

Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Nonsurgical Treatments for Urinary Incontinence in Adult Women: Diagnosis and Comparative Effectiveness*

Draft review available for public comment from February 2, 2011 to March 2, 2011.

Research Review Citation: Shamliyan T, Wyman J, Kane RL. Nonsurgical Treatments for Urinary Incontinence in Adult Women: Diagnosis and Comparative Effectiveness. Comparative Effectiveness Review No. 36. (Prepared by the University of Minnesota Evidence-based Practice Center under Contract No. HHSA 290-2007-10064-I.) AHRQ Publication No. 11(12)-EHC074-EF. Rockville, MD. Agency for Healthcare Research and Quality. April 2012. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Commentator & Affiliation	Section	Comment	Response
AUA American Urologic Association Suzanne Pope Victor Nitti, MD, President, Society of Urodynamics and Female Urology J. Christian Winters, MD, Vice-President, Society of Urodynamics and Female Urology	Executive Summary	The intended audience of the report is unclear as well as the type of incontinence that is addressed (stress urinary incontinence, urge urinary incontinence). It might be more useful to organize the document by condition and by treatment and to improve its readability; it seems to jump around topics.	We revised the report emphasizing the baseline type of UI.
AUA	Executive Summary	<p>We are also concerned about bias in the report. Of particular concern, is the uneven weighting of subjects (duloxetine? E-Stim?) and little to nothing on the behavioral therapies that are mainstays of therapy. Also, there seems to be gaps in the references used</p> <p>Figure ES2 criteria for inclusion, exclusion of the literature searched should be referenced in the text. Are these papers equally weighted? The level of evidence for some of these papers is extremely weak; some are in obscure journals with low impact factor and are even unavailable.</p>	<p>To minimize selection bias we conducted an exhaustive search: We sought studies from a wide variety of sources, including MEDLINE® via OVID and via Pub Med®, 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."</p> <p>We clarified that we cannot estimate a degree of selection bias. Our review has limitations. We restricted our review to English language studies published in journals, presented at scientific meetings, reviewed by the FDA, 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.</p> <p>We did not weight the studies but evaluated quality of the studies and incorporated quality assessment into the synthesis of evidence.</p>

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AUA	Executive Summary	<p>ES-1 The definition of urinary incontinence as the involuntary loss of urine “that reflects a failure to inhibit urination” is a poor definition, suggesting that one is dealing with failure to inhibit a detrusor contraction (the normal result of a detrusor contraction) rather than other causes of urinary incontinence, i.e. sphincteric leakage. The ICS definition is preferable: Urinary incontinence is the complaint of any involuntary leakage of urine. (Standardization of Terminology of LUTS, ICS)</p> <p>UI’s impact on an individual may range <u>from no impact on QOL</u> to debilitating. Emphasis on the multiple circumstances that lead to UI is more important than blaming one problem (immobility or dementia or pelvic floor weakness). It is a multi-factorial problem that leads to UI in most cases.</p> <p>ES-2 Incontinence is more than urge and stress. It is also mixed, overflow, functional and extrameatal as in fistulae, congenital abnormalities, and may need to be differentiated from vaginal leakage or sweating. Given that this is true, why are we lumping all types of UI into one evidence report? Doesn’t this weaken the strength of the final recommendations? (Would we address all diabetics or all hypertensives or all obesity in the same manner?) 878 references will mean that the resulting information will risk being lumped, not nuanced.</p> <p>Some of the descriptors are of concern. “Urgency incontinence is associated with the muscle in the wall of the bladder” is most confusing. What is that wall doing that gives the urge?</p> <p>Stress incontinence more commonly <u>presents</u> in younger women (it’s not like it</p>	<p>We revised this definition. We used the definitions of UI promoted by the ICS, please see ES Table 1..</p> <p>We revised the introduction pointing out that variation in baseline mechanisms of UI result in different types of incontinence. We clarified that this review focuses specifically on the problems associated with sphincter function and bladder overactivity in women.</p> <p>We revised the definition of urgency UI: “Urgency incontinence is defined as involuntary loss of urine associated with the sensation of a sudden, compelling urge to void that is difficult to defer.”</p> <p>We revised age group definition in the report.</p> <p>We revised the section on clinical evaluation of women with complains about UI. Please see responses above.</p> <p>We specified lifestyle interventions that have been examined in RCTs. We did not aim to create a decision model about first and consequent treatment choices.</p> <p>We revised the report in relation to clinically important reductions in UI episodes and the role of quality of life. We emphasized the role of patient-centered outcomes in comparative effectiveness research.</p> <p>We revised the definition of stress UI: “Stress incontinence is associated with impaired sphincter function and results in an inability to retain urine during coughing or sneezing.”</p> <p>We defined pure stress UI as the finding of involuntary leakage during filling cystometry, associated with increased intra-abdominal pressure (stress test), in the absence of a detrusor contraction.</p>

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		<p>goes away untreated as we age...). Likewise, urgency and mixed UI more commonly <u>present</u> in older women (or post-menopausal women) <u>not elderly.</u>" We don't think this is meant to imply that the 55 to 65 year old with urge incontinence is elderly.</p> <p>"Although the diagnosis of UI <u>generally</u> can be made....the objective diagnosis of different UI types <u>that stratify treatment</u> ..."</p> <p>And we don't do a CMG to differentiate the diagnoses...you start with that as your first method, and then go directly to multichannel urodynamics. There is no mention of the history or physical exam, the urinalysis, the post void residual, the bladder diary- these are the mainstays of diagnosis.</p>	
AUA	Executive Summary	<p>Lifestyle changes must be specified. If these are advocated as the first in the "standard UI treatments, they need to be delineated.</p>	We made recommended change.

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AUA	Executive Summary	Is continence what women want? A fair amount of time is devoted in the executive summary to this but then just two pages later the threshold of “70 reduction” is used. That is, we want improvement in QOL, and that often does not mean that one is dry through all activities and in all circumstances. The patient perception of improvement is what is missing in the synthesis of evidence, not the complete alleviation of involuntary urinary leakage.	<p>We revised the section about our focus on patient-centered outcomes justifying consistent definitions of continence as a primary outcome for the review: “Standard UI treatments for women include lifestyle changes, PFMT, and surgical treatments for predominant stress UI. In addition, several drugs have been approved for adults with overactive bladder with or without urgency UI. Clinical interventions to reduce the frequency of UI episodes in women have been extensively reviewed in recent years but without emphasis on continence and women’s perceptions of treatment success and satisfaction. Continence, however, was considered as a primary goal when treating UI. 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.</p> <p>“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. 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. Treatments for overactive bladder aimed decrease in frequency of urgency, voiding, and urgency UI. Statistically significant decrease in frequency of UI episodes and voiding were considered as a clinical success in a comprehensive review for treatments for overactive bladder, irrespective of women’s perception of clinical improvement. Recommended clinically meaningful levels of improvement in the number of incontinence episodes per day as greater than 50 percent reduction from baseline was not a primary outcome in original studies and published systematic literature reviews. 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. 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. Moreover, experts, not patients, define standard care by statistically significant reduction in UI episodes or improvement in pad, urodynamic, or other tests. 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.”</p>

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AUA	Executive Summary	ES2 – 3 rd paragraph Remove “ultrasound examination” before (Table ES1) ES3 – remove ultrasound from list of diagnostic methods and replace with measurement of post void residual urine. Ultrasound in UI is only used to evaluate a post void residual amount and isn’t used to diagnose the type of incontinence. See later comments on page 17.	We made corrections in Introduction. We reviewed diagnostic value of ultrasound for question 1 following the recommendations from the TEP and according to the public comments. Ultrasound is a diagnostic test feasible for ambulatory settings.
AUA	Executive Summary	ES2 - 1 st paragraph Stress incontinence occurs when bladder or intra-abdominal pressure is raised. Although this is true since a rise in abdominal pressure causes a rise in bladder pressure it will be confused by many to be seen as being bladder driven. If it is to be left in then it has to be specified that a rise in detrusor pressure (bladder pressure – abdominal pressure) does not cause stress incontinence. ES-6The internal inconsistency of “no advantage with urodynamic diagnosis” for presumably non-neurogenic SUI and “baseline urodynamic evaluation resulted in better benefits with surgery” is not helpful to the reader. And the utility of UDS and the outcomes of SUI surgery is the subject of a large UITN trial.	We clarified the scope of our review: “Other diagnoses for female pelvic floor dysfunction including UI associated with poor bladder emptying, voiding dysfunction, pelvic organ prolapse, or recurrent urinary tract infections as well neurogenic UI associated with spinal cord injury or stroke are beyond of our scope. We revised this section We added in the discussion: “Ongoing trial conducted by the Urinary Incontinence Treatment Network will shed light on the association between utility of urodynamic testing and the outcomes of stress UI surgery.”
AUA	Executive Summary	ES2- last paragraph The authors should state that because of these differences in definitions of improvement as well as the differences in populations studied that it is difficult or impossible to compare any of the treatments that they review in this document.	We clarified that definitions of continence were consistent across the studies while definitions of improved UI and quality of life were not. Variability in definitions hampered synthesis of evidence.

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AUA	Executive Summary	<p>“Evidence was insufficient for the association between baseline urodynamics evaluation and nonsurgical treatment outcomes” is absolutely false. The spinal cord injured female with UI MUST have urodynamics to assess risk and assure successful management. What is the definition of urodynamics? Isn't a uroflowmetry and post void residual urodynamics testing? There is great correlation between those measures and the management/outcomes of geriatric voiding dysfunction. Again, we are concerned that the problem is with lumping this entire field of UI into one symptom, rather than the various diagnoses.</p> <p>We are all aware of limitations holding urodynamics to the gold standard – however few use it before the primary management of UI. So, we think this is a weak metric of comparison. It would be nice to review these diagnostic modalities and compare outcomes, not urodynamic findings to see which diagnostic tests would be most useful to select RX.</p>	<p>We clarified the scope of our review: “Other diagnoses for female pelvic floor dysfunction including UI associated with poor bladder emptying, voiding dysfunction, pelvic organ prolapse, or recurrent urinary tract infections as well neurogenic UI associated with spinal cord injury or stroke are beyond of our scope (Table ES1).: We revised the report emphasizing limitations holding urodynamics to the gold standard.</p>
AUA	Executive Summary	Do you mean “absolute risk reduction” rather than absolute risk difference?	We examined absolute risk differences that can be positive when the rates of the outcome are greater in active group versus control or negative when the rates of the outcome are smaller in active versus control group.
AUA	Executive Summary	ES-7Estrogen and continence is very controversial; there are conflicting data. The text is different here from the body of the report and will give the reader of the executive summary the wrong impression.	We clarified exclusion of systemic estrogens: “Systemic estrogens have been associated with increased risk of UI. Selective estrogen receptor modulators did not demonstrate consistent benefits on prevention of UI.” After discussion with key informants and TEP members estrogen treatments were excluded from our review.
AUA	Executive Summary	Duloxetine is not indicated for the treatment of SUI in the US. Why is this included?	Duloxetine is commonly used as an off-label drug for women with UI in the United States.

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AUA	Executive Summary	<p>The comment on each of the pharmacotherapies compared to placebo, followed by discontinuation rates is confusing. All FDA-approved PhRMA drugs have some efficacy. That is the point of the executive summary. All treatments have risk-benefit assessments, with drug discontinuation occurring in many. If you are you just cataloging what the literature you reviewed found, it might be more helpful to list-as you do later in the text- the number needed to treat (13 women to achieve improvement in UI in one woman, e.g Table 7.) , the number of AEs per people treated.</p> <p>Also- it would be helpful to discuss at some point: is this any worse than other drugs for non-life-threatening symptomatic conditions (maybe with simple UTIs, chronic bronchitis, osteoarthritis as examples?) Lastly, isn't the reader going to be more interested in what the side effects were that are likely associated with these medications? These AEs are shifted down a couple pages. They should be here as most will read this executive summary and nothing more.</p>	<p>We pointed out that FDA reviews concluded efficacy based on significant reduction in UI episodes. This estimation can't be used in decisionmaking that needs evaluation of balances between benefits and harms. We focused on continence and treatment discontinuation.</p> <p>We included the rates of the common adverse effects in the Executive Summary. We examined the role of comorbidities in treatment effects but found only one study that examined it.</p> <p>We added the tables with the rates of adverse effects into the executive summary (Table ES6).</p>
AUA	Executive Summary	<p>ES-8 "To conclude differences in benefits between the types of UI" is mis-stated. Does it mean "to conclude difference in benefits in the treatment of urge urinary incontinence?" And only urge urinary incontinence, since there is no drug approved for stress urinary incontinence.</p>	<p>We revised our conclusions about strength of evidence: "Overall, evidence was not sufficient to conclude differences in benefits by the predominant type, frequency, and severity of UI."</p>
AUA	Executive Summary	<p>Would one expect a difference in comorbidities for duloxetine, a non-approved drug, which you have already stated is not better than placebo? Why is this statement necessary or important in the executive summary?</p>	<p>We clarified that average treatment benefits may not reflect differences in benefits and harms among subjects with comorbidities. Duloxetine may have the same effects than placebo in all enrolled patients but provided between benefits in patients with depression. We could not find the studies that analyzed the role of comorbidities in effect modification with other drugs.</p>

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AUA	Executive Summary	Specialized Continence services: what is usual care? Shouldn't the reader understand more about these several studies which are directly at odds with much of the pioneering and higher impact work of Burgio et al?	We included all RCTs conducted by Burgio et al. Their conclusions do not contradict the results of our analysis.
AUA	Executive Summary	Weight loss: In one of the pivotal studies of the topic reported recently in NEJM, there is but one sentence "some improvement" – this is editorializing in the executive summary and gives this important subject the exact opposite conclusion of its authors. E-stim gets more positive coverage than the sentinel paper on weight loss? This must be corrected in the final executive summary.	We revised the abstract and the Executive Summary: "Weight loss improved UI in obese women." We included the study by Subak et al (N Engl J Med, 2009) that reported "a greater decrease in the frequency of stress-incontinence episodes (P=0.02), but not of urge-incontinence episodes (P=0.14)." More women reported 70 percent or more reduction in UI episodes. Intervention improved some but not all aspects of quality of life.
AUA	Executive Summary	ES-page 9 In the voiding diary, they report incontinence episodes and severity, but do they report patient characterization of incontinence; ie what self-reported type of incontinence they experienced. All voiding diaries are not the same. ES-10 There are some very valid points that should be a part of the prior text and not sequestered to discussion (examples, tolterodine and hallucinations, cardiac arrhythmias in the elderly.) These should be in the results section of the ES, and highlighting the deficiency of current literature in the discussions.	We revised the section about clinically important differences in frequency of UI clarifying the reduction in diary among women with stress and urgency UI. We included in the analysis the studies that analyzed outcomes among eligible treatments. Many studies of active postmarket monitoring lump all drugs from the same pharmacological group together. We included such studies in the discussion but not in the analysis. We concluded that routine monitoring of long-term harms is needed.
AUA	Executive Summary	ES-11Key findings should reiterate the text, not have new information (first bullet point) and we disagree most strongly with the conclusion that outcomes of non-surgical treatments are not known. There is an internal inconsistency with "nonpharmacological treatment resulting in significant clinical benefit" with the prior statement of "insufficient to conclude difference in outcomes of non-surgical management."	We revised the section about association between baseline urodynamic diagnosis and patient outcomes: "Evidence was insufficient to conclude significant association between urodynamic diagnosis and nonsurgical treatment outcomes. Urodynamic examination was associated with clinical benefits when performed for women undergoing surgical treatments for stress UI or invasive treatments for urgency UI after they failed conservative treatments."

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AUGS The American Urogynecologic Society Board of Directors	Executive Summary	<p>Abstract and Executive Summary: Current comments in regards to diagnostic value of different diagnostic modalities are confusing and conflicting as presently stated. Specifically, the document appears to simultaneously recommend and reject the value of urodynamic studies:</p> <ul style="list-style-type: none"> • “(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. • (2) Multichannel urodynamics was not associated with better outcomes after nonsurgical treatments and was useful only for women who underwent invasive treatments for UI.” (ES-6) <p>versus</p> <ul style="list-style-type: none"> • “Self- reported symptoms of UI have a low diagnostic value when compared to urodynamic diagnosis of stress UI or detrusor overactivity” (ES-11) <p>We found these conclusions difficult to reconcile. It was also difficult to understand how a thorough evaluation of urodynamics were performed if studies that involved surgery for stress incontinence with (or without) pelvic organ prolapse were excluded.</p>	<p>We revised key finding to clarify that self-reported symptoms of UI have a low diagnostic value compared to urodynamic diagnosis of stress UI or detrusor overactivity. Since urodynamic diagnosis is not associated with better outcomes, decisions to start treatments are based on assessment of frequency, severity, and bother of UI with validated tools.</p> <p>We revised key finding to clarify that self-reported symptoms of UI have a low diagnostic value compared to urodynamic diagnosis of stress UI or detrusor overactivity. Since urodynamic diagnosis is not associated with better outcomes, decisions to start treatments are based on assessment of frequency, severity, and bother of UI with validated tools.</p> <p>We clarified inclusion of the large observations of women with UI who failed conservative treatments.</p> <p>We revised the section about the association between baseline urodynamic diagnosis and patient-centered outcomes, please see responses above.</p>
AUGS	Executive Summary	<p>We also feel that the report’s conclusion about pelvic floor muscle training vs. drugs (“Benefits from pelvic floor muscle training combined with bladder training and electrical stimulation are greater than benefits from drugs”) is in opposition to the conclusions drawn on page 98 of the document (“Evidence was insufficient to draw valid conclusions about comparative effectiveness and safety of nonpharmacological treatments when compared to drugs or combined modalities”).</p>	<p>We revised the report and focused on head-to-head randomized trials that examined comparative effectiveness of combined modalities, drugs, and nonpharmacological treatments.</p>

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AUGS	Executive Summary	The document as a whole lacks a focus on the difference in the evaluation and management of Stress Incontinence versus Urge Incontinence. This is a key distinction, influencing both diagnostic and therapeutic decision making in clinical practice. We strongly recommend that this distinction be underscored throughout the document, where appropriate, and especially in the abstract, Executive Summary and treatment sections of the manuscript.	We distinguished drugs treatments for stress and urgency UI. The vast majority of nondrug studies included women with mixed UI. We analyzed the results separately by the presence of pure versus mixed UI. We added this information in the report.
AUGS	Executive Summary	While the document is ostensibly written for primary care clinicians, the document does not clarify the respective roles of primary care providers versus specialists.	Stakeholders recommended reviewing patient-centered outcomes and interventions most relevant for ambulatory care and not yet systematically evaluated. Stakeholders also recommended reviewing nonsurgical interventions relevant to women with refractory UI. Comprehensive information about all nonsurgical treatment choices can lead to evidence based referral practices for women with refractory UI. We included the drugs available in the United States for predominant stress UI (topical estrogens and antidepressants). We excluded systemic estrogens and selective estrogen receptor modulators that failed to prevent or improve UI. The roles of PCPs versus specialists are not for the EPC to define. The EPC's charge is to determine what conclusions can be reached about the body of evidence. We explored whether conclusions vary depending on populations and settings and describe if the evidence supported different conclusions.
AUGS	Executive Summary	We agree that improvement in urinary incontinence, leading to improvement in quality of life, is an important treatment goal and is a meaningful outcome; however do not believe the document provides convincing evidence to support the 70% improvement threshold selected.	We revised the sections in the report about clinically important improvement in UI frequency. Please review the responses above.

