Comparative Effectiveness Review Disposition of Comments Report

Research Review Title: *Newer Medications for Lower Urinary Tract Symptoms Attributed to Benign Prostatic Hyperplasia*

Draft review available for public comment from August 4, 2015 to August 25, 2015.

Research Review Citation: Brasure M, MacDonald R, Dahm P, Olson CM, Nelson VA, Fink HA, Risk M, Rwabasonga B, Wilt TJ. Newer Medications for Lower Urinary Tract Symptoms Attributed to Benign Prostatic Hyperplasia: A Review. Comparative Effectiveness Review No. 178. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 290-2012- 00161-I.) AHRQ Publication No. 16-EHC024-EF. Rockville, MD: Agency for Healthcare Research and Quality; May 2016. 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.

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Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #1	Abstract	Search through January or March, 2015? Mention abnormal ejaculation as a major side effect with silodosin?	Thank you. The search has been updated and goes through July 2015; added 'abnormal ejaculation' to abstract.
TEP Reviewer #2	Abstract	In the Structured Abstract, oxybutynin is listed as a beta-3 adrenoceptor agonist. This is incorrect. The authors meant mirabegron.	Thank you. It is corrected
TEP Reviewer #3	General	This is a well-prepared report outlining the evidence for the use of newer medicatuions for LUTS attributed to BPH. The population is well defined and the key questions are clearly stated.	Thank You.
TEP Reviewer #1	General	The reviewer believes the report is valid and helpful. key questions and applicable population is carefully defined.	Thank You.
TEP Reviewer #4	General	Key questions are appropriate and explicitly stated. My main concern relates to the issue of clinically meaningful and target audience for the section on medications for overactive bladder.	We have revised the methods section to clarify what we mean by clinical significance: "When there were statistically significant differences between treatment groups in specific LUTS/BPH outcomes, we interpreted efficacy and comparative effectiveness using established thresholds indicating clinical significance…" The target audience for the report is providers treating men with LUTS attributable to BPH. Many of the anticholinergic trials did enroll men with LUTS attributable to BPH and OAB, so this should be taken into consideration when interpreting these results.

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TEP Reviewer #4	General	As a general internist, I'm leery of using anticholinergics for LUTS. While the results indicated when studies excluded patients for high post-void residuals, I would like to see explicit comments regarding whether any flowmetry studies were used to determine enrollment, the setting (i.e., urology practices) where these studies were conducted, and the specific clinical criteria used to determine OAB--which symptoms, what degree of severity. While some of these data appear in the appendices, I'd like to see it in the results text. I'd also like to know more about subjects in these studies--duration of symptoms, previous treatment.	We have added tables to the Appendices and summaries to the Results section providing baseline characteristics for enrolled populations for each drug class. As outlined in Appendix E, Table E5, many of the studies with anticholinergics utilized PFR/Qmax > 5 cc/sec as part of the inclusion/exclusion criteria, thus uroflowmetry was used in many of the studies. Many also required at least one OAB symptom including frequency, urgency or nocturia and some with specific requirements in terms of quantity.
TEP Reviewer #2	General	I think that the authors' may want to use "antimuscarinic" instead of the term "anticholinergic." There are two kinds of cholinergic antagonists ("anticholinergics"): nicotinic receptor antagonists, acting either on the skeletal muscle, autonomic ganglia and adrenal medulla, or central nervous system. In contrast, muscarinic receptor antagonists include not only the naturally occurring alkaloids but also semisynthetic and synthetic derivatives of these alkaloids (e.g., oxybutynin, tolterodine)	We understand the concern, since the term anticholinergic is commonly used in practice. We decided not to make the change to antimuscarinic.
Peer Reviewer #1	General	This report addresses the clinically relevant issue of concern to practicing primary care practitioners and urologists. The key questions are all of great relevance to current medical practice and are clearly defined. The target audience for this report is also clear.	Thank you.
TEP Reviewer #5	General	OVERALL A missed opportunity is that the treatment of AUR with these agents (AB) was not attempted. This is an unmet need and this effort would have been ideal to address this issue. The patients presenting with provoked or spontaneous AUR is a common urologic emergency in the Emergency Department, for inpatient urologic consultations and in office setting. This clinical issue is separate from chromic urinary retention which has it's own set of issues. AUR is managed strictly as an "art" as there is not single unified voice on the existing data. This leads to a large variable practice which introduces expense, unnecessary patient risk and prolonged suffering. An organized approach to the existing literature would bring these distinct approaches into a comparative publishable effort that would promote a best practices in urology that so far has escaped an organized approach.	Acute urinary retention (AUR) is an important condition, but beyond the scope of our key questions. While this issue was discussed during topic refinement process of this project, stakeholders agreed it was out of scope. Additionally, representatives from AUA (Am.Uro.Assoc) stated that a research question regarding the treatment for AUR would be included in a review they were currently working on.
Peer Reviewer #2	General	The report is logically organized and clearly written. I found the tables very helpful and liked the format. I understand the SOE classification.	Thank You.

