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European Association of Urology

Guidelines

EAU Guidelines on the Treatment and Follow-up of Non-neurogenic Male Lower Urinary Tract Symptoms Including Benign Prostatic Obstruction

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Transurethral needle ablation

Abstract

Objective: To present a summary of the 2013 version of the European Association of Urology guidelines on the treatment and follow-up of male lower urinary tract symptoms (LUTS).
Evidence acquisition: We conducted a literature search in computer databases for relevant articles published between 1966 and 31 October 2012. The Oxford classification system (2001) was used to determine the level of evidence for each article and to assign the grade of recommendation for each treatment modality.
Evidence synthesis: Men with mild symptoms are suitable for watchful waiting. All men with bothersome LUTS should be offered lifestyle advice prior to or concurrent with any treatment. Men with bothersome moderate-to-severe LUTS quickly benefit from α_1-blockers. Men with enlarged prostates, especially those >40 ml, profit from 5α-reductase inhibitors (5-ARIs) that slowly reduce LUTS and the probability of urinary retention or the need for surgery. Antimuscarinics might be considered for patients who have predominant bladder storage symptoms. The phosphodiesterase type 5 inhibitor tadalafil can quickly reduce LUTS to a similar extent as α_1-blockers, and it also improves erectile dysfunction. Desmopressin can be used in men with nocturia due to nocturnal polyuria. Treatment with an α_1-blocker and 5-ARI (in men with enlarged prostates) or antimuscarinics (with persistent storage symptoms) combines the positive effects of either drug class to achieve greater efficacy. Prostate surgery is indicated in men with absolute indications or drug treatment–resistant LUTS due to benign prostatic obstruction. Transurethral resection of the prostate (TURP) is the current standard operation for men with prostates 30–80 ml, whereas open surgery or transurethral holmium laser enucleation is appropriate for men with prostates >80 ml. Alternatives for monopolar TURP include bipolar TURP and transurethral incision of the prostate (for glands <30 ml) and laser treatments. Transurethral microwave therapy and transurethral needle ablation are effective minimally invasive treatments with higher retreatment rates compared with TURP. Prostate stents are an alternative to catheterisation for men unfit for surgery. Ethanol or botulinum toxin injections into the prostate are still experimental.
Conclusions: These symptom-oriented guidelines provide practical guidance for the management of men experiencing LUTS. The full version is available online (www.uroweb.org/gls/pdf/12_Male_LUTS.pdf).

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1. Introduction

Lower urinary tract symptoms (LUTS) in elderly men were traditionally attributed to the enlarging prostate. The mechanisms invoked were one or all of the following: histologic benign prostatic hyperplasia (BPH), benign prostatic enlargement (BPE), or benign prostatic obstruction (BPO). However, during the last decade the causal link between the prostate and the pathogenesis of LUTS has come into question [1]. Although the enlarged prostate can contribute to the onset of LUTS in a proportion of men >40 yr of age, other factors are of equal importance. Figure 1 illustrates the many causes of LUTS. In any single person complaining of LUTS, it is common for more than one of these factors to be present. This multifactorial view of the aetiology of LUTS has led most experts to regard the whole urinary tract as a single functional unit. This broader, more complex approach to the pathogenesis of LUTS meant that this guidelines panel modified the title (to reflect the change in perspective) from the former "EAU [European Association of Urology] Guidelines on LUTS Suggestive of BPO (BPH)" [2] to the more contemporary and precise "EAU Guidelines on Non-neurogenic Male LUTS Including BPO."

Because patients seek help for LUTS and not an underlying attribute of the prostate such as BPH or BPE, these updated guidelines have been written from the perspective of men who complain about a variety of bladder storage, voiding, and/or postmicturition symptoms. The recommendations made within the guidelines are based on the best available evidence. These recommendations apply to men ≥40 yr of age who seek professional help for various forms of non-neurogenic benign forms of LUTS, for example, LUTS/BPO, detrusor overactivity/overactive bladder (OAB), or nocturnal polyuria. EAU guidelines on LUTS due to neurologic diseases [3], urinary incontinence [4], urogenital infections [5], ureteral stones [6], or malignant diseases of the lower urinary tract [7] have been published elsewhere.

2. Evidence acquisition

The recommendations of these guidelines are based on a literature search using articles in the English language published in the PubMed/Medline, Web of Science, and Cochrane databases between 1966 and 31 October 2012, including the search terms *lower urinary tract symptoms, benign prostatic hyperplasia, detrusor overactivity, overactive bladder, nocturia*, and *nocturnal polyuria* in combination with the various treatment modalities and the search limits *humans, adult men, review, randomised clinical trials, clinical trials*, and *meta-analysis* (Table 1). Each extracted article was separately analysed, classified, and labelled with a level of evidence (LE) according to a classification system modified from the Oxford Centre for Evidence-based Medicine in 2001 (Table 2a) [8]. Subsections for the

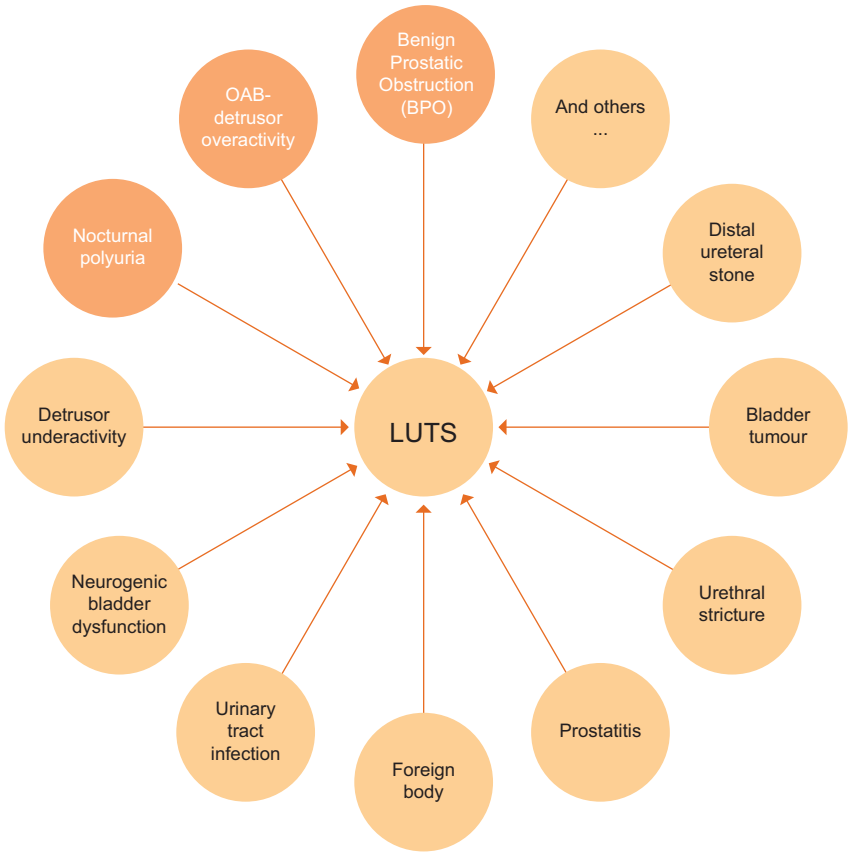

Fig. 1 – Multifactorial aetiology of lower urinary tract symptoms (LUTS). The European Association of Urology (EAU) guidelines on non-neurogenic male LUTS mainly covers LUTS secondary to benign prostatic enlargement (BPE) or benign prostatic obstruction (BPO), detrusor overactivity or overactive bladder (OAB), and nocturia due to nocturnal polyuria. Other causes of male LUTS are covered by separate EAU guidelines [3–7].

Table 1 – Literature search methodology

Databases: PubMed/Medline (http://www.ncbi.nlm.nih.gov/pubmed/) Web of Science (http://apps.webofknowledge.com) Cochrane (http://www.cochrane.org/) Language: English Literature search: February 1, 2012, to October 2012		
Search limits	For group search terms (AND)	In combination with investigated drugs, operations, or synonyms (AND)
humans AND adult men AND review OR randomised clinical trials OR clinical trials OR meta-analysis	Lower urinary tract symptoms Benign prostatic hyperplasia Detrusor overactivity Overactive bladder Nocturia Nocturnal polyuria	Alpha-adrenoceptor antagonist Adrenergic alpha-1 receptor antagonists Alpha-blocker Alfuzosin Doxazosin Tamsulosin Terazosin 5α-reductase inhibitor Dutasteride Finasteride PDE5 Tadalafil Sildenafil Vardenafil Prostatectomy Open Monopolar transurethral Bipolar transurethral Laser Ablation Resection Vaporisation Enucleation Microwave thermotherapy Transurethral needle ablation Ethanol injections Botulinum injections

Table 2 – (a) Level of evidence and (b) grade of recommendation, modified from the Oxford Centre for Evidence-based Medicine [8]

a.

Level of evidence	Type of evidence
1a	Evidence obtained from meta-analysis of randomised trials
1b	Evidence obtained from at least one randomised trial
2a	Evidence obtained from one well-designed controlled study without randomisation
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study
3	Evidence obtained from well-designed nonexperimental studies, such as comparative or correlation studies and case reports
4	Evidence obtained from expert committee reports or options or clinical experience of respected authorities

b.

Grade	Recommendation
A	Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial
B	Based on well-conducted clinical studies but without randomised clinical trials
C	Made despite the absence of directly applicable clinical studies of good quality

various types of conservative treatments, drugs, and operations are presented in a homogeneous structure listing (1) mechanism of action, (2) available drugs with a table of key pharmacokinetic profiles (for this article summarised in Table 3), (3) efficacy with a table of trials with the highest LE, (4) tolerability and safety, (5) practical considerations, and (6) recommendations drawn from the relevant articles using a grade of recommendation (GR) according to a classification system modified from the Oxford Centre for Evidence-based Medicine (Table 2b) [8]. The full analysis of the literature with all tables, recommendations, and conclusions is available online on the EAU home page (www.uroweb.org/gls/pdf/12_Male_LUTS.pdf); this article summarises these analyses and lists all LEs and GRs of analysed treatment modalities in one table (Table 4).

Table 3 – Key pharmacokinetic properties and standard doses of drug therapy licensed in Europe for treating lower urinary tract symptoms

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 wk	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
Vasopressin analogue (for treating nocturnal polyuria)			
Desmopressin tablet	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 type 5 inhibitors (for treating signs or symptoms of BPH with or without erectile dysfunction)			
Tadalafil	2 (0.5–12)	17.5	1 × 5 mg

BPH = benign prostatic hyperplasia; ER = extended release; GITS = gastrointestinal therapeutic system; IR = immediate release; LUTS = lower urinary tract symptoms; 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.

The guidelines panel consisted of urologists, a pharmacologist, and an epidemiologist and statistician who have been working on the topic for the last 6 yr. The guidelines are primarily written for urologists but can also be used by general practitioners, patients, or other stakeholders. The guidelines panel intends to update the content and recommendations according to the given structure and classification systems every 2 yr.

