of life in one woman.[412] Several RCTs reported quality of life scores with continence services when compared to usual care[413,414,674-676] (Appendix Table F102). The differences rarely achieved statistical significance. Significant differences were not consistent across domains of quality of life (Table 13). The magnitude of the differences was unlikely of any clinical importance.

Clinical Effects of Behavioral Modification Program

Evidence was not sufficient to draw valid conclusions about the effectiveness of behavioral modification programs in women with mixed UI.

A single study randomized 44 adult women with mixed UI to a behavioral modification program consisting of a group lecture by two trained urology nurses with individualized meetings and assessment of knowledge and modification of behavioral changes.[677] The control group did not receive any treatments for UI. The behavioral modification program significantly improved UI (ARD 0.38,95 percent CI 0.13; 0.63).[677] The program improved UI in every third woman (NNT 3 95 percent, CI 2 ;8) when compared to no active treatment.[677] Improvement in UI was achieved in 379 per 1,000 treated women (95 percent CI 126; 632).

Clinical Effects of Magnetic Stimulation

A moderate level of evidence indicated that magnetic stimulation improved UI but did not increase urinary continence more than sham stimulation. Evidence of improved quality of life was low.

Five RCTs examined magnetic stimulation.[407-411] The studies of magnetic stimulation included women with UI**,**[408] stress UI,[407,410] mixed,[410] or predominant urgency UI[409] (Appendix Table F80). Magnetic stimulation was described with different levels of detail using 10 Hz,[408,411] 15Hz,[407,410] or 18.5Hz[409] for 1,[407] 2,[410] 6,[411] or 8 weeks.[408,409] The studies compared active with sham stimulation using double blind,[407,409,410] single blind,[408] or open label[411] designs.

Continence. Magnetic stimulation increased continence in one RCT[408] of three[407,409,411] that examined this outcome (Appendix Table F103)**.** Pooled analysis did not demonstrate a significant increase in continence after active versus sham stimulation.[407,409,411]

Improvement in UI. Active magnetic stimulation, however, improved UI in two[407,408] of three RCTs[407-409] that examined this outcome (Appendix Table F103). Pooled analysis demonstrated a 130 percent relative increase in improved UI[407-409] (Appendix Table F104). Magnetic stimulation had to be administered in four women to achieve improvement in UI in one woman (Appendix Table F86).

Limited evidence from nonrandomized studies demonstrated that 28 percent of women reported continence with magnetic innervations (ExMI) therapy[678] (Appendix Table F26).

Magnetic stimulation improved quality of life in one[411] of two RCTs[410,411] that examined this outcome (Appendix Table F105).

Clinical Effects of Medical Devices

Evidence was insufficient to draw valid conclusions about the benefits of using vaginal cones. Uncontrolled studies of other intravaginal and intraurethral devices demonstrated improvement in UI but also high discontinuation rates due to adverse effects.

Clinical outcomes were reported when using vaginal cones, intravaginal devices, and intraurethral devices. Two RCTs compared clinical outcomes with vaginal cones and no active treatments[383,388] (Appendix Table F80). One study treated women with clinical and urodynamic stress UI with vaginal cones of 20, 40, and 70g for 20 minutes per day.[383] Another study examined nine cones of equal shape and volume, increasing in weight from 20 to 100g.[388]

Continence. Vaginal cones increased continence (pooled RR 2.88, 95 percent CI 1.10; 7.55) (Appendix Table F106), but the absolute rate difference was not statistically significant.

Improvement in UI. Use of vaginal cones improved UI[388] (Appendix Table F106). Use of vaginal cones reduced the Leakage Index but did not change the Social Activity Index (Appendix Table F107).[386]

Clinical outcomes with a variety of medical devices were reported in nonrandomized, noncontrolled studies[679-701] (Appendix Table F26). Continence rates were 82 percent after using the CapSure (Re/Stor) continence shield[679] and 20 percent[680] to 54 percent[681] after using the Contiform intravaginal device. Rates of continence and improved UI were 58 percent[684] to 69 percent[682,683] after using the Conveen Continence Guard. Improvement in quality of life was reported by 50 percent[686] to 59 percent[687] of women after using the FemAssist silicone cup. The continence rate was 93 percent at 48 months after using the FemSoft urethral insert.[688] Some studies reported discontinuation rates that varied from 27 percent[687] to 41 percent.[688] Adverse effects were reported in a few studies and included urinary tract infection in 31.3 percent, mild trauma in 6.7 percent, hematuria in 3.3 percent,[688] local discomfort in 62 percent,[683] acute bacterial cystitis in 5 percent, a small degree of fracture of the curvature of the device in 22 percent,[680] or residual volume >100 ml in 5.4 percent of women after using the devices.[681]

Several noncontrolled studies reported clinical outcomes after pessary use.[689-695,702]

Continence rates varied from 36 percent among women with urgency UI to 47 percent among those with stress UI after using Pessary Uresta/EastMed Inc.[694] More than half the women (53 percent) reported improvement.[694] Women that used the pessary ring with floor, Gellhorn (Milex), reported improved stress UI in 45 percent and improved urgency UI in 21 percent; however, 6 percent reported newly developed urgency UI.[702] Discontinuation rates varied from 11 percent[692] after different pessaries to 34 percent[694] after Pessary Uresta/EastMed Inc, and to 47 percent after Pessary Gelhorn.[693] Unsuccessful fitting was the most commonly reported reason for discontinuation.

Clinical Effects of Weight Loss

A moderate level of evidence indicated improvement in UI after weight loss and exercise in obese women with UI. The evidence was insufficient to conclude if there was an increase in continence or improved quality of life.

Three studies reported clinical outcomes after weight loss programs[416-418] (Appendix Table F108). An intensive 6-month weight loss program compared to no active treatment was examined in one RCT.[416] The trial enrolled women with a body mass index (BMI) of 25 to 50kg/m^2 with any daily UI. The program included self-administered diet, exercise, and behavior

modification, and aimed to produce an average loss of 7 to 9 percent of initial body weight. The second study treated women with a BMI between 25 and 45 kg/m^2 and at least four incontinent episodes per week.[417] A feeding study provided a 3-month standard low calorie liquid diet (800kcals/day or less), increased physical activity to 60 minutes/day, and training by a nutritionist, exercise physiologist, or behavioral therapist.[417]

Continence. Weight loss did not increase continence rates when compare to regular care[416] (Appendix Table F108).

Improvement in UI. Significant improvement in UI was demonstrated in both studies [416,417] (Appendix Table F108). Weight loss had to be maintained in four women to achieve improvement in UI in one woman (Appendix Table F86). Bayesian analysis also found improvement in UI after weight loss in obese women with UI.

Quality of life after weight loss was examined in two RCTs[416,418] (Appendix Table F109). Women reported that UI became somewhat or much less of a problem more often after 6 months of treatment. The PRIDE study (Program to Reduce Incontinence by Diet and Exercise) examined the effects of intensive weight loss on sexual function in overweight and obese women with BMI of 25 to 50 kg/m^2 and daily UI.[418] The study did not find a significant increase in the odds of overall sexual satisfaction (OR 1.28, 95 percent CI 0.83; 1.99) or sexual desire (OR 1.12, 95 percent CI 0.79; 1.61).[418]

An uncontrolled study of a low calorie diet and exercise with a target loss of 5-10 percent of body weight reported significant improvement in quality of life when compared to baseline.[703]

Discontinuation rates were significantly lower with weight loss programs than with structured education[416,418] (Appendix Table F110).

Clinical Outcomes of Soy-Enriched Diet

One study tested the effects of the soy-enriched diet on urogenital symptoms in perimenopausal and postmenopausal Thai women and did not demonstrate a reduction in UI (Appendix Table F111).[704]

Clinical Effects of Acupuncture

Evidence was insufficient to conclude improvement in UI after acupuncture. Low evidence suggested possible improvement in quality of life after active acupuncture.

Clinical outcomes after acupuncture versus acupuncture of inactive points were reported in two RCTs of 137 women[705,706] (Appendix Table F80) and one uncontrolled study.[707] The RCTs enrolled women with symptoms of overactive bladder with urgency incontinence[705] or with stress UI.[706] Active acupuncture did resolve urgency UI[705] (Appendix Table F112). An uncontrolled study reported an improvement rate of 80 percent in elderly women who failed previous treatments.[707] Improvement in quality of life was inconsistent across two RCTs[705,706] (Appendix Table F113).

