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REVIEW ARTICLE

Review of medical management of BPH

SINGH I

ABSTRACT

Aim: The aim of this study is to review the literature regarding the medical management of benign prostatic hyperplasia (BPH), with emphasis on the current mechanistic insights and drugs, so as to provide an update and present recent data to the urologists, surgeons, and clinicians involved in managing the BPH disease.

Methods: The National Library of Medicine and PubMed were searched for major published data and trials on the medical management of BPH using the key words benign prostatic hyperplasia, medical management, lower urinary tract symptoms (LUTS), α-blockers, 5-α reductase inhibitors, phytotherapy, and evidence-based medicine. Important landmark trials published in the last 15 years were analysed and tracked for recent changes, newer drugs, and medical therapies currently being used to manage BPH.

Results: Major randomised, placebo-controlled landmark trials involving the three major prescriptions, namely α-adrenergic blockers, 5-α reductase inhibitors, and phytotherapeutic agents, were reviewed and discussed.

Conclusions: Medical management of LUTS due to BPH is undoubtedly the first choice of BPH therapy, and it has drastically reduced the number of patients that were initially treated by surgery. Combination drug therapy is currently the most efficacious means to prevent BPH progression in terms of patient quality of life and morbidity. Successful medical management of BPH needs an integrated approach tailored to the patient's symptoms so as to achieve a durable and sustained realistic goal.

Key words: Benign prostatic hyperplasia, LUTS, α-adrenergic blockers, 5-α-reductase inhibitors, phytotherapy, evidence-based medicine

Introduction

Benign prostatic hyperplasia (BPH) is the non-malignant enlargement of prostate gland owing to stromal and epithelial proliferation.

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Hyperplasia of the prostate begins at 45 years, with the incidence increasing with age, viz. 8% of men being symptomatic at 40 years, 50% of men at 50–60 years, 70% of men at 70 years, and 100% of men at 80 years [1],[2]. It is also the commonest benign neoplasm of men [3], significantly affecting the quality of lives of many men world over. Advances in the understanding of the receptors and various growth mechanisms involving the prostate and lower urinary tract symptoms (LUTS) have resulted in the emergence of medical

management as a preferred initial modality to treat this condition and a consequent reduction in the need for surgery in the management of symptomatic BPH. The present manuscript attempts to holistically review and discuss the current literature, mechanistic insights, and drugs being used to medically manage the BPH disease.

MECHANISTIC INSIGHTS AND NEWER DEVELOPMENTS IN THE α-ADRENERGIC RECEPTORS

All α-adrenergic receptors (α-ARs) are G-protein-coupled trans-membrane glycoprotein receptors that mediate catecholaminergic actions in the sympathetic nervous system (act by binding to norepinephrine) [4]. Based on their binding sites (prazosin ~high-affinity sites), these were initially divided into a and b subtypes; later these a-receptors were further subdivided into α_1 and α_2 receptors, and finally the α_1-ARs were sub-classed into α_{1a}, α_{1d}, and α_{1b} (current terminology). According to the International Union of Pharmacology (IUPHAR), three native α_1-ARs (α_{1a}, α_{1b}, and α_{1c} exist – based on their prazosin high-affinity sites – older terminology] and their cloned counterparts (α_{1a}, α_{1b}, α_{1d} – new terminology) with their genomes exist on chromosomes number 8, 5, and 20.