3. Evidence synthesis

3.1. *Conservative treatment*

Many men with LUTS are not bothered enough by their symptoms to need drug treatment or surgical intervention. Most of these men can be managed conservatively by a process known as watchful waiting (WW). All men with LUTS should be formally assessed prior to any allocation of treatment. The aim of this assessment is to establish the severity of LUTS and to discriminate the vast majority of men with so-called uncomplicated LUTS that pose no threat to life expectancy from the more unusual presentation of complicated LUTS that might do. Men with mild-to-moderate uncomplicated LUTS, who are not too bothered by their symptoms, are suitable for WW. It is customary for this type of management to include the following components: education, reassurance, lifestyle advice, and periodic monitoring [9–12] that include:

- Reduction of fluid intake at specific times aimed at reducing urinary frequency when most inconvenient (eg, at night or going out in public).
- Avoidance or moderation of caffeine or alcohol that may have a diuretic and irritant effect, thereby increasing fluid output and enhancing frequency, urgency, and nocturia.
- Use of relaxed and double-voiding techniques.
- Urethral milking to prevent postmicturition dribble.
- Distraction techniques such as penile squeeze, breathing exercises, perineal pressure, and mental tricks to take the mind off the bladder and toilet, to help control storage symptoms.
- Bladder retraining that encourages men to hold on when they have sensory urgency to increase their bladder capacity and the time between voids.
- Reviewing the medication and optimising the time of administration or substituting drugs for others that have fewer urinary effects. These recommendations apply especially to diuretics.
- Providing necessary assistance when there is impairment of dexterity, mobility, or mental state.
- Treatment of constipation.

Table 4 – Level of evidence and grade of recommendation for the various treatments of male lower urinary tract symptoms and follow-up

		LE	GR
Conservative treatment: watchful waiting			
	Men with mild symptoms are appropriate for watchful waiting.	1b	A
	Men with LUTS should always be offered lifestyle advice prior to or concurrent with treatment.	1b	A
Drug treatment			
1.	α_1-Blockers can be offered to men with moderate-to-severe LUTS.	1a	A
2.	5α-Reductase inhibitors can be offered to men who have moderate-to-severe LUTS and an enlarged prostate (>40 ml). 5α-Reductase inhibitors can prevent disease progression with regard to acute urinary retention and need for surgery.	1b	A
3.	Muscarinic receptor antagonists may be used in men with moderate-to-severe LUTS who have predominantly bladder storage symptoms.	1b	B
	Carefulness is advised in men with BOO.	4	C
4.	Phosphodiesterase type 5 inhibitors reduce moderate-to-severe (storage and voiding) LUTS in men with or without erectile dysfunction. Only tadalafil (5 mg once daily) has been licensed for the treatment of male LUTS in Europe.	1b	A
5.	Vasopressin analogue can be used for the treatment of nocturia due to nocturnal polyuria.	1b	A
6.	Combination treatment with an α_1-blocker together with a 5α-reductase inhibitor can be offered to men with bothersome moderate-to-severe LUTS, enlarged prostates, and reduced Q_{max} (men likely to develop disease progression).	1b	A
7.	Combination treatment with an α_1-blocker together with a muscarinic receptor antagonist may be used in patients with bothersome moderate-to-severe LUTS if relief of storage symptoms has been insufficient with the monotherapy of either drug.	1b	B
	Combination treatment should carefully be prescribed in men who may have BOO.	2b	B
Surgical treatment			
1.	M-TURP is the current surgical standard procedure for men with prostate sizes of 30–80 ml and bothersome moderate-to-severe LUTS secondary of BPO. M-TURP provides subjective and objective improvement rates superior to medical or minimally invasive treatments.	1a	A
	The morbidity of M-TURP is higher than for drugs or other minimally invasive procedures.	1a	A
	B-TURP achieves short- and midterm results comparable with M-TURP.	1a	A
	B-TURP has a more favorable perioperative safety profile compared with M-TURP.	1a	A
	TUIP is the surgical therapy of choice for men with prostate sizes <30 ml, without a middle lobe, and bothersome moderate-to-severe LUTS secondary to BPO.	1a	A
2.	Open prostatectomy or holmium laser enucleation is the first choice of surgical treatment in men with prostate sizes >80 ml and bothersome moderate-to-severe LUTS secondary to BPO needing surgical treatment.	1b	A
	Open prostatectomy is the most invasive surgical method with significant morbidity.	1b	A
3.	TUMT and TUNA achieve symptom improvement comparable with TURP, but they are associated with decreased morbidity and lower flow improvements.	1a	A
	Durability is in favour of TURP with lower retreatment rates compared with TUMT or TUNA.	1a	A
4.	HoLEP and 532-nm laser vaporisation of the prostate are alternatives to TURP in men with moderate-to-sever LUTS due to BPO leading to immediate, objective, and subjective improvements comparable with TURP.	1a	A
	The intermediate-term functional results of 532-nm laser vaporisation of the prostate are comparable with TURP.	1b	A
	The long-term functional results of HoLEP are comparable with TURP/open prostatectomy.	1b	A
	Diode laser operations lead to short-term objective and subjective improvement.	3	C
	ThuVaRP is an alternative to TURP for small- and medium-size prostates.	1b	A
	ThuVEP leads to short-term objective and subjective improvement.	3	C
	With regard to intraoperative safety and hemostatic properties, diode and thulium lasers appear to be safe.	3	C
	With regard to intraoperative safety, 532-nm laser vaporization is superior to TURP.	1b	A
	532-nm laser vaporization should be considered in patients receiving anticoagulant medication or with a high cardiovascular risk.	3	B
5.	Prostatic stents are an alternative to catheterisation for men unfit for surgery.	3	C
6.	Intraprostatic ethanol injections for men with moderate-to-severe LUTS secondary to BPO are still experimental and should be performed only in clinical trials.	3	C
7.	Intraprostatic BTX injections for men with bothersome moderate-to-severe LUTS secondary to BPO or men in urinary retention are still experimental and should be performed only in clinical trials.	3	C
Follow-up			
	Follow-up for all conservative, medical, or operative treatment modalities is based on empirical data or theoretical considerations but not on evidence-based studies.	3–4	C

BOO = bladder outlet obstruction; BPO = benign prostatic obstruction; B-TURP = bipolar transurethral resection of the prostate; BTX = botulinum toxin; GR = grade of recommendation; HoLEP = holmium laser enucleation; LE = level of evidence; LUTS = lower urinary tract symptoms; M-TURP = monopolar transurethral resection of the prostate; Q_{max} = maximum flow rate; ThuVEP = thulium:yttrium-aluminium-garnet vapoenucleation; TUIP = transurethral incision of the prostate; TUMT = transurethral microwave therapy; TUNA = transurethral needle ablation; TURP = transurethral resection of the prostate.

3.2. *Drug treatment*

3.2.1. *α_1-Adrenoceptor antagonists (α_1-blockers)*

3.2.1.1. Mechanisms of action. Contraction of the human prostate is mediated predominantly, if not exclusively, by α_{1A}-adrenoceptors [13]. α_1-Adrenoceptors in blood vessels, other nonprostatic smooth muscle cells, and the central nervous system are considered mediators of adverse events during α_1-blocker treatment, and all three receptor subtypes (α_{1A}, α_{1B}, and α_{1D}) seem to be involved. This concept has favoured the use of α_{1A}-selective blockers.

3.2.1.2. Available drugs. Five types of α_1-blockers are currently in mainstream use: alfuzosin, doxazosin, silodosin, tamsulosin, and terazosin (Table 3). Indoramin and naftopidil are also available in a few countries but not discussed in these guidelines.

3.2.1.3. Efficacy. Indirect comparisons between α_1-blockers and limited direct comparisons demonstrate that all α_1-blockers have a similar efficacy in appropriate doses [14]. Although these improvements take a few weeks to develop fully, significant efficacy over placebo was demonstrated within hours to days. α_1-Blockers have a similar efficacy, expressed as a percentage improvement in International Prostate Symptom Score (IPSS) in patients with mild, moderate, or severe LUTS [15]. Controlled studies have shown that α_1-blockers typically reduce IPSS, after a placebo run-in period, by approximately 30–40% and increase the maximum flow rate (Q_{max}) by approximately 20–25%. In open-label studies (without a run-in period), an IPSS improvement of up to 50% and Q_{max} increase of up to 40% were documented. α_1-Blockers are able to reduce both storage and voiding LUTS. Prostate size does not affect α_1-blocker efficacy in studies with follow-up periods of $\leq$1 yr, but patients with smaller prostates (<40 ml) seem to have better efficacy compared with those with larger glands in longer-term studies [16–19]. α_1-Blocker efficacy is similar across age groups [15]. α_1-Blockers neither reduce prostate size nor prevent acute urinary retention in long-term studies [16–18,20]; therefore, some patients must be treated surgically. Nevertheless, IPSS reduction and Q_{max} improvement during α_1-blocker treatment appears to be maintained over at least 4 yr.

3.2.1.4. Tolerability and safety. Distribution into lower urinary tract tissues, subtype selectivity, and the pharmacokinetic profiles of certain formulations may contribute to the tolerability profile of specific drugs. The most frequent adverse events of α_1-blockers are asthenia, dizziness, and (orthostatic) hypotension. In particular, patients with cardiovascular comorbidity and/or vasoactive comedication may be susceptible to α_1-blocker–induced vasodilatation [21]. In contrast, the frequency of hypotension with the α_{1A}-selective blocker silodosin is comparable with placebo. The intraoperative floppy iris syndrome was only discovered in 2005 in the context of cataract surgery [22], and tamsulosin has the greatest risk. A systematic review concluded that α_1-blockers do not adversely affect libido. They have a small beneficial effect on erectile function but sometimes cause abnormal ejaculation (ie, decrease or absence of seminal fluid during orgasm) [23]. Silodosin has the highest incidence of abnormal ejaculation; however, efficacy seems to be increased in patients experiencing abnormal ejaculation [24].

3.2.1.5. Practical considerations. α_1-Blockers are often considered the first-line drug treatment of male LUTS because of their rapid onset of action, good efficacy, as well as the low rate and severity of adverse events. Ophthalmologists should be informed about α_1-blocker use prior to cataract surgery.

3.2.2. 5α-reductase inhibitors

3.2.2.1. Mechanism of action. 5α-reductase inhibitors (5-ARIs) block the conversion of testosterone to dihydrotestosterone in prostatic stroma cells by blocking the enzyme 5α-reductase and inducing apoptosis of prostate epithelial cells leading to a 18–28% prostate size reduction and about a 50% reduction in circulating prostate-specific antigen (PSA) levels after 6–12 mo of treatment [25,26].

3.2.2.2. Available drugs. Dutasteride and finasteride are available for clinical use (Table 3). Finasteride inhibits only 5α-reductase type 2, whereas dutasteride inhibits 5α-reductase types 1 and 2 with similar potency (dual 5-ARI). However, the clinical benefit of dual inhibition remains unclear.

