Medical therapy for benign prostatic hyperplasia: a review

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Introduction: *Benign prostatic hyperplasia (BPH) is a common disease that affects men as they age. Historically the treatment has been primarily surgical in nature, but over the past 25 years significant advances in medical therapy have been made, sparing some men from interventional procedures.*

Materials and methods: *This article highlights the current state-of-the-art with respect to medical therapy for lower urinary tract symptoms secondary to BPH (BPH-LUTS) including a review of landmark studies and recent areas of research in the field.*

Results: *Alpha blockers are considered first line when treating BPH-LUTS in men with small prostates and 5-alpha reductase inhibitors (5-ARIs) are recommended in men with large symptomatic prostates. While, phosphodiesterase-5 (PDE-5) inhibitors are the mainstay of erectile dysfunction therapy, they also play a role in treating BPH-LUTS. If men have persistent irritative storage symptoms after first line BPH therapy then overactive bladder (OAB) medications can be added or substituted. Combination therapies can be used to provide short term symptom relief with long term disease management.*

Conclusions: *Medical therapy remains the main treatment option for men suffering from BPH-LUTS. Numerous medical options are available that can be tailored to meet the individual's needs depending on their personal and prostate characteristics. An algorithmic approach, as we have defined within this article, can be a helpful guide to this decision-making process.*

Key Words: BPH, benign prostatic hyperplasia, benign prostatic obstruction, medical therapy, medical management, 5-ARI, PDE-5 inhibitor, alpha blocker, overactive bladder, OAB

Introduction

Prostatic enlargement secondary to benign prostatic hyperplasia (BPH) resulting in lower urinary tract symptoms (LUTS) is a common disease experienced by 50% of men 60 years of age or older and 80% of men 80 years of age or older.[1] With prostate enlargement the resistance to urinary flow through the prostatic urethra is increased, resulting in LUTS such as urgency, frequency, nocturia, weak stream, double voiding, and hesitancy. Symptoms can also be created due to increase in the smooth muscle tone at the bladder neck and in the prostatic capsule in men with smaller prostates (i.e., < 30 cc). With continued growth of the prostate and progression of the urinary symptoms, a man may eventually develop acute urinary retention. At this point, resulting hydronephrosis and renal damage are serious possibilities as well as the need for surgery. The prevalence of overactive bladder (OAB) in patients with BPH is estimated at 45%.[2] Compared with surgical management for BPH, medical management is much more contemporary with significant advances in the past 25 years.

This article aims to provide a comprehensive review of the literature pertaining to the medical management of BPH and to distill the information into clinical pearls and suggestions that can help to guide the specialist.

Discussion

Prostate-specific antigen (PSA) is correlated with prostate volume when cancer isn't present.[3] A digital rectal exam (DRE) is recommended along with PSA measurement to suggest prostate cancer risk as well as estimate prostate volume. It has been shown that DRE and prostate volume are significantly correlated

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but DRE routinely underestimates the size of larger prostates.[4] Given that all prostate cells produce PSA, both PSA and DRE are important tests to quantify the severity of BPH and its risk of progression over time.

The American Urological Association (AUA) created and validated a symptom index for BPH also known as the International Prostate Symptom Score (IPSS) which features seven questions encompassing frequency, nocturia, weak urinary stream, hesitancy, intermittence, incomplete emptying and urgency with a maximum total score ranging between 0 and 35.[5] A score less than 8 signifies mild symptoms, while scores of 8-19 signify moderate symptoms, and scores of 20 or greater indicate severe symptoms. The IPSS has become a common tool to evaluate symptoms before and after BPH treatments. An eighth question provides information about quality of life (QoL) relating to urinary symptoms and more importantly the degree of bother the patient is experiencing, which may indicate his potential level of acceptance of management suggestions.[6]

Alpha blockers

The development of alpha adrenergic blockers (α blockers) follows a course from least uro-receptor selective and most likely to cause bothersome side effects (especially vascular side effects such as orthostatic hypotension), to most uro-selective with a more tolerable side effect profile. Alpha blockers relax the smooth muscle present in the prostate and bladder neck thereby reducing the resistance to urinary flow.

