Chapter 9
Male Lower Urinary Tract Symptoms (MLUTS)

Odunayo Kalejaiye, Hashim Hashim, and Matthias Oelke

Background

Introduction

Lower urinary tract symptoms (LUTS) are common in the ageing male and represent a significant burden on both the patient and the health-care system worldwide. There are a large number of high-quality trials and guidelines to support clinical practice. In this chapter, we will be exploring the assessment of men with voiding LUTS and the recommended medical and surgical therapies, as well as their outcomes. Treatment of storage LUTS is being discussed in other chapters.

Prevalence and Bother

The two largest contemporary population surveys to investigate the prevalence and bother of LUTS are the EpiLUTS and EPIC studies. The overall prevalence of any

O. Kalejaiye, MBBS, BSc, FRCS (Urol)
Southmead Hospital, Bristol, UK

Bristol Urological Institute, Southmead Hospital,
3rd Floor Learning & Research, Southmead BS10 5NB, UK

H. Hashim, MBBS, MRCS, MD, FEBU, FRCS (Urol) (✉)
Bristol Urological Institute, Southmead Hospital,
3rd Floor Learning & Research, Southmead BS10 5NB, UK
e-mail: h.hashim@gmail.com

M. Oelke, MD, FEBU
Department of Urology, Hannover Medical School,
Carl-Neuberg-Str. 1, Hannover 30625, Germany
e-mail: Oelke.Matthias@mh-hannover.de

J. Heesakkers et al. (eds.), *Practical Functional Urology*,
DOI 10.1007/978-3-319-25430-2_9

LUTS was estimated to be 62.5 % in the EPIC study. This increases with age from 51.3 % in men under 40 years to 80.7 % in men aged over 60 years. Storage symptoms are the most common symptoms with 51.3 % of men reporting this compared with 25.7 and 16.9 % who reported voiding and post-micturition symptoms, respectively. The most common storage symptoms are nocturia (48.6–69.4 %) and urgency (10.8–22.4 %). There is an overlap between storage, voiding and post-micturition symptoms. It is estimated that 9–10 % will present with a combination of voiding and storage symptoms and 24.2 % with all three symptom groups. In addition, 62.5 % will present with one or more LUTS. Understandably as the number of LUTS increases, the proportion bothered significantly by their symptoms also rises. Although storage symptoms remain the most bothersome and prevalent symptoms, voiding symptoms are more likely to be the reason for referral to secondary care. In addition, voiding symptoms are more likely to be treated initially as treatment is often prostate focused.

Definitions

LUTS was a term coined in the late 1990s to dissociate urinary symptoms from the assumed source of their origin, traditionally perceived to be the prostate in men. In 2002, the International Continence Society (ICS) divided LUTS into three groups with symptoms defined from the patient's perspective. The groups are:

- Storage: urgency, frequency, nocturia, urgency and urinary incontinence
- Voiding: slow stream, hesitancy, intermittency, straining and terminal dribbling
- Post-micturition: feeling of incomplete emptying and post-micturition dribble

Aetiology

The underlying aetiology of LUTS is multifactorial with causes being split into urological and non-urological causes. For this chapter, we will focus on the urological causes; however, when assessing the patient in the office, it is also important to consider all the non-urological causes. The urological causes may be broadly divided into:

- Bladder: overactive bladder (OAB), impaired contractility and detrusor underactivity (DUA) during voiding, bladder tumour, cystitis and neurogenic bladder dysfunction
- Prostate: benign prostatic enlargement (BPE), bladder outlet obstruction (BOO) or benign prostatic obstruction (BPO), benign prostatic hyperplasia (BPH) and prostatitis
- Others: urethral stricture, ureteral stones, foreign body and ketamine abuse

Assessment

Objectives

The correct management is dependent on eliciting all the individual's symptoms, determining the degree of bother of each symptom and managing expectations (see Tables 9.1 and 9.2). The reason for presentation is another key aspect of the consultation. Men may present for a variety of reasons not always associated with symptom bother, i.e. public health campaigns and anxiety about the association of their symptoms with prostate cancer. Lastly, it is important to exclude underlying significant pathologies and establish the clinical profile of their condition.

Table 9.1 History and examination

Symptoms	Storage versus voiding versus post-micturition Duration Severity: i.e. incontinence episodes Degree of bother Which symptom is most bothersome Any treatment previously trialled Impact on quality of life Any precipitating factors
Drug history	Diuretics, herbal formulations, illicit drug use (especially ketamine)
Co-morbidities	Diabetes mellitus/insipidus Previous surgery: penile, prostatic or rectal (e.g. for inflammatory bowel disease) Previous trauma Neurological disorders: Parkinson's, multiple sclerosis, cerebrovascular accident, spinal cord injury, disc prolapse, spina bifida Cardiorespiratory disease: heart failure, sleep apnoea Renal disease

Table 9.2 Examination

Examination	Abdomen
	  Urinary retention
	  Surgical scars
	External genitalia
	  Phimosis
	  Meatal stenosis
	  Balanitis xerotica obliterans
	  Penile cancer
	Digital rectal examination
	  Anal tone, sensation
	  Prostate: size, irregularity, tenderness, bogginess
	  Rectal mass
	Perineal/lower limbs: motor and sensory function

Symptom Questionnaires

There are several available questionnaires which are validated in a variety of languages. They are usually sensitive to changes in symptoms and therefore can be used to monitor responses to treatment. The most widely used questionnaire is the International Prostate Symptom Score (IPSS). This eight-item questionnaire has seven symptom and one quality of life (QoL) questions. The symptom questions assess four voiding and three storage symptoms for the previous month (see Fig. 9.1). The response options range from 'not at all' (0 points) to 'almost always' (5 points). The minimum score is 0 and the maximum score 35. The symptom severity is determined based on the basis of the total symptom scores as:

- Asymptomatic: 0 points
- Mildly symptomatic: 1–7 points
- Moderately symptomatic: 8–19 points
- Severely symptomatic: 20–35 points

The QoL scores range from 0 to 6. The main limitation of the IPSS is the lack of assessment of incontinence. This means that LUTS severity may be underestimated.

International Consultation on Incontinence Questionnaire (ICIQ-MLUTS)

This validated questionnaire resulted from the ICS-BPH study. This 11-item questionnaire assesses a large spectrum of LUTS and bother scores for individual symptoms.

Bladder Diary

These are useful adjuncts in providing information about patients' drinking and voiding habits. A bladder diary records volumes voided and their times, incontinence episodes, pad usage, fluid intake and degree of urgency. Information about fluid intake allows counselling regarding fluid reduction at specific times of the day and avoidance of stimulants. The diary may also be used to diagnose nocturnal polyuria (nocturnal urine production >20 % in young individuals and >33 % in elderly of the total 24-h urine production) or 24-h polyuria (24-h urine production >40 ml/kg bodyweight). Frequent small-volume voids may indicate OAB. The time between voids may be utilised in counselling in bladder training techniques. Lastly, the maximum volume voided may be useful when performing invasive urodynamics in guiding volumes to which the patient's bladder can be filled. This also provides information about bladder capacity.

International Prostate Symptom Score (I-PSS)

Patient Name: Date:	Not At All	Less Than 1 Time In 5	Less Than Half The Time	About Half The Time	More Than Half The Time	Almost Always	YOUR SCORE
1. Incomplete Emptying Over the past month, how often have you had a sensation of not emptying your bladder completely after you finish urinating?	0	1	2	3	4	5	
2. Frequency Over the past month, how often have you had to urinate again less than two hours after you have finished urinating?	0	1	2	3	4	5	
3. Intermittency Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Urgency Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. Weak Stream Over the last month, how often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Straining Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5	
	None	Once	Twice	3 times	4 times	5 or more	YOUR SCORE
7. Nocturia Over the past month how many times did you most typically get up each night to urinate from the time you went to bed until the time you got up in the morning?	0	1	2	3	4	5	
Total I-PSS Score							

Quality of Life due to Urinary Symptoms	Delighted	Pleased	Mostly satisfied	Mixed	Mostly unhappy	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	0	1	2	3	4	5	6

The I-PSS is based on the answers to seven questions concerning urinary symptoms. Each question is assigned points from 0 to 5 indicating increasing severity of the particular symptom. The total score can therefore range from 0 to 35 (asymptomatic to very symptomatic).

Although there are presently no standard recommendations into grading patients with mild, moderate or severe symptoms, patients can be tentatively classified as follows: **0 - 7 = mildly symptomatic; 8 - 19 = moderately symptomatic; 20 - 35 = severely symptomatic.**

The International Consensus Committee (ICC) recommends the use of only a single question to assess the patient's quality of life. The answers to this question range from "delighted" to "terrible" or 0 to 6. Although this single question may or may not capture the global impact of BPH symptoms on quality of life, it may serve as a valuable starting point for doctor-patient conversation.

Fig. 9.1 International Prostate Symptom Score (IPSS)

Bright et al. have recently illustrated that the validated ICIQ-bladder diary is as reliable when completed over 3 days versus 4 days. They recommend the 3-day version.

Urinalysis

This is an inexpensive tool to exclude underlying pathologies such as diabetes, UTI, renal disease or urogenital malignancy. The European Association of Urology (EAU) expert panel recommends its use, although there is no strong evidence for its use in LUTS.

Prostate-Specific Antigen (PSA)

The serum PSA concentration may be used as a surrogate for prostate volume. A prostate volume >30 mL is associated with 3 times greater risk of acute urinary retention (AUR) and BPO-related surgery. The PSA thresholds for volumes greater than 30 mL are:

- 1.3 ng/mL for ages 50–59 years
- 1.5 ng/mL for ages 60–69 years

Recent studies have also used PSA to predict the likelihood of BPO; a PSA >4 ng/mL was shown to have an 89 % chance of being associated with BPO. The EAU currently recommends that the PSA should only be measured if it will change the patient's management or in those at risk of disease progression.

Renal Function Measurement

There is a very low risk of renal impairment in men with LUTS, less than 1 % in the Medical Therapy of Prostatic Symptoms Study (MTOPS). However, renal impairment is associated with an increased risk of complications following TURP.

The EAU recommends renal function should be checked if:

- Renal insufficiency is suspected.
- Hydronephrosis is seen on imaging.
- Surgical therapy is being considered for LUTS.

Post-void Residual (PVR) Measurement

This can be measured by transabdominal ultrasound, bladder scan or catheterisation. It can be calculated by $height \times width \times length \times 0.7$.