Clinical Effects of Bulking Agents

A low level of evidence suggests that bulking agents did not demonstrate improvement in UI when compared to placebo. Evidence was insufficient to draw valid conclusions about

improvement in quality of life in women with UI. Uncontrolled studies reported high rates of improvement but also adverse effects.

Clinical outcomes after bulking agents compared to placebo were reported in two RCTs of 241 women[708,709] (Appendix Table F80). The studies enrolled women with urodynamic stress UI and without detrusor overactivity. Women were treated with transurethral radiofrequency energy collagen micro-remodeling[708] or periurethral injections of autologous fat.[709] Active treatments did not improve UI[708,709] (Appendix Table F114). Periurethral injections of autologous fat did not improve the mean incontinence quality of life score[709] (Appendix Table F115).

Uncontrolled studies reported outcomes after injection of copolymer system[710] or nonendoscopic injection of nonanimal stabilized hyaluronic acid/dexranomer (NASHA/Dx) gel.[711,712] The improvement rate after NASHA/Dx was 76 percent,[712] improvement in quality of life was 67 percent,[711] but 36 percent had adverse effects.[712]

Comparative Effectiveness of Nonpharmacological Treatments

We concluded with high confidence that PFMT alone and in combination with bladder training or biofeedback, electrical stimulation, or weight loss with exercise were effective to achieve continence and improvement in UI. These treatments had comparable effects when compared to each other. Evidence was not sufficient to conclude better effects from medical devices or bulking agents when compared to each other.

Clinical outcomes with one nonpharmacological treatment versus another were reported in 54 RCTs (Appendix Table F80). These trials rarely examined the same active and control arms on the same outcomes, which decreased the level of evidence to low or insufficient.

Comparative Effectiveness of Continence Services

Evidence was insufficient to draw valid conclusions about comparative effectiveness of continence services when compared to other tested individual treatments (Table 14).

Outpatient continence services involving bladder retraining and physiotherapy resulted in the same continence as treatment with an inpatient 5-day hospital stay in 74 women with any UI[713] (Appendix Table F116).

The Continence Efficacy Intervention Program increased continence rates more often than PFMT in 48 women with stress or mixed UI.[413] Quality of life scores, however, did not differ between the two treatments[413] (Appendix Table F117). Face-to-face behavioral consultation by the nurse specialist giving digital assessment feedback on pelvic floor contraction resulted in the same continence as videoconferences with continence nurses in 32 older women with symptoms of urgency or stress incontinence[714] (Appendix Table F116).

Comparative Effectiveness of Group Versus Individual Physiotherapy Sessions

Evidence was insufficient to draw conclusions about comparative effectiveness of group versus individual therapy for UI.

Women reported lower benefits from group versus individual physiotherapy sessions for mixed UI at 5 months of followup (RR 0.79, 95 percent CI 0.65; 0.98) in one RCT.[715] Symptom severity or quality of life outcomes did not differ between treatment groups.[715]

Comparative Effectiveness of Behavioral Weight Loss and Education

Evidence was insufficient to conclude comparative effectiveness between behavioral weight loss intervention and education. Women reported more frequent improvement in mixed UI (defined as more than 70 percent reduction in weekly UI episodes) at 12 months with behavioral weight loss intervention than after education[716] (Appendix Table F116). The differences remained significant only for urgency UI at 18 months posttreatment.[716]

Comparative Effectiveness of Bladder Training

Evidence indicated that continence did not differ between bladder training combined with PFMT and bladder training alone. Evidence was insufficient to draw conclusions based on other tested comparisons.

Bladder training by listening to an audiotape daily improved UI more often than bladder training without the audiotape (Table 30)[717] (Appendix Tables F116 and F118).

Continence did not differ between bladder training and PFMT.[718] Satisfaction with current UI and feelings of no impact from UI on quality of life did not differ between bladder training and PFMT.[386] Bladder training combined with PFMT did not improve UI more often than PFMT alone[422,718-722] (Appendix Table F119). Bladder training combined with PFMT did not increase continence or improve UI more often than bladder training alone[36,723] (Appendix Table F120). Bladder training did not increase continence more often than use of vaginal cones (Appendix Table F116).[386]

Comparative Effectiveness of Supervised PFMT and Self-Administered PFMT

A high level of evidence indicated no difference in UI outcomes between supervised PFMT combined with bladder training and self-administered PFMT.

Supervised PFMT combined with bladder training was not more effective than self-administered PFMT[419-422,724] (Appendix Table F121). Continence rates were similar between the two interventions (Table 15).[419-422,724] Improvement in UI was similar between supervised and self-administered PFMT (Appendix Table F122).[419-422,724] Rates of treatment failure and treatment discontinuation did not differ between the two treatments (Appendix Tables F121 and F123).[419-422] One RCT reported better patient satisfaction with supervised versus self-administered PFMT in 44 women with urodynamic stress UI.[421]

Differences in quality of life were inconsistent across studies. One RCT did not demonstrate better quality of life with supervised versus self-administered PFMT in 88 women with mixed UI[725] (Appendix Table F124). Supervised PFMT versus self-administered PFMT worsened two domains of King's Health Questionnaire, physical limitations, and physical activity limitations, with no differences in other domains in 61 women with urodynamic stress UI[420] (Appendix Table F125).

Prevalence of UI did not differ between supervised and self-administered PFMT.[419,725-727] Only one RCT of intensive PFMT under the supervision of a physical therapist for 6 months in 52 women with urodynamic stress UI demonstrated sustained reduction in prevalence of severe

UI (RR 0.18, 95 percent CI (0.02; 1.33) and urgency UI (RR 0.37, 95 percent CI 0.12; 1.18) at 15 years (Appendix Table F124).[419]

The studies of individual PFMT did not report better outcomes than group PFMT in individual RCTs of women with different types of UI[728,729] (Appendix Table F126).

Comparative Effectiveness of PFMT with and without Biofeedback Using Vaginal EMG Probe

A high level of evidence indicated no differences in clinical outcomes between PFMT with or without biofeedback using vaginal EMG probe.

The studies that compared PFMT with or without biofeedback using vaginal EMG probe did not find consistent differences in continence[422,718-722] (Table 15). Failure rates of the two treatments also did not differ[718,720] (Appendix Table F123), nor did quality of life rates. Scores of Leakage Index,[718,730] Social Activity Index,[718] Incontinence Impact Questionnaire,[731] or IIQ-7 scores[732] did not differ between PFMT with and without biofeedback (Appendix Table F127). Prevalence and impact of UI did not differ between treatments either[718,731] (Appendix Table F128).

Comparative Effectiveness of PFMT and Electrical Stimulation

A moderate level of evidence suggested no differences in UI with PFMT and electrical stimulation. PFMT did not result in better outcomes than electrical stimulation[388,733,734] (Appendix Table F129). Rates of improvement in UI and treatment failure also did not differ between the two treatments[388,733,734] (Appendix Table F122).

Comparative Effectiveness of PFMT Combined with Electrical Stimulation Versus PFMT

Evidence was insufficient to draw conclusions about comparative effectiveness of PFMT combined with electrical stimulation versus PFMT alone. A combination of PFMT with electrical stimulation reduced the frequency of UI and improved quality of life more often than PFMT alone[735] (Appendix Table F116).

Comparative Effectiveness of PFMT and Medical Devices

A moderate level of evidence indicated no difference in outcomes for UI treated with PFMT compared to vaginal cones. Evidence was insufficient to draw valid conclusions about comparative effectiveness of PFMT and vaginal rings and balls.

Relative benefits of PFMT compared to medical devices were not consistent across the studies. The rates of continence or improvement in predominant stress UI did not differ between PFTM and vaginal cones[386,388,736] (Appendix Table F130). PFMT combined with biofeedback did not result in greater continence rates than use of vaginal cones[737] (Appendix Table F116). Rates of treatment discontinuation did not differ between the two treatments.[737] PFMT with biofeedback resulted in the same quality of life as vaginal cones[738,739] (Appendix Table F131).

PFMT using weighted vaginal balls 50-100g resulted in increased continence and improvement in UI compared to regular PFMT in one study that examined this association[740] in 37 women with stress UI (Appendix Table F116).

PFMT resulted in greater improvement in UI and lower treatment discontinuation than vaginal rings[741] (Appendix Table F116).

PFMT combined with the use of a vaginal ring resulted in greater improvement in UI and lower rates of treatment discontinuation than a ring alone[741] (Appendix Table F116).

PFMT and the use of a vaginal ring did not differ from PFMT alone in causing improvement of UI or treatment discontinuation[741] (Appendix Table F116).