The first generation of α blockers was considered non-selective and was associated with a large number of cardiovascular and gastrointestinal side effects. The second generation of α blockers including terazosin (Hytrin) and doxazosin (Cardura) require dose titration due to their cardiovascular impact and risk of hypotension. The third generation α blockers, including tamsulosin (Flomax), alfuzosin (Xatral, Uroxatral) and silodosin (Rapaflo), are better tolerated and don't require dose titration.[7]

A Cochrane review evaluating terazosin for BPH found significant improvement in urinary symptoms as measured by IPSS score and urinary flow rate, with efficacy comparable to other α blockers.[8] The most common side effects were dizziness, asthenia, headache and postural (orthostatic) hypotension. A subsequent Cochrane review assessing tamsulosin for BPH found similar results, with tamsulosin providing a small to moderate improvement in urinary symptoms and flow versus placebo.[9] The noticeable effects of α blockers on urinary symptoms are seen within 1 week of starting the medication.[10]

A study by Moon et al specifically appraised the efficacy of the most recently approved α blocker, silodosin (8 mg), for BPH in 100 men at multiple centers. This study considered men who were 50 years of age or older and had an IPSS score of 20 or greater, indicating severe LUTS.[11] Over 12 weeks, there was a significant improvement in IPSS scores, QoL and maximum urinary flow rate. The change in post void residual (PVR) was not significant and ejaculatory dysfunction was present in 13% of patients.

A large multi-center European study by Chapple et al involved 955 men (≥ 50 years old, IPSS ≥ 13 and a urine maximum flow rate (Qmax) > 4 mL/s and ≤ 15 mL/s) randomized to silodosin 8 mg, tamsulosin 0.4 mg or placebo for a period of 12 weeks.[12] Improvement in IPSS and QoL was equally significant in both tamsulosin and silodosin groups over placebo. Only silodosin significantly decreased nocturia over placebo. Peak flow was surprisingly increased in all groups, with the α blockers not showing significant improvement over placebo. The incidence of ejaculatory dysfunction was 2% with tamsulosin and 14% with silodosin, but only 1.3% of sildosin-treated men discontinued the medication for this reason. Noted discontinuation rates were small in all three groups (2.1% sildosin, 1.0% tamsulosin, and 1.6% placebo). Silodosin and tamsulosin appear to be equally efficacious, with silodosin having a higher incidence of ejaculatory dysfunction, which may or may not be bothersome to the patient.

Although there is very little difference in the overall efficacy of the α blockers, the side effect profile and need for titration are some of the reasons for differences in physician and patient preferences.[13] An overview of α blockers used for the treatment of BPH-LUTS can be found in Table 1.

5-alpha reductase inhibitors

Dihydrotestosterone (DHT) is a metabolite of testosterone after conversion by the enzyme 5-alpha reductase and is the driving force behind the growth of the prostate. 5-alpha reductase inhibitors (5-ARI) inhibit the conversion of testosterone to DHT. The two commonly used 5-ARIs are finasteride (Proscar) and dutasteride (Avodart). Despite both being 5-ARIs, finasteride acts only on type 2 of the 5-alpha reductase enzyme while dutasteride acts on both type 1 and type 2 of the 5-alpha reductase enzyme. The additional enzymes impacted by dutasteride contribute to its larger clinical reduction in men's DHT levels. Despite this, a study by Nickel et al comparing

TABLE 1. **LUTS due to symptomatic obstruction: small prostate (< 30 cc)**

Indication	Name (brand)	Dose	Action	Side effects/notes
Symptomatic BPH	Terazosin (generic)	1 mg-20 mg daily at bedtime	Alpha blocker; non uro-selective	Start with low dose to test for "First-Dose" syncope; dizziness, tachycardia, orthostatic hypotension, headache; rhinitis, asthenia. Take before bed. Titrate to balance efficacy versus side effects at weekly intervals; Fast response 3-7 days. Terazosin may also be used to treat hypertension.
Symptomatic BPH	Doxazosin (Cardura, generic, Cardura XL-USA)	1 mg-8 mg daily, titrate; XL 4 mg w/ breakfast meal	Alpha blocker; non uro-selective	Same as above. Doxazosin (immediate release) may also be used to treat hypertension.
Symptomatic BPH	Alfuzosin (Xatral-Canada; Uroxatral-USA, generic)	10 mg daily w/food	Alpha blocker; more uro-selective	Dizziness; headache, asthenia; less cardiovascular effects since more selective; less ejaculatory dysfunction versus tamsulosin.
Symptomatic BPH	Tamsulosin (Flomax CR, generic CR, generic SR)	CR: 0.4 mg daily SR: 0.4 mg-0.8 mg daily w/food	Alpha blocker; more uro-selective	Ejaculatory dysfunction; rhinitis and occasional asthenia.
Symptomatic BPH	Silodosin (Rapaflo)	4 mg-8 mg daily w/food	Alpha blocker; most uro-selective	Highest rate of ejaculatory dysfunction (among alpha blockers). Reduce dose to 4 mg daily if CrCL 30-50 mL/min.
Symptomatic BPH	Tadalafil (Cialis)	5 mg daily	PDE-5 inhibitor	Headache, dyspepsia, back pain, nasal congestion. Contraindicated in patients treated with nitrates. May be used as monotherapy if small prostate, or in combination with 5-ARI to treat irritative voiding symptoms and ED (as an alternative to an alpha blocker and 5-ARI combination).