3.2.2.3. Efficacy. Clinical effects relative to placebo are seen after minimum treatment duration of $\geq$6–12 mo. After 2–4 yr of treatment, 5-ARIs reduce LUTS (IPSS) by 15–30%, decrease prostate volume by 18–28%, and increase Q_{max} by 1.5–2.0 ml/s in patients with LUTS due to BPE. Indirect comparison between individual studies and one direct comparative trial indicate that dutasteride and finasteride are equally effective in the treatment of LUTS [26,27]. Symptom reduction depends on initial prostate size and may not be more efficacious than placebo in patients with prostates <40 ml [28]. Comparative studies with α_1-blockers and a recent meta-analysis have demonstrated that 5-ARIs reduce LUTS more slowly and that finasteride is less effective than either doxazosin or terazosin but equally effective compared with tamsulosin [20,29–31]. A long-term trial with dutasteride in symptomatic men with prostate volumes >30 ml and increased risk for disease progression showed that dutasteride reduced LUTS in these patients at least as much or even more effectively than the α_1-blocker tamsulosin [17,18,32]. The greater the baseline prostate volume (or serum PSA concentration), the faster and more pronounced the symptomatic benefit of dutasteride. 5-ARIs, but not α_1-blockers, reduce the long-term (>1 yr) risk of acute urinary retention or need for surgery [20,33,34]. In the Proscar Long-Term Efficacy and Safety Study after 4 yr, finasteride treatment reduced the relative risk of acute urinary retention (AUR) by 57% and surgery by 55% compared with placebo [34]. In the Medical Therapy of Prostatic Symptoms (MTOPS) study, a significant reduction in the risk of AUR and surgery in the finasteride arm compared with placebo was reported (68% and 64%, respectively) [20]. A pooled analysis of randomised trials with 2-yr follow-up data reported that treatment with finasteride significantly decreased the occurrence of AUR by 57% and surgical intervention by 34% relative to placebo in patients with moderately symptomatic BPH [35].

Dutasteride has also demonstrated efficacy in reducing the risks for AUR and BPH-related surgery. Pooled phase 3 studies have shown a reduced relative risk of AUR (57%) and a surgical intervention (48%) compared with placebo at 2 yr [36]. In addition, this reduction was maintained to 4 yr during the open-label phase of the study [37].

3.2.2.4. Tolerability and safety. The most relevant adverse effects are related to sexual function and include reduced libido, erectile dysfunction, and, less frequently, ejaculation disorders [18,20]. The incidence of sexual dysfunction and

other adverse events is low and decreased with trial duration. Gynaecomastia (breast enlargement with breast or nipple tenderness) develops in approximately 1–2% of patients.

Data from two important trials on Prostate Cancer chemoprevention (the Prostate Cancer Prevention Trial and the Reduction by Dutasteride of Prostate Cancer Events trial) found a higher incidence of high-grade cancers in the 5-ARI arms compared with placebo arms [38,39]. Although no causal relationship between 5-ARIs and high-grade prostate cancer has been proven, men taking a 5-ARI should be followed up regularly using serial PSA testing. Any confirmed increase in PSA while on a 5-ARI should be evaluated.

3.2.2.5. Practical considerations. Treatment with 5-ARIs should only be recommended in men with bothersome moderate-to-severe LUTS and enlarged prostates (prostate volume >40 ml) or elevated PSA concentrations (>1.4 ng/ml). Due to the slow onset of action, 5-ARIs are only suitable for long-term treatment.

3.2.3. Muscarinic receptor antagonists

3.2.3.1. Mechanism of action. Muscarinic receptors are densely expressed on detrusor smooth muscle cells and other cell types, such as epithelial cells of the salivary glands and the prostate, urothelial cells of the urinary bladder, or nerve cells of the peripheral or central nervous system. Inhibition of muscarinic receptors reduces smooth muscle cell contractions and the sensory threshold of the bladder. Antimuscarinic effects might also be induced or modulated by the urothelium and/or by the central nervous system.

3.2.3.2. Available drugs. The following muscarinic receptor antagonists are licensed for treating OAB/storage symptoms in both men and women: darifenacin, fesoterodine, oxybutynin, propiverine, solifenacin, tolterodine, and trospium chloride (Table 3).

3.2.3.3. Efficacy. Muscarinic receptor antagonists have been tested predominantly in women in the past because it was believed that LUTS in women are caused by the bladder and therefore have to be treated with bladder-specific drugs. Four post hoc analyses (two analyses with tolterodine extended release, one with solifenacin 5 mg, and one with fesoterodine 4 and 8 mg) of data from large randomised controlled trials (RCTs) on the treatment of OAB in women and men without presumed bladder outlet obstruction (BOO) were performed focusing only on the group of men [40–43]. It was demonstrated that tolterodine can significantly reduce urgency incontinence, daytime or 24-h frequency, and urgency-related voiding and improve patient perception of treatment benefit compared with placebo. Solifenacin significantly improved mean Patient Perception of Bladder Condition scores, mean scores on the OAB-q and overall perception of bladder problems, and fesoterodine had significantly greater median percentage improvements in micturition frequency, urgency episodes, and urgency urinary incontinence (UUI) episodes whereas significantly greater percentages reported a treatment response versus placebo. In open-label trials with tolterodine, daytime frequency, nocturia, urgency incontinence, and IPSS were significantly reduced compared with baseline values after 12–25 wk [44,45].

Few studies have investigated the efficacy of monotherapy with antimuscarinics for male patients with BOO and OAB symptoms with unsatisfactory findings. In the Tolterodine and Tamsulosin in Men with LUTS including OAB: Evaluation of Efficacy and Safety study, patients who received tolterodine as monotherapy were significantly improved only in urge incontinence, but they did not show any significant improvement in urgency, IPSS (either total or storage subscore), and the overall percentages of patients reporting treatment benefit compared with placebo [46]. A further analysis showed that men with PSA levels <1.3 ng/ml (smaller prostates) might profit more from antimuscarinic drugs [47]. Two other studies [44,48] found a positive effect of antimuscarinics in patients with OAB and concomitant BOO. In a small RCT without placebo, patients in the propiverine hydrochloride arm experienced improvement in urinary frequency and urgency episodes compared with baseline [48]. In an open-label study, tolterodine decreased the mean 24-h micturition and nocturia, and mean American Urological Association Symptom Index scores significantly improved [44].

3.2.3.4. Tolerability and safety. Muscarinic receptor antagonists are generally well tolerated. Compared with placebo, drug-related adverse events appear with higher frequencies for dry mouth (≤16%), constipation (≤4%), micturition difficulties (≤2%), nasopharyngitis (≤3%), and dizziness (≤5%). Increase of postvoid residual (PVR) urine in men without BOO is minimal and not significantly different compared with placebo (0–5 ml vs −3.6 to 0 ml). The incidence of urinary retention in men without BPO was comparable with placebo in trials with tolterodine (0–1.3% vs 0–1.4%). Short-term treatment with antimuscarinic drugs (tolterodine) in men with BOO appears safe [49].

3.2.3.5. Practical considerations. Although not all antimuscarinic agents have been tested in elderly men with LUTS and OAB symptoms, they likely present similar efficacy and adverse events. Long-term studies on the efficacy of muscarinic receptor antagonists in men with LUTS are not yet available; therefore, these drugs should be prescribed with caution, and regular reevaluation of IPSS and PVR urine is advised.

3.2.4. Phosphodiesterase type 5 inhibitors

3.2.4.1. Mechanism of action. PDE type 5 inhibitors (PDE5-Is) increase the concentration and prolong the activity of intracellular cyclic guanosine monophosphate, thereby reducing smooth muscle tone of the detrusor, prostate, and urethra. PDE4 and PDE5 are the predominant isoenzymes in the lower urinary tract [50]. Nitric oxide and PDEs might also be involved in the micturition cycle by inhibiting reflex pathways in the spinal cord and neurotransmission in the urethra, prostate, or bladder [51]. It has

also been proposed that PDE-Is increase blood perfusion and oxygenation of the lower urinary tract, but the exact mechanism of action of PDE-Is remains to be determined.

3.2.4.2. Available drugs. Although three selective oral PDE5-Is (sildenafil, tadalafil, and vardenafil) have been licensed in Europe for the treatment of erectile dysfunction and clinical trials have been conducted in patients with male LUTS with all of them, only tadalafil (5 mg once daily) has been licensed for the treatment of male LUTS in Europe (Table 3).

3.2.4.3. Efficacy. RCTs on the efficacy of all three available oral PDE5-Is have been published during the last few years. A recent meta-analysis (3214 men with a median follow-up of 12 wk) reported that monotherapy with a PDE5-I achieved a significant improvement in the International Index of Erectile Function (IIEF) score (+5.5) and IPSS (−2.8), but no significant improvement in Q_{max} was found (0.00) compared with placebo [52].

With regard to tadalafil 5 mg, it was found that it significantly reduces IPSS after a run-in period by 22–37% (4.7–6.6 IPSS points; IPSS points relative to placebo: 2.1–4.4) [53,54]. Significant LUTS (IPSS) reduction has been documented with tadalafil as early as 1 wk of treatment. In the latter RCT not included in the meta-analysis just cited, a statistically significant increase in Q_{max} with tadalafil compared with placebo (+2.4 ml/s) was reported for the first time [54]. Tadalafil had no significant impact on PVR.

The combination of α-blockers with PDE5-Is has also been evaluated. A meta-analysis of five RCTs with a limited number of patients and short-term follow-up on the combination of α-blockers with PDE5-Is (two studies with tadalafil 20 mg, two studies with sildenafil 25 mg, and one with vardenafil 20 mg) versus α_1-adrenergic blockers alone showed that the combination significantly improved Q_{max} (+1.5 ml/s), IPSS (−1.8), and IIEF score (+3.6) when compared with the use of α-blockers alone [52]. However, because only tadalafil 5 mg has been licensed, data on combinations of PDE5-Is and other LUTS medications are considered insufficient.

3.2.4.4. Tolerability and safety. PDE5-Is most frequently cause headache, back pain, dizziness, and dyspepsia. PDE5-Is are contraindicated in patients who use nitrates, potassium channel openers, nicorandil, or the α_1-blockers doxazosin or terazosin. They are also contraindicated in patients who have unstable angina pectoris, have had a recent myocardial infarction (<3 mo) or stroke (<6 mo), myocardial insufficiency (New York Heart Association stage >2), hypotension, poorly controlled blood pressure, significant hepatic or renal insufficiency, or if anterior ischemic optic neuropathy with sudden loss of vision is known or was reported after previous use of PDE5-Is.