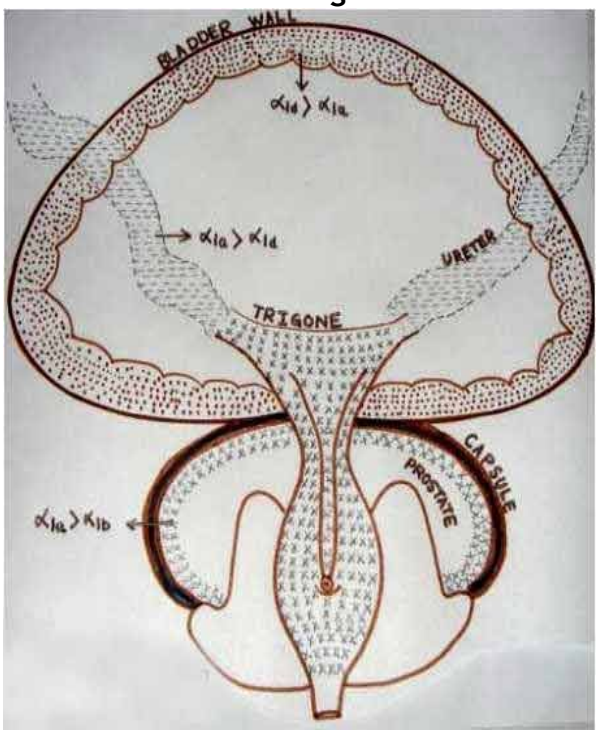
α-AR DISTRIBUTION AND QUANTIFICATION

α_{1a}-ARs overwhelmingly predominate in the prostatic stroma, whereas α_{1d}-ARs are present to a lesser extent. α_{1b}-ARs are chiefly involved in peripheral vasoconstriction. α_{1d}-ARs are restricted to the liver, spleen, lungs, urinary bladder, spinal cord, ganglia (sacral ventral motor nucleus), and nerve terminals. Normally in the human vessels, in patients <55 years, α_{1a}-ARs predominate, while in patients >65 years, α_{1b}-ARs predominate. In the human urinary bladder tissue, hypertrophy after prolonged bladder outlet obstruction leads to an enhanced bladder α_{1d}-ARs expression. Based on the RNase protection assays of the prostatic tissue, Nasu et al. has shown that the α_1-ARs (α_{1a}:α_{1b}:α_{1d}) in the normal human prostate exist in the ratio of 70:3:27%, which in patients of BPH changes to 85:1:14% [5].

CLINICO-PATHOLOGICAL CORRELATION OF α_1-ARS WITH LUTS

Receptor distribution studies [6] reveal that 70% of the α_{1a}-ARs are located in the bladder neck, prostate, and urethra; the α_{1d}-receptors predominate in the bladder and sacral spinal cord and the α_{1b}-ARs predominate in the glandular epithelium. Thus, in the human bladder ($\alpha_{1d} > \alpha_{1a}$) predominates, while in the prostate ($\alpha_{1a} > \alpha_{1b}$) prevail. This pattern of receptor distribution is in conformity with the embryology, as the bladder trigone + prostate + urethra develops from the same embryologic tissue where it mediates smooth muscle contraction, while the bladder (mesodermal derivative) has mainly α_{1d}-ARs, which also predominate in the spinal cord [6]. [Table/Fig 1] shows the distribution of α-ARs in the human bladder and prostate tissues.

Table/Fig-1



The α-AR distribution in the human bladder, trigone, and prostate tissues

UROSELECTIVITY OF THE α-BLOCKERS

The discovery of different subtypes of α-ARs has resulted in the emergence of the term "uroselectivity" **[7]**, which is chiefly of three types, namely (i) pharmacological uro-selectivity, viz. receptor selectivity for the particular α-AR-mediating contraction of the prostatic or urethral smooth muscle, (ii) physiological uro-selectivity, viz. functional selectivity as displayed in laboratory animals in respect of a preferential reduction of the prostatic urethral pressure, and

(iii) clinical uro-selectivity, viz. clinical efficacy of the drug in patients with BPH and its association with improvement of LUTS (reduction in the incidence of clinically significant adverse events). In this manuscript, the uro-selectivity term implies clinical uro-selectivity.

MANAGEMENT OF BPH-LUTS

Management of bladder and prostatic outlet obstruction involves administration of drugs that primarily target (i) the α_1-ARs to relax the smooth muscles and (ii) the 5-α reductase enzyme to block the intra-prostatic conversion of testosterone into dihydro-testosterone. With prostate hypertrophy, the proportion of α_{1b}-ARs decreases and that of α_{1a} and α_{1d} increases. Bladder outlet obstruction due to BPH results in obstructive and irritative symptoms. The obstructive symptoms (hesitancy, poor stream, prolonged urination, and incomplete emptying) are usually alleviated by the α_{1a}-ARs blockade. The storage symptoms (irritative symptoms – frequency, urgency, nocturia, and involuntary detrusor contractions) may persist despite normalised uro-flow. This is explained by the detrusor overactivity and development of uninhibited detrusor contractions [8].

