Lower urinary tract symptoms: Evidence Update March 2012

A summary of selected new evidence relevant to NICE clinical guideline 97 'The management of lower urinary tract symptoms in men' (2010)

Evidence Update 11

Evidence Updates provide a regular, often annual, summary of selected new evidence published since the literature search was last conducted for the accredited guidance they update. They reduce the need for individuals, managers and commissioners to search for new evidence and inform guidance developers of new evidence in their field. In particular, Evidence Updates highlight any new evidence that might reinforce or generate future change to the practice described in the most recent, accredited guidance, and provide a commentary on the potential impact. Any new evidence that may impact current guidance will be notified to the appropriate NICE guidance development centres. For contextual information, Evidence Updates should be read in conjunction with the relevant clinical guideline, available from the NHS Evidence topic page (www.nice.org.uk/guidance/CG97). NHS Evidence is a service provided by NICE to improve use of, and access to, evidence-based information about health and social care.

Evidence Updates do not replace current accredited guidance and do not provide formal practice recommendations.

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Contents

Introduction

This Evidence Update identifies new evidence that might reinforce or generate future change to the practice laid out in the following reference guidance:

[1]**Lower urinary tract symptoms. NICE clinical guideline 97 (2010). Available from** www.nice.org.uk/guidance/CG97

Just over 1400 pieces of evidence were identified and assessed, of which 21 were selected for the Evidence Update (see Appendix A for details of the evidence search and selection process). An Evidence Update Advisory Group, comprised of subject experts, reviewed the prioritised evidence and provided a commentary.

Feedback

If you have any comments you would like to make on this Evidence Update, please email contactus@evidence.nhs.uk

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[1] NICE-accredited guidance is denoted by the Accreditation Mark

Key messages

The following table summarises what the Evidence Update Advisory Group (EUAG) decided were the key messages for this Evidence Update. It also indicates the EUAG's opinion on whether new evidence identified by the Evidence Update reinforces or has potential to generate future change to the current guidance listed in the introduction.

The relevant NICE guidance development centres have been made aware of this evidence which will be considered when guidance is reviewed. For further details of the evidence behind these key messages and the specific guidance which may be affected, please see the full commentaries.

Key message	Effect on guidance	
	Potential change	No change
Conservative management *Self management of lower urinary tract symptoms* • Self-management (including behavioural and life-style changes) may have a role in the management of lower urinary tract symptoms (LUTS).		✓
Drug treatment *5-alpha reductase inhibitors* • There is limited evidence that dutasteride in combination with testosterone may be effective in treating hypogonadism in men with enlarged prostates and LUTS.		✓
• Finasteride may be better than placebo, but not as effective as doxazosin for treating LUTS.		✓
• Dutasteride and finasteride seem to be equally effective in the treatment of LUTS.		✓
• Combination therapy with dutasteride plus tamsulosin may be effective for the treatment of LUTS in men at risk of progression.		✓
Antimuscarinics • Antimuscarinics (anticholinergics) as monotherapy, in combination with alpha blockers or in sequential use with alpha blockers do not seem to be associated with acute urinary retention in men.		✓
• Solifenacin is effective add-on therapy in men with LUTS that are also under treatment with tamsulosin.		✓
Alpha blockers • Both silodosin[2] and naftopidil[3] may be effective treatments for LUTS.		✓

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[2] At the time of publication of this Evidence Update, silodosin did not have UK marketing authorisation, and was not available in the UK.
[3] At the time of publication of this Evidence Update, naftopidil did not have UK marketing authorisation and was not available in the UK.

	Effect on guidance	
Key message	**Potential change**	**No change**
Desmopressin • There is limited evidence that the number of nocturnal voids may be reduced with desmopressin[4] treatment for nocturnal polyuria.		✓
Surgery for voiding symptoms ***Laser vaporisation*** • There is limited evidence that a method of laser vaporisation using the green light laser technique may be as effective as transurethral resection of the prostate (TURP).		✓
Holmium laser enucleation • Holmium laser enucleation of the prostate (HoLEP) and TURP appear to be equally effective in the treatment of LUTS. There is limited evidence that HoLEP may be associated with shorter catheterisation times and hospital stay.		✓
Bipolar versus monopolar TURP • Bipolar and monopolar TURP may be equally effective in improving symptoms of LUTS, but bipolar TURP may be associated with lower rates of complications.		✓
Cost effectiveness of surgical treatments • Diathermy vaporisation with subsequent HoLEP if initial treatment fails may be a cost-effective approach to surgical treatment for LUTS.		✓
Alternative and complementary therapies • *Serenoa repens* does not seem to improve symptoms of LUTS.		✓

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[4] At the time of publication of this Evidence Update, desmopressin did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.

1 Commentary on new evidence

These commentaries analyse the key references identified specifically for the Evidence Update, which are identified in bold text. Supporting references are also provided.

In NICE clinical guideline (GC) 97, the term benign prostatic enlargement (BPE) was used in preference to the term benign prostatic hyperplasia (BPH). The explanation in the full version of NICE GC97 states: 'BPH should be reserved for histopathologically confirmed hyperplastic changes…' and that 'BPE refers to an increase in size of prostate gland due to BPH. Only about half of men with BPH will develop BPE.'

The full version of the guideline additionally defined the minimum important difference relating to clinical benefit as: a 3-point change in International Prostate Symptom Score (IPSS); a 0.5-point change in the quality of life domain of the IPSS (IPSS-QoL); and a 2 ml per second increase in maximum urinary flow rate.

1.1 Initial assessment

No new key evidence was found for this section.

1.2 Specialist assessment

No new key evidence was found for this section.