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Peer Reviewer #3	General	Key questions are appropriate and explicitly stated throughout the review -Target population and audience was defined – however, the definition of "newly used" is initially unclear. While this is written in the introduction (new within past 10 years), I would also include in the abstract to clarify. -The report itself is clinically meaningful in that it synthesizes new medications and aids clinicians seeks evidence-based review on appropriate patient selection for these medications.	Thank You, we have defined newly used in the abstract.
Peer Reviewer #3	General	Minor comments (most likely will be picked up in the editing process, but included nonetheless): -p6 line 10, comparative is misspelled	Thank you. We corrected the mistake. The final report will undergo extensive copyediting before publication.
TEP Reviewer #6	General	The AHRQ report on Newer Medications for LUTS Attributed to BPH will be a comprehensive addition, as it seems to be a thorough evaluation of all new medications in this area. The evaluation touches on all the appropriate points: comparisons of new medications and classes (in the case of mirabegron), comparisons of new medications (and combinations thereof) versus traditional medications, an evaluation of adverse effects, and analysis that includes a lack of long term trials that use disease progression and need for surgery as endpoints. Clinicians will be able to use these recommendations to make therapeutic decisions, with some caveats. A discussion regarding two of the classes follows.	Thank You.
TEP Reviewer #6	General	For example, it is reported in the Key Points section with New Alpha Blocker Silodosin that it was similarly effective when compared with tamsulosin. However, six of the eight studies comparing these medications were conducted with 0.2 mg dosing of tamsulosin, below the FDA recommended dosing of this medication. This may need to be mentioned in the Key Points section (page 8).	Only one of the six trials showed a difference between silodosin and tamsulosin, it was a silodosin, 8 mg vs. tamsulosin, 0.2 mg. trial. All other trials and the pooled results showed no statistical difference. Silodosin, 8 mg and tamsulosin, 0.4 mg had similar mean change in IPSS scores from baseline. We analyzed the dosages separately to see if lack of difference may be due to the lower dose of tamsulosin. Results were similar with lower dose and standard dose. The lower dose of tamsulosin is commonly used in Asian studies.
TEP Reviewer #6	General	With regards to PDE-5 inhibitors, studies seems to show tadalafil in combination with alpha blockers is more effective than alpha blocker therapy alone. However, the fact that these studies had an overall risk of bias from moderate to high is concerning and should, if applicable, be included in the Key Points section. (Overall, because there seems to be varying levels of potential bias in the studies within each class of medications, including these points in the Key Points section might be helpful for clinicians.)	Thank you. The Key Points are a summation of the body of evidence and strength of evidence which incorporates risk of bias; The limitations of these trials is discussed in the discussion section.

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TEP Reviewer #6	General	Also, the FDA warnings/precautions for the PDE-5 inhibitors include statements that use of alpha blockers and PDE-5 inhibitors together is not recommended because adequate studies of both used together have not been conducted. A potential for significant blood pressure reduction using both classes together is also noted. Thus, it would be prudent for the section discussing this (e.g., Efficacy of Tadalafil Added to AB Monotherapy, pages 21 and 22) to include an evaluation of whether significant blood pressure lowering occurred in the studies.	Thank you. Included trials did not report the impact of the combination of these drugs on blood pressure and we did not speculate reasons this was not addressed. We have added this point to our discussion: "Trials did not report how the combination therapy affected blood pressure."
TEP Reviewer #6	General	In short, this AHRQ report on Newer Medications for LUTS Attributed to BPH will be very beneficial for clinicians making therapeutic decisions, and I appreciate the chance to review and discuss the report. Thank you.	Thank You.
TEP Reviewer #3	Introduction	It is short and a nice summary of the status.	Thank You.
TEP Reviewer #1	Introduction	Page 1, line 9: Histologic BPH?	Thank you. We are not sure how to address this comment.
TEP Reviewer #1	Introduction	Page 1, lines38-39: In part, because BPE/BOO and OAB can coexist.	We agree, this is explained in the introduction section: "Anticholinergics have been used more frequently for LUTS/BPH since the TIMES trial reported in 2006 that significantly more men with overactive bladder plus LUTS had treatment benefit from combined tolterodine ER plus tamsulosin than from either monotherapy or placebo."
TEP Reviewer #1	Introduction	Page 1, line 42: Typo Abs	Thank you. It is corrected.
TEP Reviewer #1	Introduction	Page 2, line 2: The reviewer suggests that it is effectiveness, not efficacy, that's most important in clinical practice.	Thank you. We revised the text: "Based on the wide variety of medications available to treat LUTS/BPH, it is possible that tailoring treatment with single medications or medication combinations can maximize efficacy or effectiveness and minimize adverse effects."
TEP Reviewer #1	Introduction	Page 2, lines 13-14: Might mention the IPSS is just the AUASI plus one question about global bother, scored separately.	Thank you. We added sentence: "These two instruments are identical with the exception of an additional question in the IPSS regarding global bother."

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TEP Reviewer #4TEP Reviewer #4	Introduction	Well organized, concise, informative.	Thank You.
TEP Reviewer #2	Introduction	No comments.	Thank You.
Peer Reviewer #1	Introduction	The introduction is an outstanding overview of the clinical questions to be addressed by the review.	Thank You.
TEP Reviewer #5	Introduction	Adequate review	Thank You.
Peer Reviewer #2	Introduction	Good review of the clinical problem. Clear statement of need for the review.	Thank You.
Peer Reviewer #2	Introduction	Might have referenced existing Clinical Guidelines for treatment of LUTS/BPH	It is unclear which guidelines the reviewer is referring to. We cited the AUA guideline on the management of LUTS secondary to BPH several times. These were references #1 and #6 in the report. 1. McVary KT, Roehrborn CG, Avins AL, et al. Update on AUA guideline on the management of benign prostatic hyperplasia. J Urol 2011 May;185(5):1793-803. PMID: 2011194442. 6. McVary K, Roehrborn C, Avins A. American Urological Association Guideline: Management of Benign Prostatic Hyperplasia (BPH) Revised, 2010. American Urological Association Education and Research: Inc; 2010.

