Continuing Medical Education

Current Treatment for Benign Prostatic Hyperplasia

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Summary

Background: Benign prostatic hyperplasia (BPH) is characterized by the occurrence of.disorders of urine storage and bladder emptying. Most men over the age of 60 years are affected to some degree.

Methods: A selective literature search with additional scrutiny of guidelines and meta-analyses.

Results: The management of patients with BPH is complex. Emptying and retention disorders can be treated by various pharmacological and surgical means. Transurethral resection of the prostate (TURP) has long been considered the gold standard for operative treatment. Transurethral enucleation procedures show a better risk profile in some uses, however, and have, above all, largely displaced suprapubic prostatectomy. Numerous innovative treatment options have been developed in recent years, but their long-term effects remain to be determined. These treatment techniques can nevertheless be used in individual cases after thorough discussion with the patient.

Conclusion: The care of patients with BPH should be interdisciplinary. The efficacy and safety of many new developments in the area of pharmacological and minimally invasive treatment remain to be demonstrated in randomized trials.

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Strictly speaking, the definition of benign prostatic hyperplasia (BPH) relates to a purely histological increase in volume of the prostate; only when there is an increase in bladder outlet resistance that affect urodynamics is the term "benign prostatic obstruction" (BPO) used, often also called "bladder outlet obstruction" (BOO) (1). In affected patients, BPO causes various lower urinary tract symptoms (LUTS) which in terms of the differential diagnosis can occur in various diseases, especially diseases of the bladder (e.g., overactive bladder, bladder carcinoma, cystitis), complicating identification of the symptoms and their cause.

The first category is storage symptoms such as pollakiuria (increased frequency of urination), nocturia (urination at night), urinary urgency, and urinary incontinence.

The second category is voiding symptoms, e.g.:

- Reduced, split, intermittent urinary stream
- Dysuria (delayed, difficult, painful urination)
- Postvoid residual urine volume (PVR)
- Need to strain to urinate
- Postmicturition dribble
- Postmicturition symptoms
- Ischuria paradoxa (continuous dribble in overflow incontinence)
- Feeling of incomplete emptying

The course and severity of these symptoms can vary greatly.. They mainly affect older men, with prevalence increasing with age: on average, 50% of men over 60 years of age and 80% of men over 80 years of age experience LUTS caused by BPH (2–4). For this reason, symptomatic BPH is regarded as one

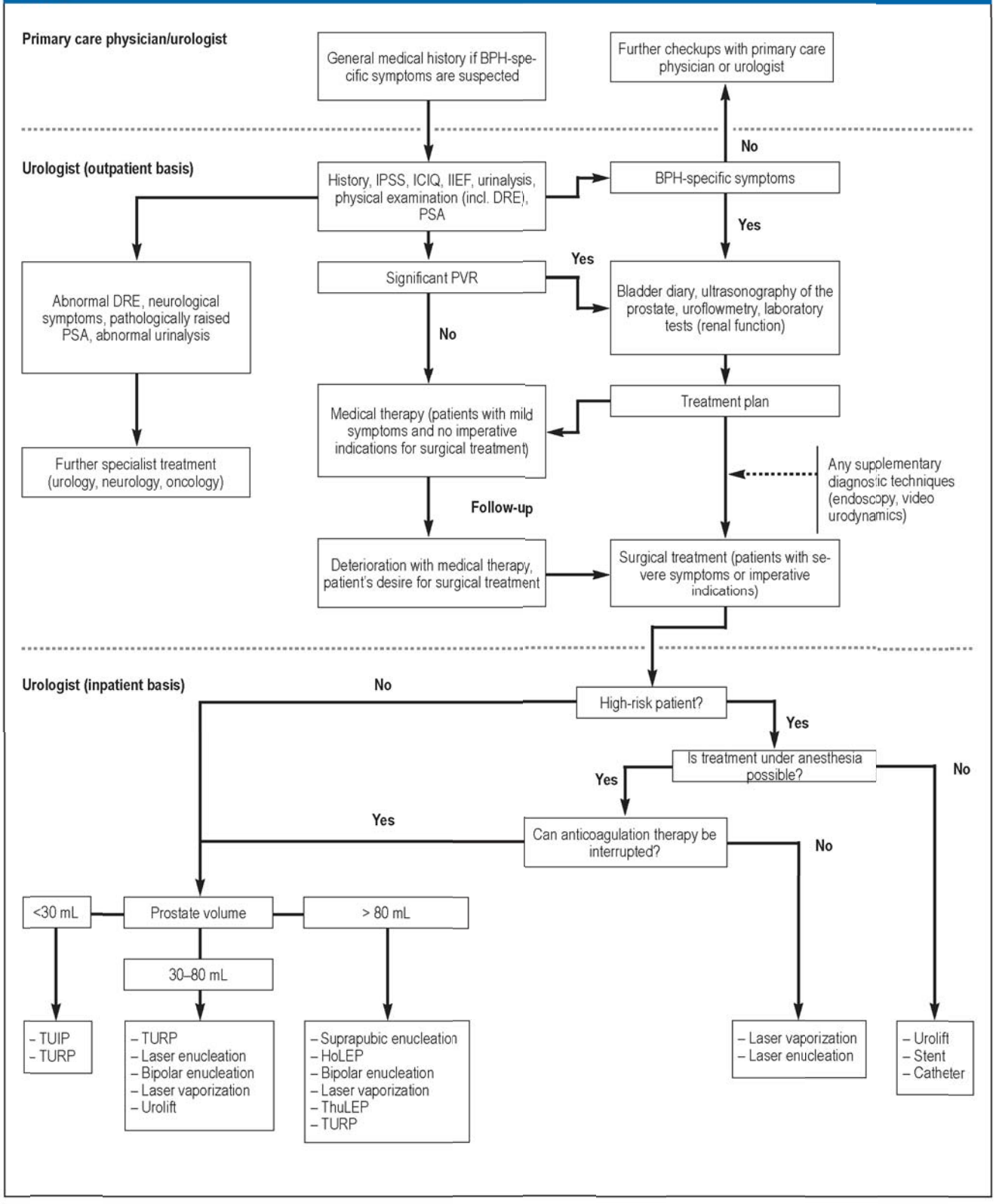
Definition

If a histological increase in volume of the prostate (BPH) leads to lower urinary tract symptoms (LUTS), the term "benign prostatic obstruction" (BPO) or "bladder outlet obstruction" (BOO) is used.

