

Comparative Effectiveness Review Disposition of Comments Report

Research Review Title: *Chronic Urinary Retention: Comparative Effectiveness and Harms of Treatments*

Draft review available for public comment from November 12, 2013, to December 9, 2013.

Research Review Citation: Brasure M, Fink HA, Risk M, MacDonald R, Shamliyan T, Ouellette J, Xu D, Butler M, Kane RL, Wilt TJ. Chronic Urinary Retention: Comparative Effectiveness and Harms of Treatments. Comparative Effectiveness Review No. 140. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 290-2007-10064-I.) AHRQ Publication No. 14-EHC041-EF. Rockville, MD: Agency for Healthcare Research and Quality; September 2014. 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
Peer Reviewer #1	Executive Summary		
	Introduction	Succinct and adequate.	Thank you.
	Methods	May be helpful to explain justification for exclusion criteria. Otherwise description of methods is transparent and outcomes selected are clinically relevant (specifically symptom outcomes)	We added text in the methods section to justify the exclusion criteria: Controlled studies are especially important because the natural history of chronic urinary retention (CUR) is poorly understood. Therefore, without a control group, we would not know whether changes in CUR outcomes were due to interventions or part of the natural history of the condition.
	Results	Results description is adequate, tables and figures are adequate.	Thank You.
	Discussion	For some reason, first sentence was a little confusing in the Discussion. I think the authors' point is better made in the Limitations section, but I had to read the first sentence multiple times to realize it was referring to the 9 studies excluded because population was not solely CUR population.	Reworded sentence for clarification: Overall, we identified few studies that enrolled patients with CUR.
	Conclusion	Conclusions are valid.	
	Figures		
	References		
	Appendix		
	General	The report is helpful to clinicians to understand the limited evidence that exists in the treatment of symptomatic CUR. Report is helpful because clinically, we have been treating CUR based on "what was always done". This report has value because it highlights the little evidence we have for treating symptomatic CUR.	Thank you.
Peer Reviewer #2	Executive Summary		
	Introduction	Questions asked are appropriate and explicitly stated	Thank you.

Commentator & Affiliation	Section	Comment	Response
	Methods	<p>Exclusion criteria are justifiable</p> <ul style="list-style-type: none"> - Regarding inclusion criteria authors in the table 1 (PICOTS framework) stated CUR as a persistently elevated PVR volume of 100 ml or greater. PVR > 100 mL is not the ICS accepted definition of CUR. In the absence of an evidence-based definition ICS is still the accepted one (although it does show many critical point). Author please clarify the choice of this definition - Search strategies are explicitly stated and logical - Definitions or diagnostic criteria: Hindley et al paper (2004) was allocated in the neurogenic CUR group despite only one patient included in the study showed a neurogenic aetiology of his detrusor under-activity; as many as 8 patients showed a myogenic aetiology. Author please clarify such allocation - outcome measures: Regarding primary outcomes PVR was not included but in the second group 2 of the studies included considered PVR as a primary outcome. From the clinical point of view PVR in neurogenic CUR is of primary importance, despite it might not be felt by patients. 	<p>Inclusion criteria were purposely broad to include as many studies of CUR treatments as possible. If there had been more available data, an analysis based upon how CUR was defined would have been conducted and may have provided meaningful information regarding PVR thresholds.</p> <p>Allocation of studies to etiology categories was challenging. We have revisited the groupings and now group studies into obstructive vs. non-obstructive.</p> <p>PVR was not considered a primary outcome because it is not patient-centered. We did, however, include it as an intermediate outcome and evaluated strength of evidence for this intermediate outcome.</p>
	Results	<p>The amount of detail presented in the results section is appropriate</p> <ul style="list-style-type: none"> - Characteristics of the studies are well described? - The key messages are explicit but not completely applicable in the clinical setting 	Thank you.
	Discussion	<p>The implications of the major findings are clearly stated</p> <ul style="list-style-type: none"> - The limitations of the review/studies are well described - The future research section is clear 	Thank you.
	Conclusion		
	Figures	- Figures, tables and appendices are adequate and descriptive	Thank you.
	References		
	Appendix	Appendix K is particularly well designed	Thank you.
	General	<p>The report is clinically meaningful and meets most of the question of clinician everyday life when addressing such patients.</p> <p>The report well structured and organized; methodological problems has been addressed in the appropriate section</p> <ul style="list-style-type: none"> - The main points are clearly presented with all limitations - The conclusions could be used to inform policy and/or practice decisions, but they are low-strength evidence. They should not be used or considered as guidelines on this topic. 	<p>Thank you.</p> <p>We agree that because the conclusions were assessed as low strength at best, this comparative effectiveness review is more likely to inform future research needs than evidence-based clinical guidelines.</p>

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Published Online: September 15, 2014