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Peer Reviewer #3	Introduction	-p8, lines 9-10. The statement that ½ of men with BPH develop BPE (and among these, about half develop BOO) may be true. But this implies that patients with BPH (but not true prostatic enlargement) don't develop BOO (this is not true). This should be clarified. Prostate size has not been shown to correlate well with BPH-related LUTS (small prostates with BPH can cause LUTS, in those patients, the urethral channel is smaller, not the entire gland- but still termed BPH). Would favor removing the "prostatic enlargement piece" altogether- or at least not ordering in a way that suggests you need enlargement to have LUTS/BOO.	Thank you. We agree with this comment. Introduction section states that LUTS can result from BPH due to BOO or changes in smooth muscle tone: "BOO and/or changes in smooth muscle tone and resistance that can accompany BPH often result in lower urinary tract symptoms (LUTS)." We respectfully disagree that our introduction implies the necessity of enlarged prostate for LUTS.
Peer Reviewer #3	Introduction	-p8, lines26-27. For the statement that treatment decisions can be based on sx and no uroflowmetry and PVR—could also reference the AUA guidelines here	Thank you. We added AUA guideline reference.
Peer Reviewer #3	Introduction	p9, lines 16-17- first sentence is missing reference	Reference added.
Peer Reviewer #3	Introduction	Table 1 – oxybutynin is bolded as if it is a new medication- I assume that the patch is intended (by writing oxytrol)- but there is oral oxybutynin that is often used (both IR and ER)- that should be added (as older medication, below the newer ones)—I would add these because you include other older meds (like finasteride, terazosin, etc)- but don't include older anticholinergics for some reason. Also, Detrol is not a new medication within 10 years (unless I'm missing something—I think it was on the market in 2001)- so also should not be bolded. The others should also be rechecked regarding whether or not they are considered new meds. Also, in the footnote on the table, Bolded medications "are the medications that are the focus of this review" whereas on the top, bolded indicates newer medication. Are these the same thing?	Newer medications refers to both newly FDA approved medications and off-label medications newly used to treat BPH. Many of the later have been approved and used for other indications for several years. We revised the sentence to clarify: "Recently, newer drugs and drug in other classes approved for other indications (off label use) have shown promise in treating LUTS/BPH."
Peer Reviewer #3	Introduction	-overall, the introduction is written in a very disjointed way. Topic sentences that naturally lead from one paragraph are needed to better link paragraphs and help the reader navigate through the section.	Thank you. We elaborated in some cases to enhance the transition and improve readability.
TEP Reviewer #3	Methods	Inclusion and exclusion criteria are well defined and justifiable. Search strategies are logical. Outcome measures are standard and classically used criteria and acceptable. The statistical methods used are also appropriate.	Thank You.
TEP Reviewer #1	Methods	Page 4: Again, would mention the search cut-off date in the Methods section.	We added search cutoff date to methods section.

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TEP Reviewer #1	Methods	Page 5, lines 16-33. Very clear description of the different SoE definitions. The reviewer really likes the provision of the rationale for the SoE assessments in the subsequent data tables.	Thank You.
TEP Reviewer #4	Methods	Inclusion and exclusion criteria are justifiable, though I could not tell whether there was a minimum RCT study duration inclusion criterion--the structured abstract mentions only that no trials exceeded 3 months.	Thank you. We clarified the sentence in the methods section: “Inclusion criteria did not restrict trials by minimal sample size or minimum study duration.”
TEP Reviewer #4	Methods	The criterion for eligible long-term studies of adverse events (> 1 year) appears only in the structured abstract--should also be in the methods.	Thank you. We added definition of long term to methods section: “We additionally searched for large (n≥100), longer-term (≥1 year duration) observational studies to assess long-term or rare treatment associated harms.”
TEP Reviewer #4	Methods	Similarly, the methods should indicate whether there was a minimal sample size criterion for the RCT; the methods indicate a requirement for > 100 subjects in the long-term studies.	Thank you. We added a sentence to methods section: “Inclusion criteria did not restrict trials by minimal sample size or minimum study duration.”
TEP Reviewer #4	Methods	Diagnostic criteria and statistical methods are appropriate, emphasizing assessments of MDD and MID is a helpful approach. However, while I assumed that the "threshold relevant to assessing effectiveness" could be interpreted as the MDD, this wasn't clearly stated.	Thank you. We edited the methods section to clarify use and interpretation of clinical significance.
TEP Reviewer #2	Methods	Did the authors consider scientific meeting abstracts as a source of fugitive literature?	Only published trials were considered for inclusion in our review. Meeting abstracts typically do not provide sufficient information to conduct risk of bias assessments and or sufficient details for extraction. We did search clinicaltrials.gov and compare registered trials to published trials to assess publication bias. This is mentioned in the footnotes of the strength of evidence assessment tables in the appendices.
TEP Reviewer #2	Methods	The authors are clear on their assessment of bias risk for experimental studies, but did not describe their methods for assessing bias in observational studies.	We did not formally assess risk of bias or strength of evidence on long-term observational studies.
TEP Reviewer #2	Methods	Not everyone is familiar with AHRQ's Key Question (KQ) abbreviation. The authors may want to define this upfront.	Thank you. We defined KQs at first occurrence in the Introduction.