1.3 Conservative management

Urisheaths and absorbent products

A crossover randomised controlled trial (RCT) by **Chartier-Kastler et al. (2010)** assessed the effect of a particular urisheath compared with absorbent products on the quality of life (QoL) in men with moderate to severe urinary incontinence.

Sixty-one men (with no concomitant faecal incontinence) participated in the 14-centre study and tested urisheaths with collecting bags against their standard absorbent products in random order for 2 weeks each. The impact on QoL was assessed using the King's Health Questionnaire and the short-form-12 acute questionnaire.

Collected data suggested an improvement on QoL with use of urisheaths, with reductions in mean scores for limitations of daily activities (−10.24, p = 0.01) and incontinence impact (−7.05, p = 0.045).

However, this study had a number of limitations that could lead to bias; for example, no information was provided on the comparator absorbent products and only a single type of sheath was used. In addition, the study population was small and the short study duration means that transferring the findings to long-term use in normal clinical practice is difficult.

Data from this study have no impact on NICE GC97, which recommends either sheaths or pads, because this study simply provides some evidence that one particular sheath device has some QoL benefit over incontinence pads. However, the low quality of data from this study highlights the need for further research of aspects relating to incontinence devices.

Key reference
Chartier-Kastler E, Ballanger P, Petit J et al. (2010) Randomized, crossover study evaluating patient preference and the impact on quality of life of urisheaths vs absorbent products in incontinent men. British Journal of Urology International 108: 241–7.
Abstract: www.onlinelibrary.wiley.com/doi/10.1111/j.1464-410X.2010.09736.x/abstract;jsessionid=98B231B30A3CDD43CA73E207C2903822.d04t03

Self-management of lower urinary tract symptoms

In a post-hoc analysis, **Yap et al. (2009)** presented data from a, single centre RCT (previously reported by Brown et al. [2007]) to assess the effect on voiding behaviour of a self-management programme plus standard care versus standard care alone. This new analysis reports actual voiding behaviour based on frequency–volume chart (FVC) data.

A total of 140 men with uncomplicated lower urinary tract symptoms (LUTS) were randomly assigned to a self-management programme plus standard care (n = 73) or standard care alone (n = 67). The self-management programme comprised three sessions addressing behaviour and problem solving strategies, and standard care comprised watchful waiting, with escalation to medical treatment or surgery at the discretion of the clinician. Patients were assessed at 3, 6 and 12 months.

The mean volume per void in the self-management group was 57 ml (95% confidence interval [CI] 33 to 83 ml) higher than in the control group at the 3-month assessment. In addition, the total number of voids and episodes of nocturia were lower in the self-management group, with mean reductions of 2.6 (95% CI −3.6 to −1.5) and 0.7 (95% CI −1.1 to −0.3) voids per 24 hours, respectively. The observed changes were maintained at the 6-month and 12-month assessments.

The study had a number of significant weaknesses: it had a small patient population and was conducted in a single tertiary treatment centre. In addition, the comparator arm of standard care was poorly defined and identifying which elements of the intervention produced the improvement, or whether the intervention only works as part of a complete package, was not possible.

Evidence from this study has no impact on NICE GC97. A multicentre RCT would be needed to determine whether these results could be replicated in everyday clinical practice.

Key reference
Yap TL, Brown C, Cromwell DA et al. (2009) The impact of self-management of lower urinary tract symptoms on frequency-volume chart measures. British Journal of Urology International 104: 1104–8.
Full text: www.onlinelibrary.wiley.com/doi/10.1111/j.1464-410X.2009.08497.x/full

Supporting reference
Brown CT, Yap T, Cromwell DA et al. (2007) Self management for men with lower urinary tract symptoms: randomised controlled trial. British Medical Journal 334: 25–8.
Full text: www.bmj.com/content/334/7583/25

1.4   Drug treatment

5-alpha reductase inhibitors

The US Food and Drug Administration has issued safety information that 5-alpha reductase inhibitors are linked to an increased risk of high-grade prostate cancer. This advice recommends ruling out other urological conditions that mimic BPH (such as prostate cancer) before starting treatment with drugs from this class.

Dutasteride plus testosterone

A double-blind, single centre RCT by **Page et al. (2011)** compared changes in prostate size, prostate-specific antigen (PSA) and androgen levels (primary outcomes) after 6 months of treatment with testosterone plus dutasteride compared with testosterone alone in hypogonadal men (n = 53, aged 51–82 years) with enlarged prostates and moderate LUTS. Patients were randomly assigned to daily transdermal 1% testosterone gel plus oral placebo or the gel plus dutasteride for a 6-month treatment period. Outcome assessments included prostate volume, serum PSA and androgen levels.

Forty-six patients completed all study procedures. After 6 months of treatment, there was a mean reduction in prostate volume and PSA of 12% (standard error of the mean [SEM] = ± 2.5%) and 35% (SEM = ± 5%), respectively, in the testosterone plus dutasteride group, compared with the testosterone alone group, in which prostate volume and PSA increased by 7.5% and 19% ($p = 0.03$ and $p = 0.008$), respectively.

Additionally, serum testosterone levels increased significantly from baseline in both groups into the mid-normal range ($p < 0.05$). Serum dihydroxytestosterone levels increased significantly from baseline in the testosterone only group to around double the limit of the normal range ($p < 0.05$); however, in the testosterone plus dutasteride group, it was significantly lower than baseline ($p < 0.05$), falling below the lower end of the normal range.

IPSS was measured as a secondary outcome, at 6 months a reduction of 2.4 points was seen ($p < 0.05$ from baseline) in the testosterone only arm, and in the dutasteride plus testosterone arm the reduction was 3.0 points ($p < 0.05$ from baseline).

This study was small and had a short follow-up so evidence from this study is not likely to affect recommendations in NICE GC97. However, the study provides some evidence that dutasteride plus testosterone leads to improvement in biological outcomes. A larger study using clinical outcomes as the primary endpoint is needed to determine whether these treatments have clinical benefits.