Lower urinary tract symptoms

Lower urinary tract symptoms are divided into two categories: storage symptoms and voiding symptoms.

FIGURE



Flow chart for recommendation medical management of patients with possibly BPH-related symptoms, based on the guidelines of the European Society of Urology [recommended scope of follow-up: history, IPSS, ICIQ, IIEF, urinalysis, physical examination (including DRE), PSA, urinary tract ultrasonography as appropriate] (1)

BPH, benign prostatic hyperplasia; DRE, digital rectal examination; HoLEP, holmium laser enucleation of the prostate; ICIQ, International Consultation on Incontinence Questionnaire; IIEF, International Index of Erectile Function; IPSS, International Prostate Symptom Score; PSA, prostate-specific antigen; PVR, postvoid residual urine; TUIP, transurethral incision of the prostate; ThuLEP, thulium laser enucleation; TURP, bipolar transurethral prostateresection

of the most common disorders in men and, because it is widespread, one that has significant socioeconomic impact (5). Apart from increasing age, risk factors include metabolic syndrome (elevated abdominal fat, elevated plasma glucose, low HDL cholesterol), obstructive sleep apnea, and thyroid dysfunction (6,7).

Learning goals

After reading this CME article, the reader should

- have acquired a basic knowledge of the clinical picture of LUTS caused by BPH.
- be familiar with new drug therapies and their place in clinical treatment.
- be familiar with new surgical treatment procedures and understand their uses and limitations.

Diagnosis

Particularly in men over 50 years of age, micturition-related symptoms should be specifically addressed in the general medical history. Dividing them into storage symptoms and voiding symptoms is helpful for the choice of drug therapy (8). Complications such as urinary retention, recurrent or persistent urinary tract infections (UTIs), renal dysfunction, or suspected malignancy should always prompt referral of the patient for further evaluation by a specialist (*Figure*) (9).

After the initial urological referral, the specific tests outlined below are carried out to determine the severity of the disease and whether active treatment is required.

Special questionnaires are used for the patient history; the most commonly used is the International Prostate Symptom Score (IPSS) questionnaire (also available in German) (*Table 1*) (2).

For continence assessment, the International Consultation on Incontinence Questionnaire (ICIQ), with 13 specific questions, is now widely in use (10). Another aid to objectifying complaints can be a symptom or "bladder" diary. Symptom diaries can provide very accurate information, both quantitative and qualitative, on LUTS in patients with BPH (11).

One of the oldest and simplest examinations is the digital rectal examination (DRE) to assess prostate size and consistency. The physiological volume is approximately 25 mL, with average values increasing in an age-specific manner (12). However, correlation of the volume as measured by DRE to actual size, especially in the case of markedly enlarged glands, is poor (0.4 to 0.9) (13, 14).

TABLE 1

International Prostate Symptom Score (IPSS)*

IPSS question		Possible answers (points)
1.	How often did you have the feeling that your bladder was not completely empty after urinating?	– Never (0) – Less than 1 time in 5 (1) – Less than half of the time (2) – About half the time (3) – More than half the time (4) – Almost always (5)
2.	How many times did you have to urinate a second time within 2 hours?	
3.	How often have you had to stop and start again several times over while urinating (urinary hesitancy)?	
4.	How often have you had difficulty delaying urination?	
5.	How often have you had a weak stream when urinating?	
6.	How often did you need to make an effort or strain to start urinating?	
7.	On average, how often did you get up to urinate during the night (i.e., between going to bed and getting up in the morning)?	– Never (0) – Once (1) – Twice (2) – Three times (3) – Four times (4) – Five times or more (5)
8.	How would you feel if your current symptoms around urination did not change in the future?	– Totally happy (0) – Happy (1) – Mostly happy (2) – A bit unhappy (3) – Mostly unhappy (4) – Unhappy (5)

* 0–7 points: mild LUTS; 8–19 points: moderate LUTS; 20–35 points: severe LUTS (2).
LUTS, lower urinary tract symptoms.

For every patient with BPH a urinalysis should also be performed. The dipstick test usually provides semiquantitative information on the presence of any urinary tract infection, proteinuria, hematuria, and glycosuria. Although the usefulness of routine urinalysis in patients with micturition-related symptoms has been questioned, both the current guideline of the European Association of Urology (EAU) on the management of LUTS (1) and the current recommendations of the National Institute of Health and Care Excellence (NICE) (9) support it.

If either the patient history or the clinical presentation suggests the possibility of renal dysfunction, or if surgery is being considered, renal function should be assessed by determining the serum creatinine concentration and glomerular filtration rate (1, 9).

The widespread use of ultrasound diagnostics in urology allows not just the morphology of the upper urinary tract to be checked (pyelocaliceal system

Prevalence

On average, 50% of men over 60 and 80% of men over 80 have symptoms caused by BPH. Symptomatic BPH is therefore regarded as one of the most common disorders in men and, because it is widespread, one that has significant socioeconomic impact.

Diagnosis

Particularly in men over the age of 50, micturition-related symptoms should be specifically addressed in the general medical history. Classifying them into storage and voiding symptoms is helpful for the choice of drug therapy.

dilatation; thickening of the bladder wall) but also the volume of residual urine to be assessed (physiologic: <50 mL). The medical significance of residual urine in patients who are asymptomatic is disputed. Only clinical checkups are recommended (15). Two large BPH studies, MTOPS (Medical Therapy Of Prostatic Symptoms) and ALTESS (Alfuzosin Long-Term Efficacy and Safety Study), showed that high levels of residual urine were associated with significantly more rapid worsening of BPH symptoms (16, 17). Determining the ratio of residual urine volume to bladder capacity (pathologic: >15%) seems to be most valuable measure to estimate disease severity. In addition, increased post void residual volume (PVR) is regarded as a risk factor for development of a urinary tract infection. However, at present evidence from studies about the causal relationship between BPH and increasing risk of urinary tract infections is inadequate (18, 19).