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Executive Summary		
	Introduction	The report addresses that CUR duration and PVR volume are not clearly defined, but does go on to give examples of PVRs identified in some studies. Were there any examples of CUR duration at all mentioned in the studies? Why is pessary placement/management not listed as a non-surgical intervention under the PICOTS section, and therefore part of the inclusion criteria?	Revised text to clarify that we found that CUR duration was rarely specified in the eligible intervention studies; PVR volumes used to diagnose CUR were typically reported: “CUR duration was rarely specified in eligible studies. We included any study that treated CUR related to chronic conditions or that specified persistent or multiple measurements.” We listed interventions identified in our initial screen of the literature and discussions with Key Informants. We intended to include any intervention type used specifically to treat CUR. Pessary placement would have been included had we found studies assessing their efficacy or comparative effectiveness in treating CUR. We have added pessary placement to our listed interventions.
	Methods	The inclusion and exclusion criteria are justifiable. The search strategies were explicitly stated and logical. The definitions and diagnostic criteria for outcome measures are appropriate. (Of note, the acronym “IPSS” is first introduced in this section without clarification of its meaning.) The statistical methods used are appropriate.	We have revised the text to provide the meaning of IPSS in first use of the acronym: “International Prostate Symptom Scores (IPSS)”
	Results	The amount of detail in the results section is appropriate. Characteristics of the studies are clearly described. The key messages are explicit and applicable to the extent that they state clearly that there is no strong evidence to direct clinical care/interventions for CUR. The investigators state clearly the reasons for inclusion and exclusion of each reviewed study.	Thank you.

Commentator & Affiliation	Section	Comment	Response
	Discussion	The implications of the major findings are clearly stated, however it is interesting that with the limited strong evidence discovered in this report that the investigators would define the applicability of the conclusions as “good”. The limitations are described adequately. The future research section of the discussion was a good overview, however some of the suggestions mentioned in this paragraph were not mentioned in the appendix: management of CUR in females with pelvic organ prolapse, for instance. The “general’ key questions addressed in Appendix K was very comprehensive and provided suggestions which could be easily translated into new research.	We have revised the text to clarify what we mean by applicability (or generalizability) of the results of the eligible studies to the broader populations for which the studies aim to test interventions: “The applicability or generalizability of our conclusions is good for patients with conditions similar to those examined in the eligible studies. Eligible studies did not address all possible populations in which CUR is common. Age and sex of subjects appear similar to the populations experiencing CUR from those causes in practice. Recruitment methods varied but were overall judged as likely to represent their respective populations. While the conclusions were not strong due to limited evidence, participants in the eligible studies reflected the populations they represented.” We have revised Appendix K to include “management of CUR in females with pelvic organ prolapse.”
	Conclusion		
	Figures	The figures, tables, and appendices are adequate and descriptive.	Thank you.
	References		
	Appendix		
	General	Because there is no strong evidence revealed by this report, it is difficult to consider it clinically meaningful. It is most significant in its revaluation of the dearth of meaningful, applicable studies and in the identification of opportunities for future research. The target audience and population are explicitly defined. The key quesstions are appropriate and explicitly stated. The report is well-structured and organized. The main points are clearly presented. Due to the lack of any strong evidence found in current literature, there are few conclusions which can be gleaned from this report to inform anything except opportunities for future research. There is little included here to inform practice decisions.	Thank you. We agree that further research on CUR treatments is necessary to inform evidence-based practice.
Peer Reviewer #4	Executive Summary		

Commentator & Affiliation	Section	Comment	Response
	Introduction	<p>The categorization of CUR into obstructive and neurogenic is first mentioned in the introduction. I believe this categorization is not optimal.</p> <p>Causes of CUR - the categorization of obstructive and neurological as the most common causes of CUR are not really accurate. More appropriately the two “etiologies” are:</p> <ol style="list-style-type: none"> 1. Obstruction 2. Detrusor underactivity <p>Neurological conditions can cause either obstruction (e.g. detrusor-sphincter dyssynergia) or detrusor underactivity (e.g. acontractile detrusor secondary to cauda equine or peripheral nerve injury)</p> <p>It is more appropriate to use the term benign prostatic obstruction (BPO) which is secondary to BPH, rather than BPH to describe retention caused by prostatic obstruction.</p> <p>In 2013, one of the most common causes of urinary retention in females is incontinence surgery. While it is often acute, it can also be chronic. Surgical interventions to relieve obstruction after incontinence surgery (urethrolisis, slig incision) are highly effective. Should this etiology be mentioned in the document?</p>	<p>Allocation of studies to etiology categories was challenging. We have revisited the groupings and now divide studies into two groups based upon underlying etiology (obstructive vs. non-obstructive).</p> <p>We have revised the text to clarify that while the men included in the eligible studies did have BPH, it was the bladder outlet obstruction caused by the BPH that was more immediately related to CUR:</p> <p>“In men, the most prevalent obstructive cause of CUR is bladder outlet obstruction associated with benign prostatic enlargement.”</p> <p>We understand that incontinence surgery is a common cause of CUR in women. We initially listed several potential causes, but revised the background section to address those for which we found eligible studies given the pilot format which strived to create a streamlined report around 20 pages.</p>
	Methods	<p>The concept of CUR secondary to detrusor underactivity (or acontractile bladder, or hypocontractile bladder) is not addressed. Often this is not caused by an obvious neurological etiology. Thus the patient population with detrusor underactivity (DU) and no neurological disease are completely ignored. The differentiation of obstruction from DU is often paramount in deciding if and how to treat a patient</p>	<p>We included studies of patients with DU if they were diagnosed with CUR and met eligibility criteria (i.e., must have a comparison group). These studies are categorized with CUR from non-obstructive etiologies.</p>
	Results	<p>It would be helpful if more space was spent on describing the outcomes measured in particular studies. From on of the studies presented, the omission of important outcomes (including time to follow up) may actually mis-represent the conclusions of the studies. Here are 2 examples:</p> <ol style="list-style-type: none"> 1. Men with BPH. In reading the document one might get the impression that, from a single study, microwave therapy is as effective as TUR-P/open surgery in relieving CUR. I do not think the study design allows that conclusion. First, the primary and only endpoint for CUR was 3 months. Also, it is curious that the change in PVR is not reported. This would be an obvious outcome to report on instead of a totally arbitrary PVR for catheterization of 300 ml (most US clinicians would not institute 	<p>Time to follow-up is not reported in the outcomes tables in the body of the report. These are described in the more detailed appendix H tables. We have revised the tables to include this key information in the body of the report.</p> <p>We have revised the text to clarify the findings of this study and added text to describe how PVR was addressed and reported in that study:</p> <p>“Schelin et al. reported no significant differences in primary outcomes between men that underwent TURP and men who received microwave therapy group; both treatment groups showed similar improvements over baseline. Low-strength evidence suggested no significant difference in the rate of UTI (diagnostic criteria not specified); 79 percent of the microwave</p>

