Pharmacological therapy options for patients with benign prostatic hyperplasia and lower urinary tract symptoms

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Abstract

Lower urinary tract symptoms (LUTS) can be found in patients with benign prostatic hyperplasia (BPH). They can be further subcategorized as storage and voiding disorders, comprising symptoms like urinary urgency, an elevated urinary frequency as well as an attenuated urinary stream. Objective parameters like prostate volume, residual urine and blood level of prostate-specific antigen help to determine the patients' individual risk.

Apart from operative therapy, several different pharmacological treatment regimes have been developed, focussing on either symptom relief, disease progression or both.

Common substances for symptom-oriented monotherapies include administration of α_1-receptor blockers and PDE_5-inhibitors (PDE_5-I) for voiding disorders and muscarinic receptor antagonists (MRA) for bladder storage dysfunctions, while 5α-reductase inhibitors (5-ARI) have a greater influence on disease progression.

Recent studies have also demonstrated a synergistic benefit for certain combination therapies of existing pharmacological substances, e.g. for a combination of α_1-receptor blockers and 5-ARI, thus providing the physician and the patient with numerous possibilities of individual treatment regimes.

This aim of this review was to deliver a short overview of current pharmacological treatment strategies in urologic BPH therapy.

Introduction

Benign prostatic hyperplasia (BPH) can be associated with lower urinary tract symptoms (LUTS), subdivided into storage and voiding dysfunctions. These symptoms may be accompanied by benign prostate enlargement and a consecutive bladder outlet obstruction [1]. BPH is a progressive disease, with an increased risk for men at a higher age, higher symptom score, a higher prostate volume and an extended grade of obstruction [2].

Symptom relief, enhancement of life quality as well as the prevention of secondary complications like acute urinary retention, hydronephrosis and infection are central goals of BPH therapy. Aside from operative interventions, there are several options regarding a pharmacological approach, depending on the severity of symptoms and the individual progression risk.

Monotherapy with single substances can be distinguished from a combination therapy with multiple agents. Below, commonly used substances are described in detail, with regard to their onset of effect as well as their impact on symptom relief, disease progression and their individual risk profile [3].

α_1-receptor blockers

A contraction of smooth muscle cells in the bladder outlet and the prostate, caused by a postsynaptical endogenous liberation of noradrenaline and a consequent activation of α1-adrenoceptors, was long thought to elevate bladder outlet resistance and thus cause a higher bladder outlet obstruction [4]. Recent studies showed an only marginal effect of α_1-receptor blockers on the bladder outlet resistance and a more essential impact on afferent nerve fibers as well as on non-prostatic α_1-receptors in the bladder. Furthermore, the different subtypes of the α_1-receptor family (α_{1a}, α_{1b}, α_{1d}) seem to play an important part [5-7].

In Germany, there are several approved α_1-blockers available: alfuzosin, doxazosin, tamsulosin, terazosin and silodosin. While the different substances, given a correct intake in the right dosage, show the same clinical effect, they differ with regard to their selectivity for α_1-receptors, their pharmacocinetic properties and possible adverse events. For instance, tamsulosin and silodosin show a high selectivity for α_{1a}-adrenoreceptors [8].

Many studies have demonstrated the beneficial effects of the α_1-blockers regarding the therapy of BPH and associated LUTS [9]. A change for the better is regularly noted hours to days after start of medication. By objective evaluation of symptoms, using the International Prostate Symptom Score (IPSS) questionnaire and measurement of the urinary stream via uroflowmetry, an improvement of 50 % on the IPSS-Score and an increase of the maximum urinary flow (Q_{max}) by 1.4 -3.7 ml/sec can be registered.

Due to their rapid onset of effect α_1-blockers are often used as a short-term or intermediate-term therapy. While the improvement of symptoms often remains constant over the years, they do not contribute to a reduction of bladder outlet obstruction or disease progression. Also, they do not have an effect on the prevention of acute urinary retention [2].

Most common reported adverse events comprise vertigo, headache, ejaculation disorders, diarrhea and nasal congestion, as well as hypotonic circulatory problems, which is more often found in terazosin and doxazosin and less often in the most recently available silodosin [10, 11]. All adverse events are reversible after discontinuation of medication.
Orthostatic dysregulation predominantly affects patients under antihypertensive medication (such as beta-blockers, ACE inhibitors, calcium channel blockers, diuretics and PDE_5-inhibitors), making a

more continuous therapy surveillance for these patients necessary.

