Guidelines on the Treatment of Non-neurogenic Male LUTS

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TABLE OF CONTENTS PAGE

1. INTRODUCTION

In the past, lower urinary tract symptoms (LUTS) in elderly men were always assumed to be directly or indirectly related to benign prostatic hyperplasia (BPH), benign prostatic enlargement (BPE), or benign prostatic obstruction (BPO). However, it is sometimes difficult or even impossible to make a direct link between symptoms and BPH. The latest knowledge and developments suggest that not all bladder symptoms of elderly men are necessarily linked to the prostate (BPH-LUTS), but instead might be caused by the bladder (detrusor overactivity-overactive bladder syndrome [OAB], detrusor underactivity) or kidney (nocturnal polyuria) (1). Because of the great prevalence of BPH in elderly men, which is as high as 40% in men in their fifth decade and 90% in men in their ninth decade (2), microscopical changes of the prostate seem to co-exist silently with other bladder or kidney malfunctions in some men. This more distinguished view on LUTS has lead to re-formation of the content and panel of the EAU guidelines on BPH (3), which have been renamed the EAU Guidelines on Non-neurogenic Male LUTS. Because patients seek help for LUTS and not BPH, it is expected that symptom-oriented guidelines will deliver a more realistic and practical guide to the clinical problem than disease-specific guidelines. Assessment and treatment of neurogenic LUTS has been published elsewhere and is valid only for men and women with bladder symptoms due to neurological diseases (4).

The new guidelines panel consists of urologists, a pharmacologist, an epidemiologist, and a statistician and has been working on the topic for the last 3 years without financial interests. The new Guidelines are intended to give advice on the pathophysiology and definitions, assessment, treatment, and follow-up of the various forms of non-neurogenic LUTS in men aged 40 years or older. These guidelines cover mainly BPH-LUTS, OAB, and nocturnal polyuria. Lower urinary tract symptoms in children or women and LUTS due to other causes (e.g. neurological diseases, urological tumours of the lower urinary tract, stones disease, or urinary incontinence) are covered by separate EAU guidelines. The new guidelines are primarily written for urologists but can be used by general practitioners as well.

The recommendations of the EAU Guidelines on Non-neurogenic Male LUTS are based on a nonstructured literature search, which used the Pubmed-Medline, Web of Science, and Cochrane databases between 1966 and 31st December 2009, covered all languages, and used the search terms, '(randomised) clinical trials', 'meta-analyses', and 'adult men'. 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 Levels of Evidence, ranging from meta-analysis (LE: 1a, highest evidence level) to expert opinion (LE: 4, lowest evidence level) (5). For each subsection, the conclusion(s) drawn from the relevant articles and evidence levels have been judged using a Grade of Recommendation (GR), ranging from a strong (Grade A) to a weak (Grade C) recommendation.

The panel on Non-neurogenic Male LUTS intend to update the Guidelines, according to the given structure and classification systems, every 2 years thereafter.

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2. CONSERVATIVE TREATMENT OF MALE LUTS

2.1 Watchful waiting-behavioural treatment

Many men with LUTS do not complain of high levels of bother and are therefore suitable for non-medical and non-surgical management - a policy of care known as watchful waiting (WW). It is customary for this type of management to include the following components: education, reassurance, periodic monitoring, and lifestyle advice. In many patients, it is regarded as the first tier in the therapeutic cascade and most men will have been offered WW at some point. WW is a viable option for many men as few, if left untreated, will progress to acute urinary retention and complications such as renal insufficiency and stones (1,2). Similarly, some symptoms may improve spontaneously, while other symptoms remain stable for many years (3).

2.2 Patient selection

All men with LUTS should be formally assessed prior to starting any form of management in order to identify those with complications that may benefit from intervention therapy. Men with mild to moderate uncomplicated LUTS (causing no serious health threat), who are not too bothered by their symptoms, are suitable for a trial of WW. A large study comparing WW and transurethral resection of the prostate (TURP) in men with moderate symptoms showed that those who had undergone surgery had improved bladder function over the WW group (flow rates and postvoid residual [PVR] volumes), with the best results being in those with high levels of bother. Thirty-six per cent of patients crossed over to surgery in 5 years, leaving 64% doing well in the WW group (4). Approximately 85% of men will be stable on WW at 1 year, deteriorating progressively to 65% at 5 years (5,6). The reason why some men deteriorate with WW and others do not is not well understood; increasing symptom bother and PVR volumes appeared to be the strongest predictors of failure.

2.3 Education, reassurance, and periodic monitoring

There now exists LE 1b that self-management as part of WW reduces both symptoms and progression (7,8) (Table 1). In this study, men randomised to three self-management sessions in addition to standard care had better symptom improvement and improved quality of life at 3 and 6 months when compared to men treated with standard care only. These differences were maintained at 12 months. Nobody is quite sure which key components of self-management are effective, but most experts believe the key components are:

- education about the patient's condition;
- reassurance that cancer is not a cause of the urinary symptoms;
- framework of periodic monitoring.

Table 1: Self-management as part of watchful waiting reduces symptoms and progression (7)

Trial	Duration (weeks)	Treatment	Patients	IPSS	Q_{max} (mL/s)	PVR (mL)	LE
Brown et al. (2007) (7)	52	Standard care	67	-1.3	-	-	1b
		Standard care plus self-management	73	-5.7 * †	-	-	

** significant compared to standard care (p < 0.05); † significant compared to baseline (p < 0.05).*
IPSS = International Prostate Symptom Score; Q_{max} = maximum urinary flow rate during free uroflowmetry; PVR = postvoid residual urine.

2.4 Lifestyle advice

The precise role of lifestyle advice in conferring benefit seen in the studies reported to date remains uncertain. Minor changes in lifestyle and behaviour can have a beneficial effect on symptoms and may prevent deterioration requiring medical or surgical treatment. Lifestyle advice can be obtained through informal and formal routes. If it is offered to men, it should probably comprise the following:

- Reduction of fluid intake at specific times aimed at reducing urinary frequency when most inconvenient, e.g. at night or going out in public. The recommended total daily fluid intake of 1500 mL should not be reduced.
- Avoidance or moderation of caffeine and alcohol which 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 stripping to prevent post-micturition 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 irritative symptoms.
- Bladder re-training, by which men are encouraged to 'hold on' when they have sensory urgency to

increase their bladder capacity (to around 400 mL) and the time between voids.

- Reviewing a man's medication and optimising the time of administration or substituting drugs for others that have fewer urinary effects.
- Providing necessary assistance when there is impairment of dexterity, mobility or mental state.
- Treatment of constipation.

2.5 Practical considerations

The components of self-management have not been individually subjected to study. The above components of lifestyle advice have been derived from formal consensus methodology (9). Further research in this area is required.

2.6 Recommendations

	LE	GR
Men with mild symptoms are suitable for watchful waiting.	1b	A
Men with LUTS should be offered lifestyle advice prior to or concurrent with treatment.	1b	A

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3. DRUG TREATMENT

3.1 α-adrenoceptor antagonists (α-blockers)

3.1.1 Mechanism of action

Historically, it was assumed that α-blockers act by inhibiting the effect of endogenously released noradrenaline on prostate smooth muscle cells, thereby reducing prostate tone and bladder outlet obstruction. Contraction of the human prostate is mediated predominantly, if not exclusively, by α_{1A}-adrenoceptors (1). However, it has been shown that α-blockers have little effect on urodynamically determined bladder outlet resistance (2) and treatment-associated improvement of LUTS is correlated only poorly with obstruction (3). Hence, there has been a lot of discussion about the role of α_1-adrenoceptors located outside the prostate (e.g. in the urinary bladder and/or spinal cord) and other α-adrenoceptor subtypes (α_{1B}- or α_{1D}-adrenoceptors) as mediators of beneficial effects of α-blockers. α_1-adrenoceptors in blood vessels, other non-prostatic smooth muscle cells, and central nervous system are considered to be mediators of side-effects during α-blocker treatment, and all three receptor subtypes seem to be involved. This concept has favoured the use of α_{1A}-selective adrenoceptor antagonists. However, it remains to be determined whether α_{1A}-selectivity is the only and main factor determining good tolerability.

3.1.2 Available drugs

Following the early use of phenoxybenzamine and prazosin in BPH-LUTS treatment, four α-blockers are currently mainly used:

- alfuzosin HCL (alfuzosin);
- doxazosin mesylate (doxazosin);
- tamsulosin HCL (tamsulosin);
- terazosin HCL (terazosin).

Over a period of time, alfuzosin has been clinically available in Europe in three formulations, doxazosin and tamsulosin in two formulations each, and terazosin in one formulation (Table 2). Although different formulations result in different pharmacokinetic behaviours and, perhaps, tolerability profiles, the overall clinical impact of the different formulations is modest. Although some countries also have available indoramin, naftopidil and more recently silodosin, there is only limited clinical data for these agents and they will therefore not be discussed in these guidelines.

Table 2: Key pharmacokinetic properties and standard doses of α-blockers licensed in Europe for treating symptoms of BPH

Drug	t_{max} (hours)	t½ (hours)	Recommended daily dose
Alfuzosin IR	1.5	4-6	3 x 2.5 mg
Alfuzosin SR	3	8	2 x 5 mg
Alfuzosin XL	9	11	1 x 10 mg
Doxazosin IR	2-3	20	1 x 2-8 mg
Doxazosin GITS	8-12	20	1 x 4-8 mg
Tamsulosin MR	6	10-13	1 x 0.4 mg
Tamsulosin OCAS	4-6	14-15	1 x 0.4 mg
Terazosin	1-2	8-14	1 x 5-10 mg

t_{max} = time to maximum plasma concentration; t½ = elimination half-life; IR = immediate release; SR = sustained release; GITS = Gastrointestinal Therapeutic System; MR = Modified Release; OCAS = Oral Controlled Absorption System.

3.1.3 Efficacy

Indirect comparisons between α-blockers, and limited direct comparisons, demonstrate that all α-blockers have a similar efficacy in appropriate doses (4). Controlled studies have shown that α-blockers typically reduce the International Prostate Symptom Score (IPSS), after a run-in period, by approximately 35-40% and increase the maximum urinary flow rate (Q_{max}) by approximately 20-25% (Table 3). However, considerable improvements also occurred in the corresponding placebo arms (4,5). In open-label studies (without a runin period), an IPSS improvement of up to 50% and Q_{max} increase of up to 40% were documented (4,6).

Although these improvements take a few weeks to develop fully, statistically significant efficacy over placebo was demonstrated within hours to days. α-blockers seem to have a similar efficacy, expressed as a percent improvement in IPPS, in patients with mild, moderate and severe symptoms (6). α-blocker efficacy does not depend on prostate size (7) and is similar across age groups (6). However, α-blockers do not reduce prostate size and do not prevent acute urinary retention in long-term studies (8), so that eventually some patients will have to be surgically treated. Nevertheless, the efficacy of α-blockers appears to be maintained over at least 4 years.

Table 3: Randomised, placebo-controlled trials with α-blockers in men with LUTS (drugs in chronological order; selection of trials)

Trials	Duration (weeks)	Treatment (daily dose)	Patients (n)	Change in symptoms (%)	Change in Q_{max} (mL/s)	PVR change (%)	LE
Jardin et al. (1991) [14]	24	Placebo Alfuzosin 3 x 2.5 mg	267 251	-32 [a] -42 [a,b]	+1.3 [a] +1.4 [a]	-9 -39 [a,b]	1b
Buzelin et al. (1997) [15]	12	Placebo Alfuzson 2 x 5 mg	196 194	-18 -31 [a,b]	+1.1 +2.4 [a,b]	0 -17 [a,b]	1b
van Kerrebroeck et al. (2000) [16]	12	Placebo Alfuzosin 3 x 2.5 mg Alfuzosin 1 x 10 mg	154 150 143	-27.7 -38.1 [a,b] -39.9 [a,b]	+1.4 +3.2 [a,b] +2.3 [a,b]	- - -	1b
MacDonald and Wilt (2005) [17]	4-26	Placebo Alfuzosin: all formulations	1039 1928	-0.9 [b] (Boyarski) [†] -1.8 [b] (IPSS) [†]	+1.2 [b]	-	1a
Kirby et al. (2001) [18]	13	Placebo Doxazosin 1 x 1-8 mg IR Doxazosin 1 x 4-8 mg GITS	155 640 651	-34 [a] -45 [a,b] -45 [a,b]	+1.1 [a] +2.6 [a,b] +2.8 [a,b]	- - -	1b
McConnell et al. (2003) [8]	234	Placebo Doxazosin 1 x 4-8 mg	737 756	-29 -39 [b]	+1.4 +2.5 [a,b]	- -	1b
Chapple et al. (1996) [19]	12	Placebo Tamsulosin MR 1 x 0.4 mg	185 364	-25.5 -35.1 [a,b]	+0.6 +1.6 [a,b]	-13.4 -22.4 [a]	1b
Lepor (1998) [20]	13	Placebo Tamsulosin MR 1 x 0.4 mg Tamsulosin MR 1 x 0.8 mg	253 254 247	-28.1 -41.9 [a,b] -48.2 [a,b]	+0.5 +1.8 [a,b] +1.8 [a,b]	- - -	1b
Chapple et al. (2005) [21]	12	Placebo Tamsulosin MR 1 x 0.4 mg Tamsulosin OCAS 1 x 0.4 mg Tamsulosin OCAS 1 x 0.8 mg	350 700 354 707	-32 -43.2 [b] -41.7 [b] -42.4 [b]	- - - -	- - - -	1b
Wilt et al. (2002) [22]	4-26	Placebo Tamsulosin 1 x 0.4-0.8 mg	4122	-12 [b] (-1.1 Boyarski [†]) -11 [b] (-2.1 IPSS [†])	+1.1 [b]	-	1a
Brawer et al. (1993) [23]	24	Placebo Terazosin 1 x 1-10 mg	72 69	-11 -42 [a,b]	+1.2 +2.6 [a,b]	- -	1b
Roehrborn et al. (1996) [24]	52	Placebo Terazosin 1 x 1-10 mg	973 976	-18.4 -37.8 [a,b]	+0.8 [a] +2.2 [a,b]	- -	1b
Wilt et al. (2000) [25]	4-52	Placebo Terazosin	5151	-37 [b] (-2.9 Boyarski [†]) -38 [b] (IPSS [†])	+1.7 [b]	-	1a

Q_{max} = maximum urinary flow rate (free uroflowmetry); PVR = postvoid residual urine; a = significant compared to baseline (indexed wherever evaluated); b = significant compared to placebo; † = absolute value.

*3.1.4 **Tolerability and safety***

Although alfuzosin, doxazosin, and terazosin are similar in terms of molecular structure and lack of α_1-adrenoceptor subtype selectivity, the side-effect profile of alfuzosin is more similar to tamsulosin than to doxazosin and terazosin. The mechanisms underlying such differential tolerability are not fully understood, but may involve better distribution into lower urinary tract tissues by alfuzosin and tamsulosin. Other factors, such as subtype selectivity and the pharmacokinetic profiles of certain formulations, may also contribute to the tolerability profile of specific drugs.

The most frequent side-effects of α-blockers are asthenia, dizziness and (orthostatic) hypotension. Although a reduction in blood pressure may benefit hypertensive patients, at least some of the observed asthenia and dizziness can be attributed to a decrease in blood pressure. Vasodilating effects are most pronounced with doxazosin and terazosin, and are much less common for alfuzosin and tamsulosin (odds ratio for vascular-related adverse events 3.3, 3.7, 1.7 and 1.4, respectively; the latter two not reaching statistical significance; [5]). In particular, patients with cardiovascular co-morbidity and/or vasoactive co-medication may be susceptible to α-blocker-induced vasodilatation (9). This includes anti-hypertensive drugs, such as α-adrenoceptor antagonists, diuretics, Ca^{2+}-channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor antagonists, but also phosphodiesterase (PDE) inhibitors prescribed for erectile dysfunction or male LUTS (9).

Despite the long-standing and widespread use of α-blockers, an adverse ocular event, termed intraoperative floppy iris syndrome (IFIS), has been discovered only recently in the context of cataract surgery (10). Although IFIS has been observed with all α-blockers, most reports have been related to tamsulosin. Whether this reflects a greater risk with tamsulosin than with other α-blockers, or rather its more widespread use, is not clear, particularly as the ratio between doses yielding ocular effects and those acting on the lower urinary tract are similar for all α-blockers (11). It therefore appears prudent not to initiate α-blocker treatment prior to cataract surgery, while existing α-blocker treatment should be stopped though it is not clear how long before surgery takes place. It should be noted that the occurrence of IFIS complicates cataract surgery and makes it technically more demanding, however, there are no reports about increased health risks of these patients.

As LUTS and erectile dysfunction often co-exist, medical BPH treatment should not further impair sexual function. A systematic review concluded that α-blockers do not adversely affect libido, have a small beneficial effect on erectile function, but sometimes cause abnormal ejaculation (12). Originally, the abnormal ejaculation was thought to be retrograde, but more recent data demonstrate that it is due to (relative) anejaculation, with young age being an apparent risk factor. Although abnormal ejaculation has been observed more frequently with tamsulosin than with other α-blockers, this difference did not reach statistical significance in direct comparative studies with alfuzosin and is not associated with an overall reduction of overall sexual function (12). The apparently greater risk for abnormal ejaculation with tamsulosin is intriguing as even more α_{1A}-selective drugs, such as silodosin, carry a greater risk (13), however, all α-blockers are dosed to block α_{1A}-adrenoceptors effectively. Hence, the mechanism underlying abnormal ejaculation remains to be elucidated.

*3.1.5 **Practical considerations***

α-blockers represent the first-line drug treatment of male LUTS. All α-blockers are available in formulations, which are suitable for once-daily administration. To minimise adverse events, it is recommended that dose titration is used to initiate treatment with doxazosin and terazosin; however, this is not necessary with alfuzosin and tamsulosin. Because of their rapid onset of action, α-blockers can be considered for intermittent use in patients with fluctuating intensity of symptoms not needing long-term treatment.

*3.1.6 **Recommendations***

	LE	GR
α-blockers should be offered to men with moderate to severe LUTS.	1a	A

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3.2 5α-reductase inhibitors

3.2.1 ***Mechanism of action***

Androgen effects on the prostate are mediated by dihydrotestosterone (DHT), which is converted primarily in the prostatic stroma cells from its precursor testosterone by the enzyme 5α-reductase, a nuclear-bound steroid enzyme (1). Two isoforms of this enzyme exist:

- 5α-reductase type 1, with minor expression and activity in the prostate but predominant activity in extraprostatic tissues, such as skin and liver.
- 5α-reductase type 2, with predominant expression and activity in the prostate.

Finasteride inhibits only 5α-reductase type 2, whereas dutasteride inhibits 5α-reductase types 1 and 2 with similar potency (dual 5α-reductase inhibitor). However, the clinical role of dual inhibition remains unclear. 5α-reductase inhibitors act by inducing apoptosis of prostate epithelial cells (2) leading to prostate size reduction of about 15-25% and circulating PSA levels of about 50% after 6-12 months of treatment (3). Mean prostate volume reduction may be even more pronounced after long-term treatment.

3.2.2 ***Available drugs***

Two 5α-reductase inhibitors are available for clinical use: dutasteride and finasteride (Table 4). The elimination half-time is longer for dutasteride (3-5 weeks). Both 5α-reductase inhibitors are metabolised by the liver and excreted in the faeces. Continuous treatment reduces the serum DHT concentration by approximately 70% with finasteride and 95% with dutasteride. However, prostate DHT concentration is reduced to a similar level (85-90%) by both 5α-reductase inhibitors.