LUTS = lower urinary tract symptoms; BPH = benign prostatic hyperplasia; CR = controlled release; SR = sustained release; CrCL = creatinine clearance; PDE-5 inhibitor = phosphodiesterase-5 inhibitor; 5-ARI = 5-alpha reductase inhibitor

1630 men randomized to receive finasteride (5 mg) or dutasteride (0.5 mg) over a period of 12 months, found no difference in terms of prostate volume reduction, LUTS severity and urinary flow.[14] There was no difference in side effects between the two groups, with the most common adverse effects being impotence (8%), decreased libido (5%) and ejaculation disorders (2%). The reason for this lack of differentiation may have been because of the fact that the prostates were quite large, the impact on the shrinkage of the prostate is slow and the study only lasted for 1 year.

TABLE 2. **LUTS due to symptomatic obstruction: large prostate (> 30 cc)**

Indication	Name (brand)	Dose	Action	Side effects/notes
Symptomatic BPH with an enlarged prostate	Finasteride (Proscar, generic)	5 mg daily	5-ARI (Type 2 only)	Decreased libido, decreased volume of ejaculate, erectile dysfunction, gynecomastia, breast tenderness. Slow response 3-6 months. May reduce PSA level by 50% over 6 months.
Symptomatic BPH with an enlarged prostate	Dutasteride (Avodart)	0.5 mg daily	5-ARI (Types 1 and 2)	Same as above. Approved for use alone or in combination with tamsulosin.
Symptomatic BPH with an enlarged prostate	Tamsulosin with dutasteride (Jalyn)	1 tab daily w/food	Alpha blocker with 5-ARI (Types 1 and 2)	Fixed single dose combination of dutasteride (0.5 mg) and tamsulosin (0.4 mg).

LUTS = lower urinary tract symptoms; BPH = benign prostatic hyperplasia; PSA = prostate-specific antigen; 5-ARI = 5-alpha reductase inhibitor

Finasteride has been shown in large numbers of men (n = 3040) to reduce the risk of BPH surgery and acute urinary retention (AUR) as well as improve symptoms over placebo throughout 4 years of treatment.[15] This provides evidence for a 5-ARI's ability to change the progression of BPH and be a possible alternative to surgical management.

In another 4 year trial comparing dutasteride to placebo, similar results were found demonstrating significant symptom response, prostate volume reduction, reduced progression of the disease, and a lower incidence of the need for surgery. All measures were statistically significant.[16] An overview of the 5-ARIs used for the treatment of BPH-LUTS can be found in Table 2.

Phosphodiesterase-5 inhibitors

Phosphodiesterase-5 inhibitors (PDE-5 inhibitors) act by increasing levels of cyclic guanosine monophosphate (cGMP) by inhibiting the actions of phosphodiesterase-5 resulting in smooth muscle relaxation, which is mediated by nitric oxide (NO) release.[17] PDE-5 inhibitors were first approved for treatment of erectile dysfunction (ED) but recent work has shown that the nitric oxide pathway is also at least partially responsible for LUTS associated with BPH in the aging male.[18]

The International Index of Erectile Function (IIEF) questionnaire is a validated measure containing 15 questions that are used to evaluate erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction.[19] It has become a commonly used tool in BPH studies where PDE-5 inhibitors are evaluated.