Aforementioned ejaculation disorders often present themselves as a relative anejaculation, most often appearing under therapy with silodosin [8].

A more particular side effect was described in 2005 by Chang and Campbell concerning the „intraoperative floppy iris syndrome“ (IFIS) in patients planned for a cataract operation.
During therapy with tamsulosin an increased mobility of the iris was observed, complicating the operation. Since the IFIS is presumed to appear under all α_1-blockers, these substances should be discontinued 3-5 days before ophthalmologic operations [12].

5α-reductase inhibitors (5-ARI)

Androgenous effects on the prostate are caused by dihydrotestosterone, which is formed out of testosterone under enzymatic impact of 5α-reductase. There are two known isoforms of 5α-reductase, namely types 1 and 2 steroid enzymes [13].
Approved 5-ARI agents in Germany are dutasteride and finasteride, which differ regarding their pharmacological properties as well as their selectivity towards the mentioned enzyme isoforms.
Dutasteride inhibits both type 1 and 2 isoforms, while finasteride only causes an inhibition of type 2. The main effect of 5-ARI is an induction of apoptosis in prostatic epithelial cells, which brings about a reduction of size by 18-28 % as well as a halving of the prostate-specific antigen (PSA) level in the blood after 6-12 months of therapy [14]. Studies have shown comparable results after 12 months for both substances regarding prostate volume, maximum urinary flow and symptom relief. Whether a dual inhibition is associated with a therapeutic benefit after a treatment period of 12 months, has not been clarified so far [15].

Since the therapeutic effects of 5-ARI are to be expected only after 6-12 months, an initial treatment of patients with LUTS in the sense of a monotherapy is contraindicated.
In asymptomatic patients with an elevated progression risk, a treatment with the aim of progression inhibition – with consideration of possible adverse effects – can be discussed.
Significant improvement of symptoms by 15-30 %, a volume reduction of the prostate by 18-28 % and an increased Q_{max} by 1.5-2 ml /sec has been registered under a treatment period of 2-4 years [16]. Especially patients with a high prostate volume (greater than 30 ml) seem to benefit from a 5-ARI treatment. In these patients, besides the improvement of parameters like IPSS, uroflowmetry and prostate volume, the risk for acute urinary retention or an operative intervention could be significantly lowered [2, 17, 18]. Treatment with 5-ARI is to be regarded as a long-term therapy, with a lifelong necessity for the patient to take the medication, making a pretherapeutic thorough discussion with the patient an imperative factor.

Examining the effects of dutasteride, Andriole et al. could show a lowering of incidentally found prostate cancer as well as an improvement with regard to LUTS.
However, the REDUCE study, which examined patients over four years under medication with dutasteride, found a higher incidence of high-risk prostate cancer (Gleason 8-10) in the therapy group.
Analogous to α_1-blockers, adverse events are reversible after substance discontinuation, comprise ejaculatory disorders (about 2 %), loss of libido (about 2 %), erectile dysfunction (4 %) and gynecomastia (1-2 %) [2, 14].

PDE_5-inhibitors (PDE_5-I)

Nitric oxide (NO) is produced by the NO-synthase in different tissues out of L-Arginine.

Given a sufficient concentration, NO diffuses into the cell and stimulates synthesis of cyclic guanosine monophosphate (cGMP), which leads to an activation of protein kinases, ion channels and cGMP-associated phosphodiesterases (PDE), resulting in a relaxation of smooth muscle cells, e.g. in the lower urinary tract [20].
Since PDE activity inhibits cGMP-related effects, PDE-inhibitors (PDE-I) make for a higher intracellular concentration and increased activity of cGMP, leading to an enhancement of smooth muscle relaxation.
11 different isoenzymes of PDE have been identified, so far. Isoenzymes PDE_4 and PDE_5 can be found - beside the cavernous bodies of the penis - in the bladder, the urethra and the prostate [21]. There have been suggestions that PDE_5-inhibition (PDE_5-I) causes a diminished Rho-kinase activity, which leads to reduced inflammation and autonomous overactivity, resulting in an increased perfusion of the pelvis [22].
Sildenafil, tadalafil and vardenafil are approved substances for the treatment of erectile dysfunction in Germany, while sildenafil is also being used in the therapy of pulmonary hypertension.