Comparative Effectiveness of Circular Muscle Exercises and PFMT

Evidence was insufficient to draw valid conclusions about comparative effectiveness of muscle training regimens.

Continence and improvement in predominant stress UI were greater with circular muscle exercises (Paula method) than PFMT[742] in women with UI (Appendix Table F132). Quality of life was reported in two RCTs that compared circular muscle exercises with PFMT and did not find consistent differences[742,743] (Appendix Table F133). With circular muscle exercises, women experienced less "leakage annoyance" but not less frequency of UI[742] (Appendix Table F134). Adverse back pain was more common with the Paula method than with regular PFMT.[742]

Quality of life was not significantly different in studies that compared PFMT with other active treatments[386,718,720,742,744] (Appendix Tables F135 and F136).

Comparative Effectiveness of Interventions to Increase Adherence to PFMT

Evidence was insufficient to draw valid conclusion about comparative effectiveness of interventions to increase adherence to PFMT.

Adding personal reminders to enhance adherence to PFMT did not improve outcomes in 129 women with UI[745] (Appendix Table F137). Providing women with an audiocassette tape to enhance adherence to PFMT increased routine pelvic floor muscle exercise more often than usual verbal instructions for PFMT.[746] Women performed pelvic floor exercises twice per day more often after listening to audiocassette tapes.[746] Providing audiocassette tapes resulted in better adherence to PFMT in 698 women per 1,000 treated (Appendix Table F137).

Comparative Effectiveness of PFMT in Different Positions

Available evidence did not indicate differences in benefits between different regimens and combinations of PFMT treatments.

Pelvic-floor muscle exercises with EMG biofeedback in both supine and upright positions versus supine position resulted in the same outcomes in 44 women with stress UI.[747]

Comparative Effectiveness of Physiotherapeutic Methods

Evidence was insufficient to conclude comparative effectiveness of electrical stimulation and other nonpharmacological treatments for UI.

Comparative effectiveness of weekly versus three times per week posterior tibial nerve simulation resulted in the same outcomes in 35 subjects with urgency UI who failed oxybutynin treatment.[748] Frequency of UI episodes, pad test, quality of life, and treatment discontinuation rates did not differ between electrical stimulation with or without biofeedback[749] (Appendix Table F116).

Electrical stimulation compared to the use of vaginal cones resulted in the same rates of continence, improvement in UI, and discontinuation of treatments due to failure to improve UI[388] (Appendix Table F116).

Physiotherapy that included PFMT in combination with biofeedback compared to physiotherapy alone increased rates of continence and improvement in UI in one study of 40 women with stress UI.[720]

Comparative Effectiveness of Medical Devices

Evidence was insufficient to conclude comparative effectiveness of examined medical devices.

Clinical outcomes were examined in seven RCTs of vaginal cone therapy, Contrelle Continence Tampon, CCT, Conveen Continence disposable Intravaginal device Guard, CCG, Hodge pessary with support and Durasphere and Urethral device (NEAT), sterile urethral insert[386,738,750-753] (Appendix Table F138). The studies did not demonstrate significant differences in outcomes. One RCT of 94 women with the predominant symptom of stress UI found that women reported "no bother from UI" more often after Contrelle Continence Tampon versus Conveen Continence Disposable Intravaginal Device Guard.[750] Quality of life did not differ after examined devices[386,738,752] (Appendix Tables F139 and F140). One cross-over RCT of 20 women with light UI examined patient comfort, absorbency, and leakage performance after different pads and did not find significant differences[754] (Appendix Table F141).

Comparative Effectiveness of Various Bulking Agents

Evidence was insufficient to conclude comparative effectiveness of examined bulking agents.

Seven RCTs examined clinical outcomes after different bulking agents in women with pure stress UI and did not find consistent differences[755-761] (Appendix Table F142). Continence was greater after Macroplastique versus Contigen® in 260 women[762] and after autologous myoblasts and fibroblasts versus collagen in 63 women.[759] Autologous myoblasts and fibroblasts versus collagen improved quality of life scores in 63 women with intrinsic sphincter insufficiency or stress UI[759] (Appendix Table F143). Adverse effects were more common with Zuidex Implacer than with Contigen Endoscopic guidance in 344 women with stress UI[761] (Appendix Table F144). Continence rates were greater with durasphere than with contigen in one RCT in 52 women with stress UI.[752]

Indirect Evidence of Comparative Effectiveness of Nonpharmacological Treatments

Indirect comparisons indicated comparable effectiveness of nonpharmacological treatments on continence.

We evaluated the effectiveness of different nonpharmacological treatment compared to no active treatment. Such indirect evidence from all RCTs indicated that all active treatments increased continence without evident differences between treatments (Figure 20). Absolute rate differences were significant for electrical stimulation, PFMT, and PFMT combined with bladder training. Attributable cases of continence were 299 per 1,000 for PFMT compared to 162 cases for electrical stimulation, and 166 cases for PFMT combined with bladder training. Rates of continence were similar between different treatments: 38 percent of women became continent with PFMT, 23 percent became continent with electrical stimulation, and 21 percent became continent with PFMT combined with bladder training.

Statistical indirect comparisons were difficult because of substantial variability in continence rates with control treatment (Figure 20). We analyzed which factors potentially contribute to such differences in continence with the control treatment and did find statistically significant associations.

Comparative Effectiveness of Nonpharmacological Treatments when Compared to Drugs or Combined Modalities

Evidence was insufficient to draw valid conclusions about comparative effectiveness and safety of nonpharmacological treatments when compared to drugs or combined modalities (Table 16).

Duloxetine. Evidence was insufficient to conclude comparative effectiveness or harms of duloxetine combined with PFMT compared to duloxetine alone on UI.

One study, Duloxetine/Pelvic Floor Muscle Training Clinical Trial Group, compared clinical outcomes of duloxetine with and without PFMT in 201 women with stress UI.[235] Women were enrolled in 17 continence clinics in the Netherlands, United Kingdom, and United States and randomized to one of four combinations of 80 mg duloxetine daily, placebo, PFMT, and imitation PFMT.[235] Combined treatment with duloxetine and PFMT resulted in a greater reduction in UI episode frequency than PFMT alone.[235] Response rates (defined as >50 percent decrease in incontinent episode frequency), clinically important improvement in I-QOL score, and perceived treatment success did not differ between treatment groups.[235] Women who completed paper diaries at each visit experienced greater improvement in UI, quality of life, and perceived treatment success with PFMT than with duloxetine. Any adverse effects and treatment discontinuation due to adverse effects were more often associated with duloxetine combined with PFMT than with PFMT or placebo.[235]

Oxybutynin.

Oxybutynin compared to biofeedback-assisted PFMT. Evidence was insufficient to conclude effectiveness and safety with behavioral biofeedback-assisted PFMT versus oxybutynin in elderly women.

Adjustable doses of oxybutynin and behavioral biofeedback-assisted PFMT resulted in the same rates of continence and improvement in UI in 197 elderly women with urgency or predominant urgency UI.[266,634,635] Women perceived their bladder condition as "much better"[634] and were completely satisfied with the treatment more often with biofeedback-assisted training.[635] Adverse effects, including inability to void, constipation, and dry mouth were less common with biofeedback-assisted PFMT than with oxybutynin.[634]

Oxybutynin combined with PFMT and urge suppression techniques compared to individualized drug therapy alone. Evidence was insufficient to conclude comparative

effectiveness of oxybutynin combined with PFMT and urge suppression techniques compared to individualized drug therapy alone. Adjustable doses of oxybutynin combined with behavioral therapy resulted in the same reduction in UI episodes, perceived improvement in UI, and treatment satisfaction as oxybutynin alone[610] (Appendix Table F145).

Oxybutynin compared to electrical stimulation. Available limited evidence was insufficient to draw valid conclusions about comparative effectiveness of electrical stimulation compared to oxybutynin or with combined treatments compared to electrical stimulation alone.

Electrical stimulation with a 10-Hz frequency resulted in greater effects on UI episodes and quality of life scores than oxybutynin 7.5 mg/day.[637] The rates of resolved urgency and reduction in OAB symptoms did not differ between the electrical stimulation and drug therapy groups[637] (Appendix Table F145).

Electrical stimulation with frequency 20 Hz and amplitude 0.5-10 mA combined with 5 mg of oral oxybutynin resulted in the same rates of urinary continence and UI improvement as electrical stimulation alone[763](Appendix Table F145).