Table 4: 5α-reductase inhibitors licensed in Europe for treating benign prostatic enlargement (BPE) due to benign prostatic hyperplasia (BPH); key pharmacokinetic properties and standard doses

Drug	tmax (hours)	t ½	Recommended daily dose
Dutasteride	1-3	3-5 weeks	1 x 0.5 mg
Finasteride	2	6-8 hours	1 x 5 mg

*3.2.3 **Efficacy***

Clinical effects relative to placebo are seen after minimum treatment duration of at least 6 to 12 months. After 2 to 4 years of treatment, 5α-reductase inhibitors reduce LUTS (IPSS) by approximately 15-30%, decrease prostate volume by approximately 18-28% and increase Q_{max} of free uroflowmetry by approximately 1.5-2.0 mL/s in patients with LUTS due to prostate enlargement (Table 5) (4-13).

Symptom reduction by finasteride depends on initial prostate size and may not be more efficacious than placebo in patients with prostates smaller than 40 mL (14).

However, dutasteride seems to reduce IPSS, prostate volume, and the risk of acute urinary retention. It also increases Q_{max} even in patients with prostate volumes between 30 and 40 mL at baseline (15,16). Indirect comparison between individual studies and one unpublished direct comparative trial indicate that dutasteride and finasteride are equally effective in the treatment of LUTS (3). Comparative studies with α-blockers have demonstrated that 5α-reductase inhibitors reduce symptoms more slowly and, for finasteride, less effectively (5,10,17,18). A long-term trial with dutasteride in symptomatic men with a prostate volume greater than 30 mL (average prostate volume in the CombAT trial was approximately 55 mL) showed that the 5α-reductase inhibitor reduced LUTS in these patients at least as much or even more effectively than tamsulosin (11,12). The greater the baseline prostate volume (serum PSA concentration), the faster and more pronounced the symptomatic benefit of dutasteride (19). IPSS reduction was significantly greater in men with prostate volumes of 58 mL or more (PSA > 4.4) at treatment month 15 or later compared to men with lower baseline prostate volumes (PSA concentrations).

5α-reductase inhibitors, but not α-blockers, reduce the long-term (> 1 year) risk of acute urinary retention or need for surgery (8,10,19,20). Prevention of disease progression by 5α-reductase inhibitors is already detectable with prostate sizes considerably smaller than 40 mL (12,13,20). The precise mechanism of action of 5α-reductase inhibitors in reducing disease progression remains to be determined, but it is most likely attributable to reduction of bladder outlet resistance. Open-label trials demonstrated relevant reductions of voiding parameters after computer-urodynamic re-evaluation in men who were treated at least 3 years with finasteride (21,22).

Table 5: Randomised trials with 5α-reductase inhibitors in men with LUTS and benign prostatic enlargement due to BPH

Trials	Duration (weeks)	Treatment (daily dose)	Patients (n)	Change in symptoms (% IPSS)	Change in Q_{max} (mL/s)	Change in prostate volume (%)	LE
Lepor et al. (1996) [4]	52	Placebo	305	-16.5 [a]	+1.4	+1.3	1b
		Finasteride 1 x 5 mg	310	-19.8 [a]	+1.6	-16.9 [b]	
Kirby et al. (2003) [5]	52	Placebo	253	-33.1	+1.4	-	1b
		Finasteride 1 x 5 mg	239	-38.6	+1.8	-	
Andersen et al. (1995) [6]	104	Placebo	346	+1.5	-0.3	+11.5 [a]	1b
		Finasteride 1 x 5 mg	348	-14.9 [a,b]	+1.5 [a,b]	-19.2 [a,b]	
Nickel et al. (1996) [7]	104	Placebo	226	-4.2	+0.3	+8.4 [a]	1b
		Finasteride 1 x 5 mg	246	-13.3 [a,b]	+1.4 [a,b]	-21	
McConnell et al. (1998) [8]	208	Placebo	1503	-8.7	+0.2	+14 [a]	1b
		Finasteride 1 x 5 mg	1513	-22 [a,b]	+1.9 [a,b]	-18 [a,b]	
Marberger et al. (1998) [9]	104	Placebo	1452	-9.8 †	0.8	+9	1b
		Finasteride 1 x 5 mg	1450	-21.4 [†b]	+1.4 [b]	-15 [b]	
McConnell et al. (2003) [10]	234	Placebo	737	-23.8	+1.4 [a]	+24 [a]	1b
		Finasteride 1 x 5 mg	768	-28.4 [a,b]	+2.2 [a,b]	-19 [a,b]	
Roehrborn et al. (2002) [11]	104	Placebo	2158	-13.5 [a]	+0.6	+1.5 [a]	1b
		Dutasteride 1 x 0.5 mg	2167	-26.5 [a,b]	+2.2 [a,b]	-25.7 [a,b]	
Roehrborn et al. (2008) [12]	104	Tamsulosin 1 x 0.4 mg	1611	-27.4 [a]	+0.9	0	1b
		Dutasteride 1 x 0.5 mg	1623	-30.5 [a]	+1.9	-28 [b]	
Roehrborn et al. (2010) [13]	208	Tamsulosin 1 x 0.4 mg	1611	-23.2 [a]	+0.7	+4.6	1b
		Dutasteride 1 x 0.5 mg	1623	-32.3 [a]	+2.0	-28 [b]	

Q_{max} = maximum urinary flow rate (free uroflowmetry); IPSS = International Prostate Symptom Score; † Boyarski Score; a = significant compared to baseline (indexed wherever evaluated); b = significant compared to placebo/ active control.

*3.2.4 **Tolerability and safety***

The most relevant adverse effects of 5α-reductase inhibitors are related to sexual function and include reduced libido, erectile dysfunction and, less frequently, ejaculation disorders, such as retrograde ejaculation, ejaculation failure, or decreased semen volume (3,10,13). The incidence of sexual dysfunction and other adverse events is low and even decreased with trial duration. Gynaecomastia (breast enlargement with breast or nipple tenderness) develops in approximately 1-2% of patients.

*3.2.5 **Practical considerations***

Treatment with 5α-reductase inhibitors should only be considered in men with LUTS and an enlarged prostate. Due to the slow onset of action, 5α-reductase inhibitors are only suitable for long-term treatment (many years). Their effect on the serum PSA concentration needs to be considered for prostate cancer screening. Of interest,

5α-reductase inhibitors (finasteride) might reduce blood loss during transurethral prostate surgery, probably due to their effects on prostatic vascularisation (23).

3.2.6 ***Recommendations***

	LE	GR
5α-reductase inhibitors should be offered to men who have moderate to severe LUTS and an enlarged prostate. 5α-reductase inhibitors can prevent disease progression with regard to acute urinary retention and need for surgery.	1b	A

3.2.7 ***References***

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3.3 Muscarinic receptor antagonists

3.3.1 Mechanism of action

The predominant neurotransmitter of the urinary bladder is acetylcholine that is able to stimulate muscarinic receptors (m-cholinoreceptors) on the surface of detrusor smooth muscle cells. However, muscarinic receptors are not only densely expressed on smooth muscle cells but also on other cell types, such as epithelial cells of the salivary glands, urothelial cells of the urinary bladder, or nerve cells of the peripheral or central nervous system. Five muscarinic receptor subtypes (M_1-M_5) have been described in humans, of which the M_2 and M_3 subtypes are predominantly expressed in the detrusor. Although approximately 80% of these muscarinic receptors are M_2 and 20% M3 subtypes, only M_3 seems to be involved in bladder contractions in healthy humans (1,2). The role of M_2 subtypes remains unclear. However, in men with neurogenic bladder dysfunction and in experimental animals with neurogenic bladders or bladder outlet obstruction M_2 receptors seem to be involved in smooth muscle contractions as well (3).

The detrusor is innervated by parasympathic nerves which have their origin in the lateral columns of sacral spinal cord on the level S_2-S_4 which itself is modulated by supraspinal micturition centres. The sacral micturition centre is connected with the urinary bladder by the pelvic nerves which release acetylcholine after depolarisation. Acetylcholine stimulates postsynaptic muscarinic receptors leading to G-protein mediated calcium release in the sarcoplasmatic reticulum and opening of calcium channels of the cell membrane and, finally, smooth muscle contraction. Inhibition of muscarinic receptors by muscarinic receptor antagonists

inhibit/decrease muscarinic receptor stimulation and, hence, reduce smooth muscle cell contractions of the bladder. Antimuscarinic effects might also be induced or modulated by the urothelium of the bladder and/or by the central nervous system (4,5).

*3.3.2 **Available drugs***

The following muscarinic receptor antagonists are licensed for treating overactive bladder/storage symptoms in men and women (Table 6):

- darifencacin hydrobromide (darifenacin);
- fesoterodine fumarate (fesoterodine);
- oxybutynin HCL (oxybutynin);
- propiverine HCL (propiverine);
- solifenacin succinate (solifenacin);
- tolterodine tartrate (tolterodine);
- trospium chloride.

This drug class is still officially contraindicated in men with BPH/bladder outlet obstruction due to the possibility of incomplete bladder emptying or development of urinary retention.

Table 6: Antimuscarinic drugs licensed in Europe for treating overactive bladder/storage symptoms; key pharmacokinetic properties and standard doses

Drug	t_{max} [h]	t ½ [h]	Recommended daily dose
Darifencacin	7	13 - 19	1 x 7.5-15 mg
Fesoterodine	5	7	1 x 4-8 mg
Oxybutynin IR	0.5 - 1	2 - 4	3-4 x 2.5-5 mg
Oxybutynin ER	5	16	2-3 x 5 mg
Propiverine	2.5	13 - 20	2-3 x 15 mg
Propiverine ER	7	20	1 x 30 mg
Solifenacin	4 - 6	45 - 68	1 x 5-10 mg
Tolterodine IR	1 - 3	2-10	2 x 1-2 mg
Tolterodine ER	4	6 - 10	1 x 4 mg
Trospium chloride	4 - 6	5 - 15	3 x 10-15 mg 2 x 10-20 mg

IR = immediate release; ER = extended release; t_{max} = time to maximum plasma concentration; t½ = elimination half-life;

** oral bioavailability increased by about 50% for the parent compound, whereas that of the active metabolite is decreased by about 30%; † absolute bioavailability dependent on genotype for CPY 2D6 ranging from 17% in extensive metabolizers to 65% in poor metabolizers.*

*3.3.3 **Efficacy***

Muscarinic receptor antagonists have been predominantly tested in females 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. In contrast, it was believed that LUTS in men are caused by the prostate and need to be treated with prostatespecific drugs. However, there is no scientific data for that assumption (6). A sub-analysis of an open-label trial of 2,250 male or female patients with overactive bladder symptoms treated with tolterodine showed that age but not gender has a significant impact on urgency, frequency, or urgency incontinence (7).

The efficacy of the anticholinergic drug tolterodine, and lately also fesoterodine, was tested as a single agent in adult men with bladder storage symptoms (OAB symptoms) but without bladder outlet obstruction (Table 7). Maximum trial duration was 25 weeks, but most of the trials lasted for only 12 weeks. In open-label trials with tolterodine, daytime frequency, nocturia, urgency incontinence, and IPSS were all significantly reduced compared to baseline values after 12-25 weeks (8,9). In an open-label study with α-blocker nonresponders, each answer of the IPSS questionnaire was improved during tolterodine treatment irrespective of storage or voiding symptoms (8). Randomised, placebo-controlled trials demonstrated that tolterodine can significantly reduce urgency incontinence and daytime or 24-hour frequency compared to placebo. It was also demonstrated that urgency related voiding is significantly reduced by tolterodine (10-12). Although nocturia, urgency, or IPSS were reduced in the majority of patients, these parameters did not reach

statistical significance in most of the trials. However, if treatment outcome was stratified by PSA-concentration (prostate volume) tolterodine significantly reduced daytime frequency, 24h voiding frequency and IPSS storage symptoms in those men with PSA concentrations below 1.3 ng/mL, which was not the case in men with PSA concentrations of 1.3 ng/mL or more indicating that men with smaller prostates might profit more from antimuscarinic drugs (13).

Table 7: Trials with antimuscarinic drugs only in elderly men with LUTS, predominantly with overactive bladder symptoms (trials in chronological order)

Trials	Duration (weeks)	Treatment	Patients	Voiding frequency [%]	Nocturia [%]	Urgency incontinence [%]	IPSS [%]	LE
Kaplan et al. (2005) [8]	25	Tolterodine 1x4 mg/d (after α-blocker failure)	43	-35.7 a	-29.3 a	-	-35.3 a	2b
Roehrborn et al. (2006) [16]	12	Placebo	86	-4	-	-40	-	1b
		Tolterodine 1x4 mg/d	77	-12	-	-71 b	-	
Kaplan et al. (2006) [11]	12	Placebo	374	-7.9	-17.6	-	-	1b
		Tolterodine 1x4 mg/d	371	-10.8 b	-18.8	-	-	
Kaplan et al. (2006) [17]	12	Placebo	215	-13.5	-23.9	-13	-44.9	1b
		Tolterodine 1x4 mg/d	210	-16.5	-20.1	-85 b	-54	
Dmochowski et al. (2007) [12]	12	Placebo	374	-5.6	-17.6	-	-	1b
		Tolterodine 1x4 mg/d	371	-8.7 b	-18.8	-	-	
Höfner et al. (2007) [9]	12	Tolterodine 1x4 mg/d	741	-20 a	-42.9 a	-100 a	-37.9 a	2b
Herschorn et al. (2009) [14]	12	Placebo	124	-10.2	-	-59.3	-	1b
		Fesoterodine 1x4 mg/d	111	-13.2 b	-	-84.5 b	-	
		Fesoterodine 1x8 mg/d	109	-15.6 b	-	-100 b,c	-	

IPSS = International Prostate Symptom Score; a = significant compared to baseline ($p < 0.01$; indexed wherever evaluated); b = significant compared to placebo ($p < 0.05$); c = significant compared to fesoterodine 4 mg ($p < 0.05$)

3.3.4 Tolerability and safety

Muscarinic receptor antagonists are generally well tolerated and associated with approx. 3-10% study withdrawals which were not significantly different compared to placebo in most of the studies. Compared to placebo, drug-related adverse events appear with higher frequencies for dry mouth (up to 16%), constipation (up to 4%), micturition difficulties (up to 2%) nasopharyngitis (up to 3%), and dizziness (up to 5%).

Increase of postvoid residual urine in men without bladder outlet obstruction is minimal and not significantly different compared to placebo (0 to 5 mL vs. -3.6 to 0 mL). Nevertheless, fesoterodine 8 mg showed higher postvoid residuals (+20.2 mL) compared to placebo (-0.6 mL) or fesoterodine 4 mg (+9.6 mL) (14). The incidence of urinary retention in men without bladder outlet obstruction was comparable with placebo in trials with tolterodine (0 to 1.3 vs. 0 to 1.4%). In men under fesoterodine 8 mg treatment, 5.3% had symptoms suggestive of urinary retention that was higher compared to placebo or fesoterodine 4 mg (0.8% each). These symptoms appeared during the first 2 weeks of treatment and affected men aged 66 years or older.

In men with bladder outlet obstruction, antimuscarinic drugs are not recommended due to the theoretical decrease of bladder strength which might be associated with postvoid residual urine or urinary retention. A 12-week placebo-controlled safety study dealing with men who had mild to moderate bladder outlet obstruction (median bladder outlet obstruction index, BOOI, in the placebo or tolterodine group 43

and 49 cm H2O, respectively) demonstrated that tolterodine significantly increased the amount of postvoid residual urine (49 vs. 16 mL) but was not associated with increased events of acute urinary retention (3% in both study arms) (15). Urodynamic effects of tolterodine included significant larger bladder volumes to first detrusor contraction, higher maximum cystometric bladder capacity, and decreased bladder contractility index. Maximum urinary flow remained unchanged in both the tolterodine and placebo groups. This single trial indicated that the short-term treatment with antimuscarinic drugs in men with bladder outlet obstruction is safe.

*3.3.5 **Practical considerations***

Although studies in elderly men with LUTS and overactive bladder symptoms were exclusively carried out with tolterodine or fesoterodine it is likely that similar efficacy and adverse events will also appear with other antimuscarinic agents. Long-term studies on the efficacy of muscarinic receptor antagonists in men with LUTS are still missing, therefore, these drugs should be prescribed with caution, and regular re-evaluation of IPSS and post-void residual urine is advised.

*3.3.6 **Recommendations***

	LE	GR
Muscarinic receptor antagonists might be considered in men with moderate to severe LUTS who have predominantly bladder storage symptoms.	1b	B
Caution is advised in men with bladder outlet obstruction.	4	C

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3.4 Plant extracts - phytotherapy

3.4.1 ***Mechanism of action***

Phytotherapy comprises the medical use of various extracts of different plants. It remains controversial which components of the extracts are responsible for symptom relief in male LUTS. The most important compounds are believed to be phytosterols, ®-sitosterol, fatty acids, and lectins (1). In vitro studies have shown that plant extracts:

- have anti-inflammatory, antiandrogenic, or oestrogenic effects;
- decrease sexual hormone binding globulin (SHBG);
- inhibit aromatase, lipoxygenase, growth-factor stimulated proliferation of prostatic cells, α-adrenoceptors, 5α-reductase, muscarinic cholinoceptors, dihydropyridine receptors, or vanilloid receptors;
- improve detrusor function;
- neutralize free radicals (1-3).

However, most in vitro effects have not been confirmed in vivo and the precise mechanisms of action of plant extracts remain unclear.

3.4.2 ***Available drugs***

Herbal drug preparations are made of roots, seeds, pollen, bark, or fruits of a single plant (monopreparations); others combine the extracts of two or more plants to one pill (combination preparations). A large number of different plants are used for the preparation of extracts. 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);
- *Urtica dioica* (roots of the stinging nettle).

Different producers use different extraction techniques, distribute active ingredients with different qualitative and quantitative properties, or combine two or more herbal compounds in one pill. The extracts of the same plant produced by different companies do not necessarily have the same biological or clinical effects so that the effects of one brand cannot be extrapolated to others (4). To complicate matters, even two different batches of the same producer might contain different concentrations of active ingredients and cause different biological effects (5). Thus, the pharmacokinetic properties can differ significantly between different plant extracts.

3.4.3 ***Efficacy***

Each class of plant extract is discussed separately because of the above-mentioned reasons (Table 8).

Whenever possible, the brand name is mentioned to demonstrate possible differences between products. In general, no phytotherapeutic agent has been shown to significantly reduce prostate size and no trial has proven reduction of bladder outlet obstruction or decreased disease progression.