(i) *α-Blockade*: α_1-blockers form the current first-line management modality for medically treating symptomatic BPH. Their onset of action is fairly rapid (within the first week), and they are clinically efficacious in relieving the obstructive symptoms, as revealed by urodynamic flow studies, and in lowering the risk of long-term complications like acute urinary retention (AUR) [9]. The incidence of clinical adverse events is extremely low, making them highly tolerable to a majority. The adverse events include dizziness, headache, asthenia, somnolence, postural hypotension, and abnormal ejaculation.

Table/Fig 2

Comparison of clinico-pharmacological properties of various α-blockers

Drug	Prazosin	Terazosin	Doxazosin	Alfuzosin 15	Tamsulosin 16, 17
Half-life (hour)	2–3	12	20	5	10
Dosage	BD(2)	OD(1)	OD(1)	TDS(3) and , OD(1)* ~10 mg	OD(1) ~0.4–0.8 mg
Efficacy vs. Placebo	Yes	Yes	Yes	Yes	Yes
Clinical adverse events, in order of frequency				Body pain > nausea > dizziness> fatigue > postural hypotension > syncope	Dizziness > abnormal ejaculation > headache > hypotension > GI disorder > nausea> CVS disorder > impotence > dry mouth > sweating > arrythmia > postural hypotension > pruritis
% Increase in IPSS vs. placebo	–	9–31	3–26	6–15	3–11
Comments		Devoid of significant receptor subtype selectivity	No receptor subtype selectivity	Clinically uro-selective – efficacy very low incidence – postural symptom. Lowest incidence of ejaculatory disturbances; hence, sexual function is best preserved.	Very good safety profile [9] Lowest re-treatment rate
Selectivity ratio [20] for prostate vs. vascular tissue	–	19	51	144 (highest)	90 (second highest)

*Extended release OD formulation is the best.

Table/Fig 3

Important landmark studies on α-adrenergic antagonists and 5-α reductase inhibitors

No	Study	Nos.	Content	Conclusions
1	MTOPS (2002) [37] (Medical Therapy of Prostatic Symptoms)	3047	Randomised men with symptomatic BPH to P, DO, F, or a combination of DO + F	1. SS deterioration was less in the DO + F. 2. 5-αRI not α-blockers reduced prostate volume, AUR, risk of surgery vs. P. 1. 3. Combination was safe and more effective than either drug alone.
2	SMART-1 (2003) [38] (Symptom Management after Reducing Therapy)	327	Randomised men to D + T × 36 weeks or D + T × 24 weeks, followed by D- and T-matched placebo × 12 weeks	1. Examined dual combination of D +T, followed by withdrawal of T. 2. D + T × 24 weeks for rapid onset of symptom relief, which is maintained in a majority after removal of T. Patients with severe symptom scores benefit from long-term D + T therapy.
3	PLESS (1998) [39] (Proscar* – long-term safety and efficacy study)	3040	Men with mod-severe BPH were randomised to daily F vs. placebo × 4 years	1. SS and PFR improvement was modest. 2. Durable symptom-flow improvements. 3. Cumulative incidence of AUR at 4 years was 7% with F and 3% with P. 4. No significant difference in prostate cancer detection rate.
4	PREDICT (1999) [40] (Prospective European DO, F & (C) Combination Therapy Trial)	1089	Men randomised to placebo, DO, F, or DO + F therapy to four groups × 1 year	1. Overall F therapy was the best relative to the P in the long term (1 year).
5	PROSPECT (1996) [26]		2-year randomised control trial of the efficacy and safety of finasteride vs. placebo for BPH	1. F can halt and reverse the natural course of BPH and is able to maintain the improvement for at least 2 years.
6	ALFAUR (2005) [15] (ALFAUR study group)	360	AUR patients – emergency catheterisation and randomised to Alfuzosin. (10 mg OD) vs. P × 3 days (first phase). TWOC patients were randomised to A vs. P × 6 months (second phase)	1. A – increased success TWOC rate (62%) in men with first episode of spontaneous AUR. 2. A – should be continued beyond the acute phase as it lowered the need for BPH surgery during a 6-month therapy period
7	ALFORTI TRIAL [13]	447	447 patients in the 3-month randomised double-blind multicentric study and 311 in extension phase. (PR)-A, 10 mg OD (*n* = 94) vs. (IR)-A, 2.5 mg TID (*n* = 111) × 3 months followed by (PR)-A, 10 mg OD in all patients in extension phase	1. Clinical benefits of pronged-release alfuzosin 10 mg were maintained for 12 months. 2. Moderate symptoms (IPSS = 7–20) decreased from 78% (baseline) to 55% patients (end point). 3. Severe symptoms (IPSS = 20–35) decreased from 22% (baseline) to 4% patients (end point).
8	ALTESS [41] (study group)	1522	Patients with LUTS/BPH were randomised to A-10 mg OD vs. placebo for 2 years	1. A – significantly improves LUTS and QOL × 2 years and is well tolerated. 4. A – prevents overall clinical progression of BPH but does not reduce primary AUR