Commentator & Affiliation	Section	Comment	Response
(cont'd)	Results	<p>CISC for a PVR of 300 ml). It makes me believe that in this industry sponsored study that there probably were differences in PVR between the two therapies. This needs to be highlighted in the document.</p> <p>2. Neurogenic Bladder. The primary reasons and outcomes for the treatment of CUR in the neurogenic population as not addressed in the document. Most cases of CUR in the neurogenic population involve “upper motor neuron lesions” and are associated with DSD. In these cases, the primary goals of therapy are to reduce storage pressures (treat detrusor overactivity and/or impaired bladder compliance) and improve incontinence. The goals are rarely to improve bladder emptying (unless surgical or chemical sphincterotomy are preformed). For these patients we are not looking to treat CUR, but rather induce and manage it. The incidence of UTI is of less importance as it is often defined by bacterial counts and not symptoms in these studies. Pyelonephritis and sepsis is what one is trying to prevent. The 2 most extensive studies on the effects of onabotulinumtoxinA on patients with neurogenic bladder are excluded. They are:</p> <p>Ginsberg D et al: Phase 3 efficacy and tolerability study of onabotulinumtoxinA for urinary incontinence from neurogenic detrusor overactivity J Urol. 2012 Jun;187(6):2131-9.</p> <p>Cruz F, et al: Efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: a randomised, double-blind, placebo-controlled trial Eur Urol. 2011 Oct;60(4):742-50.</p>	<p>therapy group and 88 percent of the successful TWOC between TURP group were catheter free at 6 months; 7 percent of the microwave therapy group and 4 percent of the TURP group maintained PVR volumes above 300 ml”</p> <p>There are a wide variety of etiologies for CUR. Given space constraints for this report format, we were not able to provide detailed background on each underlying etiology.</p> <p>This focus of this review was to assess the efficacy and/or comparative effectiveness of treatments for chronic urinary retention not neurogenic bladder. Eligible studies enrolled patients with CUR. Systematic reviews that assess the efficacy and effectiveness of bladder management interventions for neurogenic bladder would include a wider variety of urinary dysfunction; however this was not the objective of our review. The studies mentioned do not meet eligibility criteria of this review because chronic urinary retention is not a criterion for patient enrollment. Both of these studies used urinary incontinence as an enrollment criterion, While these two conditions can occur together, urinary incontinence is different than chronic urinary retention. A recent systematic review that addresses the population and key questions suggested by your comments can be found here:</p> <p>Soljanik I. Efficacy and Safety of Botulinum Toxin A Intradetrusor Injections in Adults with Neurogenic Detrusor Overactivity/Neurogenic Overactive Bladder: A Systematic Review. Drugs. 2013:1-12.</p> <p>We have reviewed the title and key questions of our report and feel that they accurately describe the scope and objectives of our review.</p> <p>We have revised the categorization of CUR etiologies to clarify the intent of this review and prevent future misunderstanding of our scope and objectives.</p>