Key reference
Page ST, Hirano L, Gilchriest J et al. (2011) Dutasteride reduces prostate size and prostate specific antigen in older hypogonadal men with benign prostatic hyperplasia undergoing testosterone replacement therapy. The Journal of Urology 186: 191–7.
Abstract: www.jurology.com/article/S0022-5347(11)03273-3/abstract

Finasteride

A Cochrane review undertaken by **Tacklind et al. (2010)** compared the clinical effectiveness and side effects of finasteride versus placebo and active controls in the treatment of LUTS. A total of 23 studies were identified as suitable for inclusion, 19 of which were placebo-controlled and included 20,821 men. The review's primary outcome was change in IPSS. A clinically meaningful change was defined as 4 points from baseline in either score. Outcomes were also categorised by trial length, with durations of 1 year or less defined as 'short-term' and longer than 1 year referred to as 'long-term'.

The main results were that finasteride consistently improved urinary symptom scores more than placebo in trials of more than 1 year in duration (standard mean difference = −0.19, 95% CI −0.31, −0.07). Finasteride had an increased risk of decreased libido (relative risk [RR] = 2.12, 95% CI 1.40 to 3.23), ejaculation disorder (RR = 2.86, 95% CI 1.79 to 4.56) and impotence (RR = 2.02, 95% CI 1.38 to 2.97) compared with placebo (all analyses for studies of up to 1 year duration). By comparison with alpha-blocker monotherapy, finasteride was less effective than either doxazosin or terazosin, but equally effective compared with tamsulosin (no statistical analysis reported).

The authors concluded that finasteride improves long-term urinary symptoms versus placebo, but is less effective than doxazosin, and that long-term combination therapy with alpha blockers (doxazosin, terazosin) improves symptoms only in men with medium (25 to < 40 ml) or large prostates (≥ 40 ml), but not in men with small prostates (25 ml).

Evidence from this study supports current guidance in NICE GC97, which recommends treatment with alpha blockers for moderate to severe LUTS and 5-alpha reductase inhibitors

(such as finasteride) alone or in combination for men with prostates larger than 30 g (or PSA level of more than 1.4 ng/ml).

Key reference
Tacklind J, Fink HA, MacDonald R et al. (2010) Finasteride for benign prostatic hyperplasia. Cochrane Database of Systematic Reviews 10: CD006015.
Full text: www.onlinelibrary.wiley.com/doi/10.1002/14651858.CD006015.pub3/full

Dutasteride versus finasteride

Nickel et al. (2011) is the first report of a head-to-head study of dutasteride versus finasteride that began in 1998, and finished in 2003. This multicentre double-blind, randomised 12-month parallel group study (the Enlarged Prostate International Comparator study; EPICS) compared the efficacy and safety of dutasteride and finasteride in the treatment of men (aged ≥ 50 years) with symptomatic BPH.

Participating patients received once daily dutasteride (0.5 mg, n = 813) or finasteride (5 mg, n = 817). After a 4-week placebo run-in period, patients were randomly assigned to 48 weeks' treatment with dutasteride or finasteride, with the option of joining a subsequent 24-month open-label study of dutasteride. The primary endpoint was the change in prostate volume at 12 months. A total of 1454 patients completed the 12-month assessments, 719 and 735 patients in the dutasteride and finasteride groups, respectively.

Dutasteride and finasteride were equally effective in reducing prostate volume; at 12 months there was a 26.7% reduction in the finasteride group compared with a 26.3% reduction in the dutasteride group (p = 0.65). Secondary endpoints were also similar – both agents resulted in comparable reductions in the mean American Urological Association Symptom Score (AUASS) (−5.8 vs −5.5 respectively, p = 0.38) and improvements in maximum urinary flow rate (2.0 ml vs 1.7 ml, respectively, p = 0.14). Adverse events (including impotence, decreased libido, ejaculation disorders, gynaecomastia, hypertension, and acute urinary retention) were reported by 50% of people on finasteride and 49% of those on dutasteride (no p value reported).

Evidence from this study that both 5-alpha reductase inhibitors are equally effective treatments for LUTS reinforces current clinical practice and recommendations in NICE GC97, which does not indicate a preferred drug in this class.

Key reference
Nickel JC, Gilling P, Tammela TL et al. (2011) Comparison of dutasteride and finasteride for treating benign prostatic hyperplasia: the Enlarged Prostate International Comparator Study (EPICS). British Journal of Urology International 108: 388–94.
Abstract: www.onlinelibrary.wiley.com/doi/10.1111/j.1464-410X.2011.10195.x/abstract

Dutasteride and tamsulosin combination therapy

A multicentre, double-blind, parallel group RCT (the Combination of Avodart and Tamsulosin [CombAT] study) by **Roehrborn et al. (2010)** assessed whether dutasteride and tamsulosin combination therapy is more effective than either drug as monotherapy in increasing the time to acute urinary retention or BPH-related surgery over 4 years (primary endpoint) in men at increased risk of progression. A total of 4844 men (aged ≥ 50 years) received daily treatment with tamsulosin (0.4 mg, n = 1611), dutasteride (0.5 mg, n = 1623) or a combination of tamsulosin and dutasteride (n = 1610).

Combination therapy with dutasteride and tamsulosin was significantly better than tamsulosin monotherapy (p $<$ 0.001), but not dutasteride monotherapy (p = 0.18), in the length of time to acute urinary retention and BPH-related surgery. The 4-year incidence of acute urinary

retention or BPH-related surgery was 4.2% for the combination, 5.2% for dutasteride, and 11.9% of tamsulosin.