*Proscar™ – finasteride brand.

F, finasteride; D, dutasteride; A, alfuzosin; PR, prolonged release; IR, intermittent release; DO, doxazosin; SS, symptom scores; P, placebo; AUR, acute urinary retention; PFR, peak flow rate; TWOC, trial without catheter; LUTS, lower urinary tract symptoms; QOL, quality of life.

Tamsulosin: It is a methoxybenzene sulphonamide [YM-617] (quinazoline derivative), FDA-approved, stereoisomer ([R(−)] enantiomer) with a 13–38 (α_{1a} over α_{1b}) times higher selectivity for prostatic smooth muscles. Tamsulosin is a highly protein-bound hydrophilic compound, with a $T_{1/2}$ of 10 hours. At the clinical dose of 0.4 or 0.8 mg/d, its pharmacological selectivity is $\alpha_{1a} \geq \alpha_{1d} \geq \alpha_{1b}$-ARs, with no effect on serum prostate-specific antigen (PSA) levels; it is free from any untoward cardiovascular side effects, is safe and effective, and is well tolerated by a majority in BPH. It is the latest-generation α-blocker that can be administered without the need for dose titration. It is also the first α_1-blocker with receptor subtype selectivity (moderate higher affinity to α_{1a} than to α_{1b} and intermediate affinity to α_{1d}). This explains its mild cardiovascular effects and functional uro-selectivity [10], [11]. Abnormal ejaculation is the only consistent dose-related adverse event, i.e. 10% at 0.4 mg/d and 26% at 0.8 mg/d; due to slight α_{1a} selectivity it may negatively affect vas deferens function and thereby ejaculation (post-junctional α_{1a} or $\alpha_{1A/L}$-ARs may play an important role in contraction of the human vas deferens). The long-term incidence of AUR and development of cancer prostate are about 2% and 1.4%, respectively. It has the lowest re-treatment percentage when compared with alfuzosin and terazosin [12].

Alfuzosin: It is also a quinazoline derivative, devoid of significant receptor subtype selectivity (on the cloned receptors), but in isolated human tissue it exhibits the highest selectivity ratio for prostate over vascular tissue. It is a selective competitive α_1-ARs antagonist with a $T_{1/2}$ of 5 hours, with an overall good safety profile. Alfuzosin is currently available as an extended release (10 mg) – once-daily-administered preparation that is as efficacious as the other α-blockers. The 10 mg prolonged-release preparation of alfuzosin provides an equivalence of drug release that is sustained for up to 20 hours and is well tolerated and the clinical improvement is well maintained for up to 1 year [13]. The incidence of cardiovascular side effects is low, with fewer incidences of postural hypotension, which does away with the need for any dose titration (clear advantage over other α-blockers). Overall adverse events have been reported in only 1–2% of patients receiving alfuzosin hydrochloride (body pain, dyspepsia, nausea, and sinusitis). It also appears to be the first α-blocker to demonstrate a clinically significant positive correlation, with a reduction in the post-void residue (PVR) on the trans-abdominal ultrasound [14].