- ***Cucurbita pepo**:* Only one trial has evaluated the efficacy of pumpkin seeds extracts (Prosta Fink™ forte) in patients with BPH-LUTS (6). A total of 476 patients were randomly assigned to placebo or Prostat Fink™ forte. After a follow-up of 12 months, IPSS and daytime voiding frequency were significantly reduced in the pumpkin seed group. However, uroflowmetry parameters (Q_{max}), postvoid residual urine, prostate volume, PSA concentration, nocturia, or quality of life (QoL) Score were not statistically different between the groups.
- ***Hypoxis rooperi**:* These phytopharmacological extracts contain a mixture of phytosterols bonded with glycosides of which ®-sitosterol is the most important compound (Harzol™, Azuprostat™). Four randomised, placebo-controlled trials with durations between 4 and 26 weeks were published and summarised in a Cochrane report (7). Daily doses of plant extracts ranged from 60 to 195 mg. Two trials evaluated symptoms (8,9) and all four trials investigated Q_{max} and postvoid residual urine. A meta-analysis calculated weighted mean differences of -4.9 IPSS points, +3.9 mL/s in terms of Q_{max} and -28.6 mL in terms of postvoid residual urine in favour of ®-sitosterol. Prostate size remained unchanged in all trials. No further trials have been carried out since the Cochrane report was published in 2000.
- ***Pygeum africanum**:* A Cochrane report dealing with the clinical results of *Pygeum africanum* extracts (mono- or combination preparations) summarised the results of 18 randomised, placebo-controlled trials (10). Most trials used the *Pygeum africanum* extract Tadenan™. The meta-analysis comprised 1,562 men, but individual trials were small in size and lasted only between 30 and 122 days. Most trials were performed in the 1970s and 1980s and did not use validated questionnaires such as the IPSS. Men treated with *Pygeum africanum* were twice as likely to report symptom improvement (relative risk [RR] 2.07) compared to men treated with placebo. The mean weighted difference of Q_{max} was +2.5 mL/s and of postvoid residual volume -13.2 mL in favour of *Pygeum africanum*. No further trials have been published since the Cochrane report in 2002.
- ***Secale cereale**:* A Cochrane report dealt with the clinical results of the main *Secale cereale* product Cernilton™ and comprised 444 men who were enrolled in two placebo-controlled and two comparative trials (Tadenan™, Paraprost™) lasting between 12 and 24 weeks (11). Men treated with Cernilton™ reported that they were twice as likely to benefit from therapy compared to placebo (RR 2.4). However, there were no significant differences between Cernilton™ and placebo with regard to Q_{max}, postvoid residual urine, or prostate volume. No additional placebo-controlled trial with the mono preparation of *Secale cereale* has been published since the Cochrane report in 2000.
- ***Sabal serrulata*/*Serenoa repens**:* A recently updated Cochrane report summarised the clinical results of 30 randomised trials comprising 5,222 men (12). *Serenoa repens* (mainly Permixon™ or Prostaserene™) was compared as mono or combination preparations either with placebo, other plant extracts (*Pygeum africanum, Utica dioica*), the 5-reductase inhibitor finasteride, or the α-blocker tamuslosin. Mean follow-up of these trials varied between 4 and 60 weeks. The Cochrane report concluded that *Serenoa repens* was not superior to placebo, finasteride, or tamsulosin with regard to IPSS improvement, Q_{max}, or prostate size reduction. Similar levels of IPSS or Q_{max} improvements in trials with finasteride or tamsulosin might be interpreted as treatment equivalence (13). For nocturia, *Serenoa repens* was significantly better than placebo (mean weighted difference -0.78).
- ***Utica diocia**:* Two trials investigated the efficacy of stinging nettle mono preparations compared to placebo (14,15). One trial investigated 246 men with BPH-LUTS over a period of 52 weeks (14); only IPSS decreased significantly in the phytotherapy group (Bazoton™ uno), whereas Q_{max} and postvoid residual urine were not statistically different between the groups at the end of the trial. The second trial investigated 620 patients with BPH-LUTS over a period of 26 weeks (15); IPSS, Q_{max}, and postvoid residual urine significantly improved compared to placebo.
- **Combination preparations**: Trials have been carried out, especially with the extract combination of *Sabal serrulata* and *Utica dioica* (PRO 160/120, Prostatgutt™ forte). A 24-weeks placebo-controlled trial demonstrated a significant improvement in IPSS in the phytotherapy arm (-2 IPSS points difference) (16); Q_{max} reduction was similar in both groups. A 24-week open label extension trial of the same patients, in which all patients were treated with PRO 160/120, showed similar improvements of IPSS at week 48 in both groups (-7 IPSS points). A second trial, in which PRO 160/120 was randomised against finasteride, showed similar results for IPSS and Q_{max} in both groups (17).

Table 8: Trials with plant extracts in patients with BPH-LUTS (selection; in alphabetical order)

Trials	Duration (weeks)	Treatment	Patients (n)	Change in symptoms (IPSS) †	Change in Q_{max} [mL/s]	PVR [mL]	LE
Bach (2000) (6)	52	placebo Cucurbita pepo (Prosta Fink™forte)	243 233	-5.5 -6.7 a	n.s. n.s.	n.s. n.s	1b
Berges et al. (1995) (8)	24	placebo *Hypoxis rooperi* (Harzol™)	100 100	-2.3 -7.4 [a]	+1.1 +5.2 [a]	-16.8 -35.4 [a]	1b
Klippel et al. (1997) (9)	26	placebo *Hypoxis rooperi* (Azuprostat™)	89 88	-2.8 -8.2 [a]	+4.3 +8.8 [a]	-4.1 -37.5 [a]	1b
Wilt et al. (2000) (7)	4-26	placebo Hypoxis rooperi	475	-4.9 [b]	+3.9 [b]	-28.6 [b]	1a
Wilt et al. (2002) (10)	4-18	placebo *Pygeum africanum* (β-sitosterol)	1562	RR 2.07 [b]	+2.5 [b]	-13.2 [b]	1a
Wilt et al. (2000) (11)	12-24	placebo *Secale cereale* (Cernilton™)	444	RR 2.4 [b]	-1.6	-14.4	1a
Wilt et al. (2002) (18)	4-48	placebo Serenoa repens/ Sabal cerrulata	3139	-1.41 [b]	+1.86 [b]	-23 [b]	1a
Bent et al. (2006) (19)	52	placebo Serenoa repens	113 112	-0.7 -0.7	-0.01 +0.42	-19 -14	1b
Carraro et al. (1996) (20)	26	finasteride *Serenoa repens* (Permixon™)	545 553	-6.2 -5.8	+3.2* +2.7	- -	1b
Debruyne et al. (2002) (21)	52	tamsulosin *Serenoa repens* (Permixon™)	354 350	-4.4 -4.4	+1.9 +1.8	- -	1b
Schneider & Rübben (2004) (14)	52	placebo *Urtica dioica* (Bazoton uno™)	122 124	-4.7 -5.7 [a]	+2.9 +3.0	-4 -5	1b
Safarinejad (2005) (15)	26	placebo Urtica dioica	316 305	-1.5 -8.0 [a]	+3.4 +8.2 [a]	0 -37	1b
Lopatkin et al. (2005) (16)	24	placebo *Sabal cerrulata* + *Urtica dioica* (Prostatgutt™ forte)	126 127	-4 -6 [b]	+1.9 +1.8	- -	1b
Sökeland & Albrecht (1997) (17)	48	finasteride *Sabal cerrulata* + *Urtica dioica* (Prostatgutt™ forte)	244 245	-5.6 -4.8	+2.8 +2.0	-17.1 -10.2	1b

IPSS = International Prostate Symptom Score; Q_{max} = maximal urinary flow rate (free uroflowmetry); PVR = postvoid residual urine; n.s. = not significant; RR = relative risk
† absolute values; a = significant reduction compared to placebo/comparison treatment arm ($p<0.05$); b = in favour of plant extract.

3.4.4 ***Tolerability and safety***

Side-effects during phytotherapy are generally mild and comparable to placebo with regard to severity and frequency. Serious adverse events were not related to study medication. Gastrointestinal complaints were the most commonly reported side-effects. In formulations with *Hypoxis rooperi*, erectile dysfunction appeared in

0.5% of patients. Trial withdrawals were almost equal in both placebo and phytotherapy groups.

3.4.5 ***Practical considerations***

Phytotherapeutic agents are a heterogeneous group of plant extracts used to improve BPH-LUTS. Phytotherapy remains problematic to use because of different concentrations of the active ingredient(s) in different brands of the same phytotherapeutic agent. Hence, meta-analyses of extracts of the same plant do not seem to be justified and results of these analyses have to be interpreted with caution.

3.4.6 ***Recommendations***

The guidelines committee is unable to make specific recommendations about phytotherapy of male LUTS because of the heterogeneity of the products and the methodological problems associated with meta-analyses.

3.4.7 ***References***

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3.5 Vasopressin analogue - desmopressin

3.5.1 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 V_2 receptor in the renal collecting ducts. AVP increases water re-absorption as well as urinary osmolality and decreases water excretion as well as total urine volume. AVP might be therapeutically used to manipulate the amount of urine excretion but, however, AVP also has V_1 receptor mediated vasoconstrictive / hypertensive effects and a very short serum half-life, which makes the hormone unsuitable for the treatment of nocturia / nocturnal polyuria.

3.5.2 Available drugs

Desmopressin acetate (desmopressin) is a synthetic analogue of AVP with high V_2 receptor affinity and antidiuretic properties. It is the only registered drug for antidiuretic treatment (Table 9). In contrast to AVP, desmopressin has no relevant V1 receptor affinity and hypertensive effects. Desmopressin may be used by intravenous infusion, nasal spray, tablet, or MELT formulation. Nasally or orally administered desmopressin is rapidly absorbed and, later, excreted 55% unchanged by the kidneys (1). Desmopressin has been used for over 30 years in the treatment of diabetes insipidus or primary nocturnal enuresis. More recently, it has been approved in most European countries for the treatment of nocturia on a polyuric background in adult male and female patients. After intake before sleeping, urine excretion during the night decreases and, therefore, the urge to void is postponed and the number of voids at night is reduced (2,3). The clinical effects - in terms of urine volume decrease and an increase in urine osmolality - last for approximately 8-12 hours (2).

Table 9: Antidiuretics licensed in Europe for treating nocturia due to nocturnal polyuria; key pharmacokinetic properties and standard doses

Drug	t_{max} (hours)	t ½ (hours)	Recommended daily dose
Desmopressin	1-2	3	1 x 0.1-0.4 mg orally before sleeping

t_{max} = time to maximum plasma concentration; t½ = elimination half-life.

3.5.3 Efficacy

The majority of clinical trials have used desmopressin in an oral formulation. A dose-finding study showed that the nocturnal urine volume/nocturnal diuresis was more reduced by oral desmopressin 0.2 mg than 0.1 mg; however, this study also showed that a 0.4 mg dose taken once before sleeping had no additional effects on

the nocturnal diuresis compared to a 0.2 mg dose (4). In the pivotal clinical trials, the drug was titrated from 0.1 to 0.4 mg according to the individual clinical response. 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%) (-2 in the long-term open-label trial), and extended the time until the first nocturnal void by approximately 1.6 hours (-2.3 in the long-term open-label trial) (Table 10). Furthermore, desmopressin significantly reduced night-time urine volume as well as the percentage of urine volume excreted at night (5,8).

The clinical effects of desmopressin were more pronounced in patients with more severe nocturnal polyuria and bladder capacity within the normal range at baseline. The 24-hour diuresis remained unchanged during desmopressin treatment (6). The clinical effects were stable over a follow-up period of 10-12 months and returned to baseline values after trial discontinuation (12). A significantly higher proportion of patients felt fresh in the morning-time after desmopressin use (odds ratio 2.71) (11).

Table 10: Clinical trials with desmopressin in adult men with nocturnal polyuria

Trials	Duration (weeks)	Treatment, i.e. oral daily dose before bedtime unless otherwise indicated	Patients (n)	Change nocturnal urine volume (mL/min)	Change nocturnal voids (n)	Time to first void (hours)	LE
Asplund et al. (1998) [4]	3	1 x 0.1 mg	23*	-0.5 (-31%)	-	-	2b
		1 x 0.2 mg	23*	-0.7 (-44%)	-	-	
		2 x 0.2 mg	23*	-0.6 (-38%)	-	-	
Cannon et al. (1999) [5]	6	Placebo	20	-	+0.1 (+3%)	-	1b
		1 x 20 µg intranasal	20	-	-0.3 (-10%)	-	
		1 x 40 µg intranasal	20	-	-0.7 (-23%)[a]	-	
Asplund et al. (1999) [6]	2	Placebo	17*	-0.2 (-11%)	-0.2 (-11%)	+0.2	1b
		1 x 0.1-0.4 mg	17*	-0.8 (-44%)[a]	-0.8 (-42%)[a]	+1.6	
Chancellor et al. (1999) [7]	12	1 x 20-40 µg intranasal	12	-	-1.8 (-50%)	-	2b
Mattiasson et al. (2002) [8]	3	Placebo	65	-0.2 (-6%)	-0.5 (-12%)	+0.4	1b
		1 x 0.1-0.4 mg	86	-0.6 (-36%)[a]	-1.3 (-43%)[a]	+1.8[a]	
Kuo 2002 [9]	4	1 x 0.1 mg	30*	-	-2.72 (-48.5)	-	2b
Rembratt et al. (2003) [10]	0.5	1 x 0.2 mg	72*	-0.5	-1.0	+1.9	2b
van Kerrebroeck et al. (2007) [11]	3	Placebo	66	-	-0.4 (-15%)	+0.55	1b
		1 x 0.1-0.4 mg	61	-	-1.25 (-39%)[a]	+1.66[a]	
Lose et al. (2004) [12] ‡	52	1 x 0.1-0.4 mg	132	-	-2	+2.3	2b

**Majority of study participants were men; ‡ only male data; a = significant compared to placebo.*

*3.5.4 **Tolerability***

The absolute number of adverse events associated with desmopressin treatment were higher compared to placebo but usually mild in nature. The most frequent adverse events in short-term (up to 3 weeks) and long-term studies (12 months) were headache, nausea, diarrhoea, abdominal pain, dizziness, dry mouth, and hyponatraemia. These events were comparable with the established safety profile of desmopressin in the treatment of polyuria due to other conditions. Peripheral oedema (2%) and hypertension (5%) were reported in the long-term treatment trial (12).

Hyponatraemia (serum sodium concentration < 130 mmol/L) was observed mainly in patients aged 65 years or older and seemed to occur less frequently in men compared to women of the same age (3). Hyponatraemia of all degrees, not necessarily associated with symptoms, occurs in approximately 5% (13) to 7.6% of patients (14) early after treatment initiation. The risk of developing hyponatraemia significantly increases with age (odds ratio 1.16 per year of age), lower serum sodium concentration at baseline (odds ratio

0.76), and higher basal 24-hour urine volume per bodyweight (odds ratio 1.09) (13). The chance of developing hyponatraemia in patients younger than 65 years is less than 1%, whereas the risk for older patients increases to 8% with normal sodium concentration and up to 75% in patients with low sodium concentration at baseline (13).

Therefore, the treatment of men aged 65 years or older should not be initiated without monitoring the serum sodium concentration. At the time of treatment initiation or dose change, older men with normal values of serum sodium should be monitored by Na+ measurement at day 3 and day 7 of treatment as well as at 1 month later. If serum sodium concentration has remained normal and no dose adjustment is intended, Na^+ should be monitored every 3-6 months thereafter (15). Furthermore, patients should be informed about the prodromal symptoms of hyponatraemia, such as headache, nausea, or insomnia.

*3.5.5 **Practical considerations***

Desmopressin should be taken once daily before sleeping. As the optimal dose differs between patients, desmopressin treatment should be initiated at a low dose (0.1 mg/day) and may be gradually increased every week until maximum efficacy is reached. The maximal daily dose recommended is 0.4 mg/day. Patients should avoid drinking fluids at least 1 hour before using desmopressin until 8 hours thereafter. In men aged 65 years or older, desmopressin should not be used if the serum sodium concentration is below the normal value. In all other men aged 65 years or older, serum sodium concentration should be measured at day 3 and 7 as well as after 1 month and, if serum sodium concentration has remained normal, every 3-6 months subsequently.

*3.5.6 **Recommendations***

	LE	GR
Desmopressin can be used for the treatment of nocturia based on a polyuric background.	1b	A

*3.5.7 **References***

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3.6 Combination therapies

3.6.1 α-blockers + 5α-reductase inhibitors

3.6.1.1 Mechanism of action

Combination therapy of α-blockers and 5α-reductase inhibitors aims to combine the differential effects of both drug classes to create synergistic efficacy in symptom improvement and prevention of disease progression.

3.6.1.2 Available drugs

Combination therapy consists of an α-blocker (alfuzosin, doxazosin, tamsulosin, or terazosin; pharmacokinetic properties *see* Section 3.1.2) together with a 5α-reductase inhibitor (dutasteride or finasteride; pharmacokinetic properties *see* Section 3.2.2). The α-blocker exhibits clinical effects within hours or days, whereas the 5α-reductase inhibitor needs several months to develop significant clinical efficacy. Of all drug combinations possible, so far finasteride together with alfuzosin, doxazosin, or terazosin, and dutasteride together with tamsulosin, have been tested in clinical trials. Both compounds show class effects with regard to efficacy and adverse events. No differences in pharmacokinetic or pharmacodynamic properties of the combined use of both drugs have been reported compared to single drug.

3.6.1.3 Efficacy

Several studies have investigated the efficacy of combination therapy against the efficacy of an α-blocker, 5α-reductase inhibitor, or placebo alone (Table 11). Initial studies with follow-up periods between 6 and 12 months used symptom (IPSS) change as their primary endpoint (1-3). These trials consistently demonstrated that the α-blocker was superior to finasteride in symptom reduction, whereas the combination treatment was not superior to the α-blocker alone. In studies which included a placebo arm, the α-blocker was consistently more effective than placebo, whereas finasteride was consistently not more effective than placebo. Data from the 1-year time point of the MTOPS (Medical Therapy of Prostatic Symptoms) study, which have been published but not specifically analysed for this time point, showed similar results (4).

More recently, 4-year data analysis from MTOPS, as well as the 2- and 4-year results from the CombAT (Combination of Avodart® and Tamsulosin) trials, have been reported (4-6). 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 to 12 months follow-up, long-term data have demonstrated that combination treatment is superior to either monotherapy with regard to symptom reduction and Q_{max} improvement and superior to α-blocker in reducing the risk of acute urinary retention and the need for surgery (4-6). The CombAT study demonstrated that combination treatment is superior to either monotherapy with regard to symptom improvement and Q_{max} starting from month 9 and superior to α-blocker with regard to the reduction in the risk of acute urinary retention and the need for surgery after month 8 (6). The different results between the CombAT and MTOPS trials appear to arise from different inclusion and exclusion criteria rather than the types of α-blockers or 5α-reductase inhibitors. Dutasteride or finasteride alone reduced prostate volume as effectively as combination treatment (-20 to -27%).

Three studies addressed the issue of discontinuation of the α-blocker (7-9). One trial evaluated the combination of tamsulosin with dutasteride and the impact of tamsulosin discontinuation after 6 months (7). After cessation of the α-blocker, almost three-quarters of patients reported no worsening of symptoms. However, patients with severe symptoms (IPSS > 20) at baseline may benefit from longer combination therapy. A more recently published trial evaluated the symptomatic outcome of finasteride monotherapy at 3 and 9 months after discontinuation of 9-month combination therapy (finasteride plus α-blocker) (8). LUTS

improvement after combination therapy was sustained at 3 months (IPSS difference 1.24) and 9 months (IPSS difference -0.44).

In a retrospective study, the likelihood of α-blocker discontinuation, which was based on the individual decision of the patient, was evaluated over a 12-month period in men aged > 65 years receiving α-blockers in combination with either dutasteride or finasteride (9). Dutasteride patients discontinued α-blocker therapy 64% faster than finasteride patients at any time point. At 12 months, 62% of patients were treated with dutasteride alone compared to 43.7% of men treated with finasteride alone.

Combination therapy was shown to be superior to monotherapy in both the MTOPS and CombAT trials in preventing overall clinical progression, as defined by an IPSS increase of at least 4 points, acute urinary retention, urinary tract infection, incontinence, or an increase in serum creatinine > 50% compared to baseline values). For combination therapy in the MTOPS trial versus the CombAT trial, the following reductions were observed:

- overall risk of disease progression was 66% versus 44%;
- symptomatic progression, 64% versus 41%;
- acute urinary retention, 81% versus 68%;
- urinary incontinence, 65% versus 26%;
- BPH-related surgery, 67% versus 71%.

Monotherapy with 5α-reductase inhibitor appeared to reduce the risks of acute urinary retention and prostaterelated surgery as effectively as combination treatment (differences not significant), although the preventive effects were more pronounced with combination therapy (4,6). The MTOPS trial results suggested that the α-blocker alone might also reduce the risk of symptom progression.

Table 11: Randomised trials using α-blocker, 5α-reductase inhibitor, and the combination of both drugs in men with LUTS and benign prostatic enlargement due to benign prostatic hyperplasia (Of note: references 5 and 6 reflect different time points of the same study.)

