NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

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NICE CLINICAL GUIDELINE 97: *LOWER URINARY TRACT SYMPTOMS – THE MANAGEMENT OF LOWER URINARY TRACT SYMPTOMS (LUTS) IN MEN* (MAY 2010)

It is the purpose of this special edition of the *PACE Bulletin* to summarize the key recommendations of the guideline and to give Lincolnshire prescribers clear advice on preferred treatments at each stage.

Key Prescribing Recommendations

Drug treatment should be considered only in men with bothersome LUTS when conservative options have been unsuccessful or are inappropriate

Recommendation 1: Offer an alpha blocker (alfuzosin, doxazosin, tamsulosin or terazosin) to men with moderate to severe LUTS but with normal prostates.

- **Offer an alpha blocker (alfuzosin, doxazosin, tamsulosin or terazosin) to men with moderate to severe LUTS but with normal prostates.**
- **As NICE make no differentiation between the four alpha blockers reviewed in terms of effectiveness and safety, the lowest cost agent should be preferred. Standard release generic doxazosin is the first line alpha blocker of choice; any remaining doxazosin MR prescribing (Cardura XL) should be switched to generic doxazosin wherever possible.**
- **Tamsulosin is a suitable alternative for elderly patients or those with a history of cardiovascular disease. Where tamsulosin is indicated, it should be prescribed as generic capsules. Patients currently prescribed a premium price tamsulosin MR formulation such as Flomaxtra XL or MR tablets, should be switched to tamsulosin MR capsules.**
- **Alfuzosin is a premium price alpha blocker and should not be prescribed routinely. It may be considered for men who have had ejaculatory problems associated with the use of other alpha blockers. It has a rapid onset of action and would be an appropriate choice if rapid relief from symptoms is required or the patient is in acute urinary retention. It is also licensed for use in urinary retention to enable early catheter removal.**
- **Indoramin and prazosin should no longer be prescribed for the treatment of LUTS; no new patients should be initiated on these therapies for the management of LUTS.**

Recommendation 2: Offer a 5 alpha reductase inhibitors (5-ARI) to men with LUTS who have prostates estimated to be larger then 30g or a PSA level greater then 1.4ng/ml and who are considered to be at high risk of progression (e.g. older men)

- **PACEF has evaluated the clinical evidence for both finasteride and dutasteride and can find no compelling evidence of one treatment being superior to another. NICE have conducted a similar review and have also failed to find reason to differentiate clinically between the two 5-ARIs.**
- **Finasteride is the first line 5-ARI of choice; it should be prescribed generically to avoid the high cost of branded Proscar. Generic finasteride tablets 5mg are designated GREEN. All new 5-ARI initiations should be for finasteride; any existing Proscar prescribing should be switched to generic finasteride.**
- **All patients prescribed finasteride should be made aware of the risk of male breast cancer and advised to promptly report any changes in breast tissue (e.g. lumps, pain or nipple discharge) to their doctor. Dutasteride has been associated with breast disorders (including breast enlargement and tenderness) and there have been a small number of cases of breast cancer reported in dutasteride treated patients. The link between dutasteride and breast cancer remains unclear, but similar vigilance among patients and clinicians is advised.**
- **Dutasteride (Avodart) should be reserved for those patients unable to tolerate or inappropriate for finasteride. It is designated AMBER and should only be initiated by a specialist; a shared care guideline is not required.**
- **Review of dutasteride prescribing is encouraged where finasteride is appropriate for use, but has never previously been prescribed.**

Recommendation 3: Offer a combination of an alpha blocker and 5-ARI to men with bothersome moderate to severe LUTS and prostates estimated to be larger than 30g or a PSA level greater the 1.4ng/ml

- **Finasteride in combination with doxazosin is the 5-ARI/alpha blocker combination of choice.**
- **Alternative alpha blockers in combination with finasteride may be a more appropriate choice dependent on individual patient circumstances as detailed under Recommendation 1.**
- **Dutasteride/alpha blocker combination therapy is only indicated where finasteride is not tolerated or inappropriate. Combodart (a dutasteride/ tamsulosin combination) is only appropriate where both components are specifically indicated; the combination product is lower in cost that the two components prescribed separately. Combodart is also designated AMBER and should only be initiated by a specialist; no shared care guideline is required.**

Recommendation 4: Consider offering an anticholinergic as well as an alpha blocker to men who still have storage symptoms after treatment with an alpha blocker.