In a secondary endpoint analysis, combination therapy reduced the IPSS by 2.5 points over the alpha blocker (p < 0.001), and by 1.0 points over dutasteride alone (p < 0.001). However, the change in IPSS score did not reach the definition of clinical significance (that is a change of 3 points from baseline) stated in the full version of NICE GC97.

This study looked at men with large prostates (≥ 30 cm^3), and these data reinforce the recommendation in NICE GC97 that combination therapy can be considered for men with large prostates.

Key reference
Roehrborn CG, Siami P, Barkin J et al. (2010). The effects of combination therapy with dutasteride and tamsulosin on clinical outcomes in men with symptomatic benign prostatic hyperplasia: 4-year results from the CombAT study. European Urology 57: 123–31.
Full text: www.europeanurology.com/article/S0302-2838(09)00970-1/fulltext

Phosphodiesterase-5 inhibitors

Tadalafil for the treatment of BPH has been proposed for consideration in a NICE technology appraisal. A decision on inclusion in NICE's work programme is expected by April 2012.

Antimuscarinics

A systematic review by **Athanasopoulos et al. (2011)** assessed 71 articles (17 trials, n = 5986) published between 1990 and September 2010 that were relevant to the treatment of overactive bladder (OAB) and bladder outflow tract obstruction with antimuscarinic drugs (previously known as anticholinergics). This was a narrative review of the data without meta-analysis so no statistical analyses were provided to support the authors' conclusions.

Monotherapy with antimuscarinic drugs did not seem to have much effect on the risk of developing acute urinary retention, and people with mild obstruction, smaller prostates, low PSA levels and symptoms of OAB were most likely to benefit from this treatment. However, in some combination studies of alpha blockers and antimuscarinics that measured post-void residual volume, a clinically non-significant increase was seen. Studies that used alpha-blockers and antimuscarinics sequentially, also appeared to show little risk of acute urinary retention. The sequence was usually an alpha-blocker followed by an antimuscarinic drug if OAB symptoms continued.

The findings of this review support the recommendations in NICE GC97, which suggest offering antimuscarinics (referred to as anticholinergics in the guideline) to men with OAB, and combination treatment with alpha-blockers and antimuscarinics for those with persisting storage symptoms.

A large multicentre double-blind RCT by **Yamaguchi et al. (2011)** evaluated the effects of solifenacin as an additional treatment for men (aged ≥ 50 years) with LUTS who were also receiving treatment with tamsulosin. A total of 638 men across 84 sites in Japan were randomly assigned to receive tamsulosin 0.2 mg plus placebo, 0.2 mg tamsulosin plus 2.5 mg solifenacin or 0.2 mg tamsulosin plus 5 mg solifenacin. The primary endpoint was change from baseline to the end of treatment in the number of urgency episodes in a 24-hour period.

Urgency was reduced by 2.2 and 2.4 episodes per 24 hours in the tamsulosin plus 2.5 mg solifenacin and tamsulosin plus 5 mg solifenacin groups, respectively. The tamsulosin plus solifenacin 5 mg group demonstrated significant improvement in urgency episodes per day compared with tamsulosin plus placebo (2.4 vs 1.9, p = 0.049).

Although patients with polyuria (> 3 litres in 24 hours) were excluded, there was no mention of any modification of fluid intake that would be part of normal conservative treatment measures.

However, the number of micturitions at the end of treatment in both tamsulosin plus solifenacin combination therapy groups were significantly lowered (−1.27 micturitions for solifenacin 2.5 mg, −1.06 micturitions for solifenacin 5 mg) compared with the tamsulosin plus placebo group (−0.22 micturitions, 95% CI −0.51 to 0.06, p = 0.001 for both comparisons). No significant differences were seen for IPSS or quality of life.

Evidence from this study reinforces current recommendations to consider combination therapy for men who still have symptoms after treatment with an alpha blocker.

Key references

Athanasopoulos A, Chapple C, Fowler C et al. (2011) The role of antimuscarinics in the management of men with symptoms of overactive bladder associated with concomitant bladder outlet obstruction: an update. European Urology 60: 94–105.
Full text: www.europeanurology.com/article/S0302-2838(11)00361-7

Yamaguchi O, Kakizaki H, Homma Y et al. (2011) Solifenacin as add-on therapy for overactive bladder symptoms in men treated for lower urinary tract symptoms--ASSIST, randomized controlled study. Urology 78: 126–133.
Abstract: www.goldjournal.net/article/S0090-4295(11)00258-5/abstract

Alpha blockers

A multicentre, randomised, double-blind, placebo- and active-controlled parallel group study by **Chapple et al. (2011)** evaluated the superiority of silodosin (an alpha blocker not available in the UK at the time of publication of this Evidence Update) over placebo and non-inferiority to tamsulosin in the treatment of LUTS in men with suspected BPH. A total of 1228 men (aged ≥ 50 years) were recruited at 72 sites in 11 European countries; 955 patients were randomly assigned to silodosin 8 mg (n = 381), tamsulosin 0.4 mg (n = 384) or placebo (n = 190) once daily for 12 weeks. The primary endpoint was the change from baseline in IPSS total score.

The change from baseline in the IPSS total score with silodosin and tamsulosin was significantly superior to placebo ($p < 0.001$ for both analyses). In the intent-to-treat analysis, silodosin reduced IPSS by 2.3 points more than placebo compared with a reduction of 2.0 points more than placebo for tamsulosin (the authors specified non-inferiority as a difference up to 1.5 points on IPSS).

However, the results for both drugs in this trial were less than the minimum important difference in IPSS (3 points) defined in the full version of NICE CG97. In terms of adverse events, there was an increase in reduced or absent ejaculation during orgasm with silodosin (14%) compared with tamsulosin (2%), but there was no difference between either tamsulosin or silodosin in the incidence of orthostatic hypotension.