Trials	Duration (weeks)	Treatment (daily dose)	Patients (n)	Symptom change (% IPSS)	Change in Q_{max} (mL/s)	Change in prostate volume (%)	LE
Lepor et al. (1996) [1]	52	Placebo	305	-16.5 [a]	+1.4	+1.3	1b
		Terazosin 1 x 10 mg	305	-37.7 [a,b,d]	+2.7 [b,d]	+1.3	
		Finasteride 1 x 5 mg	310	-19.8 [a]	+1.6	-16.9 [b,c]	
		Terazosin 1 x 10 mg + finasteride 1 x 5 mg	309	-39 [a, b ,d]	+3.2 [b,d]	-18.8 [b,c]	
Debruyne et al. (1998) [2]	26	Alfuzosin 2 x 5 mg	358	-41.2 [d]	+1.8	-0.5	1b
		Finasteride 1 x 5 mg	344	-33.5	+1.8	-10.5 [c]	
		Alfuzosin 2 x 5mg + finasteride 1 x 5 mg	349	-39.1 [d]	+2.3	-11.9 [c]	
Kirby et al. (2003) [3]	52	Placebo	253	-33.1	+1.4	-	1b
		Doxazosin 1 x 1-8 mg	250	-49.1 [b,d]	+3.6 [b,d]	-	
		Finasteride 1 x 5 mg	239	-38.6	+1.8	-	
		Doxazosin 1 x 1-8 mg + finasteride 1 x 5mg	265	-49.7 [b,d]	+3.8 [d]	-	
McConnell et al. (2003) [4]	234	Placebo	737	-23.8 [a]	+1.4 [a]	+24 [a]	1b
		Doxazosin 1 x 1-8 mg	756	-35.3 [a,b,d]	+2.5 [a,b]	+24 [a]	
		Finasteride 1 x 5 mg	768	-28.4 [a,b]	+2.2 [a,b]	-19 [a,b,c]	
		Doxazosin 1 x 1-8 mg + finasteride 1 x 5 mg	786	-41.7 [a,b,c,d]	+3.7 [a,b,c,d]	-19 [a,b,c]	
Roehrborn et al. (2008) [5]	104	Tamsulosin 1 x 0.4 mg	1611	-27.4	+0.9	0	1b
		Dutasteride 1 x 0.5 mg	1623	-30.5	+1.9	-28 [c]	
		Tamsulosin 1 x 0.4 mg + dutasteride 1 x 0.5 mg	1610	-39.2 [c,d]	+2.4 [c,d]	-26.9 [c]	

Roehrborn et al. (2009) [6]	208	Tamsulosin 1 x 0.4 mg	1611	-23.2	+0.7	+4.6	1b
		Dutasteride 1 x 0.5 mg	1623	-32.3	+2.0	-28 [c]	
		Tamsulosin 1 x 0.4 mg + dutasteride 1 x 0.5 mg	1610	-38 [c,d]	+2.4 [c]	-27.3 [c]	

Q_{max} = maximum urinary flow rate (free uroflowmetry); IPSS = International Prostate Symptom Score; a = significant compared to baseline (indexed wherever evaluated); b = significant compared to placebo; c = significant compared to α-blocker monotherapy; d = significant compared to 5α-reductase inhibitor monotherapy.

3.6.1.4 Tolerability and safety

In both the CombAT and MTOPS trials, overall drug-related adverse events were significantly more frequent during combination treatment than during either monotherapy. The adverse events observed during combination treatment were typical of an α-blocker and 5α-reductase inhibitor. The frequencies of adverse events were significantly higher for combination therapy for most adverse events (4).

3.6.1.5 Practical considerations

Compared to α-blocker or 5α-reductase inhibitor monotherapy, combination therapy result in a greater improvement in LUTS, an increase in Q_{max}, and superior prevention of disease progression. However, combination therapy is also associated with more adverse events. Combination therapy should therefore be used primarily in men who have moderate to severe LUTS and are at risk of disease progression (higher prostate volume, higher PSA concentration, advanced age, etc). Combination therapy should only be used when long-term treatment (more than 12 months) is intended; this issue should be discussed with the patient before treatment.

Discontinuation of the α-blocker after 6 months might be considered in men with moderate LUTS.

3.6.1.6 ***Recommendations***

	LE	GR
Combination treatment with α-blocker together with 5α-reductase inhibitor should be offered to men with moderate to severe LUTS, enlarged prostates, and reduced Qmax (men likely to develop disease progression). Combination treatment is not recommended for short-term therapy (< 1 year).	1b	A

3.6.1.7 References

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3.6.2 α-blockers + muscarinic receptor antagonists

3.6.2.1 Mechanism of action

Combination therapy of an α-blocker together with a muscarinic receptor antagonist aims to antagonize both α_1-adrenoceptors and muscarinic cholinoreceptors (M_2 and M_3) in the lower urinary tract, hereby using the efficacy of both drug classes to achieve synergistic effects.

3.6.2.2 Available drugs

Combination treatment consists of an α-blocker (alfuzosin, doxazosin, tamsulosin, or terazosin; pharmacokinetic properties chapter 3.1.2) together with a muscarinic receptor antagonist (darifencacin, fesoterodine, oxybutynin, propiverine, solifenacin, tolterodine, or trospium chloride; pharmacokinetic properties chapter 3.3.2). However, only the combinations of the α-blocker doxazosin, tamsulosin, or terazosin and the muscarinic receptor antagonist oxybutynin, propiverine, solifenacin, or tolterodine have been tested in clinical trials so far. Until now, both drug classes have to be taken as separate pills as no combination pill is yet available. No differences in terms of pharmacokinetic or pharmacodynamic properties of the combined use of both drugs have been described compared to the use of the single drugs.

3.6.2.3 Efficacy

At least nine trials have been published investigating the efficacy of the combination treatment with α-blockers and muscarinic receptor antagonists in adult male patients with LUTS (1-8). Additionally, one trial was published using the α-blocker naftopidil (not registered in most European countries) with and without anticholinergic agents (9). Only one of those trials had a placebo arm (LE: 1b) and also tested the drug combination against the α-blocker as well as against the muscarinic receptor antagonist (4); all other trials compared the efficacy of the combination therapy with the efficacy of an α-blocker alone (Table 12) (LE: 2b). Maximum trial duration was 25 weeks but the majority of trials lasted 4-12 weeks only.

The combination of drugs was in general more efficacious in reducing voiding frequency, nocturia, or IPSS compared to α-blockers or placebo alone. Furthermore, the combination treatment significantly reduced urgency urinary incontinence episodes as well as urgency and significantly increased QoL (4).

Overall symptom improvement in the combination therapy arm was significantly higher compared to placebo regardless of PSA serum concentration, whereas tolterodine alone significantly improved symptoms predominantly in men with a serum PSA concentration less than 1.3 ng/mL (10). Three trials investigated the efficacy of combination treatment in patients with persistent LUTS during α-blocker treatment by adding a muscarinic receptor antagonist to the existing α-blocker therapy (add-on approach) (6-8). These trials demonstrated that persistent LUTS can be significantly reduced by the additional use of a muscarinic receptor antagonist (tolterodine) especially if detrusor overactivity had been demonstrated (Table 12). Patient reported QoL, treatment benefit, symptom bother, or patient perception of bladder condition was significantly improved in the combination treatment arm.

Table 12: Efficacy of muscarinic receptor antagonists together with α-blockers

Trials	Duration (weeks)	Treatment	Patients	Voiding frequency [%]	Nocturia [%]	IPSS [%]	LE
Saito et al. (1999) [1]	4	Tamsulosin 1 x 0.2 mg/d	59	-29.6	-22.5	-	1b
		Tamsulosin 1 x 0.2 mg/d + propiverine 1 x 20 mg/d	75	-44.7	-44.4 [a]	-	
Lee et al. (2005) [3]	8	Doxazosin 1 x 4 mg/d	67	-11.8	-37.5	-54.9	1b
		Doxazosin 1 x 4 mg/d + propiverine 1 x 20 mg/d	131	-27.5 [a]	-46.7	-50.7	
Kaplan et al. (2006) [4]	12	Placebo	215	-13.5	-23.9	-44.9	1b
		Tolterodine 1 x 4 mg/d	210	-16.5	-20.1	-54	
		Tamsulosin 1 x 0.4 mg/d	209	-16.9	-40.3	-64.9 [b]	
		Tolterodine 1 x 4 mg/d + tamsulosin 1 x 0.4 mg/d	217	-27.1 [b]	-39.9 [b]	-66.4 [b]	
MacDiarmid et al. (2008) [5]	12	Tamsulosin 1 x 0.4 mg/d + placebo	209	-	-	-34.9	1b
		Tamsulosin 1 x 0.4 mg/d + oxybutynine 1 x 10 mg/d	209	-	-	-51.9 [b]	
Kaplan et al. (2005) [7] ‡	25	Tolterodine 1 x 4 mg/d	43	-35.7 [a]	-29.3 [a]	-35.3	2b
Yang et al. (2007) [8] ‡	6	Tolterodine 2 x 2 mg/d	33	-	-	-35.7 [a]	2b
Kaplan et al. (2009) [11] ‡	12	Tamsulosin 1 x 0.4 mg/d + placebo	195	-6.2 [a]	-	-29	1b
		Tamsulosin 1 x 0.4 mg/d + solifenacin 5 mg/d	202	-9.1 [a]	-	-31.8	

IPSS = International Prostate Symptom Score
‡ persisting LUTS during α-blocker treatment (add-on approach)
a = significant compared to baseline (p ≤ 0.05, indexed wherever evaluated)
b = significant reduction compared to placebo (p < 0.05)

3.6.2.4 Tolerability and safety

Adverse events of both drug classes appear during combination treatment of αblockers and muscarinic receptor antagonists. The most frequently reported side effect in all trials was xerostomia. Some side effects (e.g. xerostomia or ejaculation failure) appear with increased frequency and cannot simply be explained by adding the frequencies of adverse events of either drug. Postvoid residual urine increased in most trials. Although the mean increase of postvoid residual urine was low (+6 to +24 mL) some men developed higher postvoid residuals or even urinary retention (0.9 to 3.3%). It remains unknown which men are at risk of developing post-void residual urine or urinary retention during the combination treatment.

3.6.2.5 Practical considerations

Class effects are likely to be responsible for increased efficacy and QoL in patients treated with α-blocker and muscarinic receptor antagonist. Measuring of postvoid residual urine is recommended during combination treatment to assess increase or urinary retention.

3.6.2.6 Recommendations

	LE	GR
Combination treatment with α-blocker and muscarinic receptor antagonist might be considered in patients with moderate to severe LUTS if symptom relief has been insufficient with the monotherapy of either drug.	1b	B
Combination treatment should cautiously be prescribed in men who are suspicious of having bladder outlet obstruction.	2b	B

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3.7 New emerging drugs

*3.7.1 **Phosphodiesterase (PDE) 5 Inhibitors (with or without α-blockers)***

*3.7.2 **Mechanism of action***

Nitric oxide (NO) represents an important non-adrenergic, non-cholinergic neurotransmitter in the human body and is involved in signal transmission in the human urinary tract. NO is synthesised from the amino acid L-arginine by NO synthases (NOS), which are classified based on their original tissues of detection as neuronal (nNOS), endothelial (eNOS), and immune cells (inducible NOS, iNOS). After being synthesised, NO diffuses into cells and stimulates the synthesis of cyclic guanosine monophosphate (cGMP) mediated by the enzyme guanylyl-cyclase. cGMP can activate protein kinases, ion channels, and cGMP-binding phosphodiesterases (PDEs) leading to smooth muscle cell relaxation via depletion of intracellular Ca^{2+} and desensitisation of contractile proteins (1). The effects of cGMP are terminated by PDE isoenzymes catalysing the hydrolysis of cGMP to an inactive form. PDE inhibitors increase the concentration and prolong the activity of intracellular cGMP, hereby reducing smooth muscle tone of the detrusor, prostate, and urethra. Until now, 11 different PDEs have been identified of which the PDEs 4 and 5 are the predominant ones in the transition zone of the human prostate, bladder, and urethra (2,3). NO might also be involved in the micturition cycle by inhibiting reflex pathways in the spinal cord and neurotransmission in the urethra, prostate, or bladder (4).

3.7.3 *Available drugs*

Three selective oral PDE5 inhibitors (sildenafil citrate [sildenafil], tadalafil, and vardenafil hcl [vardenafil]) have been licensed in Europe for the treatment of erectile dysfunction or pulmonary arterial hypertension (sildenafil and tadalafil), but these drugs have not yet been officially registered for the treatment of male LUTS (Table 13). The available PDE5 inhibitors differ primarily in their pharmacokinetic profiles (5). All PDE5 inhibitors are rapidly resorbed from the gastrointestinal tract, have a high protein binding in plasma, and are metabolised primarily by the liver and eliminated predominantly by the faeces. However, their half-lives differ markedly. PDE5 inhibitors are taken on-demand by patients with erectile dysfunction but tadalafil is also registered for daily use in lower dose (5 mg) than for on-demand use.

Table 13: PDE5 inhibitors licensed in Europe for treating erectile dysfunction; key pharmacokinetic properties and doses used in clinical trials

Drugs	t_{max} (hours)	t ½ (hours)	Daily doses in clinical trials of patients with male LUTS
Sildenafil	1 * (0.5-2)	3-5	1 x 25-100 mg
Tadalafil	2 (0.5-12)	17.5	1 x 2.5-20 mg
Vardenafil	1 * (0.5-2)	4-5	2 x 10 mg

*t_{max} = time to maximum plasma concentration; t½ = elimination half-life; * dependent on food intake (i.e. slower resorption of the drug and an increase in t_{max} by approximately 1 hour after a fatty meal).*

3.7.4 *Efficacy*

A post-hoc analysis of patients with erectile dysfunction treated with sildenafil initially showed that the PDE5 inhibitor was capable of significantly reducing concomitant LUTS and increasing bladder symptoms-related QoL, as measured by the IPSS questionnaire (6,7). LUTS improvement was found to be independent of improvement of erectile function. Randomised, placebo-controlled trials on the efficacy of all three available oral PDE5 inhibitors have been published during the last years and have investigated changes in symptoms (IPSS), uroflowmetry parameters (Q_{max}), and postvoid residual urine (6-16). The maximum trial duration was 12 weeks. These trials demonstrated that all PDE5 inhibitors significantly and consistently reduced IPSS by approximately 17-35% (Table 2). Both bladder storage and voiding symptoms decreased equally during treatment with PDE5 inhibitors. Postvoid residual urine remained unchanged in most of the trials. Q_{max} of free uroflowmetry increased in a dose-dependent fashion (tadalafil [16]), but was not significantly different to placebo (sildenafil, tadalafil, and vardenafil). In contrast to the EBM level 1b-trials listed in Table 14, two singlecentre uroflowmetry studies documented improvements of Q_{max} and Q_{ave} following oral administration of 50 or 100 mg sildenafil in up to 76% of men (mean Qmax increase 3.7-4.3 mLs or 24-38%) (17,18). PDE5 inhibitors significantly improved QoL compared to placebo-treated patients.

Three trials compared the efficacy of PDE5 inhibitors (sildenafil or tadalafil) with or without α-blockers (alfuzosin or tamsulosin) (9,12,13). These trials were conducted in a small number of patients and with a limited follow-up of 6 to 12 weeks. The drug combination improved IPSS, Q_{max}, and postvoid residual urine to a greater extent than the single drug alone of each class (Table 14), although the difference compared to PDE5 inhibitor or α-blocker alone was only statistically significant in one of the three trials (12).

Table 14: Efficacy of PDE5 inhibitors in adult men with LUTS who participated in clinical trials with EBM Level 1b

Trials	Duration (weeks)	Treatment	Patients	IPSS	Qmax (mL/s)	PVR (mL]	LE
McVary et al. 2007 [8] ‡	12	Placebo	180	-1.93	+0.16	-	1b
		Sildenafil 1 x 50-100 mg/ day or 1 x 50-100 mg before sexual intercourse	189	-6.32 *	+0.32	-	
Kaplan et al. 2007 [9]‡	12	Alfuzosin 1 x 10 mg/day	20	-2.7 (-15.5%) †	+1.1 †	-23 †	1b
		Sildenafil 1 x 25 mg/day	21	-2.0 (-16.9%) †	+0.6	-12	
		Alfuzosin 1 x 10 mg/day + sildenafil 1 x 25 mg/day	21	-4.3 (-24.1%) †	+4.3 †	-21 †	
McVary et al. 2007 [10]	12	Placebo	143	-1.7 (-9.3%)	+0.9	-2.6	1b
		Tadalafil 1 x 5-20 mg/day	138	-3.8 (-21.7%) *	+0.5	+1.4	
Roehrborn et al. 2008 [11]	12	Placebo	212	-2.3 (-13.3%)	+1.2	+4.81	1b
		Tadalafil 1 x 2.5 mg/day	209	-2.7 (-22.2%) *	+1.4	+12.1	
		Tadalafil 1 x 5 mg/day	212	-4.9 (-28.2%) *	+1.6	+6.6	
		Tadalafil 1 x 10 mg/day	216	-5.2 (-29.1%) *	+1.6	+10.6	
		Tadalafil 1 x 20 mg/day	209	-5.2 (-30.5%) *	+2.0	-4	
Bechara et al. 2008 [12]	6	Tamsulosin 1 x 0.4 mg/day	15	-6.7 † (-34.5%)	+2.1 †	-35.2 †	1b
		Tamsulosin 1 x 0.4 mg/day + tadalafil 1 x 20 mg/day	15	-9.2 †[a] (-47.4%)	+3.0 †	-38.7 †	
Liguori et al. 2009 [13] ‡	12	Alfuzosin 1 x 10 mg/day	22	-5.2 † (-27.2%)	+1.7 †	-	1b
		Tadalafil 1 x 20 mg every 2 days	21	-1.3 (-8.4%)	+1.2 †	-	
		Alfuzsosin 1 x 10 mg/day + tadalafil 1 x 20 mg every 2 days	23	-6.3 † (-41.6%)	+3.1 †	-	
Porst et al. 2009 [14]‡	12	Placebo	115	-2.1	+1.9	-6.8	1b
		Tadalafil 1 x 2.5 mg/day	113	-3.6 *	+1.4	+8.6 *	
		Tadalafil 1 x 5 mg/day	117	-4.2 *	+1.7	-1.8	
		Tadalafil 1 x 10 mg/day	120	-4.7 *	+1.3	+3.8	
		Tadalafil 1 x 20 mg/day	116	-4.7 *	+2.0	-14	
Stief et al. 2008 [15]	8	Placebo	113	-3.6 (-20%)	+1.0	.+1.92	1b
		Vardenafil 2 x 10 mg	109	-5.8 (-34.5%) *	+1.6	-1.0	

*IPSS = International Prostate Symptom Score; Q_{max} = maximum urinary flow rate during free uroflowmetry; PVR = postvoid residual urine; ‡ trial included patients with both erectile dysfunction and LUTS; * significant compared to placebo ($p \leq 0.05$); † significant compared to baseline ($p \leq 0.05$ (indexed wherever evaluated); [a] significant compared to α-blocker (tamsulosin, $p < 0.05$).*

3.7.5 *Tolerability and safety*

PDE5 inhibitors in general can cause headache, flushing, dizziness, dyspepsia, nasal congestion, myalgia, hypotension, syncope, tinnitus, conjunctivitis, or altered vision (blurred, discoloration). However, the frequencies of side-effects vary between the individual PDE5 inhibitors. The probability of developing priapism or acute urinary retention is considered minimal.

PDE5 inhibitors are contraindicated in patients using nitrates or the potassium channel opener, nicorandil, due to additional vasodilatation, which might cause hypotension, myocardial ischaemia in patients with coronary artery disease, or cerebrovascular strokes (5). Additionally, all PDE5 inhibitors should not be used in patients who are taking the α-blockers doxazosin or terazosin, have unstable angina pectoris, have had a recent myocardial infarction (previous 3 months) or stroke (previous 6 months), myocardial insufficiency NYHA > 2, hypotension, poorly controlled blood pressure, significant hepatic or renal insufficiency, or if non-arteritic anterior ischemic optic neuropathy (NAION) with sudden loss of vision is known or has appeared after previous use of PDE5 inhibitors. Sildenafil and vardenafil are also contraindicated in patients with retinitis pigmentosa. Caution is advised if PDE5 inhibitors are used together with other drugs which are metabolised by the same hepatic elimination pathway (CYP3A4), which is associated with an increased serum concentration of the PDE5 inhibitor.