Noninvasive uroflowmetry (measurement of urinary flow) can be used to investigate functional parameters such as urination volumes, maximum urinary flow rate (Q_{max}, pathologic: <10 mL/s) and the shape of the urine flow curve (physiologic: bell shape). In addition, bladder diaries can provide a more accurate picture of urination volumes and characteristics (frequency and type of urination). Since uroflowmetry can be affected by many factors, this investigation is nonspecific and is not included in the initial diagnostic workup. However, the guideline committee recommends that it should be carried out before the start of medical therapy or any intervention (1).

A particularly important step is to measure the concentration of prostate-specific antigen (PSA). Clinical interpretation of the test result is a complex task that depends on the expertise of the physician in question, and it should therefore be carried out by an interdisciplinary team or a urologist. PSA level, unless influenced by other pathologic processes, correlates with prostate volume (20) and is a strong predictor of prostate growth (21). In addition, baseline PSA is a predictor of risk of urinary retention and surgical risk (16, 17). However, there is no known direct association between BPH and prostate cancer (22), and patients with BPH should be advised about the advantages and disadvantages of prostate cancer screening (23).

Interventional diagnostic techniques should only be used after noninvasive techniques have been exhausted. Interventional techniques include urethrocystoscopy, which is used, for example, in patients with hematuria, urethral stricture, bladder carcinoma, or known anomalies of the lower urinary tract, or those who have previously undergone surgery relevant to the condition. Urethrocystoscopy as a diagnostic procedure should never be considered routine before interventional procedures (24). The same is true of noninvasive urodynamic testing, where pressure sensors are placed in the bladder and rectum and electrodes are placed in the pelvic floor region to measure functional parameters of the lower urinary tract in real time. Although it provides the most detailed description so far of pathological function in BPH, this technique should be reserved for selected cases only (patients with neurologic disorders of the lower urinary tract that may possibly correlate with BPH-related LUTS, such as neurogenic detrusor overactivity, detrusor-sphincter dyssynergia, or hypotonic bladder) (25). The much-respected recent Upstream study showed that measuring bladder pressure does not lead to a reduction in BPH-related surgery (26).

Options for conservative treatment and medical therapy

The main factor in the decision about treatment is, in the first place, the patient's perceived burden of suffering, which is best assessed using the IPSS and Quality of Life (QoL) score. Uroflowmetry results, PVR measurements, and IPSS and ICIQ are all included in the overall assessment, making cut-off values for treatment decisions impracticable. In patients with mild distress, the natural course of the BPH can be initially monitored by watchful waiting (27–29). Patients can also be offered counseling on lifestyle and nutritional changes. The following suggestions can, if followed, have a positive impact on BPH-related symptoms and may potentially slow disease progression (30):

- Avoiding alcohol and caffeine
- Adjusting timing of fluid intake to daily routine
- Ongoing monitoring of symptoms
- Using relaxation exercises and distraction techniques
- Adjusting other medications (especially diuretics)

Drug therapy should be considered if the patient's symptom burden requires it or if initial watchful waiting has not led to satisfactory improvement in symptoms. The choice of drug therapy depends on the symptoms. The most important clinical effects of the various drug classes, their respective adverse effects profile, and recommended follow-up schedules can be found in *Table 2*.

High residual urine volumes

Two large studies on BPH showed that high residual urine volumes were associated with significantly faster progression of BPH-related symptoms.

Decision making

The primary main factor on which treatment decisions are based is the patient's subjective perception of symptom burden, which can best be captured by the IPSS and Quality of Life (QoL) score.

TABLE 2

Main therapeutic effects and adverse effects of drug therapy options and EAU recommended approaches to follow-up (1).