Data from this paper suggest that silodosin has efficacy comparable to, but without additional benefits over, tamsulosin. These results would not affect recommendations in NICE CG97, because silodosin is not available in the UK.

A Cochrane review by **Garimella et al. (2009)** evaluated the efficacy and safety of naftopidil, a selective alpha-1d antagonist (not licensed in the UK at the time of publication of this Evidence Update), for the treatment of LUTS associated with BPH. Eight Japanese trials (including 774 men, mean age 68 years), lasting a maximum of 17 weeks were identified. The primary efficacy measure was a 4-point decrease in IPSS. Five trials (including 419 men) compared naftopidil with 0.2 mg tamsulosin, and one each compared high-dose naftopidil with low-dose naftopidil, naftopidil with a plant extract and naftopidil with combination therapy with antimuscarinics. Randomisation in the studies was poorly described.

Naftopidil achieved similar effects to tamsulosin in all variables (including a mean IPSS improvement of 8.4 versus 8.9 points respectively). No statistically significant result between the two drugs was clinically meaningful. However, the tamsulosin dose used was half that

licensed for use in the UK. Naftopidil was statistically significantly better than phytotherapy in all variables, except change in post-void residual volume. Combination therapy resulted in no added change in the variables measured, compared with naftopidil alone.

The evidence on naftopidil would not affect recommendations in an update to NICE CG97 because this drug is not licensed in the UK.

Key references

Chapple CR, Montorsi F, Tammela TLJ et al. (2011) Silodosin therapy for lower urinary tract symptoms in men with suspected benign prostatic hyperplasia: results of an international, randomized, double-blind, placebo- and active-controlled clinical trial performed in Europe. European Urology 59: 342–52.
Abstract: www.europeanurology.com/article/S0302-2838(10)01058-4/fulltext

Garimella PS, Fink HA, MacDonald R et al. (2009) Naftopidil for the treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia. Cochrane Database of Systematic Reviews 7: CD007360.
Full text: www.onlinelibrary.wiley.com/doi/10.1002/14651858.CD007360.pub2/full

Desmopressin

A placebo-controlled study by **Wang et al. (2011)** evaluated the long-term efficacy and safety of low dose (0.1 mg) desmopressin in men aged ≥ 65 years with BPH and nocturnal polyuria of more than 30% of total daily urine volume. A total of 115 patients were enrolled into the study and randomly assigned to placebo (n = 58) or desmopressin (n = 57) at bedtime. The study was powered to detect a 40% difference in the proportion of those with nocturnal polyuria, nocturia and non-interrupted first sleep between the groups.

A clinical response (defined as a decrease of ≥ 2 voids per night) was attained by 35 (61.4%) patients treated with desmopressin and 8 (13.8%) patients treated with placebo ($p < 0.001$). The total nocturnal urine volumes were 392.1 ± 60.1 ml and 533.1 ± 93.3 ml in the desmopressin and placebo groups respectively. In addition, the mean first sleeping period was 120.0 ± 17.2 minutes in the desmopressin group compared with 101.6 ± 19.5 minutes for placebo ($p < 0.01$).

Study limitations included: people who dropped out of the study appear to have been excluded from the analysis and the method of blinding was not reported. Hyponatraemia, the main side-effect of concern in patients aged over 65 years occurred in 10 patients in the placebo group and 9 patients in the desmopressin group; this was said to be asymptomatic and not clinically relevant. The authors stated that serum electrolytes were monitored closely but did not specify when the electrolytes were measured. However, in the discussion, the authors commented on the need to measure electrolytes 1 week after starting desmopressin treatment and after any dose adjustment.

This study supports the recommendations in NICE CG97, which suggest using desmopressin for nocturnal polyuria if other medical causes have been excluded and other treatments have not worked, with serum sodium measured 3 days after the first dose and stopping treatment if sodium is below normal. At the time of publication of this Evidence Update, desmopressin did not have UK marketing authorisation for this indication.

Key reference

Wang CJ, Lin YN, Huang SW et al. (2011) Low dose oral desmopressin for nocturnal polyuria in patients with benign prostatic hyperplasia: a double-blind, placebo controlled, randomized study. The Journal of Urology 185: 219–23.
Absract: www.jurology.com/article/S0022-5347(10)04536-2/abstract

1.5   Surgery for voiding symptoms

Laser vaporisation

A randomised, open-label trial by **Capitan et al. (2011)** assessed the safety and efficacy of GreenLight HPS 120-W laser vaporisation compared with transurethral resection of the prostate (TURP) in men with LUTS caused by BPH. Fifty patients were randomised to laser vaporisation or TURP. Primary endpoints were IPSS, IPSS-QoL, and changes in the maximum urine flow rate at 2 years of follow-up.

Laser vaporisation and TURP showed no difference in IPSS reductions (−15.7 and −14.9, respectively, $p = 0.48$) or maximum urine flow rate (+14.5 ml/s and +13.1 ml/s, respectively, $p = 0.65$). Similarly, IPSS-QoL was the same for both treatment options (no data provided). With respect to clinical outcomes, the main differences were in the length of hospital stay and length of time using a catheter, with shorter times for laser vaporisation (both $p < 0.0001$).

The finding of better early symptom score in the laser vaporisation group was unusual – the authors explained in their conclusion that this could be because no specific questions about dysuria were asked. Although this symptom is not part of the IPSS, its omission is surprising because dysuria is known to clinicians and is important to patients.

Long-term data would be needed to demonstrate lasting efficacy compared with the gold standard of TURP. Evidence from this study has no impact on NICE CG97, although this modality is referenced in the guideline, it is not recommended because there is no evidence of adequate lasting efficacy compared with the gold standard of TURP.

