Guidelines on Conservative Treatment of Non-neurogenic Male LUTS

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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, which have been renamed from the EAU Guidelines on BPH (3) to 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. LUTS 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 non-structured 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, according to a classification system modified from the Oxford Centre for Evidence-based Medicine Levels of Evidence, ranging from meta-analysis (Level 1a, highest evidence level) to expert opinion (Level 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, ranging from a strong (Grade A) to a weak (Grade C) recommendation.

The new Guidelines Panel has completely finished the sections on conservative treatment of male LUTS, which are presented here for the first time. The sections on pathophysiology and definitions, assessment and surgical treatment of non-neurogenic LUTS in adult men are still under discussion and will therefore be published later (expected in the autumn of 2010). The Panel on Non-neurogenic Male LUTS intends 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. Watchful waiting 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 men's symptoms may improve spontaneously, while others' 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 strongest predictors of failure.

2.3 Education, reassurance, and periodic monitoring

There now exists level 1b evidence 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	Qmax (mL/s)	PVR (mL)	Level of evidence
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 ($p \leq 0.05$); † significant compared to baseline ($p \leq 0.05$)*
IPSS = International Prostate Symptom Score; Qmax = 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 according to 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 not therefore 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)	t ½ (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 run-in 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 [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] (-3.9 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 intra-operative 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 through to be retrograde, but more recent data demonstrate that it is due to (relative) anejaculation, with a 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	t_{max} (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 [a, b]	
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 [a]	+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 [a]	+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

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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% M_3 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), and
- 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 prostate-specific 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 non-responders, each answer of the IPSS questionnaire was improved during tolterodine treatment irrespective of storage or voiding symptoms (8). Randomized, 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 H_2O, 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, β-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 extracts 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 QoL Score were not statistically different between the groups.

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

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 V_1 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 consistently was 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 has 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 prostate-related 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 Q_{max} (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 (Level 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 (Level 2b; table 12). Maximum trial duration was 25 weeks but the majority of trials were 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 quality of life (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 quality of life, 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 α-blockers 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 residulas 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 quality of life 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 quality of life (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 single-centre 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 Q_{max} 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

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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.

3.9 Summary conservative 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 15 provides differential information about conservative treatment options described in the EAU Guidelines on Non-Neurogenic Male LUTS. Note that treatment modalities may be combined leading to different effects.

Table 15: Conservative treatment options for non-neurogenic male LUTS.

Treatment	Onset	LUTS	Uroflowmetry (Q_{max})	Prostate size	PVR	Disease progression
Conservative treatment						
Watchful waiting, behavioural treatment	(+)	+	(+)	-	(+)	?
α-adrenoceptor antagonists	+++	++	++	-	(+)	+++ (Symptoms)
5α-reductase inhibitors	(+)	+	++	+ - ++	(+)	+++ (Urinary retention)
Muscarinic receptor antagonists	++	++ (Filling symptoms)	-	-	++ (increase)	?
Plant extracts	++	+	(+)	-	- / (+)	+
α-adrenoceptor antagonists + 5α-reductase inhibitors	++	++	++	+ -++	(+)	+++ (Symptoms + retention)
α-adrenoceptor antagonists + muscarinic receptor antagonists	+++	++	++	-	(+)	?
PDE5-inhibitors	++	+	-	-	-	?

Key to Table

Speed of Onset:

(+) Very slow (many months)
+ Slow (few months)
++ Intermediate (weeks)
+++ Fast (days)
++++ Very fast (hours)

Influence:

- No influence
(+) Discrete influence
+ Mild influence
++ Moderate influence
+++ Strong influence
++++ Very strong influence
? Unknown

Abbreviations

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

4. FOLLOW-UP

4.1 Watchful waiting – behavioural treatment

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:

- IPSS
- Uroflowmetry and postvoid residual urine volume.

4.2 Medical treatment

Patients receiving α-blockers, muscarinic receptor antagonists, or the combination of α-blockers with muscarinic receptor antagonists or 5α-reductase inhibitors 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 side-effects, α-blockers, muscarinic receptor antagonists, or the combinations 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:

- IPSS
- Uroflowmetry and postvoid residual urine volume.

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

- IPSS
- 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 3-6 months subsequently. The following tests are recommended at follow-up visits:

- Serum sodium concentration
- Frequency-volume chart.

4.3 Recommendations	LE	GR
Follow-up for all conservative treatment modalities is based on emperical data or theoretical considerations but not on evidence based investigations	3-4	C

5. 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
Qmax	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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