3.2.4.5. Practical considerations. To date, only tadalafil 5 mg once daily has been officially licensed for the treatment of male LUTS, with or without erectile dysfunction. Therefore, only tadalafil should be used clinically for the treatment of male LUTS. The meta-analysis on PDE5-Is suggested that younger men with a low body mass index and more severe LUTS profit the most from PDE5-I treatment [52]. Long-term experience with tadalafil in patients with LUTS is limited to one trial, and therefore judgement of efficacy or tolerability >1 yr is not possible. There is limited information at present about the reduction of prostate size and no information on slowing of disease progression.

3.2.5. Plant extracts: phytotherapy

Herbal drug preparations are made of roots, seeds, pollen, bark, or fruits of a single plant (mono-preparations); others combine the extracts of two or more plants into one pill (combination preparations). The most widely used plants are *Cucurbita pepo* (pumpkin seeds), *Hypoxis rooperi* (South African star grass), *Pygeum africanum* (bark of the African plum tree), *Secale cereale* (rye pollen), *Serenoa repens* (syn. *Sabal serrulata*; berries of the American dwarf palm, saw palmetto), and *Urtica dioica* (roots of the stinging nettle).

Various producers use different extraction techniques, distribute active ingredients with different qualitative and quantitative properties, or combine two or more herbal compounds into one pill. The extracts of the same plant produced by different companies do not necessarily have the same biologic or clinical effects; therefore, the effects of one brand cannot be extrapolated to others [55]. To complicate matters further, even two different batches of the same producer might contain different concentrations of active ingredients and cause different biologic effects [56]. Thus the pharmacokinetic properties can differ significantly between different plant extracts.

Available Cochrane meta-analyses suggest that (1) men treated with *Pygeum africanum* were twice as likely to report symptom improvement (although analysed trials did not use validated questionnaires, eg, the IPSS), (2) men treated with *Secale cereale* were twice as likely to benefit from therapy compared with placebo, and (3) *Serenoa repens* was not superior to placebo, finasteride, or tamsulosin with regard to IPSS improvement (similar levels of IPSS improvements in trials with finasteride or tamsulosin might be interpreted as treatment equivalence) [57–59].

The guidelines committee has not made any specific recommendations on phytotherapy for the treatment of male LUTS because of the heterogeneity of the products, lack of regulatory framework, and the considerable methodological problems associated with the published trials and meta-analyses.

3.2.6. Vasopressin analogue: desmopressin

3.2.6.1. Mechanism of action. The antidiuretic hormone arginine vasopressin (AVP) plays a key role in body water homeostasis and the control of urine production by binding to the V2 receptor in the renal collecting ducts. AVP increases water reabsorption as well as urinary osmolality and decreases water excretion as well as total urine volume. AVP might be used therapeutically to manipulate the amount of urine excretion; however, AVP also has V1

receptor–mediated vasoconstrictive/hypertensive effects and a very short serum half-life, which makes the hormone unsuitable for the treatment of nocturia/nocturnal polyuria.

3.2.6.2. Available drugs. Desmopressin is a synthetic analogue of AVP with high V2 receptor affinity and antidiuretic properties but has no relevant V1 receptor affinity and hypertensive effects. Desmopressin has been approved in most European countries for the treatment of nocturia secondary to nocturnal polyuria in adult patients (Table 3). The clinical effects, in terms of urine volume decrease and an increase in urine osmolality, last for approximately 8–12 h [60].

3.2.6.3. Efficacy. In pivotal clinical trials, desmopressin significantly reduced nocturnal diuresis by approximately 0.6–0.8 ml/min (−40%), decreased the number of nocturnal voids by approximately 0.8–1.3 (−40%), and extended the time until the first nocturnal void by approximately 1.6–2.1 h. Desmopressin significantly reduced nighttime urine volume and the percentage of urine volume excreted at night [61–63].

A meta-analysis of the available RCTs found that desmopressin reduced significantly the overall number of nocturnal voids and increased significantly the hours of undisturbed sleep in comparison with placebo. However, these RCTs were conducted in extremely heterogeneous populations with variable dosages [64].

3.2.6.4. Tolerability and safety. The most frequent adverse events in short-term (≤3 wk) and long-term studies (12 mo) were headache, nausea, diarrhoea, abdominal pain, dizziness, dry mouth, and hyponatremia (serum sodium concentration <130 mmol/l). Peripheral oedema (2%) and hypertension (5%) were reported in the long-term treatment trial [63].

Hyponatremia of all degrees, not necessarily associated with symptoms, occurs in 5–7.6% of patients early after treatment initiation [65,66]. The risk of developing hyponatremia is significantly lower in men and significantly increases with age, lower serum sodium concentration at baseline, and higher basal 24-h urine volume per bodyweight [65]. The risk of hyponatremia in patients <65 yr of age is <1%, whereas the risk for older patients increases to 8% with normal sodium concentrations and up to 75% in patients with low sodium concentrations at baseline [65]. A recently published subanalysis suggests that oral doses of 50–100 μg desmopressin (Melt) are safe in men [67].

3.2.6.5. Practical considerations. Desmopressin is indicated in patients with nocturia secondary to nocturnal polyuria and should be taken once daily before sleeping. Because the optimal dose differs between patients, desmopressin treatment should be initiated at a low oral dose (0.1 mg/d) and may be gradually increased every week until maximum efficacy is reached. The maximum oral daily dose recommended is 0.4 mg/d. Patients should avoid drinking fluids at least 1 h before using desmopressin and for 8 h after dosing. Serum sodium concentrations should be monitored at days 3 and 7 after starting therapy and regularly thereafter.

3.2.7. Combination therapies

3.2.7.1. α_1-Blockers plus 5α-reductase inhibitors. An α_1-blocker together with a 5-ARI aims to combine the differential effects of both drug classes with regard to symptom improvement and prevention of disease progression. Four-year data analysis from MTOPS, as well as the 2- and 4-yr results from the Combination of Avodart and Tamsulosin (CombAT) trials, have been reported [17,18,20]. The latter trial included older men with larger prostates and higher serum PSA concentrations and therefore appears to represent men at greater risk of disease progression. In contrast to earlier studies with only 6–12 mo of follow-up, long-term data have demonstrated that combination treatment is superior to monotherapy with regard to symptom reduction and improvement in Q_{max} [17,18,20]. The MTOPS study found that the risk of long-term clinical progression (primarily due to increasing IPSS) was reduced by 66% with combined therapy (vs placebo) and to a greater extent than with either finasteride or doxazosin monotherapy (34% and 39%, respectively) [20]. In addition, finasteride, alone or in combination, but not doxazosin significantly reduced both risks of AUR and the need for BPH-related surgery over the 4-yr study. In the CombAT study, combination therapy reduced the relative risks of AUR by 67.8%, BPH-related surgery by 70.6%, and symptom deterioration by 41.3% compared with tamsulosin, after 4 yr [18].

Discontinuation of the α_1-blocker after 6–9 mo of combination therapy was investigated by an RCT and open-label multicentre trial [68,69]. However, the main limitations of those studies include the short duration of the combination therapy and the short follow-up period after discontinuation.

Adverse events of both drug classes are reported with combination treatment [17,18,20]. α_1-Blockers together with 5-ARIs should be prescribed primarily in men with moderate-to-severe LUTS who are at risk of disease progression (eg, higher prostate volume, higher PSA concentration, advanced age) and when the patient accepts long-term treatment (>12 mo).

3.2.7.2. α_1-Blockers plus muscarinic receptor antagonists. An α_1-blocker together with a muscarinic receptor antagonist aims to antagonise both α_1-adrenoceptors and M_2- and M_3-receptors in the lower urinary tract, thereby using the efficacy of both drug classes to achieve synergistic effects.

Several RCTs [70–75] and prospective studies have evaluated the efficacy of the combination of α_1-blockers and muscarinic receptor antagonists either as initial treatment in men with OAB and presumed BPO or as sequential treatment in men with persistent storage symptoms despite treatment with an α_1-blocker. Combination treatment was more efficacious in reducing voiding frequency, nocturia, or IPSS compared with α_1-blockers or placebo alone.

Combination treatment significantly reduced UUI episodes as well as urgency and significantly increased quality of life (QoL) [75]. Persistent LUTS during α_1-blocker treatment can be significantly reduced by the additional use of a muscarinic receptor antagonist, especially when detrusor overactivity had been demonstrated. Two systematic reviews (no statistical analyses were provided) of studies on the efficacy and safety of antimuscarinic agents (including tolterodine, oxybutynin, propiverine, solifenacin, trospium, and fesoterodine) for the treatment of LUTS, including OAB in men, supported that combination treatment provides significant benefit to those men [76,77].

Adverse events of both drug classes are reported with combination treatment with α_1-blockers and muscarinic receptor antagonists. Some side effects (eg, xerostomia or ejaculation failure) may appear with increased frequency and cannot simply be explained by adding the frequencies of adverse events of either drug. Combination studies of α_1-blockers and antimuscarinics that measured PVR volume showed an increase (but not clinically significant) in PVR, and the risk of AUR seems to be low [76,77]. A recent RCT investigated the safety in terms of maximum detrusor pressure and Q_{max} of the combination of solifenacin (6 and 9 mg) and tamsulosin in men with LUTS and BOO compared with placebo [78]. At the end of treatment the combination therapy was noninferior to placebo for the primary urodynamic variables; Q_{max} was increased versus placebo [78].

Class effects are likely to be responsible for increased efficacy and QoL in patients treated with an α_1-blocker and muscarinic receptor antagonist. Trials used mainly storage symptom end points, were of short duration, and included only men with low PVR volumes at baseline. Therefore, measuring PVR urine is recommended during combination treatment to assess increased PVR or urinary retention.

3.3. Surgical treatment

3.3.1. Transurethral resection and transurethral incision of the prostate

3.3.1.1. Mechanism of action. Transurethral resection of the prostate (TURP) aims to resect tissue from the transition zone of the prostate to treat LUTS secondary to BPO. TURP is still regarded as the standard surgical procedure for the treatment of LUTS secondary to BPO in prostates $\leq$80 ml. Transurethral incision of the prostate (TUIP) reduces BPO by splitting the bladder outlet without tissue removal.

3.3.1.2. Efficacy. In 1999, a meta-analysis of 29 RCTs found a mean decrease in LUTS of 70.6% and a mean increase in Q_{max} by 125% after TURP [79]. In a recent analysis of 20 contemporary RCTs published between 2005 and 2009 and a maximum follow-up of 5 yr, TURP resulted in a substantial improvement of mean Q_{max} (+162%) and a significant reduction of mean IPSS (−70%), mean QoL scores (−69%), and mean PVR urine (−77%) [80]. TURP also delivers durable clinical outcomes. One study with a mean follow-up of 13 yr reported a significant and sustained decrease in most symptoms and an improvement of urodynamic parameters following TURP; subjective and objective failures were associated with detrusor underactivity rather than redevelopment of BPO [81].

A meta-analysis of short- and long-term data from 10 RCTs comparing TUIP with TURP found similar LUTS improvements and lower but not significant improvements in Q_{max} for TUIP patients with small prostates but without enlarged prostate median lobes [82].