Doxazosin: Another quinazoline derivative with a $T_{1/2}$ of 20 hours, it has been associated with mild-to-moderate side effects of dizziness, headache, fatigue, and a clinically significant BP reduction. It is ideally suited for treating BPH associated with hypertension.

Terazosin: It is also a quinazoline derivative with a $T_{1/2}$ of 12 hours, with a demonstrable superior reduction of the symptom scores and uro-flow rates. Minor reversible side effects include asthenia, hypotension, and dizziness (minimised by dose titration). No sexual dysfunction or alteration in the serum PSA has been observed on long-term therapy with terazosin. [Table/Fig] 2 shows the salient features, properties, and adverse events associated with the commonly used α-blockers [15–17].

(ii) *5-Alpha reductase inhibitors (5-ARI)*: The role of 5-ARI in BPH therapy stemmed from the discovery of the fact that congenital deficiency of the 5-α reductase in adult men was associated with a non-palpable prostate [18], leading to the correlation that dihydro-testosterone (DHT) has an obligatory role in the development of BPH [19].

Dutasteride: It is a 4-azasteroid compound with a 60% bioavailability rate and a terminal elimination $T_{1/2}$ of about 5 weeks. Due to its long half-life, significant detectable serum concentrations of dutasteride can exist for up to 4–6 months after discontinuation of therapy.

Thus 5-ARI drug therapy may be superior to α-blockade alone in preventing AUR- and BPH-related surgery [20]. Both finasteride and dutasteride at a daily dose of 0.5 and 5 mg have shown to reduce DHT levels by 70% and 90.2%, respectively, leading to prostatic stromal atrophy and a reduction in the prostate volume by up to 30% [20–22]. Whereas finasteride is a selective inhibitor of 5-ARI (type-1), dutasteride is a dual inhibitor of both types of 5-ARI isoenzymes. Pharmacogenetic analysis and mapping studies of the genotypes of the human 5-α reductase type-2 isoenzyme has shown that dutasteride is a more efficient inhibitor as compared to finasteride [23]. While both the drugs are of similar clinical efficacy and safety, dutasteride is significantly

capable of an earlier and more rapid powerful bio-chemical action, thereby having a faster onset of action in a monotherapy trial setting.
Important adverse events attributed to 5-ARI include a lowering of the ejaculatory volume and libido in 9–16% and gynaecomastia in 0.4%. Ejaculatory dysfunction associated with finasteride ranges from decreased volume of ejaculate to complete failure of ejaculation. The overall incidence of ejaculatory dysfunction associated with finasteride in several randomised clinical trials in men with symptomatic BPH ranges from 2.1% to 7.7% [24],[25]. The incidence of erectile dysfunction in the PROSPECT trial [26] involving 472 men who received 2 years of finasteride therapy was 15.8% (versus 6.3% in the placebo arm), whereas in the finasteride study [24] it was 4.9%, both of which were statistically significant with respect to the placebo. Dutasteride has been shown to be well tolerated in several randomised controlled trials when administered on a long-term basis for the management symptomatic BPH [27–29]. The most common adverse events encountered with dutasteride are impairment of sexual function and gynaecomastia (1–4%); however, the withdrawal rates on account of this have been less than 1% (0.3–1%) [27]. A longer duration of therapy with dutasteride (2 versus 4 years) has shown a greater sustained and continued symptom improvement [28]. The lowering of the serum PSA levels by about 50% by both these drugs also causes problems in PSA interpretation, which needs to be kept in the mind [28],[30].