Several studies have shown the improvement in urinary symptoms secondary to BPH with the use of tadalafil (Cialis), a PDE-5 inhibitor. Porst et al reported the results of a 12 week trial where men with BPH-LUTS were randomized to receive either placebo or tadalafil (5 mg).[20] The tadalafil group experienced a significant improvement in LUTS demonstrated by reduction in IPSS scores compared to placebo. The improvement was apparent after 1 week and significant after 4 weeks. Another 12 week study by Egerdie et al evaluated results from men with BPH-LUTS who were treated with tadalafil (2.5 mg), tadalafil (5 mg) or placebo.[21] Only the 5 mg dose resulted in significant improvement of IPSS scores over placebo. Both mentioned studies showed significant improvement in IIEF scores with either dose of tadalafil. A dose finding study by Roehrborn et al found that 5 mg of tadalafil provided the best risk-benefit profile.[22] It was also noted that no dose of tadalafil resulted in significant changes to peak urinary flow rate compared to placebo. In 2012, tadalafil 5 mg (Cialis) was approved by Health Canada for the treatment of BPH-LUTS. Please see Table 1 for additional information regarding tadalafil.

A post-hoc analysis by Oelke et al evaluated the speed of onset of BPH-LUTS improvements with tadalafil 5 mg.[23] An analysis of four prior trials showed IPSS score improvement in two thirds of patients,

with at least 50% of responders showing significant improvement at the 1-week mark and at least 70% exhibiting improvement at 4 weeks. The speed of onset of PDE-5 inhibitors is comparable with α blockers.

Another study by Oelke et al involving 511 men with BPH-LUTS were randomized to receive placebo, tamsulosin (0.4 mg) or tadalafil (5 mg).[24] After 12 weeks, IPSS scores improved similarly for both tamsulosin and tadalafil over placebo. BPH impact index was improved at both 4 weeks and at 12 weeks, equally, for both tamsulosin and tadalafil over placebo. The IIEF score was improved for tadalafil compared to placebo but not tamsulosin. The results of this study show similar efficacy for the treatment of BPH-LUTS with either tamsulosin or tadalafil but only tadalafil provides improvement in erectile function.

These results have added another treatment approach for the male patient with a small prostate who was treated with an α blocker and still has frequency or urgency, and may have some ED. PDE-5 inhibitors may also be used to primarily treat LUTS/ED, if the patient has a small prostate and the physician does not believe there is any obstruction.[25]

PDE-5 inhibitor combination therapies

With evidence supporting the use of PDE-5 inhibitors for the treatment of BPH-LUTS, there has been growing interest in combination therapies involving PDE-5 inhibitors and 5-ARIs.

A study of 695 men with BPH-LUTS by Glina et al evaluated the effects of treatment with tadalafil (5 mg) plus finasteride (5 mg) compared to placebo plus finasteride (5 mg).[26] The men were randomized into the two treatment groups with some men having pre-existing ED and others not. Using the IIEF to identify men with impaired erectile function, it was determined that combined treatment with tadalafil and finasteride was associated with significant improvement of BPH-LUTS symptoms, regardless of whether the men had pre-existing ED or not.

Combination 5-ARI and alpha blocker therapy

The initial combination therapy approaches used an α blocker and 5-ARI which in theory offered both short term and long term medical management.

The MTOPS study by McConnell et al compared 3047 men randomized into four groups; placebo, finasteride (5 mg), doxazosin (4 mg-8 mg), or combination therapy with finasteride plus doxazosin.[27] The results indicated that combination therapy resulted in a greater reduction of disease progression and symptom improvement scores compared to either monotherapy group. The reduction in risk of urinary retention and BPH-related surgery was only significant in the combination therapy and finasteride groups, but not the doxazosin group. This evidence is significant, showing that α blockers do not slow the progression of the disease, but only treat symptoms. It also demonstrates the efficacy of combination therapy over monotherapies.

The 4 year results of the CombAT study (n = 4844) published by Roehrborn et al included men who had a PSA ≥ 1.5 ng/mL, a prostate volume (PV) ≥ 30 cc and an IPSS score of at least 12.[28] Patients were randomized into three groups where they would receive tamsulosin (0.4 mg), dutasteride (0.5 mg) or both. At 48 months, combination therapy resulted in significantly reduced IPSS and improved QoL compared to tamsulosin monotherapy in all subgroups (PV, PSA, age, body mass index (BMI)). Combination therapy also reduced IPSS significantly more than dutasteride monotherapy but only in the lower baseline PV (< 60 mL) or PSA level (< 4 ng/mL) subgroups. QoL was improved with combination therapy over dutasteride in all PSA groups and in those with a PV of 40 mL-60 mL. Overall the CombAT data supports the use of combination therapy for improvement of LUTS and QoL. Intuitively, the 5-ARI appears to be the move effective therapy over time, in men with larger prostates (> 30 cc).