Transdermal oxybutynin combined with behavioral intervention compared to transdermal oxybutynin alone. Evidence was insufficient to conclude significant benefits from combined therapy compared to the drug alone. The Multicenter Assessment of Transdermal Therapy in Overactive Bladder with Oxybutynin trial compared 3.9 mg of transdermal oxybutynin plus the behavioral intervention of enhanced patient education with transdermal oxybutynin alone.[276] Combined treatment resulted in lower negative impact from UI on sexual life (RR 0.77, 95 percent CI 0.69; 0.86).[276]

Tolterodine.

Tolterodine combined with PFMT, bladder control techniques, fluid management versus tolterodine alone. Evidence was insufficient to conclude comparative effectiveness and safety of tolterodine combined with PFMT, bladder control techniques, fluid management versus tolterodine alone. The Urinary Incontinence Treatment Network compared clinical outcomes in 307 women with predominant urgency UI treated with a combination of tolterodine plus supervised behavioral training versus tolterodine alone[764-766] (Appendix Table F146). Combined therapy resulted in greater rates of complete satisfaction with therapy at the end of the treatment and at 8 months followup.[765] The rates of perceived improvement with UI as “better” or “much better” were also higher with combined treatment at the end of the trial and at 8 months followup.[765]

Standard educational programs that included printed information and an explanation about OAB, medication use, and behavioral treatments combined with tolterodine were compared to tolterodine alone in one RCT of 84 adults with OAB (Kegel exercise, bladder stretching, fluid regulation with medication treatment alone).[767] Self-reported perception of treatment success and the use of behavior modification therapies were greater with combined therapy than with tolterodine alone.[767] More women used Kegel exercises and urge suppression techniques, regulated fluid intake, and limited caffeine intake with combined treatment than with drugs alone.

Tolterodine versus percutaneous tibial nerve stimulation. Evidence from one study was insufficient to conclude better effectiveness of percutaneous tibial nerve stimulation compared to tolterodine. The Overactive Bladder Innovative Therapy trial compared clinical outcomes with percutaneous tibial nerve stimulation and extended-release tolterodine in 100 adults with urinary frequency[768] (Appendix Table F147). Patient assessment and investigator assessment of improvement or cure were greater with stimulation than with tolterodine.

Tolterodine combined with simplified bladder training vs. tolterodine alone. The Tolterodine Scandinavian Study Group compared clinical outcomes with tolterodine combined with simplified bladder training versus tolterodine alone. This randomized trials enrolled adults with OAB, including 75 percent of women.[769] The number of UI episodes and perceived improvement in symptoms did not differ between treatment groups.[769] Symptom deterioration tended to be lower with combined treatment, but the difference did not reach statistical significance.[769] Total number of adverse effects, including dry mouth, headache, and constipation were similar between combined treatment and drug treatment alone.[769]

Solifenacin. Evidence was insufficient to conclude comparative effectiveness and safety of a combination of solifenacin with bladder training and the drug alone. The SOLifenacin Alone and with simplified bladder Re-training (SOLAR) RCT compared clinical outcomes of flexible-dose solifenacin 5/10 mg with and without bladder training in patients with overactive bladder[770] (Appendix Table F148). Combined therapy was better in reducing micturition frequency.[770] Quality of life scores did not differ between treatment groups.[770] Adverse effects did not differ between treatments.[770]

Trospium. Evidence was insufficient to conclude comparative effectiveness and safety of trospium and electrical stimulation. Trospium was compared with intravaginal electrical stimulation in women with overactive bladder syndrome [611] (Appendix Table F149). Improvement in UI did not differ between trospium and electrical stimulation.[611] Both treatments improved VAS urgency severity and Beck Depression Inventory scores when compared to baseline levels. However, neither post-treatment VAS urgency severity nor Beck Depression Inventory scores differed between drug and electrical stimulation. Dry mouth was more common with drug administration (ARD 0.29, 95 percent CI 0.07; 0.52).[611]

Darifenacin.

Darifenacin compared to behavioral modification program. Evidence was not sufficient to conclude differences in benefits and harms with combined therapy of the drug with behavioral modification compared to darifenacin alone. The ABLE trial randomized adults with OAB to the flexible dose of darifenacin (7.5-15mg/day) alone or combined with behavioral brochures on modification of diet and daily habits and training for pelvic floor muscle exercise.[771] The differences between the two groups for both the Overactive Bladder Questionnaire (OAB-q) and the Overactive Bladder Satisfaction with Treatment Questionnaire (OAB-SAT-q) at week 12 were not significant. However, the rate of adverse effects leading to discontinuation of treatment was higher in the combined treatment group (RR 3.24, 95 percent CI 1.34; 7.86).[771]

Table 12. Continence with nonpharmacological treatments compared to no active treatment

Treatment	Studies Patients	Rate in Active/ Control	Relative Risk (95% CI)	Absolute Risk Difference 95% CI)	Number Needed to Treat (95% CI)	Attributable Events (95% CI)	Bayesian Odds Ratio Median (2.5%; 97.5%)	Level of Evidence
Continence Service	3[412-414] 3,939	28.8/20.4	1.58 (1.07; 2.34)	0.30 (-0.01; 0.60)				Moderate
Bladder Training	1[376] 131	12.3/3	4.06 (0.90; 18.41)	0.09 (0.00; 0.18)	10 (5; 353)	93 (3; 18)		Insufficient
Pelvic Floor Muscle Training	10[379,380,382,383,385-389] 959	37.5/12.3	3.77 (2.09; 6.80)	0.30 (0.19; 0.41)	3 (2; 5)	299 (188; 410)	8 (5; 15)	High
Pelvic Floor Muscle Training + Bladder Training	5[390-392,394,395] 1,369	21.2/12.2	3.79 (1.55; 9.27)	0.17 (0.06; 0.27)	6 (4; 16)	166 (63; 268)	18 (5; 1)	High
Pelvic Floor Muscle Training With EMG Biofeedback	2[382,385] 185	42.0/2.4	11.17 (2.21; 56.44)	0.494 (-0.10; 1.08)				Low
Electrical Stimulation	7[397,399,400,404 383 401 388] 420	22.7/7.7	2.86 (1.57; 5.23)	0.16 (0.06; 0.26)	6 (4; 16)	162 (64; 259)	4 (2; 9)	High
Magnetic Stimulation	3[407,409,411] 171	30.7/17.8	1.22 (0.78; 1.88)	0.09 (-0.01; 0.18)				Moderate
Vaginal Cones	2[383,388] 118	23/8	2.88 (1.10; 7.55)	0.14 (-0.01; 0.29)				Low
Weight Loss	1[416] 338		Urgency UI 1.78 (0.98; 3.23)	0.08 (0.01; 0.16)	12 (6; 16)	83 (6; 160)		Insufficient
			Stress: 1.78 (1.09; 2.90)	0.12 (0.03; 0.21)	8 (5; 33)	118 (30; 206)		Insufficient

Table13. Improvement in severity of incontinence and quality of life with nonpharmacological treatments compared to no active treatment

Treatment	Studies Reference	Number of Subjects	Significance of the Effect	Evidence
Continence service	2 studies[412,674]	3,847	Significant improvement in both RCTs	Moderate
Continence service	5 studies that reported scores[413,414,674-676]	1,598	Inconsistent differences in scoring	Moderate
Bladder training	1 study[378]	131	Significant improvement in scoring	Insufficient
Pelvic floor muscle training	2 studies[380,384]	125	Significant improvement	Moderate
Pelvic floor muscle training	6 studies that reported scores[384,385,772-774]	199	Significant improvement in scoring	Moderate
Pelvic floor muscle training + bladder training	1 study[395]	164	Significant improvement in scoring	Insufficient
Pelvic floor muscle training + biofeedback	1 study[385]	30	Significant improvement in scoring	Insufficient
Supervised pelvic floor muscle training	1 study[383]	61	Significant improvement in scoring	Insufficient
Acupuncture	2 studies[705,706]	137	Inconsistent differences in scoring	Low
Electrical stimulation	4 studies[383,400,402,774]	274	Significant improvement in scoring	Moderate
Magnetic stimulation	2 studies[410,411]	90	Improvement in scoring in one of two RCTs	Low
Vaginal cones	1 study[383]	61	Significant improvement in scoring	Insufficient
Bulking agent	1 study[709]	68	Not significant changes in scoring	Insufficient
Weight loss	2 studies[416,418]	651	Inconsistent differences	Low

Table 14. Continence with nonpharmacological treatments (insufficient evidence)