Drug class	Main clinical effects [95% confidence limits](range)	Most important adverse effects (value/range)	Recommended follow-up
Alpha-blocker	Versus placebo: absolute effects Q_{max} 1.9 [0.01; 3.76] to 2.91 [1.05; 4.74] IPSS –5.46 [–8.79; –2.1] to –7.06 [–10.41; –3.71] (e22)	– Asthenia (OR: 1.38; 2.434) – Dizziness (OR: 1.35; 3.06) – Orthostatic intolerance (dizziness, hypotension, or syncope) (OR: 1.42; 3.71) – Intraoperative floppy iris syndrome (IFIS) (OR: 5.5; 393.1) – Ejaculatory dysfunction (retrograde ejaculation, delayed ejaculation, ejaculate volume reduction) (OR: 0.8; 32.5) (e23–e25); *note:* preparations vary greatly)	1. After 4–6 weeks 2. After 6 months, then 3. Once a year Patient history, IPSS, uroflowmetry, residual urine volume Assess: bladder diaries, frequency–volume diagrams
5-Alpha-reductase-inhibitor	Versus placebo: SMD Q_{max} 0.29 [0.22; 0.36] Prostate volume –0.63 [–0.74; –0.52] (e26)	– Reduced libido (2.36%–5%) – Erectile dysfunction (4.53%–7%) – Ejaculatory dysfunction (1%–1.78%) – Gynecomastia (1%–2%) (16, e2, e54).	1. After 12 weeks 2. After 6 months Patient history, IPSS, uroflowmetry, residual urine volume + serial PSA testing (from 6 months) if life expectancy > 10 years or treatment-modifying PCA diagnosis
PDE5 inhibitor	Versus placebo: MD IPSS: –1.89 [–2.27; –0.33] (e3)	– Flushing (OR: 4.888; range: 1.546; 15.459) – Gastroesophageal reflux (OR: 2.214; range: 0.556; 5.123) – Headache (OR: 1.876; range: 1.181; 2.98) – Dyspepsia (OR: 1.85; range: 1.064; 3.216) – Back pain (OR: 1.177; range: 0.731; 1.897) – Sinusitis (1.376; range: 0.428; 4.426) (e28)	See Alpha-blocker
Muscarinic receptor antagonist	Mean ± SD IPSS 9.9 ± 4.6; 16.1 ± 7.1 (e29–e31)	– Dry mouth (up to 16%) – Constipation (up to 4%) – Urinary problems (up to 2%) – Nasopharyngitis (up to 3%) – Dizziness (up to 5%) (1) – Increased residual urine volume (+ 9.6–49 mL) (1, e32, e33)	See Alpha-blocker
β_3-Receptor agonist	50 mg mirabegron vs. placebo: WMD Urinary frequency –0.6Urgency episodes –0.53 (31)	– Hypertension (5.9%–9.2%) – Urinary tract infections (1.4%–5.9%) – Headache (3.2%–4.1%) – Nasopharyngitis (0.9%–3.9%) (e34–e37)	See Alpha-blocker
Vasopressin analog	Versus placebo: MD nocturnal urinary frequency –0.87 [–1.15; –0.60] (e39)	– Headache (up to 12%) – Hyponatremia (up to 4%) – Insomnia (up to 2%) – Dry mouth (up to 3%) – Hypertension (up to 3%) – Abdominal pain (up to 4%) – Peripheral edema (not specified) – Nausea (up to 4%) (e39)	On days 3 + 7 and after 1 month, then periodically (every 3 months for routine values, more frequently for-patients >65 and/or at increased risk of hyponatremia) Serum sodium concentration Frequency–volume diagram
Alpha-blocker + 5-alpha reductase inhibitor	MTOPS: Risk reduction clinical progression 66% [54; 76] (16) ComBAT: risk reduction for clinical progression 44.1% [33.6; 53], (e2)	– Typical adverse effects of both drug classes (see above) – Combination: 28% vs. monotherapy: 19%–21%, (P < 0.001) (e2) During first year 3.4– to 10.6-fold increased incidence (P < 0.001) (e1)	See Alpha-blocker
Alpha-blocker + muscarinic receptor antagonist	Versus alpha-blockers: SMD IPSS storage symptoms –0.28 [–0.4; –0.17] QoL –0.29 [–0.5; –0.07] (e40).	– Typical adverse effects of both drug classes (see above) – Combination: 16.9%–20.1% vs. monotherapy 8.3% (e6) – Increased residual urine volume may occur, but low risk of acute urinary retention (0.7%) (e41)	See Alpha-blocker

AUASS, American Urological Association Symptom Score; EAU, European Association of Urology; IPSS, International Prostate Symptom Score; MD, mean difference; MTOPS, medical therapy of prostatic symptoms; QoL; Quality of Life; OR, odds ratio; PCA, prostate cancer; PDE, phosphodiesterase; SMD, standardized mean difference; WMD, weighted mean difference

In patients with predominantly storage symptoms, muscarinic receptor antagonists and β3-adrenoceptor agonists may be used. Muscarinic receptor antagonists inhibit M3-receptor-mediated contraction of the detrusor muscle of the bladder. Drugs approved for the treatment of BPH symptoms are: darifenacin hydrobromide (darifenacin), fesoterodine fumarate (fesoterodine), oxybutynin hydrochloride (oxybutynin), propiverine hydrochloride (propiverine), solifenacin succinate (solifenacin), tolterodine tartrate (tolterodine), and trospium chloride. If voiding dysfunction worsens, discontinuing drug therapy should be considered. Treatment is strongly recommended for patients with predominantly storage symptoms and a PVR below 150 mL. The β3-adrenoceptor agonist mirabegron, acting directly on the receptor, mediates detrusor muscle relaxation exclusively during the storage phase, thus improving urination frequency, urgency, incontinence, and nocturia (31). However, because existing data were collected primarily in women with an overactive bladder, there is only a weak recommendation for use of the drug in men with predominantly storage symptoms.

Treatment with alpha$_1$-receptor inhibitors (alpha-blockers), phosphodiesterase 5 (PDE5) inhibitors, or 5-alpha-reductase inhibitors may be considered in patients with predominantly voiding dysfunction.

Alpha-blockers such as terazosin, doxazosin, alfuzosin, tamsulosin, and silodosin act by inhibiting norepinephrine-mediated contraction of the smooth muscle cells of the prostate and the bladder outlet, reducing tissue tone (32). Their effect on extraprostatic receptors can lead to floppy iris syndrome during cataract surgery, and the surgeon should be informed in advance that alpha-blockers are being used (*eTable*). Because of their rapid onset of action and efficient improvement of IPSS and Q_{max} scores, they are strongly recommended in patients with moderate to severe LUTS. However, despite bringing significant symptom relief, alpha-blockers do not reduce the risk of urinary retention, disease progression or, hence, the need for surgery (33).

PDE5 inhibitors also lead to reduced prostate smooth muscle tone, in that diminished breakdown of cGMP enhances smooth muscle cell relaxation in the prostate, urethra, and detrusor muscle. This improves IPSS and IIEF (International Index of Erectile Function) scores as erectile function is also influenced. Currently, only tadalafil 5 mg/day is approved for BPH. Numerous contraindications exist, such as nitrate therapy or recent myocardial infarction or stroke, and must be clarified with the patient before therapy is started. Due to their rapid onset of action and functional efficacy, PDE5 inhibitors are strongly recommended in patients with moderate to severe LUTS with or without erectile dysfunction (34).

In patients with predominantly voiding dysfunction who have a prostate volume above 40 mL and wish to start long-term therapy, 5-alpha-reductase inhibitors (finasteride, dutasteride) can be given. These drugs inhibit the enzymatic conversion of testosterone into the biologically important dihydrotestosterone (DHT). Apoptosis is thus induced in the epithelial cells of the prostate tissue, reducing prostate size, PSA levels, and thus progression of hyperplasia (35). However, it takes months for the drug to start to take effect, and for this reason it is only suitable for long-term therapy.