There are a variety of available formulae for calculating PVR, usually varying in the multiplication factor used in the formula. A high PVR was found to be associated with an increased risk of symptom progression in both MTOPS and ALTRESS. A significant PVR may be associated with BOO/BPO and/or DUA. EAU recommendation: PVR measurement should be part of routine assessment.

Uroflowmetry

This is a non-invasive urodynamic test which produces a visual representative of the strength of urinary flow. It evaluates the function of the lower urinary tract. It is a quick test which may be easily performed and interpreted in the office.

The key parameters of the test are:

- Maximum urinary flow rate (Q_{max})
- Voided volume (VV)
- PVR
- Flow pattern

Ideally, uroflowmetry should be performed twice to maximise the reliability of the results, especially when flow parameters are pathological, and the voided volume should exceed 150 mL. The flow pattern may provide suggestions regarding a diagnosis:

- Bladder outlet obstruction: reduced Q_{max}, prolonged tail
- Urethral stricture: reduced Q_{max} with plateau flat trace
- Detrusor underactivity: reduced Q_{max}, intermittent, fluctuating flow

A normal flow trace is bell shaped with Q_{max} attained with 3–10 s. Q_{max} may be affected by age, voided volume, bladder contractility and urethral resistance. The values give an indication of probability of BOO/BPO (Table 9.3). Q_{max} >15 mL/s can exclude BOO/BPO in 97 % of patients and is associated with a poorer outcome after TURP; therefore, Q_{max} >15 mL/s is one of the indications for performing invasive urodynamics prior to prostate surgery in symptomatic patients.

Invasive Urodynamics (UDS)

This invasive test involves the insertion of intravesical and rectal catheters which allows for simultaneous bladder filling, vesical and rectal pressure measurements and the

Table 9.3 Risk factors for bladder outlet obstruction

Q_{max} (mL/s)	% Obstructed
≥15	3
<15	59
≥10	28
<10	69

calculation of detrusor pressure. The test consists of filling and voiding phases. It allows for the diagnosis of bladder detrusor overactivity (DO) during filling and BOO and/or DUA during voiding which may significantly affect management. BOO and DUA may be determined using the bladder outflow obstruction index (BOOI, previously known as the Abrams-Griffiths number) and bladder contractility index (BCI), respectively (Fig. 9.2). BOO is characterised by increased detrusor pressure and reduced flow, while DUA is characterised by reduced detrusor pressure and flow during the voiding phase. The importance of establishing a UDS diagnosis is that in men with 'clinical' BOO, 57–61 % may have DO, 29 % BOO and 11 % DUA. The prevalence of DUA in men with LUTS ranges between 11 and 40 %. A study by Cannon et al. revealed that there are no UDS or symptomatic gains from TURP in men shown to have DUA. Lastly, the other advantage of invasive UDS prior to surgery is in determining the presence of preoperative DO which, after bladder outlet surgery, may result in DO incontinence. This allows for better patient counselling prior to surgery (Table 9.4).

Others

- Ultrasound: only if large PVR or history of urolithiasis (EAU 2014) (Tables 9.5 and 9.6)

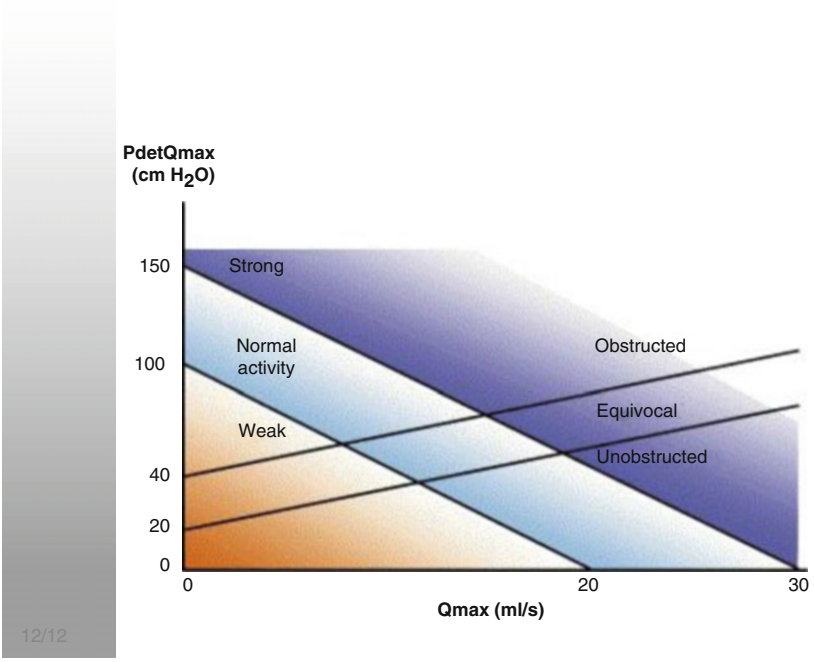

Fig. 9.2 Composite Bladder outlet obstruction index (BOOI) and Bladder contractility index (BCI) nomograms. (Hashim Hashim et al. *Eur Urol* 2007;4:1186–94)

Table 9.4 EAU recommendations for invasive urodynamics

Voided volume on uroflowmetry ≥150 ml
$Q_{max} \geq 15$ ml/s
Age <50 years or >80 years
PVR >300 mL
Suspicion of neurogenic bladder dysfunction
Bilateral hydronephrosis
Previous radical pelvic surgery
Previous failed invasive treatment

Table 9.5 Predictors for progression of LUTS/BPO

Predictor	Risk increase
Age >70 years	8
PSA >1.4 ng/mL	3
IPSS >7	3
Q_{max} <12 mL/s	4
Prostate volume >30 mL	3
PVR >50 mL	3
Prostatic inflammation	
Failure to respond to medical treatment	

Table 9.6 Complications of LUTS/BPO

Complication	Risk
Symptom progression	17–40 %
Acute urinary retention	1–2 %/year
UTI	0.1–12 %
Bladder stone	0.3–3.4 %
Renal impairment	<2.5 %
Urinary incontinence	<1 %
Haematuria	10 %

Conservative Treatment of Male LUTS

The origin of LUTS in adult men, as described above, is multifactorial and shifted away from the prostate (BPH, BPE or BPO). Although the prostate may be responsible for LUTS in some men, different organs or structures can also cause or contribute to LUTS in others, for example, the urinary bladder, pelvic floor, central or peripheral nervous system and even the kidney in case of nocturia due to nocturnal polyuria. It is sometimes difficult or even impossible to detect the primary origin of LUTS in individual patients. Therefore, symptomatic therapy of LUTS with conservative treatment modalities, regardless the exact cause, should always be the first and an essential part of the treatment in all patients without absolute indications for surgery. Conservative treatment modalities consist of:

- Education: explanation of the anatomy of the lower urinary tract, physiology of urine storage and voiding and pathologies which can lead to LUTS, instructions concerning drinking volumes as well as fluid types and explanation of the

correlation between fluid volume intake and voiding frequency (www.patients.uroweb.org/library-bpe/).

- Reassurance: explanation that not (bladder or prostate) cancer is the cause for LUTS.
- Lifestyle advice: is diverse, should be applied according to the predominant complaint and includes:
  - Reduction of the fluid volume in cases of excessive fluid intake, emptying the bladder before going to bed or when urinary frequency is most inconvenient (e.g. during travels or going out in public)
  - Avoidance of, or moderation in, caffeinated and/or alcoholic beverages which can have a diuretic or irritant effect on the bladder
  - Distraction techniques (e.g. penile squeeze, breathing exercises, perineal pressure or mental tricks) to take the mind off the bladder or toilet and to control bladder storage symptoms, i.e. the brain controlling the bladder and not the other way round
  - Bladder retraining to encourage men to hold on when they have urgency in order to increase bladder capacity and increase the time between voids
  - Providing assistance in cases of cognitive dysfunction or impairment of dexterity and mobility
  - Reviewing medications (for other indications than LUTS) and optimising the time of administration or replacement in case of urinary adverse events (e.g. diuretics)
  - Treatment of constipation
  - Use of relaxed or double-voiding techniques, pelvic floor muscle exercises with or without biofeedback support
  - Urethral milking or use of absorbents to cope with post-micturition dribble
- Periodic monitoring: regular follow-up examinations of the patient with re-evaluation of LUTS, the prostate and pathologies which have been identified and quantified during initial workup, offer to return to the clinic in case of symptom deterioration.

Conservative treatment has shown to significantly reduce LUTS to a greater extent than standard care when three self-management sessions were offered. Approximately 64 % of men do well with conservative treatment over a period of 5 years. Conservative treatment has level 1b evidence (randomised-controlled trials, RCTs), and the EAU guidelines on male LUTS recommend this treatment approach for patients with mild (to moderate) symptoms in the absence of complicated LUTS, absolute indications for surgical treatment or parameters of disease progression. Physicians should always offer conservative treatment prior or concurrent to drug treatment (grade of recommendation A).

Drug Treatment of Male LUTS

If symptom relief has been insufficient with conservative treatment modalities alone and the patient still suffers of LUTS, drug treatment can be added. There are

currently five different drug classes available which have been licensed for the treatment of male LUTS and can be used either alone or in combination:

- α-Adrenoceptor antagonists (α-blockers)
- 5α-Reductase inhibitors (5ARI)
- Muscarinic receptor antagonists (antimuscarinics)
- Phosphodiesterase type 5 inhibitors (PDE5i)
- Arginine-vasopressin analogues (desmopressin)

Approved drug classes, drugs within the different classes, the key pharmacokinetic features and recommended daily doses are listed in Table 9.7. This chapter focuses only on the drugs which have been analysed by the NICE, EAU and AUA guidelines.

In some European countries, phytotherapy is also popular and has a market share as high as 50 % of the national male LUTS market. However, plant extracts are a heterogeneous group of drugs, not universally available, and can contain different concentrations of active ingredients when comparing the extract of different producers and even different brands of the same producer. Additionally, it has yet not been clarified which active ingredient is responsible for LUTS improvement. Phytotherapy was excluded from the NICE, EAU and AUA guidelines due to methodological reasons but may be a viable treatment option for some men with mild to moderate LUTS who refuse using chemical drugs. Therefore, phytotherapy could be used to support conservative treatment.

The prescription of one drug of the above-mentioned five chemical drug classes depends on baseline values determined during systematic assessment of the patient and is largely dependent on the type of symptom (storage, voiding, storage + voiding or nocturnal polyuria), concomitant erectile dysfunction, prostate volume and the patient's willingness to use the drug long term. The flow diagram (Fig. 9.3) illustrates the evidence-based drug treatment of male LUTS with key results of the initial diagnostic tests, as described in the EAU guidelines on male LUTS in the year 2013.