Active	Control	Studies Reference	Number of Subjects	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat (95% CI)	Attributable Events 95% CI)	Evidence
Continence service	Bladder training	1 study[713]	74	Not significant				Insufficient
Continence service	PFMT	1 study[413]	33	7.44 (2.00; 27.70)	0.76 (0.53; 0.98)	1 (1; 2)	757 (534; 980)	Insufficient
Continence service	Tele continence service	1 study[714]	58	Not significant				Insufficient
PFMT+ reminder	PFMT+ bladder training	1 study[745]	103	Not significant				Insufficient
PFMT in the supine position	PFMT in both supine and upright positions	1 study[747]	44	Not significant				Insufficient
Group physiotherapy	Biofeedback	1 study[728]	40	Not significant				Insufficient
Individual PFMT+BT	Group PFMT	1 study[729]	530	1.58 (1.05; 2.36)	0.08 (0.00; 0.16)	12 (6; 1003)	81 (1; 161)	Insufficient
Circular muscle exercises (Paula method)	PFMT	1 study[742]	245	1.50 (1.11; 2.03)	0.17 (0.05; 0.29)	6 (3; 21)	171 (48; 295)	Insufficient
PFMT	PFMT+ Balls	1 study[740]	37	0.11 (0.01; 1.83)	-0.22 (-0.43; -0.02)	-5 (-52; -2)	-222 (-425; -19)	Insufficient
Physiotherapy in combination with biofeedback	Physiotherapy	1 study[720]	40	3.67 (1.20; 11.19)	0.40 (0.13; 0.67)	3 (1; 8)	400 (132; 668)	Insufficient
Weekly posterior tibial nerve simulation	Posterior tibial nerve simulation three times per week	1 study[748]	35	Not significant				Insufficient
Vaginal cone	behavioral intervention	1 study[386]	238	Not significant				Insufficient
Conveen Continence device Guard, CCG	Contrelle Continence Tampon, CCT	1 study[750]	94	Not significant				Insufficient

Table 14. Continence with nonpharmacological treatments (insufficient evidence) (continued)

Active	Control	Studies Reference	Number of Subjects	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat (95% CI)	Attributable Events 95% CI)	Evidence
Hodge pessary with support	Super tampon	1 study[751]	40	Not significant				Insufficient
Durasphere	Contigen	1 study[752]	52	3.33 (1.03; 10.74)	0.27 (0.05; 0.49)	4 (2; 22)	269 (46; 493)	Insufficient
Urethral device (NEAT)	Reliance insert sterile balloon	1 study[753]	24	Not significant				Insufficient
Calcium hydroxylapatite (CaHA	Bovine Dermal Collagen	1 study[755]	296	Not significant				Insufficient
Peri or transurethral porcine dermal implant injection (Permacol)	Transurethral silicone injection (Macroplastique	1 study[756]		Not significant				Insufficient
Periurethral route of injection of bulking agent-dextran copolymer	Transurethral route of injection of bulking agent-dextran copolymer	1 study[757]		Not significant				Insufficient
Macroplastique	Contigen®	1 study[758]	247	1.49 (1.01; 2.18) NS for self reported continence	0.12 (0.01; 0.24)	8 (4; 152)	121 (7; 235)	Insufficient
Autologous myoblasts and fibroblasts	Collagen	1 study[759]	63	9.50 (2.53; 35.63)	0.81 (0.66; 0.96)	1 (1; 2)	810 (656; 963)	Insufficient
Zuidex Implacer	Contigen Endoscopic guidance	1 study[761]	344	Not significant				Insufficient

Table 15. Continence rates compared between nonpharmacological treatments

Active Treatment	Control Treatment	Studies	Patients	Rate Active/ Control, %	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Level of Evidence
Pelvic floor muscle training + bladder training	Bladder training	3[36,723]	406	22/19	1.17 (0.60; 2.28)	0.03 (-0.10; 0.16)	High
Pelvic floor muscle training +biofeedback	Pelvic floor muscle training	6[422,718-722]	542	30/25	1.27 (0.88; 1.85)	0.08 (-0.03; 0.19)	High
Supervised pelvic floor muscle training	Pelvic floor muscle training	4[419-422]	300	35/22	1.92 (0.87; 4.23)	0.20 (-0.03; 0.43)	High
Pelvic floor muscle training	Electrical stimulation	3[388,733,734]	99	24/29	0.85 (0.45; 1.61)	-0.04 (-0.20; 0.11)	Moderate
Pelvic floor muscle training	Vaginal cone	3[386,388,736]	320	22/27	0.78 (0.58; 1.06)	-0.11 (-0.26; 0.04)	Moderate

Figure 20. Continence with nonpharmacological treatments for UI when compared to no active treatment (pooled results from RCTs

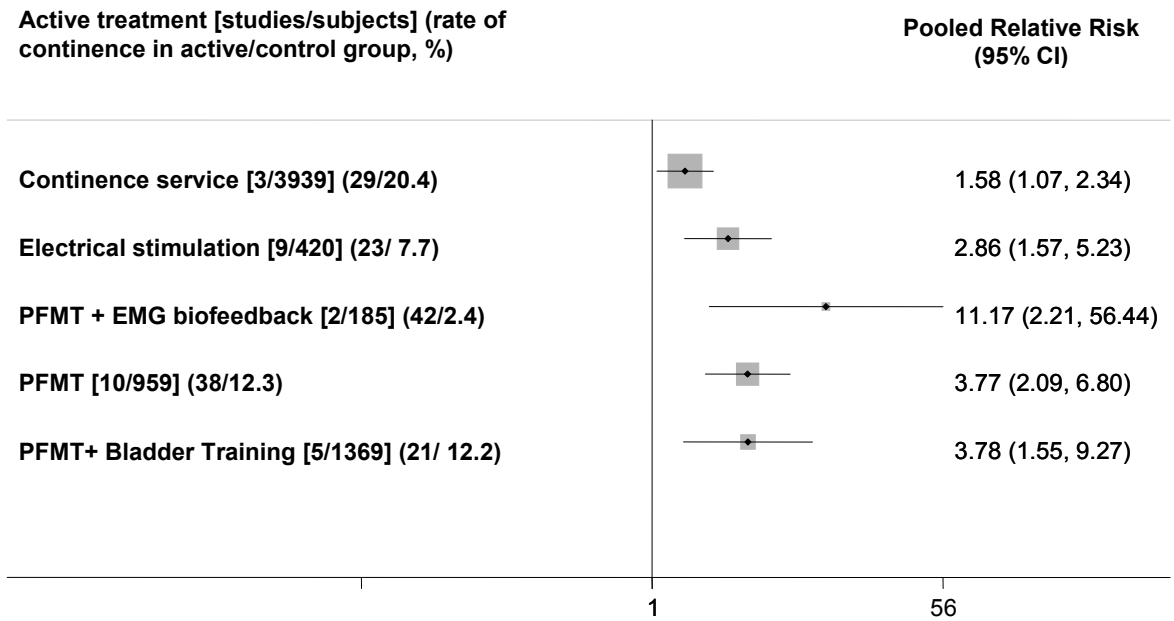

Table 16. Continence with pharmacological treatments compared to nonpharmacological treatments or combined modalities

Outcome	Active	Control	Reference	Patients	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Evidence
Cured from urgency UI	Stoller afferent neurostimulation	Stoller afferent neurostimulation + oxybutynin	Karademir, 2005[763]	44	1.10 (0.25; 4.84)	0.01 (-0.19; 0.22)	Insufficient
Subject assessment OAB symptom cured	Percutaneous Tibial Nerve Stimulation	Tolterodine tartrate	Peters, 2009[768]	100	0.50 (0.05; 5.34)	-0.02 (-0.09; 0.05)	Insufficient
Investigator assessment OAB symptom cured	Percutaneous Tibial Nerve Stimulation	Tolterodine tartrate	Peters, 2009[768]	100	1.00 (0.15; 6.82)	0.00 (-0.08; 0.08)	Insufficient
Totally dry	Tolterodine + PFMT	Tolterodine	Burgio, 2008[765]	307	1.22 (0.77; 1.95)	0.04 (-0.05; 0.13)	Insufficient
Continence	PFMT biofeedback-assisted	Oxybutynin, 7.5 to 15	Goode, 2004[635]	132	1.37 (0.77; 2.44)	0.08 (-0.07; 0.23)	Insufficient
Continence	PFMT biofeedback-assisted	Oxybutynin, 7.5 to 15	Burgio, 1998[634]	132	1.31 (0.73; 2.34)	0.07 (-0.08; 0.22)	Insufficient

Chapter 4. Discussion

Key Findings

A number of important findings emerged from this review.