Most guidelines today suggest that "degree of bother" is a significant factor in the recommendation for medical therapy. It appears that in men with large prostates, the QoL improvement and patient satisfaction is significant with combination therapy.[29]

In the PROACT study, Nickel et al sought to compare the 3 month durability of LUTS improvement in 275 men after removal of only the α blocker following 9 months of combination therapy (finasteride 5 mg and an α blocker).[30] A subset (n = 124) of these patients continued on finasteride monotherapy for a total of 9 months after the discontinuation of the α blocker. The results demonstrated that both durations of monotherapy (3 months and 9 months) were equivalent to combination therapy in terms of LUTS determined by IPSS scores. This study demonstrated the durability of 5-ARI monotherapy following initiation with combination therapy. This supports the treatment approach of using both an α blocker to gain control of symptoms in the short term and discontinuation once the 5-ARI has sufficiently shrunk the prostate.

Barkin et al performed a similar trial called SMART (Symptom Management After Reduction of Therapy), this time testing withdrawal of the α blocker tamsulosin after only 6 months of combination

therapy with tamsulosin and dutasteride. At month 9 (3 months after discontinuation of tamsulosin), the patients were asked if they "felt the same, better or worse now" compared to 3 months ago. Three months later (month 12), they were asked the same question. At month 9, 76% of patients felt the same or better. At month 12, 92% of the 76%, felt the same or better.[31]

Both trials suggested that α blocker withdrawal was possible. However, long term combination trials of 4 years still demonstrated a benefit of the combination of the 5-ARI and the α blocker, compared to the 5-ARI alone. This would suggest that if there is no compelling reason such as side effects or cost, to stop the α blocker, that there is benefit to maintain combination therapy.[32]

Roehrborn et al published the 2-year results of the CONDUCT study (n = 742), which compared fixed dose combination therapy (dutasteride 0.5 mg and tamsulosin 0.4 mg) with watchful waiting plus initiation of tamsulosin (0.4 mg), if subsequent IPSS score remained the same or worsened with time.[33] Both groups of patients were given lifestyle and fluid management advice. The treatment naïve male population was selected based on IPSS score (8-19), PSA and prostate volumes to target men who had moderately symptomatic BPH and were at risk of progression. Results show that early treatment with combination therapy resulted in improved and lasting urinary QoL and IPSS scores compared to men in the watchful waiting plus possible treatment group. This study reinforces the belief that an α blocker and 5-ARI offered earlier in the course of the disease provide symptom relief and help prevent the progression of the disease.

Overactive bladder

With such a large portion of BPH-LUTS men experiencing OAB (45%)[2] and their associated storage symptoms, it is important to consider this therapy as part of BPH-LUTS management.

Tolterodine (Detrol), an antimuscarinic, has been used to treat OAB outside the realm of BPH for some time. A trial by Chung et al evaluated the use of extended release (ER) tolterodine in men (n = 137) with storage symptoms and BPH.[34] The men were randomized to be treated with or without tolterodine ER (0.4 mg), in combination with an α blocker and/or a 5-ARI. The IPSS, QoL and peak urinary flow rate were equal in both groups. The only difference was with regard to IPSS storage symptoms, where the tolterodine group was significantly improved over the group that did not receive tolterodine. This study helps to illustrate the benefits of using an antimuscarinic in men with BPH-LUTS who have bothersome storage symptoms.

Fesoterodine (Toviaz) was evaluated as add-on therapy in men with persistent storage symptoms following 6 weeks of treatment with an α blocker, in a study by Kaplan et al.[35] A total of 943 men were randomized to receive either fesoterodine 4 mg or placebo. Fesoterodine dose escalation and reduction was done at week 4 and week 8, respectively, at the behest of the patient. At 12 weeks the fesoterodine group had significantly improved frequency and OAB bother score compared to placebo. Urinary urgency was not significantly different between the two groups and urinary retention was noted in 2% of the fesoterodine group and < 1% of the placebo group. Dry mouth (fesoterodine 21%, placebo 6%) and constipation (fesoterodine 6%, placebo 2%) were the most common side effects. This study helps to illustrate the role for an antimuscarinic following α blocker therapy in men who have continued storage symptoms, as might be found in men with BPH and OAB.