α-Adrenoceptor Antagonists (α-Blockers)

The urinary bladder, bladder neck and prostate contain α_1-adrenoceptors in high density which can increase, after noradrenaline stimulation, smooth muscle tone. The effect on smooth muscle cells in the bladder outlet is primarily mediated by α_{1A}-adrenoceptors. In contrast, α_{1B}- and α_{1D}-adrenoceptors are mainly located in blood vessels, central nervous system and in the urinary bladder proximal to the bladder outlet and may also contribute to LUTS. α-Blockers act by reversible inhibition of these α_1-adrenoceptors, thereby reducing the tone of smooth muscle cells of the prostate and bladder neck and, eventually, reducing BPO and LUTS. However, the effect on BPO is only modest and does not fully explain the effects of α-blockers; other factors may therefore be responsible for LUTS reduction, such as central nervous effects.

Table 9.7 Drug classes, drugs within the classes, key pharmacokinetic properties and standard doses of drugs licensed for the treating of male LUTS (license text added next to the drug class) [Oelke M et al. *Eur Urol*. 2013;64:118–40]

Drug (class)	t_{max} [h]	$t½$ [h]	Recommended daily dose
α_1-Adrenoceptor antagonists (for treating signs or symptoms of BPH)			
Alfuzosin IR	1.5	4–6	3×2.5 mg
Alfuzosin SR	3	8	2×5 mg
Alfuzosin XL	9	11	1×10 mg
Doxazosin IR	2–3	20	1×2–8 mg
Doxazosin GITS	8–12	20	1×4–8 mg
Silodosin	2.5	11–18	1×4–8 mg
Tamsulosin MR	6	10–13	1×0.4 mg
Tamsulosin OCAS	4–6	14–15	1×0.4 mg
Terazosin	1–2	8–14	1×5–10 mg
5α-Reductase inhibitors (for treating benign prostatic enlargement due to BPH)			
Dutasteride	1–3	3–5 weeks	1×0.5 mg
Finasteride	2	6–8	1×5 mg
Antimuscarinic drugs (for treating OAB/storage symptoms)			
Darifenacin	7	12	1×7.5–15 mg
Fesoterodine	5	7	1×4–8 mg
Oxybutynin IR	0.5–1	2–4	3–4×2.5–5 mg
Oxybutynin ER	5	16	2–3×5 mg
Propiverine	2.5	13	2–3×15 mg
Propiverine ER	10	20	1×30 mg
Solifenacin	3–8	45–68	1×5–10 mg
Tolterodine IR	1–3	2–10	2×1–2 mg
Tolterodine ER	4	6–10	1×4 mg
Trospium IR	5	18	2×20 mg
Trospium ER	5	36	1×60 mg
B3 agonist (for treating OAB/storage symptoms)			
Mirabegron	3.5	50	1×50 mg
Antidiuretic (for treating nocturnal polyuria)			
Desmopressin tbl.	1–2	3	1×0.1–0.4 mg orally before sleeping
Desmopressin oral lyophilisate (MELT)	0.5–2	2.8	1×60–240 μg* sublingually before sleeping
Phosphodiesterase 5 inhibitors (for treating signs or symptoms of benign prostatic hyperplasia with or without erectile dysfunction)			
Tadalafil	2 (0.5–12)	17.5	1×5 mg

LUTS lower urinary tract symptoms, *BPH* benign prostatic hyperplasia, *ER* extended release, *GITS* gastrointestinal therapeutic system, *IR* immediate release, *MR* modified release, *OAB* overactive bladder, *OCAS* oral controlled absorption system, *SR* sustained release, t_{max} time to maximum plasma concentration, $t½$ elimination half-life, * equivalent to tablet doses of 0.1–0.4 mg

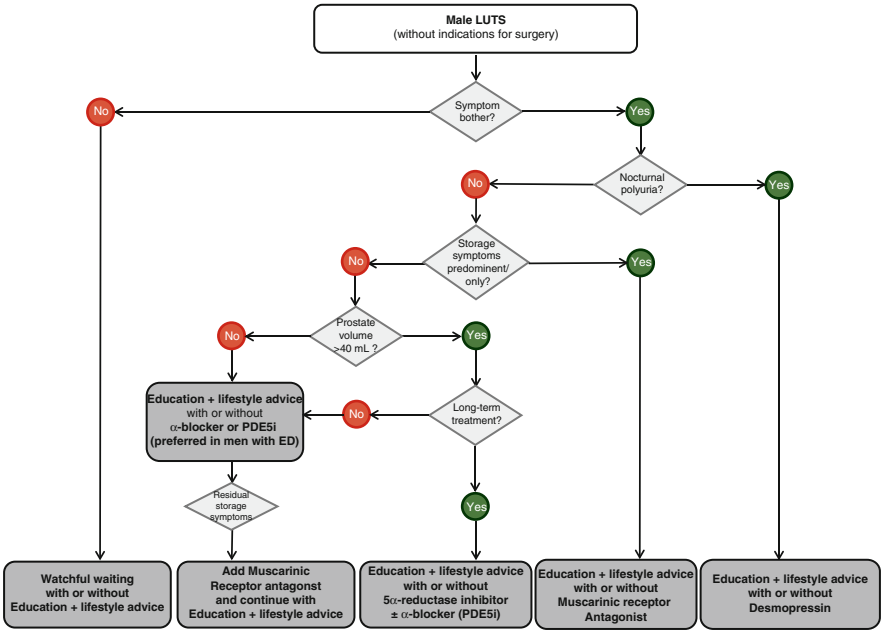

Fig. 9.3 Treatment algorithm of male LUTS with conservative treatment options and drugs, EAU guidelines on male LUTS, including BPO. *PDE5i* phosphodiesterase type 5 inhibitor, *ED* erectile dysfunction [Oelke M et al. *Eur Urol*. 2013;64:118–40]

α-Blockers are available in different formulations (Table 9.7) and have become the most popular drug class for the treatment of male LUTS during the past 25 years. Primary candidates for α-blocker therapy are men with bothersome moderate-to-severe voiding or voiding + storage LUTS. Reasons for this first-line treatment choice are obvious:

- α-Blockers can be administered in the majority of symptomatic men because the majority suffer of voiding or voiding + storage symptoms.
- They are efficacious after a few days.
- They significantly and substantially reduce storage and voiding LUTS within weeks (IPSS decrease by 30–40 % on average after placebo run-in and up to 50 % in open-label trials).
- About 60 % of men experience a clinically meaningful LUTS reduction within the first treatment month.
- They significantly improve maximum urinary flow rate (Q_{max}) within hours (by 20–25 %).
- Work independent of patients' age, prostate volume and initial symptom severity.
- Have long-lasting effects on symptoms, thereby reducing symptomatic disease progression.
- They are able to significantly improve health-related quality of life and decrease bother from LUTS.

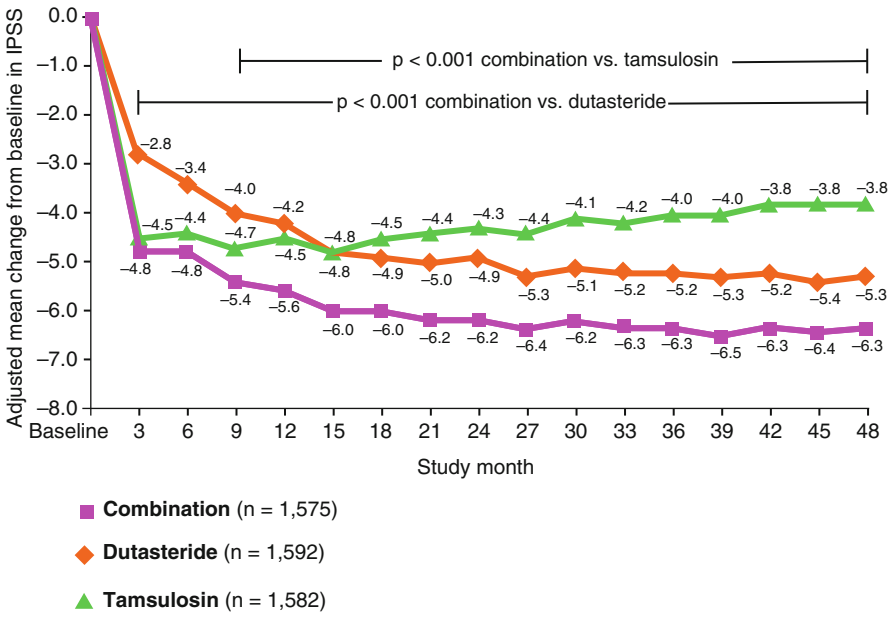

Fig. 9.4 IPSS reduction with combination therapy using α-blocker (tamsulosin 0.4 mg once daily) together with 5α-reductase inhibitor (dutasteride 0.5 mg once daily) compared to α-blocker and 5α-reductase inhibitor monotherapies (CombAT study). Combination therapy is significantly more efficacious than both monotherapies, starting at treatment month 3 for dutasteride and month 9 for tamsulosin monotherapy [Roehrborn CG et al. *Eur Urol*. 2010;57:123–31]

All available α-blockers have a significant impact on LUTS in adult men in the short-term (≤3 months) and long-term RCTs (≥12 months). No α-blocker has consistently shown superiority over other α-blockers despite differences in α_1-adrenoceptor subtype inhibition; therefore, all α-blockers are considered to be equally efficacious. However, α-blockers do not influence prostate size or PSA concentration and do not consistently reduce PVR in RCTs. Additionally, α-blockers (tamsulosin) seem to have reduced long-term efficacy in men with prostate volumes ≥40 mL (Fig. 9.4). α-Blockers have level 1a evidence (meta-analyses) and grade A recommendation in the EAU guidelines on male LUTS.

Although there are no relevant differences between the different α-blockers and formulations in terms of efficacy, the adverse event profiles are substantially different. Consequently, the choice of the α-blocker in the individual patient is largely dependent on the expected adverse event profile.