A study by Rosen et al. reports of a higher risk of libido loss as well as erectile and ejaculatory dysfunction in men with LUTS, making PDE_5-I administration a rational therapy strategy [23]. For all three approved PDE_5-I placebo controlled studies have shown an improvement of symptoms by 17-35 % (measured by IPSS -5.2 - -6.3 points) after 8-12 weeks of therapy. Uroflowmetry showed an enhancement of Q_{max} by 0.32 – 3.2 ml/sec.
The recent approval of the use of tadalafil in men with BPH and patients with both BPH and erectile dysfunction led to an integration of this substance into daily therapy algorithms.
Due to its higher half-life period of 17.5 hours - compared to other PDE_5-I - it is suitable for a „once-a-day“ therapy regime. In one study, which compared oral therapies of tamsulosin 0.4 mg/d vs. tadalafil 5 mg/d, no significant differences could be observed regarding symptom relief or the improvement of maximum urinary flow [25]. Because of missing long-term studies, no final statement can currently be made about the influence of PDE_5-I on disease progression. Patient satisfaction under PDE_5-I therapy seems to be high, presumably due not only to the symptom relief concerning LUTS, but also to the additional positive effects on erection and ejaculation [26]. A meta-analysis by Gacci et al. demonstrated a special benefit for younger patients with a lower body-mass-index (BMI) and distinct LUTS [27].

Adverse events in PDE_5-I are rare. Compared to placebo, patients reported a higher occurrence of side effects like headaches, dyspepsia, rhinitis, lumbago and flush [27].

Muscarinic receptor antagonists (MRA)

There are 5 known muscarinic receptors in the human body, with 80 % of M_2-receptors and 20 % of M_3-receptors to be found in the bladder and the bladder outlet.
These postsynaptic receptors are activated by acetylcholine and are targets of MRA, which primarily inhibit M_3-receptors and consecutively the muscular contraction of the bladder [28].

About 40-50 % of patients with BPH do not have a bladder outlet obstruction. Those men suffer from bladder storage dysfunctions and a so called „overactive bladder (OAB)“ [1].
OAB symptoms include urinary urgency, nycturia and increased urinary frequency. About a third of patients with OAB suffer from urge incontinence, also known as „wet-OAB“. Beside special behavioral therapies, treatment with MRA is a standard procedure in those patients.

Studies with an administration of tolterodine (4 mg/d) over a period of 12 weeks have

shown an improvement regarding micturition frequency, urge incontinence, nycturia and IPSS [29].
Another study by Kaplan et al. examined patients with no symptom improvement under α_1-blockers, who were given tolterodine 4 mg/d, leading to a significant enhancement of IPSS, Q_{max} and a reduction of residual urine volume after micturition [30].
Known adverse effects comprise oral and pharnygeal dryness, constipation, nasopharyngitis and vertigo. Frequency of side effects, which are all reversible after discontinuation of medication, depend on receptor distribution and administered substance.
In patients with confirmed bladder outlet obstruction MRA are contraindicated due to the possibility of acute urinary retention, although this danger has never been proven in various studies.

Side effects are fully reversible after discontinuation, differences in occurring adverse events depend on the affinity of a substance to different muscarinic receptors. While usage of MRA in patients with bladder outlet obstruction is contraindicated due to the possible danger of acute urinary retention, this particular fact has never been confirmed in studies.

Phytotherapeutic agents

Phytotherapeutic agents for the treatment of BPH include several extracts of different plants, such as:

Saw palmetto fruit (Saba serrulata or *serenoa repens)*
Nettle root (Urtica dioica)
Pumpkin seeds (Curcubita pepo)
Rye pollen (Secale cereale)
South African Star Grass (Hypoxis rooperi)

While there are several studies, which tested the efficacy of certain phytotherapeutic agents, an evidence-based comparison of those studies is not possible, due to the differences in used dosages and in the extraction procedures of active substances. This also applies to combined preparations of different substances.
None of the publicated studies could demonstrate a positive effect on bladder outlet obstruction, prostate volume or disease progression.
The „Complementary and Alternative Medicine for Urological Symptoms (CAMUS)“-study examined the effect of „serenoa repens“ in a dosage of 320 mg/day on LUTS in 329 patients, in comparison to placebo, over a period of 72 weeks.
The study, apart from methodological flaws and missing objective parameters like urinary flow and prostate volume, could not show statistically significant results.
Based on this lack of evidence, there is no recommendation given by the guidelines for a therapy with phytotherapeutic agents in patients with BPH, at the moment [31, 32].