- Self-reported symptoms of UI have a low diagnostic value compared to urodynamic diagnosis of stress UI or detrusor overactivity. Decisions to start treatments are based on assessment of frequency, severity, and bother of UI with validated tools.
- Evidence was insufficient to conclude differences in outcomes with nonsurgical treatments in association with baseline urodynamic diagnosis of UI. Urodynamic examination resulted in clinical benefit when performed for women undergoing surgical treatments for stress UI or invasive treatments for urgency UI.
- Women considered treatment successful when it reduced frequency of UI episodes by 70 percent or more according to voiding diaries. Important differences for women in validated scales for quality of life are available to judge treatment effectiveness.
- Nonpharmacological treatments result in significant clinical benefit with low risk of adverse effects. Women with predominant stress UI can achieve continence performing PFMT. Continence rates are similar between those who undergo PFMT with and without biofeedback.
- Women with predominant urgency UI can achieve continence performing PFMT with bladder training and/or electrical stimulation.
- Weight loss may improve UI in obese women.
- Low-dose local estrogen formulations may improve UI in postmenopausal women.
- Duloxetine showed an unfavorable balance between improvement in UI and treatment discontinuation due to adverse effects.
- Women with predominant urgency UI may achieve continence taking antimuscarinic drugs including trospium, solifenacin, fesoterodine, tolterodine, or oxybutynin. The degree of benefit was low for all drugs (absolute risk difference <20 percent).
- Drugs demonstrated similar effectiveness, but treatment discontinuation due to adverse effects was most common with oxybutynin and least common with solifenacin.
- Dry mouth, constipation, and blurred vision are among the most frequent adverse effects. Evidence of long-term safety of pharmacological treatments is insufficient.

These findings provide several important implications for clinicians regarding UI diagnosis and treatment. Salient findings include: (1) Diagnosis of predominant stress or urgency UI in primary care setting can be based on clinical history, voiding diary, stress cough test, and validated scales.[15,423] (2) Multichannel urodynamics was not associated with better outcomes for nonsurgical treatments, and was useful only for women undergoing invasive treatments for UI.[227] (3) To define and assess treatment outcomes for women with UI, investigators must consider the issues women deem important: continence, 70 percent or more reduction in UI episode frequency, meaningful changes in quality of life measures, and treatment satisfaction.[424 424] (4) Women may achieve continence with PFTM combined with bladder training and electrical stimulation, or with drugs for overactive bladder. (5) The magnitude of benefit is similarly low for all drugs for overactive bladder; however, adverse effects are common, with oxybutynin

having greater rates of discontinuation due to adverse effects. (6) Nonpharmacological treatments offer a greater magnitude of benefit than drugs, and adverse effects are uncommon.

Our findings agree with previously published systematic reviews of UI diagnosis and treatment by AHRQ,[21,22] the Cochrane Collaborative Group,[23,25-28,31-35,37-50,425-428] and the ICI.[1,51]

UI Diagnosis

Diagnosis of different types of UI. Self-reported symptoms offer lower diagnostic value than urodynamic diagnosis for stress UI or detrusor overactivity. However, urodynamic diagnosis was not associated with better outcomes for nonsurgical UI treatments. Diagnosis of pure urodynamic stress UI or detrusor overactivity can influence treatment decisions for women undergoing surgical treatments for urogenital prolapse or pelvic floor trauma.[227] Previously published systematic reviews also demonstrated a weak association between self-reported UI symptoms and instrumental urodynamic findings.[15,423] However, investigators still use urodynamic evaluation as a reference method. In contrast, guidelines recommend urodynamic evaluation as one component of the complex algorithm for women with pelvic floor dysfunction.[11] Evaluations of women who report UI symptoms begin with exclusion of urinary tract infection, pelvic organ prolapse, and poor bladder emptying.[10] Examination methods for urinary tract infection and pelvic organ prolapse have been addressed by previous reviews, and are beyond our scope.[10,775] Measurement of postvoid residual (PVR) urine volume can be used to diagnose UI associated with poor bladder emptying. Some experts consider urinary catheterization as the gold standard for measuring PVR.[776] Invasive urinary catheterization can be performed only in specialized care settings. Portable ultrasound is an accurate and feasible method for estimating PVR urine volume in primary care settings.[777,778] Ultrasound is preferable to catheterization, and should be used when decreased bladder emptying is suspected.[10] Vaginal and transrectal ultrasound accurately diagnosed urodynamic stress UI.[454,595] Other instrumental radiological and magnetic resonance imaging is useful for diagnosis of anatomical pelvic pathology including fibroids, ovarian and uterine tumors, foreign bodies, or diverticulum.[11] Associations are unclear between the criteria for excessive bladder neck mobility identified via ultrasound or MRI and the severity and frequency of self-reported UI, or UI treatment outcomes.

Diagnosis of baseline frequency, severity, and bothersomeness of UI. Urodynamic or ultrasound evaluations diagnose the presence of UI but not baseline severity, frequency, or bothersomeness of the condition, all of which are important in determining the best treatment options. Primary care physicians may choose between several validated tools for diagnosing predominant stress or urgency UI, and for judging treatment effectiveness. Treatment effectiveness for female UI should be assessed according to issues women value: 70 percent or greater reduction in UI episode frequency, meaningful changes in quality of life measures, and overall treatment satisfaction.[424] Women do not consider small reductions in UI frequency or in urinary loss as treatment success, even though such reductions are statistically significant.[213] Clinically important differences have been determined for several questionnaires and scales.[175,180,204,598-600] Many validated tools are available to monitor quality of life in women with different UI types. Several tools that define clinically important differences in scores can be used to assess treatment success in clinical settings.[601-603] All tools for assessing symptom bother have been validated. The Incontinence Severity Index,[195,196] Patient Global Impression of Improvement and of Severity,[197] Urogenital Distress Inventory,[136,201,202] and Patient Perception

of Bladder Condition[198-200] developed definitions of minimal important differences in any UI that can be used to define treatment success in clinical settings.

UI Treatment

Defining and measuring outcomes of treatments for UI. Meaningful assessment of treatment outcomes depends on how those outcomes are defined. Market approval and coverage decisions have been made based on intermediate outcomes, not based on continence or on women's treatment satisfaction. Despite intensive discussions about the importance of patient centered outcomes, the majority of drug studies aimed to detect statistical differences in frequency of UI episodes. The most common outcome examined by RCTs was a reduction in UI episode frequency.[224,257,263,264,278,287,293,301,303,308,320,326,327,346,349,357,362,606-611] Previous reviews of drugs for overactive bladder also focused on a reduction in frequency of UI episodes and frequency of micturitions.[52,429,430] The FDA reviews focused primarily on the same continuous reduction in UI episode frequency, and not on continence or self-reported treatment success and satisfaction.[264,326,327,360,361,431,432]. In contrast, our review emphasized the role of clinical outcomes, including continence, quality of life, and adverse effects of the treatments.

Treatments for UI. Women can achieve continence with PFMT, bladder training, and electrical stimulation. Obese women can improve UI with weight loss and exercise. Long-term adherence to and benefits of these treatments are not clear. Specific characteristics of women associated with better benefits and compliance are not clear. Adverse effects with nonpharmacological treatments are not common. The magnitude of the effect of nonpharmacological treatments was large. The best time to start pelvic muscle floor exercise and bladder training in relation to either menopause or the onset of UI is not clear.

All drugs for overactive bladder resulted in continence and improved UI. All drugs offered similar benefits, but treatment discontinuation due to adverse effects was most common with oxybutynin. Informed decisions, therefore, should consider the drugs' adverse effects. RCTs rarely reported long-term comparative drug safety. In contrast with RCTs, continuous prescription-event monitoring as a part of postmarketing surveillance provided valuable information about unfavorable long-term safety of tolterodine, which posed significantly higher risk of hallucinations than ten drugs of other therapeutic classes.[433] Postmarketing surveillance may provide data on long-term safety of UI drugs when combined with other medications for comorbidities. RCTs did not examine the role of concurrent treatments. For instance, limited information exists on the cognitive effects of drugs in older adults. The relative risks of ventricular arrhythmias (adjusted RR or sudden death 5.5, 95 percent CI 1.3; 22.3) or sudden death (adjusted RR or sudden death 21.5, 95 percent CI 5.2; 88.3) were very high in elderly patients using UI medications in combination with antihistamine/cytochrome inhibitors.[434]

Very few studies provided evidence for individualized treatment decisions. Both patient comorbidity and baseline type and severity of UI were associated with differences in treatment benefits, but this information was available for only a few drugs. Which factors are associated with differences in harms remains unclear.