3.7.6 *Practical considerations*

To date, PDE5 inhibitors have been officially licensed only for the treatment of erectile dysfunction and pulmonary arterial hypertension. Treatment beyond this indication (e.g. male LUTS) is still experimental and should not be used routinely in the clinical setting. Long-term experience in patients with LUTS is still lacking. The value of PDE5 inhibitors in the context of other available potent drugs (e.g. α-blockers, 5α-reductase inhibitors, or muscarinic receptor antagonists) remains to be determined. Insufficient information is available about combinations between PDE5 inhibitors and other LUTS medications.

3.7.7 *Recommendations*

	LE	GR
PDE5 inhibitors reduce moderate to severe male LUTS.	1b	
PDE5 inhibitors are currently restricted to men with erectile dysfunction, pulmonary arterial hypertension, or to those who have LUTS and participate in clinical trials.		A

3.7.8 *References*

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3.8 Other new drugs

Several new drugs are currently under clinical investigation (phase II-III trials) of which none has been licensed for male LUTS so far. These new drugs target:

- the prostate, e.g. gonodotrophin-releasing hormone antagonists, oestrogen receptor antagonists, apoptosis-inducing agents, vaccines, vitamin D agonists, or androgen replacement therapies;
- the bladder, e.g. β_3-adrenoceptor agonists;
- the nervous system, e.g. neuromuscular blocking agents, tachykinin receptor antagonists. Published results of those drugs are preliminary and sparse. Therefore, these new drugs were excluded from further analyses, but will be re-evaluated for the next version of the guidelines on male LUTS.

4. SURGICAL TREATMENT

4.1 Transurethral resection of the prostate (TURP) and transurethral incision of the prostate (TUIP)

4.1.1 Mechanism of action

Transurethral resection of the prostate (TURP) was first performed in 1932. Whereas the material has changed substantially since the first procedure, the basic principle of TURP has remained unchanged. It is still, firstly, the removal of tissue from the transition zone of the prostate to reduce benign prostatic obstruction (BPO) and, secondly, to reduce lower urinary tract symptoms (LUTS).

TURP is still regarded as the gold standard for the treatment of BPO in prostates between 30 and 80 mL. However, there is no strong evidence in the literature regarding the upper size limit of the prostate suitable for TURP. The suggested threshold sizes reflect the Panel's opinion who has assumed that this limit depends on the surgeon's experience, resection speed, and resectoscope sizes.

During the last decade, there has been a continuous decline in the rate of TURPs performed. In 1999, TURP represented 81% of all surgery for benign prostatic hypertrophy (BPH) in the USA, but by 2005, TURP represented only 39% of surgical procedures for BPH, due to the combined effect of fewer prostatic operations and more minimally-invasive procedures (1).

Transurethral incision of the prostate (TUIP) was initially described by Orandi in 1969. TUIP reduces BPO by splitting the bladder outlet without tissue removal. This technique has been rediscovered and may replace TURP as the first choice of treatment in selected men with benign prostate enlargement (BPE), especially men with prostate sizes ≤ 30 mL and without prostate middle lobes.

4.1.2 Operative procedure

During TURP, hyperplastic prostatic tissue of the transition zone is removed endoscopically using special resectoscopes and cutting loops, which enable ablation of prostatic tissue in small slices that are then removed from the bladder at the end of surgery. The cutting of prostatic tissue and coagulation of blood vessels is achieved by using adaptable electrical current.

During the TUIP procedure, one or two cuts are made into the prostatic parenchyma and capsule, thereby reducing urethral resistance (BPO). The technique has been modified by several authors. The most popular unilateral incision is located at the 6 o'clock position and the most commonly performed bilateral incisions are at the 5 and 7 o'clock positions.

Urinary tract infections (UTIs) should be treated prior to TURP or TUIP (2,3). The routine use of prophylactic antibiotics in TURP has been well evaluated with a considerable number of RCTs. Three systematic reviews of the available RCTs resulted in similar conclusions favouring the use of antibiotic prophylaxis (4-6). Antibiotic prophylaxis significantly reduces bacteriuria, fever, sepsis, and the need for additional antibiotics after TURP. There was also a trend towards higher efficacy in favour of short-course antibiotic administration than for a single-dose regimen (4). However, further studies are required to define the optimal antibiotic regimen and cost-effectiveness of antibiotic prophylaxis in TURP.

4.1.3 Efficacy

Symptom improvement

TURP provides durable clinical outcomes, as shown by studies with a long follow-up of 8-22 years. There are no similar data on durability for any other surgical treatment for BPO (7). One study with a mean follow-up of 13 years reported a significant and sustained decrease in most symptoms and improvements in urodynamic parameters following TURP. The study also found that subjective and objective failures were associated with decreased detrusor contractility rather than BPO (8). A study in 577 men who underwent TURP reported excellent functional outcomes with a mean IPSS of 4.9 and a mean QOL score of 1.2 after 10 years of followup (9). A meta-analysis of 29 RCTs reported a mean LUTS improvement of 70.6% (95% CI: 66.4-75.5%) after TURP (10).

RCT comparison of TUIP with TURP

Eleven RCTs comparing TUIP with TURP are currently available (10-14) (Table 15). These studies evaluated similar LUTS improvements in patients with small prostates (< 20-30 mL) and no prostate median lobe (10-14). The findings are reported below.

Uroflowmetry: the mean Q_{max} increase following TURP was 125% with an absolute mean improvement of +9.7 mL/s (95% CI: 8.6-11.2 mL/s) (10). All RCTs comparing TUIP with TURP 12 months after the procedure reported a lower mean or median Q_{max} following TUIP with an overall mean Q_{max} improvement of 70% (95% CI: 27-112) (10,13).

Postvoid residual (PVR) volume: PVR volume decreased by 60.5% (95% CI: 48-71) after TURP (10). The decrease in PVR after TUIP varied across available studies, but was always lower than with TURP (10,13).

Re-treatment rate: a second prostatic operation, usually performed as TURP again, was reported at a constant rate of approximately 1-2% per year. The review analysing 29 RCTs found a re-treatment rate of 2.6% (96% CI: 0.5-4.7) after a mean follow-up of 16 months (10). In a recent large-scale study of 20,671 men, who underwent TURP in Austria, the overall reported re-treatment rates (including secondary TURP, urethrotomy, and bladder neck incision) were 5.8%, 12.3%, and 14.7% at 1, 5, and 8 years of follow-up, respectively (14). The incidence of secondary TURP was 2.9%, 5.8% and 7.4% for the same follow-up periods (14). Analyses of RCTs comparing TURP with TUIP showed that re-treatment was more likely following TUIP (17.5%) than after TURP (9%) (13).

4.1.4 Tolerability and safety

Intra- and peri-operative complications

Mortality following prostatectomy has decreased constantly and significantly during the past decades and is less than 0.25% in contemporary series (10,15,16). In the most recent study of 10,564 men who underwent TURP, peri-operative mortality (during the first 30 days) was 0.1% (17). The risk of transurethral resection (TUR) syndrome has also decreased during the last decades to less than 1.1% (10,16). Risk factors associated with TUR syndrome are excessive bleeding with opening of venous sinuses, prolonged operation time, large prostates, and past or present nicotine abuse (17). No cases of TUR syndromes were recorded in patients undergoing TUIP. The incidence of blood transfusion following TURP in the analysis of 29 RCTs was 8.4% (95% CI: 3.9-13.4) (10). Contemporary real-life data from 10,564 TURP procedures reported procedure-related bleeding requiring blood transfusion in 2.9% of patients. The risk of bleeding following TUIP is negligible (10).

Long-term risk of mortality

The possibility of an increased long-term risk of mortality after TURP compared to open surgery has been raised by Roos et al. (15). However, these findings have not been replicated by others (18-20). Recently, data from 20,671 TURPs and 2,452 open prostatectomies (OP) showed that the 8-year incidence of myocardial infarction was identical after TURP (4.8%) and OP (4.9%). Similarly, mortality rates at 90 days (0.7% vs. 0.9%), one year (2.8% vs. 2.7%), 5 years (12.7% vs. 11.8%) and 8 years (20% vs. 20.9%) were almost identical (14).

Long-term complications

Urinary incontinence: the median probability of post-operative stress urinary incontinence ranges from 1.8% following TUIP to 2.2% following TURP (1-6,13,15). A meta-analysis of three trials investigating urinary incontinence showed no statistically significant difference between the TUIP and TURP groups, although there were fewer events in the TUIP group (13).

Urinary retention and UTIs: a recent meta-analysis found no statistically significant differences between TURP and TUIP in the development of urinary retention and UTIs (13).

Bladder neck stenosis and urethral stricture: the risk of developing urethral strictures after TURP is 3.8% (95% CI: 1.7-5.8) and after TUIP 4.1% (10). The risk of bladder neck stenoses is 4.7% (95% CI: 0.3-9.2) after TURP (10). A systematic review reported an overall incidence of 8.7% for strictures after TUIP, but did not distinguish between urethral strictures and bladder neck stenoses (13).

Sexual function: retrograde ejaculation results from resection/destruction of the bladder neck and is reported by 65.4% (95% CI 53.4-77.5) of patients after TURP and 18.2% after TUIP (10). There is a long-standing controversy on the impact of prostatectomy, particularly TURP, on erectile function. The only RCT that compared TURP to a 'wait and see' policy with a follow-up of 2.8 years reported identical rates of erectile dysfunction (ED) in both arms (19% and 21%, respectively) (21). In the analysis of 29 RCTs, the incidence of ED following TURP was 6.5% (95% CI: 0.2-12.7%) (10). The frequently reported increase in ED after TURP seems to be caused by confounding factors (e.g. age) rather than being the direct consequence of TURP.

4.1.5 Practical considerations

TURP and TUIP are both effective primary treatments for men with BPO, BPE, and moderate-to-severe LUTS. The choice between TURP and TUIP should be primarily based on prostate volume, with prostates < 30 mL being mainly considered for TUIP and prostates of 30-80 mL for TURP. The advantages of TUIP are reduced bleeding incidents, shorter operation time, avoidance of TUR syndrome, minimal and shorter post-operative bladder irrigation, low risk of retrograde ejaculation, and shorter times for catheterisation and hospitalisation.

The disadvantages are a higher rate of symptom recurrence and the need for additional surgery.

*4.1.6 **Modifications of TURP: bipolar resection of the prostate***

4.1.6.1 Mechanism of action

One of the most important recent improvements in TURP is the incorporation of plasmakinetic bipolar technology (B-TURP). To date, five types of bipolar resection devices have been developed: the plasmakinetic (PK) system (Gyrus), Vista Coblation/CTR (controlled tissue resection) system (ACMI) [withdrawn], transurethral resection in saline (TURis) system (Olympus), Karl Storz, and Wolf (22). The devices differ in the way in which bipolar current flow is delivered to achieve the plasmakinetic effect.

4.1.6.2 Operative procedure

Prostatic tissue removal during B-TURP is identical to monopolar TURP. In contrast to monopolar TURP, B-TURP uses a specialized resectoscope loop, which incorporates both the active and return electrodes. It permits electrosurgical tissue cutting in a conductive saline medium. After activation of the high frequency current, the physiological saline around the loop is heated up to the boiling point. The resulting bubbles create an environment with high electrical resistance; the voltage between electrode and saline solution spikes forms an arc. The tissue is heated indirectly by the heat of the ignition of the arc; this enables both resection and coagulation. As with other endoscopic operations, UTIs should be treated before the procedure and prophylactic antibiotic therapy is advised.

4.1.6.3 Efficacy

The efficacy of bipolar TURP devices has been demonstrated in case series and RCTs. Three systematic reviews have provided important information on the efficacy of bipolar TURP (23-25). Almost identical outcomes were reported with monopolar and bipolar TURP concerning the improvement of Q_{max} (10.5 mL/s vs. 10.8 mL/s) and the AUA-SS/IPSS (-15.2 vs. -15.1) (23).

Long-term results of B-TURP are still awaited. In a RCT comparing B-TURP with plasmakinetic energy with a mean follow-up of 18.3 months, the re-operation rate was 4.1% and 2.1% for the PK system and TURP, respectively (26). In a recent study with a follow-up of 3 years, the initially observed significant improvements remained durable for the bipolar and monopolar arm in terms of IPSS (6.8 vs. 6.2) and Q_{max} (20.5 vs. 21.5 mL/s) (27).

4.1.6.4 Tolerability and safety

The overall rate of adverse events was significantly lower with B-TURP compared to monopolar TURP (28.6% vs. 15.5%) (23). Main advantages of B-TURP include reduced blood loss and decreased incidences of postoperative clot retention and blood transfusions. Both post-operative catheterisation and hospitalization times were shorter with bipolar TURP compared to monopolar TURP; this was thought to be due to reduced bleeding associated with improved coagulation abilities. Post-operative storage symptoms, particularly dysuria, were less common with B-TURP. However, most of these results were trends favouring B-TURP rather than statistically significant differences (23).

TUR syndrome has not been reported with B-TURP, due to the use of physiological saline irrigation fluid and reduced fluid absorption during the procedure (23,24). Several RCTs have suggested that urethral strictures are more common with B-TURP, with possible contributory factors being a larger resectoscope size (27F), the type of return electrode, and higher current densities (22). However, the most recent systematic review of RCTs did not reveal statistically significant differences between monopolar and bipolar TURP treatment arms (1.7% vs 2.4, respectively, p = 0.280) (24). Nevertheless, larger studies with increased numbers of patients and/or longer follow-ups may change these results. Regarding the impact of B-TURP on sexual function, it was found that post-operative retrograde ejaculation (57 vs 60%) (24) or erectile dysfunction (both about 14%) (23) did not differ significantly between B-TURP and monopolar TURP.

4.1.6.5 Practical considerations

B-TURP offers an attractive alternative to monopolar TURP in patients with BPO, BPE, and LUTS with similar efficacy but lower morbidity. Furthermore, the safety of B-TURP allows more time for training and teaching of urology residents. However, since there remains a lack of sufficient long-term data, it is not possible to draw definite conclusions about the duration of improvements and advantages of B-TURP over monopolar 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.

4.1.7 *Recommendations*

	LE	GR
Monopolar TURP is the current surgical standard procedure for men with prostate sizes of 30-80 mL, BPO and moderate-to-severe LUTS. Monopolar TURP provides subjective and objective improvement rates superior to medical or minimally invasive treatments. However, the morbidity of monopolar TURP is higher than for TUIP, bipolar TURP, drugs, or other minimally-invasive procedures.	1a	A
Bipolar TURP achieves short-term results comparable to monopolar TURP.	1a	A
TUIP is the surgical therapy of choice for men with BPO, LUTS, and prostate sizes < 30 mL and without middle lobes.	1a	A

BPO = benign prostatic obstruction; LUTS = lower urinary tract symptoms; TUIP = transurethral incision of the prostate; TURP = transurethral resection of the prostate.

Table 15: Efficacy of transurethral resection of the prostate (TURP) or transurethral incision of the prostate (TUIP) in level 1 trials at 12 or 24 months. Absolute and relative changes compared to baseline with regard to symptoms (Madson-Iverson or IPSS) and maximum urinary flow rate (Q_{max})

Trials	Intervention	Patients (n)	Absolute decrease (%) in symptoms at 12 months		Q_{max} (mL/s) at 12 months		Blood trans-fusion	Re-operation rate at 12 months	LE
			absolute	[%]	absolute	[%]	[%]	[%]	
Dorflinger et al. (1992) (28)	TURP	31	-11.6 [a]	-88 [a]	+22.9 [a, b]	+294 [a, b]	13	3.2 [b]	1b
	TUIP	29	-12.6 [a]	-85 [a]	+16.3 [a]	+223 [a]	0 [c]	20.7	
Jahnson et al. (1998) (29)	TURP	43	-13 [a]	-82 [a]	+19.5 [a, b]	+229 [a, b]	2.4	7.1 [b]	1b
	TUIP	42	-11.8 [a]	-77 [a]	+13.8 [a]	+148 [a]	0	23.2	
Riehmann et al. (1995) (30)	TURP	61	-9.5 [a]	-67 [a]	no significant difference between groups			16	1b
	TUIP	56	-10 [a]	-63 [a]				23	
Saporta et al. (1996) (31)	TURP	20	-9.4 [a]	-63 [a]	+17.3 [a]	+266 [a]		0 [b]	1b
	TUIP	20	-9.3 [a]	-64 [a]	+14.6 [a]	+197 [a]		15	
Soonwalla et al. (1992) (32)	TURP	110			+20.1 [a]	+251 [a]	34.5		1b
	TUIP	110			+19.5 [a]	+246 [a]	0 [c]		
Tkoocz et al. (2002) (12)	TURP	50	-12 *[a]	-70*	6.9 *[a]	+255 [a]			1b
	TUIP	50	-13 *[a]	-77*	7.6 *[a]	+222 [a]			
Lourenco et al. (2009) (33)	TURP	345	no significant difference between groups		no significant difference between groups		28.3	7.2 [b]	1a
	TUIP	346					1.1 [c]	18	
Yang et al. (2001) (11)	TURP	403	-11.2 to -13	-63 to -82	+17.3 to +22.9 [b]	+266 to +352 [b]	25.1	5.5	1a
	TUIP	392	-10 to -13.5	-63 to -83	+13.8 to +16.3	+189 to +223	0.87 [c]	9.3	

** 24 month post-operatively; [a] significantly different compared to baseline; [b] significantly different in favour of TURP; [c] significantly different in favour of TUIP*

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4.2 Open prostatectomy

*4.2.1 **Mechanism of action***

Open prostatectomy is the oldest surgical treatment modality for BPE. Obstructive prostatic adenomas are enucleated using the index finger, either from the inside of the bladder (Freyer procedure) or through the anterior prostatic capsule (Millin procedure), allowing unobstructed voiding.

4.2.2 ***Operative procedure***

Indications for surgery

The most frequent indication for surgical management is bothersome LUTS refractory to medical management (1,2). The following complications of BPH/BPE/BPO are considered strong indications for surgery:

- refractory urinary retention;
- recurrent urinary infection;
- recurrent haematuria refractory to medical treatment with 5-alpha reductase inhibitors;
- renal insufficiency due to BPE/BPO;
- bladder stones.

Increased post-void residual volume (PVR) may also be used as an indication for surgery. However, there is great intra-individual variability and an upper limit requiring intervention has not been defined. Variables most likely to predict the outcome of prostatectomy are severity of LUTS, the degree of bother and the presence of BPO.

Procedure

A transurethral balloon catheter is inserted and the bladder is filled with saline solution. Access to the bladder or anterior prostatic capsule is obtained through a midline or transverse suprapubic incision.

Transvesical procedure (Freyer)

A transverse incision is made in the anterior bladder wall. The index finger is then placed in the urethra and with forward pressure towards the symphysis, the urethral mucosa is broken, and the plane between the surgical capsule and the adenomas is defined. The prostatic adenomas are then bluntly separated from the capsule with the finger. Special care must be taken when dividing the urethra at the apex in order not to harm the urethral sphincter. Haemostatic sutures are placed in the posterior corners of the cavity and the posterior margin, taking care not to include the ureteral orifices. Post-operative haemostasis might be obtained using gauze packing and/or traction on a large balloon catheter. For sufficient drainage, both a transurethral and a suprapubic catheter are placed.

Transcapsular procedure (Millin)

A transverse incision is made in the anterior prostatic capsule and the adenomas freed bluntly with a scissor and the index finger. Care is taken when dividing the urethra. Many surgeons will resect the posterior bladder neck to avoid late bladder neck stricture. The prostatic capsule is closed after insertion of a transurethral balloon catheter for drainage.