Cardiovascular Adverse Events

Cardiovascular tolerability (e.g. [orthostatic] hypotension, dizziness or asthenia) is a great concern for many α-blockers, especially for α_1-subtype unselective blockers

and when administered as immediate-release formulation. Doxazosin and terazosin are unspecific for α_1-adrenoceptor subtypes and lower blood pressure significantly, especially upon treatment initiation ('first dose hypotension'); consequently, these α-blockers have to be dose titrated when immediate-release formulation is used. The doxazosin extended-release formulation GITS (gastrointestinal therapeutic system) and alfuzosin formulations have a better tolerability profile but still lower blood pressure significantly. In contrast, tamsulosin reduces blood pressure less frequently. Nevertheless, in a recently published study of first-time users of tamsulosin in the USA (compared to users of 5ARIs), tamsulosin had significantly higher rates of severe hypotension during the first two treatment months. The hazard ratio for severe hypotension requiring hospital admissions was 2.12 for the first and 1.51 for the second treatment month but was no longer significant afterwards. Consequently, it is recommended to use α-blockers after meals and in the evening to prevent rapid lowering of blood pressure (or the clinical consequences of blood pressure decrease) and to prescribe extended-release formulations. In contrast to the other α-blockers, silodosin is highly selective for the α_{1A}-adrenoceptor subtype and does not significantly affect the blood pressure, as shown in phase III trials.

Abnormal Ejaculation

α-Blockers in general do not adversely affect libido or erectile function but may alter ejaculation. It was long believed that ejaculation disorders (reduced semen volume or dry ejaculation) were caused by retrograde ejaculation but recent studies have demonstrated that α-blockers cause (relative) anejaculation as no sperm cells were detected in the bladder after ejaculation. Of all available α-blockers and formulations, only tamsulosin and silodosin have consistently shown to cause anejaculation which occurred in RCTs with silodosin 8 mg once daily in up to 28 % of patients. However, post hoc analyses have shown that anejaculation was often associated with a more pronounced LUTS reduction and high-treatment persistence. Therefore, anejaculation seems to be a good predictor of LUTS treatment response and satisfaction. Anejaculation is no special threat for the patient and is reversible. As the majority of men are in their mid-60s or older when treated for voiding LUTS, (relative) anejaculation and subsequent infertility are often no major issues for this patient group anymore.

Intraoperative Floppy Iris Syndrome (IFIS)

Ocular adverse events have first become evident in the year 2005 when three phenomena during cataract surgery were described in tamsulosin users: (1) an iris that flutters and billows to normal intraoperative fluid movements, (2) prolapse of iris tissue to surgical incisions and (3) progressive intraoperative miosis despite standard preoperative pupil dilation. This triad has also been described for almost all α-blockers (including those for the treatment of arterial hypertension, e.g. prazosin,

indoramin or labetalol) and, interestingly, also for drugs with partial α-adrenoceptor blocking abilities (e.g. antipsychotics, antidepressants, benzodiazepines, serenoa repens) as well as finasteride. IFIS can occur in one eye only, may be incomplete (appearance of only 1 or 2 phenomena of the triad), can be seen in both men and women and can be seen even after a long time after cessation of α-blocker therapy. Preliminary results suggest that IFIS is irreversible and a consequence of pharmacologic inhibition of the smooth musculature of the iris and smooth muscle atrophy due to drug accumulation in the iris pigment. Although IFIS is not life threatening, precautions should be taken in patients who are scheduled for cataract surgery, such as delaying α-blocker use, prescribing PDE5i instead and performing cataract surgery only by an experienced ophthalmologists (overview and recommendations of the American Academy of Ophthalmology).

5α-Reductase Inhibitors (5ARIs)

The hormonal environment of the prostate and prostate growth is mainly regulated via testosterone which is converted to the active androgen dihydrotestosterone by the enzyme 5α-reductase located in prostatic stromal cells. In the male body, two isoforms of 5α-reductase have been detected: 5α-reductase type 1 with major activity in the liver and skin (hair follicles) and minor activity in the prostate and 5α-reductase type 2 with predominant expression and activity in the prostate. Inhibition of the enzyme 5α-reductase (by 5ARIs) reduces the intraprostatic dihydrotestosterone concentration, induces apoptosis of prostatic epithelial cells and reduces prostate size by approximately 18–28 % after 1–4 years and serum PSA concentration by about 50 % after 6–12 months of treatment. Prostate size reduction can significantly lower the BPO grade and eventually improve LUTS. Because the serum PSA concentration is used for prostate cancer screening and detection, serum PSA concentration has to be multiplied by 2 during 5ARI treatment.

Two 5ARIs have been licensed for the treatment of male LUTS due to BPE: finasteride inhibits 5α-reductase type 2 only, whereas dutasteride inhibits both 5α-reductase types 1 and 2 ('dual inhibition') (Table 9.7). Although dutasteride reduces serum dihydrotestosterone concentration to a greater extent than finasteride (95 % vs. 70 %), the intraprostatic concentration of dihydrotestosterone is reduced to a similar level with both 5ARIs (~85–90 %). No relevant differences in terms of efficacy or adverse events have been detected between the two drugs.

Reduction of LUTS versus placebo is first seen after several months of treatment; the time of onset is mainly determined by the initial prostate volume. The larger the prostate at baseline, the faster the effects on LUTS become evident. 5ARIs are usually not more efficacious than placebo in men with prostate volumes <40 mL. After treatment duration of 2–4 years, 5ARIs reduce LUTS (IPSS) by approximately 15–30 % and increase Q_{max} by 1.5–2.0 mL/s. In direct comparison to α-blockers, 5ARIs reduce LUTS slower and less effectively; however, 5ARIs (dutasteride) were able to reduce LUTS to a greater extent than α-blockers (tamsulosin) after a

treatment duration of 15 months if initial prostate volume was >30–40 mL (Fig. 9.4); the longer the treatment, the stronger the effects of dutasteride were versus tamsulosin (after 4 years: IPSS −5.3 vs. −3.8, Q_{max} +2.4 vs. +0.7 and quality of life [BPH Impact Index] −1.8 vs. −1.2). Therefore, long-term treatment with 5ARIs is necessary to significantly reduce LUTS and improve quality of life.

5ARIs are currently the only drug class which can prevent disease progression with regard to acute urinary retention or need for prostate surgery. BPH disease progression and acute urinary retention appear especially in older men with enlarged prostates (see section assessment and Table 9.5). Several trials have proven that both 5ARIs can significantly reduce acute urinary retention after minimum treatment duration of 6–12 months (relative risk reduction 57–68 % after 1–4 years). In the CombAT trial, in which dutasteride was compared against tamsulosin (and combination treatment) for a total duration of 4 years only in men with prostate volumes >30 mL, dutasteride was able to significantly reduce acute urinary retentions already after 8 months. BPO-related surgery is reduced with 5ARIs by 34–70 % after 1–4 years of treatment; the large variation between the numbers is possibly reflecting the missing standardisation when to perform surgery in patients without urinary retention. The EAU guidelines on male LUTS recommended using 5ARIs only in patients with moderate-to-severe LUTS, prostate volumes >40 mL and men who are willing to use 5ARIs for at least 1 year. 5ARIs have level 1a evidence and grade A recommendation.

Adverse events of 5ARIs are mainly related to sexual function and include decreased libido, erectile dysfunction and ejaculation disorders (e.g. retrograde ejaculation, reduced semen volume or anejaculation). Patient-reported sexual adverse events appear in RCTs in low frequency (<10 %) and especially during the first 1–2 years of treatment, but open-label studies suggest higher frequencies in real-life practice. Similar to anejaculation in patients with α-blockers, the majority of sexual adverse events are no major issue for patients with ARIs. Interestingly, the addition of PDE5i (tadalafil 5 mg once daily) can antagonise the sexual adverse events during 5ARI therapy (finasteride 5 mg once daily). Additionally, gynecomastia and nipple pain are reported by patients with 5ARIs with low frequency (approximately 1–2 % of study participants). Long-term trials with 5ARIs have also detected (slightly) increased rates of breast cancer (4/3047 cases of the MTOPS study), but the relationship between 5ARIs and male breast neoplasia is currently unknown. The same is true for the development of high-risk prostate cancers in patients treated with 5ARIs.

Muscarinic Receptor Antagonists (Antimuscarinics)

The main neurotransmitter of the urinary bladder is acetylcholine which binds to muscarinic receptors on the surface of the bladder urothelial and smooth muscle cells in order to initiate detrusor contractions. There are five different muscarinic receptor subtypes in the human body ($M_{1–5}$) of which only M_2 and M_3 are mainly

expressed in the bladder. Reversible inhibition of muscarinic receptors (by antimuscarinics) decreases muscarinic receptor stimulation and, consequently, increases the threshold for urothelial receptor depolarisation (afferent loop) and smooth muscle cell contraction (efferent loop). Measurable urodynamic effects of antimuscarinics are, besides others, increased bladder capacity, reduction of the amplitude as well as frequency of involuntary detrusor contractions and (slight) decrease of detrusor contraction power. Although approximately 80 % of muscarinic receptors of the human bladder are M_2 subtypes, only the M_3 receptor subtype (~20 %) seems to be involved in detrusor contractions in healthy humans. All available antimuscarinics (Table 9.7) inhibit to a variable amount M_2 and M_3 receptors, and some have also inhibitory function on calcium channels and α-adrenoceptors (e.g. propiverine).

Based on the mechanism of action, antimuscarinics are particularly useful for the treatment of bladder storage symptoms, such as urgency, frequency and urgency incontinence. Approximately 45–50 % of adult men with LUTS have storage symptoms, of which 10 % of men have them alone and 35–40 % in combination with voiding symptoms. Antimuscarinics have been evaluated for the treatment of LUTS in men with bothersome moderate-to-severe storage and voiding symptoms (alone or in combination with α-blockers). The greatest amount of data on the treatment of male LUTS or male OAB exists with the three antimuscarinics, fesoterodine, solifenacin and tolterodine, but it is assumed that there is a class effect and all antimuscarinics exhibit similar effects in this patient group. Muscarinic receptor antagonists have level 1b evidence and grade B recommendation in the EAU guidelines on male LUTS.

The majority of participants investigated in RCTs or post hoc analyses were men without BOO. It was demonstrated that antimuscarinics can significantly:

- Reduce daytime and 24-h frequency.
- Suppress urgency episodes, urgency intensity and urgency-related voiding.
- Reduce urgency urinary incontinence.
- Improve scores of disease-specific questionnaires (e.g. IPSS or IPSS-QoL) of which some are specifically addressed to bladder storage symptoms/OAB (e.g. patient perception of bladder condition [PPBC], overactive bladder questionnaire [OAB-q] or patient perception of intensity of urgency scale [PPIUS]).

Improvement of LUTS with antimuscarinic monotherapy (tolterodine) seems to be more pronounced and significantly superior in men with serum PSA concentrations <1.3 μg/L. Because serum PSA is a proxy parameter for prostate volume, tolterodine is especially efficacious and useful in men with smaller prostates (<30 mL).