Meta-analysis of six trials showed that the need for reoperation was more common after TUIP (18.4%) than after TURP (7.2%) (relative risk: 2.40) [82].

3.3.1.3. Tolerability and safety. Perioperative complications include mortality during the first 30 d (0.1% after TURP), TUR syndrome (<1.1% after TURP and 0% after TUIP), and blood transfusion (8.6% after TURP and negligible for TUIP) [79]. Similar results on TURP complications were reported by the analysis of the contemporary RCTs having TURP as comparator: bleeding requiring blood transfusion 2% (range: 0–9%), TUR syndrome 0.8% (range: 0–5%), AUR 4.5% (range: 0–13.3%), clot retention 4.9% (range: 0–39%), and urinary tract infection (UTI) 4.1% (range: 0–22%) [80].

Long-term complications comprise urinary incontinence (1.8% following TUIP to 2.2% following TURP), urinary retention and UTIs, bladder neck stenosis (4.7% after TURP), urethral stricture (3.8% after TURP and 4.1% after TUIP), retrograde ejaculation (65.4% after TURP and 18.2% after TUIP), and erectile dysfunction (6.5% after TURP) [79].

3.3.1.4. Practical considerations. TURP and TUIP are both effective primary treatments for men with moderate-to-severe LUTS secondary to BPO. The choice between TURP and TUIP should be based primarily on prostate volume, with prostates <30 ml suitable for TUIP and prostates 30–80 ml for TURP. UTIs should be treated prior to TURP or TUIP [83]. No studies on the optimal cut-off value are available, but the rate of complications increases with size [84]. The upper limit depends on the experience of the surgeon and is mostly suggested as 80 ml.

3.3.2. Modifications of transurethral resection of the prostate: bipolar resection of the prostate

3.3.2.1. Mechanism of action. Bipolar TURP (B-TURP) addresses the fundamental flaw of monopolar TURP (M-TURP) by allowing performance in normal saline (NaCl 0.9%) irrigation. Contrary to M-TURP systems, in B-TURP systems, the energy does not travel through the body to reach a skin pad. Bipolar circuitry is completed at the resection site between an active and a return pole attached to a single support on the resectoscope [85].

3.3.2.2. Efficacy and safety. B-TURP is the most widely and thoroughly investigated alternative to M-TURP. A meta-analysis based on 17 RCTs [86] concluded that no clinically relevant differences exist in short-term (up to 12 mo) efficacy, urethral stricture, and bladder neck contracture rates but that B-TURP is preferable due to a more favourable perioperative safety profile (elimination of transurethral

resection syndrome; less bleeding, ie, lower clot retention and blood transfusion rates; shorter irrigation, catheterisation, and possibly hospitalisation times) [86]. Two subsequent RCT-based meta-analyses supported these conclusions [80,87], which despite the relatively low trial quality appear reliable and currently reflect the best available evidence. A contemporary update [88] of a meta-analysis detected 16 additional RCTs published during the last 3 yr (33 RCTs; 3601 randomised patients in total). Updated pooled results are still awaited, but no individual RCT favours M-TURP in any aspect [88]. Midterm, short-term, and perioperative complication rates did not differ significantly between arms [89–91]. The effect on overall sexual function, efficacy, and all other secondary outcomes were comparable throughout follow-up [89–91]. Seven RCTs published to date have follow-up durations >12 mo (range: 18–60 mo) showing no differences in terms of IPSS and Q_{max} between B-TURP and M-TURP at midterm [90,92–97].

3.3.2.3. Practical considerations. B-TURP offers an attractive alternative to M-TURP in patients with moderate-to-severe LUTS secondary to BPO with similar efficacy but lower perioperative morbidity [86]. The duration of improvements with B-TURP was documented in a number of RCTs with a follow-up >12 mo. Midterm results (up to 5 yr) of B-TURP safety/efficacy are comparable with those of M-TURP. The choice of B-TURP should currently be based on the availability of the bipolar armamentarium, the surgeon's experience, and the patient's preference.

3.3.3. Open prostatectomy

3.3.3.1. Mechanism of action. Open prostatectomy is the oldest surgical treatment modality for moderate-to-severe LUTS secondary to BPO. Removal of prostatic tissue resolves BPO and, secondarily, LUTS.

3.3.3.2. Efficacy. Open prostatectomy results in reduction of LUTS by 63–86% (12.5–23.3 IPSS points), improvement of the IPSS-QoL score by 60–87%, mean increase of Q_{max} by 375% (range: 88–677%; in absolute terms +16.5–20.2 ml/s), and reduction of PVR by 86–98% [98,99]. Efficacy is maintained after long-term observations >5 yr.

3.3.3.3. Tolerability and safety. Perioperative complications include mortality (<0.25% in contemporary series) and blood transfusion (7–14%) [98,99]. Long-term complications are urinary incontinence (≤10%) and bladder neck stenosis or urethral stricture (approximately 6%) [98,100].

3.3.3.4. Practical considerations. Open prostatectomy is the most invasive but also the most effective and durable procedure for the treatment of LUTS/BPO. Only holmium enucleation delivers similar results but with less morbidity [98,100]. In the absence of endourologic armamentarium and a holmium laser, open prostatectomy is the surgical treatment of choice for men with prostates >80 ml who have absolute indications for surgery or experience moderate-to-severe LUTS secondary to BPO who have been treated insufficiently by drugs.

3.3.4. Transurethral microwave therapy

3.3.4.1. Mechanism of action. Microwave thermotherapy works by emitting microwave radiation through an intraurethral antenna to deliver heat into the prostate, which leads to tissue destruction, apoptosis, and denervation of α-receptors and thus reduces BPO and LUTS.

3.3.4.2. Efficacy. Although one RCT obtained comparable clinical results 5 yr after transurethral microwave therapy (TUMT) or TURP [101], a systematic review found TUMT somewhat less effective than TURP in reducing LUTS [102]. The pooled mean symptom score for TUMT decreased by 65% in 12 mo compared with 77% in TURP, which results in a weighted mean difference of −1.0 in favour of TURP. TURP achieved a greater Q_{max} improvement (119%) than TUMT (70%), with a weighted mean difference of 5.08 ml/s in favour of TURP [102]. In addition, TUMT was associated with increased risks for retreatment for BPH symptoms. TUMT also improved IPSS symptom scores (weighted mean difference [WMD]: −4.20) and peak urinary flow (WMD: 2.30 ml/s) in the one comparison with α-blockers [102].

3.3.4.3. Tolerability and safety. Treatment is well tolerated, although most patients experience perineal discomfort and urinary urgency and require pain medication prior to or during therapy. In the Cochrane systematic review of RCTs comparing TURP with TUMT, it was shown that catheterisation time, incidence of dysuria/urgency, and urinary retention were significantly less with TURP, whereas the incidence of hospitalisation, haematuria, clot retention, transfusions, TUR syndrome, and urethral strictures were significantly less for TUMT [102]. Sexual dysfunction and retreatment rates for strictures of the meatus, urethra, or bladder neck were higher after TURP than after TUMT.

3.3.4.4. Practical considerations. Endoscopy prior to TUMT is essential to identify the presence of a prostate middle lobe or an insufficient length of the prostatic urethra. Because of the low peri- and postoperative morbidity and no need for anaesthesia, TUMT is a true outpatient procedure and an alternative for older patients with comorbidities and those at risk for anaesthesia otherwise unsuitable for invasive treatment [103]. Independent baseline parameters predicting an unfavourable outcome include small prostates, mild-to-moderate BOO, and low energy delivered during treatment [104]. Predictive factors for particular devices cannot necessarily be applied to systems of other producers.

3.3.5. Transurethral needle ablation of the prostate

3.3.5.1. Mechanism of action. The transurethral needle ablation (TUNA) device delivers low-level radiofrequency energy to the prostate via needles inserted transurethrally into the prostatic parenchyma. The energy induces coagulation necroses in the prostatic transition zone resulting in prostate volume reduction and BPO reduction/resolution.

3.3.5.2. Efficacy. A meta-analysis of two randomised trials, two nonrandomised protocols, and 10 single-arm studies conducted on TUNA showed that it achieved a 50% decrease

of the mean IPSS and a 70% improvement in Q_{max} from baseline at 1 yr after treatment [105]. A more recent meta-analysis of 35 studies (9 comparative, 26 noncomparative) confirmed these results [106]. TUNA significantly improved IPSS and Q_{max} with respect to baseline values, but in comparison with TURP this improvement was significantly lower at 12 mo. TURP versus TUNA differences in means were −4.72 and 5.9 ml/s for the IPSS and Q_{max}, respectively [106].

TUNA has a significant higher retreatment rate compared with TURP (odds ratio [OR]: 7.44 (2.47–22.43). The overall retreatment rate after TUNA was 19.1% (95% confidence interval [CI], 18.7–39.7) as calculated from 17 noncomparative studies [106].

3.3.5.3. Tolerability and safety. Postoperative urinary retention with a mean duration of 1–3 d is seen in 13–42% of patients; within 1 wk, 90–95% of patients are catheter free [107]. Bladder storage symptoms are common for the first 4–6 wk after the operation [108]. TUNA is associated with fewer adverse events compared with TURP including mild haematuria, urinary infections, strictures, incontinence, erectile dysfunction, and ejaculation disorders (OR: 0.14; 95% CI, 0.05–0.41) [106].

3.3.5.4. Practical considerations. TUNA can be performed as a day-case procedure under local anaesthesia or sedation. TUNA is unsuitable for prostates >75 ml or isolated bladder neck obstruction. Because TUNA cannot effectively treat prostatic middle lobes, it remains unclear whether men with large middle lobes will benefit from this treatment.

3.3.6. Laser treatments of the prostate

3.3.6.1. Holmium laser enucleation or holmium resection of the prostate

3.3.6.1.1. Mechanism of action. The holmium:yttrium-aluminium-garnet (Ho:YAG) laser with a wavelength of 2140 nm is a pulsed solid-state laser that is promptly absorbed by water and water-containing tissues. Holmium laser resection of the prostate (HoLRP) or holmium laster enucleation of the prostate (HoLEP) results in BPO relief and, secondarily, in LUTS reduction.

3.3.6.1.2. Efficacy. In a meta-analysis of studies comparing HoLRP with TURP, no difference in symptom improvement could be detected at 6 or 12 mo postoperatively, but HoLRP achieved a significantly greater increase in Q_{max} compared with TURP with a WMD of 4.8 ml/s [109]. One RCT comparing TURP with HoLRP with a minimum follow-up of 4 yr showed no difference in urodynamic parameters between the two techniques after 48 mo [110]. Three meta-analyses that analysed RCTs comparing HoLEP and TURP [111–113] reported a significantly longer operation time for the laser operation. Symptom improvement was comparable or superior with HoLEP. Furthermore, Q_{max} at 12 mo was significantly better with HoLEP [111–113]. One RCT comparing photoselective vaporisation of the prostate (PVP) and HoLEP in patients with prostates >60 ml showed comparable symptom improvement but significantly higher flow rates and lower PVR volume after HoLEP [114].