A recent prescription review study in over 10,000 men with BPH-LUTS, who were refractory to α blocker monotherapy and treated with an antimuscarinic agent, suggested that the greatest treatment persistence was found with the combination of solifenacin and tamsulosin.[36]

A newer OAB medication, mirabegron (Myrbetriq) a beta-3 agonist, was recently approved for use in treating OAB in Canada. Studies evaluating it specifically for men with BPH are limited. A study by Otsuki et al evaluated 52 men newly diagnosed with OAB and 45 OAB men who were unresponsive to antimuscarinics.[37] Each group was given mirabegron 50 mg for 8 weeks. Recently diagnosed OAB patients treated with antimuscarinics were used as a control. Both groups had significant improvement in IPSS score and OAB symptom score over the course of the study. There was no difference between either of the groups and the control, indicating similar efficacy to antimuscarinics. Adverse events were reported in 8.4% of patients, with dry mouth being most common. No serious adverse events were reported. This study lacked a placebo group and was relatively small. Despite this, mirabegron appears to have similar efficacy to antimuscarinic agents with an improved side effect profile.

Mirabegron is the first in its class and appears to have a profound impact on OAB symptoms, without the anti- cholinergic side effects. It also appears to be very safe in the elderly.[38] An overview of medications used for the treatment of OAB or residual irritative storage symptoms is provided in Table 3.

TABLE 3. **Overactive bladder or residual irritative storage symptoms after benign prostatic hyperplasia therapy**

Indication	Name (brand)	Dose	Action	Side effects/notes
Overactive bladder	Darifenacin extended release (Enablex)	7.5 mg-15 mg daily	Antimuscarinic	Maximum 7.5 mg/day in patients with moderate hepatic impairment (Child Pugh B) or when co-administered with potent CYP3A4 inhibitors; no dose adjustment required in renal impairment. May be better tolerated by elderly patients since does not cross blood brain barrier.
Overactive bladder	Fesoterodine (Toviaz)	4 mg-8 mg daily	Antimuscarinic	Maximum 4 mg/day if CrCL < 30 mL/min or if combined with potent CYP3A4 inhibitors. Not recommended for use in severe hepatic impairment (Child Pugh C). No dose adjustments required in elderly patients.
Symptoms of bladder instability associated with voiding	Oxybutynin immediate release (Ditropan, generics)	5 mg daily to QID (max 20 mg daily)	Anticholinergic	Titrate to efficacy versus side effects.
Overactive bladder	Oxybutynin ER (Ditropan XL)	5 mg-30 mg daily	Anticholinergic	Not studied in renal or hepatic impairment. Crosses blood brain barrier.
Overactive bladder	Oxybutynin transdermal patch (Oxytrol)	One patch applied twice per week	Anticholinergic	Not studied in renal or hepatic impairment. Oxytrol 36 mg patch delivers oxybutynin 3.9 mg/day. Apply to the abdomen, hip, or buttock; rotate application sites.
Overactive bladder	Oxybutynin gel 10% (Gelnique)	Apply 1 gram (one sachet) to skin daily	Anticholinergic	Apply to the abdomen, upper arms/shoulders, or thighs; rotate application sites daily.
Overactive bladder	Solifenacin (Vesicare, generics)	5 mg-10 mg daily	Antimuscarinic	Maximum 5 mg/day if CrCL < 30 mL/min, or if moderate hepatic impairment (Child-Pugh B), or if combined with potent CYP3A4 inhibitors.
Overactive bladder	Tolterodine (Detrol)	1 mg-2 mg BID	Antimuscarinic	Maximum 1 mg BID for patients with impaired hepatic or renal function. No safety studies for doses of 8 mg/day.
Overactive bladder	Tolterodine long acting (Detrol LA)	2 mg-4 mg once daily		Maximum 2 mg once daily for patients with impaired hepatic or renal function. No safety studies for doses of 8 mg/day.
Overactive bladder	Trospium (Trosec-Canada, Sanctura, Sanctura XR-USA)	20 mg BID XR: 60 mg daily	Antimuscarinic	Recommended dose of Trosec in severe renal impairment (CrCL 15-30 mL/min) is 20 mg daily at bedtime; Sanctura XR is not recommended for use in patients with CrCL < 30 mL/min. Minimal blood brain barrier crossing.
Overactive bladder	Mirabegron (Myrbetriq)	25 mg-50 mg daily	Beta-3 agonist	Maximum 25 mg/day if Cr CL 15-30 mL/min, or if moderate hepatic impairment (Child-Pugh B), or if combined with drugs metabolized by CYP2D6 with a narrow therapeutic index.