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TEP Reviewer #2	Methods	I was curious why the authors excluded nonEnglish studies.	Non-English trials were not eligible because the majority of research and the higher quality research is published in English. All drugs are FDA-approved and therefore likely to have trials published in English.
Peer Reviewer #1	Methods	In general, methods described and used in this report are typical for systematic reviews and quantitative meta-analyses of this type. The authors have applied these techniques with great expertise and care. These techniques include a thorough search strategy, explicitly stated inclusion and exclusion criteria, multiple reviewers, carefully managed data extraction and outstanding application of modern statistical methods for meta-analyses.	Thank You.
TEP Reviewer #5	Methods	The authors use of the the term "BPH" is evidence of a naivety. This should be corrected throughout.	Our review focuses on treating LUTS attributable to BPH. The topic was nominated to update a guideline titled “LUTS secondary to BPH” and the American Urological Association (AUA) used the term “BPH” in that nomination. We discussed the terminology extensively with experts during the Topic Refinement and protocol process and decided that “LUTS attributable to BPH” was preferable to “secondary to” or “associated with”. As of October 1, 2015 the AUA still uses the “benign prostatic hyperplasia” terminology and “BPH” abbreviation on their website. It is unclear what terminology the reviewer prefers/suggests
Peer Reviewer #2	Methods	Clear tree of exclusions. The lack of definition of MID in the questionnaires is clearly problematic, but the authors' strategy to estimate important clinical differences makes sense.	Thank you.
Peer Reviewer #3	Methods	-Inclusion & exclusion criteria are clearly stated and justifiable -Search strategies were explicitly stated and logical	Thank you.
Peer Reviewer #3	Methods	Definition/diagnostic criteria for outcome measure were not explicitly stated in the methods (but elsewhere throughout the paper)- this could be expanded upon here- Table 3 does demonstrate symptom scores used- but there were other additional outcomes not discussed in the methods that were also reported in the results and discussion (e.g. adverse effects)	We did not specify specific diagnostic criteria for outcomes that were diagnoses We used the criteria provided by authors of the primary studies. .

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Peer Reviewer #3	Methods	Statistical methods were appropriate	Thank you.
TEP Reviewer #3	Results	the results are clear and well presented. Figures and tables are appropriate. The review is thorough.	Thank you.
TEP Reviewer #1	Results	Page 11, Table 5. Most of the trials underdosed tamsulosin. In the 2nd column, could the doses of the trials for each row be included?	We have added the dosage to each row.
TEP Reviewer #1	Results	Page 11, lines 49-53: This paragraph doesn't make sense. Page 12, lines 41 and 47: Typos.	Thank you. These were corrected.
TEP Reviewer #1	Results	Page 17, line 3: What about the range of tamulosin doses?	Thank you. It is added.
TEP Reviewer #1	Results	Page 19, line 3: The dose response looks unusual. Are the effects by dose correct? If so, deserves comment.	Thank you. We have added text to describe the wide confidence intervals associated with each dose.
TEP Reviewer #1	Results	Page 20, 4: Greater than MDD?	Thank you. It is corrected.
TEP Reviewer #1	Results	Page 21, 43-45: Please provide the AB doses.	Thank you. AB doses are noted in the first paragraph.
TEP Reviewer #1	Results	Page 21, line 55: …greater than MDD.	Thank you, It is corrected.
TEP Reviewer #1	Results	Page 21/Table 11: The reviewer would like to see more descriptions of the study limitations of the 4 trials of Tadalafil/AB versus AB, without having to dig through the appendices. The confidence intervals don't seem that broad, and exclude no effect. Why specifically is SoE low? This finding might be the one "positive" result (especially with equivalent withdrawal rates) with clinical implications in the entire review, so a thorough discussion is warranted.	The text describes that three of the four trials were open label, meaning not blinded; this is primary reason for the study limitations for this comparison. Additionally, after revising our analysis approach the confidence intervals for the main outcome now include that there is no effect.