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AUGS	Executive Summary	Because this document focuses on non-surgical management options, surgical treatments are not addressed. However, the document includes some options that require surgical intervention for their delivery, such as Botox injections of the detrusor and urethral bulking agents. We believe these should not be discussed in this document, as these treatments necessitate surgical delivery. Future systematic reviews focusing on surgical treatments for stress incontinence would likely include bulking agents.	We clarified how we formulated a list of eligible interventions, please see responses above. Neurotoxins and bulking agents were included because we aimed to review all nonsurgical treatment options for women with refractory UI.
AUGS	Executive Summary	<p>Question 1. What Constitutes an Adequate Diagnostic Evaluation in the Primary Care Setting?</p> <p>In multiple sections, the document states that UI diagnosis should be made based on “clinical history, voiding diary, stress cough test and validated scales”. We believe the initial evaluation should include pelvic examination and urinalysis (e.g., to evaluate for pelvic organ prolapse and urinary tract infection).</p> <p>One suggestion would be modifying “clinical history” to “clinical evaluation” for completeness. Also, insufficient evidence is provided to support the routine use of the cough stress test and “validated scales” as part of the primary evaluation of urinary incontinence. We question the inclusion of these tests as a part of an evidence-based initial evaluation in clinical practice.</p> <p>A larger issue is that the document does not explain what is meant by “the primary care setting”. Is this targeted at Primary Care Physicians? If so, the report should acknowledge that the majority of research cited in this review was not performed in the primary care setting. As a result, we question whether these findings are</p>	<p>We aimed to evaluate all available methods to diagnose UI and judge treatment effectiveness in nonsurgical settings. We did limit the methods to initial evaluation of UI.</p> <p>We clarified our focus on ambulatory care interventions that were not previously reviewed by an EPC report and nonsurgical interventions for women with refractory UI.</p> <p>We use the term clinical evaluation following your suggestions. We clarified that initial evaluation should include pelvic examination and urinalysis. Reference method to evaluate value of noninvasive diagnostic tests in original studies does not need to be applicable to primary care settings. We found that clinical evaluation with validated tools for diagnosis of UI, its type, frequency, severity, and impact on quality of life informs nonsurgical treatment decisions. We concluded that in comparison to diagnosis by patients’ symptom reports, multichannel urodynamics did not better predict which patients would benefit from nonsurgical treatments. We did not conclude that cough stress test is a part of the primary evaluation of urinary incontinence. We clarified that the evidence about diagnosis and treatment of UI is applicable for ambulatory care settings. We clarified that stakeholders also recommended reviewing nonsurgical interventions that can be relevant to women with refractory UI. Comprehensive information about all nonsurgical treatment choices can lead to evidence based referral practices for women with refractory UI.</p> <p>We did not aim evaluation of utility of UDS or other diagnostic tools in different settings. We found the studies that compared treatment outcomes by the diagnoses made in different settings. However, we did not find the studies evaluating how diagnostic tools might perform in the ambulatory care setting versus in a more tertiary setting.</p> <p>We clarified our findings about low diagnostic value of the tools for urodynamic diagnosis of UI that, in fact, was not associated with patient</p>

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		<p>applicable, or even appropriate, in the primary care setting. We believe the majority of Primary Care Physicians are not trained to perform many of these recommended diagnostic methods, such as cystometry, Q-tip tests, or even home pad tests. If the “primary care setting” refers to “initial evaluation” by a care provider with appropriate training, then this should be further clarified in the document. Also, the armamentarium of diagnostic tools that should be utilized by primary care providers for the evaluation of urinary incontinence is not well defined. We recommend that the EHC consider how diagnostic tools might perform in the primary care setting versus in a more tertiary setting.</p>	<p>outcomes. Instead, validated tools are available for diagnosis and treatment monitoring of UI. We clarified that diagnosis of neurogenic UI or overflow was beyond our scope. Our systematic review is intended to help clinicians, consumers, and policymakers make clinical recommendations and informed decisions based on synthesized evidence and other relevant factors. This CER is not a practice guideline; therefore, it does not make practice recommendations or statements about what constitutes standard initial evaluation.</p>

Commentator & Affiliation	Section	Comment	Response
AUGS		<p>Finally, the document and conclusions are unclear regarding the role and value of urodynamic testing. At one point, the conclusions suggest that urodynamic diagnosis is superior to self-reported symptoms of UI. However, later the document suggests that urodynamic diagnosis is not associated with treatment outcomes. This will likely be confusing for a clinician attempting to make a clinical decision regarding how to proceed with diagnostic evaluation. In addition, the document does not address for which clinical scenarios urodynamic testing may provide valuable information (e.g. evaluation of refractory UI, settings in which the diagnosis is unclear after initial evaluation). Clarifying these points will likely lead to increased clinical relevance of the document.</p>	<p>We revised the introduction: “Our report also addresses the role of urodynamic testing, which is not typically performed in primary care. We include it here primarily as background information for primary care practitioners and because it raises a perplexing conundrum. As we have emphasized, the primary outcome for UI should be patient-centered reports of the UI experience, especially the presence or absence of UI. Although we typically think of physiologic testing as more objective, these results are, at best, akin to intermediate outcomes. In the diagnostic context, physiologic testing can inform in one of three ways: (1) establishing a diagnosis; (2) determining an etiology with therapeutic implications; and (3) generating a prognosis. In the case of UI, it is unclear whether physiologic measures represent a gold standard against which other measures can be compared or whether they should be viewed as information that may predict key patient-centered outcomes. Hence, we may be more interested in levels of agreement between physiological measures and patient outcomes but hard pressed to interpret differences between them. We examine the role of urodynamic testing in diagnosing and treating UI to provide insight into this conundrum.</p> <p>Our systematic review is intended to help clinicians, consumers, and policymakers make clinical recommendations and informed decisions based on synthesized evidence and other relevant factors.”</p> <ul style="list-style-type: none"> • We revised key messages: “Clinical evaluation with validated tools for diagnosis of UI, its type, frequency, severity, and impact on quality of life informs nonsurgical treatment decisions. • In comparison to diagnosis by patients’ symptom reports, multichannel urodynamics did not better predict which patients would benefit from nonsurgical treatments.” <p>We also explored potential relationships between different sources of clinical diversity and heterogeneity of results.</p>

Commentator & Affiliation	Section	Comment	Response
AUGS	Executive Summary	<p>Question 2. How Effective is the Pharmacologic Treatment of UI in Women?</p> <p>The data are well organized, with separation of “cure” rates versus improvement rates for UI, and with results expressed in number needed to treat (NNT) to achieve continence or improvement. We believe that practicing clinicians will find this approach useful. However, in this section, the distinction should be made explicit between options for the treatment of stress incontinence versus options for the treatment of urge incontinence. This is especially important with respect to Duloxetine, which has been used as a treatment for stress incontinence (while most of the other pharmacologic treatments are directed at urge incontinence). This is an important distinction. Typically the clinical trials restrict enrollment to women with one type of urinary incontinence and therefore it is imperative that the results be interpreted in that light.</p> <p>We believe the report could provide the clinician with a “big picture” conclusion regarding anticholinergic therapy for treatment of overactive bladder and urge incontinence. While there are differences between the agents considered, we believe the data could be summarized as follows: All anticholinergic medications 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 and the side effects are frequently bothersome enough to affect compliance and continuation of prescription. These summary finding should be highlighted.</p>	<p>We revised the report to distinguish the predominant type of UI; please review responses above.</p> <p>We revised: “Women with predominant urgency UI may achieve continence taking antimuscarinic drugs including trospium, solifenacin, fesoterodine, tolterodine, or oxybutynin. All anticholinergic medications were more effective than placebo in achieving continence and improving UI. The degree of benefit was low for all drugs (absolute risk difference with placebo <20 percent).</p> <p>Drugs demonstrated similar effectiveness, but treatment discontinuation due to adverse effects was most common with oxybutynin and least common with solifenacin.</p> <p>The side effects are frequently bothersome enough to affect compliance and continuation of prescription. Dry mouth, constipation, and blurred vision were among the most frequent adverse effects. Evidence of long-term safety of pharmacological treatments is insufficient.”</p>

Commentator & Affiliation	Section	Comment	Response
AUGS	Executive Summary	<p>The document focuses on studies examining efficacy of the pharmacological treatments; the <i>effectiveness</i> of these agents can be very different from their efficacy. In clinical practice, parameters such as cost should be taken into consideration. It should be mentioned in the document that only oxybutynin is currently available as a generic formulation. (With respect to oxybutynin, we also recommend that the report consider separately short-acting versus extended release preparations. Outcomes have been more favorable for extended release preparations and that distinction is not clear in the current draft.)</p> <p>While all anticholinergic medications seem to have similar clinical effectiveness in curing and improving UI, this conclusion should be interpreted with caution given paucity of head-to-head comparisons of various medications and variability in outcome measures between studies.</p>	<p>We revised subheadings following your recommendations. We analyzed formulations of all drugs separately. We revised the section on comparative effectiveness between anticholinergic medications that seem to have similar clinical effectiveness in curing and improving UI. We discussed that variability in outcome measures between studies section and limited data from head-to-head RCT reduced strength of evidence, please review responses above.</p>

Commentator & Affiliation	Section	Comment	Response
AUGS	Executive Summary	We disagree with the conclusions reported for the effectiveness of transvaginal estrogen for the treatment of urinary incontinence. One of the two studies cited to support the effectiveness (reference #630) was a study of multiple simultaneous interventions (including transvaginal estrogen) and therefore cannot be used to assess outcomes with estrogen alone. Moreover, while the other cited study (reference #631) demonstrated short term improvement in a small number of women, the biological plausibility for an effect is lacking. Specifically, there is evidence that systemic estrogen does not improve urinary incontinence and may even worsen symptoms (WHI and HERS studies). Thus, we believe there is insufficient evidence that vaginal estrogen preparations cure/improve urinary incontinence.	We clarified exclusion of systemic estrogens from the review. We used consistent criteria across the drug studies for grading of evidence.
AUGS	Executive Summary	Question 3. How Effective is the Nonpharmacological Treatment of UI? The section on non-pharmacological therapies should acknowledge that outcomes of non-pharmacological therapies will differ for stress incontinence symptoms versus overactive bladder symptoms. This is a <u>critical distinction</u> in interpreting outcome data. Without this distinction, it is difficult to make meaningful comparisons between the effectiveness of pharmacological therapy and non-pharmacological therapy. In fact, the lack of distinction, the selection criteria used and the fact that the majority of the pharmacologic studies focus on urge incontinence almost guarantee erroneous conclusions.	We made a clear distinction between treatments for stress or urgency UI when the authors clearly indicated that all participants have pure UI. In fact, the vast majority of the studies either included women with mixed UI or did not specify the type of UI. We analyzed the data using subgroup analysis and metaregression to explore differences in treatment effects among the studies with pure vs. mixed UI.

Commentator & Affiliation	Section	Comment	Response
AUGS	Executive Summary	Also missing from this section is an important discussion of efficacy versus effectiveness. We believe that the lack of effectiveness data should be specifically addressed in the report. Moreover, the report should specifically address possible difference in outcome from supervised versus unsupervised programs. The report should also discuss how the outcomes from these therapies may be affected by compliance and adherence. Specifically, Discontinuation Rates are discussed throughout the "pharmacological" section but are insufficiently addressed with respect to non-pharmacological, non-surgical therapies.	We revised the subheadings to distinguish efficacy versus effectiveness. We concluded that the evidence of comparative effectiveness was insufficient and made recommendations for future research.
AUGS	Executive Summary	We were disappointed that weight loss was not emphasized as an effective treatment. On page 91, the report notes that "a moderate level of evidence indicated improvement in UI after weight loss and exercise in obese women with UI". This is an important conclusion with public health significance. This is an intervention that can be introduced in the primary care setting. Given the nation's increasing problem with obesity, we suggest that the report emphasize weight loss as an evidence-based intervention for obese women with UI. Specifically, we feel that this intervention deserves mention in the abstract and executive summary.	We revised the section about weight loss in the abstract and in the report, please review responses above.

Commentator & Affiliation	Section	Comment	Response
AUGS	Executive Summary	<p>Finally, a critical issue is the apparent contradiction between one of the key conclusions of the report (“Benefits from pelvic floor muscle training combined with bladder training and electrical stimulation are greater than benefits from drugs”) and the conclusion on page 98 (“Evidence was insufficient to draw valid conclusions about comparative effectiveness and safety of nonpharmacological treatments when compared to drugs or combined modalities”). This is one of our central concerns. While we agree that individual studies can be used to calculate the “number needed to treat” for individual therapies, and while we acknowledge that these calculations suggest the superiority of non-pharmacological options, however, these comparisons are relevant only if the populations are similar and the outcomes are consistently defined across studies. We believe that the report misses an important distinction between outcomes for women with stress versus urge incontinence. We further believe that a review that considers this important and clinically relevant distinction might reach different conclusions than those stated in the report.</p>	<p>We revised the section about indirect comparisons between drug and nonpharmacological treatments; please review responses above.</p>

Commentator & Affiliation	Section	Comment	Response
AUGS	Executive Summary	<p>Some additional, specific comments regarding the content of this section:</p> <ul style="list-style-type: none"> Pessaries should be considered in this review. Pessaries have been used successfully for the treatment of UI and should be considered as a “medical device”. Vaginal cones are an adjunct to PFMT, not an anti-incontinence device. Therefore, cones should be addressed under the section on Medical Devices. Bulking agents are a surgical treatment and therefore should not be addressed in this report. However, if bulking agents are included in this report, the conclusions should be revised. The conclusion is based in part on a study (reference #708) of “transurethral radiofrequency energy”; this treatment is not related to bulking agents. We suggest that the report should conclude “There is insufficient evidence to assess the value of bulking agents in comparison to placebo.” 	<p>We included all RCTs and uncontrolled studies of pessaries that we found. We included RCTs that examined vaginal cones as adjunct to PFMT. We included bulking agents and neurotoxins because we aimed to review all nonsurgical treatment options for women with refractory UI. We concluded insufficient evidence of benefits with bulking agents.</p>
Doug Campos-Outcalt, MD	Executive Summary	The research review was well done.	Thank you.
Mary Ann Forciea, MD	Executive Summary	It might have been useful to state why the report focuses on 1) women, and 2) diagnosis and management in the primary care office. The use of Number Needed to Treat statistics is easy to understand.	We focus on female UI diagnosis and management in ambulatory care settings following the nomination of the topic, public comments, and recommendations from the TEP.
Nancy Kolb, MSN, RN VP Global Marketing Uroplasty, Inc.	Executive Summary	Executive Summary: Urinary incontinence (UI) is only one facet of the many urinary problems facing adult women. This report would better serve consumers and health care providers if the report reflected the complex constellation of symptoms that comprise Lower Urinary Tract Symptoms (LUTS), which encompasses the entire spectrum of urinary problems women face – frequency, urgency, nocturia, quality of life implications, co-morbidities such as urinary tract infections, fractures and falls.	We revised the Introduction adding information about overactive bladder and other urinary problems. We pointed out that our scope focuses on stress, urgency, or mixed UI.

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Commentator & Affiliation	Section	Comment	Response
Nancy Kolb, MSN, RN	Executive Summary	Also missing from this review is overactive bladder syndrome (OAB) defined by the International Continence Society (ICS) as a syndrome with or without urge incontinence, usually associated with urinary frequency and nocturia in the absence of proven infection or other obvious pathology. Many of the studies used in this literature review focus on OAB syndrome and yet have been evaluated only on the symptom of incontinence instead of the combination of all symptoms impacting the patient's health and quality of life. This is an incorrect way to view these studies, and many are excluded not because the study is lacking, but because the criteria for inclusion are too narrow. <u>This review attempts to distinguish, in most cases, between stress UI and urgency UI, but neglects to mention that urgency UI is only one component of OAB as defined by the ICS.</u>	We clarified our analysis of urgency UI in women with OAB. We revised the report providing definition of OAB and the outcomes to judge treatment effectiveness for adults with OAB. We clarified that we focus on clinical outcomes relevant to UI including continence, improvement in UI, quality of life, and harms.
Nancy Kolb, MSN, RN	Executive Summary	Additionally, this report would <u>be more clinically relevant if it addressed all therapies for incontinence, including surgical treatments.</u> T	We excluded surgical treatments because the primary objective of our review was management of UI in ambulatory care settings. Surgical treatments were extensively reviewed in a previously published evidence report ⁷ .

Commentator & Affiliation	Section	Comment	Response
Nancy Kolb, MSN, RN	Executive Summary	<p>Perhaps the best example of the flawed methodology in this report is the use of reference # 213, Yalcin et al., as the sole rationale for using a 70% reduction in incontinence episodes as the indicator of success of a treatment. Within the urology community, a > 50% reduction in symptoms is the reasonable and accepted standard of care. The Yalcin study focused on stress urinary incontinence (SUI), and within the study admonishes that "First, the findings and thresholds apply to women with predominant SUI and cannot be extrapolated to women with other types of incontinence, particularly urge urinary incontinence where even a single large volume incontinence episode may be completely unacceptable" (p. 346). Yet, the investigators use it to generalize to all forms of incontinence in just the way the authors state it should not be used. Also, this study is derived from 4 studies of duloxetine, a drug not FDA cleared for the indication of SUI in women. Lastly, the study results are misquoted and improperly extrapolated to define this draft review's measure of success. On page 346, the Yalcin study defines the clinical importance of reductions in incontinence episodes by stating, "Reductions in IEF (incontinence episode frequency) <40% do not appear to be clinically important for women with SUI. Patients appear to recognize important clinical value at reductions of approximately 50% and important incremental clinical value at reductions of approximately 75% and 90-100%." Note the 50% which is similar to the current standard of care.</p>	<p>We revised the section about what women consider clinically important reductions in UI frequency episodes; please see responses above. We revised the section about importance of patient-centered outcomes. Women's perception of improvement should be taken into consideration defining "current standard of care."</p>

Commentator & Affiliation	Section	Comment	Response
Nancy Kolb, MSN, RN	Executive Summary	LUTS is an altered health state with many complex causes and a constellation of symptoms. This report confuses only one symptom with the entire complexity of the disease. This simplification does not result in clinically relevant endpoints.	We defined our scope after public discussion with key informants and according to the public comments. One review could not possible address all “complex causes and a constellation of symptoms” of LUTS.
Nancy Kolb, MSN, RN	Executive Summary	The object is to help consumers, health care providers and others in making informed choices among treatment alternatives.” This report does not meet that goal. There is a plethora of data and statistics reported, however, it is not a practical nor clinically applicable document.	We synthesized the evidence following principles outlined in the Cochrane Handbook of Systematic reviews and the AHRQ Methodological guideline. We revised the discussion pointing out applicability of the findings to ambulatory care. Practicality of our review is the same as practicality of the original studies included in the review.
Nancy Kolb, MSN, RN	Executive Summary	This review focuses specifically on the problems associated with sphincter function and bladder overactivity in women.” Bladder overactivity includes many more symptoms than just incontinence; it also includes problems with urinary frequency, nocturia and urinary urgency.	We revised clarifying our focus on incontinence, not all symptoms of OAB.
Nancy Kolb, MSN, RN	Executive Summary	“Ultimately, discussions of UI are complicated by the wide variety of measures used to describe the problem and its treatment outcomes...Thus we focus on continence as the primary outcome for this comparative effectiveness review.” This is the crux of the problem with this report. Separating out only one part of this complex clinical picture is not helpful. It is precisely because LUTS is a complex problem that it must be studied in aggregate, as it is more than just the sum of its parts.	We revised the section about primary outcomes in our review justifying out focus on patient-centered outcomes. We revised the report providing more information about quality of life with different treatments. Diagnosis and treatment of all variances of the complex LUTS problem was outside of out scope.

Commentator & Affiliation	Section	Comment	Response
Nancy Kolb, MSN, RN	Executive Summary	The focus is on diagnosing UI in primary care settings. However, the skill and knowledge to use pad weight tests, bladder ultrasound, and multichannel urodynamics to diagnose incontinence is part of specialty urology care and is outside the scope of primary care practitioners.	We clarified that the studies used urodynamic as a reference standard. Evaluated index methods were applicable to ambulatory care. Our approach is similar to examining diagnostic value of ECG for coronary stenosis when index method (ECG) is applicable ambulatory care settings while reference standard (angiography) is not.
Nancy Kolb, MSN, RN	Executive Summary	While complete continence is a laudable goal, the reason that it is rarely examined as a primary outcome is that the usual therapeutic treatment goal for urinary disorders is to ameliorate symptoms to a level that is acceptable to the patient. What has been demonstrated repeatedly is that even small changes in voiding symptoms may result in large changes in quality of life parameters. With multiple symptoms, cumulative modest changes across the patient's entire symptom range may be enough to change a patient's life even if full continence is not reached.	We analyzed all available patient-centered outcomes including continence, improvement in UI, quality of life, and harms.