In patients whose predominant symptom is nocturia, the vasopressin analog desmopressin may be used; this mimics the action of the endogenous antidiuretic hormone that promotes water reabsorption and reduces urine production. Compared with placebo, nocturnal urinary frequency can be reduced in the medium term (3–12 months) without a significant increase in adverse effects (36). Monitoring of serum sodium concentration in order to detect hyponatremia early on is essential, especially in patients aged over 65. Regarding herbal preparations (phytotherapeutics), no definite recommendation has so far been made by the European Association of Urology (EAU) (1), because of the lack of clear evidence that these preparations are effective (37–40).

In addition to the existing options for monotherapy, combination therapies can also be considered. When prescribing combination therapy, costs, adverse effects, and possible drug interactions must be assessed and taken into account. It is also important to continuously follow patients to monitor their compliance and the effect of the drugs.

Alpha-blockers + 5-alpha-reductase inhibitors can further increase improvement in LUTS and Q_{max}, so long as increased rates of adverse effects are accepted, and can also reduce the risk of acute urinary retention and the need for surgery. This combination is therefore recommended in patients with moderate to severe LUTS and increased risk of progression (prostate volume >40 mL) (16, e1, e2). Similarly, a combination of 5-alpha-reductase inhibitors + PDE5 inhibitors is also an option (e3). In patients with persistent storage symptoms, further combination (triple therapy) with muscarinic receptor antagonists

The following lifestyle changes can improve BPH-related symptoms:

- Avoiding alcohol and caffeine
- Adapting fluid intake to daily routine
- Ongoing monitoring of symptoms
- Using relaxation exercises and distraction techniques

Predominantly voiding symptoms

Alpha-1 receptor inhibitors (alpha-blockers), PDE5 inhibitors, or 5-alpha-reductase inhibitors may be considered for treating patients with predominantly voiding symptoms.

TABLE 3

Statistical overview of the most important surgical procedures[*1]

Procedure	Prostate size, symptom burden	LE	Main effects Unit, follow-up time	Most important complications (sources of further information)
Transurethral incision of the prostate (TUIP)	<30 mL, moderate–severe	1	**Versus TURP: MD [95% CI], 1 year** IPSS –1.0 [–1.73; –0.27] Q_{max} –2.71 [–5.77; –0.35] (e42)	Bladder neck contracture, Urethral stricture, Disease progression (e42)
Monopolar or bipolar transurethral resection of the prostate (M-TURP)	30–80 mL, moderate–severe	1	**Percentage change, max. 5 years**IPSS –70%, QoL –69% Q_{max} +162%, PVR –77% (e43)	Postoperative bleeding, TUR syndrome, adenoma recurrence (e9, e10, e44)
Bipolar transurethral prostate-resection (TURP)	30–80 mL, moderate–severe	1	**Versus M-TURP: MD [95% CI], 1 year**IPSS –0.24 [–0.39;–0.09],QoL –0.12 (–0.25; –0.02] (e45)	Postoperative bleeding, adenoma recurrence, urethral stricture (e43, e44)
Bipolar vaporization of the prostate (TUVP)	30–80 mL, moderate–severe	1	**Versus TURP: MD [95% CI], max. 3 years**IPSS (SMD) 0.09 [–1.56; 1.73], (e46)QoL –0.286 [–2.806; 2.234] Q_{max} –1.696 [–3.416; 0.024] (e44)	Adenoma recurrence, dysuria, urethral stricture (e44, e46)
Open simple prostatectomy	>80 mL, moderate–severe	1	**Mean ± SD, 5 years**AUASS 3 ± 1.7 (1–9) Q_{max} 24.4 ± 7.4 (11–49) PVR 5.3 ± 11.2 (0–40) (e27)	Intra- and postoperative bleeding, long hospital stay, transient stress incontinence (e8)
Endoscopic enucleation of the prostate	>80 mL, moderate–severe	1	**Versus TURP: MD [95% CI], 1 year**IPSS –0.48 [–1.33; 0.37], QoL –0.14 [–0.37; 0.09]Q_{max} 0.83 [0.26; 1.4] (e10)	Transient stress incontinence, urethral stricture, postoperative bleeding (e10, e38, e44)
Green light laser vaporization of the prostate(80 W, 120 W KTP)	30–80 mL, moderate–severe	1b	**Versus TURP: MD [95% CI], 2 years**IPSS 0.02 [–0.28; 0.32], QoL –0.07 [–0.14; 0.01] Q_{max} 0.74 [–0.8; 2.29] (e10, e13, e44)	Dysuria, postoperative urinary retention, stress incontinence (e10, e13, e44)
Laser vaporization of the prostate 120 W, 980 nm	30–80 mL, moderate–severe	1b	**Mean ± SD, 2 years**IPSS 10.4 ± 8.7 Q_{max} 18.5 ± 2.2 (e47)	Dysuria, postoperative urinary retention, stress incontinence (e47, e49)
Thulium laser vaporization of the prostate (ThuVARP)	30–80 mL, moderate–severe	1a	**Versus TURP: WMD [95% CI], 1 year** IPSS –0.64 [–1.14; –0.13], QoL –0.16 [–0.72; 0.41] Q_{max} –1.19 [–1.89; –0.49] (e48)	Dysuria, adenoma recurrence, transient stress incontinence (e48)
UroLift	30–80 mL, moderate	1b	**Percentage change [95% CI], 5 year** IPSS –35% [–41; –29], QoL –44.4% [–50.5; –37.7] Q_{max} 49.9% [37.4; 62.3] (e50)	Rapid disease progression, preexisting low urinary flow rate, dysuria (e14)
Laparoscopic/robot-assisted simple prostatectomy	>80 mL, moderate–severe	2a	**Median (interquartile range), median 1 year** IPSS 4 (2–5) Q_{max} 22 (20–27) (e51)	Intra- and postoperative bleeding, long hospitalization times, transient stress incontinence (e52)
iTIND (temporarily implanted nitinol device)	<50 mL, moderate	No RCT	**Percentage change ± SD, 3 years** IPSS –19 ± 0.5%Q_{max} +41 ± 1% (e21)	Rapid disease progression, preexisting low urinary flow rate, dysuria (e53)
Aquablation	30 – 80 mL, moderate–severe	1b	**Main change/improvement ± SD, 2 years** IPSS –14.7 ± 7.1 Q_{max} + 11.2 ± 11 (e17)	Intra-/perioperative bleeding, adenoma recurrence (e16-e18)
Rezum	30 – 80 mL, moderate–severe	*2	**Percentage change, 4 years** IPSS –46, QoL –42.9 Q_{max} +49.5 (e15)	Rapid disease progression, preexisting low urinary flow rate, dysuria/UTI (e15)
Prostate artery embolization	30 – 80 mL, moderate–severe	1a	**Versus TURP/SP: MD [95% CI], 1 year** IPSS 3.8 [2.77; 4.83], QoL 0.73 [0.56; 0.91] (e20) Q_{max} –3.62 [–2.9; –4.34]	Preexisting very low urinary flow, iatrogenic compression of blood supply to other organs, insufficient predictive power (e19, e20)