All of the above anticholinergic/antimuscarinic medications have similar side effects (e.g., dry eyes, dry mouth, constipation) and are contraindicated in narrow angle glaucoma. Drugs should be taken for at least 30 days to obtain maximum impact and balance side effects. CrCL = creatinine clearance

TABLE 4. **Nocturia (high volume) and nocturnal enuresis**

Indication	Name (brand)	Dose	Action	Side effects/notes
Nocturia	Desmopressin ODT (Nocdurna-Canada)	Daily dose (at bedtime): Female: 25 µg; Male: 50 µg	Anti-diuretic hormone	Fluid restriction should be observed. Gender specific dose that obtained maximum response. Not recommended for use if baseline sodium < 135 mEq/L.
Primary nocturnal enuresis	Desmopressin ODT (DDAVP MELT-Canada)	120-240 µg daily (1 hour before bedtime)	Anti-diuretic hormone	Restricted fluid intake is recommended a few hours before administration, especially 1 hour before, and until the next morning (at least 8 hours) after administration.
Nocturnal enuresis	Desmopressin (DDAVP tablets, generics)	0.2 mg daily (1 hour before bedtime)	Anti-diuretic hormone	A restricted fluid intake is recommended a few hours before administration, especially 1 hour before bedtime.
	Imipramine (generic)	25 mg-50 mg nightly	Central suppressant	May cause drowsiness. Similar side effect profile as anticholinergic/ antimuscarinic medications.

ODT = orally disintegrating tablet

Desmopressin

Nocturia is a storage urinary symptom that can have significant impact on a patient's sleep and quality of life. Desmopressin (Nocdurna) was studied in 385 men who were randomized to 50 µg desmopressin oral disintegrating tablet (ODT), 75 µg desmopressin ODT, or placebo.[39] Desmopressin significantly reduced the number of nighttime voids, improved sleep quality and QoL. The authors recommended the minimum effective dose (50 µg) for treatment of nocturia in men. This opens up the possibility of targeting nocturia in men with BPH who are especially bothered by their nighttime symptoms. Previously, there was a major concern of the development of hyponatremia in the patients treated with this type of agent. However, the study demonstrated significant safety as long as the baseline sodium was greater than 135 mEq/L.

Desmopressin (Nocdurna) is indicated for "high volume" nocturia. In contrast, nocturnal enuresis (bed wetting) can also be treated with desmopressin, but in a different preparation that requires very careful monitoring. An overview of medications used for the treatment of nocturia and nocturnal enuresis can be found in Table 4.

Guidelines

The 2010 AUA guideline[40] recommends watchful waiting in men who don't have bothersome urinary symptoms and suggests an α blocker (2nd or 3rd generation) as initial therapy, if the prostate volume is less than 30 cc. The AUA recommends 5-ARIs only in patients who have confirmed enlarged prostates (greater than 30 cc) and significant bother. Combination 5-ARI and α blocker therapy is supported and there is no mention of PDE-5 inhibitors. The use of saw palmetto is not recommended due to the lack of evidence. Saw palmetto (Permixon) seems to be quite popular in Europe.

The 2010 Canadian Urological Association (CUA) guideline update features similar recommendations however they specifically do not recommend the use of PDE-5 inhibitors due to lack of current evidence.[41]

The more recent European Association of Urology (EAU) guideline recommends the use of antimuscarinics for storage symptoms, PDE-5 inhibitors in addition to an α blocker, and 5-ARIs as monotherapy and in combination if the prostate volume is greater than 40 cc.[42] It is important to note that guidelines have been updated at varying times and this is likely the cause of the differences.

Author's pearls

There are a growing number of options for the specialist treating patients with BPH-LUTS, Figure 1. Our belief is that first line therapy should be either an α blocker or PDE-5 inhibitor as they offer quick onset and equivalent treatment of BPH-LUTS in the small prostate. It is important to ensure the patient knows these treatments are not altering the course of