Commentator & Affiliation	Section	Comment	Response
Nancy Kolb, MSN, RN	Executive Summary	<p>The authors of this report have misconstrued the correlation between objective voiding parameters such as urine leak tests and the subjective reports of improved overall perception of bladder conditions. Pad weight tests and voiding diaries that document improvements in voiding symptoms provide statistical data that symptoms have changed. Note that a study by Peters et al found a correlation between improved voiding symptoms and subjective response.⁵ Note also, that while the goal of having women be the arbiters of their symptom improvement is laudable, this is not a stance that is accepted by the professional, scientific, nor payer communities. Recent publications do state that conditions such as OAB that are essentially lifestyle issues and should be studied with patient perception as the standard for judging improvement.⁶</p> <p>The statement that “meaningful differences in questionnaires or scales have not been systematically reviewed” is irrelevant, as most are validated measurement tools. Any difference between them is immaterial as they all have the ability to measure differences within a study group.</p>	<p>We included all available evidence about differences of clinical important for women as reported in voiding diaries, scales, and questionnaires. We revised the report analysis all available studies of PTNS including Peters et al studies. Validation of the tools does not necessarily provided cut offs in continuous measures that reflected women’s perception of clinically important differences</p>

Commentator & Affiliation	Section	Comment	Response
Nancy Kolb, MSN, RN	Executive Summary	<p>If the focus of this study is on diagnosis and treatment of UI in adult women by primary care setting, then it should not include diagnostic methods nor treatments that are part of specialty care delivered by urologists, gynecologists, physical therapists or continence care professionals.</p> <p>KQ1, 1-Primary care practitioners do not have expertise in and do not administer pad weight tests, bladder ultrasounds, and multichannel urodynamics. These are diagnostic tests performed by specialty care and continence experts.</p>	<p>We revised the discussion with applicability of our results to ambulatory care settings.</p> <p>We clarified applicability of index methods, not reference standards to ambulatory care practice. We revised the discussion with applicability of the results to ambulatory care settings.</p>
Nancy Kolb, MSN, RN	Executive Summary	<p>KQ1,4-This is a question that is trying to imply causality between diagnosis and patient outcomes. There is none. The treatment, not the diagnosis, determines patient outcome. For example, what is the association between a positive strep throat culture and patient outcome? There is none because the association is between the correct choice of antibiotic to treat the infection, and not the diagnostic method by which the infection was found.</p>	<p>The question about urodynamic diagnosis and patient outcomes is testing associated hypothesis, not causality. The studies examined this association and demonstrated no association with conservative treatment outcomes.</p>

Commentator & Affiliation	Section	Comment	Response
Nancy Kolb, MSN, RN	Executive Summary	<p>KQ1, 1-The comparison between pharmacologic choices has not been examined in a clinically relevant way. The bottom line is that all anticholinergic drugs work to some extent, patients have different tolerances for them, physicians have different preferences for using them, they can be used in combination with one another, and they all have side effects. A clinically useful statement arising from a comparative effectiveness review would be which medication to use first based upon an effectiveness ratio and low adverse events profile, which to use second, and what therapies should be used if pharmacological therapy fails or cannot be tolerated.</p> <p>KQ3-The better question is, when pharmacologic treatment has not resulted in sufficient therapeutic effect, what are the next treatment options that can be used for patients? The algorithm of care for LUTS, as with most chronic conditions, is to begin with the least invasive, least costly, lowest risk therapy, and move toward those that are more costly, have more potential adverse effects, and are more invasive.</p>	<p>The order of treatment choices was not examined in the original studies. We examined outcomes by the response to prior treatments and clarified that solifenacin only provided benefits irrespective of the response to prior treatments. We recommended that future research may clarify the best treatments for women who failed nonpharmacological nonsurgical treatments for UI.</p>

Commentator & Affiliation	Section	Comment	Response
Nancy Kolb, MSN, RN	Executive Summary	Study selection: "For Key Question 1 we included studies that evaluated different methods to diagnose UI in women that are applicable for primary care settings." Again, pad weight tests, bladder ultrasound, and multichannel urodynamics are not primary care setting diagnostic tests. <input type="checkbox"/> We excluded studies of surgical treatments for UI or urogenital-prolapse and studies of drugs not approved by the FDA." If this is true, then Botulinum Toxin and duloxetine should not be included in this review. They are not FDA cleared for the indication of incontinence or overactive bladder.	We clarified how we determined a list of interventions eligible for the review; please see responses above. We included bulking agents and neurotoxins to provide the audience with conservative treatment options for women who failed other treatments.
Nancy Kolb, MSN, RN	Executive Summary	There is inconsistency in the number of overall studies identified and included in the review between what is reported here, what is in figure ES2, and what is reported in the structured abstract. Only 17% of identified studies were included in the review. This seems extremely low and again draws attention to the inconsistent and overly restrictive exclusion criteria.	We revised the abstract adding all studies from updated searchers that were included in the study flow. Precision of our search is larger than in other evidence based reports (~6%). Proportions of included among retrieved studies reflect how exhaustive comprehensive search was.
Nancy Kolb, MSN, RN	Executive Summary	Page ES-6 Comparing drugs to placebo gives enough evidence. Why does comparing other interventions (such as percutaneous tibial nerve stimulation) to placebo (sham) not do the same, especially when the sham was independently validated in a completely separate study?	We added information about PTNS; please see responses above. We revised the Methods section clarifying how we evaluated strength of evidence. We followed the methodological guidelines from AHRQ that define evidence from individual RCT as insufficient; please review responses above.

Commentator & Affiliation	Section	Comment	Response
Nancy Kolb, MSN, RN	Executive Summary	<p>There are inconsistencies throughout this section when referring to urgency of urination and urinary incontinence. Measuring treatment success-A 70% reduction of urinary episodes assessed by voiding diary is not the standard in the urology community. This is an example of using statistics outside of their clinical context. Sometimes even modest reductions in urinary episodes may be sufficient for a patient to reclaim their quality of life.</p> <p>Additionally, reference 213 (Yalcin I, Peng G, Viktrup L, et al. Reductions in stress urinary incontinence episodes: what is clinically important for women? Neurourol Urodyn 2010; Mar; 29(3): 344-7) has been severely misused as the rationale for the success rate. We are particularly disturbed by the use of reference 213 to set the level of 70% reduction in urinary episodes as the measure of clinical success, as previously discussed.</p> <p>Effectiveness of pharmacological treatments-Note that the report reviewed "drugs for overactive bladder," but then only evaluated one of the studied parameters-urinary incontinence. The drug effects are designed to work on multiple symptoms with improvements evaluated in aggregate, not individually. With modest improvements in several symptoms, patients may experience sufficient therapeutic improvement to have acceptable quality of life changes. To look at only one symptom does not represent a sound methodology.</p>	<p>We used the definitions of urgency and urgency UI recommended by the ICS.</p> <p>We revised the report adding all information about quality of life. We did not look at one symptom but analyzed all available patient centered outcomes: continence, improvement in UI, quality of life, and harms.</p> <p>We revised the section about clinically important differences in voiding diaries and other tools.</p>
Nancy Kolb, MSN, RN	Executive Summary	<p>Page ES-8</p> <p>Percutaneous tibial nerve stimulation (PTNS) is lumped with electrical stimulation and magnetic stimulation. PTNS is a method of neuromodulation,</p>	<p>We revised the report adding all available information about PTNS.</p> <p>We analyzed comparative effectiveness of treatments in head-to-head studies when available. We conducted indirect comparisons without format statistical tests because of clinical diversity and variability in control rates.</p> <p>We clarified what our report offers in addition to previously published</p>

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Published Online: April 2012

Commentator & Affiliation	Section	Comment	Response
		<p>and it should be considered separate from electrical and magnetic stimulation. "Evidence was insufficient to conclude positive effects from percutaneous tibial nerve stimulation." There are 3 RCTs in the literature that demonstrate effectiveness in the short term and the long term. The UK's NICE guidance document IPG362, using a very comprehensive review of the literature, concluded that PTNS is effective in the short and medium term. A copy of the guidance document is included in our comments.</p> <p>An essential flaw in the methodology of this review can be found in the statement "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." Comparative effectiveness is a relatively new concept, yet this report looks at published studies that are as old as 1989. To begin performing comparative effectiveness studies, a reasonable person cannot possibly expect that individual studies would contain comparisons to other treatments. 10-15 years into the future when comparative effectiveness is an established standard, then it may be reasonable to expect studies to examine treatments head-to-head with similar controls. The only way to perform a comparative effectiveness review now is to look at studies individually and the results they report. Then those results should be reported as a way to support clinically effective therapies that can be used appropriately by physicians as</p>	<p>reviews.</p>

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Published Online: April 2012

Commentator & Affiliation	Section	Comment	Response
		warranted by the individual patient's condition. If a conclusion is not possible, then the judgment should be "we were unable to draw a conclusion" rather than that the evidence was insufficient. It's a subtle difference in language that has large implications for how good scientific evidence of efficacy is perceived. The statement on ES-9 "Indirect comparison indicated comparable effectiveness of nonpharmacological treatments on continence" is a correct statement.	
Nancy Kolb, MSN, RN	Executive Summary	Page ES-9 The report states "our findings are in agreement with previously published systematic reviews of diagnosis and treatment of UI by AHRQ, the Cochrane Collaborative Group, and International Consultation on Incontinence." If this is true, why was it necessary to spend the resources to create and revise this report if it introduces no new knowledge?	We clarified that in addition to previously published reports our review provides a comprehensive synthesis of evidence about benefits and harms from treatments for UI using patient centered prospective.
Nancy Kolb, MSN, RN	Executive Summary	Page ES-10 "Policy makers should consider patient-centered outcomes including continence on QoL when making regulatory decisions." Studies on PTNS demonstrate both. Why then is only continence used as the sole indicator of success? Page ES-11 "Non-pharmacologic treatments result in significant clinical benefit with a low risk of adverse effects." PTNS is a non-pharmacologic treatment. This statement contradicts the statement on page 88-"Evidence was insufficient to conclude positive effects from PTNS on continence or improved UI in adults with overactive bladder." "Evidence of long-term safety of pharmacological treatments is	We revised the report appraising all published studies about PTNS. We included all patient centered outcomes. Clinical Effects of Percutaneous Tibial Nerve Stimulation Percutaneous tibial nerve stimulation improved UI in adults with OAB. Four RCTs examined clinical effects of percutaneous tibial nerve stimulation, including the Study of Urgent PC versus Sham Effectiveness in Treatment of Overactive Bladder Symptoms (SUmT) trial and the Overactive Bladder Innovative Therapy Trial (OrBIT) (Appendix Table F108). The studies treated adults with either active stimulation with a current level of 0.5 to 9 mA at 20 Hz or sham stimulation. Continence No RCTs compared continence after percutaneous tibial nerve stimulation versus sham stimulation in adults with UI. Participants in OrBIT Trial reported 16-20 percent cure rates with 12 months of active stimulation. The study did not report cure rates with sham stimulation. Continence rates were 94 percent among women with predominant urgency UI and 91 percent in women with mixed UI in an uncontrolled trial. ⁶⁴⁵ Continence did not differ with more frequent stimulation (three versus one time/week). Improvement in UI Percutaneous tibial nerve stimulation improved UI. Three women need to

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Published Online: April 2012

Commentator & Affiliation	Section	Comment	Response
		<p>insufficient...”</p> <p>PTNS has safety data available out to one year, but that study was excluded from the draft review.</p> <p>Table ES4 Conclusions about the management of UI in women</p> <p>PTNS is omitted from the table</p> <p>Table ES5-Clinical outcomes with treatments for UI (direct evidence from pooled with random effects models RCTs)</p> <p>This title does not make sense</p> <p>PTNS has a similar or lower number needed to treat than many drugs. PTNS has a number needed to treat of 7. For drugs, the range is 9-12 for tolterodine, 6 for solifenacin, and 31 for fesoterodine. Yet PTNS was given an insufficient evidence rating, while the drugs are endorsed as treatment options.</p>	<p>be treated with percutaneous tibial nerve stimulation to achieve improvement in one woman (Appendix Table F97). Improvement in UI was attributable to active treatment in 308 women per 1,000 treated (95% CI, 40 to 557). Participants in OrBIT Trial experienced 76-80 percent improvement rates with 12 months of active stimulation. Nonrandomized studies reported 63-64 percent success rate with active stimulation.</p> <p>Adverse Effects</p> <p>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. Treatment discontinuation did not differ with active versus sham stimulation. One patient did not complete the treatment because of aggravating pre-existing cardiac arrhythmia in an uncontrolled clinical trial of 39 subjects with voiding dysfunction.</p> <p>Tolterodine versus percutaneous tibial nerve stimulation</p> <p>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 (Appendix Table F153). Patient assessment and investigator assessment of improvement or cure were greater with stimulation than with tolterodine. Self-reported change in health-related quality of life score did not differ with stimulation versus drug treatment. Subjects reported worsening of the symptoms less often with stimulation than with the drug.</p>
Peer Reviewer #1	Introduction	1. The title is grammatically odd. It sounds as if treatments will be diagnosed. The title should reflect that only pharmacological and non-surgical treatments are included in this report. Consider: Diagnosis of urinary incontinence and comparative effectiveness of non-surgical treatments in adult women.	We revised the title following your suggestions.
Peer Reviewer #2	Introduction	The introduction provides a strong background justifying the need for the report. Key terms are clearly defined.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Introduction	Overall, the introduction is appropriate. As noted, above further clarification of who the intended audience of the report is would be valuable. Additionally, some discussion of the current standard of care for first-line and 2nd line treatments for different types of UI seems necessary to frame the rest of the report.	We clarified that this CER is not a practice guideline, therefore it does not make practice recommendations or statements about what constitutes standard of care: "This report aims to synthesize published evidence about diagnosis and management of UI in adult women. We focused on adult women in ambulatory care settings and on nonsurgical nonpharmacological treatments and pharmacological agents available in the United States. The comprehensive synthesis of evidence is intended to provide clinicians, consumers, and policymakers with information for informed decision making."
Peer Reviewer #4	Introduction	<p>on page ES-1, please provide a more complete list of causes of incontinence. In listing dementia and loss of inhibition first, this implies a greater weight to this etiology.....which is not true.</p> <p>Urgee incontinence (p. ES-2) may have NOTHING to do with the detrusor muscle in some patients. please reword the sentence as it is physiologically inaccurate. it is also misstated on p. 1.</p> <p>UDS can be performed with many FLUIDS. please correct this on ES-2 and on p.2.</p> <p>UDS measure many aspects of urination. please clarify and reword lines 7-8 on p. 2. it is inaccurate.</p> <p>UDS have many utilities other than diagnosis (p. ES-2) including prognosis and deciding between treatments. Please include this on p. ES-2 in the 3rd paragraph.</p>	<p>We revised this section:""Voluntary voiding requires a balance between sphincter activity and bladder function. UI in women is related to actions of the bladder and the urinary sphincter. Stress incontinence is a sphincter failure attributed to intra-abdominal pressure. Urgency incontinence is attributable to sphincter failure with or without overactive bladder contractions. Conversely, an inactive bladder may result in overflow incontinence, whereby urine is retained until bladder capacity is exceeded. In many women stress and urgency occur together in what is called mixed incontinence. Sphincter failure in women is often associated with weakness of the pelvic floor muscles. Nonpharmacological therapy targets strengthening the pelvic floor, whereas pharmacologic therapy addresses innervating the bladder and sphincter.</p> <p>The etiology of incontinence is multifactorial. Known risk factors include age, pregnancy, pelvic floor trauma after vaginal delivery, menopause, hysterectomy, obesity, urinary tract infections, functional impairment, cognitive impairment, chronic cough, and constipation. Assessments of women complaining of UI begin with exclusion of underlying causes such as pelvic organ prolapse, urinary tract infection, and poor bladder emptying, all of which are conditions beyond the scope of this review, as well neurogenic UI associated with spinal cord injury or stroke (Table ES1).</p> <p>We focus specifically on women with stress UI associated with sphincter function, and with urgency UI, often associated with overactive bladder."</p> <p>We corrected sentences about types of UI following your suggestions. We revised the definition: "Urgency incontinence is defined as involuntary loss of urine associated with the sensation of a sudden, compelling urge to void that is difficult to defer."</p> <p>We reworded the text to make clarifications requested by the reviewer.</p> <p>We could not find the studies that demonstrated predictive value of UDS for prognosis and deciding between nonsurgical treatments.</p>

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Introduction	<p>It states on ES-2 that treatment outcomes SHOULD be patient centered. I would argue that patient centered outcomes are important (and may even be most important) but there are other outcomes that should be included also (objective efficacy endpoints such as diaries, pads, etc., cost, adverse events, etc.) especially as a composite. Furthermore whether these SHOULD (as stated by the authors) be reported as questionnaires or scales only, is debatable. These statements are OPINIONS and subjective and are not based on ANY scientific data whatsoever. Therefore they should be classified as such or removed from this document.</p>	<p>The Effective Health Care program focuses on patient centered outcomes over physiologic intermediate outcomes that are easier to quantify. We clarified that “continence (complete voluntary control of the bladder) has been considered a primary goal in UI treatment. Continence is also the most important outcome associated with quality of life in women with UI, but it is rarely examined as a primary outcome in syntheses of evidence. Thus, we focus on continence and quality of life as primary outcomes for this comparative effectiveness review.</p> <p>While definitions of continence are similar, commonly used definitions of improvement of UI varied across studies and included different degrees of change in frequency and severity of symptoms. Furthermore, improvement in UI has been viewed by women and researchers very differently. Women have defined improvement according to reduced lifestyle restrictions or improved overall perception of bladder conditions. 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.</p> <p>Treatments for overactive bladder aim to decrease the frequency and intensity of urgency sensations, as well as the frequency of urgency UI episodes. Previous reviews of treatments for overactive bladder have considered clinical success as any statistically significant decrease in frequency of UI episodes and voiding, irrespective of whether women perceived any clinical improvement. Measurement of treatment outcomes should be patient-centered and based on factors important to women, rather than on the results of invasive tests. Thus, treatment success and failure should be evaluated according to what women report in validated questionnaires or scales. 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). This review examines improvement thresholds of clinical importance in validated scales and checklists that can be applied to judge UI treatment success according to women's own perceptions.</p>

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Introduction	<p>Continence may NOT be the most important outcome for some individuals (p. ES 2 and p. 2). reword this sentence. It may not be the MOST important outcome in an individual with frequency x 15 daily but only one minor episode of UI weekly. Is urinary retention (complete continence) a desired outcome??? How many normal people have some incontinence (e.g. post void dribbling)? Is this what is MOST IMPORTANT to them?</p> <p>It is inaccurate to state that reviews and prior studies have not emphasized continence or patient perspectives of treatment. There are volumes of papers with PRO's, and continence outcomes.</p>	<p>We clarified that continence is considered as a primary goal when treating UI. 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.</p> <p>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. While definitions of continence are similar, improvement in UI has been judged very differently by researchers and women. 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. Treatments for overactive bladder decrease in urgency, voiding, and urgency frequency. Statistically significant decreases in frequency of UI episodes and voiding were considered as a clinical success in a comprehensive review for treatments for overactive bladder, irrespective of women's perception of clinical improvement. Recommended clinically meaningful levels of improvement in the number of incontinence episodes per day as greater than 50% reduction from baseline was not a primary outcome in original studies and published systematic literature reviews. 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. 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. Moreover, experts, not patients, define standard care by statistically significant reduction in UI episodes or improvement in pad, urodynamic, or other tests. 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.</p>
Peer Reviewer #5	Introduction	The introduction is well written and provides valuable context.	Thank you.
AUA	Introduction	<p>Page 1 – same comment as under the executive summary about the definition of stress.</p> <p>Page 2 – 1st paragraph – remove ultrasound</p> <p>Hyperactive bladder should be replaced by detrusor overactivity incontinence.</p>	We made suggested corrections.