Commentator & Affiliation	Section	Comment	Response
	Discussion	<p>1. There should be more mention of comments made in Result section for men with BPH.</p> <p>2. The Discussion regarding Botulinum Toxin and UTI's in MS patients is completely off-base and thus the concluding statement is incorrect. The whole idea behind using botulinum toxin is to reduce storage pressures and reduce incontinence. The exclusion of the Ginsberg and Cruz manuscripts here is unfortunate.</p>	<p>We have added text to the discussion section to elaborate on the treatments for men with bladder outlet obstruction due to BPH:</p> <p>"We identified only three studies that examined the treatment for CUR from obstructive causes. All addressed CUR associated with bladder outlet obstruction from benign prostatic enlargement and enrolled men with CUR and urinary symptoms. Data was insufficient to draw conclusions regarding most outcomes for each comparison. Low-strength evidence of reported suggested no statistical difference between TURP and microwave therapy in the rate at which men were catheter free at 6 months. Evidence was insufficient to draw conclusions for all other outcomes. Future research is necessary before information is useful in informing practice.</p> <p>We found no data to assess the impact of treating CUR independent of treating benign prostatic enlargement and other lower urinary tract symptoms."</p> <p>Ginzberg and Cruz manuscripts were not included in this review because they do not evaluate treatments for CUR, The Ginzberg study enrolled 'patients with neurogenic detrusor overactivity and urinary incontinence' and more than half of the enrollees were taking anticholinergics, which are associated with urinary retention.</p> <p>The Cruz study enrolled "patients with multiple sclerosis (MS; n = 154) or spinal cord injury (SCI; n = 121) with UI due to NDO [Neurogenic detrusor overactivity] (<14 UI episodes per week."</p> <p>These studies both include urinary retention as an adverse event of Botulinum Toxin treatment affecting between 17 and 31 percent of the treatment groups. This could be interpreted as strengthening our conclusion that this treatment is not effective for CUR.</p>

Commentator & Affiliation	Section	Comment	Response
	Conclusion	<p>1. “ In men with symptomatic BPH, TURP is as effective as microwave therapy at reducing rates of UTI and increasing ability to go without catheterization and more effective than laser at improving symptoms and reducing rates of treatment failure”. This is much too broad and strong a statement (see comments above). I believe the document would not be taken seriously with the statement as is. It must be modified to include the fact that the time point was 3 months and there is no assessment of PVR change.</p> <p>2. “In patients with neurogenic bladder, may not be effective.” This statement is completely incorrect. It addresses the wrong outcome measure (UTI) and it is well established and recognized by many international societies and guideline panels that botulinum toxin is extremely effective in treating neurogenic bladder as evidenced by multiple RTC’s not included in this review. The conclusion as stated shows a complete misunderstanding of the concept of treating neurogenic bladder. The future research section is spot on and really is the main conclusion of the manuscript. Another thing that I would suggest is that future research should not only guide the clinician on how to treat, but maybe even more importantly, who to treat.</p>	<p>We revised text to describe the timeframe of the results that were reported in the study, and reworded to clarify that the strength of evidence for this conclusion was assessed as low: “Low-strength evidence of reported suggested no statistical difference between TURP and microwave therapy in the rate at which men were catheter free at 6 months.”</p> <p>PVR was assessed in the study, dichotomized into a variable called ‘treatment failure’ which indicated that PVR remained above 300 ml.</p> <p>Chronic urinary retention is thought to be associated with an increased risk of urinary tract infections. This is why our team of clinical experts identified a reduced rate of symptomatic urinary tract infections as an important outcome for CUR treatment. Our review does not conclude that botulinum injections are not effective for treating neurogenic bladder. We cannot draw conclusion for this condition because this was not within the scope of our review. The evidence we analyzed for CUR patients suggested that botulinum injections into the urethral sphincter may not be effective in treating chronic urinary retention (see title and Key Questions of current review). A brief scan of the literature on botulinum injections in the treatment of neurogenic bladder identifies that one adverse effect of this treatment is urinary retention. This is consistent with our results and conclusion that this treatment may not be effective for chronic urinary retention. We apologize for this misunderstanding and have revised the text to emphasize the scope of our review.</p>
	Figures		
	References		
	Appendix		

Commentator & Affiliation	Section	Comment	Response
	General	<p>As constructed, I do not believe that the report is clinically meaningful or certainly not as meaningful as it could be (see comments below).</p> <p>I believe that the key questions are appropriate, but sub categorization into “obstructive” and “neurogenic” categories is not helpful and in my opinion is detrimental to the manuscript. I do not think that the conclusions of the manuscript as constructed and be used to inform policy and/or practice decisions. It believe it offers little guidance to the clinician and in many cases statements are incomplete or incorrect based on current literature and well established clinical principals. I believe that the categorization of CUR into obstructive and neurogenic is not helpful and it should rather be obstructive vs. detrusor underactivity. Basic questions of if and when to treat are not answered. I realize that the evidence-base may not allow such questions to be answered and if that is the case so be it. Perhaps that’s all such a document can say. Then it can be used to guide future research.</p> <p>The “treatment” of CUR in the neurogenic population is misguided with the goals of therapy, even on a most superficial level, not reflected in the document. In my opinion, the neurogenic section is so misleading and incorrect that I would recommend eliminating it from the document.</p> <p>Re-categorizing CUR into obstruction vs. DU would be extremely helpful in my opinion.</p>	<p>We agree. The lack of high quality evidence on this condition suggests that further research is necessary to guide clinical decisions.</p> <p>We have recategorized CUR into obstructive and non-obstructive for clarification.</p> <p>We believe that the reviewer misunderstood the scope and objectives of the review and do not agree that results are incorrect. We have reviewed the report for “incomplete” statements and revised when necessary.</p> <p>Questions of if and when to treat are important and answers to those questions may have priority over those addressed in this review. However, the key questions we addressed were prioritized during a Topic Refinement period with guidance from several Key Informants identified as experts on the topic of urinary retention. These Key Questions were publicly posted for comment. Comments received did not suggest revisions to the Key Questions.</p>
Peer Reviewer #5	Executive Summary		
	Introduction	<p>The discussion is again in a different direction that I would expect with the title “Chronic Urinary Retention”. This comparative study could be titled “Incomplete bladder emptying due to Obstruction (in contrast to obstruction without CUR), Neurogenic bladder and others” or “Partial Urinary Retention”. Totally missed in the introduction is the fact that the Urinary retention could be due to detrusor failure that may or may not be related to obstruction or neuropathic disturbance.</p>	<p>During our review process, we noted inconsistency in the terminology used to describe this condition. We settled on chronic urinary retention because it appears to be most commonly used in literature.</p> <p>We have revised the groupings of CUR studies into obstructive and non-obstructive to avoid confusion.</p>
	Methods	<p>The method was appropriate but I believe the outcome of the review went to the direction of treatment of etiologies rather than that of urinary retention per-se because of their definition of the subject matter.</p>	<p>This is true; we found no studies that evaluated the treatment of CUR that were not also treatments for the underlying condition.</p>