Combination therapies

A different, still not regularly implemented treatment strategy, is the combination therapy of different substances with the idea of a synergistic effect between independent pharmacologial mechanisms, with the goal to attain both risk progression and symptom relief.

1. <u>α_1-blockers/5-ARI</u>

A benefit of a α_1-blocker/5-ARI combination therapy in patients with a prostate volume greater than 30-40 ml could be shown in large, prospective multi-center studies („MTOPS/CombAT“).
Compared to a treatment with a single substance, combination therapy led to significant symptom relief, a gain in maximum urinary flow and a reduction of prostate volume, which is associated with a reduced disease progression [2, 33].
An individual pretherapeutic discussion with each patient is necessary, due to the summed up side effects of both substances.

An early combination therapy with dutasteride and tamsulosin, compared to a monotherapy with tamsulosin after an unsuccessful „watchful waiting“ approach, has been evaluated in the CONDUCT study by Roehrborn et al., in which patients, beyond the medicinal therapy, received lifestyle consultation.
Based on the evaluated parameters, the early combination therapy was associated with significantly better results [34].

A different study by Nickel et al. examined the effect of finasteride after 3 and 9 months, following the discontinuation of the α_1-blocker in a preceding combination therapy.
No deterioration of IPSS after 3 and 9 months could be shown, leading to the conclusion that a discontinuation of an initially administered α_1-blocker in a combination therapy has no negative effect on symptomology [35].
On grounds of the delayed onset of effect of 5-ARI agents, the combination therapy is also to be regarded as a long-term treatment concept, including an individual discussion with the patient about the occurrence of adverse effects over a life-long period.

2. α_1-blockers/MRA

As mentioned earlier in the article, patients with BPH may also show bladder storage dysfunctions. Only a few randomized controlled trials have examined a combination therapy of α_1-blockers and MRA.
One study by Kaplan et al. compared a combined treatment of tamsulosin and tolterodine both against a monotherapy with mentioned substances and additionally against placebo.
Concerning micturition frequency, urge and incontinence rate, the combination therapy showed a significantly better outcome compared to the other study arms [36].
The α_1-blocker/MRA combination can be adminstered both as a primary and also as a secondary "add-on therapy". If irritative symptoms persist under an initiated α_1-blocker, the addition of a MRA remains a possibility.

3. α_1-blockers/PDE_5-I

So far, no official recommendation by the guidelines for a combination therapy of α_1-blockers and PDE_5-inhibitors exists, due to missing study data and major flaws in existing trials [32]. However, this treatment concept may be considered in individual cases.

4. PDE_5-I/5-ARI

Comparison of a combination of finasteride and tadalafil, each in a daily dosage of 5 mg and over a period of 6 months, versus a monotherapy with finasteride vs. placebo was the subject of a study by Casabe et al. A significant reduction of IPSS and an improvement of storage and voiding dysfunctions as well as an increase of general life quality for the study arm of the combination treatment could be registered.
Additionally, in sexual active patients improvement of erectile function could be noted.
Thus, finasteride-related side effects like erectile and ejaculatory dysfunctions were significantly lowered in the group with a combined therapy of PDE_5-I and 5-ARI [37].

Tab. 1: Effect of different therapeutic substances - as mono- and combination treatment regimes - on certain parameters in management of BPH (modified after current EAU guidelines)

Therapeutic	Onset of effect	LUTS	Qmax	Prostate volume	Residual urine	Disease progression
α_1-blockers	hours - days	++	++	-	(+)	+++ (symptoms)
5-ARI	months	+	++	+ - ++	(+)	+++ (acute urinary retention)
MRA	weeks	++ (storage disorder)	-	-	++ (increase)	?
Phytotherapy	weeks	+	(+)	-	-	+
PDE_5-I	weeks	+	+	-	-	?
α_1-blockers + 5-ARI	days	++	++	+ - ++	(+)	+++ (symptoms and acute urinary retention)
α_1-blockers + MRA	days	++	++	-	(+)	?