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TEP Reviewer #4	Results	8. Would also highlight the high rate of long-term sexual side effects in key points.	Thank you. We revised key point to say "Adverse effects with silodosin were higher than with placebo, most commonly, abnormal ejaculation (High SoE)." We do not know about long-term, most trials were short in duration.
TEP Reviewer #4	Results	8. Paragraph 2, the responders had a 19 PERCENTAGE POINT increase in response--not 19%.	Thank you. It is corrected
TEP Reviewer #4	Results	12. Clarify for tolterodine added to AB (and for all studies in the anticholinergic section) that subjects had OAB (or storage symptoms).	We have reviewed the anticholinergic trials and have reported on the percentage of participants with OAB. This data is also reported in the appendix overview tables.
TEP Reviewer #4	Results	12. Indicate whether the 1.8 point improvement in mean I-PSS between combination and placebo met criterion for clinical improvement. My interpretation is that a 3 point improvement would be necessary to establish clinical superiority.	Thank you. We revised methods section to clarify that we would judge a weighted mean difference as clinically significant when it is statistically significant and the weighted mean difference is at least half of the MDD.
TEP Reviewer #4	Results	15. Consider highlighting that the 0.2 mg tamsulosin dose is below the generally recommended starting dose.	Thank you. it is explained
TEP Reviewer #4	Results	19. The key points should emphasize that these studies were conducted among cohorts where most, if not all, subjects had ED.	Thank you. It is added.
TEP Reviewer #4	Results	26. The 2 mg dose of doxazosin in the comparative studies with sildenafil is quite low; where doses titrated in these studies? If not, this would bias results against AB.	Thank you. These trials were rated high risk of bias, the potentially non-therapeutic dose of the comparator contributes to that risk.

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TEP Reviewer #2	Results	I was curious why the authors didn't consider breaking out storage and voiding symptoms from the IPSS for their evaluation of antimuscarinic therapy. The touted benefit for these medications is in the treatment of the former. Along these lines, many of the antimuscarinic studies on OAB/BPH include bladder diary data. If it's not too much work, the authors might consider looking at related outcomes. These might be meaningful to patients and providers, too.	No, we did not break out storage and voiding symptoms. We agree that antimuscarinics would be more useful for storage symptoms, but storage specific outcomes were beyond the scope of our review as we were not interested in treatments for OAB, but LUTS attributed to BPH. It was important to compare treatments using outcomes and instruments with established validity, reliability, and a demonstrated threshold indicating the clinically significance of treatment. We identified these outcomes and thresholds a priori (responders or IPSS total scores, BII) with input from our Technical Expert Panel. Because sub-scale score analyses were never suggested by team or TEP members, we did not explore the validity, reliability, sensitivity, and magnitude of change associated with clinical significance associated with these subscales that would be necessary in that analyses.
TEP Reviewer #2	Results	The authors make several notes of those trials that report industry sponsorship. Is this a part of their bias assessment? If not, I don't see that it's necessary to make these call-outs.	We feel into is important to note that almost all of these trials received industry sponsorship. While industry sponsorship is not a component of risk of bias assessment of the studies, disclosure information is important for transparency of our report.
TEP Reviewer #2	Results	I also found it confusing for the authors to say things like "Vardenafil improved mean I-PSS score more than placebo ... suggesting that an appreciable number will benefit from vardenfail treatment (insufficient evidence." Maybe instead they could say "While vardenfail use was associated with significant improvement in mean I-PSS scores, because of study limitations and imprecision in measurement, it remains unclear if an appreciable number of patient would benefit from treatment." That seems clearer to me. There are several other instances of this throughout the report.	Thank you. We agree and have amended.
Peer Reviewer #1	Results	The authors have done a tremendous job of finding the right combination of detail and clarity in the presentation of the results. In general, tables are extremely well done, easy to interpret, and contain the essential information.	Thank you.

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Peer Reviewer #1	Results	One minor suggestion: when comparing two active agents, tables could be made a little easier to read by substituting the name of the actual intervention for the words "Treatment" and "Control."	We agree and have amended.
Peer Reviewer #1	Results	Another minor point is that it may be somewhat misleading to state that longer-term observational studies show increasing rates of adverse effects (e.g., page 19, rows 32 and 33). This is basically a tautology: rates of adverse effects will increase with increasing length of follow-up for both active agents and placebo. To state that adverse event rates increase in cohort studies of an intervention implies that patients can expect to experience increasing rates of treatment-related adverse effects; but without a placebo comparison group, there is really no way to know whether the increasing rates of adverse events are, in fact, treatment-related.	This was not a conclusion of our report; longer term studies were provided for descriptive purposes. We changed the wording to 'adverse events' to clarify that we do not know if they can be attributed to treatment.
Peer Reviewer #1	Results	Finally, I would be interested to see more data on the potential interaction between PDE-5 inhibitors and alpha blockers, as many clinicians are still under the impression that this combination is strongly contraindicated.	None of the PDE-5 trials addressed this issue. We report adverse effects for combination therapy versus monotherapy; Trials did not report specific cardiovascular adverse effects..
TEP Reviewer #5	Results	Line 31-32, page 5: Comments concerning discontinuation of silodosin. It should be stated that these discontinuation rates are similar amongst the entire drug class.	Thank you for the comment. We did not synthesize evidence on discontinuation rates across all alpha-blockers (not within the scope of our Key Questions) and therefore cannot generalize our findings for the entire AB class..
TEP Reviewer #5	Results	Line 35-36, page 5: "Tadalafil improved LUTS more than placebo but had more adverse effects." It should be stated that these side effects attributed to the active drugs were predominantly improved sexual function related.	The only adverse effects specifically mentioned in our report when comparing tadalafil to placebo are dyspepsia and myocardial infarction; these are not necessarily related to improved sexual function.
TEP Reviewer #5	Results	Line 12-14, page 9: "The two most widely used, validated instruments for assessment of LUTS are the American Urological Association Symptom Index (AUA-SI) and the International Prostate Symptom Score (I-PSS)." The authors should note that these two instruments differ only by the addition of a single QoL (Question #8 on the IPSS).	Thank you. It is explained.
TEP Reviewer #5	Results	Table 1, Medications used to treat LUTS attributed to BPH, Page 10: "Phospodiesterase type 5 (PDE-5) inhibitors: selectively inhibits PDE5 and increases cyclic guanosine monophosphate (cGMP). The smooth muscle cells of the prostate, bladder and surrounding vasculature contain PDE5; inhibiting PDE5 and increasing cGMP levels in these tissues causes smooth muscle relaxation". This putative MOA has not been validated and is likely not correct. The true MOA is controversial and not established.	Thank you. The table reads "Presumed to selectively inhibit PDE-5…"