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Commentator & Affiliation	Section	Comment	Response
Mary Ann Forciea, MD	Introduction	This is well written. The key questions are clearly presented and relevant to the target audience selected.	Thank you.
Peer Reviewer #1	Methods	Page 16, paragraph 1: Should clearly detail how this report differs from recent AHRQ report by Hartman et al (ref 52), as it appears that many of the items noted in this paragraph were in fact covered in that report.	We clarified. Following guidelines and recommendations from key informants and TEP members we focused on patient centered outcomes including continence, improvement in UI, quality of life, adverse effects, and discontinuation due to adverse effects. Voiding frequency in women with overactive bladder was reviewed previously and was outside of our scope. We clarified. Statistically significant decreases in frequency of UI episodes and voiding were considered as a clinical success in a comprehensive review for treatments for overactive bladder, irrespective of women's perceptions of clinical improvement. Recommended clinically meaningful levels of improvement in the number of incontinence episodes per day as greater than 50% reduction from baseline was not a primary outcome in original studies and published systematic literature reviews.
Peer Reviewer #1	Methods	Page 16: notes that the focus of this report is on primary care settings. Yet, most of the references are not conducted in primary care populations.	We clarified: "The index methods that are applicable to ambulatory care settings were compared in eligible studies with urodynamic or clinical diagnosis of UI that was made by investigators in specialized clinics."
Peer Reviewer #1	Methods	Page 16: Notes that one objective is to present valid methods to monitor treatment benefits and harms. Were methods to evaluate harms assessed for validity?	We clarified: "Methods to evaluate harms were not assessed for validity"
Peer Reviewer #2	Methods	The methods are clearly presented. The search strategies are presented in detail and should have identified the majority of relevant studies. Inclusion and exclusion criteria were clearly stated and appropriate. Data extraction methods were explained and follow current recommendations. Data extraction tools were included in the appendices. The methods used grade the evidence were presented in adequate detail. The meta-analysis methods were clearly presented and appropriate.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Methods	<p>1) Inclusion/exclusion criteria - the inclusion criteria are inadequately described in my opinion, particularly with regard to what constitutes "eligible" interventions. Explicit and coherent criteria for what interventions are included in this review should be provided. On page 8 "eligible interventions" is not defined. Even a careful study of appendix D does not give enough clarity in my opinion. As noted in general comment #2 above, the exclusion of some surgical treatments but the inclusion of other treatments that require a surgical or procedure based intervention is confusing; similarly the inclusion of first-line treatments and some but not all 2nd-line treatments seems inconsistent with a focus on the primary care setting. Even the choice of which drugs are included in the report seems inconsistent; for instance vaginal estrogen preparations are included but data from trials of oral estrogen preparations are not; duloxetine for SUI is included in the review but other medications that have been used for SUI including imipramine and alpha agonists are not included.</p>	<p>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. According to the public comments we formulated a list of interventions eligible for this review. Stakeholders recommended reviewing patient-centered outcomes and interventions most relevant for ambulatory care and not yet systematically evaluated. Stakeholders also recommended reviewing nonsurgical interventions relevant to women with refractory UI. Comprehensive information about all nonsurgical treatment choices can lead to evidence based referral practices for women with refractory UI. We included the drugs available in the United States for predominant stress UI (topical estrogens and antidepressants). We excluded systemic estrogens and selective estrogen receptor modulators that failed to prevent or improve UI.</p> <p>We developed a protocol with detailed information about included interventions. The protocol was posted online for the public view: on http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=497</p>
Peer Reviewer #3	Methods	<p>In the executive summary (ES-5, line 7) it is noted that "drugs not approved by the FDA" were excluded from this report. First, does this mean not approved by the FDA for UI or for anything? If not approved for UI then duloxetine and vaginal estrogen preparations would not qualify; if FDA approval for any indication is the inclusion criteria then the exclusion of oral estrogen and the other meds mentioned above is not consistent. Second, I cannot find this "not approved by the FDA" exclusion listed explicitly in the Methods section.</p>	<p>We revised the report: "This report synthesizes published evidence about diagnosis and management of UI in adult women. We focused on adult women in ambulatory care settings and on nonsurgical nonpharmacological treatments and pharmacological <u>agents available in the United States</u>. Our systematic review will help clinicians, consumers, and policymakers make clinical recommendations and informed decisions based on synthesized evidence and other relevant factors."</p>

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Methods	Meaningful conclusions can only be drawn from pooling studies with similar types of UI. I have significant concerns that pooling as it was performed for this report will draw inappropriate conclusions particularly for the non-pharmacologic interventions where a wide variety of UI subtypes have been studied. The authors should limit study pooling to specific UI subtype categories (i.e urge, urge-predominant, stress, stress-predominant, Mixed UI, any UI)	We clarified the type of predominant UI in the text and the tables. We synthesized the evidence by the baseline type of UI as pure or predominant stress, pure or predominant urgency, and mixed UI. We compare clinical outcomes by the type of UI within each study and across the studies. We evaluated inclusion and exclusion criteria and baseline characteristics of the subjects to determine whether all or a proportion of the subjects had mixed UI. Then we conducted quantitative meta-regression and subgroup analysis to determine treatment effects by baseline type of UI. Pooling criteria include the same definition of the intervention and the outcome. The association between length of treatment and treatment effects was examined in meta-regression.
Peer Reviewer #4	Methods	Were studies of higher quality (better level of evidence) given more weight than poor quality studies? if not, then it calls into question ALL of the conclusions from all the sections of the paper.	We used quality of the studies in evaluating the strength of evidence. Evidence quality was high from the studies with low risk of bias. We clarified in the executive summary That we evaluated the quality of studies and classified them by design. We evaluated studies for question 1 with predefined criteria for assessing quality of the diagnostic accuracy studies. 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. We examined sponsorship and conflict of interest but did not downgrade quality using this information. We incorporated quality in synthesis of evidence conducting meta-regression, subgroup and sensitivity analysis for each quality criteria rather than overall quality score. We described quality of the studies for each section. We report differences in results by quality of individual studies when we detected them. We used quality assessment in grading of evidence (see risk of bias assessment).

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Methods	the authors use a 70% reduction in UI episodes as a cutoff for clinical meaningfulness. is this based on a single reference (reference 213)? this is inadequate. This was a study on SUI. This may not apply at all to those with UUI or MUI. how do we know that any other percent, such as 50% is not meaningful to an individual patient? furthermore, there are patients in whom only a 100% reduction is meaningful.	<p>We revised the section about minimal clinical important reduction in daily UI episodes.</p> <p>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. The authors examined the relationship between relative reduction in UI episode frequency and meaningful improvement for women in the Incontinence Quality of Life questionnaire. Women with daily stress UI perceived important clinical benefit at reductions of approximately 50% and important incremental clinical value at reductions of 75% and 90–100%. The study concluded that women noticed improvement in quality of life when UI episode frequency was reduced by more than 70 percent. 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. Quality of life impact was similar for stress UI episode reductions of >40% to 70%. Women with persistent urge, stress, or mixed urinary incontinence reported reduction in UI episodes using voiding diaries and satisfaction with treatment using Global Perception of Improvement and Incontinence Impact Questionnaire. More than 60% of women reported complete treatment satisfaction when they experienced more than 70% reduction of UI episodes No studies examined clinically important reduction in UI episode frequency for women with predominant urgency UI.</p>

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Methods	<p>In the comparative data analysis such as comparing drugs and behavior, was baseline severity taken into account? how was it corrected for especially as regards pharmacology?</p> <p>how were differing inclusion/exclusion criteria across studies accounted for? I think (.....I am not a statistician) that p. 11-12 attempt to explain these corrections however, I am not sure. Does such a "random effects model"/metanalysis paradigm allow corrections between such disparate populations that are enrolled in drug studies vs. PFMT studies? how does it account for patient motivation, etc.? were these studies and analysis corrected for inclusion/exclusion criteria, severity of UI, types of UI, age, co-morbidities, prolapse and other selection factors/confounding variables? is this REALLY possible??</p>	<p>We analyzed the role of baseline severity: 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.</p> <p>Three secondary data analyses of drug trials examined clinical outcomes among subgroups with different baseline frequency of UI. 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.</p> <p>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). 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. 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. 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. In contrast, trospium was better than placebo at resolving UI only in subjects with fewer than five UI episodes/day. Trospium did not resolve UI in subgroups with more than 5 episodes of UI /day.</p> <p>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).</p> <p>We followed consensus recommendations for quantitative analysis of evidence and used random effects model to analyze the results from randomized head-to-head trials.</p> <p>First, randomization provides equal distribution of all factors among treatment groups. Thus estimates are valid. Second, we avoided indirect comparisons because of clinical diversity across the studies and variability in baseline rates. We incorporated baseline rates in meta-regression analysis when possible. Third, random effects models take into account differences in treatment effects across studies.</p>
Peer Reviewer #5	Methods	<p>The methods are well stated, including the inclusion and exclusion criteria and statistical methods, which are appropriate.</p>	<p>Thank you.</p>

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Commentator & Affiliation	Section	Comment	Response
AUA	Methods	<p>Prioritization of data: How are data prioritized and weighed?</p> <p>"Potential for bias": How is this determined? For example is a blinded, randomized placebo controlled trial given less weight because it was funded by pharma?, even if an FDA submission?</p> <p>The methods of grading the evidence must be more clearly defined. This is an area where significant bias can be introduced.</p>	<p>We clarified prioritizing patient-centered outcomes.</p> <p>We clarified: "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."</p> <p>We clarified: "We evaluated studies for question 1 with predefined criteria for assessing quality of the diagnostic accuracy studies. 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. We examined sponsorship and conflict of interest but did not downgrade quality using this information. We incorporated quality in synthesis of evidence conducting meta-regression, subgroup and sensitivity analysis for each quality criteria rather than overall quality score."</p> <p>We clarified definitions of risk of bias. "Well designed RCTs are believed to have 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."</p> <p>We clarified domains to judge strength of evidence: "We assessed strength of evidence and judged it according to the domains of risk of bias, consistency, directness, and precision for each major outcome. We judged with high confidence that the evidence reflects the true effect when we found direct consistent evidence from several well designed RCTs with low risk of bias. Significant dose response association or large magnitude of the treatment effects increase level of evidence. We defined insufficient evidence when a single study examined treatment effects or associations."</p>

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Published Online: April 2012

Commentator & Affiliation	Section	Comment	Response
Mary Ann Forciea, MD	Methods	Clear. I am not sure where a brief discussion of selection bias in populations might be introduced. Results on women recruited from speciality practices (gyn or urology) may not be the same as data from primary care offices. I do not see a breakdown table which reports what percentage of papers were based on women recruited in primary care.	We analyzed recruitment across different settings. Available information was not sufficient to conclude differences in the results of the studies among specialized versus ambulatory care settings. We revised the discussion: "Nonsurgical treatments included in this review are applicable to ambulatory care settings. Appropriately trained continence nurses and physical therapists can provide high quality care. Women with UI were satisfied with care provided by continence nurses. A large cross-sectional community postal survey of women with UI in France, Germany, Spain, and the UK found that many women actually prefer to be treated for UI in ambulatory care settings despite easy access to specialized services. Adherence to evidence-based recommendations by ambulatory care providers is not satisfactory and should be improved."
Nancy Kolb, MSN, RN	Methods	Page 8-Chapter 2, Methods Inclusion criteria: Studies that examined eligible outcomes of UI (total, mixed, stress, urgency), quality of life in women with UI, and harms of the treatments Then why were studies listed in the appendix excluded from the review with the reason that they did not compare two interventions? Drug adverse events were taken from case reports and observational studies, yet case reports were not used for effectiveness data. This is a double standard and poor methodology.	We clarified inclusion of non RCTs when they provided adjusted estimated of treatments' effects or provided information about patient outcomes not available in RCTs; please see responses above. We revised the report adding nonrandomized studies about PTNS.

Commentator & Affiliation	Section	Comment	Response
Nancy Kolb, MSN, RN	Methods	<p>Page 19</p> <p>Women only consider treatment a success when there is a greater than 70% of urinary incontinence episodes, per the pooled results from a study of 4 RCTs of women with predominant SUI. However, according to p19, this was only determined in studies about SUI, and “no studies examined clinically important reduction in UI episode frequency in women with predominant urgency UI.” However, this 70% reduction number is applied to all interventions, even those not indicated for SUI (like PTNS). Again, this reference created a faulty basis on which to draw conclusions regarding the success of a UI intervention.</p> <p>The clinical standard for symptom reduction is 50%, not 70%. This is too high. Even modest decreases in voiding symptoms can yield high improvements in quality of life measures that are clinically meaningful for patients.</p>	<p>We clarified inclusion of non RCTs when they provided adjusted estimated of treatments’ effects or provided information about patient outcomes not available in RCTs; please see responses above.</p> <p>We revised the report adding nonrandomized studies about PTNS.</p> <p>We revised the section about clinically important reduction in UI frequency.</p> <p>We revised the report adding information about PTNS.</p>
Peer Reviewer #1	Results	Page 18, line 7: Clarify here whether you mean drugs not approved by FDA or drugs not indicated to treat UI by the FDA.	We clarified that we excluded the drugs not available in the United States.
Peer Reviewer #1	Results	Page ES-6, line 49: It seems a curious omission that neither systemic estrogens nor SERMs were assessed.	<p>Stakeholders recommended reviewing patient-centered outcomes and interventions most relevant for ambulatory care and not yet systematically evaluated. Stakeholders also recommended reviewing nonsurgical interventions relevant to women with refractory UI. Comprehensive information about all nonsurgical treatment choices can lead to evidence based referral practices for women with refractory UI.</p> <p>We included the drugs available in the United States for predominant stress UI (topical estrogens and antidepressants). We excluded systemic estrogens and selective estrogen receptor modulators that failed to prevent or improve UI.</p>
Peer Reviewer #1	Results	Page ES-9: I’m confused about why the rate of continence is not the same as the cases of continence achieved per 1000 women. This distinction should be better explained in Methods.	We clarified that we calculated the number of attributable to active treatment events per 1000 treated multiplying absolute risk difference by 1000. These estimates reflect absolute risk differences in the rates of the outcomes in active vs. control groups.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Results	Table ES5: As you did in table ES2, insert references for studies in the table.	We inserted the reference in the table in the text of the report. We did not include all reference in the ES due to restrictions in the number of the references in the posted documents.
Peer Reviewer #2	Results	Overall, the amount of detail presented in the results section was appropriate. Studies were clearly described in the accompanying tables and overall, findings in the tables were consistent with those presented in the text. I believe that all relevant studies were included.	Thank you.
Peer Reviewer #2	Results	I think that statements that appear throughout the document that women consider treatment successful when UI episodes are reduced by 70% or more needs more support than references 213 (all subjects in this study had SUI and percent reductions in incontinent episodes were compared to mean changes in scores on the I-QOL questionnaire, a UI-specific quality of life measure) and 424 (which does not, as far as I can see, address the percent reduction in UI that women consider important). Adding reference 603 (Burgio et al, 2006 which included women with both urgency and stress UI) would strengthen this assertion.	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. The authors examined the relationship between relative reduction in UI episode frequency and meaningful improvement for women in the Incontinence Quality of Life questionnaire. Women with daily stress UI perceived important clinical benefit at reductions of approximately 50% and important incremental clinical value at reductions of 75% and 90–100%. The study concluded that women noticed improvement in quality of life when UI episode frequency was reduced by more than 70 percent. 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. Quality of life impact was similar for stress UI episode reductions of >40% to 70%. Women with persistent urge, stress, or mixed urinary incontinence reported reduction in UI episodes using voiding diaries and satisfaction with treatment using Global Perception of Improvement and Incontinence Impact Questionnaire. More than 60% of women reported complete treatment satisfaction when they experienced more than 70% reduction of UI episodes No studies examined clinically important reduction in UI episode frequency for women with predominant urgency UI.
Peer Reviewer #2	Results	The positive likelihood ratio for the diagnostic value of the pad test compared to multichannel urodynamics presented for detrusor overactivity on page 56 of 960 (line 56) is 1.7; in Table F18 it is listed as 1.555 (the CI is the same in both places).	Correct number is 1.56. We made this correction.
Peer Reviewer #2	Results	On page 57 (line 40) the sample size for study 174 is listed as 488 while in Table 3 is it listed as 488 in one row (urodynamic stress UI) and 388 in the next row (detrusor overactivity). Is this correct?	Both numbers should be 488. We corrected this typo.

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Results	On page 57 (line 40) the sample size for study 174 is listed as 488 while in Table 3 is it listed as 488 in one row (urodynamic stress UI) and 388 in the next row (detrusor overactivity). Is this correct? The positive predictive values for urodynamic stress UI reported for reference 170 on page 58 (90.2%) and in table 3 (98%) are not the same. In the text it sounds like the sample size in this study was 1,455 while in table 3 it is listed as 173. Is there a reason for this large discrepancy?	Although the sample size is 1455, only 184 received urodynamic study in which 173 data are interpretable. There is some data interpreting issue: The abstract stated: "The clinical algorithm had a positive predictive value of 90.2% for urodynamic SUI with or without detrusor overactivity and 76.9% for urodynamic SUI only (pure urodynamic SUI). The positive predictive value for the condition of pure SUI was 85.0%, while for the condition of SUI in pure and mixed forms the positive predictive value was 98.3%." The authors argued that when UD study did not demonstrate DO and SUI they classified as patients as having SUI. Therefore, the PPV increased from 0.90 to 0.98. We reported both data.
Peer Reviewer #2	Results	On page 59 (lines 10 and 11) it states that "Urge symptoms accurately diagnosed urodynamic urgency UI in 69 percent of women." In Figure 2, it looks like the accuracy is 66%. The corresponding numbers reported in the text and tables need to be checked for consistency and if they are different to be sure the discrepancy is accurate.	We corrected to: "Urge symptoms accurately diagnosed urodynamic urgency UI in 66 percent of women." We rechecked accuracy of the numbers in the text and the tables.
Peer Reviewer #2	Results	Page 150: For the key findings that women with stress UI can achieve continence with PFMT and urgency UI can achieve continence with PFMT combined with bladder training and/or electrical stimulation, I think that the supporting evidence should presented more clearly in the text or table (by type of UI). One suggestion is to list the specific types of UI included in the studies in the last column in Table 87 and 88.	We clarified the type of predominant UI in the text and the tables. We examined the association between age, race, obesity, comorbidities, type of UI, baseline severity of UI, and response to prior treatments with clinical outcomes as reported by the authors of the original studies. We synthesized the evidence by the baseline type of UI as pure or predominant stress, pure or predominant urgency, and mixed UI. We compare clinical outcomes by the type of UI within each study and across the studies. We evaluated inclusion and exclusion criteria and baseline characteristics of the subject to determine whether all or a proportion of the subjects had mixed UI. We then conducted quantitative meta-regression and subgroup analysis to determine treatment effects by baseline type of UI.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Results	Question 1 1) Overall the data is clear and well presented however I found the tables (Table 3 and similar tables in the ES and appendix) a bit confusing particularly the columns labeled Method Index/Standard. It would be easier to view and interpret if this column was divided into two separate columns labeled "Test" and "Reference Standard" or something similar. Additionally, many acronyms including UD, BND, BIDI are not defined in the table legends.	We added a new column in Table ES2. We spelled out all abbreviations in Table 3.
Peer Reviewer #3	Results	The finding on page 16, line 42-44 "questionnaires had little diagnostic value for stress and urgency UI" seems inconsistent with the conclusion (page 109, line 47-48) that diagnosis of UI in primary care setting can be based on ..validated scales."	We clarified that the studies defined urodynamics as a reference standard. Thus index methods had low diagnostic value for urodynamic diagnosis of pure stress UI or detrusor overactivity. Urodynamic diagnosis at the same time was not associated with better prediction of clinical outcomes. Thus clinical diagnosis and monitoring of treatment effectiveness can be made using validated tools.
Peer Reviewer #3	Results	Section on Minimal clinically important differences in diagnostic tools to monitor effectiveness of treatments (page 18-19) - see general comment #4 above.	We revised the report. 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 stress UI perceived important clinical benefit at reductions of approximately 50% and important incremental clinical value at reductions of 75% and 90–100%. Women reported improved quality of life and a clinical success only when they experienced a greater than 70 percent reduction in urinary episode frequency assessed by a voiding diary. 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). Quality of life impact was similar for stress UI episode reductions of >40% to >70%. Women with persistent urge, stress, or mixed UI reported reduction in UI episodes using voiding diaries and satisfaction with treatment using Global Perception of Improvement and Incontinence Impact Questionnaire. More than 60 percent of women reported complete treatment satisfaction when they experienced more than 70% reduction of UI episodes.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Results	Table 4 - presenting Likelihood ratios rather than PPV by age group seems a more appropriate way to present this relationship. (also PPV + and PPV - is confusing as most people are familiar w/ PPV meaning positive predictive value)	We presented likelihood ratios in the executive summary and Table 3. We present positive and negative predictive values (PPV) using Bayesian approach with population prevalence: "The predictive values in primary settings depend on prevalence of UI in community dwelling women. 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."
Peer Reviewer #3	Results	Table 5 - nice summary; well presented. For IQOL change MID to 50% or more for incontinence episode frequency (see general comment #4) Question 2	We made the suggested change.
Peer Reviewer #3	Results	Question 2. Throughout this section, the authors should clearly indicate in the text which UI type a given study applies to. I would recommend separating this question into sections: (1) Medications for SUI or SUI predominant and (2) Meds for Urge UI or urge predominant to avoid this confusion. Also, as noted above, studies should not be pooled across UI subtypes.	We could distinguish baseline UI type only if the authors clearly indicated exclusion of other types of UI from the sample. We report drug studies for stress (estrogen and duloxetine) and for urgency UI. The majority of non drug studies included women with mixed UI or did not clearly indicate that all women had only pure UI. The same treatments were tested in predominant stress or urgency UI. We conducted subgroup analysis and meta-regression by the presence of mixed UI. We report differences in estimates by the type of UI (pure stress, pure urgency or mixed) when detected. Please see previous responses. We revised the report clarifying the type of UI.
Peer Reviewer #3	Results	The evaluation of the clinical effectiveness of estrogen therapy is incomplete without including studies of oral estrogen preparations. Several RCTs evaluating oral estrogen preparations exist (one example is Fantl et al, Obstet Gynecol 1996; 88:745-8) and all fail to show efficacy. Moreover, the exclusion of the results from the HERS and WHI studies that demonstrate a worsening of UI with systemic estrogens is a substantial oversight.	We agree. We clarified in Introduction: Systemic estrogens have been associated with increased risk of UI. Selective estrogen receptor modulators did not demonstrate consistent benefits on prevention of UI. After discussion with key informants and TEP members estrogen treatments were excluded from our review. We clarified in the Methods section: We excluded systemic estrogens and selective estrogen receptor modulators that failed to prevent or improve UI. This decision was made a priori and was reflected in the posted protocol.
Peer Reviewer #3	Results	As noted previously, botox and resiniferatoxin should not be included in this report and would be better suited for a systematic review on treatments for refractory or 2nd line UI treatments	We included f Botox and resiniferatoxin as treatment options for refractory UI.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Results	The authors use the term "effectiveness" too liberally throughout the report. The vast majority of the studies included in Question 2 are FDA phase 3 placebo controlled studies - "efficacy" studies. There are very few, if any studies that would meet the commonly understood definition for an "effectiveness" study. The authors should change the headings in this section (and correspondingly the language in the text) to "Clinical Efficacy of...."	We revised subheadings following your recommendations.
Peer Reviewer #3	Results	Reporting outcomes as "cure" and "improvement in UI" and "harms" with NNT and NNH is an excellent way to present this data.	Thank you.
Peer Reviewer #3	Results	Tables 9 and 10 should indicate in their title that they apply to pharmacological treatments for "Urge" UI, not just UI.	We made suggested changes.
Peer Reviewer #3	Results	Figure 10. Treatment persistence over what period of time?	We revised adding 1 year of followup.
Peer Reviewer #3	Results	Question 3 As noted previously, the authors fail to adequately distinguish the UI type that the studies apply to and appear to inappropriately pool studies across UI types throughout this section. It is imperative that when describing a study or group of studies that they clearly distinguish in the text who the study population is (Urge, Urge predominant, Stress, Stress predominant, Mixed, Any UI) and report results by UI type. They may want to consider separating this question into sections as described for meds above (#6) for clarity.	We could distinguish baseline UI type only if the authors clearly indicated exclusion of other types of UI from the sample. We report drug studies for stress (estrogen and duloxetine) and for urgency UI. The majority of nondrug studies included women with mixed UI or did not clearly indicate that all women had only pure UI. The same treatments were tested in predominant stress or urgency UI. We conducted subgroup analysis and meta-regression by the presence of mixed UI. We reported differences in estimates by the type of UI (pure stress, pure urgency or mixed) when detected. Please see previous responses. We revised the report clarifying the type of UI.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Results	Tables 12- 16 need a column that describes the UI type of the study populations; similarly in Tables in the appendix, tables F83 and beyond, the UI type of the study population needs to be clearly defined for each population and pooling only occur across similar UI types. Listing "Mixed UI included" y/n is not by itself adequate.	We revised the tables adding the predominant type of UI when it was possible. We did pool the studies by the type of UI as pure stress, pure urgency, mixed, not reported. We reported the differences in the results by the type UI when we could find them.
Peer Reviewer #3	Results	As noted previously, percutaneous nerve stimulation, bulking agent injection and radiofrequency ablation are not first line UI treatments and not available in the primary care setting and should not be included in this report. Moreover the section on bulking agents appears to be missing several studies evaluating Contigen.	We included percutaneous nerve stimulation as a feasible treatment option for women with refractory urgency UI. We did not review radiofrequency ablation. We did include bulking agents because it is a feasible nonsurgical treatment option for women with refractory stress UI. We conducted additional searches using Contigen as a key word, identified three randomized trials we did not have, but excluded them because they did not report incontinence outcomes. We clarified in limitations that radiofrequency ablation and surgical treatments were beyond our scope.
Peer Reviewer #4	Results	on page ES-6, it is stated that the magnitude of the effect of drugs on continence and improving UI was "low". what was this subjective judgement based on? was it determined a priori ? if so, what were (are) the levels upon which this judgement was based? what was/is the threshold for a judgement of 'good'? Please provide the reference criteria/points/values for such a subjective assessment. If the authors do not have such a categorization a priori, then remove the value judgement statement.	We clarified: "We evaluated strength of the association defining a priori large effect when relative risk was >2 or <0.5) and very large effect when relative risk was >5 <0.2. We defined low magnitude of the effect when relative risk was significant but <2."
Peer Reviewer #4	Results	Reference 708 did not use a true injectable saline placebo as an injection. please correct this on p.93.	We revised: "Clinical outcomes after bulking agents compared to placebo or sham treatments were reported in two RCTs of 241 women."
Peer Reviewer #4	Results	There are many uncontrolled bulking agent studies (approx 50) and several RCT's vs. collagen. Why were these not included in this analysis on p. 92-93 and only 7 studies included on p. 97? There is data on collagen, coaptite, tegress, duraspHERE, macropLASTIQUE, teflon and others.	We included uncontrolled studies when the data from RCTs were not available or uncontrolled studies included important harms in treated women with UI. We also excluded studies of bulking agents that did not report clinical outcomes.