Commentator & Affiliation	Section	Comment	Response
	Results	The detail was very appropriate but then I believe the papers that came through were very few (1-2 per diagnosis) and of very low strength and with moderate to high bias that most readers will wonder the value of these findings. Some may use the report to their advantage without caution as to the relevance of the findings due to low strength and bias.	The literature on this topic is indeed sparse and not high quality. Therefore, strength of evidence for any finding was not higher than low.
	Discussion	The major findings were clearly stated but again with such a weak database and poor quality of the studies, the findings in my mind are not clinically sound and may be misinterpreted or used by others to their advantage (especially the in the treatment of BPH).	We have revised the text to emphasize the low and insufficient strength of evidence: "Overall, we identified few studies that enrolled patients specifically because they had CUR. Studies that did enroll CUR patients comprised mainly adults with CUR as well as the contributing condition such as benign prostatic enlargement or multiple sclerosis. Eligible studies were generally small and had moderate risk of bias. We grouped similar populations for analysis. We found that many treatment options depend on etiology; we analyzed data from eligible studies by etiology category. Many possible CUR etiologies had not been studied in controlled trials. In those that were, evidence was in most cases insufficient to draw conclusions about efficacy and comparative effectiveness of various interventions."
	Conclusion		
	Figures		
	References		
	Appendix		

Commentator & Affiliation	Section	Comment	Response
	General	<p>The report is not clinically meaningful because the topic “Chronic Urinary Retention” is a very vague clinical entity and the definition used is very arbitrary that clinicians reading this report will have different opinions as to the appropriateness of the population reviewed.</p> <p>The vagueness of the definition made the reviewers review various diagnostic categories such as BPH, Neurogenic bladders, Fowlers syndrome (unknown or poorly recognized in the US). The condition reported here are obstruction cases that could be either in CUR because of a) active obstruction yet the detrusor muscle is still having good contractility or b) because they may have already an under active detrusor due to the obstruction or c) may be totally due to other non-obstructive cases.</p> <p>The neurogenic bladder cases are in CUR because of detrusor overactivity and dyssynergic sphincter and botox is used to paralyze the bladder yet many CUR is due to lower motor paralytic bladder and will not need botox.</p> <p>The Fowler syndrome is recognized only in certain areas and is considered uncommon.</p> <p>The questions asked where gender specific rather than problem specific which means asking question for the treatment of the CUR and of course, it cannot be asked because of the variety of conditions that are unrelated to the main issue of CUR.</p> <p>This study could be more specific into CUR due to under active detrusor (failed contractility due to obstruction leading to CUR and measured by pressure flow urodynamic study or failed contractility due to neuropathic disturbance to innervation causing a paralytic detrusor). Then the comparative study could be surgical versus non-surgical (pharmacologic or intermittent catheterization or even nerve stimulation).</p> <p>The results are of questionable value because of very limited studies that qualified and because of moderate to high bias. Are the studies powered and if not, are the significance relevant?</p>	<p>The Key Questions arose from a publicly nominated topic on various aspects of urinary retention and were prioritized during a Topic Refinement period with guidance from several Key Informants identified as experts on the topic of urinary retention. These Key Questions were then publicly posted for comment. Comments received suggested these were important questions and did not suggest revisions to the Key Questions.</p> <p>We agree that future research on urinary retention may be best approached separately for each underlying etiology. The literature on this topic is sparse and not high quality. Therefore, strength of evidence for any finding was not higher than low.</p> <p>In systematic review, we do not assess power separately for each study. This construct is a key component of the precision element in assessing strength of evidence and the inadequate power of studies is reflected in this assessment for the body of the literature for each comparison/outcome.</p>
Peer Reviewer #6	Executive Summary		