Adverse events of antimuscarinics in men are mainly related to M_2 and M_3 muscarinic receptor inhibition outside of the bladder (e.g. in salivary glands, intestine or vessels). These adverse events are typical for antimuscarinics, have already been described for female OAB and are not different in frequency or severity in men. Compared to placebo, the following adverse events appear with a higher frequency in men treated with antimuscarinics: most frequently dry mouth, followed by dizziness, constipation, nasopharyngitis, blurred vision and voiding difficulties. Based

on the mechanism of action of antimuscarinics and M_2 as well as M_3 receptor inhibition in the bladder, it is possible that a decrease of detrusor contraction power could significantly increase PVR and provoke (acute) urinary retention. Although some RCTs have shown a (slight) decrease of Q_{max} and a (slight) increase of PVR/urinary retention, others could not confirm this finding or even observe opposite effects. It was shown in one post hoc analysis of pooled data of two fesoterodine studies that especially older men (≥66 years of age) during the first weeks of treatment using the higher dose (8 mg once daily) have a (slightly) increased risk to develop PVR or urinary retention. It therefore appears safe to use antimuscarinics in men but it is still recommended to control PVR during the first treatment weeks to detect PVR increase. Additionally, patients should be informed about the symptoms and signs of (acute) urinary retention.

Phosphodiesterase Type 5 Inhibitors (PDE5i)

Nitric oxide is an important neurotransmitter in the human body and also involved in the signal transmission of the urinary bladder. Nitric oxide stimulates the synthesis of cyclic guanosine monophosphate (cGMP) in the cell where it activates protein kinases and ion channels which are responsible for (detrusor) smooth muscle cell relaxation. The effects of PDE are stopped by PDE isoenzymes which catalyse the hydrolysis of cGMP to inactive molecules. PDEi increase the intracellular concentration of cGMP by blocking the hydrolysis and, therefore, prolong the relaxing effects on smooth muscle tone of the urinary bladder, prostate and urethra. Of the 11 PDEs in the human body, especially PDE4 and PDE5 are expressed in the lower urinary tract and transition zone of the prostate. Next to relaxation of the smooth musculature of the bladder outlet, other mechanisms of action may also contribute to the clinical effects of PDE5i, such as modulation of autonomic innervation of the bladder, downregulation of the Rho-kinase activity in the prostate and increase of blood flow in pelvic organs. However, the exact mechanism of action of PDE5i still remains to be determined.

Of the PDE5i in clinical use, RCTs have been performed with sildenafil, tadalafil and vardenafil (Table 9.7). While all oral PDE5i are used for the treatment of erectile dysfunction, only tadalafil (5 mg once daily) has been licensed for the treatment of male LUTS (with or without erectile dysfunction). Clinical studies have shown that approximately 60–70 % of elderly men with LUTS also have erectile dysfunction; therefore, PDE5i (tadalafil) seems to be especially suitable for co-morbid patients with bothersome moderate-to-severe LUTS and erectile dysfunction. PDE5i have level 1a evidence and grade A recommendation in the EAU guidelines on male LUTS. PDE5i have shown in RCTs to subjectively significantly improve:

- Storage and voiding LUTS (IPSS decrease 17–37 %) as early as 1 week after start of treatment
- Nocturia (nocturnal voiding frequency)

- LUTS over a period at least 12 months
- Quality of life (IPSS-QoL, BPH Impact Index)
- Treatment satisfaction (TSS-BPH scale)
- Erectile and ejaculatory function in those men with erectile dysfunction at baseline (IIEF-questionnaire)

Treatment effects of tadalafil are independent on pre-existing erectile dysfunction and similar to the α-blocker tamsulosin; however, treatment satisfaction is greater with tadalafil versus placebo or tamsulosin. Treatment effects (and adverse events) are not influenced by baseline parameters, such as age, LUTS severity, prior α-blocker or PDE5i use, baseline serum testosterone concentration or prostate volume. However, it is important to realise that PDE5i have not demonstrated to objectively influence prostate volume, PVR, Q_{max} (only in one RCT and in subgroups) or disease progression.

Adverse events of PDE5i in studies of men with LUTS are nearly identical to studies in men with erectile dysfunction. Adverse events include headache, flushing, dizziness, dyspepsia, nasal congestion, myalgia, back pain, hypotension, syncope, tinnitus and altered vision (blurred or discoloration). All adverse events appear with low frequency, are reversible and usually do not cause harm to the patient. The appearance of priapism or (acute) urinary retention is unlikely, and both adverse events have not been seen in RCTs in patients with LUTS. Caution is advised in men with coronary or cerebral artery diseases who use potassium channel openers or the α-blocker doxazosin or terazosin (for the treatment of arterial hypertension) because PDE5i can cause hypotension which, together with other blood pressure-lowering drugs, can lead to myocardial infarction or cerebrovascular strokes.

Arginine-Vasopressin Analogues (Desmopressin)

Arginine-vasopressin (AVP) is a hormone secreted by the hypothalamus in a circadian rhythm which can increase blood pressure by binding to V1 receptors in blood vessels and retain water by binding to the V2 receptor of the renal collecting duct. Stimulation of the V2 receptor leads to cAMP- and protein kinase A-mediated activation of aquaporin channels which are responsible for reabsorption of water in the kidney, thereby decreasing urine excretion and increasing urine osmolality.

Desmopressin is a synthetic AVP analogue with V2 receptor-binding activity only, avoiding V1 receptor-induced vasoconstriction. Vasopressin is available as tablet or MELT formulation (Table 9.7) and has been used for the treatment of diabetes insipidus or nocturnal enuresis for decades. Lately, desmopressin has also been licensed for the treatment of nocturia, in those under the age of 65, due to nocturnal polyuria (i.e. nocturnal urine production >33 % of the 24 h urine production). It was shown in adult men with nocturia that more than 80 % had nocturnal polyuria of whom 20 % had nocturnal polyuria alone and more than 60 % had

nocturnal polyuria in combination with decreased functional bladder capacity due to LUTS/BPE or BPO. Desmopressin should be taken before going to sleep at night. Additionally, the patient has to be instructed to avoid drinking fluids 1 h before until 8 h after using desmopressin. Clinical effects (i.e. decrease of urine excretion) are apparent for approximately 8 h. Desmopressin has level 1b evidence and grade A recommendation in the EAU guidelines on male LUTS.

Dose titration of desmopressin is recommended, starting with 0.1 mg tablets and escalating until 0.4 mg (or equivalent doses when using the MELT formulation) in intervals of at least 1 week. Desmopressin showed in RCTs the following significant effects:

- Reduction of diuresis by 0.6–0.8 mL/min (~40 %)
- Decrease of the frequency of nocturnal voids by 0.8–1.3 (~40 %)
- Reduction of the night-time urine volume
- Increase of the hours of undisturbed sleep and the time until the first void at night by 1.6–2.1 h
- Improvement of the quality of sleep as well as health-related quality of life

Desmopressin effects are more pronounced in patients with more severe nocturnal polyuria compared to those with a less severe condition. However, the 24-h diuresis with desmopressin is unchanged as diuresis is increased after the antidiuretic effects of the drug have diminished in the morning; therefore, retained water during night time is excreted during the daytime. Clinical effects of antidiuresis at night with desmopressin are stable over an observational period of 12 months and return to baseline values once desmopressin treatment should be stopped again.

Nocturia has been identified to be the leading cause for sleep disturbance and sleep fragmentation, causes daytime fatigue, impacts daily activities and deteriorates psychomotor performance, cognitive function and mood. Nocturia can also cause depression, immune suppression, increases vulnerability for cardiovascular diseases and may contribute to the development of diabetes mellitus type II. Additionally, nocturia ($\geq$2 times per night) significantly increases accidents, falls and fractures. It is expected that antidiuretic treatment with desmopressin can also prevent patients from these consequences of nocturia, although studies to demonstrate these beneficial effects have not been conducted for most of the parameters. However, studies could show that patients feel fresher in the morning and have less daytime fatigue after using desmopressin.

Adverse events with desmopressin are rare and usually mild in nature. The most frequently seen adverse events with desmopressin are headache, diarrhoea, nausea, abdominal pain, dizziness, dry mouth and hyponatraemia (serum sodium concentration <130 μmol/L). In long-term trials (12 months), peripheral oedema (2 %) and arterial hypertension (5 %) were also documented. Of all adverse events, only hyponatraemia is potentially dangerous as it could cause nausea, vomiting, headache, short-term memory loss, confusion, lethargy, restlessness, muscle weakness, cramps, seizures, decreased consciousness and coma. Hyponatraemia, not necessarily associated with symptoms or signs, appears during desmopressin treatment in men and women in 5–7.6 %. However, hyponatraemia predominantly develops in

women and patients aged ≥65 years. Studies in experimental animals and humans have suggested that women have a higher sensitivity of vasopressin to the V2 receptor in the kidney, leading to a fivefold higher risk of hyponatraemia in women aged >50 years. Therefore, equivalent doses of desmopressin result in lower overall efficacy in men compared to women but also lower risk of hyponatraemia, suggesting no major threat of developing hyponatremia in men with the standard doses between 0.1 and 0.4 mg once daily (or equivalent doses of the MELT formulation). Known risk factors for developing hyponatraemia are, besides age and gender, low serum sodium concentration at baseline (at the bottom of the normal serum sodium range of 135–145 μmol/L) and higher basal 24-h urine volume per bodyweight. Although the risk of hyponatraemia appears to be low in men, it is still recommended to monitor serum sodium concentration at baseline and days 3, 7 and 30 of treatment. Once the patient is on a stable dose and serum sodium has not decreased, it is recommended to check serum sodium concentration every 3–6 months. If the dose of desmopressin needs to be escalated, the same time intervals for monitoring serum sodium concentration should be chosen again.