Peri-operative antibiotics

A known urinary tract infection should be treated before surgery (10,11). The routine use of prophylactic antibiotics remains controversial. However, antibiotics are recommended in patients on catheterization prior to surgery.

4.2.3 ***Efficacy***

Open prostatectomy is the treatment of choice for large glands (> 80-100 mL). Associated complications include large bladder stones or bladder diverticula (4-6). Three recent RCTs have shown that Holmium laser enucleation and PVP lead to similar outcomes compared to open prostatectomy in men with large glands (> 70, 80 and 100 mL) at a significantly lower complication rate (7-9).

Treatment outcome

The results of open prostatectomy studies for treating BPH-LUTS or BPO are summarised in Table 16.

- LUTS: open prostatectomy results in an improvement of LUTS of 63-86% and in the IPSS Quality of Life score of 60-87% (8,9,12).
- Uroflowmetry: the mean increase of Q_{max} following open prostatectomy is 375% (range, 88-677%) (8,9,12) in absolute terms +16.5-20.2 mL/s (6,8,9,12).
- PVR: a reduction of 86-98% is seen in the PVR volume after open prostatectomy (8,9,12).

Long-term outcome and re-treatment rate

A favourable long-term outcome is common after open prostatectomy. A secondary prostatic operation has not been reported in the open prostatectomy arm in randomized studies up to 5 years follow-up (8,9,12) (Table 17).

4.2.4 *Tolerability and safety*

Intra-/peri-operative complications

Mortality following open prostatectomy has decreased significantly during the past two decades and is less than < 0.25% in contemporary series (13) (Table 17). The estimated need for blood transfusion following is about 7-14% (9,12,13).

Long-term complications

Long-term complications are incontinence and bladder neck contracture and urethral stricture. The risk of developing stress incontinence is up to 10% (4), while the risk for developing bladder neck contracture and urethral stricture is about 6% (7-9).

4.2.5 *Practical considerations*

Open prostatectomy is the most invasive, but also the most effective and durable, procedure for the treatment of BPH-LUTS or BPO. Only Holmium enucleation delivers similar results, but with less morbidity. In the absence of an endourological armamentarium and a Holmium laser, open prostatectomy appears to be the treatment of choice for men with prostates > 80-100 mL, BPO, and drug-treatment-resistant LUTS. The choice between the Freyer or Millin procedures depends upon the surgeon's preference.

Table 16: Results of open prostatectomy studies for treating BPH-LUTS or BPO

Studies	Duration (weeks)	Patients (*n*)	Change in symptoms (IPSS)		Change in Q_{max}		Change in PVR		Change in prostate volume		LE
			Absolute	%	mL/s	%	mL	%	mL	%	
Kuntz et al. 2008 (9)	260	32	-18.2	86	21.4	677	-287	98			1b
Skolarikos et al. 2008 (8)	78	60	-12.5	63	7	86	-77	86	-86	88	1b
Naspro et al. 2006 (7)	104	39	-13.2	62	15.9	291					1b
Varkarakis et al. 2004 (12)	151	232	-23.3	84	16.5	329	-104	90			3
Gratzke et al. 2007 (13)		868			13	218	-128	88	85	88	2b

IPSS = international prostate symptom score; PVR = postvoid residual urine; Q_{max} = maximum urinary flow rate (free uroflowmetry)

Table 17: Tolerability and safety of open prostatectomy

	Peri-operative mortality (%)	Post-operative stress incontinence (%)	Re-operation for BPO (%)
Kuntz *et al*. 2008 (9)	0	0	0
Skolarikos *et al*. 2008 (8)	0		0
Naspro *et al*. 2006 (7)	0	2.5	0
Varkarakis *et al*. 2004 (12)	0	0	
Gratzke *et al*. 2007 (13)	0.2		

BPO = benign prostatic obstruction.

4.2.6 *Recommendation*

	LE	GR
Open prostatectomy is the first choice of surgical treatment in men with BPH-LUTS refractory to drugs, BPO, and prostate sizes > 80-100 mL in the absence of Holmium lasers.	1b	A

4.3 Transurethral microwave therapy (TUMT)

*4.3.1 **Mechanism of action***

Microwave thermotherapy of the prostate works by emitting microwave radiation through an intra-urethral antenna in order to deliver heat into the prostate. Tissue is destroyed by being heated at temperatures above cytotoxic thresholds (> 45°C) (coagulation necrosis). Heat is mainly produced by electrical dipoles (water molecules) oscillating in the microwave field and electric charge carriers (ions) moving back and forth in the microwave field.

It is also thought that the heat generated by TUMT also causes apoptosis and denervation of α-receptors, thereby decreasing the smooth muscle tone of the prostatic urethra.

*4.3.2 **Operative procedure***

Transurethral microwave therapy is a registered trademark of Technomed Medical Systems, the pioneer of microwave thermotherapy. Currently, the main devices in the field of microwave thermotherapy are the Prostatron™ device (Urologix, Minneapolis, MN, USA), Targis™ (Urologix, Minneapolis, MN, USA), CoreTherm™ (ProstaLund, Lund, Sweden), and TMx-2000™ (TherMatrx Inc, Northbrook, ILL, USA). Most published data on thermotherapy has been on the Prostatron device.

Conceptually, TUMT devices are all similar in delivering microwave energy to the prostate with some type of feedback system. All TUMT devices consist of a treatment module that contains the microwave generator with a temperature measurement system and a cooling system. The main difference between TUMT devices is the design of the urethral applicator. The applicator consists of a microwave catheter connected to the module, which is inserted into the prostatic urethra. Differences in the characteristics of applicators have a significant effect on the heating profile (1). Other less important differences between TUMT devices are found in the catheter construction, cooling systems, treatment time, and monitoring of TUMT effects (2).

*4.3.3 **Efficacy***

Clinical outcome

A systematic review of all available RCTs on TUMT attempted to assess therapeutic efficacy (Table 18) (3) in different TUMT devices and software, including Prostatron (Prostatsoft 2.0 and 2.5) and ProstaLund Feedback. Weighted mean differences (WMD) were calculated with a 95% confidence interval (CI) for the between-treatment differences in pooled means. The review found that TUMT was somewhat less effective than transurethral resection of the prostate (TURP) in reducing LUTS. The pooled mean symptom score for men undergoing TUMT decreased by 65% in 12 months compared to 77% in men undergoing TURP, which is a WMD of -1.83 in favour of TURP. TURP achieved a greater improvement in Q_{max} (119%) than TUMT (70%), with a WMD of 5.44 mL/s in favour of TURP (3).

Similarly, a pooled analysis of three studies (two RCTs and one open label) of ProstaLund Feedback TUMT (PLFT) with 12-month follow-up showed that the responder rate was 85.3% in the PLFT group and 85.9% in the TURP group (4). In addition, pooled IPSS data indicated that a subjective, non-inferior improvement with PLFT compared to TURP (4). However, one-sided 95% CI analysis showed that the non-inferiority of PLFT compared to TURP did not reach the predetermined level, even though both PLFT and TURP appeared to improve Q_{max} significantly.

Previously, urinary retention was considered to be a contraindication for TUMT. Nowadays, level 2b evidence studies have reported an 80-93% success rate for TUMT, defined as the percentage of patients who regained their ability to void spontaneously (5-7). However, these studies had a short follow-up ($\leq$ 12 months), which makes it difficult to estimate the durability of TUMT outcome in patients with retention. In a study with a longer follow-up of up to 5 years, treatment failure was 37.8% in the retention group, with a cumulative risk of 58.8% at 5 years (8).

One RCT compared TUMT with the α-blocker, terazosin (9). After 18 months' follow-up, treatment failure in the terazosin-treated patients (41%) was significantly greater than in TUMT patients (5.9%), with TUMT also achieving a greater improvement in IPSS and Q_{max} (10).

Durability

Low-energy TUMT has disappointing results for durability. Several studies have reported a re-treatment rate after low-energy TUMT as high as 84.4% after 5 years (11-14), while other studies have reported re-treatment rates of 19.8-29.3% after high-energy TUMT, though with a lower mean follow-up of 30-60 months (15-18). The re-treatment rate due to treatment failure has also been estimated by a systematic review of randomized TUMT trials (3). The trials had different follow-up periods and the re-treatment rate was expressed as the number of

events per person per year of follow-up. The re-treatment rate was 0.075/person years for patients treated by TUMT and 0.010/person years for TURP.

However, a prospective, randomised, multicentre study after 5 years has obtained comparable clinical results with TUMT to those seen with TRUP. The study compared TUMT (PLFT; the Core-Therm device) and TURP (19). No statistically significant differences were found in Q_{max} and IPSS between the two treatment groups at 5 years. In the TUMT group, 10% needed additional treatment versus 4.3% in the TURP arm. These data suggest that, at 5 years, clinical results obtained with PLFT-TUMT were comparable to those seen after TURP. It should be noted that most durability studies have a high attrition rate; in this study, less than half of the initial group of patients treated were analyzed at 4-5 years. In addition, patients who remained in the study were likely to represent the best data (responders).

4.3.4 ***Tolerability and safety***

Treatment is well tolerated, even though most patients experience perineal discomfort and urinary urgency and require pain medication prior to or during therapy. Pooled morbidity data of randomised studies comparing TUMT and TURP have been published (3,4,20). Catheterization time, incidence of dysuria/urgency and urinary retention were significantly less with TURP, while the incidence of hospitalisation, haematuria, clot retention, transfusions, transurethral resection (TUR) syndrome, and urethral strictures were significantly less for TUMT. In a systematic review of randomized trials (3), the re-treatment rate due to strictures during follow-up was estimated and expressed as the number of events per person per year of follow-up. TURP patients (5.85/100 person years) were more likely than TUMT patients (0.63/100 person years) to require surgical re-treatment for strictures (meatal, urethral, or bladder neck). Pooled data showed that TUMT had less impact on sexual function (erectile dysfunction, retrograde ejaculation) than TURP (3,4,20).

4.3.5 ***Practical considerations***

Endoscopy is essential because it is important to identify the presence of an isolated enlarged middle lobe or an insufficient length of the prostatic urethra. Reported low morbidity and the absence of any need for anaesthesia (spinal or general) make TUMT a true outpatient procedure, providing an excellent option for older patients with co-morbidities at high operative risk and, therefore, unsuitable for invasive treatment (21). Independent baseline parameters predicting an unfavourable outcome include advanced age of the patient, small prostate volume, mild-to-moderate bladder outlet obstruction and a low amount of energy delivered during treatment (22). However, it should be remembered that a predictive factor for a particular device cannot necessarily be applied to other devices.

Table 18: Efficacy of TUMT. Absolute and relative changes compared to baseline are listed for symptoms (IPSS), maximum urinary flow rate (Q_{max}), postvoid residual urine (PVR), and prostate volume (PVol)

Trials	Duration (weeks)	Patients (n)	Change IPSS (absolute [%])	Change Q_{max} (mL/s, [%])	Change QoL (absolute [%])	Change PVR (absolute [%])	Change PVol (absolute [%])	LE
Hoffman et al. (2007) (3)	52	322	-12.7[a] (-65.0)	5.6[a] (70.0)	-2.4[a] (58.5)	NA	NA	1a
Gravas et al. (2005) (4)	52	183	-14.5[a] (-69.0)	8.4[a] (109.0)	-2.97[a] (70.9)	NA	-17.0 [a] (-33.0)	1b
Mattiasson et al. (2007) (19)	260	100	-13.6[a] (-61.5)	3.8[a] (50.0)	-3.2[a] (-74.4)	-36.0 (-34.0)	-4.0 (-8.1)	1b
Floratos et al. (15)	156	78	-8.0[a] (-40.0)	2.7[a] (29.3)	-2.0[a] (-50.0)	NS	NA	1b
Thalmann et al. (2002) (17)	104	200	-20.0[a] (-87.0)	7.0[a] (116.6)	-4.0[a] (-80.0)	-143 [a] (-84.1)	-17.7 [a] (-30.7)	2b
Miller et al. (2003) (18)	260	150	-10.6[a] (-47.0)	2.4[a] (37.0)	-2.3[a] (-54.7)	NA	NA	2b
Trock et al. (2004) (23)	208	541	-8.9[a] (-42.7)	2.8[a] (35.0)	-2.1[a] (-50.1)	NA	NA	2b

a = significant compared to baseline (indexed whenever evaluated); NS = not significant; NA = not available.

*4.3.6 **Recommendations***

	LE	GR
TUMT achieves symptom improvement comparable to TURP, but is associated with decreased morbidity and lower flow improvements.	1a	A
Durability is in favour of TURP with lower re-treatment rates compared to TUMT	1a	A

*4.3.7 **References***

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4.4 Transurethral needle ablation (TUNA™) of the prostate

4.4.1 ***Mechanism of action***

The TUNA™ procedure works by inducing a coagulative necrosis within the transition zone of the prostate. As a result of scar maturation, there may be a reduction in transition zone volume and, therefore, a reduction of BPO. There may also be a poorly understood neuromodulatory effect.

4.4.2 ***Operative procedure***

The TUNA™ device delivers low-level radiofrequency energy to the prostate via needles inserted transurethrally into the prostatic parenchyma. The needles are insulated, except at their tips, so that energy is only delivered into the prostatic parenchyma and not to the urethra. Needles are placed under direct vision using an attachment to the standard cystoscope. TUNA™ is carried out under anaesthetic (local or general) or sedation.

4.4.3 ***Efficacy***

Several, non-randomized, clinical trials have documented the clinical efficacy of TUNA™ with a fairly consistent outcome (3-7). Symptomatic improvement has ranged from 40-70%. Improvements in Q_{max} vary widely from 26-121% in non-retention patients. A recent report with 5 years' follow-up in 188 patients demonstrated symptomatic improvement in 58% and improved flow in 41%. However, 21.2% of patients required additional treatment (8).

Randomized clinical trials

TUNA™ has been compared with TURP in randomized studies (8-11) with varying follow-up. The studies found both TUNA™ and TURP produced symptomatic improvement. However, TURP produced greater symptom improvement and a better quality of life than TUNA™, as well as a significant improvement in Q_{max} after TUNA™ (Table 19). More detailed comparisons between TUNA™ and TURP can be found in some very high-quality and comprehensive, systematic reviews and meta-analyses (12,13).

Impact on bladder outlet obstruction

Seven clinical studies on the impact of TUNA™ on BPO (14,15) have demonstrated a statistically significant decrease in maximum detrusor pressure or detrusor pressure at Q_{max}, even though a number of patients were still obstructed following TUNA™ therapy.

There is no convincing evidence that prostate size is significantly reduced following TUNA™ (6). Recent reports have suggested that gadolinium-enhanced MRI can be used to assess TUNA™-related treatment effects (16).

Durability

Because most studies have been short-to-medium term, concerns have been risen about the durability of effects. Even short term (12 months), up to 20% of patients treated with TUNA™ need to be re-treated with TURP (1). A recent French report described a failure rate (incorporating re-treatment) of up to 50% over a 20-month period (17).

4.4.4 ***Tolerability and safety***

TUNA™ is usually performed as an outpatient procedure under local anaesthesia, although intravenous sedation is sometimes required (1). Post-operative urinary retention is seen in 13.3-41.6% of patients and lasts for a mean of 1-3 days; within 1 week, 90-95% of patients are catheter-free (1). Irritative voiding symptoms up to 4-6 weeks are common (2). Continence status is not affected.

4.4.5 *Practical considerations*

Few selection criteria have been identified. However, TUNA™ is unsuitable for patients with prostate volumes > 75 mL or isolated bladder neck obstruction. Because TUNA™ cannot treat median lobes effectively it is not clear whether men with significant median lobes will experience the benefit in published studies. There is anecdotal evidence for TUNA™ in men receiving aspirin and anti-coagulants. TUNA™ can be performed as a day-case procedure and is associated with fewer side-effects compared to TURP (e.g. bleeding, erectile dysfunction, urinary incontinence). However, there remain concerns about the durability of the effects achieved by TUNA™.

4.4.6 *Recommendations*

	LE	GR
TUNA™ is an alternative to TURP for patients who wish to defer/avoid (complications of) TURP, but patients should be aware of significant re-treatment rates and less improvement in symptoms and quality of life.	1a	A

Table 19: Summary of comparative level of evidence (LE) 1 data (TUNA™ vs TURP) (12)

	TUNA™	TURP	TUNA™ vs TURP 95% CI	LE
Symptoms (IPSS): mean (% improvement)				
3 months (8,10)	-12 (56%)	-14 (62%)	-2 (-0.9 to 3.1)	1b
1 year (9-11)	-12 (55%)	-15.5 (70%)	3.4 (2.1 to 5.2)[a]	1b
3 years (9,11)	-10 (45%)	-15 (67%)	4.8 (4.2 to 5.4)[a]	1b
Quality of life scores: mean (% improvement)				
3 months (8,10)	-4.5 (54%)	-3.7 (48%)	-0.8 (-1.3 to 0.5)	1b
1 year (9-11)	-4 (50%)	-4.3 (56%)	0.63 (0.1 to 1.2)[a]	1b
3 years (9,11)	-4.2 (50%)	5.2 (67%)	1 (0.2 to 1.9)[a]	1b
Q_{max} (mL/s): mean (% improvement)				
3 months (8,10)	4.7 (54%)	11.5 (150%)	-5.8 (-6.3 to -5.4)[a]	1b
1 year (9-11)	6.5 (76%)	12.2 (160%)	-5.9 (-7.7 to -4.1)[a]	1b
3 years (9,11)	5.6 (66%)	10.8 (141%)	-5.3 (-6.8 to -3.9)[a]	1b
PVR (mL): mean (% improvement)				
1 year (10,11)	-20 (22%)	-42 (41%)	22 (-18 to 27)[a]	1b

IPSS = International Prostate Symptom Score; Q_{max} = maximum urinary flow rate; PVR = postvoid residual urine. a = TURP significantly better compared with TUNA™.

4.4.7 *References*

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4.5 Laser treatments of the prostate

*4.5.1 **Holmium laser enucleation (HoLEP) and holmium resection of the prostate (HoLRP)***

4.5.1.1 Mechanism of action

The holmium:yttrium-aluminum-garnet (Ho:YAG) laser (2140 nm) is a pulsed, solid-state laser that has been used in urology for a variety of endourological applications in soft tissues and for the disintegration of urinary calculi (1). The wavelength of the Ho:YAG laser is strongly absorbed by water. This means that the area of tissue coagulation and the resulting tissue necrosis is limited to 3-4 mm, which is enough to obtain adequate haemostasis (2). Peak power produces intense, non-thermal, localized, tissue destruction, resulting in precise and efficient cutting of prostatic tissue. Resection is usually performed when the prostate is smaller than 60 mL, while enucleation is used for larger glands.

4.5.1.2 Operative procedure

Instrumentation for this technique includes a 550 µm, end-firing, quartz fibre and an 80 W Ho:YAG laser. A continuous-flow resectoscope is required with a working element, while physiological saline solution is used as an irrigant. The basic principle of the HoLRP technique is retrograde resection of the prostate and fragmentation of resected tissue inside the bladder to allow its evacuation through the operating channel of the resectoscope (2,3). The introduction of holmium laser enucleation (HoLEP) has been a significant improvement.

Mimicking open prostatectomy, the prostatic lobes are completely enucleated and pushed into the bladder, before being fragmented and aspirated afterwards by a morcellator (8).

4.5.1.3 Efficacy

Gilling et al. (4) has presented the results of a prospective RCT comparing TURP with HoLRP. To date, 120 patients have been enrolled with urodynamically-confirmed BPO (Schäfer grade ≥ 2) and prostate sizes < 100 mL (Table 20). Preliminary analysis has revealed a significantly longer mean resection time (42.1 vs. 25.8 minutes) for HoLRP patients, while symptomatic and urodynamic improvement were equivalent in both treatment groups. In 2004, long-term results with a minimum follow-up of 4 years were published (7), which showed that there was no difference in urodynamic parameters between HoLRP and TURP after 48 months.