Commentator & Affiliation	Section	Comment	Response
	Introduction	Line 22, page1, in introduction, could modify as below. “ CUR is typically caused by another, OFTEN CONCOMITANT medical conditon” or “CUR is typically caused by another COEXISTENT medical conditon. This would highlight that CUR and the causal conditon often exist simultaneously. Table 1 PICOTS framework is very helpful.	Modified text as suggested: “CUR is typically is caused by another (often concomitant) medical condition.”
	Methods	Inclusion and exclusion criteria are justifiable. Referring to Table in APPENDIX D is very helpful. Search strategies are thorough, well stated and logical. Overall methodolgy is very clearly stated with appropriate detail. Strength of evidence assessments were thoroughly explained.	Thank you.
	Results	Figure 1, Results section is very clear and easy to read and understand. The characteristics of the studies are clearly outlined and described. Amount of detail in results section is appropriate. The tables and appendices are adequate, generally clear and descriptive. PAGE 6 Line 35. Could make last sentence under benefits section clearer by Adding; “WHEN COMAPRING TURP WITH CISC, the mean change from baseline for CISC.....”	Thank you. We have revised the text to clarify: “All treatments tested in the three trials reduced PVR volumes; the trials reported no statistically significant differences between comparisons.”.
	Discussion	In Discussion Section, PAGE 12, paragraph starting on line 23. Discussing men with CUR due to BPH. This paragraph includes the most significant findings of the review, but I found it somewhat difficult to follow. Some of the sentences are very long and need to be read a few time through to get the full meaning. Could a small chart or table help? The part that is least clear begins on line 33, “Low-strength evidence...” The discussion of CUR due to neurogenic bladder and other causes was clearer. The section on future research is made clearer if one also looks at the appendix. Suggestions can be fairly easily translated into new research.	We have revised the text to clarify: “Data was insufficient to draw conclusions regarding most outcomes for each comparison. Future research is necessary before information is useful in informing practice.” We found no data to assess the impact of treating CUR independent of treating benign prostatic enlargement and other lower urinary tract symptoms.

Commentator & Affiliation	Section	Comment	Response
	Conclusion	<p>In Conclusions, PAGE 14, line 10. The sentence beginning with “In men with symptomatic BPH...”</p> <p>The sentence is also quite long and as with the previous comments, somewhat difficult to understanding without reading it through a few times.</p> <p>Conclusions can help inform practice decisions by helping clinicians to counsel patients on the the possible outcomes of TURP verses microwave and laser therapy when suffering from CUR due to BPH. Even though the amount and quality of the studies was low, this is a very common problem and many of these procedures are performed.</p> <p>It is also important to know that neuromodulation may be effective for Fowler’s syndrome and that botulinim toxin injections may not be effective in neurogenic bladder.</p> <p>I am not sure if any of the evidence is strong enough to inform policy.</p>	<p>We have revised the text to clarify findings: “Low-strength evidence suggested no statistical difference between TURP and microwave therapy in the rate at which men were catheter free at 6 months. However, the study was only powered to detect fairly large differences between groups. Evidence was insufficient to draw conclusions for all other outcomes.”</p> <p>We agree. Further high-quality research would better inform practice.</p>
	Figures		
	References		
	Appendix		
	General	<p>This report is clinically meaningful as it provides information to clinicians they can use to help guide patients in choosing between the available therapies available for CUR. It is especially useful in the case of male patients with CUR due to BPH. Here the evidence can help to choose between the options of TURP, laser and microwave therapy for CUR caused by BPH.</p> <p>Target population studied is very well defined.</p> <p>Target audience is mentioned in the Preface.</p> <p>Key questions are appropriate and clearly stated.</p> <p>Except as commented above the overall report is logical, well structured and well organized. The figures, tables and appendices provide additional clarity to the text.</p>	Thank you.
Peer Reviewer #7	Executive Summary		
	Introduction	Concise summary of problems with definition standards for CUR (100-500 ml). Good review of general categories of causation.	Thank you.

Commentator & Affiliation	Section	Comment	Response
	Methods	I do understand the logic of searching by etiology of the CUR. In the logic model outlined in Appendix Fig B1, 3 treatment strategies are proposed (surgical, catheters, and drugs). I remain unclear if these 3 treatments were analyzed for all etiologies - the role of drugs for BPH related CUR seems to have dropped out of the results discussions. Also, why is diabetes not included in the 'neurogenic' group of etiologies? In practices seeing women, diabetic neuropathy can be an important cause of CUR.	We searched for studies on a wide variety of interventions and etiologies. However we found no studies of drugs used in treating CUR in men with BPH and no studies of treating diabetic patients with CUR; therefore, due to space limitations, we did not further discuss these interventions in the report.
	Results	I believe the text and tables are clear regarding the papers selected.	Thank you.
	Discussion	The conclusions of the analyses of such a small number of studies is clearly stated. I am not aware of any missed literature.	
	Conclusion		
	Figures		
	References		
	Appendix		
	General	The standard for setting the population was the most strict (PVR>100) to capture any relevant studies. The small number of articles which ultimately met inclusion standards unfortunately limited the power of the report (accurately reflecting the state of the evidence-based literature). The report is likely to be useful for men with BPH related urinary retention, but not to the wider array of patients seen in primary care (diabetes, neurodegenerative diseases). Other than the findings of the limited superiority of TURP in BPH related CUR, there is little here that will influence practice.	The literature on this topic was sparse and not of high quality. Future high quality research would better inform practice decisions.
Peer Reviewer #8	Executive Summary		
	Introduction	See above.	
	Methods	1. The authors limited their search criteria to papers which directly compared various treatments for urinary retention. This resulted in exclusion of the vast majority of papers which have been published on the subject. The result is a document which unfortunately has very little value. In fact, some of the conclusion drawn by using these methods are false and will mislead the reader.	This is not an inaccurate depiction of our search criteria. While our inclusion criteria did require a comparison group, the criteria allowed for efficacy studies with passive control groups. However, even then, we identified few studies with comparison groups. This was not a function of our search strategy, but a function of the state of the literature on the topic. The bibliographic databases searches were supplemented with citation searching and hand searching. We discussed the small number of identified studies with our Technical Expert Panel and they were unable to suggest studies that were missing. We would be happy to review studies for inclusion if the reviewer knows of studies meeting our inclusion criteria.