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Results	The authors found that specialized health care providers provided no benefit over usual care (p. ES-8) based on 3 studies. Other studies have arrived at exactly the opposite conclusion. how is this possible?	We focused on the highest quality data from RCTs that included at least 75 percent of community dwelling women. The studies of specialized care for men with UI related to prostate diseases were not included.
Peer Reviewer #5	Results	The results section is complete with an appropriate amount of detail. The review seems to be both appropriately targeted and comprehensive	Thank you.
AUA	Results	page 14: Does it make a difference if a patient has UDS proven -DI or not?	We clarified that evidence was not sufficient to draw valid conclusions that treatment effects differ by the urodynamic diagnosis of DO.
AUA	Results	Page 14 – 3 rd paragraph - We are told that studies included fewer than 100 women yet on page 8 we are told that case series with fewer than 100 subjects were excluded. Clarification is needed.	We clarified: “We included observational studies with adjusted treatment estimates or when the provided evidence of treatment effects not available in the RCT.”

Commentator & Affiliation	Section	Comment	Response
AUA	Results	<p>Page 16: “Women with symptoms of stress UI had a minimal likelihood of a clinical diagnosis of stress UI.” But you report that the pooled sensitivity was 88% (95% CI 68;96%). Why is this minimal likelihood? Sensitivity of 88% seems pretty good for a pure symptom to correlate with a diagnosis. We would have greater issue with the lack of syllogism here. The clinical diagnosis of SUI is most often based on symptoms; it is begging the question perhaps? Similarly on page 18 where you state the “majority of women without symptoms of UI did not have the clinical diagnosis of UI,” of course not. They didn’t have the symptoms inherent to the diagnosis.</p> <p>The utility of UDS will be answered very soon for the SUI patient undergoing surgery. We understand that it is difficult to time this evidence report with future literature to be published, but the huge VALUE study should be out soon. Is this report coming out too soon for some of the important federally funded multi-site studies on SUI, the role of UDS, etc? IS there a mechanism to ensure that this report is timely at publication? An addendum, perhaps?</p>	<p>We concluded diagnostic value based on likelihood ratios: Clinical interpretations of likelihood ratios:</p> <p>Likelihood Interpretation Ratio</p> <p>>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</p> <p>We revised the section about association between UDS diagnosis and treatment outcome. We revised the discussion pointing out the ongoing studies will shed light on such association; please see responses above.</p>
AUA	Results	Cost will be increasingly important in the analyses, but is absent here. We hope that support can be obtained for these studies in future work.	We clarified that our analysis of patient outcomes should be used for cost effectiveness analysis that was beyond our scope. Please see responses above.

Commentator & Affiliation	Section	Comment	Response
AUA	Results	Page 17 – Diagnostic values of ultrasound vs. urodynamics as a reference standard. This section should be removed. These 5 studies of 540 women were performed from 1988 to 1997. These tests are not used in common clinical practice in the evaluation of the incontinent woman in North America today. Once this paragraph is removed all mention of ultrasound as a diagnostic test should be removed from the document except when discussing measurement of post void residual.	We analyzed diagnostic value of ultrasound vs. UDS because ultrasound examination is a feasible and accurate test applicable for ambulatory settings.
AUA	Results	Page 88-9 – There is a discrepancy regarding Percutaneous Tibial Nerve Stimulation. Throughout the document it says that there is insufficient evidence to conclude positive effects for tibial nerve stimulation on continence or improved UI in adults with overactive bladder yet in the two RCTs examined urinary incontinence was improved. Page 92-93 – In this section of bulking agents conclusions are drawn from 2 studies that examined transurethral radiofrequency energy collagen remodeling which is not a bulking agent and the periurethral injection of autologous fat which is not a commonly used method of bulking agent in North America.	We revised the evidence about Percutaneous Tibial Nerve Stimulation with an updated literature search, new studies, and comparative effectiveness between PTNS with bladder training vs. bladder training alone. We clarified how we formulated a list of eligible interventions, please see responses above. We included the drugs available in the United States for predominant stress UI (topical estrogens and antidepressants). We included the drug approved by the FDA for overactive bladder. We excluded systemic estrogens and selective estrogen receptor modulators that failed to prevent or improve UI. We included bulking agents and neurotoxins to review all nonsurgical treatment options for women with refractory UI.
AUGA	Results	Questions about whether these recommendations translate to the "Primary care setting"	We discussed applicability of the results to ambulatory care settings. Our systematic review will help clinicians, consumers, and policymakers make clinical recommendations and informed decisions based on synthesized evidence and other relevant factors.
Mary Ann Forciea, MD	Results	The relatively low specificity of historical information will likely be disappointing to clinicians. The report seems to favor questionnaires over time spent talking with patients. Still, the data is what it is. The comparative efficacy data is well presented and highly likely to be useful.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Nancy Kolb, MSN, RN	Results	<p>Page 88-89-Chapter 3. Results. Question 3</p> <p>The investigators have included the same study twice. The SUMiT study is included as the publication in the Journal of Urology, as well as a paper of the same study presented at ICS. Thus, some of the information is misleading.</p> <p>“Percutaneous tibial nerve stimulation improved UI.” “Evidence was insufficient to conclude positive effects from PTNS on continence or improved UI in adults with OAB.” These two statements seem inherently contradictory. The first statement alone provides acknowledgement regarding the clinical effectiveness of PTNS.</p> <p>“No studies examined continence after PTNS in adults with UI.” This is a vague statement. As the indication of PTNS is not for UI alone, of course it would not be the only outcome evaluated.</p> <p>A long-term extension of the OrBIT study, a RCT comparing PTNS to tolterodine, with 12 month follow up and data on the therapeutic effect of PTNS was not included.</p>	<p>We mentioned in the text all publications including duplicative publications of the same study. Pooled analysis included one estimate from each study. We conducted a separated search for all studies that examined PTNS and revised the report with updated information.</p> <p>We revised the report including all studies of percutaneous tibial nerve stimulation.</p>
Nancy Kolb, MSN, RN	Results	<p>Page 96-97-Chapter 3. Results. Question 3</p> <p>Lists the Finazzi study-“Comparative effectiveness of weekly versus three times per week posterior tibial nerve stimulation (note, misspelled in the paper) resulted in the same outcomes in 35 subjects with urgency UI who failed oxybutynin treatment.” This study demonstrates that PTNS is effective in decreasing voiding symptoms whether it is used weekly or more often.</p> <p>Page 99-Chapter 3. Results. Question 3</p> <p>“Tolterodine vs. PTNS: Evidence from one study was insufficient to conclude</p>	<p>We synthesized evidence to answer our research question irrespective of the primary outcomes or the goals to show noninferiority of the treatments from original studies.</p> <p>We revised the report adding all studies of PTNS; please see responses above.</p> <p>We did not evaluate standards of care or treatment utilization including drugs or nondrug therapies.</p> <p>We could not analyze the order of available treatments.</p>

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Published Online: April 2012

Commentator & Affiliation	Section	Comment	Response
		<p>better effectiveness for PTNS compared to Tolterodine.” “...Patient assessment and investigator assessment of improvement or cure were greater with stimulation than with Tolterodine.” Once again, these statements are contradictory. Also, the objective of the study was not to show that one treatment was better; the goal was to demonstrate comparable efficacy, which the study does.</p> <p>Page 111-Chapter 4</p> <p>Effect of non-pharmacologic treatments is “large.” This statement should include PTNS, as it is a non-pharmacologic treatment. This contradicts the earlier conclusions stated about PTNS. Page 112-Chapter 4</p> <p>“Non-pharmacological treatments offer a better balance between benefits and adverse effects than do drugs.” Again, PTNS is a non-pharmacological treatment. This contradicts the conclusion on page 88.</p> <p>“...better drugs are needed. Few of the currently used medications are sustained for even a year and fewer still are very effective.”</p> <p>Drugs are still considered the standard of care and are widely used in clinical practice.</p> <p>“First treatment choice, therefore, might be based on known benefits and harms with non pharma and drug treatments, along with patient preferences.” We know the benefits of PTNS, as listed on page 88, it “improves UI” with no serious safety considerations. This treatment is well-tolerated by patients. Do the investigators conclude that it should be a first choice treatment?</p>	

Commentator & Affiliation	Section	Comment	Response
Elizabeth Loughren	Results	Was this recent RCT reviewed for inclusion for PTNS? It fell into the search dates you provided in the abstract of the systematic review (last search December, 2010): Finazzi-Agro Et al. Percutaneous tibial nerve stimulation effects on detrusor overactivity incontinence are not due to a placebo effect: A randomized, double-blind, placebo controlled trial. J Urol, 184. Vol. 184, 2001-2006, November 2010	We revised the report to include all studies with PTNS; please review responses above.
Kristine Zinkgraf	Results	This review leaves patients who are intolerant to drugs with few, if any, options. Patients who fail behavioral therapy and who cannot tolerate, or who experience no improvement from drugs may be left with no options, especially if payers use this review as a mechanism to deny coverage of proven therapies. The review chose a single outcome measure, continence, to measure improvement in quality of life. Patients who have suffered with severe urgency & frequency, but no incontinence, have experienced significant improvement in QOL after treatment with tibial nerve stimulation. Validated tools such as the UDI-6, which evaluate quality of life, are the mainstay in measuring outcomes in pelvic floor disorders. Our Pelvic Center has found that percutaneous tibial nerve stimulation serves a purpose in the treatment algorithm. We offer it only after behavior modification and pharmacotherapy have been tried. It is a less costly alternative to direct stimulation sacral nerve modulation.	We revised the report emphasizing the available evidence about quality of life. We added information about PTNS; please see responses above.
Peer Reviewer #1	Discussion/ Conclusion	Page ES-9, line 56: State whether your results are in agreement with recent AHRQ report, reference 52.	We clarified that our findings are in agreement with a previously published AHRQ report. In addition, our report offers a comprehensive analysis of patient-centered outcomes including continence, improvement in UI, and harms with nonsurgical treatments available in the United States for female UI.

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Published Online: April 2012

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Discussion/ Conclusion	Table ES3, second row: This seems an odd statement: "Women in primary care settings have been diagnosed with UI..." Does this mean that they "can be" or that they can accurately be? In 3rd row, "have been" again seems an odd choice of words.	We revised this sentence: "Women in ambulatory care settings can be accurately 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."
Peer Reviewer #2	Discussion/ Conclusion	The major findings are clearly stated. Limitations are appropriately acknowledged. Future directions for research presented in the text and Table 19.	Thank you.
Peer Reviewer #2	Discussion/ Conclusion	The first recommendation for "What constitutes an adequate diagnostic evaluation for women in the primary care setting on which to base treatment of urinary incontinence (UI)" is to "Examine the association between physiological measures using bladder ultrasound and frequency and severity of self-reported stress and urgency UI." The rationale for this recommendation is not clear. Is there a reason you would expect bladder ultrasound measures to be related to the severity of stress and urge UI?	We excluded this recommendation.
Peer Reviewer #3	Discussion/ Conclusion	As noted previously, the key finding on page 109, line 19 should be substantially altered or eliminated as should similar statements on page 110 line 45-47, page 112 line 34-5.	We revised key findings following your recommendations.
Peer Reviewer #3	Discussion/ Conclusion	As noted on page 110, line 23-24 "evaluations of women who report UI symptoms begin with the exclusion of UTI, pelvic organ prolapse and poor bladder emptying." Given this, Salient finding (1) on page 109, line 46 should include a urinalysis, physical examination in addition to those listed; adding "post-void residual volume determination" also seems appropriate.	We revised: "Evaluations of women who report UI symptoms begin with, physical examination, exclusion of urinary tract infection using urinalysis, pelvic organ prolapse, poor bladder emptying, and post-void residual volume determination."

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Discussion/ Conclusion	Salient finding (6) page 110, line 4 is inappropriate - see general comment #5. A more appropriate finding would be "Evidence was insufficient to draw valid conclusions about comparative effectiveness and safety of nonpharmacological treatments when compared to drugs or combined modalities" or something similar	We revised: (6) Nonpharmacological treatments offer a large magnitude of benefit, and adverse effects are uncommon. Drugs offer a low magnitude of benefit and adverse effects are common. Evidence from few head-to-head RCTS was insufficient to draw valid conclusions about comparative effectiveness and safety of nonpharmacological treatments when compared to drugs or combined modalities.
Peer Reviewer #4	Discussion/ Conclusion	This paper did not fully address or review urodynamics and outcomes following invasive therapy. Therefore the statement (ES-9) in the Discussion regarding their utility in patients undergoing invasive therapy is really irrelevant and unsubstantiated (though it may be true....).	We revised this section pointing out that women with UI who failed conservative treatments may benefit from urodynamic testing.
Peer Reviewer #4	Discussion/ Conclusion	Why should policy makers consider patient centered outcomes (p ES-10)? Did this paper make a case for such a consideration? No, it did not. Again, though the statement may be true, it is not supported by the data in this paper. It should be removed.	The Effective Health Care program focuses on patient centered outcomes over physiologic intermediate outcomes that are easier to quantify. We clarified: "Policymakers should consider patient-centered outcomes when making regulatory decisions. Patient-centered outcomes research gives patients and clinicians the information they need for effective informed decisions about the provision of health care services."
Peer Reviewer #4	Discussion/ Conclusion	There are MANY limitations of this data set other than the 4 lines on page ES-10. See other comments. Any discussion of cost and resources, including those attributable to the patient, or healthcare system were excluded. Please include these as an important factor in deciding whether to initiate treatment and in choosing between treatments.	Evidence-based reports do not analyze cost-effectiveness of treatments. Cost-effectiveness analyses 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. We recommended that comparative effectiveness, safety, and adherence to treatments should be incorporated into cost-effectiveness analyses.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Discussion/ Conclusion	A significant limitation which was not discussed is that, when comparing interventions such as drugs to behavioral therapy, powerful biases are introduced. Selection bias, for example, is introduced in studies enrolling patients for PFMT and/or behavioral modification. These are highly motivated patients and likely represent a different patient population from those who enroll in drug studies. It is expected that these highly motivated individuals will do well.....and they generally do!!!	We analyzed head-to-head randomized trials that examined drugs, nonpharmacological treatments, and combined modalities. We avoided indirect comparisons between drugs and nondrug treatments. We revised the discussion: "Comparative effectiveness of drug versus nonpharmacological treatments was examined in few head-to-head RCTs. Direct evidence was insufficient to draw valid conclusions that combined modalities result in greater benefits than monotherapy. Existing guidelines recommend PFMT as the first treatment choice for women with stress UI and bladder training for women with urgency UI but do not provide evidence based recommendations about combined therapy including drugs. Other guidelines list many treatment options, including electrical intravaginal stimulation and percutaneous tibial nerve stimulation, but do not provide evidence based recommendation about first therapy options or combined modalities. Existing guidelines may provide individualized treatment recommendations based on age or predominant type of UI but do not address baseline severity of UI or comorbidities."
Peer Reviewer #4	Discussion/ Conclusion	REgarding key question 1: it is preposterous to assume that any one instrument, symptom or test would have accuracy in the diagnosis of the type of UI. Though the analysis used in this paper was a good academic exercise, knowing that the reference standard (UDS) is VERY flawed, the authors were destined to find that any of the other instruments were going to be worse. As clinicians we utilize several aspects of the history, PE, and other assorted studies as indicated to provide a diagnosis of the type of UI. Such an approach should be emphasized in the Discussion section: the synthesis of multiple pieces of interrelated data to arrive at a diagnosis.	We revised the discussion to reflect that considering the multifactorial syndromic nature of UI, any one instrument, symptom, or test would not have accuracy in the diagnosis of the type of UI. Clinicians utilize several aspects of the history, pelvic exam, and other assorted studies synthesizing multiple pieces of interrelated data to arrive at a diagnosis of the type and severity of UI.
Peer Reviewer #4	Discussion/ Conclusion	The lack of data for Botulinum toxin and PTNS should be attributed to the relative newness of these therapies. This should be mentioned in the Discussion.	We added more studies that examined percutaneous tibial nerve stimulation.
Peer Reviewer #5	Discussion/ Conclusion	The implications are clearly stated, as are the limitations. I do not find any important omissions. Areas for future research are clearly identified and presented in table 19 and summarized in the text.	Thank you.