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Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #5	Results	Line 47-54, Page 17 This is quite liable to bias given the nature of the report and the lack of appropriate baseline scores Sakata et al. interviewed patients who had been taking silodosin of 6.7 months at one hospital to evaluate the extent and impact of associated ejaculatory dysfunction. Associated with the drug.102 Of the 91 patients prescribed silodosin, 42 percent considered, 95 percent experienced ejaculatory disorder. Seventy-six percent of those patients were bothered by the adverse effect.	We added qualification that information on longterm effects was meant for descriptive purposes. No conclusions were drawn from this data.
TEP Reviewer #5	Results	Line 36, Page 18 Anticholinergics, Supporting tables and figures relevant to anticholinergics appear in Appendix E, Key Points These article are using a different cohort, OAB not LUTS from BPH correct? If true then this is a critical point in the response rates and should be mentioned and the implications and shortcomings discussed in that light. This impacts the discussion section (page 36, line 20-30)	These trials enrolled men with LUTS attributed to BPH and OAB. This is mentioned in the text and described in detail in the appendices for each study.
TEP Reviewer #5	Results	Line 49, Page 20 Was it really “AUR requiring catheter drainage”? That is unusual and normally is just a rising PVR above some capricious value. This should be checked. This same issue relates to the rest of the ACH review.	We described AUR as it was described in the original trial. This evidence was insufficient to draw conclusions.
TEP Reviewer #5	Results	Line 32, Page 26 PDE5i Key Points Observational studies show high rates of adverse effects during longer-term treatment with tadalafil. These “high rates” of AE (as above) also included erection as an AE.	Results from observational studies were for descriptive purposes only and should not have been included as a Key Point. Key points refer only to adverse effects identified from RCT data; erections were not considered adverse effects in those trials.

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TEP Reviewer #5	Results	Largely well constructed and organized. The authors use of the the term "BPH" is evidence of a naivety. This should be corrected throughout.	Our review focuses on treating LUTS attributable to BPH. The topic was nominated to update a guideline titled “LUTS secondary to BPH” and the American Urological Association used the term “BPH” in that nomination. We discussed the terminology extensively with experts during the Topic Refinement and protocol process and decided that “LUTS attributable to BPH” was preferable to “secondary to” or “associated with”. As of October 1, 2015 the AUA still uses the “benign prostatic hyperplasia” terminology and “BPH” abbreviation on their website. It is unclear what terminology the reviewer prefers/suggests and confusing why this comment was made specifically with regard to our methods section. No changes made.
Peer Reviewer #2	Results	The tables are very clear and helpful. I like the inclusion of NNT where possible as an addition to confidence intervals. Personally, I prefer Forrest plots for quick review of data congruence and significance, but moving the tables into the exec summary is ok.	Thank You.
Peer Reviewer #3	Results	For key points of the new alpha blocker, it may be worthwhile to mention that no intermediate-term or long-term outcomes have been investigated -Also, for key points- may be worth noting that demographic/clinical characteristics did not impact treatment efficacy based on secondary analyses (as this was one of the key questions (KQ#3) -for key points under anticholinergics, would again note that secondary analyses shown no differences in efficacy when evaluating demographic/clinical analyses (with ___ SOE). I think it is helpful to keep these in order of key questions for organization for the reader -also for key points under anticholinergics, it may be worth saying something to the effect that fesoterodine, oxybutynin (patch?) darifenacin, and trospium showed X for efficacy but low SOE in all trials- I felt like that was missing- and had to scroll back when reading. (for example, you do say “evidence was insufficient to assess efficacy or adverse effects of mirabegron…” so I feel that it should also be mentioned for the other drugs that have the same conclusion).-	Key Points were restricted to points with moderate or high strength evidence. Our evidence was insufficient to assess effect modification of specific demographic/clinical characteristics; Insufficient evidence should not be confused with no difference of effect as the reviewer suggests. While not key points, these issues are mentioned in the discussion. We did make an exception in the mirabegron section because there were no comparison-outcomes with sufficient evidence and the insufficient evidence rose to the level of key point.
Peer Reviewer #3	Results	-p. 18, line 51 under the third bullet of key points: “…treatment of LUTS more than (moderate SOE)..” wasn’t sure if a word was left off or “more than” is supposed to be removed? This sentence should be clarified.	Thank you. It is revised.