- **Immediate release oxybutynin tablets are recommended first-line. For patients responsive to oxybutynin, but intolerant to the immediate release formulation, modified release oxybutynin tablets (Lyrinel XL) should be considered. Solifenacin (Vesicare), tolterodine (Detrusitol/Detrusitol XL), trospium (Regurin/Regurin XL) or transdermal oxybutynin (Kentara) are all endorsed by NICE as possible second line alternatives.**

Recommendation 5: Consider offering a late afternoon loop diuretic to men with nocturnal polyuria.

- **Frusemide 40mg is preferred.**

Recommendation 6: Consider offering oral desmopressin to men with nocturnal polyuria

- **This is an unlicensed indication; treatment should only be initiated after specialist assessment and advice.**

Introduction

Lower Urinary Tract Symptoms (LUTS) is an umbrella term introduced 15 years ago to dispel the perception that all urinary symptoms that arise in the male are associated with the prostate. NICE CG 97 is the first national guideline to acknowledge this and to avoid using the term BPH (benign prostatic hyperplasia). CG97 identifies four priorities for implementation:

- Initial assessment
- Conservative management
- Surgery for voiding symptoms
- Provision of information

These guidelines were developed in response to the wide variation in clinical practice across the UK in the management of LUTs. **The CG places particular emphasis on a thorough initial assessment of all patients and places conservative management of symptoms including bladder training, the use of incontinence products and appliances, before drug treatment.**

Drug Treatment

PACEF have been working with urologists from United Lincolnshire Hospitals Trust (ULHT) to develop Lincolnshire guidance on the drug treatment of this condition. **Drug treatment should be considered only in men with bothersome LUTS when conservative options have been unsuccessful or are inappropriate**.

Recommendation 1: Offer an alpha blocker (alfuzosin, doxazosin, tamsulosin or terazosin) to men with moderate to severe LUTS but with normal prostates.

- Alpha blockers are currently the most commonly used first line treatment because of their rapid onset of action. They act by reducing the contraction of the smooth muscle within the benign hyperplastic tissue of an enlarged prostate thus increasing urinary flow rate and reducing symptoms caused by obstruction.
- There are currently 6 alpha blockers licensed for the management of BPH. NICE excluded the two older alpha blockers, indoramin and prazosin, from the review as they are now little used. NICE do not differentiate between any of the four remaining alpha blockers.
- NICE concluded that alpha blockers are more effective than placebo at improving symptom scores and flow rate, although their use is associated with a number of side effects. Alpha blockers emerged from the assessment as more effective than 5-alpha reductase inhibitors (5-ARIs) in men with normal prostate size.
- Alpha blockers are associated with higher risk of orthostatic hypotension, dizziness, fatigue or asthenia and rhinitis than 5-ARIs.

- Since all alpha blockers reduce blood pressure patients receiving antihypertensive treatment may require a reduced dosage and close or specialist supervision.
- NICE also advocate a “watchful waiting “approach for men whose symptoms are either not bothersome or if they perceive that the potential adverse effects of any treatment may outweigh any benefits.