Very few studies addressed adherence to prescribed drug regimens. Observational economic evaluations[435-437] 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 drugs for overactive bladder in California Medicaid program beneficiaries.[436]

Cost-effectiveness analyses[435,438-441] were beyond the scope of our review. Our review provides valid information about treatment benefits according to patient-centered outcomes including continence as well as about adverse effects that can be used for cost-effectiveness analyses.

Our review has limitations. We restricted our review to English language studies published in journals, presented at scientific meetings, reviewed by the FDA,[442] or reported on the ClinicalTrials.gov Web site. Even after such an exhaustive review of evidence, we do not know how many studies we missed in our review. We did not review regulatory documents or grant databases from other countries.

Our findings can inform clinicians' evidence-based recommendations for UI diagnosis and management (Tables 17 and 18). In order to make treatment decisions and monitor treatment effectiveness, primary care clinicians can diagnose predominant stress or urgency UI and evaluate frequency, severity, and quality of life at baseline and with treatment. Nonpharmacological treatments offer a better balance between benefits and adverse effects than do drugs. First treatment choice, therefore, might be based on known benefits and harms with nonpharmacological and drug treatments, along with patient preferences. Evidence was insufficient to conclude better benefits from nonpharmacological treatments combined with drugs. Women's opinions about treatment success should be considered before combining nonpharmacological treatments with available drugs or increasing the doses of the drugs.

Future Research

Our report points to areas for future research (Table 19). First, future research should clarify which female characteristics are associated with benefits and lower harms of treatments, and better treatment adherence. Second, treatment success should be assessed with outcomes centered on women, including long-term continence, reduction of 70 percent or more in UI episodes, and clinically important improvement in scales of severity and quality of life. More work is needed on how physiological measures correspond with symptoms. Third, all harms should be analyzed, regardless of investigator judgment about possible association with tested treatments. Fourth, better drugs are needed. Few of the currently used medications are sustained for even a year, and fewer still are very effective. Fifth, nonsurgical treatments for predominant stress UI are limited to PFMT, with very few ongoing studies of bulking agents and devices. One issue with PFMT is sustaining it. Programs should explore how to extend the period of adherence. Future research should explore new treatment options for women with stress UI and should also address the preventive potential in premenopausal women of various nonpharmacological treatments, including PFMT, bladder training, and electrical stimulation. The results from all studies, including 25 closed and 124 ongoing registered studies, should be made available for future reviews of the evidence.

Table 17. Conclusions about diagnosis of UI in women

Conclusions	Level of Evidence
Diagnosis of UI	
Symptoms of stress UI, urgency, or urgency UI have minimal or small diagnostic value to identify women with urodynamic stress UI or detrusor overactivity.	High
Complex clinical algorithms demonstrated better diagnostic performance. Individual studies suggested a good diagnostic value of the epidemiology of prolapse and incontinence questionnaires.	Moderate
Women in primary care settings have been diagnosed with UI after obtaining clinical history, a voiding diary to assess predominant stress or urgency UI and cough stress or pad tests, and after excluding urogenital prolapse and urinary tract infections.	High
Decisions to start treatments have been based on assessment of frequency, severity, and bothersomeness of UI with validated tools.	High
Urodynamic examination was not associated with better outcomes after nonsurgical treatments for UI.	Moderate
Urodynamic examination was associated with treatment outcomes in women undergoing surgical treatments for stress UI.	
Monitoring treatment success can address differences in the voiding diary (>70 percent in frequency of UI episodes) and scales measuring quality of life that are important for women, and women's impressions of global improvement and treatment satisfaction. A variety of the validated tools are available to monitor quality of life in women with UI and with different UI types. Several tools that can define clinically important differences in scores can be used to assess treatment success in clinical settings	High

Table 18. Conclusions about management of UI in women

Conclusions	Level of Evidence
Drug treatment for predominant stress UI	
Duloxetine was worse than placebo resolving stress UI	Low
Duloxetine improved stress UI in women.	High
Risk of adverse effects was significantly higher with duloxetine compared to placebo. Women stopped taking the drug because of nausea, somnolence, insomnia, dizziness, headache, fatigue, diarrhea, and constipation.	High
Drug treatment for predominant urgency UI	
Oxybutynin compared to placebo increased continence and improved UI.	High
Oxybutynin compared to placebo increased treatment discontinuation due to adverse effects. Dry mouth was the most common adverse effect.	High
Immediate release oxybutynin when compared to controlled release oral or transdermal oxybutynin resulted in greater rates of adverse effects and dry mouth.	Low
Higher vs. lower doses of oxybutynin resulted in greater improvement in UI, the same rates of dry mouth, but in greater treatment withdrawal.	Low
Tolterodine increased continence and improved UI when tolterodine treatments when compared to placebo.	High
Tolterodine improved quality of life in women with urgency UI.	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 due to adverse effects did not differ with tolterodine compared to placebo.	High
Darifenacin, 7.5 and 15 mg, improved urgency UI and several domains of quality of life when compared to placebo.	High
Adverse effects were more common with darifenacin than placebo. Among examined adverse effects, darifenacin increased rates of constipation, dry mouth, dyspepsia, and headache.	Moderate
Larger dose, 30 mg of darifenacin/day, did not result in better benefits but caused greater rates of adverse effects.	High
Treatment discontinuation rates because of adverse effects were the same with darifenacin vs. placebo.	High
Solifenacin increased continence with greater benefits with the larger dose of the drug in women with urgency and mixed UI.	High
Solifenacin increased risk of dry mouth, constipation, and blurred vision, 10 mg of solifenacin increased the risk of severe dry mouth and constipation.	High
Treatment discontinuation because of adverse effects was more common with solifenacin compared to placebo.	High
Fesoterodine increased continence when compared to placebo.	Low
Fesoterodine improved urgency UI with fesoterodine compared to placebo, with a better response with 8 mg versus 4 mg.	High
Fesoterodine improved quality of life in women with urgency UI.	Low
Fesoterodine treatment resulted in higher rates of adverse effects and discontinuation of the treatments because of adverse effects compared to placebo. Adverse effects were more common with 8 mg compared to 4 mg of fesoterodine.	High
Trospium increased continence when compared to placebo.	High
Women experienced dry mouth, dry eye, dry skin, and constipation more often with the drug than with placebo.	Moderate
Adverse effects resulted in treatment discontinuation more often than placebo.	High
Fesoterodine resulted in greater rates of continence when compared to tolterodine.	Low
Fesoterodine resulted in greater rates of improved UI when compared to tolterodine.	High
Fesoterodine resulted in greater treatment discontinuation due to adverse effects when compared to tolterodine.	Moderate
Oxybutynin resulted in greater treatment discontinuation due to adverse effects when compared to tolterodine.	High
Improvement in UI did not differ with oxybutynin when compared to tolterodine	Moderate
Adherence to drug treatments is low, more than 50% of women stopped treatments within one year.	Moderate
Role of characteristics in women in association with treatment effects	
Age did not modify the effects from the tested drugs on examined clinical outcomes.	Moderate
Duloxetine was no better than a placebo in improving UI in elderly women.	High

Table 18. Conclusions about management of UI in women (continued)