Key reference
Capitan C, Blazquez C, Martin MD et al. (2011) GreenLight HPS 120-W laser vaporization versus transurethral resection of the prostate for the treatment of lower urinary tract symptoms due to benign prostatic hyperplasia: a randomized clinical trial with 2-year follow-up. European Urology 60: 734–39. Abstract: www.sciencedirect.com/science/article/pii/S0302283811005483

Holmium laser enucleation

An unblinded prospective randomised trial by **Eltabey et al. (2010)** assessed the safety, efficacy and medium-term durability of holmium laser enucleation of the prostate (HoLEP) combined with mechanical morcellation against the standard TURP in patients with bladder outlet obstruction due to BPH. Eighty patients were randomised to surgical treatment with HoLEP (n = 40) or standard TURP (n = 40). Primary outcomes were AUASS, maximum urine flow rate and post-voiding residual urine volume. Postoperative assessments were undertaken at 1, 6 and 12 months.

The HoLEP group had a greater improvement in AUASS ($p = 0.05$, 0.005 and < 0.0001 at 1 month, 6 months and 12 months, respectively) and post-voiding residual urine volumes scores ($p = 0.005$, < 0.0001 and < 0.0001 at 1 month, 6 months and 12 months respectively) versus the TURP group. By contrast, there was no significant difference in the maximum urine flow rate between the two groups at any follow-up assessment ($p = 0.64$, 0.72 and 0.78 at 1 month, 6 months and 12 months, respectively). At 1 month after surgery, 25% of patients in the HoLEP group and 20% of patients in the TURP group had irritative voiding symptoms ($p = 0.61$). Patients in the HoLEP treatment arm had shorter catheterisation times and shorter hospital stays compared with patients in the TURP treatment group. In addition, the mean haemoglobin reduction was lower in the HoLEP group (1.8 ±1.3 g/dl vs 2.9 ±1.5 g/dl, $p = < 0.05$).

The study did not provide information about the experience of the surgeons or details of patients lost to follow-up. The same surgeon performed both types of operations, however, no details were provided on how any potential bias was minimised in the study.

[Fayad et al. (2011)](#) conducted a randomised trial comparing HoLEP with bipolar TURP in 60 patients with BPH, who were sequentially assigned to undergo HoLEP or bipolar TURP and followed-up for 6 months.

HoLEP and bipolar TURP were equally effective in treating patients with LUTS due to BPH. At 6 months follow-up, there were no significant differences between the HoLEP and bipolar TURP group in mean IPSS (5.5 ± 1.1 and 5.3 ± 1.3 respectively), maximal urine flow rate (20.8 ± 1.2 ml/s and 20.6 ± 0.9 ml/s respectively) and mean post-void residual volume (20.3 ml/s ± 1.4 ml and 25.6 ml/s ± 1.9 ml/s respectively). No significant differences in the postoperative catheterisation time, hospital stay or blood loss were seen between the two groups; no patients in either group needed a blood transfusion or hypertonic saline administration. However, the long mean operative time (HoLEP = 110.5 minutes, bipolar TURP = 76.5 minutes), and the need for additional training for HoLEP were in favour of bipolar TURP.

Results from these studies adds to the evidence base that was available during the development of current guidance in [NICE GC97](#), which recommends either of these treatments.

Key references
Eltabey AM, Sherif H, Hussein AA (2010) Holmium laser enucleation versus transurethral resection of the prostate. The Canadian Journal of Urology 17: 5447–51.
Abstract: www.canjurol.com/abstract.php?ArticleID=&version=1.0&PMID=21172109

Fayad AS, El Sheikh MG, Zakaria T et al. (2011) Holmium laser enucleation versus bipolar resection of the prostate: a prospective randomized study. Which to choose? Journal of Endourology 25: 1347–52.
Abstract: www.online.liebertpub.com/doi/abs/10.1089/end.2010.0550

Bipolar versus monopolar TURP

A randomised trial by [Fagerstrom et al. (2011)](#) in men with BPH that did not respond the medical therapy or had urinary retention needing an indwelling catheter, compared bipolar with monopolar TURP with respect to the associated preoperative and postoperative complications and long-term outcome (no primary outcome stated). A total of 185 patients were randomised to bipolar or monopolar TURP and followed-up for 18 months. One third of the patients had a preoperative indwelling catheter. The average resection weight was approximately 27 g.

Fewer readmissions were seen in the bipolar TURP group compared with the monopolar TURP group (5 vs 13, $p < 0.05$), particularly those due to late haematuria. However, there were no differences in hospital stay (51 hours, range 22–163 hours vs 52 hours, range 27–365 respectively) and catheter duration (20 hours, range 13–115 vs 20 hours range 13–262 respectively) between the two groups.

There was less bleeding in the bipolar TURP group, with significantly fewer transfusions (4 vs 10, $p < 0.01$). Although patients appeared to recover faster in the bipolar TURP group, there was no significant difference in IPSS between groups at 18 months, both of which provided durable relief from symptoms associated with BPH.

Evidence from this study reinforces current guidance in [NICE CG97](#), which recommends either monopolar or bipolar TURP.

A systematic review and meta-analysis of RCTs by [Mamoulakis et al. (2009)](#) compared the effects of bipolar and monopolar TURP. Sixteen RCTs (1406 patients) were included in the review. No clinically significant differences were seen between the two treatment modalities with respect to short-term (12 months) efficacy. For the maximal urine flow rate, weighted mean difference (WMD) was 0.72 ml/s (95% CI 0.08 to 1.35, $p = 0.03$). Data relating to follow-up of more than 12 months were lacking for bipolar TURP, precluding assessment of long-term efficacy. Compared with monopolar TURP, treating 50 patients (95% CI 33 to 111) with

bipolar TURP results in one fewer case of TURP syndrome (risk difference [RD] = 2.0%, 95% CI 0.9 to 3.0%, p = 0.01); treating 20 patients (95% CI 10 to 100) results in one fewer case of clot retention (RD = 5.0%, 95% CI 1.0 to 10%, p = 0.03). TURP syndrome is hyponatraemia that can occur if irrigation solution used during the procedure is absorbed by the body.