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Published Online: September 15, 2014

Commentator & Affiliation	Section	Comment	Response
	Results	1. The four studies of 'neurogenic' retention (references 13-16) deserve mention. References 13 and 16 are studies which utilized botulinum toxin injections into the external urethral sphincter to treat detrusor sphincter dyssynergia. Presumably this was to try to improve their urinary retention. However, this scenario is extremely uncommon, as most patients with DSD are managed with intermittent catheterization and the goal of treatment is to maintain safe storage pressures, rather than to try to allow for volitional voiding. Reference 14 examines the effects of bethanechol or prostaglandin E2 in the treatment of detrusor failure (idiopathic urinary retention). These patients had no evidence of neurologic disease, and therefore including this study in the 'Neurogenic Bladder' section is inappropriate. Similarly, reference 15 examines the efficacy of urethral botulinum toxin injections to treat detrusor sphincter pseudodyssynergia in stroke patients. Detrusor sphincter pseudodyssynergia refers to the volitional contraction of the external urethral sphincter in response to an uninhibited detrusor contraction, and by definition does not occur in neurogenic bladder patients. Therefore, inclusion of this study in the Neurogenic Bladder section is also not appropriate.	We have revisited the groupings and now divide studies into two groups based on underlying etiology (obstructive vs. non-obstructive).
	Discussion	The conclusion that TURP and microwave therapy are similarly effective in the treatment of retention is patently false. In fact, most studies of microwave therapy have specifically excluded patients with urinary retention. Numerous large case series of microwave therapy and TURP have demonstrated inferior results following microwave therapy, and this is particularly true for retention patients. This is one example where the large volume of lower level evidence dwarfs the very few randomized trials. Excluding the former studies has resulted in an inaccurate document.	We reviewed relevant statements in the discussion section to verify that this result applies only to the population with CUR and certain outcomes. We did not include case series data in our review because case series data have no comparison groups and do not provide a sufficient strength of evidence regarding efficacy. Without a comparison group, conclusions about changes in patient reported outcomes would be difficult to credit to the intervention or to the natural course of their condition.
	Conclusion		
	Figures		
	References		
	Appendix		

Commentator & Affiliation	Section	Comment	Response
	General	<p>The paper ignores the entire construct of how urinary retention is categorized and diagnosed. Retention can be caused by obstruction or by detrusor failure. These categories are identified based on urodynamic findings, and in fact this is one area where urodynamic findings are consistently helpful in guiding treatment. The concept of detrusor failure is not specifically introduced and is only mentioned in a tangential fashion ('other' causes of retention, sacral neuromodulation for nonobstructive urinary retention).</p> <p>See above. Unfortunately, the conclusions will not be of any use in informing policy or practice decisions.</p>	<p>We have revisited the groupings and now divide studies into two groups based on underlying etiology (obstructive vs. non-obstructive).</p> <p>The literature on this topic was sparse and not of high quality. Future high quality research would better inform practice decisions.</p>
Peer Reviewer #9	Executive Summary		
	Introduction	<p>The introduction is clearly written and well referenced. A presentation describing how the key questions were selected will help to fend off criticisms for the final, narrow scope. As I recall, we had topics that included diagnosis and screening for urinary retention, evaluation for retention, as well as acute urinary retention. Clinicians may consider such topics more relevant. Explaining why these of the topics were not selected in favor of the present key questions will help defend against criticism.</p> <p>It may also be worthwhile to include in the introduction a statement regarding the relative lack of high levels evidence and generally poor study designs that were encountered. I might suggest putting this in perspective by citing other systematic reviews performed by EPC and a more typical number of Randomized controlled trials. As I recall from an earlier conversation, the gene was surprised by the lack of good evidence. This will help prepare the audience for the somewhat disappointing results.</p>	<p>Thank you. This is helpful. These are the questions that were prioritized during a Topic Refinement period from the original broad nomination. Other questions are important and relevant as well and deserve further study – some are not appropriate for comparative effectiveness review and/or have minimal literature addressing the issue.</p> <p>We will revise the text to emphasize the dearth of studies with comparison groups; however this may be more appropriate for the discussion section:</p> <p>“Overall, we identified few studies that enrolled patients specifically because they had CUR.”</p>