A cost comparison of the four key alpha blockers reveals the following:

Alpha blocker	Daily dose	Cost/pack	Annual cost
Alfuzosin tablets (Xatral)	2.5mg tds	£20.37 (60)	£370.73
Alfuzosin tablets (generic)	2.5mg tds	£10.39 (60)	£189.62
Alfuzosin m.r. tablets (Bezavar XL/ Xatral XL)	10mg daily	£12.51 (30)	£151.79
Doxazosin m.r. tablets (Cardura XL)	4-8mg daily	£5.00(28) 4mg m.r. £9.98 (28) 8mg m.r.	£65.00 - £129.74
Doxazosin tablets	4-8mg daily	£1.35 (28) 4mg	£17.60 – £35.20
Tamsulosin m.r.capsules	400mcg daily	£4.42 (30)	£53.78
Tamsulosin m.r. tablets (Flomaxtra XL)	400mcg daily	£10.47 (30)	£127.04
Tamsulosin m.r. capsules (Tabphyn MR)	400mcg daily	£5.99 (30)	£72.88
Terazosin tablets	5-10mg	£2.51 (28) 5mg £7.72 (28) 10mg	£32.71- £100.64
Terazosin tablets (Hytrin)	5-10mg	£4.13(28) 5mg £8.24 (28) 10mg	£53.84-£107.41

PACEF Recommendations: Alpha Blockers

1) Offer an alpha blocker (alfuzosin, doxazosin, tamsulosin or terazosin) to men with moderate to severe LUTS but with normal prostates.

2) As NICE make no differentiation between the four alpha blockers reviewed in terms of effectiveness and safety, the lowest cost agent should be preferred. Standard release generic doxazosin is the first line alpha blocker of choice; any remaining doxazosin MR prescribing (Cardura XL) should be switched to generic doxazosin wherever possible.

3) Tamsulosin is a suitable first line alternative for elderly patients or those with a history of cardiovascular disease. Where tamsulosin is indicated, it should be prescribed as generic capsules. Patients currently prescribed a premium price tamsulosin MR formulation such as Flomaxtra XL or MR tablets, should be switched to a lower cost formulation such as MR capsules.

4) Alfuzosin is a premium price alpha blocker and should not be prescribed routinely. It may be considered for men who have had ejaculatory problems associated with the use of other alpha blockers. It has a rapid onset of action and would be an appropriate choice if rapid relief from symptoms is required or the patient is in acute urinary retention. It is also licensed for use in urinary retention to enable early catheter removal.

5) Indoramin and prazosin should no longer be prescribed for the treatment of LUTS; no new patients should be initiated on these therapies for the management of LUTS.

Recommendation 2: Offer a 5 alpha reductase inhibitors (5-ARI) to men with LUTS who have prostates estimated to be larger then 30g or a PSA level greater then 1.4ng/ml and who are considered to be at high risk of progression (e.g. older men)

- 5-ARIs act on the 5-alpha reductase enzyme which converts testosterone into the more potent androgen dihydrotestosterone (DHT) within the prostatic cells. The use of 5-ARIs reduces the level of DHT resulting in prostate volume

reduction. As the action of the 5ARIs is predominately an intracellular effect, the incidence of sexual dysfunction is lower than compared to systemic castration. Compared to alpha blockers, reductions in symptoms are observed more slowly.

- **Based on evidence from randomised controlled trials, men with higher risk of progression, such as older men with poorer flows, higher symptom scores, greater residuals, larger prostates and higher PSAs, are more likely to benefit from 5-ARIs than men with normal prostates.**
- 5ARIs are associated with a higher risk of decreased libido, impotence and breast enlargement than alpha blockers.
- NICE concluded that 5-ARIs are not cost-effective in the general population of men with LUTS but they may be cost effective if they are reserved for men with larger prostates in whom they are more effective. NICE has not differentiated clinically between the two currently licensed 5-ARIs.

A cost comparison of the two available 5-ARIs reveals generic finasteride to be significantly less expensive than branded finasteride (Proscar) or dutasteride (Avodart):

Drug	Daily dose range	Cost per pack	Cost (£)pa
Dutasteride capsules 0.5mg (Avodart)	0.5mg daily	£19.80 (30)	£240.24
Finasteride tablets 5mg (generic)	5mg daily	£1.97 (28)	£25.68
Finasteride (Proscar)	5mg daily	£13.94(28)	£181.22

PACEF Recommendations: 5-ARIs

1) 5-ARIs should only be prescribed for men with LUTS who have prostates estimated to be larger then 30g or a PSA level greater then 1.4ng/ml and who are considered to be at high risk of progression (e.g. older men).