Conclusions	Level of Evidence
Solifenacin increased continence when compared to placebo, irrespective to age.	High
Baseline frequency of UI did not dramatically modify the effects of the drugs on clinical outcomes. Subjects with more frequent UI had slightly greater benefits when compared to placebo.	Low
Solifenacin was effective irrespective of the response to previous treatments, even though poor responders did not benefit from increasing the dose of the drug.	High
Nonpharmacological treatments	
Bladder training compared to usual care improved UI	Low
Pelvic floor muscle training increased continence and improved UI when compared to no active treatment.	High
PFMT also improved several domains of quality of life in women with UI.	Low
PFMT combined with bladder training increased continence and improved UI.	High
PFMT combined with bladder training reduced severity of UI	Low
PFMT with biofeedback when compared to usual care increased continence.	Low
PFMT with biofeedback when compared to usual care improved UI.	High
Electrical stimulation when compared to sham stimulation increased continence and improved UI.	High
Electrical stimulation when compared to sham stimulation improved quality of life.	Moderate
Continence services that were implemented by specialized health care providers increased continence and improved UI when compared to usual care.	Low
Magnetic stimulation improved UI but did not increase urinary continence when compared to sham stimulation.	Moderate
Evidence of improved quality of life.	Low
Uncontrolled studies of other intravaginal and intraurethral devices demonstrated improvement in UI but also high discontinuation rates and evident harms.	Low
Weight loss and exercise improved UI in obese women.	Moderate
Acupuncture improved quality of life after active acupuncture.	Low
Continence did not differ	
PFMT + bladder training when compared to bladder training	High
PFMT + biofeedback when compared to PFMT	High
Supervised PFMT when compared to PFMT	High
PFMT when compared to electrical stimulation	Moderate
Insufficient Evidence	
Drug treatment for predominantly stress UI	
Individual RCT demonstrated greater continence and improvement in UI with vaginal estrogen formulations and worsening of UI with transdermal patches.	Insufficient
Individual studies reported that duloxetine improved urgency UI.	Insufficient
Drug treatment for predominantly urgency UI	
Individual studies reported inconsistent improvement in quality of life with oxybutynin.	Insufficient
Solifenacin improved quality of life.	Insufficient
Trospium improved quality of life in individual RCTs.	Insufficient
Continence, improvement in UI, and adverse effects did not differ with other drugs when compared to each other.	Insufficient
Racial differences in treatment effects of duloxetine in women with stress UI.	Insufficient
Clinical outcomes with tolterodine and solifenacin did not differ in subjects with baseline mixed or pure urgency UI.	Insufficient
Subjects with mixed UI may require a larger dose and longer treatment duration to achieve clinical benefits from solifenacin.	Insufficient
One study reported that darifenacin was effective in those who failed previous treatment.	Insufficient
Tolterodine was not better than placebo in achieving clinical benefits among poor responders to the previous muscarinic antagonists in one RCT.	Insufficient
Duloxetine was no better than placebo improving stress UI in women with comorbidities.	Insufficient
Nonpharmacological treatments	
Bladder training compared to usual care improved quality of life in women with UI	Insufficient
PFMT combined with bladder training improved quality of life in women with UI.	Insufficient
PFMT with biofeedback when compared to usual care improved quality of life in women with UI.	Insufficient
PFMT performed under the supervision of physical therapists or nonmedical instructors may improve continence or quality of life in women with UI.	Insufficient
Continence services that were implemented by specialized health care providers improved quality of life.	Insufficient
Vaginal cones improved UI.	Insufficient

Table 18. Conclusions about management of UI in women (continued)

Conclusions	Level of Evidence
Weight loss and exercise improved quality of life.	Insufficient
Acupuncture improved UI.	Insufficient
Continence and improvement in UI did not differ with nonpharmacological treatment when compared to each other or combined with drug modalities.	Insufficient
Adverse effects were higher with pharmacological treatments when compared to nonpharmacological in individual head-to-head RCTs.	Insufficient

Table 19. Future research recommendations

Key Question	Results of Literature Review	Types of Studies Needed to Answer Question	Future Research Recommendation
What constitutes an adequate diagnostic evaluation for women in the primary care setting on which to base treatment of urinary incontinence (UI)?	• Symptoms of stress UI, urgency, or urgency UI have minimal or small diagnostic value to identify women with pure urodynamic stress UI or detrusor overactivity • Urodynamic examination was not associated with better outcomes after nonsurgical treatments for UI. • Monitoring treatment success can address differences in the voiding diary (>70 percent in frequency of UI episodes) and scales measuring quality of life that are important for women, and women's impressions of global improvement and treatment satisfaction.	• Observational studies	• Examine the association between physiological measures using bladder ultrasound and frequency and severity of self reported stress and urgency UI. • Examine the association between diagnostic algorithms that include voiding diary, validated questionnaires to determine frequency and severity of pure or predominant stress and urgency UI, and baseline quality of life with or without portable ultrasound with the effects of nonpharmacological treatments. • Determine minimal clinically important reduction in frequency and severity of different types of UI in women subpopulations by age, baseline severity and frequency, and bothersomeness. • Examine the association between diagnostic values with women's treatment preferences. • Determine whether women in clinical settings receive adequate diagnostic evaluation to differentiate pelvic floor trauma, pelvic organ prolapsed, urinary tract infection, and UI associated with poor bladder emptying.
How effective is the pharmacologic treatment of UI in women?	• Women with predominant urgency UI may achieve continence taking antimuscarinic drugs including trospium, solifenacin, fesoterodine, tolterodine, or oxybutynin. Degree of the benefits was low for all drugs (absolute risk difference <20 percent). • Drugs demonstrated similar effectiveness, but treatment discontinuation due to adverse effects was most common after oxybutynin and least common after solifenacin. • Dry mouth, constipation, and blurred vision are among the most frequent adverse effects. Evidence of long-term safety of pharmacological treatments is insufficient.	• Head to head trials • Pooled analysis of individual patient data	• Examine effectiveness of the drugs on long term continence and adverse effects in women with pure urgency vs. mixed UI. • Examine comparative effectiveness of all available antimusarinic drugs on continence, reduction by 70% in UI episodes, quality of life, adverse effects, and discontinuation due to adverse effects in female subgroups by age, race, baseline predominant type and severity of UI, comorbidities, and prior treatment status.

Table 18. Future research recommendations (continued)

Key Question	Results of Literature Review	Types of Studies Needed to Answer Question	Future Research Recommendation
How effective is the nonpharmacologic treatment of UI in women?	• Nonpharmacological treatments result in significant clinical benefit with low risk of adverse effects. • Women with predominant stress UI can achieve continence performing PFMT. Continence rates are similar between those who undergo PFMT with and without biofeedback. • Women with predominant urgency UI can achieve continence performing PFMT with bladder training and/or electrical stimulation. • Weight loss may improve UI in obese women.	• Head to head trials • Pooled analysis of individual patient data	• Examine effectiveness of nonpharmacological treatments on long term continence and treatment adherence in women with pure urgency or stress vs. mixed UI. • Examine comparative effectiveness of nonpharmacological treatments on continence, reduction by 70% in UI episodes, quality of life, and treatment adherence in female subgroups by age, race, baseline predominant type and severity of UI, comorbidities, and prior treatment status. • Examine continence in women with UI by the onset time of UI and the order of the prescribed nonpharmacological treatments. • Examine which women subpopulations may benefit from combined (drugs + nondrug) treatments. • Examine the effectiveness of different methods for delivering nonpharmacological treatments on short-term and long-term continence, reduction by 70% in UI episodes, quality of life, and treatment adherence in female subgroups by age, race, baseline predominant type and severity of UI, comorbidities, and prior treatment status

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List of Acronyms/Abbreviations

AHRQ	Agency for Healthcare Research and Quality
ARD	Absolute risk difference
AUA	American Urological Association
BMI	Body Mass Index
CI	Confidence interval
DESIRE	Duloxetine Efficacy and Safety for Incontinence in Racial and Ethnic Populations
EMG	Electromyography
ER	Extended release
FDA	Food and Drug Administration
ICI	International Consultation on Incontinence
ICS	International Continence Society
IMPACT	IMprovement in Patients: Assessing symptomatic Control with Tolterodine IMPACT
I-QOL	Incontinence Quality of Life
IUGA	International Urogynecological Association
LR	Likelihood ratio
LUSQ	The Leicester Urinary Symptom Questionnaire
MATRIX	Multicentre Assessment of Transdermal Therapy in Overactive Bladder With Oxybutynin
MESA	Medical, Epidemiological, and Social Aspects of Aging Questionnaire
MeSH	Medical Subject Headings
NASHA/Dx	Nonanimal stabilized hyaluronic acid/dexranomer
NIH	National Institutes of Health
NNT	Number needed to treat
OAB	Overactive bladder
OPERA	Overactive bladder: Performance of Extended Release Agents
PFMT	Pelvic floor muscle training
PGI	Patient Global Impression
PhRMA	Pharmaceutical Research and Manufacturers of America
PPBC	Patient Perception of Bladder Condition
PRIDE	Program to Reduce Incontinence by Diet and Exercise
PVR	Postvoid residual
QUID	Questionnaire for urinary incontinence diagnosis
RCT	Randomized clinical trials
RR	Relative risk
SOLAR	SOLifenacin Alone and with simplified bladder Re-training
SRC	Scientific Resource Center
TEP	Technical Expert Panel
3IQ	Three Incontinence Questions Questionnaire
UDI-SF	Urogenital Distress Inventory-Short Form
UI	Urinary incontinence
VOLT	VESIcare Open-Label Trial
WHO	World Health Organization