Commentator & Affiliation	Section	Comment	Response
	Methods	<p>The methods are clearly described for this systematic review. In appendix C, one can see a early search terms included “elevated post void residual”. Would it have made a difference to search merely for “post void residual”?</p> <p>In the methods description on page 3, it is stated that “previous systematic reviews, randomized controlled trials, and controlled before – and – after studies” were identified. In the search strategy, Cross-sectional studies, retrospective reviews, case-control studies and cohorts also included. if these studies were considered, that should be included in the methods.</p> <p>Given the overall conclusion that there is a paucity of evidence to address the key questions, might some of the lower levels of evidence not included in the final review have been of value? These studies which were not included in the final review may provide supporting evidence or even refute the few randomized trials that are included.</p>	<p>This is a good point. During our review we explored studies using this term. However the terminology retrieves many studies, the vast majority unrelated to our topic.</p> <p>The search strategy in the draft appendix retrieved studies that did not meet our eligibility criteria. We included these in the search results to better understand the research on the topic.</p> <p>Since lower level evidence is typically associated with high risk of bias and assessed with insufficient strength of evidence, the effort required to extract data from these studies is nto cost beneficial.</p>

Commentator & Affiliation	Section	Comment	Response
	Results	<p>For men with BPH, clearly the most relevant population for chronic urinary retention, there was a disappointing three randomized controlled trials included. Of these, most were plagued with design problems and bias. In table 2, why was the strength of evidence not assessed for homes in each of the three randomized controlled trials? It would appear that these would be classified as low evidence or insufficient evidence. Where the clinical trials that were evaluated individually of sufficient statistical power to draw conclusions?</p> <p>For adults with neurogenic bladder, it is difficult to draw conclusions given the different conditions actually studied. It would be unfair to lump these conditions to draw meaningful clinical conclusions. Three of the four studies examined Botox given the recent interest in this approach. Unfortunately, these studies also have significant methodologic issues.</p> <p>For the section on “adults with other courses of chronic urinary retention”, the second paragraph might include mention of the second systematic review by Herbison and the other two smaller randomized controlled trials.</p> <p>In table 4, strength of evidence for the Cochrane incontinence group report by Herbison is left as “not reported”. Why can’t the current review indicate the strength of evidence?</p> <p>I would point out that the systematic reviews by more and herbs completed a literature search through 2007 and 2009 respectively, therefore omitting potential newer data. Did the methodological process followed in this review address this gap? If so, I would say that in the results.</p>	<p>Strength of evidenced was only assessed for primary and intermediate outcomes. AHRQ reviews select which outcomes or harms for which strength of evidence assessments are conducted. A few of our primary outcomes are also harms (UTI and surgical interventions); strength of evidence was assessed for those outcomes.</p> <p>In systematic reviews, the statistical power of the evidence for each comparison is assessed with the precision component. Because each comparison only had a single study, the precision component in the strength of evidence component is essentially measuring study power.</p> <p>We are not aware of a second Herbison systematic review that addresses urinary retention. We identified 17 Cochrane reviews authored by Herbison, most address the topic of urinary incontinence. The only other Cochrane review with Herbison as first author among those we identified addresses the use of weighted vaginal cones for urinary incontinence.</p> <p>We have assessed strength of evidence from data reported in the previous SR as low.</p> <p>When systematic reviews are used, results are updated if new studies meeting eligibility criteria are identified. No new studies were identified to update results of these previous systematic reviews.</p>

Commentator & Affiliation	Section	Comment	Response
	Discussion	<p>The discussion restates key findings from the results which gives a false sense of confidence in the studies with significant limitations and generally low strength of evidence. Perhaps it is better to merely state that for all of these clinical conditions, the evidence was unacceptably weak. One does not want to lead clinician's to draw an inappropriate conclusion based on such low strength evidence. For example, statements such as perp is not more effective than microwave therapy is based on a study of only 120 men, rather than a non inferiority design. Under limitations on page 13, I would point out that there is a lack of standardization with regards to primary outcome of chronic urinary retention, elevated post void residual and inclusion criteria in various studies.</p> <p>For future needs paragraph on page 13 And appendix K, I would call for standardization of definitions either by policymakers or national society such as the American neurological Association guidelines group. I would also expand this paragraph to include all of the other key questions which this review, for various reasons, could not include, vis-à-vis my comment earlier in this review.</p>	<p>Revised text to emphasize low strength of evidence: "Low-strength evidence of reported suggested no statistical difference between TURP and microwave therapy in the rate at which men were catheter free at 6 months." We have also addressed the design of this study and added text to describe that it was only powered to detect a difference of over 27% between groups.</p> <p>It is not clear that primary outcomes and inclusion criteria for CUR should be standard across etiologies. However, standardization of diagnostic criteria within each etiology would add value to the field.</p>
	Conclusion		
	Figures		
	References		
	Appendix		
	General	<p>The team should be congratulated for completing this systematic review on chronic urinary retention. The greatest value in this report turns out to be conclusions with regards to the paucity of high levels of evidence for management of this condition. The target populations are clearly defined and include men with BPH, neurogenic disorders and others. There were two key questions examining the comparative effectiveness and harms, respectively. These questions were addressed where possible based on low levels of evidence.</p> <p>Despite chronic urinary retention being a common condition and chief complaint, the lack of good evidence with regards to management should be brought to the attention of clinicians, national institutes of health, and policymakers.</p> <p>The report itself is well organized and easy to follow. The tables are generally well done. I found minimal numbers of typographic errors. Unfortunately, given the lack of high levels of evidence, one cannot use this report to inform policy or practice beyond the need for standardization and future research.</p>	Thank You.

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Published Online: September 15, 2014