α-Blocker + 5ARI Combination Therapy

The simultaneous use of an α-blocker and a 5ARI aims to combine the beneficial effects of both drug classes which are, besides others, fast, substantial and long-lasting symptom relief with α-blockers and decrease of prostate volume as well as the ability to prevent (acute) urinary retention or the need for prostate surgery with 5ARIs. Combination therapy is more efficacious in relieving LUTS (including nocturia) or improving Q_{max} than the α-blocker or 5ARI alone (Fig. 9.4). However, prostate volume is not more reduced with combination therapy than monotherapy. Superiority of combination therapy has been demonstrated in several trials for several α-blockers and for both dutasteride and finasteride. Compared to monotherapy, LUTS decrease with combination therapy is significantly more efficacious after >1 year of treatment but, however, is dependent on initial prostate volume or PSA concentration (as a proxy parameter of prostate volume); men with prostates >40 mL (or serum PSA concentration >1.6 μg/L) have a faster symptom reduction than men with smaller prostates. For patients who completed the study period in the CombAT study, mean change in IPSS from baseline until the end of year 4 was significantly higher for the combination therapy compared to tamsulosin or dutasteride alone (Fig. 9.4). Decrease of IPSS-QoL score was significantly greater for the combination treatment (−1.5) compared to tamsulosin (−1.1) or dutasteride (−1.3). Q_{max} improvement was also significantly higher for combination treatment (2.4 mL/s) compared to tamsulosin (0.7 mL/s) or dutasteride (2.0 mL/s). There was a tendency towards a continuous decrease of IPSS and continuous increase of Q_{max} for dutasteride monotherapy and combination treatment over time, whereas both parameters worsened with tamsulosin monotherapy after 15–18 months (Fig. 9.4). Interestingly, PVR significantly decreased in the treatment arms containing dutasteride but not with tamsulosin alone. The EAU guidelines on male LUTS recommend

combination treatment with an α-blocker and a 5ARI in men with bothersome moderate-to-severe LUTS, enlarged prostates and reduced Q_{max} (men likely to develop disease progression), but combination therapy only seems useful when treatment duration exceeds 12 months. Combination therapy has level 1b evidence and grade A recommendation.

SMART was an RCT that evaluated the combination of tamsulosin with dutasteride and the impact of tamsulosin discontinuation after 6 months. After discontinuation of the α-blocker, almost three quarters of patients reported no worsening of symptoms. However, patients with severe symptoms (IPSS ≥20) at baseline showed symptom deterioration and, therefore, seem to benefit from longer combination therapy.

Prevention of disease progression (i.e. IPSS increase ≥4 points, (acute) urinary retention and need for prostate surgery but also the appearance of urinary incontinence, urinary tract infection or renal insufficiency) is also more pronounced with combination therapy compared to α-blocker or 5ARI monotherapy. Two long-term studies evaluated the ability of combination therapy to reduce disease progression, the MTOPS trial (using placebo, doxazosin, finasteride or combination for a mean follow-up of 4.5 years) and the CombAT trial (using tamsulosin, dutasteride or combination for a follow-up of 4 years). MTOPS, which included men with the entire range of prostate volumes without any lower limit, showed that combination therapy was significantly more efficacious in reducing disease progression than placebo, α-blocker and 5ARI alone but the risk of disease progression was similar with doxazosin compared to finasteride (Fig. 9.5). At the end of the study, disease progression occurred in 17 % of men with placebo, 10 % with doxazosin, 10 % with finasteride and 5 % with combination therapy. Overall, combination therapy significantly reduced the overall risk of disease progression by 66 % versus placebo and was also significantly better than the monotherapies with doxazosin or finasteride versus placebo (39 % and 34 %, respectively). Additionally, finasteride alone and in combination but not doxazosin was able to significantly reduce the disease progression parameters of acute urinary retention and need for prostate surgery. The CombAT study, which included only men with prostate volumes >30 mL, confirmed that combination therapy was significantly more efficacious than monotherapy with tamsulosin or dutasteride in terms of prevention of disease progression. The time to first clinical progression was significantly longer with combination therapy which, after 4 years, reduced the relative risk of BPE disease progression by 44.1 % compared to tamsulosin and by 31.2 % compared to dutasteride. Compared to tamsulosin monotherapy, combination therapy was significantly more efficacious in reducing the relative risk of acute urinary retention and need for prostate surgery by 67 % and 71 %, respectively. Compared to dutasteride monotherapy, combination therapy reduced the relative risk of acute urinary retention and need for prostate surgery by 18.3 % and 31.1 %, respectively, but this risk reduction with combination therapy was not significantly lower than with dutasteride monotherapy. Taken together the results of combination therapy, this treatment approach is especially useful for patients who are likely to develop BPE disease progression; patients suitable for combination therapy can be identified by careful assessment and evaluation of symptoms and signs of BPE disease progression (see section assessment and Table 9.5).

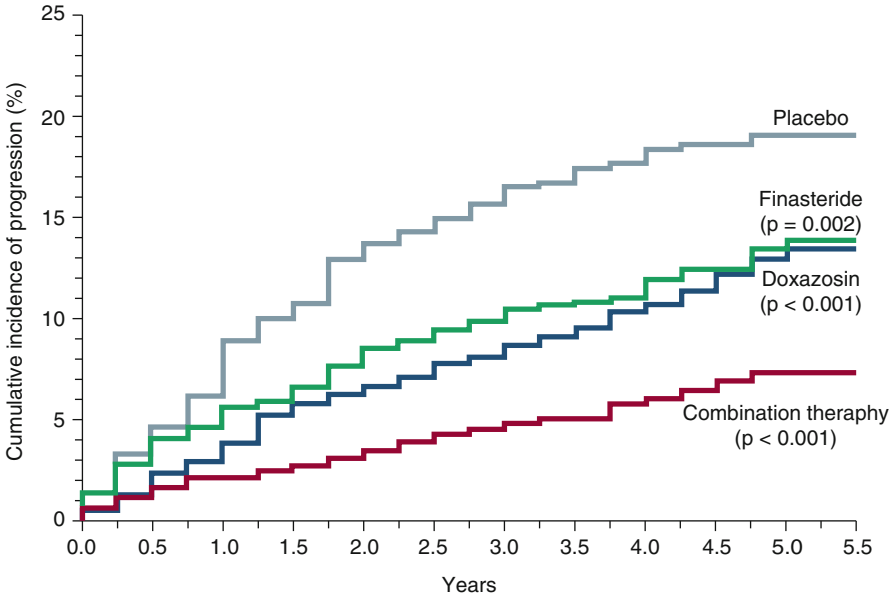

Fig. 9.5 Cumulative incidence of BPE disease progression with placebo, α-blocker (doxazosin), 5α-reductase inhibitor (finasteride) and combination therapy (doxazosin + finasteride). BPH disease progression is significantly reduced with doxazosin, finasteride or combination therapy versus placebo. Doxazosin mainly inhibited LUTS deterioration, whereas finasteride mainly inhibited (acute) urinary retention and need for prostate surgery (MTOPS study) [McConnell JD et al. *New Eng J Med*. 2003;349:2387–98]

The types of adverse events are identical to those of α-blockers or 5ARIs, but the frequency is higher for combination therapy, especially for erectile dysfunction, dizziness, postural hypotension, asthenia, decreased libido, abnormal ejaculation, peripheral oedema and dyspepsia. Therefore, physicians have to weigh the treatment benefits against potential adverse events in the individual patient before initiation of combination therapy.

α-Blocker + Antimuscarinic Combination Therapy

The simultaneous use of an α-blocker and an antimuscarinic aims to combine the beneficial effects of both drug classes which are, besides others, fast, substantial and long-lasting relief of voiding symptoms with α-blockers and fast, substantial and long-lasting relief of storage symptoms with antimuscarinics. Therefore, this combination therapy is especially useful in patients with both storage and voiding LUTS. As α-blockers are also able to reduce storage symptoms in some patients (˜35 %), it is recommended to use combination therapy only when α-blockers have failed to adequately reduce storage symptoms in patients suffering with both storage and voiding symptoms, and they are still bothered (add-on therapy). It was shown in the SATURN study that combination

therapy of an α-blocker (tamsulosin) together with an antimuscarinic (silodosin in different doses) does not add any additional effects if the patients suffer only or predominantly of voiding symptoms. However, if the patient has substantial storage and voiding LUTS, combination therapy is significantly more efficacious in reducing 24-h daytime and night-time voiding frequency, urgency intensity, total urgency-frequency score (TUFS), urgency urinary incontinence episodes and IPSS total as well as IPSS storage sub-score compared to α-blocker monotherapy or placebo. Additionally, voided volume and health-related quality of life scores improve significantly with combination therapy compared to α-blocker monotherapy or placebo. The TIMES study indicated that LUTS improvement with combination therapy works independent of prostate volume (or serum PSA concentration as a proxy parameter). Treatment effects with combinations of α-blocker (tamsulosin) and an antimuscarinic (solifenacin) are maintained for at least 12 months. A urodynamic study demonstrated that bladder contractility index and voiding efficiency remained unchanged with combination therapy using tamsulosin 0.4 mg and solifenacin 6 or 9 mg once daily. The EAU guidelines on male LUTS recommend using combination therapy in patients with moderate-to-severe LUTS if relief of storage symptoms has been insufficient with either monotherapy. Combination therapy has level 1b evidence and grade B recommendation.

The types of adverse events are identical to those of α-blockers or antimuscarinics. The most frequently reported adverse event in all trials on combination therapy is dry mouth. Some adverse events appear with increased frequency (e.g. dry mouth, dizziness or ejaculation disorders) and cannot be explained by simply adding the individual frequencies of α-blockers and antimuscarinics. Increase of PVR and the rate of (acute) urinary retention are also important issues for α-blocker and antimuscarinic combination therapy. Although PVR is significantly increased in some RCTs investigating combination therapy, studies have rarely shown a clinically relevant PVR increase or increased rates of (acute) urinary retention. The NEPTUNE II study investigated the long-term use of combination therapy and found a low retention rate (1.1 % at month 12), which is similar to the retention rate of the symptomatic male population without treatment. A recently published meta-analysis of pooled data from 7 RCTS with more than 3,600 patients concluded that combination therapy reduces Q_{max} (weighted mean difference −0.59 mL/s) and increases PVR (weighted mean difference 11.6 mL) compared to α-blocker monotherapy but the risk of (acute) urinary retention is low (101 patients needed to harm one patient). It therefore appears safe to use combination therapy in adult men with LUTS but, nevertheless, PVR should be monitored especially during early treatment.

Surgical Therapies

Monopolar Transurethral Resection of the Prostate (mTURP)

This remains the ‘gold’ standard treatment for BPO with the longest outcome data. It involves the removal of prostate tissue using monopolar electrocautery passed through inert, optically clear and non-conductive irrigation fluid. Electrical current

passes from an active electrode on the resectoscope loop to the prostate, through the body before exiting via a return electrode placed on the skin. The most common irrigating fluid used is glycine; the others in use include ethanol and mannitol. The current recommendation is that prostate sizes should be 30–80 mL, although this reflects expert opinion only. Three systematic reviews of all available RCTs have suggested that antibiotic prophylaxis significantly reduces bacteriuria, fever, sepsis and need for further antibiotics post-TURP. There was a trend towards a higher efficacy with a short course compared with a single dose. EAU guidelines recommend UTIs should be treated prior to surgery.