Available RCTs indicated that in large prostates HoLEP was as effective as open prostatectomy for improving micturition [98,100], with equally low reoperation rates after 5 yr (5% vs 6.7%, respectively) [98]. One RCT comparing HoLEP with TURP in a small number of patients who completed the 7-yr follow-up found that the functional long-term results of HoLEP were comparable with TURP; no HoLEP patient required reoperation for recurrent BPH [115]. A retrospective study of 949 treated with HoLEP with the longest follow-up (up to 10 yr; mean follow-up: 62 mo) reported durable functional results; bladder neck contracture, urethral stricture, and reoperation due to residual adenoma developed in 0.8%, 1.6%, and 0.7% of patients, respectively [116].

3.3.6.1.3. Tolerability and safety. No major intraoperative complications have been described; in a meta-analysis, no statistically significant differences were noted between HoLEP and TURP for urethral stricture (2.6% vs 4.4%), stress incontinence (1.5% vs 1.5%; $p = 0.980$), and reintervention (4.3% vs 8.8%; $p = 0.059$) [112]. Pooled data from large case series (total of 1847 patients) showed low complication rates including perioperative mortality (0.05%), transfusion (1%), UTI (2.3%), urethral stricture/bladder neck contracture (3.2%), and reoperation (2.8%) [117]. Patients using anticoagulant medication and those with urinary retention can be treated safely [118,119]. Three meta-analyses found that HoLEP resulted in a significantly shorter catheterisation time and hospital stay, reduced blood loss [111–113], and fewer blood transfusions compared with TURP [112,113]. Similarly available RCTs indicated that HoLEP was better than open prostatectomy for blood loss, catheterisation, and hospitalisation time [98,100].

3.3.6.1.4. Practical considerations. The holmium operations are surgical procedures that require experience and relevant endoscopic skills. The experience of the surgeon was the most important factor affecting the overall occurrence of complications [120,121].

3.3.6.2. GreenLight 532-nm laser vaporisation of prostate

3.3.6.2.1. Mechanism of action. The kalium-titanyl-phosphate (KTP) and the lithium triborate (LBO) lasers are both derived from the neodymium:YAG (Nd:YAG) laser. The addition of a KTP or LBO crystal to the laser resonator converts the Nd:YAG wavelength from 1064 nm to 532 nm, and laser energy is absorbed within the tissue by haemoglobin, which acts as an intracellular chromophore, and not by the water. Vaporisation leads to immediate removal of prostatic tissue, relief of BPO, and, secondarily, reduction of LUTS. In 2013, three different GreenLight lasers are in use: the 80-W (KTP), 120-W HPS (LBO), and the 180-W XPS (LBO) laser systems. They differ in maximum power output, fibre design, and maximum energy application.

3.3.6.2.2. Efficacy. A meta-analysis of the nine available RCTs comparing PVP using the 80-W and 120-W lasers with TURP was performed in 2012 [122]. No differences were found in

Q_{max} and IPSS between PVP and TURP, but only three RCTs [123–125] provided sufficient 12-mo data to be included in the meta-analysis.

The longest RCT using the 80-W KTP laser has a follow-up of only 12 mo [123]. A case series of 246 patients who completed the 5-yr follow-up showed that functional outcomes after the 80-W KTP laser were durable with an overall retreatment rate of 8.9% at 5 yr due to recurrent adenoma (7.7%) and bladder neck contracture (1.2%) [126]. Another case series of 500 patients treated with the 80-W system with a mean follow-up of 30.6 mo (5.2–60.6 mo) reported a retreatment rate of 14.8% due to recurrent or persisting adenoma (6.8%), bladder neck strictures (3.6%), or urethral strictures (4.4%) [127].

The longest RCT comparing the 120-W HPS laser with TURP had a follow-up of 36 mo and showed a comparable improvement in IPSS, Q_{max}, and PVR, whereas the percentage reductions in PSA level and prostate volume were significantly higher in the TURP group. Reoperation rate was significantly higher after PVP (11% vs 1.8%; $p = 0.04$) [128]. Similar improvement of IPSS, QoL, Q_{max}, or urodynamic parameters was reported from two RCTs with a maximum follow-up of 24 mo [124,129].

No RCTs had been published on the 180-W GreenLight laser until the end of the literature search. A multicentre case series of the 180-W laser demonstrated comparable safety and symptom improvement compared with the former GreenLight laser systems [130].

Interestingly, transurethral enucleation of the prostate using a 120-W 532-nm HPS GreenLight laser in combination with a 600-μ side-fire laser fibre has been described [131].

3.3.6.2.3. Tolerability and safety. The meta-analysis of the RCTs comparing the 80-W and 120-W lasers with TURP showed a significantly longer operating time but significantly shorter catheterisation time and length of hospital stay after PVP [122]. Postoperative blood transfusions and clot retention were significantly less with PVP. No difference was noted in the occurrence of postoperative urinary retention, infection, meatal stenosis, urethral stricture, or bladder neck contracture [122].

Safety in patients with oral anticoagulation, urinary retention, or prostates >80 ml was shown in various prospective nonrandomised trials [131–137].

3.3.6.2.4. Practical considerations. The evolution of the GreenLight laser from 80 W to 120 W and then to 180 W resulted in a wide variation in the degree of maturity of each laser therapy. Long-term results on 120 W and RCTs on 180 W are still pending.

3.3.6.3. Diode laser vaporisation of the prostate

3.3.6.3.1. Mechanism of action. In diode lasers, a semiconductor is used to generate the laser light. The wavelength of the laser beam depends on the semiconductor material used. For the application in prostate surgery, diode lasers with a wavelength of 940 nm, 980 nm, 1318 nm, and 1470 nm are available, and they are absorbed by both water and haemoglobin [138]. Depending on wavelength, power output, and fibre design, diode lasers can be used for vaporisation in noncontact and contact mode and enucleation.

3.3.6.3.2. Efficacy. A major drawback of all studies on diode laser vaporisation is the lack of RCTs in comparison with TURP or open prostatectomy and the short follow-up period (up to 12 mo). Case series as well as two comparative studies of a 980-nm diode laser to the 120-W HPS laser are available [139–148]. IPSS, QoL, Q_{max}, and PVR improved significantly in all diode laser studies compared with the baseline value. Compared with the 120-W HPS laser, the improvement of IPSS, QoL, Q_{max}, and PVR was similar at 6 mo and 12 mo [139,142].

A small RCT with a 6-mo follow-up comparing laser enucleation using a 1318-nm diode laser with B-TURP reported similar efficacy and safety results [149]. Operative time, blood loss, catheterisation, and hospitalisation time were in favour of laser enucleation.

3.3.6.3.3. Tolerability and safety. Studies on diode lasers indicate a high level of intraoperative safety. The application of the 980-nm diode laser showed no intraoperative bleeding, whereas with the 120-W HPS laser, bleeding was reported in 11% and 13% of the cases [139,142]. Notably, in these two studies, anticoagulants or platelet aggregation inhibitors were taken in 23.6% and 52% of the diode laser cases compared with 25% and 43% of the cases in the 120-W HPS group [139,142]. Comparable haemostatic properties are also reported for the 1470-nm diode laser [145].

During the postoperative course, a significantly higher rate of dysuria with sloughing tissues occurs after the 980-nm diode laser compared with the 120-W HPS laser [139,142]. The modification of the 980-nm diode laser fibre with a quartz head led to a significant reduction of dysuria lasting >1 mo from 42% to 17% [146]. Reoperation due to bladder neck stricture and obstructive necrotic tissue (33% vs 4%) and persistence of stress urinary incontinence (9.1% vs 0%) were significant higher after 980-nm diode laser compared with 120-W HPS laser [139,142]. In contrast, two cohort studies of the 980-nm diode laser reported no reoperations but only after 3 and 6 mo [143,148]. After treatment with the 1470-nm diode laser, reoperation in 2 of 10 patients was necessary during the 12 mo after surgery [145].

3.3.6.3.4. Practical considerations. Diode lasers lead to immediate, subjective, and objective improvements of LUTS due to BPO and appear to be safe due their haemostatic properties. Based on the short follow-up, the lack of RCTs in comparison with TURP or open prostatectomy, and controversial data on retreatment rate, diode lasers cannot be recommended as a standard treatment option for BPO.

3.3.6.4. Thulium:yttrium-aluminium-garnet laser

3.3.6.4.1. Mechanism of action. In thulium:YAG (Tm:YAG) lasers, a wavelength of approximately 2000 nm is emitted in continuous-wave mode. The target chromophore is water. The laser is primarily used in front-fire applications; the

continuous-wave output of the Tm:YAG allows smooth incision of tissue [138]. Four different techniques have been described: Tm:YAG vaporisation of the prostate (ThuVaP), Tm:YAG vaporesection (ThuVaRP), Tm:YAG vapoenucleation (ThuVEP), and Tm:YAG laser enucleation of the prostate (ThuLEP). ThuVEP follows a HoLEP-like approach, and ThuLEP consists mainly of blunt dissection of the tissue.

3.3.6.4.2. Efficacy. A major drawback of all studies on thulium lasers is the limited number of RCTs in comparison with TURP and the lack of RCTs in comparison with open prostatectomy. No data beyond a follow-up of 18 mo are available yet. One RCT and one non-RCT compared ThuVaRP with M-TURP [150,151]; one RCT comparing ThuVaRP and B-TURP was published recently [152]. In summary, all studies show a comparable improvement of symptoms and voiding parameters. There are only few case studies on ThuVEP showing a significant improvement in IPSS, Q_{max}, and PVR after treatment [153–156]. Interestingly, a comparative study showed that both 120-W and 200-W ThuVEP had an equivalent efficacy and safety at 12-mo follow-up [155]. ThuLEP and HoLEP were compared in one RCT with 18-mo follow-up [157]. Symptom improvement, increase of Q_{max}, and reduction of PVR volume sustained and were comparable between ThuLEP and HoLEP [157].

3.3.6.4.3. Tolerability and safety. Thulium laser prostatectomy shows high intraoperative safety in RCTs [150,152,157] as well as in case series in patients with large prostates [153] and for anticoagulation therapy or bleeding disorders [154]. Catheterisation time, hospital stay, and blood loss were significantly shorter in comparison with TURP [150–152]. In one RCT, operation time was longer with ThuLEP compared with HoLEP, whereas blood loss was reduced with ThuLEP [157]. The rate of postoperative urethral strictures after ThuVaRP was 1.9%, the rate of bladder neck contracture was 1.8%, and the reported reoperation rate was 0–7.1% during the 9- to 12-mo follow-up [150,151,158]. Urethral stricture after ThuVEP occurred in 1.6% of the patients, and the overall retreatment rate was 3.4% after a mean follow-up of 16.5 mo [159]. No urethral and bladder neck strictures after ThuLEP were reported during the 18-mo follow-up [157].