*1 Data about time refer not to experience with the technique concerned, but to follow-up times in prospective, controlled studies with the lowest risk of bias. Data in bold indicate the unit of the values listed below them.

*2 Final evaluation not yet possible.

AUASS, American Urological Association Symptom Score; IPSS, International Prostate Symptom Score; CI, confidence interval; LE, level of evidence; KTP, potassium titanyl phosphate; MD, mean difference; PVR, post-void residual urine volume; Q_{max}, maximum urinary flow rate; QoL; quality of life index; RCT, randomized controlled trial; SD, standard deviation; SMD, standardized mean difference; SP, simple prostatectomy (suprapubic enucleation); TUR, transurethral resection; UTI, urinary tract infection; WMD, weighted mean difference."

TABLE 4

Findings of the meta-analysis by Zhang et al.*

	TURP vs. EEP (favored procedure)	Remarks
Functional results		**Time since operation**
IPSS	Equivalent	24 months
Qmax	EEP	12 months
QoL	Equivalent	12 months
IIEF	Equivalent	24 months
Retrograde ejaculation	Equivalent	24 months (e38)
Perioperative results		
Operative time	TURP	EEP +11.14 min
Length of hospital stay	EEP	HoLEP –24.34 h
Reduction in hemoglobin level	EEP	HoLEP –0.46 g/dL
Reduction in sodium level	EEP	HoLEP –1.45 mmol/L; ThuLEP –1.3 mmol/L
Complications		**Risk ratio (RR; EEP vs. TURP), *P* value (statistically significant: *P* < 0.05)**
Urge incontinence	Equivalent	RR = 1.24; p = 0.13
Stress incontinence	Equivalent	No difference in subgroups; RR = 0.87; *P* = 0.75
Dysuria	Equivalent	No difference in subgroups; RR = 0.48, *P* = 0.26
Hematuria	EEP	No difference in subgroups; RR = 0.37; *P* = 0.01
Blood transfusion	EEP	RR = 0.26; *P* < 0.00001
Bladder neck contracture	Equivalent	No difference in subgroups; RR = 0.82; *P* = 0.64
Urethral stricture	EEP	No difference in subgroups; RR = 0.5; *P* = 0.009

*27 randomized controlled trials, 3283 patients (e10).
EEP, endoscopic enucleation of the prostate; HoLEP, holmium laser enucleation of the prostate; IIEF, International Index of Erectile Function; IPSS, International Prostate Symptom Score; Q_{max}, maximum urinary flow rate; QoL, quality of life; RR, risk ratio; ThuLEP, thulium laser enucleation; TURP, transurethral resection of the prostate.

or β_3-adrenoceptor agonists may also be contemplated (e4).

The combination of an alpha-blocker + a muscarinic receptor antagonist leads to improved quality of life and is more effective than alpha-blocker monotherapy in reducing urinary urgency, IPSS, urinary incontinence, urinary frequency, and nocturia (e5, e6). This combination is recommended in patients with moderate to severe LUTS, residual urine <150 mL, and inadequate improvement of storage symptoms in response to monotherapy. Residual urine volumes should be monitored.

An important aspect of drug treatment in general is patient compliance. Current data show that at the end of 12 months fewer than 10% of patients are taking their prescribed combination therapy (alpha-blocker + 5-alpha-reductase inhibitor), compared to 35% on alpha-blocker and 18% on 5-alpha-reductase inhibitor monotherapy (e7). Apart from adverse effects, other possible reasons for discontining treatment are high expectations on the part of the patient (symptom relief not quick enough or great enough) or inadequate understanding of the long-term effects. This needs to be taken into account when assessing treatment efficacy (e7).

Surgical treatment

Invasive treatment should be considered if medical therapy fails to provide adequate symptom relief or is refused by the patient (relative indication for surgery),

Phytotherapeutics

The European Association of Urology has not yet issued a definitive recommendations regarding herbal preparations, because of the lack of clear evidence that these preparations are effective.

Alpha-blockers + 5-alpha-reductase inhibitors

Alpha-blockers + 5-alpha-reductase inhibitors can further increase improvement in lower urinary tract symptoms and Q_{max}, so long as increased rates of adverse effects are accepted, and can also reduce the risk of acute urinary retention and the need for surgery.

or if any of the following are present: recurrent or refractory urinary retention, overflow incontinence, refractory macrohematuria, dilatation of the upper urinary tract with or without renal insufficiency, recurrent urinary tract infections, or bladder stones or diverticula (absolute indications for surgery).