2) PACEF has evaluated the clinical evidence for both finasteride and dutasteride in the treatment of BPH and can find no compelling evidence of one treatment being superior to another. NICE have conducted a similar review and have also failed to find reason to differentiate clinically between the two 5-ARIs.

3) Finasteride is the first line 5-ARI of choice; it should be prescribed generically to avoid the high cost of branded Proscar. Generic finasteride tablets 5mg are designated GREEN. All new 5-ARI initiations should be for finasteride; any existing Proscar prescribing should be switched to generic finasteride.

4) All patients prescribed finasteride should be made aware of the risk of male breast cancer and advised to promptly report any changes in breast tissue (e.g. lumps, pain or nipple discharge) to their doctor. Dutasteride has been associated with breast disorders (including breast enlargement and tenderness) and there have been a small number of cases of breast cancer reported in dutasteride treated patients. The link between dutasteride and breast cancer remains unclear, but similar vigilance among patients and clinicians is advised.

5) Dutasteride (Avodart) should be reserved for those patients unable to tolerate or inappropriate for finasteride. It is designated AMBER and should only be initiated by a specialist; a shared care guideline is not required.

6) Review of dutasteride prescribing is encouraged where finasteride is appropriate for use, but has never previously been prescribed.

Recommendation 3: Consider offering a combination of an alpha blocker and 5-ARI to men with bothersome moderate to severe LUTS and prostates estimated to be larger than 30g or a PSA level greater the 1.4ng/ml

- The combination of alpha blockers and 5-ARIs has been shown to be more effective than either drug used alone. Treatment with alpha blockers may result in observable symptom improvements in 4-6 weeks whereas benefits associated with a 5-ARI may require up to 6 months treatment.
- The effect almost certainly works with any combination of these two drug groups but the combinations which have been most studied are doxazosin with finasteride and tamsulosin with dutasteride.
- NICE advise that patient severity at baseline should be considered in the decision to offer combination treatment. They considered the increased benefits in terms of reduction in LUTS, risk of disease progression and need for surgical progression to outweigh the higher risk of side effects when a combination is used.
- Although an economic analysis did not demonstrate that the combination is cost effective the Guidelines Development Group concluded that it might be cost effective in a selected population (e.g. men with larger prostates).

A cost comparison reveals the following:

Drug	Daily dose range	Cost per pack	Cost (£)pa
Finasteride + doxazosin tabs	5mg + 4mg	£1.97 + £1.35	£43.28
Finasteride + doxazosin tabs	5mg + 8mg	£1.97 + £2.70	£60.88
Finasteride + tamsulosin m.r	5mg + 400mcg	£1.97 + £4.42	£79.46
Combodart (dutasteride + tamsulosin)	1 capsule daily (0.5mg + 0.4mg)	£19.80 (30)	£240.24
Dutasteride + tamsulosin m.r. caps	0.5mg +400mcg m.r	£19.80 + 4.42	£294.02
Finasteride + doxazosin m.r	5mg + 4mg	£1.97+ £5.00	£90.86
Finasteride + doxazosin m.r	5mg + 8mg	£1.97 + £9.98	£155.78

PACEF Recommendation: Combination 5-ARI/Alpha Blocker Therapy

1) 5-ARI/alpha blocker combination therapy is acknowledged to be more effective than monotherapy, but, due to concerns over cost-effectiveness, should be reserved for men with LUTS who have prostates estimated to be larger then 30g or a PSA level greater then 1.4ng/ml and who are considered to be at high risk of progression (e.g. older men).

2) Finasteride, in combination with generic doxazosin, is the preferred combination of alpha blocker and 5-ARI (prescribed as separate components).

3) Alternative alpha blockers in combination with finasteride may be a more appropriate choice dependent on individual patient circumstances as detailed under the alpha blocker recommendations.