Efficacy

A historic meta-analysis from 1999 of 29 RCTs revealed a mean reduction in LUTS of 70 % and mean increase in Q_{max} of 125 % post-TURP. In addition, a more contemporary analysis has again shown excellent outcome data. This involved 20 RCTs published between 2000 and 2009 with an overall sample size of 954 patients and a maximum follow-up of 5 years. There was an improvement in mean Q_{max} of 162 %, reduction in mean IPSS of 70 %, mean reduction in QoL scores of 69 % and mean reduction of PVR of 77 %. Similar results have been replicated in many other studies with follow-up of 8–22 years suggesting that mTURP results are durable long term.

Adverse Effects

- Retreatment rates: 14.7 % at 8 years
- TUR syndrome: 0.8 %
- Transfusions: 2.9–8.6 % (2 % in contemporary series)
- Urethral strictures: 3.8–9.3 %
- Bladder neck contractures: 1.9–9.2 %
- Urinary incontinence: 2.2 %
- Retrograde ejaculation: 65.4 %
- Erectile dysfunction: 6.5 %

Transurethral Incision of the Prostate (TUIP)

This involves one or two lateral incisions in the prostate at the 4 and 7 o'clock positions. The incision extends from below the ureteric orifice to the level of the verumontanum down to the prostatic capsule. No prostatic tissue is resected. The procedure is performed with a Collings knife, resection loop or laser. This is recommended by some authors especially in young men with small prostates (<30 mL). The efficacy is comparable or slightly inferior to mTURP; however, the re-intervention rates are higher compared to TURP (15.9 % vs. 2.6 %). Transfusion and retrograde ejaculation rates are lower than with TURP.

Bipolar Transurethral Resection of the Prostate (bTURP)

This modification of the traditional mTURP involves the passage of current between the active and return electrodes both attached to the resectoscope. Current passes from the active electrode (loop) to the saline irrigation fluid resulting in excitation of sodium ions and tissue resection. As saline irrigation fluid is used, the risk of TUR syndrome may be abolished allowing larger prostates to be resected. There are five types of bipolar devices currently available which differ in the way their current is delivered to achieve coagulation, cutting or vaporisation. There are two modalities of action:

- Resection
- Vaporesection

Efficacy

A meta-analysis of 17 RCTs has shown no significant differences in the short-term efficacy (up to 12 months) between m- and bTURP with respect to IPSS, QoL, Q_{max} and re-intervention rates. The main advantages found with bTURP are the shorter hospital stay and catheterisation times as well as reduced post-operative retention, transfusion and TUR syndrome rates.

Open Prostatectomy (OP)

This is the oldest surgical treatment for moderate-to-severe LUTS due to large prostates, usually defined as >80 mL but dependent on the resection speed of the individual surgeon. This open procedure may be performed via the perineal, retropubic or suprapubic routes. The obstructive adenoma is enucleated using the index finger either from inside the bladder (Freyer's procedure) or through the anterior prostatic capsule (Millin's procedure). Although efficacious in long term, it may be associated with higher short-term morbidity than endoscopic procedures; it is estimated that it makes up less than 5 % of all prostatectomies being performed in the UK currently.

Efficacy

Studies on OP have revealed durable long-term results with a reduction in LUTS of 63–86 %, improvements in QoL scores of 60–87 %, a mean rise in Q_{max} of 375 % and reduction of PVR by 86–98 %. These compare very favourably with TURP. In addition, three recent RCTs have demonstrated similar outcomes between Holmium laser enucleation, photoselective vaporisation of the prostate (PVP) and OP in the treatment of large prostates. EAU guidelines recommend OP or Holmium laser enucleation as the first-line treatment of LUTS/BPO in men with prostates greater than 80 mL. Although, performing a TURP on one lobe and then repeating the

process on the other lobe at a later time is also an option which may involve two anaesthetics but, however, may have less morbidity.

Adverse Effects

- Mortality: <0.25 %
- Transfusion rates: 7–14 %
- Re-intervention rates: 0–6.7 %
- Urinary incontinence: 10 %
- Urethral strictures: 1.7–6 %
- Bladder neck strictures: 3.3–5 %.

Holmium Laser Enucleation (HoLEP) and Holmium Laser Resection of the Prostate (HoLRP)

The Holmium laser has a wavelength of 2140 nm, an absorption distance of 0.4 mm and is absorbed by water and water containing tissues. This minimises the area of tissue coagulation and necrosis to 3–4 mm. The main advantages are that it may be utilised in variably sized prostates, maximal prostatic tissue is removed and sent for histological analysis and may be used in men on anticoagulation. A laser fibre is inserted via a laser bridge down a resectoscope. The procedure aims to replicate an open prostatectomy. Once a lobe has been enucleated, it is placed in the bladder, shred and retrieved with the use of a morcellator. The main disadvantage of the procedure is the longer learning curve required compared with a TURP. The NICE Institute currently recommends that this treatment modality may be offered but at a centre specialising in the technique or where a mentorship programme is in place.

Efficacy

HoLEP compares favourably with mTURP, bTURP and OP in meta-analysis and systematic reviews. Functional outcomes with respect to IPSS, Q_{max} and PVR were either equivalent or favoured HoLEP. Complication rates with respect to re-intervention and strictures were equivalent. HoLEP was associated with reduced catheter and hospital times but longer operating times. HoLEP has satisfactory results in the medium term (3–8 years).

Adverse Events

- Dysuria was the most common adverse event.
- Re-interventions: 1.4 % at 6 years follow-up.
- Urethral strictures: 3.3 %.
- Bladder neck strictures: 1.7 %.

- Transfusion rate: 0 %.
- Urinary incontinence: 1.5 %.

Greenlight Laser Vaporisation

This is a 532 nm laser. The two types are the potassium titanyl phosphate (KTP) and lithium triborate (LBO) which are derived from neodymium: yttrium-aluminium-garnet (Nd:YAG). The Nd:YAG wavelength is reduced from 1064 to 532 by the addition of KTP/LBO crystals to a laser converter. The laser energy is absorbed by haemoglobin and results in vaporisation which leads to immediate tissue removal. There are currently three green light lasers in use which differ in their power output, fibre design and energy application:

- 80 W (KTP)
- 120 W HPS (LBO)
- 180 W HPS (LBO)

The main advantages of this technique are that it is easier to learn, safe in anticoagulated men, has minimal fluid absorption and less retrograde ejaculation versus TURP and HoLEP. However, it is a slow procedure with relatively less tissue removed versus TURP or HoLEP and tissue for pathological investigation is not available.

Efficacy

A meta-analysis from 2012 of nine RCTs compared the 80 and 120 W with TURP. They found no significant difference between the two modalities with respect to Q_{max} and IPSS. However, three RCTs had sufficient 12-month data to be included. In the literature, follow-up time remains variable and short. The longest RCT using 120 W HPS had 36 months follow-up. There were comparable improvements in IPSS, Q_{max} and PVR. However, the percentage reduction in PSA and prostate volume was greater with TURP. The re-intervention rate was significantly higher with greenlight. A meta-analysis comparing the 120 W laser with mTURP found comparable functional outcomes at 12 months. Greenlight is associated with longer operating times, shorter catheter and hospital times but lower risk of transfusion. The recent prospective, randomised non-inferiority study on the 180 W with a 12-month follow-up demonstrated non-inferiority to TURP for mean IPSS, mean Q_{max} and complication-free rate. The early re-intervention rate was three times higher after TURP; however, the overall re-intervention rate was not significantly different between the two groups.

Adverse Events

- Re-intervention rates: 9.6–11 %
- Urinary incontinence: 11 %

- Transfusions: 0–0.3 %
- Urethral strictures: 3.7 %
- Bladder neck strictures: 7.4 %

Thulium:Yttrium-Aluminium-Garnet (Tm:YAG) Laser

This is a 2000 nm wavelength laser which is absorbed by water. It has a continuous wave mode which allows for the smooth incision of tissue. There are four techniques utilised in prostate removal:

- Vaporisation (ThuVaP)
- Vaporesection (ThuVaRP)
- Vapoenucleation (ThuVEP): HoLEP-like approach
- Laser enucleation (ThuLEP): blunt dissection

Efficacy

This is the newest laser technique with a limited number of RCTs comparing it with TURP. The main study outcomes have shown comparable improvements in voiding parameters, i.e. Q_{max}, PVR and QoL. However, a 4-year randomised-controlled study revealed that some of these parameters may not be maintained. The main advantages of thulium are that it is associated with a reduction in operating time, hospital stay and catheter times.

Adverse Events (Follow-Up 9–12 Months)

- Strictures (ThuVaRP): 1.9 %
- Bladder neck strictures: 1.8 %
- Re-intervention rates: 0.7–1 %

Prostatic Stents

Prostatic stents were introduced approximately 25 years ago and may be a useful alternative to long-term indwelling urethral catheters. Long-term catheters may be associated with reduction in QoL, risk of catheter-related infections as well as the ongoing costs of the catheters and staff required for their upkeep. Prostatic stents require functioning detrusor to facilitate bladder emptying and aim to maintain urethral patency. The main advantage of these stents is that they are relatively easy to insert and may be inserted under local anaesthesia in a clinical setting. Stents are either temporary or permanent. The permanent stents (Urolume Wallstent) are

biocompatible and allow epithelisation which means that they are eventually embedded in the urethra. They are less liable to encrustation and infection but removal may be difficult and often cannot be undertaken in clinic. Temporary stents are biostable or biodegradable, do not epithelise and provide short-term relief. Biodegradable stents may be inserted to allow the temporary relief of BPO until medication has a chance to reduce prostate volume. There are multiple stents currently available, all of which differ in their method of deployment. Unfortunately, the studies are generally poor quality and heterogeneous. At present, NICE and AUA do not include prostatic stents in their guidelines. The EAU recommends their use as an alternative to catheter in men unfit for surgical treatment. Prostatic stents have been used intermittently over the years by urologists but have been generally not used and have proven unpopular in the long term due to problems with encrustations and difficult removal.

Efficacy

- IPSS reduction: 10–19 points
- Mean Q_{max} increase: 3–13.1 mL/s
- Spontaneous voiding: 84–93 %

Adverse Events

- 5-year failure rates: 27–50 %
- Migration: 15 %
- Urinary incontinence: 22 %
- Haematuria: 19 %

Prostatic Urethral Lift (UroLift™)

This technique manipulates the properties of the urethra, prostate and its capsule. The compliant urethra is surrounded by the compressible prostate which in turn is supported by the tough prostatic capsule. This means that the application of an implant between the urethra and capsule lifts the urethra towards the capsule thereby expanding the urethral lumen. The implants are permanent and attached to a suture. They separate occlusive prostatic lobes and are usually placed at the 2 and 10 o'clock positions. Once an appropriate tension is attained, the excess suture is trimmed. Prostate size determines the number of implants used; however, 4–6 are usually deployed. The UroLift™ delivery system is preloaded with the implant components, a syringe and 19-gauge needle. This procedure is performed under cystoscopic guidance with regional, local or general anaesthesia. Several studies have evaluated the use of this new technology with the main exclusion being large prostates (>80–100 mL) and large or obstructing median lobes. A large median lobe

is believed to be technically more challenging to treat. At present, NICE, EAU and the American Urological Association (AUA) do not include prostatic stents in their guidelines.