The procedure chosen depends on the size of the prostate; the patient's general condition and comorbidities, fitness to undergo anesthesia, and wishes; procedure-related adverse effects; the surgical equipment available; and the surgeon's training. In the case of patients on anticoagulation therapy, the primary care physician or cardiologist must also be consulted. The timing of surgery is planned on an individual basis and depending on the clinical situation.

The main clinical effects and adverse effects of all surgical procedures presented below are shown in *Table 3*.

Conventional surgical procedures

Transurethral resection of the prostate (TURP) and suprapubic enucleation procedures have been established as the gold standard in practice. While TURP is mostly used for smaller and medium-sized prostate volumes (up to 80 mL), large adenomas are enucleated by open surgery. However, the latter procedure ("adenoma enucleation" [AE]) is now less frequently used because transurethral enucleation techniques (endoscopic enucleation of the prostate [EEP]) are now becoming increasingly widespread. Evidence-based medicine (EBM) reveals relatively high transfusion (9.5%) and revision (9.8%) rates for TURP for gland sizes greater than 60 g, and also relatively high transfusion rates (7.5%) and prolonged hospital stay (11.9 days) after AE (e8, e9). Transurethral enucleation procedures such as HoLEP (holmium laser enucleation of the prostate), ThuLEP (thulium laser enucleation of the prostate), or BipoLEP (bipolar enucleation of the prostate) have a better safety profile in this respect. Zhang et al. reviewed a total of 27 randomized controlled trials (RCTs) comparing EEP with its subgroups versus TURP (*Table 4*). Reviewing the evidence in a meta-analysis, it appears that technically correct performance of EEP does not depend on the type of energy used (holium, thulium, bipolar current) (e10).

Regarding the learning curve, recent data show that a satisfactory level of competence is reached after 25 to 50 operations. A structured mentoring program seems to allow faster progress (e11, e12).

Vaporization of the prostate by means of certain laser procedures—green light laser, plasma vaporization of the prostate (PVP)– is currently performed less frequently. A meta-analysis showed no significant differences compared to TURP in terms of IPSS, Q_{max}, PVR, quality of life, and erectile function (IIEF score), nor in the incidence of complications such as urinary tract infections, acute urinary retention, bladder neck contracture, retrograde ejaculation, and urethral stricture. PVP showed a significant advantage ($P < 0.05$) over TURP in terms of hemoglobin drop (mean difference in Hb: –1.33 g/dL), length of hospital stay (–1.83 days), catheterization time (–1.25 days), transfusion rate and clot retention (risk ratio [RR]: 0.14 for each), transurethral resection syndrome (RR: 0.19), and capsular perforation (RR: 0.09).

By contrast, PVP was inferior to TURP in terms of operative time (main difference 10.6 min), dysuria (RR: 1.76), and reintervention rate (RR: 1.81) (e13).

Newer surgical procedures

Recently, several new surgical technologies have been developed to give patients effective treatment on an outpatient basis, without general anesthesia and with short recovery times, minimal morbidity rates, preservation of sexual function, and a good safety profile. However, compared with established modes of treatment, these options generally fail to achieve sufficient gland debulking in the long term. Over the past 20 years, a variety of these minimally invasive techniques have been tested, most of which have not become widely used in clinical care to date, despite being investigated from an early stage in high-quality randomized trials.

The procedures presented below all have trademarked names. In prostatic urethral lift, or "UroLift," nitinol-coated implants are inserted under urethrocystoscopic control to compress the prostatic lobes of the prostate, creating a dilated anterior canal within the prostatic urethra. Although the urinary flow rates achieved are lower than those after TURP, the clear advantage is that erectile function and antegrade ejaculation can be preserved. This procedure is thus recommended for patients with urinary symptoms with a prostate size greater than 70 mL without a middle lobe who wish to preserve sexual function (e14).

Rezum is a procedure for convective water vapor energy (WAVE)-based ablation of the prostate in which water vapor causes necrotization of the cells, ultimately leading to volume reduction. To date, only gland volumes up to 80 mL have been studied, and

Invasive therapy should be considered if:

medical therapy fails to provide adequate symptom relief or any of the following are present: urinary retention, overflow incontinence, refractory macrohematuria, dilatation of the upper urinary tract with or without renal insufficiency, recurrent urinary tract infections, or bladder stones or diverticula.

Conventional surgical procedures

Transurethral resection of the prostate (TURP) and suprapubic enucleation procedures have become established as the gold standard of practice.

further RCTs comparing it to a reference technique are needed before a sufficiently clear evidence-based recommendation can be made (e15).

Aquablation—waterjet ablation (AquaBeam)—is based on robot-assisted hydrodissection of the prostate tissue that spares collagenous structures (blood vessels, capsule). Under transrectal ultrasound guidance, the adenoma tissue is removed within limits defined by the surgeon and without generating thermal energy. However, transurethral hemostasis may be required after ablation (e16). Functional outcome at 2 years is comparable to that after TURP, with a lower risk of ejaculatory dysfunction – in a direct comparison, the WATER study showed at 24 months follow-up an anejaculation rate of 10% for aquablation vs. 36% for TURP ($P = 0.0003$) (e17). The procedure is efficient for volumes of 30–80 mL, but long-term follow-up data are still awaited. Peri- and postoperative safety aspects of treatment of adenoma volumes greater than 80 mL also need to be investigated in further studies (e18).

In prostatic artery embolization (PAE), the prostatic arteries are probed using microcatheters under X-ray guidance, and embolization is achieved using intravascular embolic agents, leading to a reduction in size of the prostate. This technically demanding procedure seems to be more efficient for larger volumes (e19). It also requires working with a radiologist and exposes patients to ionizing radiation (e20). For this reason, this procedure is currently carried out only at specialized centers.

A temporarily implanted nitinol device (iTIND), a type of expander consisting of dimensionally stable nitinol wires left in the prostate for 5 to 7 days, induces tissue ischemia by continuous pressure, widening the prostatic urethra and improving IPSS and Q_{max}, with urinary retention-related reintervention rates of 9.9% (e21). However, long-term data from randomized trials are still awaited.