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Peer Reviewer #3	Results	-p.19, lines 38-39, add references when speaking of location of where trials were performed. Also missing reference for the study not reporting industry sponsorship	Thank you. We added References
Peer Reviewer #3	Results	-p. 21, line 7- when discussing Kaplan trial, add some information on inclusion criteria (nothing currently mentioned… e.g. PVR<200 or predominant storage LUTS, or …)	We added overview tables to the appendices describing enrolled subjects characteristics.
Peer Reviewer #3	Results	-p. 23, lines 38-48 (long-term adverse effects). In this study, was there a percentage who stopped therapy due to adverse effects? If so, can you include this piece of information also.	Withdrawal due to adverse effects was extracted and reported from all trials reporting that information.
Peer Reviewer #3	Results	-p. 23, line 52- regarding the two trials for fesoterodine + AB monotherapy, can you include exclusion criteria (e.g. PVR<200)- or specify if this was or was not present? Important to be consistent when describing these studies since including higher PVRs may contribute to increased SEs (anitcholinergics predispose to higher PVRs and can cause retention).	We added overview tables to the appendices describing enrolled subjects characteristics.
Peer Reviewer #3	Results	-p.24, line 44- many formulations of oxybutynin exist. Please specify the formulation (this was ER I believe- and not IR or patch- but please confirm).	Oxybutynin 10mg tablets is now specified in the text.
Peer Reviewer #3	Results	Also, I am a little confused as to why this was included if you are only including newer drugs in this review. In the Intro/methods, you only mention oxybutynin patch (oxytrol)- which IS new- but this study you have in the results is not about the patch- it is the oxybutynin ER which has been around >10 years (to my knowledge).	We included drugs 'newly used' to treat LUTS attributable to BPH. Many of these have been FDA approved for other indications, but only more recently been tested for LUTS attributable to BPH.
Peer Reviewer #3	Results	-p.30, lines 28-29. "Overall risk of bias was low to high for the four trials." Can you include references of which was low and which was high?	This information is in the appendices tables.
Peer Reviewer #3	Results	Minor: -p.16, line 50: a period is between dysfunction & associated -p. 20, first row of table 6, last column- "imitations" written instead of "limitations"	Thank you. We corrected them. The report will undergo copy editing prior to posting.
TEP Reviewer #3	Discussion/ Conclusion	The discussion is satisfactory, Limitations are well-described. To the "future research" section; I would like to see that "better LUTS measurement tools which are patient-centered be developed and included in clinical trials" added. There is clear need for better measurement of patient experineces with LUTS in addition to the non-urological factors and adaptive behaviors which may impact them.	It is not clear from this review that the field needs better measures. From the perspective of systematic reviewers, a commonly used instrument with an established threshold indicating clinical response is valued and highly unusual.
TEP Reviewer #1	Discussion/ Conclusion	Page 29, lines 49-50. Again, include a summary of the problems with these studies in the Results section.	We mentioned the lack of blinding in the results section.

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TEP Reviewer #4	Discussion/ Conclusion	Discussion appropriately highlights that new agents were not particularly efficacious, studies were often biased.	Thank You.
TEP Reviewer #4	Discussion/ Conclusion	I'm not aware that any important literature was omitted.	Thank You.
TEP Reviewer #4	Discussion/ Conclusion	I would suggest clarifying that the anticholinergics were being used for patients with OAB--and explicitly note (applicability) that there are little data on the effectiveness and safety of initiating this therapy in primary care settings.	Our review only included studies enrolling patients with LUTS attributable to BPH. Participants in the anticholinergic trials may have also had OAB or at least predomninantly storage symptoms. This is described in the appendix overview table for that section. Our applicability section in the discussion describes how these trials excluded patients with elevated PVRs, so these results may not be applicable to that population.
TEP Reviewer #4	Discussion/ Conclusion	I would also highlight that the short duration (and small sample sizes) of the studies substantially limit the detection of important long-term adverse events. Additionally, the durability of benefit is uncertain for the new agents that showed similar efficacy with current medications only during very limited follow up.	Thank you. We stated that we had no data from trials on long term effectiveness or adverse effects.
TEP Reviewer #4	Discussion/ Conclusion	The results make the important point that the benefit of PDE-5 on QOL is likely more due to ED than LUTS--this could be added to the discussion.	Thank you. Our revised analysis no longer shows that QoL is improved with tadalafil.
TEP Reviewer #4	Discussion/ Conclusion	I would like also see more about the subjects enrolling in these studies of second generation treatments. What was their duration of symptoms; had patients been on treatment before the study; if so, were they failing? I think this would further reinforce the message that these new drugs are clearly not first-line treatments.	We've added an appendix table and text to the report describing the population characteristics of subjects in trials.
TEP Reviewer #4	Discussion/ Conclusion	The future research section should also note the importance of conducting blinded studies.	While this was a problem with certain medications. Participant blinding in PDE-5s may not be successful given their efficacy with ED (participants could likely accurately predict which treatment group they were randomized to).
TEP Reviewer #2	Discussion/ Conclusion	The need for long-term data and responder analysis is clear.	Thank you.