(iii) *Phytotherapeutic agents*: Phytotherapy or the use of plant-derived products in the therapy of LUTS and BPH was first described in Egypt way back in the 15th century BC [31]. Phytotherapy is a popularly prescribed medication for BPH with LUTS throughout Germany, Italy, Austria, Switzerland, Spain, Poland, and Japan, and its recent awareness has risen worldwide including the United States [32]. The plants that are principally exploited are those that are rich in phytosterols (flavonoids-active compounds include β-sitosterol-β-D-glucoside, sitosterin, pentacyclic triterpenoids, and esters of long-chain fatty alcohols).Various mechanisms have been attributed to their actions such as inhibition of 5-AR, anti-inflammatory; inhibition of growth factors and aromatase, anti-androgenic and anti-oestrogenic; decreased sex hormone-binding globulin; altered cholesterol metabolism; free radical scavenger; altered lipid peroxidation; modulated prolactin-induced prostatic growth; protection of bladder function; and placebo effect [33],[34]. Plant extracts of *Pygeum africanum* (African plum tree) and *Serenoa repens* (Sao palmetto) have been used clinically. Other plants, also rich in flavinoids, include Cernilton (extract of rye grass pollen – *Secale cereale*), *Hypoxis rooperi* (South African star grass), Bazoton (*Urtica dioica* – stinging nettle), and Curbicin (*Cucurbita pepo* – pumpkin seed).therapy has been principally exploited for the relief of early and moderate symptoms of outflow obstruction due to BPH. Lack of any serious side effects (nausea and diarrhoea) has made them very popular in some countries. Several placebo-controlled trials and long-term studies evaluating the efficacy of phytotherapy in BPH are still underway [35],[36].

Discussion

[Table/Fig 3] shows a summary of the salient features of some of the clinically important landmark trials that have been carried out with α-blockers and 5-ARI drugs for the management of symptomatic BPH till date [13],[15],[37],[38], [39], [40], [41].

The MTOPS study (medical therapy of prostatic symptoms) [37] had a shortcoming in that it was not possible to conclude whether combination therapy could (i) actually prevent hospitalisation on account of AUR and (ii) whether it could be justified as a viable option for long-term therapy in patients with moderately severe LUTS. SMART-1 (symptom management after reducing therapy) [38] trial too had its lacunae: (i) it was a short-term study of a small number of patients and (ii) it lacked a placebo arm. Nevertheless, it showed that combination therapy was quite effective, and symptom deterioration following tamsulosin withdrawal was seen only in patients with prior severe symptoms.

The α-blockers currently recommended by the American Urological Association for the treatment of symptomatic BPH include doxazosin, terazosin, tamsulosin, and alfuzosin [42],[43]. A recent re-analysis of the MTOPS by Roehrborn et al. concluded that medical therapy ought to be tailored to the risk status of the patient [44]. They concluded that combination therapy of an α-adrenergic blocker with 5-ARI is more beneficial and effective for the therapy of patients of LUTS with demonstrable enlargement of the

prostate [45] than with α-blockers alone in the long run. Patients with a prostate volume >40 ml, transition zone volume >20 ml, and serum PSA >4.0 ng/dl could be the right group of patients who could be ideally subjected to a combination therapy. Recent clinical experience with tamsulosin has also shown that it is one of the safest α-blockers capable of producing a rapid and lasting symptomatic relief of LUTS, while finasteride and dutasteride reduce the risk of AUR and BPH-related surgery [46],[47]. Phase III double-blind studies have also confirmed that daily tamsulosin (0.4–0.8 mg) is effective and safe for the long-term therapy of BPH, and it is a good therapeutic alternative to surgical intervention [48]. The combination of dutasteride and tamsulosin has been shown to be well tolerated, with the additional advantage of a rapid and sustained efficacy with symptomatic relief when administered over a period of time [48],[49]. Further dutasteride has also been shown to hold an in vitro tumour regression property, and its role in chemoprevention of prostate cancer is being currently evaluated by an ongoing trial "Reduction by Dutasteride of Prostate Cancer Events" (REDUCE) [50]. This may translate into a superior advantage of using the dual inhibitor dutasteride in place of finasteride for the management of BPH in preventing the onset of possible high-grade prostate cancer, suggesting a possible chemopreventive role in future [50],[51].