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Conflict of interest statement
Prof. Miernik holds a patent for a device for enucleation of intracorporeal areas of tissue. He has received consultancy fees from Avatera Medical, Karl Storz, Medi-tate, and LISA Laser Products GmbH. He has had conference fees reimbursed by Procept. He has received fees from Richard Wolf for the preparation of medical education events related to the topic of this paper.

Prof. Gratzke has received consultancy fees from Astellas, Ipsen, Janssen, Steba, Bayer, Olympus, Medi-tate, MSD, Astra-Zeneca, and Roche. He was reimbursed for conference attendance fees by Astellas, Olympus and Recordati. He has had travel and accommodation expenses reimbursed by Procept, Olympus, Medi-tate, MSD, Astra-Zeneca, Roche, GSK, and Recordati. He has received fees from Astellas, Amgen, Ipsen, Janssen, Bayer, Takeda, and Medac for the preparation of medical education events related to the topic of this paper. He has received third-party funding from Astellas Pharma, Neotract, Medi-tate, and Recordati for conducting clinical trials. He has received funding from Recordati and Medi-tate for a research project initiated by him.

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New technology

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► **Supplementary material**

For eReferences please refer to:
www.aerzteblatt-international.de/ref4920

eTable:
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- Participation in the CME certification program is possible only over the Internet: cme.aerzteblatt.de.
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Only one answer is possible per question. Please select the answer that is most appropriate.

Question 1

What percentage of men over 60 years old are affected by benign prostatic hyperplasia?

a) 10%
b) 20%
c) 30%
d) 40%
e) 50%

Question 2

How do alpha-blockers used to treat voiding symptoms exert their therapeutic effect?

a) They increase the concentration of cyclic GMP, causing the prostate to relax.
b) They relax the smooth muscle cells of the prostatic urethra, reducing tissue tone.
c) They lead to programmed cell death of the prostatic epithelial cells and thus reduce obstruction.
d) They increase the expression of smooth muscle cells in the bladder and thus improve voiding.
e) They relax the striated muscles of the detrusor muscle, thereby reducing residual urine.

Question 3

What factors does the IPSS questionnaire investigate?

a) Factors relevant to continence
b) Male sexual function
c) BPH-related lower urinary tract symptoms (LUTS) and quality of life issues
d) The psychological state of patients with cancer
e) Lower urinary tract symptoms in children

Question 4

What drug is strongly recommended for the treatment of moderate to severe LUTS?

a) Tamsulosin
b) Pumpkin seed extract
c) Nettle root (*Urtica dioica* radix)
d) Acetylcholinesterase inhibitors
e) Baclofen

Question 5

What is the best procedure for reducing a prostate volume greater than 80 mL?

a) UroLift implantation
b) Transurethral incision of the prostate gland
c) Holmium laser enucleation of the prostate (HoLEP).
d) Femtosecond laser ablation
e) Insertion of a prostate stent

Question 6

What is the pharmacological effect of 5-alpha-reductase inhibitors?

a) They inhibit M3-mediated contraction of the detrusor muscle.
b) They lead via G-protein-coupled inhibition to relaxation of the detrusor muscle.
c) They activate MAP kinase and induce apoptosis of prostate epithelial cells.
d) They inhibit the conversion of testosterone into the biologically active dihydrotestosterone.
e) They inhibit acetylcholine receptors at the motor endplate of prostate smooth muscle cells.

Question 7

What is a common side effect of PDE5 inhibitors?

a) Flushing
b) Reduced libido
c) Dizziness
d) Insomnia
e) Gynecomastia

Question 8

What is a typical complication after transurethral incision of the prostate?

a) Long hospital stay
b) Severe intraoperative bleeding
c) Decreased blood supply to adjacent organs
d) Dysuria
e) Bladder neck contracture

Question 9

What is a risk factor for benign prostatic hyperplasia?

a) Hypertension
b) Renal insufficiency
c) Metabolic syndrome
d) Horseshoe kidney
e) Vasopressin deficiency

Question 10

What is an absolute indication for surgery in a patient with benign prostatic obstruction?

a) Residual urine volume of 30 mL
b) Erectile dysfunction
c) Ejaculatory disorder
d) Bladder diverticulum
e) Overflow incontinence

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Supplementary material to:

Current Treatment for Benign Prostatic Hyperplasia

by Arkadiusz Miernik and Christian Gratzke

Dtsch Arztebl Int 2020; 117: 843–54. DOI: 10.3238/arztebl.2020.0843

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eTABLE

Extended information on adverse effects of alpha-blockers (1)

Most important adverse effects	Quantitative information on adverse effects from selected publications	Follow-up
Asthenia	Tamsulosin OR: 1.38 Alfuzosin OR: 1.42 Terazosin OR: 2.42 Doxazosin OR: 2.434	1. Four to six weeks after the start of therapy 2. Six months after the start of therapy, then 3. Once a year
Dizziness/orthostatic intolerance	Tamsulosin OR: 1.35 Alfuzosin OR: 1.49 Doxazosin OR: 2.89 Terazosin OR: 3.06	
Dizziness, hypotension or syncope	Tamsulosin OR: 1.42 Alfuzosin OR: 1.66 Doxazosin OR: 3.32 Terazosin OR: 3.71 (e23)	
Intraoperative floppy iris syndrome	Tamsulosin OR: 393.1 Alfuzosin OR: 9.7 Doxazosin OR: 6.4 Terazosin OR: 5.5 (e24)	Patient history, IPSS, uroflowmetry, residual urine volume Assessment: bladder diaries, frequency–volume diagrams (in patients with predominantly storage symptoms or nocturnal polyuria)
Ejaculatory dysfunction (retrograde ejaculation, delayed ejaculation, ejaculate volume reduction)	Doxazosin OR: 0.8 Terazosin OR: 1.78 Tamsulosin OR: 8.57 Silodosin OR: 32.52 (e25)	

IPSS, International Prostate Symptom Score; OR, overall ratio