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Published Online: April 2012

Commentator & Affiliation	Section	Comment	Response
AUA	Discussion/ Conclusion	Page 109 - UI Diagnosis: Vaginal and transrectal ultrasound may have been shown in the past to be useful for the diagnosis of Urodynamic SUI but these are not methods that are commonly used in 2011 in the US. The two references cited here are from 1988 and these studies have not been replicated. Our concern with this comment in the Discussion section is that primary care providers are going to send patients for an ultrasound in an effort to make a diagnosis of SUI. This also links into future research recommendations in the how an ultrasound is done (perineal, transvaginal, transrectal) and who does it (radiologist, urologist) will need to be examined if this is to be addressed.	We revised the introduction, discussion, and future research needs following your recommendations. Please see responses above.
AUA	Discussion/ Conclusion	page 110: What is self reported UI during a clinical examination? Need more specificity as to how the data are captured and characterized. Future Research Recommendations. This document puts a lot of weight on the importance of a 70% reduction in incontinence episodes.	We clarified diagnostic methods for multifactorial syndrome of UI in real world settings. We revised the sections in the report with this cut off. 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. The authors examined the relationship between relative reduction in UI episode frequency and meaningful improvement for women in the Incontinence Quality of Life questionnaire. Women with daily stress UI perceived important clinical benefit at reductions of approximately 50% and important incremental clinical value at reductions of 75% and 90–100%. The study concluded that women noticed improvement in quality of life when UI episode frequency was reduced by more than 70 percent. 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. Quality of life impact was similar for stress UI episode reductions of >40% to 70%. Women with persistent urge, stress, or mixed urinary incontinence reported reduction in UI episodes using voiding diaries and satisfaction with treatment using Global Perception of Improvement and Incontinence Impact Questionnaire. More than 60% of women reported complete treatment satisfaction when they experienced more than 70% reduction of UI episodes No studies examined clinically important reduction in UI episode frequency for women with predominant urgency UI.

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Commentator & Affiliation	Section	Comment	Response
AUGA	Discussion/ Conclusion	Most of our comments and suggestions are also relevant to the Discussion section, including: Emphasize that this is a review of non-surgical treatment of urinary incontinence.	We made recommended revisions.
AUGA	Discussion/ Conclusion	Insufficient evidence to support the proposed definition of treatment success (>70% reduction in incontinence episodes)	We revised the section about clinically important differences in voiding diaries and other validated tools.
AUGA	Discussion/ Conclusion	Distinguishing between stress incontinence and urge incontinence/ overactive bladder	We revised the report distinguishing baseline types of UI.
AUGA	Discussion/ Conclusion	Apparent contradictions in the conclusions regarding the role of urodynamic testing	We clarified the role of UDS as flawed reference standard. We clarified that baseline urodynamic diagnosis was not associated with between outcomes.
AUGA	Discussion/ Conclusion	In sufficient evidence to recommend transvaginal estrogen	We do not make any recommendations about local estrogen.
AUGA	Discussion/ Conclusion	Recommendations to exclude from this document treatments that require surgical delivery (Botox, bulking agents).	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. According to the public comments we formulated a list of interventions eligible for this review. Stakeholders recommended reviewing patient-centered outcomes and the interventions most relevant for ambulatory care and not previously systematically reviewed. Stakeholders also recommended reviewing nonsurgical interventions that can be relevant to women with refractory UI. Comprehensive information about all nonsurgical treatment choices can lead to evidence based referral practices for women with refractory UI.
AUGA	Discussion/ Conclusion	Inclusion of pessary treatment as an option. In summary, we voice our strong support for the efforts of the AHRQ to bring attention to the important topic of the diagnosis and comparative effectiveness of non-surgical treatments for urinary incontinence in adult women. We appreciate the panel reviewing our comments and hope they prove instructive by allowing the final report to be both comprehensive and clearly focused on clinical outcomes relevant to both patients and their care providers.	We included all studies of pessaries we could find. Thank you.

Commentator & Affiliation	Section	Comment	Response
Mary Ann Forciea, MD	Discussion/Conclusion	Useful sections on directions for future research	Thank you.
Nancy Kolb, MSN, RN	Discussion/Conclusion	Page 117-118-Chapter 4. Discussion. Table 19 (Future Recommendations) Given the poor compliance with drugs, are long-term studies on drug adherence feasible? Comparative effectiveness studies should result in a report that has clinical significance in that it can be used in the step-by-step accepted algorithm of care for patients with urinary incontinence (Conservative therapy -> Pharmacological therapy -> Non-invasive treatments -> Minimally-invasive therapies -> Surgery). This one does not.	Long-term monitoring of harms with all treatments is feasible and moreover commonly accepted in the UK and other European countries. We did not intend creation “of step-by-step accepted algorithm,” clinical recommendations, or clinical guidelines.
Mary Ann Forciea, MD	Figures/Tables	Tables—exhaustive Figures—Forest plots well done and easy to understand	Thank you.
Peer Reviewer #2	References	For reference 144 (page 58 and table 3) the sample sizes and positive predictive value for urodynamic stress UI in the text [n=652 (line 8) and 95% (line 14)] and Table 3 [n=74 (page 22, line 23) and 97%] are not the same. Is this correct?	Reference 144 is based on 652 women of whom 74 have 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. 72 of 74 (97%) are SUI. Table 3 [n=74 and 97%] based on reference 144 seems correct. We corrected typo to 97%.
Elizabeth Loughren	References	Was this recent RCT reviewed for inclusion for PTNS? It fell into the search dates you provided in the abstract of the systematic review (last search December, 2010): Finazzi-Agro Et al. Percutaneous tibial nerve stimulation effects on detrusor overactivity incontinence are not due to a placebo effect: A randomized, double-blind, placebo controlled trial. J Urol, 184. Vol. 184, 2001-2006, November 2010	We updated our search and included all studies about PTNS; please see responses above.
Nancy Kolb, MSN, RN	Appendix	Page A-6 <ul style="list-style-type: none"> Uroplasty, Inc., the manufacturer of Urgent@PC, the only FDA cleared PTNS delivery system, was not contacted by the SRC for technical data. Page F-80, page F-427	We apologize. The SRC contacted pharmaceutical companies only. We revised all information about PTNS. We included all studies you recommended in the review for qualitative, not quantitative analysis. The NICE stated: “Current evidence on percutaneous posterior tibial nerve stimulation (PTNS) for overactive bladder (OAB) syndrome shows that it is efficacious in reducing symptoms in the short and medium term. There are no major safety concerns. Therefore the

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Published Online: April 2012

Commentator & Affiliation	Section	Comment	Response
		<ul style="list-style-type: none"> MacDiarmid et al. Inclusion and exclusion criteria for the OrBIT study were reported in the initial report by Peters et al. <p>Page F-84, page F-470</p> <ul style="list-style-type: none"> MacDiarmid OrBIT study should not be reviewed under non-pharmacologic treatment for SUI as this is not an indication for PTNS and SUI as a primary diagnosis was an exclusion criteria for entry into the study. <p>Page F-587</p> <ul style="list-style-type: none"> This reference should be excluded: Borawski KM, Foster RT, Webster GD, et al. Predicting implantation with a neuromodulator using two different test stimulation techniques: A prospective randomized study in urge incontinent women. <i>Neurourol Urodyn</i> 2007; 26(1): 14-8. It pertains to a test for a surgically implanted neurostimulator and is outside the stated scope of this study. <p>Additionally, only one NICE guideline, "Management of UI in Women," was referenced in this report. All NICE guidelines should be included or excluded equally. NICE guideline IPG362, "Percutaneous posterior tibial nerve stimulation for overactive bladder," presents a comprehensive literature review of PTNS. AHRQ's National Guideline Clearinghouse published a guideline in May 2010 "Recommendations for the Management of Urge Urinary Incontinence in Women" (NGC-7873) that rated PTNS data and clinical usefulness as "Grade B, evidence fair." It is apparent that these findings were not taken into consideration. We have also included a copy of both with</p>	<p>procedure may be used provided that normal arrangements are in place for clinical governance, consent and audit." We focused on urgency UI and concluded improvement in UI with this procedure.</p> <p>We revised the report to include all studies of PTNS.</p> <p>Clinical Effects of Percutaneous Tibial Nerve Stimulation</p> <p>Percutaneous tibial nerve stimulation improved UI in adults with OAB. Four RCTs examined clinical effects of percutaneous tibial nerve stimulation, including the Study of Urgent PC versus Sham Effectiveness in Treatment of Overactive Bladder Symptoms (SUMiT) trial and the Overactive Bladder Innovative Therapy Trial (OrBIT) (Appendix Table F108). The studies treated adults with either active stimulation with a current level of 0.5 to 9 mA at 20 Hz or sham stimulation.</p> <p>Continence</p> <p>No RCTs compared continence after percutaneous tibial nerve stimulation versus sham stimulation in adults with UI. Participants in OrBIT Trial reported 16-20 percent cure rates with 12 months of active stimulation. The study did not report cure rates with sham stimulation. Continence rates were 94 percent among women with predominant urgency UI and 91 percent in women with mixed UI in an uncontrolled trial. Continence did not differ with more frequent stimulation (three versus one time/week).</p> <p>Improvement in UI</p> <p>Percutaneous tibial nerve stimulation improved UI. Three women need to be treated with percutaneous tibial nerve stimulation to achieve improvement in one woman (Appendix Table F97). Improvement in UI was attributable to active treatment in 308 women per 1,000 treated (95% CI, 40 to 557). Participants in OrBIT Trial experienced 76-80 percent improvement rates with 12 months of active stimulation. Nonrandomized studies reported 63-64 percent success rate with active stimulation.</p> <p>Adverse Effects</p> <p>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. Treatment discontinuation did not differ with active versus sham stimulation. One patient did not complete the treatment because of aggravating pre-existing cardiac arrhythmia in an uncontrolled clinical trial of 39 subjects with voiding dysfunction.</p> <p>Tolterodine versus percutaneous tibial nerve stimulation</p> <p>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</p>

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Published Online: April 2012

Commentator & Affiliation	Section	Comment	Response
		<p>our comments.</p> <p>Stress UI and urgency UI, examined together in this report, are two very distinct diagnoses that should be considered separately. Studies that examined stress UI (i.e., most of the studies referenced for Electrical Stimulation including #383, 397-404) were extrapolated to draw conclusions about the outcomes for the intervention for all types of urinary incontinence.</p> <p>PTNS is medically necessary for the OAB patient who has <i>failed behavioral and pharmaceutical management</i>. The majority of patients in PTNS clinical trials had experienced OAB symptoms for at least 8 years. They had already tried, and failed, conservative measures. A category I CPT® code for PTNS was approved by the CPT® Editorial Panel and effective January 1, 2011. The CPT code process requires that the clinical efficacy of a procedure be well-established, documented in U.S. peer-reviewed literature, and supported as a legitimate treatment, in this case, by the American Urological Association.</p> <p>Medicare carriers and private payers may look to this report to guide coverage decisions. They need to be aware that this is NOT a technology assessment. PTNS is evaluated only through the lens of urinary incontinence in women, which is not the full indication for PTNS.</p>	<p>in 100 adults with urinary frequency (Appendix Table F153). Patient assessment and investigator assessment of improvement or cure were greater with stimulation than with tolterodine. Self-reported change in health-related quality of life score did not differ with stimulation versus drug treatment. Subjects reported worsening of the symptoms less often with stimulation than with the drug.</p>

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	General	The usefulness of this report is limited by the recent publication of the Hartman et al AHRQ report (i.e., much of the information has been presented in a similar format).	We explained differences in the scope between the report about treatments for OAB and our report. We clarified: "Standard UI treatment for women includes lifestyle changes, pelvic floor muscle training (PFMT), and surgical treatments for stress UI. In addition, several drugs have been approved for adults with overactive bladder with or without urgency UI. Clinical interventions to reduce the frequency of UI episodes in women have been extensively reviewed in recent years, but reviews have not emphasized outcomes of continence or women's perceptions of treatment success and satisfaction. However, continence has been considered a primary goal in UI treatment. Continence is also the most important outcome associated with quality of life in women with UI but is rarely examined as a primary outcome in syntheses of evidence. Thus, we focus on continence and quality of life as primary outcomes for this comparative effectiveness review."
Reviewer #1	General	The key questions are appropriate though Key Question #3 would be more precise if "non-surgical" were added between "non-pharmacologic" and "treatment".	We can't change key questions. We clarified that we focused on adult women in ambulatory care settings and on <u>nonsurgical</u> nonpharmacological treatments and pharmacological agents available in the United States.
Peer Reviewer #1	General	Clarity and Usability: The main points are clearly presented. The primary factor limiting the ability of the conclusions to inform policy is the short-term nature of the bulk of the trials (this is unavoidable as it reflects the literature). From a policy/practice point of view, 12 week results are not too worthwhile. I thought one of the best clinical messages was the summary of the little data there are about using anticholinergic drugs in the face of certain comorbidities.	We emphasized that limited evidence was available for treatment effectiveness in subpopulations with different comorbidities and poor response to the prior treatments. We revised the discussion pointing out the lack of evidence of long-term benefits and harms with nonsurgical treatments for UI.
Peer Reviewer #2	General	The report is clinically meaningful. The target population, women with stress and urgency UI, is clearly defined. The key questions are clearly stated and appropriate. Clarity and Usability: The report was well structured and presently clearly and in a manner that was easy to follow. I believe that the findings can inform clinical practice, policy and future research. This was an excellent systematic review.	Thank you

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	General	The authors provide a comprehensive review evaluating the methods to diagnose UI and and to compare clinical efficacy of pharmacologic and non-surgical treatments for UI. Overall, the target population (community dwelling adult women with UI) and key questions are well defined, appropriate, and clinically meaningful. The audience of the report appears to be primary care physicians given the emphasis of diagnosis "in the primary care setting" and the absence of evaluation of surgical treatments for stress incontinence but this is not explicitly stated. Overall the report is impressive and will provide a valuable resource to primary care physicians and incontinence specialists alike.	Thank you.
Peer Reviewer #3	General	There are a few areas that I think require further clarification or discussion however: 1) The absence evaluation of surgical treatments is notable and in many ways leaves a surprising "hole" in this otherwise comprehensive report, particularly one titled "Diagnosis and Comparative Effectiveness of Treatments for Urinary Incontinence in Adult Women". This exclusion is certainly understandable given the emphasis on the primary care setting but the title is confusing. To avoid confusion, I would strongly suggest changing the title of the report to "Diagnosis and Comparative Effectiveness of Pharmacological and Non-surgical treatments of Urinary Incontinence in Adult women" or add the qualifier "in the primary care setting" or something similar.	We revised the title to Diagnosis of Urinary Incontinence and Comparative Effectiveness of Nonsurgical Treatments in Adult Women. We explain the focus of this review in the report: "This report synthesizes published evidence about diagnosis and management of UI in adult women. We focused on adult women in ambulatory care settings and on nonsurgical nonpharmacological treatments and pharmacological agents available in the United States. This report is intended as a companion piece to an earlier EPC report that examined a wide range of treatment alternatives including surgery. The focus of this report is on techniques appropriate to primary care ambulatory practice."

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	General	Following on comment #1, the inclusion of certain interventions that are not first line therapies or typically administered by anyone other than a specialist including botox injections, bulking agent injections, tibial nerve stimulators, radiofrequency ablation devices is surprising and seems incongruous with the emphasis on the primary care setting. I would suggest removing procedures or devices that generally cannot be administered in the primary care setting or do not represent first line treatments for UI such as those listed above. Otherwise, there seems little logic in including these and excluding procedures like midurethral slings or sacral nerve stimulation.	We clarified that we created a list of interventions eligible for review following recommendations from the nominator, key informants, public comments, and TEP members: "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. According to the public comments we formulated a list of interventions eligible for this review. Stakeholders recommended reviewing patient centered-outcomes and interventions most relevant for ambulatory care and not yet systematically evaluated. Stakeholders also recommended reviewing nonsurgical interventions that can be relevant to women with refractory UI. Comprehensive information about all nonsurgical treatment choices can lead to evidence based referral practices for women with refractory UI." We acknowledged in limitations midurethral slings or sacral nerve stimulation.
Peer Reviewer #3	General	Throughout the report, but particularly in the structured abstract, executive summary, and in the section for Key question 3 non-pharmacologic treatments of UI the authors fail to adequately distinguish studies evaluating women with urge incontinence, stress incontinence and mixed or any UI when discussing or comparing treatments. This has important clinical implications and the treatment response for a particular drug or non-pharmacologic therapy cannot be assumed to be same across UI subtypes. In many cases it seems that studies are inappropriately pooled together including a mixture of different UI subtypes and in other instances the report seems to make broad conclusions about UI treatment in general when the evidence really is only appropriate for populations with certain sub-types.	We could distinguish baseline UI type only if the authors clearly indicated exclusion of other types of UI from the sample. We report drug studies for stress (estrogen and duloxetine) and for urgency UI. The majority of nondrug studies included women with mixed UI or did not clearly indicate that all women had only pure UI. The same treatments were tested in predominant stress or urgency UI. We conducted subgroup analysis and meta-regression by the presence of mixed UI. We report differences in estimates by the type of UI (pure stress, pure urgency or mixed) when detected. Please see previous responses.
Peer Reviewer #3	General	The Key Finding/Conclusion "Women defined treatment success when treatments reduced frequency of UI episodes by 70% or more according to	We revised this section: (1) we changed the threshold to 50-70% or more; (2) we provided evidence that women with refractory mixed UI define the same threshold for clinically important reduction in UI frequency; (3) we did not downgrade the level of evidence of this finding because meta-analysis

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Published Online: April 2012

Commentator & Affiliation	Section	Comment	Response
		<p>voiding diaries" is overemphasized throughout the report and, I believe, incorrect. First, the authors have based this conclusion on a single study (reference 213) and appear to have misinterpreted it. This study concludes "Reductions in IEF $\leq 40\%$ do not appear to be clinically important for women with SUI. Patients appear to recognize important clinical value at reductions of approximately 50%.." Patients in this study improved their quality of life as measured by I-QOL beyond the MCID at a threshold of 50%, not 70%. Additional benefits were seen above those seen at 50% reduction when IEF decreased 75% and again at 90% but the initial threshold where pt noted important clinical benefit was 50%. Of note, other studies have found clinically important improvements in QOL with reductions of IEF of as little as 25% (see ref 202 for instance) Second, the conclusions of this study are based on a synthesis of 4 industry sponsored RCTs in women receiving a medication (duloxetine) for stress incontinence. Yalcin et al emphasize in their paper that "These thresholds may not apply to women seeking non-pharmaceutical treatments for SUI" and "findings and thresholds apply to women with predominant SUI and cannot be extrapolated to women with other types of incontinence, particularly urge incontinence where even a single large volume incontinence episode may be completely unacceptable." In spite of this, the AHRQ report broadly applies the findings to women with all types of incontinence receiving all treatments, not just pharmaceuticals. In fact, this key finding is repeated so often throughout the report (including 2 times in the structured</p>	<p>of individual patient data from several RCTs provides high level of evidence; and (4) we emphasized the importance of outcomes meaningful for women.</p>

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Published Online: April 2012

Commentator & Affiliation	Section	Comment	Response
		<p>abstract and 7 times in the executive summary) that I worry that this misinterpreted and misapplied conclusion will become dogma should the report become published in its current form. Third, it seems inappropriate to give a "High" level of evidence for this conclusion (see Table ES 3 and Table 17) given that it is based on a single study with a very specific patient population - "Insufficient" or "Low" seems more appropriate. I strongly encourage the authors to 1) change the threshold to 50% 2) emphasize that the findings apply only to women with SUI getting medications and 3) downgrade the level of evidence of this finding and 4) de-emphasize this finding throughout the report particularly the abstract, executive summary and key findings.</p>	