The two treatment modalities did not differ significantly with respect to operation times, transfusion rates, retention rates after catheter removal and urethral complications. However, irrigation (WMD = 8.75 hours, 95% CI 6.8 to 10.7) and catheterisation (WMD = 21.77 hours, 95% CI, 19.22 to 24.32, p < 0.00001) duration was significantly longer with monopolar TURP. Studies included in this systematic review were fairly small with short and varied follow-up periods.

Data from this review show no significant difference in short-term efficacy between the two treatment modalities, a finding consistent with NICE CG97, which recommends both approaches. However, there was some suggestion that bipolar TURP may reduce bleeding and complications.

Key references
Fagerstrom T, Nyman CR, Hahn RG et al. (2011) Complications and clinical outcome 18 months after bipolar and monopolar transurethral resection of the prostate. Journal of Endourology 25: 1043–9.
Abstract: www.online.liebertpub.com/doi/abs/10.1089/end.2010.0714

Mamoulakis C, Ubbink DT, de la Rosette JJMCH (2009) Bipolar versus monopolar transurethral resection of the prostate: a systematic review and meta-analysis of randomized controlled trials. European Urology 56: 798–809.
Abstract: www.europeanurology.com/article/S0302-2838(09)00679-4/fulltext

Cost-effectiveness of surgical treatments

A cost-effectiveness study by **Armstrong et al. (2009)** attempted to determine which of the surgical treatments available for LUTS associated with BPH is most cost-effective. The cost-utility analysis used Markov modelling and Monte Carlo simulation. This study used a complex methodology and the authors stated that the outcome of this model should be interpreted cautiously because of the limitations of the data used.

The study concluded that initial ablation with diathermy vaporisation, followed by HoLEP for treatment failures, had an 85% probability of being cost-effective at £20,000 per quality adjusted life year. Diathermy vaporisation was expected to be carried out ubiquitously but HoLEP would be concentrated in a few specialist centres. However, the authors noted that a reduction in the length of hospital stay for TURP from 3 to 2 days meant that diathermy vaporisation no longer dominated the current reference strategy of TURP (repeated if needed). The length of hospital stay is therefore important to UK practice.

Limitations of the study were that bipolar diathermy resection was not considered (which is relevant to current practice) and that NHS reference costs were based on Healthcare Resource Group (HRG) code 3.5, which was superseded by HRG 4.0 in April 2009.

The evidence from this study is unlikely to affect NICE CG97, and the authors concluded that findings for the cost-effectiveness of initial ablation with diathermy vaporisation, followed by HoLEP for treatment failures, would need confirmation in a good quality, prospective RCT.

A critical abstract of this study, produced for the Centre for Reviews and Dissemination's NHS Economic Evaluation Database (NHS EED), concluded that the study was based on a valid methodology and that the author's conclusions were robust, but noted limitations in the available data.

Key reference
Armstrong N, Vale L, Deverill M et al. (2009) Surgical treatments for men with benign prostatic enlargement: cost effectiveness study. British Medical Journal 338: b1288
Full text: www.bmj.com/highwire/filestream/347872/field_highwire_article_pdf/0.pdf

Supporting reference
Centre for Reviews and Dissemination (2009) Surgical treatments for men with benign prostatic enlargement: cost-effectiveness study. NHS Economic Evaluation Database.
Available from: www.crd.york.ac.uk/crdweb/ShowRecord.asp?LinkFrom=OAI&ID=22009101385

1.6   Surgery for storage symptoms

No new key evidence was found for this section.

1.7   Treating urinary retention

No new key evidence was found for this section.

1.8   Alternative and complementary therapies

Serenoa repens

A systematic review by **Tacklind et al. (2009)** assessed the effects of the plant extract *Serenoa repens* in the treatment of LUTS associated with BPH. Overall, this systematic review included a total of 5222 men from 30 randomised trials lasting 4–60 weeks.

Serenoa repens was not more effective than placebo in improving IPSS urinary symptoms ([WMD = −0.77 points, 95% CI −2.88 to 1.34, $p > 0.05$). The effect of *Serenoa repens* on nocturia was significantly better than placebo (WMD = −0.78 nocturnal visits, 95% CI −1.34 to −0.22, $p < 0.05$); however, a sensitivity analysis showed a difference between older, small and weaker trials, which tended to show some benefits, and the larger newer trials, which did not show a difference (WMD = −0.31 nocturnal visits, 95% CI −0.70 to 0.08, $p > 0.05$). *Serenoa repens* did not appear to have any major safety concerns.

Evidence from this systematic review has no impact on NICE GC97, which states 'do not offer' phytotherapy.

Key reference
Tacklind J, MacDonald R, Rutks I et al. (2009) Serenoa repens for benign prostatic hyperplasia (review). Cochrane database of systematic review, Issue 2: CD001423
Full text: www.onlinelibrary.wiley.com/doi/10.1002/14651858.CD001423.pub2/full

1.9   Providing information

No new key evidence was found for this section.

2   New evidence uncertainties

No new evidence uncertainties were identified during the Evidence Update process, however current uncertainties for LUTS can be found in the NHS Evidence UK Database of Uncertainties about the Effects of Treatments (DUETs)at www.library.nhs.uk/duets/ and in the NICE research recommendations database at www.nice.org.uk/research/index.jsp?action=rr

DUETs has been established in the UK to publish uncertainties about the effects of treatment that cannot currently be answered by referring to reliable up-to-date systematic reviews of existing research evidence.