Gilling et al. (9) reported long-term data with a mean follow-up of 6.1 years, indicating that HoLEP results were durable and most patients remained satisfied with their procedure. Two meta-analyses, which analyzed available RCTs comparing HoLEP and TURP (10,11), reported a significantly longer operation time with HoLEP (Table 20). Symptom improvements were comparable, but Q_{max} at 12 months was significantly better with HoLEP (11). In prostates > 100 mL, HoLEP proved to be as effective as open prostatectomy for improving micturition, with equally low re-operation rates at 5-years' follow-up (12).

4.5.1.4 Tolerability and safety

No major intra-operative complications have been described; however, the technique is a surgical procedure that requires relevant endoscopic skills. There are no specific limitations to the procedure. Patients taking anticoagulant medication and those with urinary retention can be treated safely (6). Dysuria was the most common peri-operative complication with an incidence of approximately 10% (2,4,5). Compared to TURP, HoLRP has a significantly shorter catheterization time (20.0 vs. 37.2 hours), shorter hospitalization time (26.4 vs. 47.4 hours) (4), and peri-operative morbidity (7). Potency, continence, symptom scores and major morbidity at 48 months were identical between HoLRP and TURP (7). Retrograde ejaculation occurred in 75-80% of patients; no post-operative impotence has been reported (2). Both meta-analyses found that HoLEP resulted in a significantly shorter catheterization time and hospital stay, reduced blood loss and fewer blood transfusions, but had a longer operation time than TURP (10,11).

*4.5.2 **532 nm ('Greenlight') laser vaporization of prostate***

4.5.2.1 Mechanism of action

Vaporization of prostatic tissue is achieved by a sudden increase in tissue temperature from 50°C to 100°C following the application of laser energy. A rapid increase in tissue temperature results in intracellular vacuoles (bubbles), followed by an increase in intracellular cell pressure. Once the cell pressure exceeds that compatible with cellular integrity, the vacuoles are released, as can be seen during the procedure. Because of the way in which tissue interacts with oxyhaemoglobin, laser vaporization is increased within a wavelength range from 500-580 nm. Because of the green light emitted (⌊=532 nm), this laser procedure is known as 'Greenlight' laser vaporization.

It is important to include the wavelength or crystal used to produce the laser energy when describing the type of laser vaporization used. This is because tissue interaction caused by laser energy varies according to the wavelength, applied energy, fibre architecture and tissue properties. This also means that the clinical results of different wavelengths are not comparable.

4.5.2.2 Operative procedure

Laser vaporization of the prostate using an 80 W, 532 nm laser is performed by using a 600 µm side-firing laser fibre with a 70°-deflecting laser beam and a 30°-deflecting laser cystoscope. Cold sterile saline or water can be used for irrigation during the procedure. Under direct vision, vaporization is performed with a fibre-sweeping technique, usually starting at the bladder neck and continuing with the lateral lobes and the apex (13). The visible, side-fired, laser beam leads to an immediate and apparent tissue ablation.

4.5.2.3 Efficacy

Numerous studies, predominantly with 80 W lasers, have been published in recent years (Table 20). The lack of long-term data means it is not yet possible to make final conclusions about the duration of improvement. A significant improvement in symptoms and voiding parameters and a re-operation rate comparable to TURP was reported in a 5-years' follow-up study of 500 patients (14). Despite ongoing oral anticoagulation in 45% of the patients (n = 225), no severe intra-operative complications were observed. The mean catheterization and post-operative hospitalization time was 1.8 (0-10) and 3.7 (0-35) days, respectively.

Three years after photolaser vaporization in men with mean vaporized prostate volumes of 28 ± 42 mL, the mean IPSS was 8.0, quality of life score was 1.3, and Q_{max} was 18.4 mL/s. The re-treatment rate was 6.8%. Urethral and bladder neck strictures were observed in 4.4% and 3.6% of patients, respectively. However, follow-up was available only in a few patients. Significant improvements in voiding parameters at a follow-up of 12 months were demonstrated with urodynamic investigation (15). At 12 months' follow-up, the mean urethral opening pressure ($Pdet_{open}$; 76.2 vs. 37.4 cm H2O) and detrusor pressure at Q_{max} ($Pdet_{max}$; 75 vs. 36.6 cm H_2O) were significantly reduced compared to baseline. The Q_{max} improved by 113% (mean 18.6 mL/s) compared to pre-operative Q_{max} (mean 7.9 mL/s).

To date, only two prospective RCTs and three non-randomised trials have been published. The longest available follow-up of a RCT is only 12 months; this trial indicated that 532 nm laser vaporization was equivalent to TURP in symptom improvement (20). Both groups showed a significant increase in Q_{max} from baseline. In the TURP group, flow increased from 8.7 to 17.9 mL/s (149%) and in the laser vaporization group from 8.5 to 20.6 mL/s (167%). The IPSS decreased from 25.4 to 12.4 (50%) in the TURP group and from 26 to 12 (50%) in the laser vaporization group. Laser vaporization also resulted in significant decreases (averaging 119 mL pre-operatively in the TURP group and 147 mL in the laser vaporization group), with reductions to 37 and 27 mL, respectively. Similar trends were seen concerning bother and quality of life scores.

4.5.2.4 Tolerability and safety

Safety was shown in various, prospective, non-randomised trials in patients with oral anticoagulation, urinary retention, or prostates > 80 ml (16-19). Regarding intra-operative safety, 532 nm laser vaporization was reported to be superior to TURP in non-randomised trials (21,22). It is also an effective technique when compared to TURP, producing equivalent improvements in flow rates and IPSS with the advantages of markedly reduced length of hospital stay, duration of catheterisation, and adverse events in a randomized trial. The duration of catheterisation was significantly less in the laser vaporization than the TURP group, with a mean (range) of 13 (0–24) hours versus 44.7 (6–192) hours. Additionally, the length of hospital stay was significantly shorter with laser vaporization, with a mean (range) of 1.09 (1–2) and 3.6 (3–9) days in the laser vaporization and TURP groups, respectively (23).

4.5.2.5 Practical considerations

Despite the efficacy of TURP in terms of tissue removal and reduction of BPO, a higher rate of peri-operative complications has resulted in an ongoing search for less invasive and safer surgical techniques. Based on the wavelength and power, laser can be used either for coagulation, vaporization, or cutting ('enucleation'). Non-thermal effects, also known as 'ablation', also result in tissue destruction. Functional results will therefore differ in terms of peri-operative handling of different laser devices, including learning curve, debulking issue, durability of results, and type of complications. The treatment choice how to reduce BPO is dependent on the availability of the armamentarium, patient's choice, concomitant morbidity or drug use, and experience of the surgeon.

Several types of new generation lasers for prostate surgery have emerged during the last decade, including the holmium:YAG, potassium titanyl phosphate:yttrium aluminum garnet (KTP:YAG), thulium:yttrium aluminium garnet (thulium:YAG), light blue optics:yttrium aluminium garnet (LBO:YAG) and the diode lasers. Energy can be transmitted through a bare, right-angle or interstitial fibre. Each laser has wavelength-specified energy–tissue interaction. Prostatic tissue destruction results from both thermal and non-thermal effects. In 2009, published data were only available for HoLEP, 80 W Greenlight PV (photoselective vaporization), and thulium:YAG laser prostatectomy. Only a few articles have been published on thulium:YAG prostatectomy, which may be used as a vaporizing, coagulating, or cutting laser. The lack of published data means that firm conclusions are not yet possible with regard to the different laser treatments.

4.5.2.6 Recommendations

	LE	GR
Ho:LEP and 532 nm laser vaporization of the prostate are minimally-invasive alternatives to TURP in men with BPE, BPO and LUTS which lead to immediate, objective and subjective improvements comparable to TURP.	1b	A
With regard to intra-operative safety, 532 nm laser vaporization is superior to TURP and should be considered in patients receiving anticoagulant medication or with a high cardiovascular risk.	3	B
With regard to long-term complication rates, results are only available for HoLEP, and are comparable to TURP.	1b	A

Table 20: Post-operative results of holmium resection (HoLRP) or enucleation (HoLEP) vs. transurethral resection of the prostate (TURP) open prostatectomy (OP) and 'Greenlight' laser vaporization (KTP) vs. TURP. Absolute and relative changes compared to baseline, with regard to symptoms (AUA-SI/IPSS), maximum urinary flow rate (Qmax), postvoid residual urine (PVR), and prostate volume

Trials	Duration	Patients	Surgery	Change symptoms (IPSS)		Change Q_{max} (mL/s)		Change PVR (mL)		Change prostate volume (mL)		LE
	(months)	(n)		absolute	[%]	absolute	[%]	absolute	[%]	absolute	[%]	
Le Duc et al. (1999) (1)	6	42	HoLRP	-18.4	-84	+15.1	+170					1b
		43	TURP	-17.9	-78	+13.2	+145					
Westenberg et al. (2004) (7)	48	43	HoLRP	-14.7 [a]	-67 [a]	+13.4 [a]	+151 [a]	- 61.1 [a] †	-70 [a] †	- 15 [a] †	-34 [a] †	1b
		30	TURP	-16.4 [a]	-71 [a]	+9.4 [a]	+103 [a]	- 50.4 [a] †	-60 [a] †	- 17 [a]	-39 [a] †	
Fraundorfer et al. (1998) (8)	1	14	HoLEP	-14.0	-66	+18.2	+260					3
Gilling et al. (2008) (9)	72	38	HoLEP	-17.2	-67	+10.9	+135	-71.7 †	-68 †	- 31.3 †	-54 †	3
Tan et al. (2007) (10)	12	232	HoLRP	-17.5 to -21.7	-81 to -83	+13.4 to +23.0	+160 to +470	-232.7	-98			1a
		228	TURP	-17.7 to -18.0	-76 to -82	+10.1 to +21.8	+122 to +370	-189.4	-88			
Lourenco et al. (2008) (11)	12	277	HoLRP	-17.7 to -21.7	-82 to -92	+13.4 to +23.0 [b]	+160 to +470 [b]					1a
		270	TURP	-17.5 to -18.7	-81 to -82	+10.1 to +21.8	+122 to +370 [a]					
Kuntz et al. (2008) (12)	60	42	HoLEP	-19.1	-86	+ 20.5	+540	-269.4	-96			1b
		32	OP	-18.0	-86	+ 20.8	+578	-286.7	-98			
Heinrich et al. (2007) (13)	6	140	KTP (80 W)	-10.9 [a]	-55	+ 5.6	+ 43	-65 [a]	-74 [a]			3
Ruszat et al. (2008) (14)	12	302	KTP (80 W)	-11.9 [a]	-65 [a]	+ 10.2 [a]	+121 [a]	-173 [a]	-83 [a]			3
	48	88	KTP (80 W)	-10.9 [a]	-60 [a]	+ 10.2 [a]	+121 [a]	-179 [a]	-86 [a]			
Hamann et al. (2008) (15)	12	157	KTP (80 W)	-13.4 [a]	-65 [a]	+ 10.7 [a]	+135 [a]	-103.4 [a]	-78 [a]			3
Reich et al. (2005) (16)	12	51	KTP (80 W) OA	-13.7 [a]	-68 [a]	+ 14.9 [a]	+222 [a]	-122 [a]	-83 [a]			3

Ruszat et al. (2007) (17)	24	116	KTP (80 W) OA	-13.0	-70	+ 11.3	+140	-103	-80			3
		92	KTP (80 W) CG	-12.7	-71	+12.0	+168	-160	-78			
Ruszat et al. (2006) (18)	24	16	PVP RUR	-11.1	-72			-280	-88			3
		19	PVP NUR	-12.1	-65	+16.2	+228	-131	-85			
Rajbabu et al. (2007) (19)	24	38	KTP (80 W)	-17.2 [a]	-75 [a]	+11.3 [a]	+141 [a]	-85 [a]	-63 [a]			3
Bouchier-Hayes et al. (2006) (20)	12	38	KTP (80 W)	-14.0 [a]	-50 [a]	+12.0 [a]	+167 [a]	-120 [a]	-82 [a]			1b
		38	TURP	-12.9 [a]	-50 [a]	+8.6 [a]	+149 [a]	-82 [a]	-69 [a]			
Bachmann et al. (2005) (21)	6	55	KTP (80 W)	-12.9 [a]	-71 [a]	+11.2 [a]	+162 [a]	-133 [a]	-91 [a]			3
		31	TURP	-12.5 [a]	-72 [a]	+12.2 [a]	+177 [a]	-106 [a]	-88 [a]	-21	-45	
Bouchier-Hayes et al. (2008) (23)	12	46	KTP (80 W)	-16.4 [a]	-65 [a]	+9.8 [a]	+111 [a]	-107 [a]	-83 [a]	-30	-63	1b
		39	TURP	-14.5 [a]	-57 [a]	+10.5 [a]	+118 [a]	-93 [a]	-84 [a]	-27	-44	
Horasanli et al. (2008) (24)	6	39	KTP (80 W)	-5.8	-31	+4.7	+156	-104	-57			1b
		37	TURP	-13.8 [b]	-68 [b]	+11.5 [b]	+225 [b]	-154 [b]	-87 [b]			

† 6-month data; CG = control group; RUR = refractory urinary retention; OA = oral anticoagulation; NUR = no urinary retention

[a] significant compared to baseline (indexed whenever evaluated)

[b] significant difference in favour of indicated treatment

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4.6 Prostate stents

4.6.1 ***Mechanism of action***

The use of an endoprosthesis to preserve luminal patency is a well-established concept, while in 1980 Fabian first describing stenting of the prostatic urethra to relieve BPO (1). Prostatic stents were primarily designed as an alternative to an indwelling catheter in patients unfit for surgery because of co-morbidity. However, prostatic stents have also been assessed by several studies as a primary treatment option in patients without significant co-morbidities 2,3).

A prostatic stent requires a functioning detrusor, so that the bladder still has the ability to empty itself. This is in contrast to an indwelling catheter, which drains the bladder passively (4). Stents can be temporary or permanent. Permanent stents are biocompatible, allowing epithelialisation, so that eventually they become embedded in the urethra. Temporary stents do not epithelialize and may be either biostable or biodegradable. Temporary stents can provide short-term relief from BPO in patients temporarily unfit for surgery or after minimally invasive treatment (MIT) (4).

4.6.2 ***Operative procedure***

Stent insertion is mostly performed in an outpatient setting under local anaesthesia. Prior to stent insertion, the length of the prostatic urethra is measured to determine the stent length. After the patient has been placed in the lithotomy position, the stent is advanced through the urethra until the tip of the prostatic urethral segment is positioned in the bladder. It is important that the stent is not positioned inside the external urethral sphincter as it may cause stress urinary incontinence. To confirm proper positioning, abdominal ultrasonography or cystoscopy is performed. 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. It can be difficult to remove permanent stents in cases of stent migration, stent encrustation or epithelial in-growth, and general anaesthesia is usually needed. In general, antibiotic prophylaxis is not necessary unless there has been a positive urine culture.

4.6.3 ***Efficacy***

There have been several small case studies on a range of stents of different designs and materials, which have provided a low level of evidence for their use. Table 21 describes the most important studies (2,5-9). All studies during follow-up have observed a significant attrition rate. There is only one RCT that has compared two versions of a blind-placement prostatic stent (BPS) for BPO (10), and there have been no studies comparing stents with sham or other treatment modalities. The BPS system is a temporary stent consisting of a soft silicone stent, retrieval line, and delivery device, with the difference between BPS-1 and BPS-2 being an additional 2-cm bulbar segment. This bulbar segment results in a significantly lower migration rate with BPS-2 (5%) compared with BPS-1 (85%), but the bulbar segment also caused significant discomfort (10). BPS-2 also has better symptom scores and voiding function than BPS-1, but only Qmax reached statistical significance. The results from this study appear to indicate that stent design has a critical role in the efficacy and safety of prostatic stents (10).

Permanent stents (UroLume endourethral prosthesis)

The main representative of the permanent stents is the UroLume endourethral prosthesis. A recent systematic review identified 20 case series, with a total of 990 patients who received the UroLume stent (11). The 10 studies that reported symptom scores demonstrated improved symptoms following stent insertion, although

the timing of assessment varied between studies. The reported decrease in Madsen-Iversen scores ranged from 7.9 to 14.3 points, while the IPSS decreased by 10-12.4 points (11). Additionally, the mean Q_{max} increased between 4.2 and 13.1 mL/s following stent insertion. The pooled data from studies with patients using permanent transurethral catheters showed that 84% of patients (148/176) regained the ability to void spontaneously after UroLume treatment, with the mean Q_{max} ranging from 8.8 to 20 mL/s. At 12 years of follow-up, the mean IPSS, Q_{max} and PVR were 10.82, 11.5 mL/s and 80 mL, respectively (12).

Non-epitheliazing (temporary) prostatic stent (Memokath)
The best data on non-epitheliazing prostatic stent are provided by a systematic review of the efficacy of Memokath, a self-expanding metallic prostatic stent (13). In total, 14 case series with 839 patients were reviewed. Analysis of the seven studies reporting symptom scores found that Memokath insertion was associated with a reduction of 11-19 points in the IPSS and a reduction of 9 points in the Madsen-Iversen score. However, it is important to note that the assessment was made at different times after stent placement. Similarly, stent insertion resulted in a Qmax increase of 3 to 11 ml/s, although again the time of assessment was variable after placement (13).

4.6.4 ***Tolerability and safety***

In general, stents are subject to misplacement, migration, poor tolerability because of exacerbation of LUTS, and encrustation (4). The main adverse events immediately following stent placement include perineal pain or irritative voiding symptoms in most patients.

The systematic review of the UroLume reported a 16% failure rate (104/666) within 12 months of insertion, mainly due to stent misplacement or migration (37%) or recurrent obstructive or irritative voiding symptoms (14%). The overall failure rate at 5 years was 27% (50/188 stents), although many patients were lost to follow-up or died with the stent in situ (11). In the study with the longest follow-up, 18% of the patient population (11 men) completed 12 years of follow-up with the Urolume stent in situ, whereas 29 stents were removed (failure rate, 47%) and 22 patients (34%) died of diseases non related to male LUTS.

4.6.5 ***Practical considerations***

In search for the ideal prostatic stent, a range of different stent types has been developed and undergone clinical study. Because of the side effects and high migration rate, prostatic stents have a limited role in the treatment of BPO. Prostatic stents remain an alternative to transurethral catheterization for men who have (recurrent) urinary retention and are at high risk for surgery.

4.6.6 ***Recommendations***

	LE	GR
Prostatic stents are an alternative to catheterisation for men unfit for surgery. Stents may have a role in the temporary relief of BPO after minimally invasive treatment.	3	C

Table 21: Efficacy of stents: key studies

		Symptoms		Qmax (mL/s)		Failure rate (follow-up in months)	LE
Stent	***n***	**Pre-operative**	**Post-operative**	**Pre-operative**	**Post-operative**		
Urolume (P) (2)	91	14.1	4.7	9.3	17.1	Overall	3
	44	R	4.6	R	13.7	15.5% (18 mos)	
Memotherm (P) (5)	123	24.0	6.1*	7.4	16.1*	4% (48 mos)	3
TITAN (P) (6)	85	15.9[a]	9.331	8.59*	11.431	Overall	3
	59	18.0	5.21	R	11.34	19% (24 mos)	
Spanner (T) (7)	30	22.3	7.1	8.2	11.6	0% (2 mos)	3
Memokath (T-P) (8)							
	211	20.3	8.22	NA	NA	23% (7 y)3	3
Horizon Bell-shaped (T) (9)	108	22.0	15.0	9.1	9.6	46% (3 mos)	3

Q_{max} = maximum urinary flow rate (free uroflowmetry); (P) = permanent stent; R = retention; (T) = temporary stent; NA = not available.

* Immediately after insertion; [a] Madsen score; [1] At 2 years; [2] At 3 months.