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	General	<p>The reports finding "Evidence was insufficient to draw valid conclusions about comparative effectiveness and safety of nonpharmacological treatments when compared to drugs or combined modalities (page 98, line 23-27) is incongruous with the abstract conclusions that "Benefits from PMFT combined with bladder training and electrical stimulation are greater than benefits for drugs." Based on the findings of the report, the abstract conclusions should be altered. Moreover this finding of insufficient evidence to compare behavioral to drugs seems important enough to add to the Key findings of the report. On a separate note, the indirect NNT comparisons between medications and behavioral therapy are not appropriate unless the studies non-pharmacologic therapies are limited to patients with urge incontinence.</p> <p>Clarity and Usability: See comments above</p>	<p>We revised the conclusion in the abstract: Benefits from pelvic floor muscle training combined with bladder training and electrical stimulation are large, benefits from drugs are small. Drugs for predominant urgency UI had comparable effectiveness.</p> <p>We revised salient finding. Nonpharmacological treatments offer a large magnitude of benefit, and adverse effects are uncommon. Drugs offer a low magnitude of benefit and adverse effects are common. Evidence from few head-to-head RCTs was insufficient to draw valid conclusions about comparative effectiveness and safety of nonpharmacological treatments when compared to drugs or combined modalities.</p>

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	General	Clearly alot of work was put into this 1000 page document but there are significant shortcomings. This is not very clinically meaningful for the exact reasons that the authors point out on pages ES-2-3. This report has little meaning to the individual patient seen in practice, or for that matter the clinical practice of medicine. It needs to be CLEARLY stated that, given the methodology, these conclusions do not apply to complex patients or patients who have failed initial therapy or initial diagnostic evaluation.	<p>We analyzed how treatment benefits may differ in patients who have failed initial therapy:</p> <p>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).</p> <p>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). Previous nonresponders experienced a greater relative benefit than those who responded to previous treatments. Patients who did not respond to previous treatments did not benefit from increasing the dose of solifenacin. 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. Tolterodine was not better than placebo among poor responders to the previous muscarinic antagonists in one RCT.</p> <p>Darifenacin improved clinical outcomes in OAB patients who expressed dissatisfaction with prior extended-release (ER) oxybutynin or tolterodine therapy in one nonrandomized study. Darifenacin improved the Patient's Perception of Bladder Condition regardless of previous treatments by 108 percent (OR 2.08, 95% CI, 1.48 to 2.92) in oxybutynin treated patients and by 77 percent (OR 1.77, 95% CI, 1.29 to 2.43) in tolterodine treated patients.</p> <p>We emphasized in the abstract, results, and discussion the lack of evidence for individualized treatment decisions.</p> <p>We added future research recommendation to examine treatment effects in women who failed initial diagnostic evaluation (delayed diagnosis)</p>

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Published Online: April 2012

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	General	Urodynamics are NOT the reference standard for the diagnosis of UI and CERTAINLY not in the primary care setting. This calls into question ALL of the methodology and conclusions that follows concerning Key Question 1. A UDS study which reproduces the patients presenting symptoms is a valuable study which MAY be the reference standard. However, many UDS studies don't reproduce the patients symptoms. This is a severe limitation of this analysis.	We agree that UDS is not a gold standard. We based our analysis and conclusions for question 1 on all available methods to diagnose presence, type, and severity of UI as well as impact on quality of life. We emphasized that UDS should not be used as a reference standard for treatment decisions or monitoring of treatment success: "Previously published systematic reviews also demonstrated a weak association between self-reported UI symptoms and instrumental urodynamic findings. 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. Evaluations of women who report UI symptoms begin with, physical examination, exclusion of urinary tract infection using urinalysis, pelvic organ prolapse, poor bladder emptying, and post-void residual volume determination.
Peer Reviewer #4	General	the abstracts last sentence should be removed. the abstracts final sentence regarding monitoring of long term effects is philosophically correct however it is NOT based on evidence from this data set and is therefore opinion, and subjective and should be removed. This paper did not look at long term safety of ANY interventions including drugs. There is no reason to single out drugs for their potential long term ramifications. do we know that long term PFMT or e-stim is or isn't harmful??? We do not!!!	We revised conclusions in the abstract: "Routine clinical practice should include monitoring of long-term adherences and safety of all available treatments."
Peer Reviewer #4	General	The conclusion statement in the Structured Abstract and elsewhere in the paper state that "benefits from PFMT" and "electrical stimulation" are greater than the benefits from drugs. (page V in the structured Abstract). There is no clear data to support this statement in this document. In fact on p. 98 it is stated that "Evidence was insufficient to draw valid conclusions about comparative effectiveness.....". These two statements are contradictory. Please reconcile, clarify or remove this erroneous statement. Clarity and Usability: see above.	We revised: "Benefits from PFMT combined with bladder training and electrical stimulation are large, benefits from drugs are small. Drugs for predominant urgency UI had comparable effectiveness."

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #5	General	<p>This is a comprehensive and well-organized review of the literature on diagnosis and treatment of urinary incontinence in adult women. I especially appreciate the description of the strengths and limitations of the evidence. It report will be very helpful for clinicians, investigators and policy makers in this area.</p> <p>Clarity and Usability: The report is well structured and organized and the main points are clearly presented. I believe the summary and conclusions will be useful with respect to informing both practice and policy.</p>	Thank you.
AUGA	General	<p>On behalf of the American Urogynecologic Society (AUGS), we appreciate the opportunity to submit comments regarding the draft document.</p> <p>First, we recommend that the title of the report be modified to indicate more clearly that this report addresses only non-surgical treatments.</p> <p>Suggestion: Diagnosis and Comparative Effectiveness of Non-Surgical Treatments for Urinary Incontinence in Adult Women</p> <p>Per the protocol, surgical options are not addressed in this review and we recommend that this point be clarified. It is important for the public to understand that the review was specifically designed to exclude "studies of surgical treatments of urinary incontinence or urogenital prolapse.</p>	<p>We revised the title.</p> <p>We revised the section about clinically important differences in voiding fairies and other tools to assess outcomes, please see responses above.</p> <p>We clarified our scope and determination of eligible interventions that are applicable to ambulatory care.</p>

Commentator & Affiliation	Section	Comment	Response
AUGA	General	Second, we question the conclusion that reductions in incontinence frequency of less than 70 percent are not clinically meaningful. We have reservations about the strength of the evidence supporting this threshold and this definition for treatment success. Specifically, this criterion is derived from a single manuscript which was based on a coalescence of 4 randomized trials of pharmacologic treatment of stress incontinence. As such, the conclusions apply only to pharmacologic treatment of stress incontinence. Women with urge urinary incontinence often have a constellation of symptoms related to “overactive bladder” (urinary urgency, with frequency and nocturia). Therefore, reduction in incontinence episodes without reduction in these associated symptoms may not be perceived as a successful outcome. Moreover, based on the evidence cited in this report, we believe that the 70% threshold has not been sufficiently validated to warrant such a strong recommendation. We applaud efforts to identify meaningful outcomes in this field but suggest that further research is needed to identify rigorously identify meaningful patient-centered goals and outcomes.	We revised this section; please see responses above.
AUGA	General	Finally, we strongly believe that the findings of this report provide a convincing argument for additional research, including basic research to improve our understanding of the biology of incontinence; identification of new assessment tools; translational research to identify prevention strategies; and additional clinical trials to compare the effectiveness and efficacy of nonsurgical and surgical treatments.	Thank you.

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Published Online: April 2012

Commentator & Affiliation	Section	Comment	Response
Stan Bukofzer, M.D. VP Scientific & Medical Affairs Astellas Pharma US, Inc	General	<p>Astellas Pharma US, Inc. (Astellas) appreciates this opportunity to submit comments to the Agency for Healthcare Research and Quality (AHRQ) concerning its draft report, “Diagnosis and Comparative Effectiveness of Treatments for Urinary Incontinence in Adult Women” (hereinafter referred to as the Draft Report).</p> <p>We commend AHRQ on preparing a thorough report that is comprehensive in its scope, employing meta-regression and extensive analytical methodologies. In these comments we identify areas where the Draft Report can be improved with regard to certain methodologies and conclusions. Our comments are not intended to detract from the overall quality of this effort, but to offer our cumulative experience to clarify certain key concepts. In addition, while this report will make an important contribution to ongoing work to develop the knowledge base supporting better UI patient care, we believe it is important that the limitations of the evidence on which the report is based be given appropriate consideration as part of any strategies to disseminate the report to the patient and physician communities.</p>	Thank you.
Stan Bukofzer, M.D.	General	1) the definition of Treatment Success on Voiding Diaries	We revised the section about definition of treatment success in voiding diaries.
Stan Bukofzer, M.D.	General	2) the suggestion that “Benefits from pelvic floor muscle training combined with bladder training and electrical stimulation are greater than benefits from drugs.”	<p>We revised conclusions avoiding indirect comparisons between drugs and nonpharmacological treatments.</p> <p>We revised the section about clinically important differences in UI frequency.</p>

Commentator & Affiliation	Section	Comment	Response
Stan Bukofzer, M.D.	General	<p>Limitations</p> <p>We would encourage AHRQ to include in the final report a more comprehensive discussion of the limitations of this report's meta analysis.¹⁶ Among other things, this would be helpful in highlighting some of the challenges that could be addressed in future research in this important field. One limitation, for example, is described by LeLorier, et al., which examined meta analyses and large RCTs of similar populations.¹⁷ The outcomes of the large RCTs were not accurately predicted 35 percent of the time by the previously published meta analyses.</p> <p>Another limitation may include the use of meta-regression in analyzing the findings of observational studies,¹⁸ and the potential for the analysis to be subject to ecological fallacy, which occurs when associations observed at the patient level are not necessarily true at the study level.¹⁹</p> <p>A final limitation concerns the placebo effect found in OAB studies.²⁰ Work is ongoing in this area to gain a better understanding of the factors that determine the magnitude of this effect, and the difficulties it may pose in evaluating the true efficacy of incontinence treatments. This research could improve the ability of future studies to assess the relative efficacy of incontinence therapies.</p>	<p>We used a random effects model that does not overestimate the results from large trials.</p> <p>We did not include meta-regression patient level covariates: "When exploring heterogeneity we did not use subject level variables to avoid ecological fallacy."</p> <p>We added to the limitations of our report: "We could not explain substantial variability in the rates of the outcomes with placebo treatments. Future large well designed head to head randomized trials may conclude superior efficacy of combined treatment modalities with non surgical treatments."</p>
Ricardo R. Gonzalez, M.D. Clinical Asst. Professor of Urology, Baylor College of Medicine Medical Director, Center for Voiding Dysfunction,	General	<p>I acknowledge the formidable task of guiding the practice of evidence-based medicine. However, I am writing to express specific concerns about the interpretation of the data regarding percutaneous tibial nerve stimulation (PTNS). To summarize, PTNS is a safe and effective treatment for overactive bladder (OAB) and urge urinary</p>	<p>We revised the report adding all studies about PTNS; please review the responses above.</p>

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Published Online: April 2012

Commentator & Affiliation	Section	Comment	Response
Houston Metro Urology		<p>incontinence, especially for patients who fail or cannot tolerate medical therapy. However, it is presented somewhat unfavorably in the report.</p> <p>While the reviewers reference (page 88) the SUMIT study, a 220 patient, multi-center, randomized, double-blind study that compared PTNS to a validated sham, they dismissed the findings that demonstrated a statistically significant improvement in voiding parameters for the PTNS treatment arm compared to sham. Sham or placebo controlled trials are rarely performed with medical devices, and this study provides level I evidence that PTNS is safe and effective in treating OAB symptoms. Urge incontinence (UUI) episodes were not evaluated as a primary endpoint, but UUI clinically is a manifestation of OAB.</p> <p>Another randomized trial was misinterpreted on page 99. Regarding the OrBIT3 data [PTNS vs. tolterodine prospective 3 month trial] by concluding that “results were insufficient to prove better effectiveness of PTNS compared to tolterodine”. OrBIT was designed/powered only to show equivalence with drug therapy, and evaluating superiority was not in the study design. This is clinically relevant because not all patients tolerate medical therapy with agents like tolterodine; antimuscarinics are contraindicated in multiple clinical scenarios, and PTNS offers a safe and effective alternative. Of note, the OrBIT 12 month data [not referenced in the report] which documented the sustained durability of PTNS by demonstrating continued efficacy and patient symptom improvement at one year.</p> <p>It is difficult to draw conclusions in a</p>	

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Published Online: April 2012

Commentator & Affiliation	Section	Comment	Response
		comparative manner when studies have different populations, inclusion criteria and endpoints. Studies which look at quality of life (QoL) validated scores were discounted in the report—presumably because they may be difficult to interpret—but QoL data is useful when guiding therapy. When an FDA-approved nonpharmacological treatment (eg. PTNS) is compared to sham or drugs and shows efficacy and QoL improvement, it should be added to the arsenal of treatment options for patients with OAB and UI. I respectfully request that the data available be presented more objectively with acknowledgment of the study design. PTNS has a role in the management of patients with OAB and UI, and data available should be evaluated in fair, clinical context.	
Nancy Kolb, MSN, RN	General	<p>The list below summarizes our general comments and concerns. We have also provided detailed comments on the review that follow.</p> <p>The investigators chose a single symptom (urge urinary incontinence) from a constellation of symptoms within overactive bladder or lower urinary tract syndrome on which to base their conclusions. There is a complex constellation of symptoms which must be considered in the whole; studying one symptom is not useful.</p>	We analyzed all studies of urgency UI including those with OAB. Urgency UI is the most important symptom of “complex constellation of symptoms” of OAB because it affects quality of life and is associated with disability and placement in nursing homes. Most trials for OAB focused on intermediate outcomes irrespective of women perception of clinical improvement .

Commentator & Affiliation	Section	Comment	Response
Nancy Kolb, MSN, RN	General	The review uses a single outcome measure, continence, from a variety of outcome measures that patients and physicians use to judge improvement in quality of life. 3. The review discounted the fact that many patients, by experiencing mild to moderate improvement in multiple symptoms, gain a significant improvement in quality of life.	We analyzed all patient-centered outcomes including continence, improvement in UI, quality of life, and harms.
Nancy Kolb, MSN, RN	General	The review discounted any quality of life measures despite validation and wide acceptance of these measures.	We revised the report including all quality of life measures.
Nancy Kolb, MSN, RN	General	The outcome measure of continence and a 70% improvement in continence as the sole indicator of successful treatment was based on one report drawn from four studies of a single drug (duloxetine) that was not found to be effective and is not-FDA approved. ¹ The study also states that the results should only apply to women with stress urinary incontinence and should not be extrapolated to apply to other forms of incontinence, including urge urinary incontinence.	We revised the section about clinically important reduction in UI frequency.
Nancy Kolb, MSN, RN	General	Review of percutaneous tibial nerve stimulation (PTNS), excluded all of the cases series studies, while case series were included for other therapies. The Finazzi randomized trial ² was excluded for no stated reason. Including the Finazzi study would have allowed for a mini meta-analysis of over 230 patients.	We updated the report with all available studies of PTNS.

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Nancy Kolb, MSN, RN	General	<p>The PTNS review discounted the OrBIT3 results as insufficient to prove superiority of PTNS, when the study was designed only to show equivalence with drug therapy. The 12-month extension of the OrBIT study⁴ which demonstrates the long-term safety and efficacy of PTNS therapy was omitted from the review entirely.</p> <p>The authors' conclusions about PTNS contradict those from previously published guidelines (like AHRQ's National Guideline Clearinghouse NGC-7873 or the UK's NICE guideline IPG362). Their conclusions also contradict the CPT Editorial Panel and CMS.</p>	<p>We updated the report with all available studies of PTNS.</p> <p>We included 12-month followup publication of the OrBIT study.</p> <p>We revised the report analyzing all evidence about PTNS.</p>
Nancy Kolb, MSN, RN	General	<p>The authors state that they would exclude non-FDA approved drugs and therapies from the report, and yet Botox and duloxetine are included. Neither intervention is FDA approved for the indication of urinary incontinence.</p>	<p>We clarified inclusion criteria for the studies.</p>

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Nancy Kolb, MSN, RN	General	<p>The review ignores the fact that OAB is a chronic and progressive disorder, and that an algorithm of care is required to ensure that the patients receive adequate care as the disease progresses, as patients fail available therapies or as physicians and patients choose between available therapies.</p> <p>This review leaves patients who are intolerant to drugs with few, if any, options. Patients who fail behavioral therapy and who cannot tolerate, or who experience no improvement from, drugs may be left with no options, especially if payers use this review as a mechanism to deny coverage of proven therapies.</p> <p>This study states it is intended for use in primary care facilities, but diagnostic tests such as pad weight tests, bladder ultrasound, and multichannel urodynamics need to be performed by providers with specialized training who have the knowledge and skill to do them and to interpret the results.</p> <p>This review of therapies is not a technical assessment of any of them. While it does present a plethora of statistics, it lacks good clinical conclusions on the use of any of these therapies for patient care.</p>	<p>We analyzed treatment effectiveness by response to prior treatments when the studies reported this information.</p> <p>We included therapies for refractory UI, including bulking agents and neurotoxins.</p> <p>We clarified applicability of index tests; please review responses above.</p> <p>Technology assessment of PTNS or other devices was outside of our scope.</p> <p>This CER was a thorough review of the evidence producing only those conclusions supported by the evidence. It is not intended make practice or policy recommendations</p>
Nancy Muller, MBA, PhD Executive Director National Association For Continence	General	<p>Thank you for the opportunity to offer commentary on your extensive comparative literature review posted online as a final draft. I offer only a few comments, as the March 2, 2011, deadline approaches.</p> <p>I am curious that the focus of your review is on “continence” as the primary outcome of all interventions, even though evidence in the research shows that women consider an intervention to be a clinical success if urinary frequency is reduced by 70% or more. While incontinence is clearly</p>	<p>We clarified our choice of the primary outcome for this review. We revised the section about clinically important changes in UI frequency and quality of life; please review the responses above.</p>

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Published Online: April 2012

Commentator & Affiliation	Section	Comment	Response
		<p>not a relative term – a person is either continent or incontinent – it is apparent that consumers are comfortable defining success in relative terms. I fear therefore that many of the statements regarding “rates of cure” could be pulled out of context and dissuade practitioners from pursuing some interventions not considered effective as outright cures, or even fail to consider using them in combination with others. Clearly, the review does not exhaust all possible combinations of interventions. Ultimately, my gravest concern is that payers may use these statistics and statements to deny coverage of options and thus prevent access to remedies that can have meaningful and even lasting benefits for significant numbers of patients. Since the endpoint of much of this research when undertaken was not necessarily the restoration of continence, particularly in the case of overactive bladder where frequency and urgency are the chief symptoms being addressed but rather improvement in quality of life, I think your reliance on continence as the primary outcome for the determination of effectiveness forsakes many meaningful options potentially for millions of people. This is true not only for prescription drug intervention but a variety of non-surgical interventions used to manage and mitigate symptoms. I therefore suggest some qualifying language be added to the document so that its conclusions are not used for misguided purposes or misused by others</p>	

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Nancy Muller, MBA, PhD	General	As always, I object to the exclusive reliance on randomized clinical trials (RCTs) for determining the existence of evidence of effectiveness. Evidence-based healthcare must balance scientific knowledge, clinical expertise and experience in the form of provider input, and consumer and family values for balanced healthcare delivery and decision-making. Certainly, the absence of evidence from selected, published research does not mean that evidence does not exist. There needs to be language added to the document that clearly states that RCTs are but one piece of information in drawing conclusions and making recommendations. In particular, the inclusion of consumers and their families in the discussion is essential to more than symptom management as defined by clinicians, as this is the only means of articulating and integrating more relevant quality outcomes from intervention such as ability to work, live independently, and be socially connected. Otherwise, the concept of evidence-based review is misapplied and can be used to deny coverage, reimbursement, or access to care. Acknowledgement of these missing pieces needs to be made in the final document to help prevent its narrow misuse o	We clarified inclusion of observational studies when they provided adjusted estimates of treatment effectiveness or valuable information about benefits and harms that were not available in RCTs. We did include observational studies in the review.