3.3.6.4.4. Practical considerations. The limited number of RCTs evaluating thulium laser applications for the surgical management of BPO and the limited follow-up (up to 18 mo) do not permit final conclusions regarding the long-term efficacy of thulium laser prostatectomy.

3.3.7. Prostate stents

3.3.7.1. Mechanism of action. Stents are tubes that can be placed temporarily or permanently in the prostatic urethra to compress prostatic tissue and open the bladder outlet. Immediate BPO relief occurs after stent placement. A prostatic stent requires a functioning detrusor.

3.3.7.2. Efficacy. The main representative of the permanent stents is the UroLume prosthesis. A systematic review identified 20 case series, with a total of 990 patients who received the UroLume stent [160]. These trials with a varying follow-up reported relevant symptom improvement; IPSS decreased by 10–12.4 points [160]. Additionally, mean Q_{max} increased by 4.2–13.1 ml/s following stent insertion.

The best data on nonepithelising prostatic stents are provided by a systematic review of the efficacy of Memokath, a self-expanding metallic prostatic stent [161]. A total of 14 case series with 839 patients were reviewed. The Memokath stent reduced IPSS by 11–19 points. However, assessments were made at different times after stent placement; similarly, stent insertion resulted in a Q_{max} increase of 3–11 ml/s [161].

3.3.7.3. Tolerability and safety. Stents are subject to misplacement, migration, and poor tolerability because of exacerbation of LUTS and encrustation [162]. The main adverse events immediately following stent placement include perineal pain or bladder storage symptoms. It can be difficult to remove permanent stents in cases of stent migration, stent encrustation, or epithelial ingrowth, and general anaesthesia is usually needed in these cases. Removal of a temporary stent is achieved by pulling the retrieval suture until the stent is completely retracted or by using graspers under endoscopic guidance.

3.3.7.4. Practical considerations. Because of the side effects and high migration rate, prostatic stents have a limited role in the treatment of moderate-to-severe LUTS secondary to BPO. Prostatic stents remain an alternative to transurethral catheterisation for men who have (recurrent) urinary retention and are at high risk for surgery. Temporary stents can provide short-term relief from LUTS secondary to BPO in patients temporarily unfit for surgery or after minimally invasive treatment [162].

3.3.8. Emerging operations

3.3.8.1. Intraprostatic ethanol injections

3.3.8.1.1. Mechanism of action. Absolute (dehydrated, 95–98%) ethanol is injected into the prostatic parenchyma. Ethanol causes inflammation, coagulation necrosis with protein denaturation and cell membrane lysis, and, finally, atrophy and ablation of prostatic tissue resulting in cavity formation and BPO relief. However, the precise mechanism of action remains unclear.

3.3.8.1.2. Efficacy. Open trials with a mean follow-up of 3–54 mo demonstrated a significant reduction in symptoms (decrease of IPSS 40–71%, or 6.7–16.5 score points) and PVR (up to 99%, or 286 ml) as well as a significant improvement in Q_{max} (35–155%, or 3.2–11 ml/s) and QoL (IPSS-QoL) [163–165]. However, no predictive efficacy parameters and dose–response relationships have been found. Several trials demonstrated a considerable number or retreatments within the first year, and one trial reported a retreatment rate of 41% after 3 yr [166].

3.3.8.1.3. Tolerability and safety. Local anaesthesia supplemented by conscious sedation may be considered, although

Table 5 – Speed of onset and influence on basic parameters of conservative, medical, or surgical treatment modalities for the management of male lower urinary tract symptoms*

Treatment	Speed of onset	LUTS (IPSS)	Uroflowmetry (Q_{max})	Prostate size	PVR	Disease progression
Conservative and drug treatments						
Watchful waiting, behavioural treatment	Months	+ (−1.3 to −5.7 points)	–	–	–	?
α_1-Adrenoceptor antagonists	Days	++ (−31% to −48.2%)	++ (+1.4 to +3.2 ml/s)	–	–/+ (−17 to −39%)	+++ (symptoms)
5α-Reductase inhibitors	Months	+ (−13.3% to −38.6%)	++ (+1.4 to +2.2 ml/s)	+ to ++ (−15 to −28%)	–	+++ (retention)
Muscarinic receptor antagonists	Weeks	++ (storage symptoms) (−35.3% to −54%)	–	–	+ (0 to +49ml)	?
PDE5 inhibitors (tadalafil)	Days	++ (−17% to −37%)	–/+	–	–/+ (+9 to −19 ml)	?
α_1-Adrenoceptor antagonists plus 5α-reductase inhibitors	Days	++ (−38% to −49.7%)	++ (+2.3 to 3.8 ml/s)	+ to ++ (−11.9 to −27.3%)	–/+	+++ (symptoms + retention)
α_1-Adrenoceptor antagonists plus muscarinic receptor antagonists	Days	++ (−31.8% to −66.4%)	++	–		?
Surgical treatments			After catheter removal			
TURP–TUIP	Hours	++++ (−63% to −88%)	++++ (+6.9 to 22.9 ml/s)	+++	++++	++++
Open prostatectomy	Hours	++++ (−62% to −86%)	++++ (+7.0 to +21.4 ml/s)	++++ (−88%)	++++ (−86 to −98%)	++++
TUMT	Weeks	+++ (−40% to −87%)	+++ (+2.4 to 8.4 ml/s)	++ (−8.1 to −33.0%)	++ (−34 to −84.1%)	+++
TUNA	Weeks	+++ (−45% to −56%)	+++ (+4.7 to 6.5 ml/s)	++	+ (−20 ml or −22%)	++
HoLEP/HoLRP	Hours	++++ (−66% to −92%)	++++ (+10.9 to 23.0 ml/s)	++++ (−34 to −54%)	++++ (−68 to −98%)	++++
KTP/GreenLight	Days	+++ (−31% to −75%)	+++ (+4.7 to 14.9 ml/s)	+++ (−44 to −63%)	+++ (−57 to −91%)	+++
Diode laser	Hours	+++ (−55% to −84.3%)	+++ (+5.1 to 13.7 ml/s)	+++ (−30.3 to −58.1%) PSA based reduction	+++ (−58.1 to −87.7%)	+++
Thulium laser ThuVaP, ThuVaRP, and ThuVEP	Hours	+++ (−63% to 85.4%)	+++ (12.8 to 18.7 ml/s)	+++ (−35.7 to −88%) PSA-based reduction	+++ (−72.4 to −94.4%)	+++
Prostate stents	Hours	++ (−10 to −19 points)	++ (+3 to 13.1 ml/s)	–	+++	?

BTX = botulinum toxin; HoLEP = holmium laser enucleation of the prostate; HoLRP = holmium laser resection of the prostate; IPSS = International Prostate Symptom Score; KTP = K^+-titanyl-phosphate, GreenLight laser vaporisation; LUTS = lower urinary tract symptoms; PDE5 inhibitor = phosphodiesterase type 5 inhibitor; PSA = prostate-specific antigen; PVR = postvoid residual; Q_{max} = maximum flow rate; ThuVaP = thulium:yttrium aluminium garnet (Tm:YAG) vaporisation of the prostate; ThuVaRP = Tm:YAG vaporesection; ThuVEP = Tm:YAG vapoenucleation; TUMT = transurethral microwave therapy; TUNA = transurethral needle ablation; TUIP = transurethral incision of the prostate; TURP = transurethral resection of the prostate.

– = no influence; + = mild influence; ++ = moderate influence; +++ = strong influence; ++++ = very strong influence; ? = unknown.

* Note that the drug treatment studies have typically used data after a run-in phase as baseline, whereas those of interventional treatments did not.

most patients choose regional or general anaesthesia. Frequently reported adverse events included perineal or abdominal discomfort/pain, bladder storage symptoms (≤40%), haematuria (≤40%), UTI or epididymitis, and urinary retention. Two cases of severe complications have been reported; bladder necrosis required cystectomy and urinary diversion [163].

3.3.8.1.4. Practical considerations. Ethanol injections are considered a minimally invasive treatment option for patients with moderate-to-severe LUTS secondary to BPO. However, the mechanism of action, patient selection, and application of ethanol (number of injection sites and injection volume) have not been well investigated, severe adverse events occurred in some patients [163], and long-term results are sparse. Intraprostatic ethanol injections are therefore regarded as experimental procedures and should only be used in trials. RCTs with long-term follow-up comparing ethanol injections with TURP, other minimally invasive procedures, or drugs are needed to judge adequately the value of this treatment modality.

3.3.8.2. Intraprostatic botulinum toxin injections

3.3.8.2.1. Mechanism of action. Botulinum toxin (BTX) is the most potent neurotoxin known in humans. Botulinum toxin A (BoNTA) directly or indirectly reduces LUTS by induction of apoptosis of prostatic (epithelial) cells leading to tissue atrophy and prostate size reduction, inhibition of sensory neurons in the prostate and reduction of afferent signals to the central nervous system, and/or relaxation of smooth muscle cells in the prostatic parenchyma and reduction of BPO [167]. Downregulation of α_{1A}-adrenergic receptors in the prostate may contribute to smooth muscle cell relaxation [167]. The latter two mechanisms are summarised as chemical denervation that possibly has a negative influence on prostate growth.

3.3.8.2.2. Efficacy. A review of the available RCTs or prospective observational studies (until 2010) on the use of intraprostatic injection of BoNTA for LUTS/BPH showed an improvement in IPSS in 20 studies; this reduction was statistically significant in 13 studies [168]. Similarly, Q_{max} increased in all series, reaching statistical significance in 14 studies. The reduction in prostate volume varied between the different series and was statistically significant in 18 studies. Duration of the effects of treatment was also variable, ranging from 3 to 30 mo [168]. In patients with urinary retention before BoNTA injections, most men could void spontaneously within 1 mo [168]. In two recent RCTs comparing several BoNTA doses, no differences were observed between groups in term of efficacy [169,170]. In