Abbreviations: 5-ARI – 5α reductase inhibitors **;** MRA – muscarinic receptor antagonists **;** PDE_5-I – phosphodiesterase inhibitors **;** LUTS – lower urinary tract symptoms

Practical tips and conclusion:

A conservative, pharmacological treatment of patients with BPH and LUTS requires a careful diagnostic work-up. Only by an exact quantification of symptoms the selection of reasonable therapy concepts is ensured.

Decisions concerning a suitable treatment depend on the sort and extent of symptoms, the impact of those symptoms on the patients' life quality, their progression risk and also their sex life.

Advantages and drawbacks of each pharmacological therapy, listed in detail in *Tab. 1*, taking all possible adverse effects as well as treatment costs into account, have to be discussed with the patient beforehand.

A suggestion for a risk-stratified therapy algorithm is displayed in *Fig. 1*.

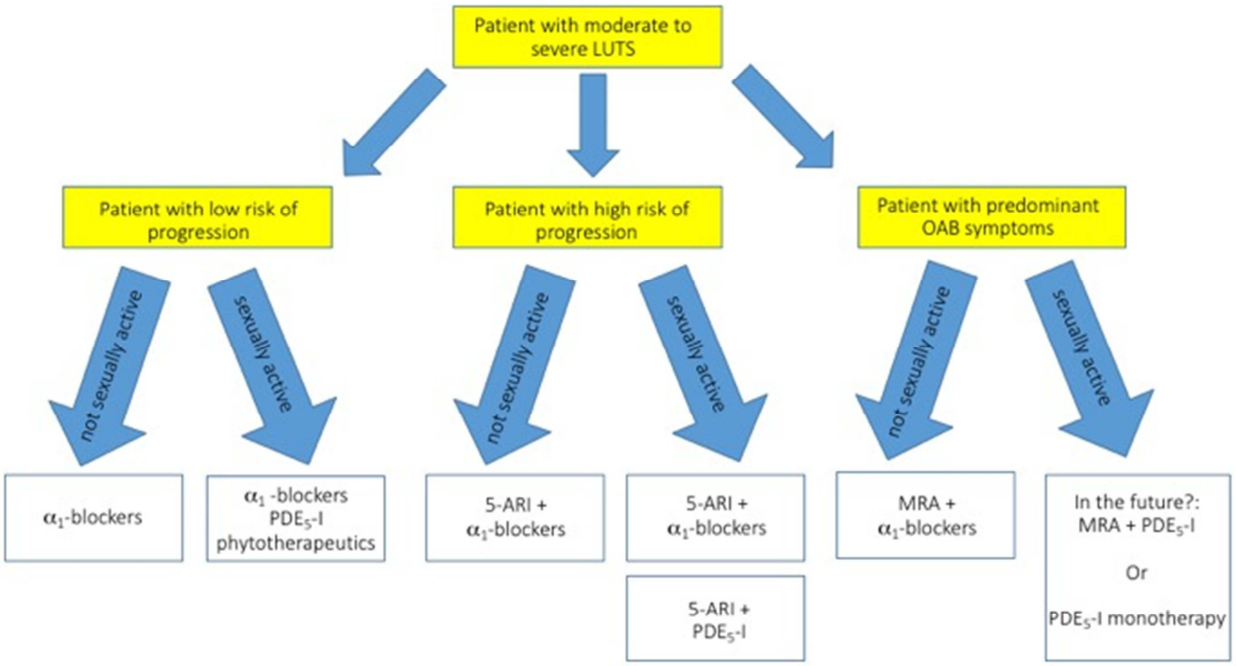
Pharmacological treatment is an adequate therapy option for BPH, when mandatory criteria for an operative approach have been excluded. Treatment concepts include monotherapies and combination therapies. A thorough diagnostic work-up, containing evaluation of symptoms, determination of the serum PSA level, the grade of obstruction, prostate volume and patient age are necessary requirements before therapy start.

While α_1-blockers and PDE_5-I lead to a quick symptom relief, 5-ARI have a positive effect on disease progression. MRA are the treatment of choice, when bladder storage disorders are involved. An official

recommendation for the application of phytotherapeutics can currently not be given. Combined regimes aim to derive a benefit from the included single substances.

An individual approach to different patients seems to be an essential factor, as BPH and accompanied LUTS often present themselves as a disease with many faces.

Fig. 1: Recommendation for a risk-stratified approach in BPH and LUTS therapy



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