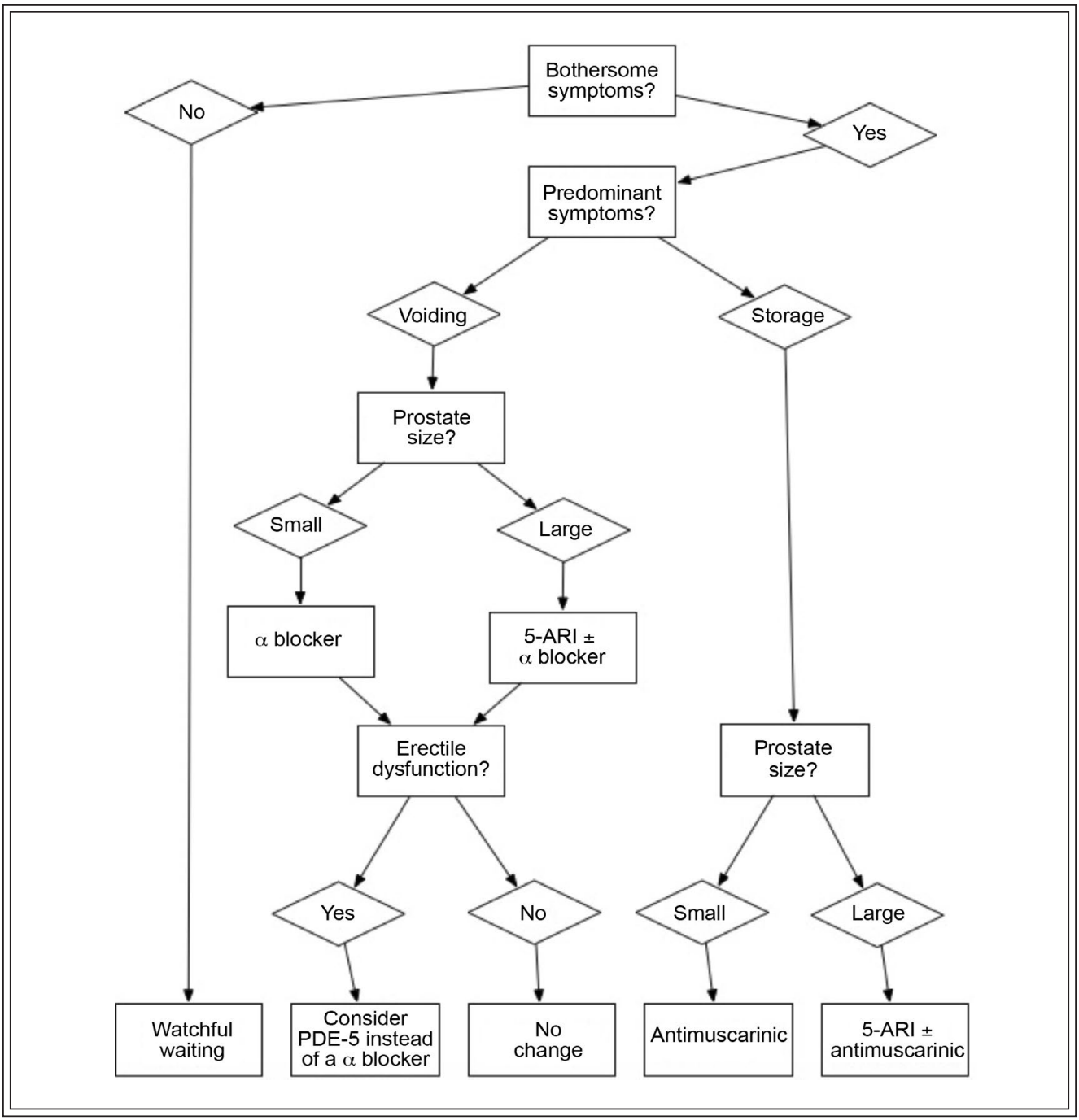

Figure 1. An algorithmic approach to the decision-making process.

their disease, merely treating symptoms. Mention of ED should support the use of a PDE-5 inhibitor over an α blocker. For men with a large prostate, use of a 5-ARI should be considered. The speed of onset will be slower than an α blocker or PDE-5 inhibitor but 5-ARIs improve urinary symptoms, reduce risk of acute urinary retention, and decrease the likelihood of surgical intervention by slowing the natural course of the disease. With combination therapy, after continued use of a 5-ARI, discontinuation of either the PDE-5 inhibitor or α blocker may be considered if the patient wishes.

Specific storage urinary symptoms may be managed with an antimuscarinic or beta-3 agonist, and bothersome nocturia can be targeted with desmopressin.

It is imperative that consideration be made for the degree of symptom bother and the number of medications a patient may already be taking.

Disclosure

Dr. Brandon Van Asseldonk has no disclosure.
Dr. Jack Barkin is a speaker and investigator for Glaxo, Actavis, Pfizer, Astellas, Merus Labs, Neotract and Merck.
Dr. Dean Elterman is a consultant/honoraria for Allergan, Astellas, American Medical Systems, Coloplast, Pfizer and Lilly. □

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