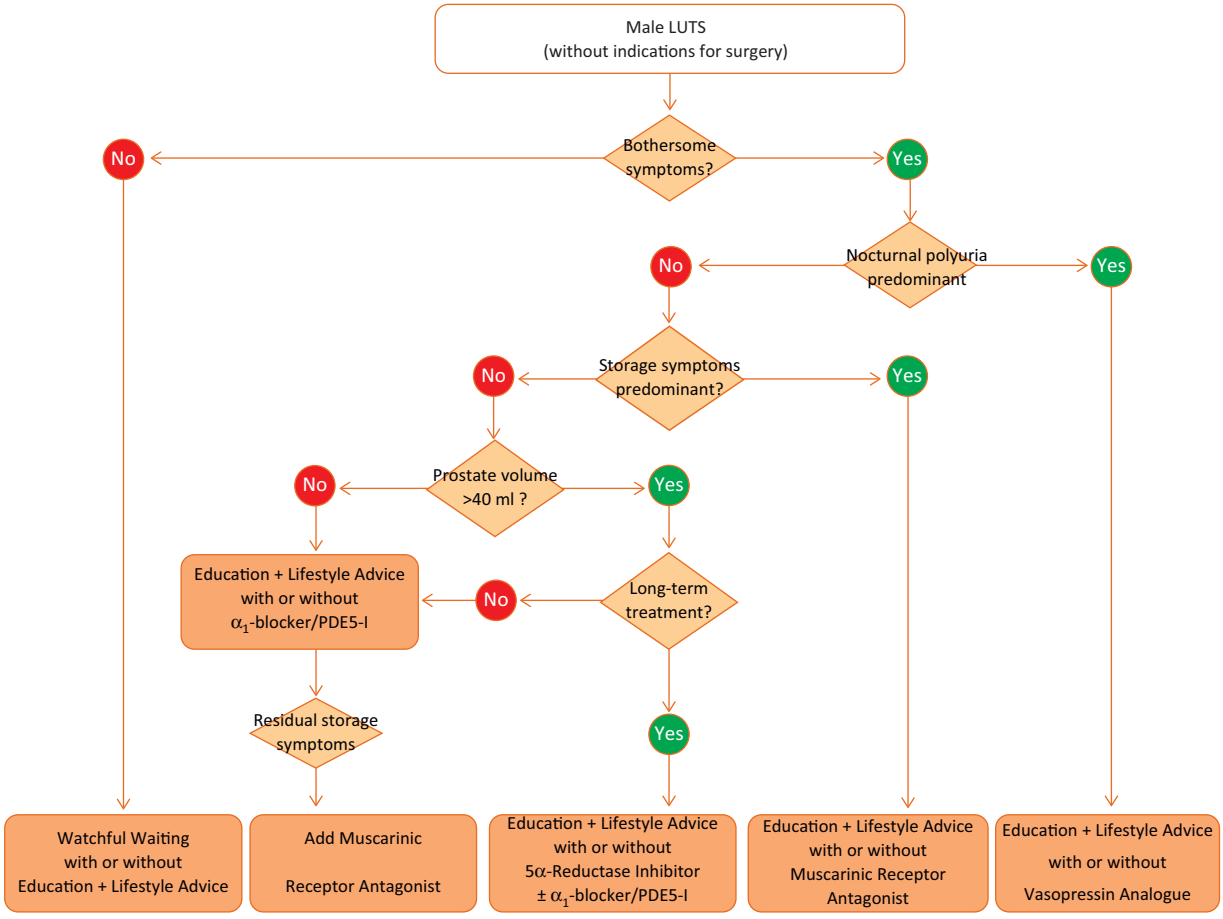

Fig. 2 – Treatment algorithm of male lower urinary tract symptoms (LUTS) using medical and/or conservative treatment options. Treatment decisions depend on results assessed during initial evaluation (◇).The absence ("No") or presence of the condition ("Yes") are indicated in circles (○). Note that patients' preferences may result in different treatment decisions. PDE5-I = phosphodiesterase type 5 inhibitor.

addition, the results from the largest placebo-controlled study on the efficacy of different doses of BoNTA (100 U, 200 U, and 300 U) in men with LUTS/BPH have been published [171]. No significant difference between BoNTA and placebo arm was observed in terms of IPSS, QoL, and Q_{max} at week 12 [171].

3.3.8.2.3. Tolerability and safety. BoNTA injections were well tolerated in all studies. The main reported complications after treatment included dysuria, haematuria, epididymitis, prostatitis, and grade 2–3 events (unspecified) among 35% of patients in the series [168]. In addition, patients may receive a transurethral catheter or perform clean intermittent catheterisation during the early postoperative period (1 wk to 1 mo) [171,172]. Intraprostatic injection of BoNTA in patients with BPE seem to have no impact on sexual function [168,173].

3.3.8.2.4. Practical considerations. BoNTA injections into the prostatic parenchyma are a promising and quick minimally invasive treatment modality with low morbidity for patients who are refractory to medical treatment or in urinary retention. Trials with a larger number of patients, randomisation against saline injections, drugs, TURP, or other minimally invasive treatments, systematic evaluation of doses and dilutions, and long-term follow-up are necessary to judge adequately the value of intraprostatic BoNTA injections in the context of other available medical or surgical treatments of LUTS/BPO.

3.4. Patient selection

The choice of treatment depends on findings assessed during evaluation, ability of the treatment to change assessed findings, treatment preferences of the individual patient, as well as expectations to be met in terms of speed of onset, efficacy, side effects, QoL, and disease progression (Table 5). Note that treatment modalities may be combined leading to different effects.

Behavioural modifications with or without medical treatments are usually the first choice of therapy. Figure 2 provides a flowchart illustrating treatment choice according to evidence-based medicine and patient profiles.

Surgical treatment is usually required when patients have experienced recurrent or refractory urinary retention, overflow incontinence, recurrent UTIs, bladder stones or diverticula, treatment-resistant macroscopic haematuria due to BPH/BPE, or dilatation of the upper urinary tract due to BPO, with or without renal insufficiency (absolute operation indications, need for surgery). Additionally,

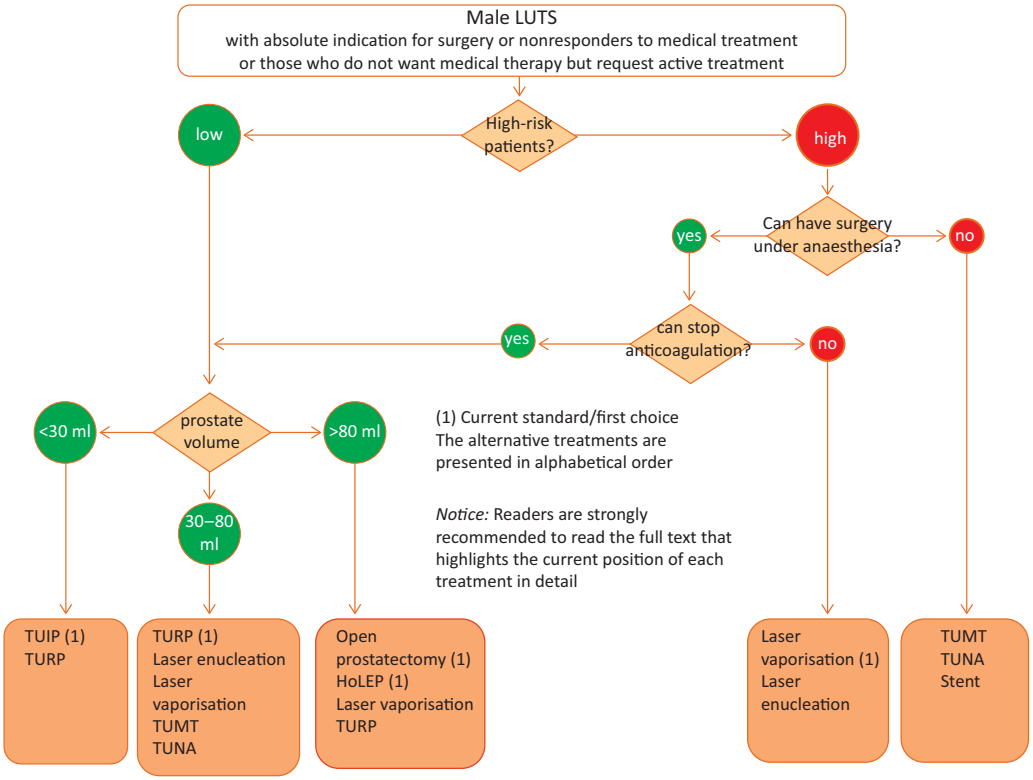

Fig. 3 – Treatment algorithm of bothersome lower urinary tract symptoms (LUTS) refractory to conservative/medical treatment or in cases of absolute operation indications (eg, urinary retention, recurrent urinary tract infections, bladder stones or diverticula, treatment-resistant macroscopic haematuria, or dilatation of the upper urinary tract due to benign prostatic obstruction [BPO] with or without renal insufficiency). Note that this flowchart has been stratified by the patient's ability to have anaesthesia, cardiovascular risk, and prostate size; however, the choice of the surgical techniques also depends on the patient's preferences, willingness to accept surgery-associated side effects, availability of the armamentarium, and surgeon's experience with the operation technique. HoLEP = holmium laser enucleation of the prostate; laser vaporisation includes GreenLight, thulium, and diode lasers vaporisation; laser enucleation includes holmium and thulium laser enucleation; TUIP = transurethral incision of the prostate; TUMT = transurethral microwave therapy; TUNA = transurethral needle ablation of the prostate; TURP = transurethral resection of the prostate (monopolar or bipolar).

surgery is usually needed when patients have had insufficient relief of LUTS or PVR after conservative or medical treatments (relative operation indications). The choice of the surgical technique depends on prostate size, comorbidities of the patient, ability to have anaesthesia, patients' preferences, willingness to accept surgery-associated specific side effects, availability of the surgical armamentarium, and experience of the surgeon with these surgical techniques. An algorithm for surgical approaches to care is provided in Figure 3.

3.5. Follow-up

Patients who elect to pursue a WW policy should be reviewed at 6 mo and then annually, provided there is no deterioration of symptoms or development of absolute indications for surgical treatment.

Patients receiving α_1-blockers, muscarinic receptor antagonists, or the combination of α_1-blockers plus 5-ARIs or muscarinic receptor antagonists should be reviewed 4–6 wk after drug initiation to determine treatment response. If patients gain symptomatic relief in the absence of troublesome adverse events, drug therapy may be continued. Patients should be reviewed at 6 mo and then annually, provided there is no deterioration of symptoms or development of absolute indications for surgical treatment.

Patients receiving 5-ARIs should be reviewed after 12 wk and 6 mo to determine their response and adverse events. Men taking a 5-ARI should be followed up regularly using serial PSA testing if life expectancy is $>$10 yr and if diagnosis of prostate cancer could alter management. A new baseline PSA should be determined at month 6, and any confirmed increase in PSA while on a 5-ARI should be evaluated.

In patients receiving desmopressin, serum sodium concentration should be measured at day 3 and 7 as well as after 1 mo, and, if serum sodium concentration has remained normal, every 3 mo subsequently. The follow-up sequence should be restarted after dose escalation.

Patients after prostate surgery should be reviewed 4–6 wk after catheter removal to evaluate treatment response and adverse events. If patients have symptomatic relief and are without adverse events, no further reassessment is necessary.

4. Conclusions

These symptom-oriented guidelines provide practical guidance for the management of men experiencing LUTS. The full version is available online (www.uroweb.org/gls/pdf/12_Male_LUTS.pdf).

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Study concept and design: Oelke, Gravas.
Acquisition of data: Oelke.
Analysis and interpretation of data: Oelke.
Drafting of the manuscript: Oelke, Gravas.
Critical revision of the manuscript for important intellectual content: Oelke, Gravas, Bachmann, Descazeaud, Emberton, Michel, N'Dow, Nordling, de la Rosette.
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