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Peer Reviewer #1	Discussion/ Conclusion	In general, I found the discussion to be a fair and evenhanded summary of the evidence presented in the report. The limitations section needs more editing as there are several editorial mistakes.	Thank you. The report will undergo copyediting prior to posting.
Peer Reviewer #1	Discussion/ Conclusion	Two minor observations: Page 30, lines 50 – 51: this sentence states, "It is unclear why investigators would choose unblinded designs for these comparisons…" This is likely due to the fact that blinding with PDE-5 inhibitors is often unlikely to be successful, given their efficacy in treating erectile dysfunction.	Thank you. We revised discussion on blinding.
Peer Reviewer #1	Discussion/ Conclusion	Finally, on Page 31, lines 20-21, the text states, "it is also important to note that the FDA-approved dose of tadalafil is 5 mg whereas doses of up to 20 mg are commonly used to treat ED." It is my understanding that the FDA has approved doses up to 5 mg for daily use; higher doses are approved only for prn use.	Thank you. We have reworded this statement to clarify our meaning.
TEP Reviewer #5	Discussion/ Conclusion	Discussion Section, page 36, line 49 Not sure this is correct. Why do the authors feel the blinding was not adequate? Provide details and justify this beyond expert opinion. Most trials making this comparison were high risk of bias because they were open label or inadequately blinded.	When we stated that blinding was inadequate, it was typically trials with combination therapy. While the authors stated that the trials was double blinded, the combination group had instructions to take one pill in the morning and another in the evening; monotherapy groups only got one of those doses (adequate blinding would have had same instructions with one placebo and one active drug). Risk of bias is summarized in the appendices; specific details are available in detailed risk of bias assessment forms which are not part of the report.
Peer Reviewer #2	Discussion/ Conclusion	Yes, this is clearly presented	Thank You.
Peer Reviewer #3	Discussion/ Conclusion	p. 36, line 43. “The associated adverse effects were higher based…” the sentence appears to end prematurely.	Thank you. The report will undergo copyediting prior to posting.
Peer Reviewer #3	Discussion/ Conclusion	-The authors may want to include more in the anticholinergics paragraph (at least including some of the newer drugs that may not have enough information...) If mirabegron was discussed as insufficient evidence, then the other anticholinergics with insufficient evidence should also be mentioned.	Drugs with insufficient evidence were added to the anticholinergics paragraph.
Peer Reviewer #3	Discussion/ Conclusion	-p. 37, lines 21-23 “To the extent that patients or providers are interested in alleviating specific individual symptoms such as nocturia, this report does may not provide that information be helpful.” I think a few words are misplaced in this sentence- not exactly sure of what was meant…	Thank you. We revised the sentence to clarify.

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TEP Reviewer #6	Discussion/ Conclusion	The Discussion, Limitations, Applicability, Future Research Needs, and Conclusions were appropriate and main points were discussed. Throughout these sections, spelling and wording for clarity and conciseness should be	Thank you. The report will undergo copyediting prior to posting.
TEP Reviewer #6	Discussion/ Conclusion	It was important to note that the new medications do not seem to offer benefit over the established medications. Also, I believe clinicians will appreciate the statement, "…new agents …viewed as alternative treatment options of similar efficacy rather than superior management options."	Thank You.
TEP Reviewer #6	Discussion/ Conclusion	As noted in the Discussion, an economic analysis was not included. I would submit that given medication choices that are equal, clinicians should strive to use cost analysis as a factor in their prescribing and thus, may need to be included in the Future Research Needs section on page 31 (i.e., more studies regarding cost analysis among agents).	We only suggest future research needs associated with our key questions. Since we did not analyze cost, we have no insight to suggest cost analysis is a research gap.
TEP Reviewer #6	Discussion/ Conclusion	Finally, this report includes interesting comparisons of combination agents with monotherapy, which will be important for clinicians making decisions regarding add-on therapy in the future.	Thank You.
TEP Reviewer #3	Clarity/Usability	The report is clear and concise and well-structured. The main points are clearly presented. Unfortunately, the new evidence from the literature is based on short-term studies. The report is a testament of the need for long-term data to better evaluate adherence, drug-related side-effects and disease progression.	Thank You.
TEP Reviewer #1	Clarity/Usability	Yes, with few exceptions, see above.	Thank You.
TEP Reviewer #4	Clarity/Usability	The report meets these criteria, my previous comments suggest potential revisions to further guide clinical decision making.	Thank You.
TEP Reviewer #2	Clarity/Usability	Yes. Yes. Yes. Yes.	Thank You.
TEP Reviewer #7	Clarity/Usability	The report is extremely well organized and presented. The authors should be congratulated on a exceptionally clear presentation.	Thank You.

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TEP Reviewer #5	Clarity/Usability	Largely well constructed and organized. The authors use of the the term "BPH" is evidence of a naivety. This should be corrected throughout.	Thank You. Our review focuses on treating LUTS attributable to BPH. The topic was nominated to update a guideline titled “LUTS secondary to BPH” and the American Urological Association used the term “BPH” in that nomination. We discussed the terminology extensively with experts during the Topic Refinement and protocol process and decided that “LUTS attributable to BPH” was preferable to “secondary to” or “associated with”. As of October 1, 2015 the AUA still uses the “benign prostatic hyperplasia” terminology and “BPH” abbreviation on their website.
Peer Reviewer #2	Clarity/Usability	This new summary of medications released in the recent past will definitely add to information available to the clinician and patient in making choices. I like the inclusion of cost information.	Thank You.
Peer Reviewer #3	Clarity/Usability	For the most part, the report was well-structured and organized. A few minor points that would improve clarity were mentioned above. Conclusions are relevant to practice decisions and provided a synthesis of existing literature to guide these decisions.	Thank You.