4) Dutasteride/alpha blocker combination therapy is only indicated where finasteride is not tolerated or inappropriate. The use of Combodart (dutasteride/tamsulosin combination) is appropriate only where both components are specifically indicated; the combination product is lower in cost that the two components prescribed separately. Combodart is also designated AMBER and should only be initiated by a specialist; no shared care guideline is required.

Recommendation 4: Consider offering an anticholinergic as well as an alpha blocker to men who still have storage symptoms after treatment with an alpha blocker.

- There is no evidence of a clinically important difference in efficacy between the various antimuscarinic drugs, although failure to tolerate immediate release (IR) oxybutynin may necessitate a trial of an alternative agent. Oxybutynin extended release (Lyrinel XL) should be considered as a second line alternative in patients responsive to oxybutynin, but intolerant to the IR formulation. Other alternatives include: **solifenacin (Vesicare)**, **tolterodine (Detrusitol/Detrusitol XL)**, **trospium (Regurin)** or **transdermal oxybutynin**

PACEF Recommendation
Immediate release oxybutynin tablets remain the first-line choice for urge urinary incontinence, overactive bladder or mixed UI. For patients responsive to oxybutynin, but intolerant to the immediate release formulation, modified release oxybutynin tablets (Lyrinel XL) should be considered. Solifenacin (Vesicare), tolterodine (Detrusitol/Detrusitol XL), trospium (Regurin/Regurin XL) or transdermal oxybutynin (Kentara) are all endorsed by NICE as possible second line alternatives. See previous *PACE Bulletin* Vol 3 No 13 (December 2009).

Recommendation 5: Consider offering a late afternoon loop diuretic to men with nocturnal polyuria.

- The Guideline Development Group (GDG) concluded that the addition of a late afternoon loop diuretic (unlicensed) could potentially improve night time frequency and that this benefit would outweigh any potential adverse effects such as hypovolaemia and orthostatic hypotension.

PACEF Recommendation
1) Consider offering a late afternoon loop diuretic (i.e. furosemide 40mg) to men with nocturnal polyuria, particularly where there is evidence of heart failure.
2) If there is any doubt in the differential diagnosis between polyuria and obstructive LUTS, refer the patient for specialist assessment.

Recommendation 6: Consider offering oral desmopressin to men with nocturnal polyuria

- NICE recommend that oral desmopressin should be offered to men with nocturnal polyuria if other medical causes have been excluded and they have not benefited from other treatments. Serum sodium should be measured 3 days after the first dose. If serum sodium is reduced to below the normal range, desmopressin treatment should be stopped.
- The Guideline Development Group (GDG) concluded that the benefit in reducing night time frequency outweighed the risk of potentially serious side effects such as hyponatraemia. This risk increases in elderly patients.
- The use of desmopressin for nocturnal polyuria is outside the marketing authorisation for both the oral and nasal forms of this product. Informed consent should be documented before treatment is commenced.
- When treatment is initiated, the oral form should be used and patients started on the lowest dose; careful biochemical monitoring is required to offset the risk of dilutional hyponatraemia.

PACEF Recommendation

1) Desmopressin preparations for this indication should only be initiated by or on the advice of a consultant urologist. Designation: AMBER.

2) Desmopressin should be offered to men with nocturnal polyuria if other medical causes have been excluded and they have not benefited from other treatments.

3) Measure serum sodium 3 days after first dose; if serum sodium is reduced to below the normal range, stop desmopressin treatment.

Recommendations for Review

- Discuss active surveillance or active intervention for men with mild or moderate bothersome LUTS or men whose LUTS have failed to respond to treatment
- Review men taking drug treatments to assess symptoms, the effect the drugs have on quality of life and ask about any adverse effects from treatment.
- Review men taking alpha blockers at 4-6 weeks and then every 6-12 months
- Review men taking 5-ARIs at 3-6 months and then every 6-12 months
- Review men taking anticholinergics every 4-6 weeks until symptoms are stable and then every 6-12 months.

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