Appendix A: Methodology

Scope

The scope of this Evidence Update is taken from the scope of the reference guidance:

- Lower urinary tract symptoms. NICE clinical guideline 97 (2010). Available from www.nice.org.uk/guidance/CG97

Searches

The literature was searched to identify studies and reviews relevant to the scope. Searches were conducted of the following databases, covering the dates 17 June 2009 (the end of the search period of the most recent Annual Evidence Update) to 22 November 2011:

- CINAHL
- Cochrane Database of Systematic Reviews – Cochrane Library
- Embase
- MEDLINE
- PsycINFO
- HMIC
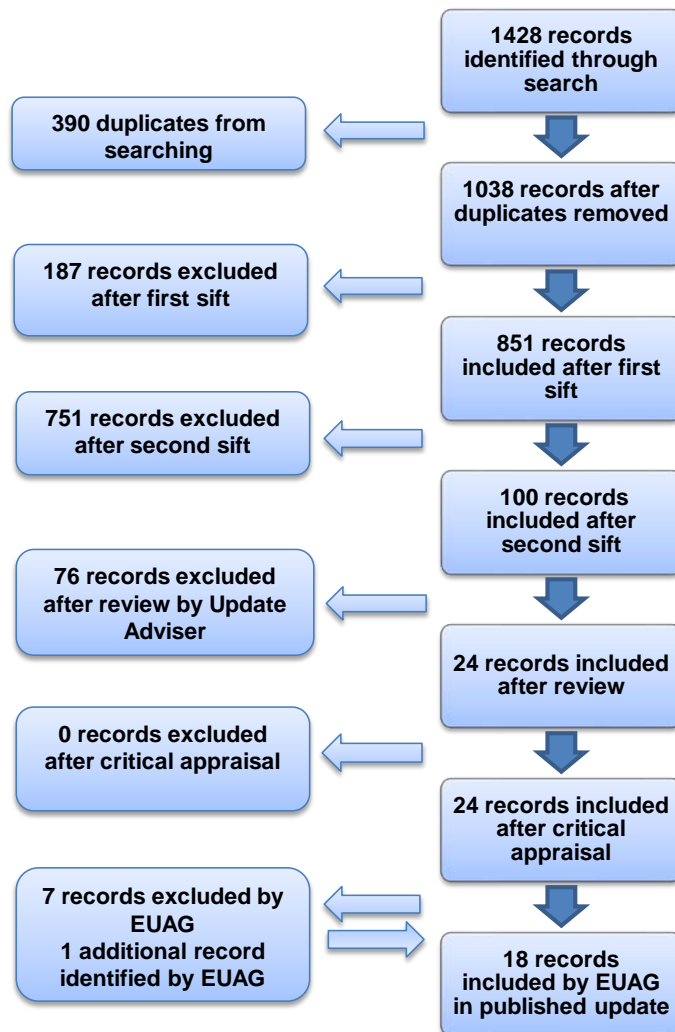- CRD databases: DARE, NHS EED and HTA

Table 1 provides details of the MEDLINE search strategy used, which was adapted to search the other databases listed above. The search strategy was used in conjunction with validated Scottish Intercollegiate Guidelines Network search filters for RCTs and systematic reviews (www.sign.ac.uk/methodology/filters.html).

One other study (Mamoulakis et al. 2009) was also identified outside of the literature search. Figure 1 provides details of the evidence selection process. The long list of evidence excluded after review by the Update Adviser (the chair of the EUAG), and the full search strategies, are available on request from contactus@evidence.nhs.uk

Table 1 MEDLINE search strategy (adapted for individual databases)

#		#	
1	Prostatic hyperplasia/	17	(retention adj5 urinary).tw.
2	Benign prostat$ disease.tw.	18	Residual urine.tw.
3	prostatism.tw.	19	urinary bladder, overactive/
4	benign prostat$ hyperplasia.tw.	20	urinary incontinence/
5	benign prostat$ enlargement.tw.	21	exp enuresis/
6	enlarged prostate.tw.	22	((micturition or urin$ or bladder or voiding) adj2 (disorder or dysfunction or symptom$ or hesitanc$ or urgency or incontinen$)).tw.
7	lower urinary tract symptom$.tw.		
8	urinary symptom$.tw.		
9	LUTS.tw.	23	(post micturition dribble or enuresis or nocturia or polakisuria or weak bladder or overactive bladder or bedwetting).tw.
10	LUTD.tw.		
11	Irritable bladder syndrome.tw.		
12	urinary retention/	24	(haematuria or hematuria).tw.
13	Bladder obstruct$.tw.	25	(male or man or men).mp,hw.
14	Incomplete bladder emptying.tw.	26	(or/7-24) and 25
15	Impaired bladder emptying.tw.	27	or/1-6
16	Storage symptom$.tw.	28	27 or 26

Figure 1 Flow chart of the evidence selection process

	1428 records identified through search
390 duplicates from searching ←	↓
	1038 records after duplicates removed
187 records excluded after first sift ←	↓
	851 records included after first sift
751 records excluded after second sift ←	↓
	100 records included after second sift
76 records excluded after review by Update Adviser ←	↓
	24 records included after review
0 records excluded after critical appraisal ←	↓
	24 records included after critical appraisal
7 records excluded by EUAG **1 additional record identified by EUAG** ← →	↓
	18 records included by EUAG in published update

EUAG – Evidence Update Advisory Group.

Appendix B: The Evidence Update Advisory Group and NHS Evidence project team

Evidence Update Advisory Group

The Evidence Update Advisory Group is a group of subject experts who review the prioritised evidence obtained from the literature search and provide the commentary for the Evidence Update.

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