Recent evidence-based medicine (EBM) reviews have shown that 5-ARI has a significantly higher efficacy in patients with larger prostates (>40 ml). Thus, patients most likely to benefit from 5-ARI therapy are those with a large prostate and serum PSA levels >1.4 ng/dl. The favourable changes in symptom scores and flow rates tend to be maintained for at least 5 years. By inducing prostate shrinkage in the pathological BPH, the 5-ARIs can potentially reverse the progress of BPH. Currently, 5-ARI therapy is advocated as a first-line therapeutic alternative for moderate-sized uncomplicated BPH (>40 ml) as an additional option for BPH patients with severe symptom scores who are either unfit or unwilling for surgery. An additional beneficial effect of 5-ARI therapy is the reversal of the male-pattern balding. However, these group of drugs need to be taken for longer periods to produce a clinically significant and durable beneficial response. 5-ARIs are principally indicated where the aim is to arrest and reverse the natural course of BPH so as to reduce the risk of BPH progression in terms of the risk for AUR, recurrent urinary tract infections, renal function deterioration, and the need for surgery related to BPH. The considerably high morbidity and mortality associated with AUR-related emergency surgical intervention and prolonged catheterisation have led to an increase in the use of trial without catheter (TWOC). TWOC involves catheter removal after 3–5 days of α-blocker therapy (success rate varying from 23% to 40%), likely predictors of an unfavourable outcome being (i) high PSA level, (ii) high PVR, and (iii) response to alfuzosin therapy following the first AUR episode managed conservatively [52].

The EBM in respect of phytotherapy for LUTS due to BPH concludes that despite their popularity and over 40 randomised control trials in 5000 men, there is no clear-cut evidence of efficacy for most phytotherapeutic products. Extracts of *S. repens* have the strongest evidence for efficacy and tolerability. The 'Committee on Other Medical Therapies of the Fourth International Consultation on BPH' had also concluded that most plant extracts have different components with unknown in vitro mechanisms, and while some short-term randomised studies suggest a clinical efficacy for some extracts, the same were inadequate due to their smaller numbers and short durations of study [53]. Phytotherapy at present appears to be useful in improving LUTS and flow measures in at least some patients.

In a major six-nation European trial comparing the efficacy of various drugs in the management of BPH/LUTS, Hutchison et al. [54] concluded that despite the difference in prescribing patterns (choice of individual drug or combination therapy), all drug therapies showed some improvement over watchful waiting in a majority, and the α-blockers were found to be the most effective.

Conclusions

About 15 years ago watchful waiting and surgery were the only two commonly practised therapeutic options for LUTS and bladder outflow obstruction due to BPH. Today worldwide medication has emerged as the dominant frontrunner, and the rates of TURP/surgery for BPH have drastically declined. α-Blockers are here to stay, as they have persistently shown a rapid improvement in the BPH-related LUTS uro-flow rates with minor side effects. Currently,

tamsulosin and alfuzosin remain the most popularly prescribed α-blockers. Prolonged therapy with 5-α reductase inhibitors produces a relatively delayed improvement in the flow rates and a reduction in the rate of BPH progression with a durable shrinkage of 20–30% in the prostate size. Dutasteride has emerged as a popular and well-tolerated, efficient dual 5-α reductase inhibitor drug both in combination with α-blockers and in monotherapy for the larger and symptomatic BPH [55]. Long-term therapy (48 months) with 5-ARIs has not shown any statistically significant increase in the overall incidence of adverse events. Combination therapy is currently the most efficacious means to prevent BPH progression. As of date no evidence exists to suggest that combination therapy is associated with any serious side effects [56].

Successful medical management of LUTS due to BPH must involve paying greater attention in detail to the monitoring of medication-related sexual side effects and following an integrated management and a holistic approach dictated by the patient symptoms and outcome goals. Tailoring of the BPH/LUTS drug management should include co-prescribing anticholinergic drugs (tolterodine) and or phosphodiesterase inhibitors (tadalafil) for selected and deserving cases of BPH syndrome associated with a proven overactive bladder and sexual dysfunction.

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