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Nancy Muller, MBA, PhD	General	Because duloxetine is not a drug used in the U.S. for incontinence, nor has it ever been because of Eli Lilly's withdrawal of the drug from FDA consideration, its inclusion potentially contributes to confusion. I suggest deleting all references to duloxetine in the final document.	We included duloxetine in the review following public discussion. We clarified how we determined eligible for this treatments. Stakeholders recommended reviewing patient-centered outcomes and interventions most relevant for ambulatory care and not yet systematically evaluated. Stakeholders also recommended reviewing nonsurgical interventions relevant to women with refractory UI. Comprehensive information about all nonsurgical treatment choices can lead to evidence based referral practices for women with refractory UI. We included the drugs available in the United States for predominant stress UI (topical estrogens and antidepressants). We excluded systemic estrogens and selective estrogen receptor modulators that failed to prevent or improve UI.
Nancy Muller, MBA, PhD	General	Exclusion of a subcutaneous medical device for sacral nerve stimulation in treating urgency and urge incontinence not responsive to medications or for patients in whom such medications are contraindicated renders a review that is incomplete and inadequate. Just as electrical stimulation is included, so likewise Interstim® (Medtronic, Minneapolis) should be. The device has been in widespread use throughout dozens of countries, including the U.S., and over 75,000 implants have been done. There is ample published literature to document its effectiveness.	We did not include sacral stimulation as surgical procedure. Sacral stimulation was extensive reviewed in previously published systematic reviews.

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Nancy Muller, MBA, PhD	General	I disagree with your interpretation of the level of evidence demonstrating effectiveness of non-surgical, percutaneous tibial nerve stimulation (PTNS) treatment for overactive bladder. On pages ES-8 and 88 - 89, the reviewers state, "evidence was insufficient to claim positive effects from PTNS." However, the published research by Peters et al. (2010) that is referenced in the document represents results of a pivotal multicenter, double-blind, randomized, sham controlled trial that provides level I evidence that PTNS therapy is both safe and effective in treating OAB symptoms. ¹ In this study, voiding diary parameters after 12 weeks of therapy showed PTNS subjects had statistically significant improvements in frequency, nighttime voids, voids with moderate to severe urgency and urinary urge incontinence episodes compared to sham. No serious device related adverse events or malfunctions were reported by researchers. Moreover, the efficacy demonstrated in this trial is consistent with other also recently published reports, supporting use of peripheral neuromodulation therapy for OAB, neither of which is referenced by the reviewers. ^{2,3} Based on such published data and findings of researchers, I propose a more positive statement be made about both the effectiveness and safety of PTNS.	We revised the report including all studies of PTNS; please see responses above. We revised ranking of evidence that included all available evidence about this treatment.
Nancy Muller, MBA, PhD	General	Again, thank you for the opportunity to submit opinion and commentary on your work. We are eager to advance science in the diagnosis, treatment, and management of all bladder and bowel control conditions regardless of their etiology, and are grateful for the professional work by AHRQ and others for the benefit of patients.	Thank you

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Kenneth M. Peters, M.D. Professor and Chairman of Urology at Oakland University William Beaumont School of Medicine in Royal Oak, Michigan	General	<p>My name is Kenneth M. Peters, M.D. I am the Professor and Chairman of Urology at Oakland University William Beaumont School of Medicine in Royal Oak, Michigan. I have been a Clinician Scientist for the past 15 years and one of the nation's experts on neuromodulation for voiding dysfunction. In addition, I developed and published a validated sham for percutaneous tibial nerve stimulation (PTNS) and I am the primary author of the OrBIT and SUMiT trials discussed in your AHRQ paper on treatment of incontinence.</p> <p>I am deeply disturbed by your comments regarding PTNS. ... This trial convinced me, a skeptic, that PTNS has an important role in our treatment algorithm for OAB. The data was overwhelming from open label trials that PTNS was efficacious and we now have 3 RCT's showing the effectiveness of this therapy for OAB. Based on this and other data on PTNS, significant support was garnered for this therapy from previously published guidelines like AHRQ's National Guideline Clearinghouse NGC-7873 or the UK's NICE guideline IPG362. In addition, the rigorous CPT editorial panel and CMS support PTNS as an important treatment option along with support from the American Urological Association and the Society for Urodynamics and Female Urology.</p>	We conducted an updated search to find all studies of PTNS. We revised the report with updated data; please review the responses above.

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Kenneth M. Peters, M.D.	General	<p>The premise of the AHRQ review is flawed on many levels. First, it focused on a single symptom (urge urinary incontinence) from a constellation of symptoms within overactive bladder or lower urinary tract syndrome to base their conclusions. The review chose a single outcome measure, <i>continence</i>, from a variety of outcome measures that patients and physicians use to judge improvement in quality of life. The review discounted the fact that many patients, by experiencing mild to moderate improvement in multiple symptoms, gain a significant improvement in quality of life. The review discounted any quality of life measures as too difficult to interpret despite validation and wide acceptance of these measures. The outcome measure of continence and a 70% improvement in continence as the sole indicator of successful treatment was based on reports written by industry employees drawn from four studies of a single drug (duloxetine) that was studied for stress urinary incontinence. Stress incontinence is leaking with valsalva such as coughing, sneezing and straining. The amount of leaking and patient distress is markedly less than that seen in urge urinary incontinence. The results of quality of life in stress incontinence cannot be extrapolated to urgency incontinence, which is much more severe and often resulting in complete loss of urine from the bladder.</p>	<p>We revised the report including all quality of life measurements from the original studies.</p> <p>We focused on all clinical outcomes, including continence, improvement in UI, patient satisfaction, treatment failure, and harms. We clarified our focus on patient-centered outcomes. We revised the report regarding clinically important decrease in UI frequency.</p>

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Kenneth M. Peters, M.D.	General	Review of percutaneous tibial nerve stimulation (PTNS), excluded the plethora of case series studies, while case series were included for other therapies. The Finazzi randomized trial was excluded for no stated reason. Including the Finazzi study would have allowed for a mini meta-analysis of over 230 patients. The review ignores the fact that OAB is a chronic and progressive disorder, and that an algorithm of care is required to ensure that patients receive adequate care as the disease progresses. This review leaves patients who are intolerant to drugs with few, if any, options. Patients who fail behavioral therapy and who cannot tolerate or experience no improvement from drugs may be left with no options, especially if payors use this review as a mechanism to deny coverage of proven therapies.	We included all studies about percutaneous tibial nerve stimulation in the report. Finazzi study was included in our analyses. We concluded moderate level of evidence that percutaneous tibial nerve stimulation improved predominant urgency UI.
Kenneth M. Peters, M.D.	General	In October 2010, the National Institute of Health and Clinical Excellence (NICE) issued guidance supporting the procedure, stating "current evidence on PTNS for overactive bladder syndrome shows that it is efficacious in reducing symptoms in the short and medium term. There are no major safety concerns." ⁵	The NICE stated: "Current evidence on percutaneous posterior tibial nerve stimulation (PTNS) for overactive bladder (OAB) syndrome shows that it is efficacious in reducing symptoms in the short and medium term. There are no major safety concerns. Therefore the procedure may be used provided that normal arrangements are in place for clinical governance, consent and audit." We focused on urgency UI and concluded improvement in UI with this procedure.

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Dr Romano Senior Vice President Pfizer	General	Pfizer is pleased to submit comments on the draft research review and evidence tables entitled, "Diagnosis and Comparative Effectiveness of Treatments for Urinary Incontinence in Adult Women." Pfizer is a global leader in life sciences and a research based organization with extensive clinical expertise in urinary incontinence (UI) and overactive bladder (OAB). We commend AHRQ for its continuing efforts to develop research intended to help inform and support improved decision making by patients and clinicians.	Thank you.
Dr Romano	General	Based on our experience with UI, we believe the evidence review will be more clinically useful and accurate if AHRQ clarifies a number of elements of the draft report. As such, we respectfully submit the following comments for your consideration: Consider reassessing the use of a 70% reduction in urinary episodes as the threshold for determining meaningful improvement in UI	We revised 70 percent reduction in urinary episodes as the threshold for determining meaningful improvement in UI.
Dr Romano	General	Stratify findings on the effectiveness of non-pharmacologic and pharmacologic treatments by the specific type of UI (urgency urinary incontinence (UUI), stress urinary incontinence (SUI), and mixed urinary incontinence (MUI)»	We revised the report stratifying findings on the effectiveness of nonpharmacologic and pharmacologic treatments by the specific type of UI when possible. We added subgroup analysis of nondrug treatments by the presence in sample patients with pure stress or mixed UI.
Dr Romano	General	When summarizing the clinical and comparative effectiveness of individual pharmacologic treatments, present data on health-related quality of life (HRQL) and other patient-reported outcomes (PRO) in a consistent manner using a systematic approach for selecting data	We revised the report providing all results on quality of life. We included all patient reported outcomes.
Dr Romano	General	Provide greater detail and clarity on randomized controlled trials (RCT) assessing nonpharmacologic treatments and pharmacologic treatments for VI.	We revised the report clarifying inclusion criteria and strength of evidence based on quality assessment of RCTs. We used consistent criteria across drug and nondrug studies for large or small treatment effects. However, we discussed the differences in

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Published Online: April 2012

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		<p>Pfizer recommends the report more explicitly denote the differences in patient populations and trial design in RCTs that evaluate non-pharmacologic and pharmacologic treatments for UI. Highlighting these details will provide end-users with the contextual information needed to appropriately evaluate the comparative effectiveness of nonpharmacologic and pharmacologic treatments for UI, as they can take into consideration the factors impacting the treatment effects.</p> <p>Most notably, the draft report should specifically clarify that the typical comparator in the inactive arm of RCTs evaluating a non-pharmacologic treatment is "no active treatment"; whereas the inactive comparator for pharmacologic interventions is usually "placebo". This distinction is important as the placebo arm of pharmacologic trials generally still includes the administration of educational and other interventions (such as patient diaries) that are not part of a "no active treatment" arm. This may lead to the misinterpretation of smaller treatment effect of pharmacological interventions when compared to nonpharmacologic interventions.</p> <p>Similarly, the draft report should note the patient populations in RCTs evaluating nonpharmacologic interventions can often differ quite substantially from the patients typically enrolled in a RCT evaluating pharmacologic interventions. By virtue of study design, patients enrolling in non-pharmacological trials are often willing to invest more time in the treatment and learn new skills to manage their symptoms. It is to be expected that the outcome of these trials of highly motivated</p>	<p>comparators using placebo in drug studies and "no active treatment" in nondrug studies.</p> <p>We explored how reported patient characteristics including baseline severity and response to prior treatments may modify the effects of pharmacological and nondrug treatments. We agree that patient populations differed in drug and nondrug studies. Thus we avoided indirect comparisons of treatment effects. We revised all statements in the report related to indirect comparisons of drug and nondrug studies.</p>

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Published Online: April 2012

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		<p>patients would yield better results than patients that are not as actively engaged in the treatment administration, as is often the case in pharmacologic trials. In addition, one of the primary motivations for participating in non-pharmacological trials is the desire to avoid taking medication. The population differences can impact results and should be made clear. It would be ideal if all patients had the opportunity and time to invest in nonpharmacological treatments, however this is often not possible for many patients. Without studies where subjects are randomized to pharmacological versus nonpharmacological treatments, independent of their preferences, there are serious limitations to claims of comparative effectiveness which should be discussed in the final report.</p>	
Dr Romano	General	Consider removing assessments of duloxetine and propiverine from final report	<p>We clarified: “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. According to the public comments we formulated a list of interventions eligible for this review. Stakeholders recommended reviewing patient-centered outcomes and interventions most relevant for ambulatory care and not systematically evaluated. Stakeholders also recommended reviewing nonsurgical interventions relevant to women with refractory UI. Comprehensive information about all nonsurgical treatment choices can lead to evidence based referral practices for women with refractory UI.”</p>
Dr Romano	General	Consider expansion of the comparative effectiveness review to include surrogate indicators of efficacy, safety, and tolerability, including medication adherence and impact on HRQL	<p>We analyzed adherence to medications. We revised the section about clinically important reduction in UI frequency; please review responses above. We revised the report pointing out baseline type of UI; please see responses above. We revised the report adding all available information about quality of life. We included head-to head RCT that compared drugs with nondrug therapies. Randomization provided valid treatment estimates because all confounding factors include patient preferences, motivations, or concomitant treatments. We avoided indirect comparisons between drug and nondrug treatments. We revised the report providing subgroup analysis of non drug treatments by baseline type of UI.</p>

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Dr Romano	General	<p>Incorporate additional methodological considerations in the updated analysis in the final report and address these items when discussing the limitations of this review</p> <ul style="list-style-type: none"> While the draft report acknowledges and assumes publication bias, in an effort to improve the scientific rigor of the final report, the authors can go further by testing for bias statistically and representing it to end-users graphically (e.g., showing a funnel plot). 	<p>We clarified “We assumed publication bias and did conduct formal statistical tests.”</p> <p>Tests for publication bias have a tendency for false negative errors and provide misleading conclusions of no publication bias when it is actually present. 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</p>
Dr Romano	General	The draft report appears to have used a causal or unadjusted form of indirect comparisons. A more formal approach (or adjusted approach) should be considered in the final report to upgrade confidence with interpretations and conclusions.	We avoided formal statistical testing for indirect comparisons because of clinical diversity and variability in control rates.
Dr Romano	General	The draft report does not state how missing data were handled in the metaanalyses. Without careful assessment of 'missing-ness', different drop-out patterns across studies may lead to biased results and conclusions, and as such, the approach to missing data should be explicitly stated in the final report.	<p>We clarified: “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 correction coefficients, forced intention to treat, and recommended calculations for missing data.”</p> <p>We clarified in the Executive Summary: “We carefully assessed missing data including loss of followup and drop-out patterns across studies and forced intention to treat analysis using the number of randomized subjects for all calculations.”</p>
Dr Romano	General	As indirect comparisons were conducted in the draft report, a graph showing the network of studies should be provided. (For example, see Figure 1 in Jansen JP, Crawford B, Bergman G, Stam W. Bayesian meta-analysis of multiple treatment comparisons: an introduction to mixed treatment comparisons. Value Health. 2008 Sep-Oct; 11 (5):956-64.)	<p>We included head-to head RCTs that compared drugs with nondrug therapies. Randomization provided valid treatment estimates because all confounding factors include patient preferences, motivations, or concomitant treatments. We avoided indirect comparisons between drug and nondrug treatments. We revised the report providing subgroup analysis of non drug treatments by baseline type of UI.</p> <p>We included Bayesian odds ratios in the report. We did not conduct indirect comparisons with Bayesian network meta-analyses. We may do so in the future.</p>

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R. Scott Ward, PT, PhD President of the APTA	General	APTA would suggest that there is support for the widespread recommendation that PFMT be included in the first treatment line of conservative management programs for women with stress, urge, or mixed incontinence. ⁵	We agree with APTA “that there is support for the widespread recommendation that PFMT be included in the first treatment line of conservative management programs for women with stress, urge, or mixed incontinence.” We clarified that our review would provide a basis for clinical recommendations and informed decisions: “Our systematic review will help clinicians, consumers, and policymakers make clinical recommendations and informed decisions based on synthesized evidence and other relevant factors.”
R. Scott Ward, PT, PhD	General	<p>APTA has concerns with the implications given to unsupervised vs. supervised PFMT in this report. It seems contradictory to most evidence and clinical practice standards. APTA would highlight three keystone studies that suggest results are not similar with individually instructed PFMT programs as compared with unsupervised or audio tape exercise training. The studies find the following outcomes instead:</p> <ul style="list-style-type: none"> • PFMT exercise programs that are closely supervised with some form of biofeedback will have the best results⁶ • High cure rates for SUI were shown in single-blind RCT’s in which women had individual instruction by a trained PT, combined with biofeedback or electrical stimulation, had close follow-up, and high adherence⁷ • “Intensive” (individualized instruction with repeated visits) appears better than “standard” (group instruction like exercise or Lamaze class) PFMT⁸ 	Our conclusions about comparative effectiveness between unsupervised vs. supervised PFMT were based on analysis of available evidence. We have reviewed three keystone studies that APTA recommended. The most favorable effects of supervised program have been demonstrated for acute UI after vaginal delivery (Morkved et al). We did not include the studies with acute UI in this report. In this report we analyzed RCTs that included community dwelling women with UI. We included all studies from the Cochrane reviews on the topic.

Commentator & Affiliation	Section	Comment	Response
R. Scott Ward, PT, PhD	General	Usage of the terminology “behavioral modification programs” is confusing. In UI treatment, this usually is composed of bladder training. However, within this report, the two are considered separately. The report should more explicitly explain and/or define what is meant by “behavioral modifications.” There are statements that seem to allude to some contradictory evidence for bladder training combined with PFMT as an intervention for UI.	We revised this section with exact definition of the program provided by the authors of the study.
R. Scott Ward, PT, PhD	General	The document states that “a high level of evidence indicated significant benefits from PFMT combined with bladder training on urinary continence and improvement in UI.” However, it then states that “the evidence was low that this treatment reduced severity of UI...” These statements cause confusion and further clarification may be warranted.	We revised this sentence: “The evidence was low that this treatment reduced bothersomeness of UI and insufficient that it can improve quality of life in women with UI.”
R. Scott Ward, PT, PhD	General	APTA recommends that there be better definitions or clarification of the difference between “improved UI” and “increased continence” as outcome measures. It is difficult to understand how these two terms are different, and therefore would also have such different levels of evidence.	We revised the term “increased continence” to “increased continence rates.” We clarified that definition of absolute outcome (continence) was consistent across the studies. Continence was the primary outcome for this review. In contrast definitions of improvement included relative reduction in UI frequency, severity, and bothersome. We concluded effectiveness of the treatments based on increased rates of continence when available. We revised the report correcting the terms.
R. Scott Ward, PT, PhD	General	APTA strongly recommends that the term “physiotherapy” be replaced for the purposes of this AHRQ report. “Physiotherapy” may have been used within one of the studies references, but “physical therapy” is the term used in the United States. “Physical therapy” is terminology that has been endorsed by the World Confederation for Physical Therapy (WCPT).	We revised the report using corrected definitions of physical therapy.

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R. Scott Ward, PT, PhD	General	Additionally, APTA has strong concerns with page 88, in which physical therapists are combined with nonmedical providers in a statement that says their supervision for PFMT is not effective in improving continence or quality of life in women with UI. Physical therapists are one of the primary health care professionals in prescribing and supervising PFMT exercises in the clinical setting, and this is within the physical therapy professional scope of practice.	We revised this sentence and clarified the effects from supervised by physical therapists PFMT on quality of life in women with UI. We described the effects of PFMT supervised by nonmedical providers separately.
R. Scott Ward, PT, PhD	General	APTA also points out that there are six recognized categories of UI: urge, stress, mixed, overflow, reflex and functional . Each type of UI has different pathophysiology, signs and symptoms, and recommended interventions. This document only designates two categories of UI (stress and urgency), which does not provide a fully comprehensive view of the variations and specificities of different types of UI. APTA understands that one of the most complicating aspects of researching UI is that there is a wide variability in treatments, which makes comparative studies difficult. However, if the reason for narrowing from six to two types is solely for simplification purposes, this intent should be described in the document.	We revised the report emphasizing the differences in the results based on predominant type of UI. Please see responses above. We used the definitions of UI by the International Urogynecological Association (IUGA)/International Continence Society (ICS), please see ES Table 1. We clarified our scope focusing on stress or urgency UI.
R. Scott Ward, PT, PhD	General	9. APTA agrees that there are areas where further research is appropriate. We agree that the strategies and benefits of long-term adherence to these treatments need to be further researched. The transferability of treatments to manage multi-system pelvic floor dysfunction needs to be further assessed. Further research also should be done with clinical outcomes, such as improvements in scales of severity and quality of life.	We discussed the importance of adherence to recommended treatments. We provided recommendations for future research including recommendations to examine quality of life with nonsurgical treatments for UI.

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Peer Reviewer #1	Additional Questions:	Quality of the Report: Good Number of Hours Spent to Review the Report: 6	Thank you.
Peer Reviewer #2	Additional Questions:	Quality of the Report: Superior Number of Hours Spent to Review the Report: 25	Thank you
Peer Reviewer #3	Additional Questions:	Quality of the Report: Good Number of Hours Spent to Review the Report: 11	Thank you
Peer Reviewer #4	Additional Questions:	Quality of the Report: Fair Number of Hours Spent to Review the Report: 10	Thank you.
Peer Reviewer #5	Additional Questions:	Quality of the Report: Superior Number of Hours Spent to Review the Report: 1	Thank you.
R. Scott Ward, PT, PhD	Additional Questions:	Finally, APTA strongly suggests that AHRQ consider the inclusion of a physical therapist on any future panels looking into the issue of treatments for UI. PFMT is a main treatment intervention for UI, which falls firmly within the domain of PT practice. We offer our assistance to serve as a resource in identifying highly qualified physical therapists to participate and contribute	We would be glad to collaborate with APTA on any future panels looking into the issue of treatments for UI.