Efficacy

In a retrospective review of 102 men across five countries with a median follow-up at 1 year found that symptom relief was achieved as early as 2 weeks. Mean improvements at 12 months were:

- IPSS: 52 %
- QoL: 53 %
- Q_{max}: 51 %

A multicentre double-blind crossover study published this year found a mean IPSS improvement of 122 % greater than sham at 3 months. Q_{max} had a stepwise improvement. The LIFT study, a multicentre randomised study with a 1-year follow-up included 206 men and compared the UroLift™ with a sham procedure. They found an 88 % greater improvement in IPSS over sham at 3 months, a reduction in voiding and storage symptoms and a significant improvement in Q_{max}. The improvements were significant at 3 months and maintained at 1 year. An additional benefit was the preservation of sexual function.

Adverse Events

- Mild and resolved within 2 weeks
- Most common:
  - Dysuria (36 %)
  - Haematuria (26 %)
  - Pelvic pain/discomfort (21 %)
  - Urgency (10 %)
- Progression to TURP: 6.5 %

Prostate Artery Embolisation (PAE)

The purpose of PAE is to cause apoptosis and necrosis with resultant shrinkage. This is a new radiological minimally invasive technique. It requires precise knowledge of prostatic anatomy and arterial supply. The prostate arteries have highly variable origins between the left and right sides of the same patient and also between different patients. The prostate has a dual supply:

- Anterolateral (from superior vesical): supplies BPH nodules
- Posterolateral

The anterolateral branch is usually the preferred vessel to embolise. In 50–60 %, there is anastomosis between the prostate artery and surrounding arteries which may result in the inadvertent injury to surrounding structures. The prostate artery may arise from the same artery or independently to give two arteries. In most studies, PAE is performed under local anaesthesia with most men discharged on the same day or after a very short hospital stay. The approach is femoral with either unilateral or bilateral embolisation. Unilateral embolisation is usually due to procedure failure on one side as a consequence of atherosclerosis or tortuosity of the vessel. The endpoint is usually interruption of flow, reflux and gland opacification.

Efficacy

Most of the studies are small and with poor quality. However, Pinheiro et al. have published one of the largest series. This was a single-centre cohort study of 365 men with moderate-to-severe LUTS at a mean follow-up of 14 months. The best outcomes were observed in men with large prostates (>100 mL) and severe symptoms (IPSS >20). Clinical success rates were 84.9 % at 3 months, 77.2 % at 18 months and 74.3 % at 24–42 months. There was a 24 % clinical failure rate. They also observed mean reductions in IPSS, QoL and prostate volume of 10.9, 2.8 and 16.2 %, respectively. The same group also evaluated the use of PAE in men with acute urinary retention with indwelling catheters. Their initial clinical success was 90 % at 3 months with 4 men having failed catheter removals. However, 3 of them had successful catheter removal after repeat PAE. Antunes et al. assessed UDS findings in 11 men with urinary retention treated with PAE. Prior to PAE, all the men had UDS proven BPO (BOOI > 40). After treatment with PAE:

- BOOI >40: 30 %
- BOOI 20–40: 40 %
- BOOI <20: 30 %

An RCT comparing PAE with TURP found greater improvements in IPSS, QoL, Q_{max} and PVR at 1 and 3 months associated with TURP. There were more adverse events associated with PAE.

Adverse Events

- UTI: 9.8 %
- Transient haematuria: 13.1 %
- Transient haematospermia: 6.6 %
- Transient rectal bleeding: 8.8 %
- Inguinal haematoma: 7.4 %
- Acute urinary retention: 1.6 %
- 1 documented case of bladder ischaemia

Botulinum Toxin A (BTX-A)

The prostate is innervated by sympathetic and parasympathetic efferents and sensory afferents. The secretory role of cholinergic nerves is mediated by muscarinic receptors. The activation of these receptors plays a role in the growth of the normal prostatic tissue and the development of BPH. Acetylcholine (ACh) activates the muscarinic receptor. BTX inhibits release of ACh at the neuromuscular junction which may therefore result in disruption of the neural pathway and subsequently symptom relief. It has proven benefit in the treatment of OAB especially in neuropathic detrusor overactivity. BTX may be injected into the prostate under local anaesthesia transrectally or transperineally.

Efficacy

A recently (2014) updated systematic review on the use of BTX in men with LUTS/BPE has found no significant changes in IPSS, Q_{max} and prostate volume when compared with placebo. There were significant changes in PSA and PVR. The main limitation of the review was that there were few studies included which had a high level of evidence. The largest level 1 trial to date by Marberger et al. included 374 men. There was a high placebo response but no significant difference between placebo and BTX. Only one study reviewed the use of BTX in men with retention who were unfit for surgery. 81 % were able to void after injection of 200 units of BTX-A. The systematic review concluded that the evidence was contradictory and BTX should not be used. A post hoc analysis by Marberger et al. revealed a significant reduction in IPSS versus placebo in men who had previously used α-blockers.

Adverse Events

The incidence of adverse events was similar across the placebo and treatment groups. These events were thought to be due to the procedure rather than BTX. Adverse events included haematuria, haematospermia, urinary urgency, dysuria and UTI.

Transurethral Microwave Therapy (TUMT) and Transurethral Needle Ablation (TUNA™)

Both these techniques are minimally invasive and may be performed under local anaesthesia or sedation in the clinical setting. They involve delivery of heat to the prostate either via microwave radiation (TUMT) or radiofrequency energy (TUNA™) in order to create coagulation necrosis. Both techniques have been shown in systematic reviews and meta-analyses to be efficacious and safe but inferior to results obtained from TURP. TURP is also associated with lower retreatment rates. However, most of the studies have limited follow-up data.

Robotic Prostatectomy

This is a technique usually reserved for the management of prostate cancer. However, there are now small series using the technique to treat very-large-volume BPH. The results reveal this is feasible with good efficacy results and minimal complications. Although the procedure costs are high when compared with open prostatectomy, there may be saving with regard to in-hospital stay. This is an exciting new robotic procedure; however, it will require a learning curve and will probably need to be reserved for high-volume surgeons. In the perspective of alternative techniques for the removal of large prostates, there is currently no place for robotic prostatectomy for the treatment of BPE.

Conclusions

LUTS/BPO remains a significantly bothersome chronic disease worldwide and is one of the most common complaints presenting to urologists. The patients may present with a variety of symptoms, anxieties and co-morbidities. Some will be worried by the concern that their symptoms are due to prostate cancer. Others will be embarrassed by symptoms such as incontinence or assume that surgical treatment of the prostate is the only way to treat their condition. The correct assessment of these patients is vitally important to determine the likely underlying correctable or non-correctable causes, which men are likely to progress, and the patient's expectation of treatment outcome. When counselling men, it is again important to stress the importance of lifestyle changes and the side effects of the various medical treatments. Although there is excellent evidence for both medical and surgical therapies, they are not without risks. Each patient must be treated on an individual basis when deciding on the most appropriate treatment. In men with LUTS who wish to preserve sexual function, consideration must be given to the PDEi tadalafil (Cialis™), UroLift™ or PAE; the patient may be willing to sacrifice some of the efficacy of TURP for their sexual function. There is a large variety of surgical options now available with growing evidence base for their use as alternatives to TURP. HoLEP and monopolar and bipolar TURP are considered at least equivalent in terms of outcomes. However, surgical experience with new technologies may lag as surgeons become as proficient in their use as they are in the performance of the 'gold' standard TURP. In addition, surgical options offered to men may be affected by the available funding and equipment.

Points of Interest
Lower urinary tract symptoms remain an important and common condition which urologists must have an efficient strategy for managing. This strategy must involve the use of evidence-based definitions which allow us to determine the underlying pathogenesis and determine exactly what a patient means

by the symptoms he describes. It is vital to remember the LUTS are often not due to prostatic pathology. The history and examination of the patient remains a critical part of the assessment. This must include a review of their current medications and conditions which may affect or cause symptoms such as diabetes mellitus or neurological dysfunction. It is possible that the urologist may be the clinician initially diagnosing these non-urological conditions. Simple adjuncts often provide a vast amount of information for the clinician which must not be overlooked. The bladder diary allows the assessment of the patient's drinking habits, bladder capacity, degree of frequency and nocturia. In addition, bladder diaries along with questionnaires allow the patient to take a more active role in their own management. Although invasive urodynamics has a role in the assessment of LUTS, this should be reserved for specific patients where there is uncertainty in the diagnosis or there is a specific question which needs an answer. UPSTREAM is a study currently recruiting which is comparing invasive urodynamics with non-invasive urodynamics in the selection of patients for TURP; the results will be eagerly awaited.

The management of LUTS may be divided broadly into conservative, medical and surgical. Conservative management should not be ignored as there is some evidence to suggest its usefulness in patients with mild symptoms. It is especially useful in those keen to avoid drugs who are self-motivated. There are now a multitude of drugs with good efficacy. However, the real challenge appears to be in choosing the correct combination for a specific patient. An example would be a man with predominant storage symptoms or another with erectile dysfunction and lastly one at high risk of disease progression. The patient plays a critical role in these decisions as the expectations must as always be balanced with treatment of adverse events. The vast variety of surgical technologies now available highlights the innovation and growing interest in this area. The more traditional monopolar TURP is now being eclipsed by bipolar TURP which has equivalent outcomes at least in short-term follow-up. In addition, bipolar has advantages with respect to lower rates of transfusion, TUR syndrome and hospital stay. There is growing interest in the use of the laser with a variety of modalities now available. However, follow-up is short and more data is still required. As post-operative sexual function becomes more important and patient preoperative morbidity grows, we may observe techniques such as the prostatic urethral lift (UroLift™), prostatic embolisation and prostatic stents gaining a more important role in selected patients. The evidence for their outcomes though limited remains promising. Lastly, as experience with robotic surgery grows, this technology may expand into the treatment of benign prostatic pathology. This is an exciting time in LUTS management with new studies challenging how we assess patients and determining the efficacies of new techniques.

Further Reading

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