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Review Article

Benign Prostatic Hyperplasia Current Medical Treatment –A Review

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Abstract

Benign Prostatic Hyperplasia (BPH) is a "histologic diagnosis that refers to the proliferation of smooth muscle and epithelial cells within the prostatic transition zone." Men are likely to develop BPH as the age advances. Half of men ages 51 – 60 years old and 80 percent of men over 80 years old have BPH according to autopsy data. About half of men with BPH develop an enlarged prostate gland, called benign prostatic enlargement (BPE), and among these, about half develop bladder outlet obstruction (BOO). BOO and/or changes in smooth muscle tone and resistance that can accompany BPH often result in lower urinary tract symptoms (LUTS). LUTS are storage disturbances, such as daytime urinary urgency and nocturia, and/or voiding disturbances, such as urinary hesitancy, weak stream, straining, and prolonged voiding Urinary hesitancy, weak stream, and nocturia are the most commonly reported LUTS.Usually, BPH diagnosis is based on clinical presentation of enlarged prostate and/or bothersome LUTS (daytime urinary urgency and nocturia, and/or voiding disturbances, such as urinary hesitancy, weak stream, straining, and prolonged voiding); other causes of LUTS should be ruled out. Despite the deceptively simple description of benign prostatic hyperplasia (BPH), the actual relationship between BPH, lower urinary tract symptoms (LUTS), benign prostatic enlargement, and bladder outlet obstruction is complex and requires a solid understanding of the definitional issues involved. The etiology of BPH and LUTS is still poorly understood, but the hormonal hypothesis has many arguments in its favor. There are many medical and minimally invasive treatment options available for affected patients. In the intermediate and long term, minimally invasive treatment options are superior to medical therapy in terms of symptom and flow rate improvement; tissue ablative surgical treatment options are superior to both minimally invasive and medical therapy.

Keywords: Benign prostatic hyperplasia, Lower urinary tract symptoms, Bladder outlet obstruction, alfa-adrenergic receptor blockers, 5-alfa reductase inhibitors, Minimally invasive surgical therapy, Interstitial laser coagulation.

Introduction

Benign prostatic hyperplasia (BPH) refers to the non-malignant growth of the prostate observed very commonly in aging men. [1-3] BPH, the actual hyperplasia of the prostate gland, develops as a strictly age-related phenomenon in nearly all men, starting at approximately 40 years of age. In fact, the histologic prevalence of BPH, which has been examined in several autopsy studies around the world, is approximately 10% for men in their 30s, 20% for men in their 40s, reaches 50% to 60% for men in their 60s, and is 80% to90% for men in their 70s and 80s. No doubt, when living long enough, most men will develop some histologic features consistent with BPH.Many person with BPH do not develop problem. [4] The condition becomes a clinical entity if and when it is associated with subjective symptoms, the most common manifestation being lower urinary tract symptoms (LUTS). [5] It must be recognized, however, that not all men with histologic BPH will develop significant LUTS, although other men who do not have histologic BPH will develop LUTS. Such men might have other conditions of the prostate (prostatitis or prostate cancer), other causes for subvesical outlet obstruction (urethral stricture, bladder neck sclerosis), conditions of the bladder (carcinoma in situ, inflammation, stones), or other conditions leading to the rather nonspecific constellation of symptoms commonly labeled as “LUTS”. [6,7]

The LUTS symptom complex can be conveniently divided into obstructive and irritative symptoms.[8]

Among the obstructive symptoms are hesitancy, straining, weak flow, prolonged voiding, partial or complete urinary retention, and, ultimately, overflow incontinence. [9] The often more bothersome irritative symptoms consist of frequency, urgency with urge incontinence, nocturia, and painful urination, as well as small, voided volumes. The prevalence of LUTS increases steadily with increasing age. [10,11] Another important part of the constellation of LUTS and BPH is the fact that, in aging men, the prostate tends to increase in size. [12,13] Studies demonstrate that across a wide spectrum of racial and ethnic groups, prostate size increases from 25 g to 30 g for men in their 40s to 30 g to 40 g for men in their 50s and to 35 g to 45 g for men in their 60s. At the same time, the transition zone of the prostate, which is quite small at approximately 15 g in men in their 40s, increases to approximately 25 g for men in their 60s and 70s. [14,15] It is well understood that the immediate periurethral glands or transition zone of the prostate is the source of the size enlargement, slowly expanding and thus compressing the peripheral zone of the prostate. [16-19]

Not all men with histologic BPH will develop benign prostatic enlargement (BPE). [20]

Furthermore, not all men with LUTS or bothersome symptomatology will have concomitant BPE, and not all men with BPE will have bothersome symptoms. Many men with significant LUTS and bother have a normal sized prostate, whereas many men with large prostates present with surprisingly few, if any, symptoms. In the past, this later condition has been called “silent prostatism.” This can be understood with help of a venn diagram shown below. [21]