4.6.7 ***References***

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4.7 Emerging operations

*4.7.1 **Intra-prostatic ethanol injections***

4.7.1.1 Mechanism of action

Absolute (dehydrated, 95-98%) ethanol is injected into the prostatic parenchyma for the treatment of BPHLUTS or BPO. The precise mechanism of action in both humans and animals remains unclear. The use of ethanol was investigated in the canine model and demonstrated the ability of ethanol to cause inflammation, coagulative necrosis with protein denaturation and cell membrane lysis, and, finally, atrophy and ablation of prostatic tissue resulting in cavity formation (1-4). Tissue necrosis was typically wedge-shaped (4). The volume of injected ethanol correlated only moderately with the size of tissue necrosis (4). Intra-prostatic cavity formation appeared in the canine model after 7 days (3).

4.7.1.2 Operative procedure

Liquid dehydrated ethanol or ethanol gel is injected into the prostatic parenchyma with a 20-22 gauge needle either transurethrally, transperineally, or transrectally. The transurethral approach (TEAP or TUEIP) has been used more frequently (5-14) than the transperineal (11,15,16) or transrectal approaches (11).

Specific devices have been developed for the transurethral delivery of ethanol (InecTx™ in the USA and Prostaject™ in Europe) (17). There is no consensus on the number of injection sites or injection volumes, which depend on total prostate volume, urethral length and/or presence of a prostate median lobe, and have ranged from 2 mL to 25 mL of ethanol per patient in different studies (with the injection volume being up to 42% of the volume of the prostate).

Local anaesthesia supplemented by conscious sedation may be considered, although regional or general anaesthesia were chosen by most patients. The procedure is usually completed within approximately 30 minutes. The majority of patients need an indwelling catheter after the procedure.

4.7.1.3 Efficacy

So far, 12 trials (5-16) have been published (Table 22), with the majority having investigated men refractory to medical treatment. Only one trial investigated patients with urinary retention (10). None of these trials was randomized against TURP or other minimally invasive procedures for BPH-LUTS or BPO. Mean follow-up varied among studies from 12 to 208 weeks (3-48 months).

The majority of trials demonstrated a significant reduction in symptoms (IPSS -41% to -71%) and PVR (-6% to -99%) as well as a significant improvement in the maximum urinary flow rate (Q_{max} +35% to +155%) and QoL (IPSS-QoL -47% to -60%). Prostate volume decreased significantly in approximately half the trials (-4% to -45%). After an initial strong reduction in prostate volume, 1-2 years post-operatively prostate size increased again, although LUTS and peak urinary flow remained significantly improved (8). No predictive efficacy parameter or dose-response relationship has been found (9,12).

Several trials demonstrated a considerable number of retreatments within the first year after the procedure (usually treated by a second ethanol injection, TURP, or open prostatectomy). Little is known about the durability of clinical effects later than 1 year after the operation; one trial with a mean follow-up of 3 years showed a retreatment rate of 41% (8).

Table 22: Results of intra-prostatic ethanol injections for treating BPH-LUTS or BPO in men refractory to medical treatment or in urinary retention

Trials	Duration (weeks)	Patients (n)	Change in symptoms (IPSS)		Change in Q_{max}		Change in PVR		Change in prostate volume		Level of evidence
			Absolute	%	mL/s	%	mL	%	mL	%	
Goya *et al.* 1999 (5)	12	10	-10.9[a]	-47	+5.1[a]	+64	-79.8[a]	-62	-2.1	-4	3
Savoca *et al.* 2001 (15)	24	8	-11[a]	-52	+5[a]	+46	-103[a]	-79	n/a	n/a	3
Ditrolio *et al.* 2002 (6)	52	15	-1 6.5	-74	+6.2	+109	n/a	n/a	-21.6	-45	3
Plante *et al.* 2002 (7)	52	5	-9.6[a]	-41	+3.2	+32	-7.6	-6.4	-15.8[a]	-30	2b
Chiang *et al.* 2003 (16)	12 (24)	11	-9.2[a]	-52	+8.2[a]	+155	-203.2[a]	-88	-2.2	-5	3
Goya *et al.* 2004 (8)	156	34	-8.7[a]	-40	+4.4[a]	+65	-65[a]	-70	+2.1	+4	3
Grise *et al.* 2004 (9)	52	115 (94)	-10.3[a]	-50	+3.5[a]	+35	n/a	n/a	-7.4[a]	-16	2b
Mutaguchi *et al.* 2006 (10)[†]	64	16	Spontaneous voiding in 87.5% Mean PVR 60 mL						-19.7[a]	-34	3
Larson *et al.* 2006 (11)	52	65	-9.4[a]	-44	+2.8[a]	+33	n/a	n/a	n/a	n/a	3
Plante *et al.* 2007 (12)*	24	79	-10.6 to -13.4[a]	-47 to -55	+3.2 to +8.1[a]	+37 to +94	-1.2 to -27.3[a]	-1 to -26	-5.6 to -11.2[a]	-13 to -25	2b
Magno *et al.* 2008 (13)	52	36	-13.3[a]	-47	+9.2[a]	+154	-286.4[a]	-99	-12.7	-19	3
Sakr *et al.* 2009 (14)	208	35	-12.1[a]	-55	+11[a]	+186	-32.6[a]	-47	-2.8[a]	-5	3

*Absolute and relative changes compared with baseline are listed with regard to symptoms (IPSS), maximum urinary flow rate (Q_{max}), post-void residual urine (PVR), and prostate volume. [a] = significant compared with baseline (indexed whenever evaluated); [†] = patients with urinary retention; * = three study arms comparing transurethral, transrectal and transperineal injections.*

4.7.1.4 Tolerability and safety

- Frequently reported adverse events included:
- perineal or abdominal discomfort/pain
- bladder storage symptoms (≤ 40%)
- haematuria (≤ 40%)
- urinary tract infection or epididymitis
- urinary retention.

Less frequently reported (< 5%) adverse events included:

- decreased libido
- retrograde ejaculation
- urgency urinary incontinence
- urethral stenosis
- erectile dysfunction.

Animal studies revealed a high percentage of urethral sphincter damage and stress urinary incontinence when ethanol was injected via the perineal route (1), but these complications have not been reported in humans (15,16). One man developed a big bladder stone six months after treatment, most probably due to calcification of sloshed necrotic prostatic masses (18). Two cases of severe complications after ethanol injections have been reported; bladder necrosis required cystectomy and urinary diversion (9).

4.7.1.5 Practical considerations

Intra-prostatic ethanol injections are considered to be a minimally invasive treatment option for patients with BPH-LUTS or BPO. However, the mechanism of action, patient selection and application of ethanol (the number of injection sites and the injection volume) have not been well investigated, severe adverse events occurred in some patients, and long-term results are sparse. Intra-prostatic ethanol injections are therefore still regarded as experimental and should be used only in trials.

Randomized-controlled trials with long-term follow-up comparing ethanol injections with TURP, other minimally invasive procedures, or drugs are needed to be able to judge adequately the value of this treatment modality.

4.7.1.6 Recommendations

	LE	GR
Intra-prostatic ethanol injections for BPH-LUTS due to BPO or BPE are still experimental.	3	
Intra-prostatic ethanol injections should be performed only in clinical trials.		C

4.7.1.7 References

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*4.7.2 **Intra-prostatic botulinum toxin injections***

4.7.2.1 Mechanism of action

BTX is the exotoxin of the bacterium *Clostridium botulinum*. This 150 kDa toxin is the most potent neurotoxin known in humans, and causes botulism (food-borne, wound or infant). Seven subtypes of BTX are known (types A-G), of which subtypes A and B have been manufactured for use in humans.

Experience with intra-prostatic injections for the treatment of BPH-LUTS/BPO exists only for BTX-A. The precise mechanism of action has been evaluated in experimental animals but is not fully understood. BTX-A blocks the release of neurotransmitters (e.g. acetylcholine or norepinephrine) from pre-synaptic nerves (1). BTX-A directly or indirectly reduces LUTS by induction of apoptoses of prostatic (epithelial) cells leading to tissue atrophy and prostate size reduction (2-4), inhibition of sensory neurons in the prostate and reduction of afferent signals to the central nervous system (3), and/or relaxation of smooth muscle cells in the prostatic parenchyma and reduction of BPO (4-6). Down-regulation of □1A adrenergic receptors in the prostate may contribute to smooth muscle cell relaxation (3). The latter two mechanisms are summarized as chemical denervation that possibly has a negative influence on prostate growth.

4.7.2.2 Operative procedure

Under ultrasound visualization, BTX-A can be injected into the prostatic parenchyma transperineally, transurethrally or transrectally, using a 21-23 gauge needle.

The transperineal approach has been described most frequently (7-13); the transurethral (5) and transrectal routes (14, 15) have also been used but applied less often. Botox™ (Allergan, Irving, CA, USA) was employed in all but one study (13).

Different therapeutic doses (100-300 units Botox™ or 300-600 units Dysport™) and dilutions (25-50 units Botox™/mL or 75 units Dysport™/mL) were used in various studies, but doses and dilutions have not been systematically tested. Doses of 100 units Botox™ have been suggested for prostate sizes < 30 mL, 200 units for sizes between 30 mL and 60 mL, and 300 units for sizes > 60 mL (9). For Dysport™, 300 units were used for prostate sizes < 30 mL, and 600 units for sizes > 30 mL were used (13). The majority of patients were treated without anaesthesia, local anaesthesia, or sedation.

4.7.2.3 Efficacy

So far, 11 trials have been published (Table 23) investigating intra-prostatic BTX-A injections in patients with BPH-LUTS who required or were resistant to medical therapy, or patients with an indwelling urethral catheter due to acute or chronic urinary retention (5, 14, 15). Only two trials were randomized, one against injection of saline solution (7), the other against α-blocker therapy (12).

The majority of patients in the published trials received only a single injection of BTX-A and mean follow-up ranged between 12 and 120 weeks (3 to 30 months). All trials reported significant improvements with regard to symptoms (IPSS -39% to -79%) and urinary flow rate (Qmax +27% to +122%), or a decrease of prostate

volume (-11% to -61%). Post-void residual urine decreased in all studies, but reduction was significant in only approximately half of the trials.

BTX-A injection therapy was significantly superior to saline injection in the randomized-controlled trial with regard to symptom and Qmax improvement as well as PVR and prostate volume reduction; all parameters were significantly different compared with baseline or saline solution within the first treatment month (7).

In patients with urinary retention before BTX-A injections, 80-100% of men could void spontaneously within one month of the operation, and maintained voiding throughout the follow-up period.

Little is known about the long-term effects and durability of the treatment; prostate volume seems to increase again after 6-12 months (11,14) despite stable improvements in symptoms, Qmax and PVR. Retreatment rates with BTX-A were as high as 29% (11).

Table 23: Results of intra-prostatic botulinum toxin (Botox™) injections for treating BPH-LUTS, BPO or urinary retention

Trials	Duration (weeks)	Patients (n)	Change in symptoms (IPSS)		Change in Q_{max}		Change in PVR		Change in prostate volume		Level of evidence
			Absolute	%	mL/s	%	mL	%	mL	%	
Maria *et al.* 2003 (7)*	52	30	-14.4[a,b]	-62	+6.9[a,b]	+85	-102[a,b]	-81	-32[a,b]	-61	1b
Chuang *et al.* 2005 (8)*	40	16	-9.8[a]	-52	+5.3[a]	+73	-41	-60	-3[a]	-16	3
Kuo 2005 (5)†	24	10	Spontaneous voiding in 100% of patients		+4.0[a]	+53	-206[a]	-85	-17[a]	-24	3
Chuang *et al.* 2006 (9)*	52	41	-11[a]	-57	+4.1[a]	+59	-68	-42	-7[a]	-13	3
Park *et al.* 2006 (10)*	24	23	-9.3[a]	-39	+2.0[a]	+28	-49[a]	-45	-7[a]	-14	3
Chuang *et al.* 2006 (4)	12	8	-15[a]	-79	+6.5[a]	+73	-155.5	-88	-12.1[a]	-20	3
Silva *et al.* 2008 (14)†*	12 (24)	21 (10)	Spontaneous voiding in 80% of patient		+11.4	n/a	Mean PVR 66 mL		-20[a]	-29	3
Brisinda *et al.* 2009 (11)*	120	77	-13[a]	-54	+5.9[a]	+69	-65[a]	-71	-27.2[a]	-50	3
Kuo and Liu 2009 (12)*	52	30	-7.1[a]	-46	+2.3[a]	+27	+21	+23	-13[a]	-14	1b
Silva *et al.* 2009 (15)†*	72	11	Spontaneous voiding in 100% of patients		+10.5	n/a	Mean PVR 58 mL		-9.2[a]	-11	3
Nikoobakht *et al.* 2010 (13)‡	52	72	-11.3[a]	-57	+7.7[a]	+122	-34[a]	-68	n/a		3

*Absolute and relative changes compared with baseline are listed with regard to symptoms (IPSS), maximum urinary flow rate (Q_{max}), post-void residual urine (PVR), and prostate volume. [a] = significant compared with baseline (indexed whenever evaluated); [b] = significant compared with placebo (saline solution) or αblockers; † = patients with acute or chronic urinary retention; * = Botox™; ‡ = Dysport™.*

4.7.2.4 Tolerability and safety

BTX-A injections were well tolerated in all studies, and no systemic adverse events have yet been reported to have arisen from BTX-A. There was no need for post-operative analgesia.

Adverse events were dysuria in ≤ 19%, haematuria in ≤ 14%, and acute prostatitis in one patient (2%). Urinary retention occurred in ≤ 6%, but many patients received a transurethral catheter or performed clean intermittent

catheterization during the early post-operative period (one week to one month) (8,14).

4.7.2.5 Practical considerations

BTX-A injections into the prostatic parenchyma seem to be a promising and quick minimally invasive treatment modality with low morbidity for patients who are refractory to medical treatment or in urinary retention. However, despite the excellent and homogeneous outcomes in published trials, BTX-A has been injected into only a few patients, and all trials have a limited follow-up. Only two randomized-controlled trials have been published so far. Trials with a larger number of patients, randomization against saline injections, drugs, TURP, or other minimally invasive treatments, and long-term follow-up are therefore necessary to judge adequately the value of intra-prostatic BTX-A injections in the context of other available medical or surgical treatments of BPH-LUTS.

4.7.2.6 Recommendations

	LE	GR
Intra-prostatic botulinum toxin injections for BPH-LUTS due to BPO, BPE or urinary retention are still experimental.	3	
Intra-prostatic botulinum toxin injections should be performed only in clinical trials.		C

4.7.2.7 References

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4.8 Summary treatment

The choice of treatment depends on:

- findings assessed during evaluation
- treatment preferences of the individual patient
- ability of the treatment modality to change assessed findings
- expectations to be met in terms of speed of onset, efficacy, side-effects, quality of life, and disease progression.

Table 24 provides differential information about conservative and surgical treatment options described in the EAU Guidelines on Non-Neurogenic Male LUTS. Note that treatment modalities may be combined leading to different effects.

Table 24: Speed of onset and influence on basic parameters with conservative or surgical treatment modalities for the management of non-neurogenic male LUTS

Treatment	Onset	LUTS	Uroflowmetry (Q_{max})	Prostate size	PVR	Disease progression
Conservative treatments						
Watchful waiting, behavioural treatment	months	+	+	-	-	?
α-adrenoceptor antagonists	days	++	++	-	- / +	+++ (symptoms)
5α-reductase inhibitors	months	+	++	+ - ++	-	+++ (retention)
Muscarinic receptor antagonists	weeks	++ (storage symptoms)	-	-	+ (increase)	?
Plant extracts	weeks	+	- / +	-	-	+
α-adrenoceptor antagonists + 5α-reductase inhibitors	days	++	++	+ -++	- / +	+++ (symptoms + retention)
α-adrenoceptor antagonists + muscarinic receptor antagonists	days	++	++	-	- / +	?
PDE5-inhibitors	weeks	++	-	-	-	?
Surgical treatments	After catheter removal					
TURP–TUIP	hours	++++	++++	+++	++++	++++
Open prostatectomy	hours	++++	++++	++++	++++	++++
TUMT	weeks	+++	+++	++	++	+++
TUNA	weeks	+++	+++	++	+	++
HoLEP	hours	++++	++++	++++	++++	++++
KTP	days	+++	+++	++	++	+++
Prostate stents	hours	++	++	-	+++	?
Ethanol injections prostate	weeks	++	++	+	+	?
Botulinum toxin injections prostate	weeks	++	+++	+	+	?

LUTS = Lower Urinary Tract Symptoms; Q_{max} = maximum urinary flow rate; PVR = postvoid residual urine

Key to Table:

- no influence
+ mild influence
++ moderate influence
+++ strong influence
++++ very strong influence
? unknown

5. FOLLOW-UP

5.1 Watchful waiting – behavioural

Patients who elect to pursue a WW policy should be reviewed at 6 months and then annually, provided there is no deterioration of symptoms or development of absolute indications for surgical treatment. The following are recommended at follow-up visits:

- I-PSS
- Uro-flowmetry and post-void residual urine volume.

5.2 Medical treatment

Patients receiving α-blockers, muscarinic receptor antagonists, or the combination of α-blockers with 5α-reductase inhibitors or muscarinic receptor antagonists should be reviewed 4 to 6 weeks after drug initiation in order 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 months and then annually, provided there is no deterioration of symptoms or development of absolute indications for surgical treatment. The following tests are recommended at follow-up visits:

- I-PSS
- Uro-flowmetry and post-void residual urine volume.

Patients receiving 5α-reductase inhibitors should be reviewed after 12 weeks and 6 months to determine their response and adverse events. Follow-up visits are similar to the above mentioned drugs. The following are recommended at follow-up visits:

- I-PSS
- Uroflowmetry and post-void residual urine volume.

Patients receiving desmopressin, serum sodium concentration should be measured at day 3 and 7 as well as after 1 month and, if serum sodium concentration has remained normal, every 3 months subsequently. The following tests are recommended at follow-up visits:

- Serum-sodium concentration
- Frequency-volume chart

After dose adjustment, follow-up should be repeated likewise.

5.3 Surgical treatment

Patients after prostate surgery should be reviewed 4 to 6 weeks after catheter removal in order to evaluate treatment response and adverse events. If patients have symptomatic relief and are without adverse events no further re-assessment is necessary. The following tests are recommended at follow-up visit after 4 to 6 weeks:

- I-PSS
- Uroflowmetry and post-void residual urine volume.

5.4 Recommendations

	LE	GR
Follow-up for all conservative or operative treatment modalities is based on empirical data or theoretical considerations but not on evidence based studies.	3-4	C

6. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations.

AVP	arginine vasopressin
BOO(I)	bladder outlet obstruction (index)
BPE	benign prostatic enlargement
BPH	benign prostatic hyperplasia
BPO	benign prostatic obstruction
cGMP	cyclic guanosine monophosphate
CombAT	combination of avodart® and tamsulosin
DHT	dihydrotestosterone
EBM	evidence-based medicine
eNOS	endothelial
ER	extended release
GITS	gastrointestinal therapeutic system
IFIS	intra-operative floppy iris syndrome
IPSS	international prostate symptom score
IR	immediate release
MR	modified release
MTOPS	medical therapy of prostatic symptoms
NAION	non-arteritic anterior ischemic optic neuropathy
NO	Nitric oxide
NOS	NO synthases
nNOS	neuronal
n.s.	not significant
OCAS	oral controlled absorption system
PDE	phosphodiesterase
PSA	prostate specific antigen
PVR	postvoid residual urine
Q_{max}	maximum urinary flow rate during free uroflowmetry
QoL	quality of life
RR	relative risk
SHBG	sexual hormone binding globulin
SR	sustained release
t_{max}	time to maximum plasma concentration
t½	elimination half-life
TURP	transurethral resection of the prostate
WW	watchful waiting

Conflict of interest

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