TABLE 1 Sym LUTS **symptoms of BPH5**

Storage symptoms

- Urinary frequency
- Urinary urgency
- Urinary incontinence
- Nocturia
- Dysuria

Voiding symptoms

- Difficulty in initiating urinary stream

- Urinary hesitancy
- Straining to void
- Decreased urinary flow
- Intermittency
- Dribbling
- Incomplete bladder emptying

Venn diagram

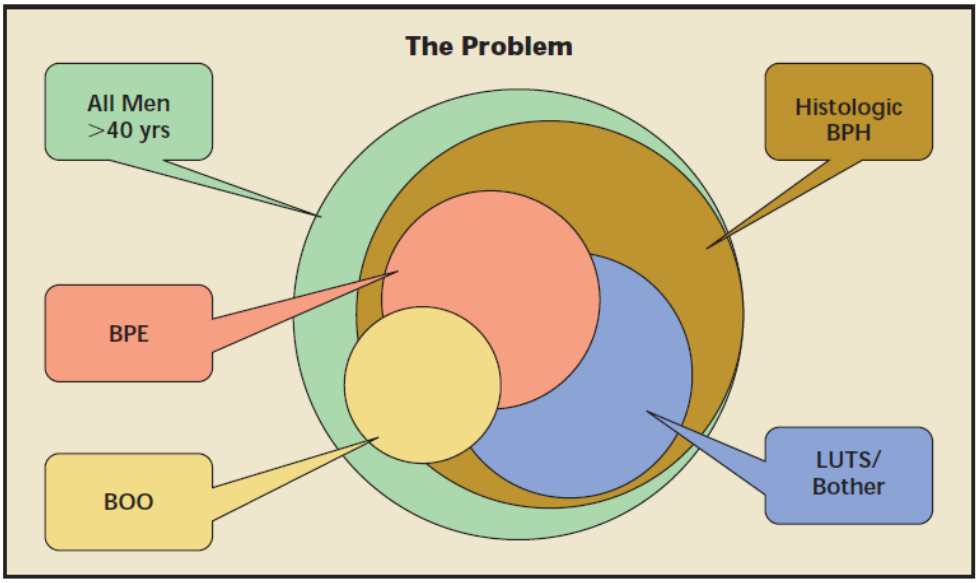

Figure 1. *Complex relationship between benign prostatic hyperplasia (BPH), lower urinary tract symptoms (LUTS), benign prostatic enlargement (BPE), and bladder outlet obstruction (BOO).*

The last part of the complex relationship is the issue of bladder outlet obstruction (BOO) (Figure 1). This refers to the presence of a pressure gradient at the bladder neck/prostatic urethra, which can be measured precisely by invasive urodynamic studies. As with the previous observation, not all men with enlarged prostates and bothersome LUTS will have BOO, whereas certainly there are other causes for BOO than BPH and BPE. For example, a primary bladder neck sclerosis, a urethral stricture, or other conditions might cause significant obstruction while not being associated with histologic BPH. BOO can be measured by invasive pressure-flow studies or noninvasively tested for by urinary flow rate recordings. It has been shown that the maximum urinary flow rate decreases with advancing age, either in the absence or presence of BPH and LUTS. Girman and colleagues have shown that the maximum urinary flow rate for men in their early 40s is approximately 20.3 mL/s, whereas it decreases for men in their 70s to 11.5 mL/s.

Abrams and others have demonstrated that a peak or maximum urinary flow rate of less than 10 mL/s indicates the presence of a sub vesical obstruction in 90% of patients, whereas in patients with a maximum urinary flow rate of greater than 15 mL/s, sub vesical obstruction is present in only 30%. Of the men in the indeterminate group, with a peak flow rate of 10 to 15 mL/s, approximately 2 out of 3 will have subvesical obstruction.

subvesical obstruction or BOO might be responsible for secondary changes of the bladder anatomy and function, urinary tract infections, formation of bladder stones, and ultimately deterioration of the upper urinary tract with renal failure.

Diagnosis and Evaluation

All patients should undergo a careful history, focusing on diseases specific to the genitourinary tracts, and a physical examination including a careful digital rectal examination (DRE). it is important to assess the prostate in terms of its shape, symmetry, nodularity, and firmness.

In addition, urinalysis and a serum prostate-specific antigen (PSA) assay, blood examination including CBC ,LFT,KFT ,Complete urine analysis is recommended as part of the additional diagnosis.

Trans abdominal or transrectal prostatic ultrasound also may be considered to accurately evaluate the size, shape, anatomy, and potential pathology of the prostate in a minimally invasive, cost-effective, and reproducible way. A transabdominal ultrasound also can assess the bladder and postvoid residual urine, which may be contributing to a patient's symptoms

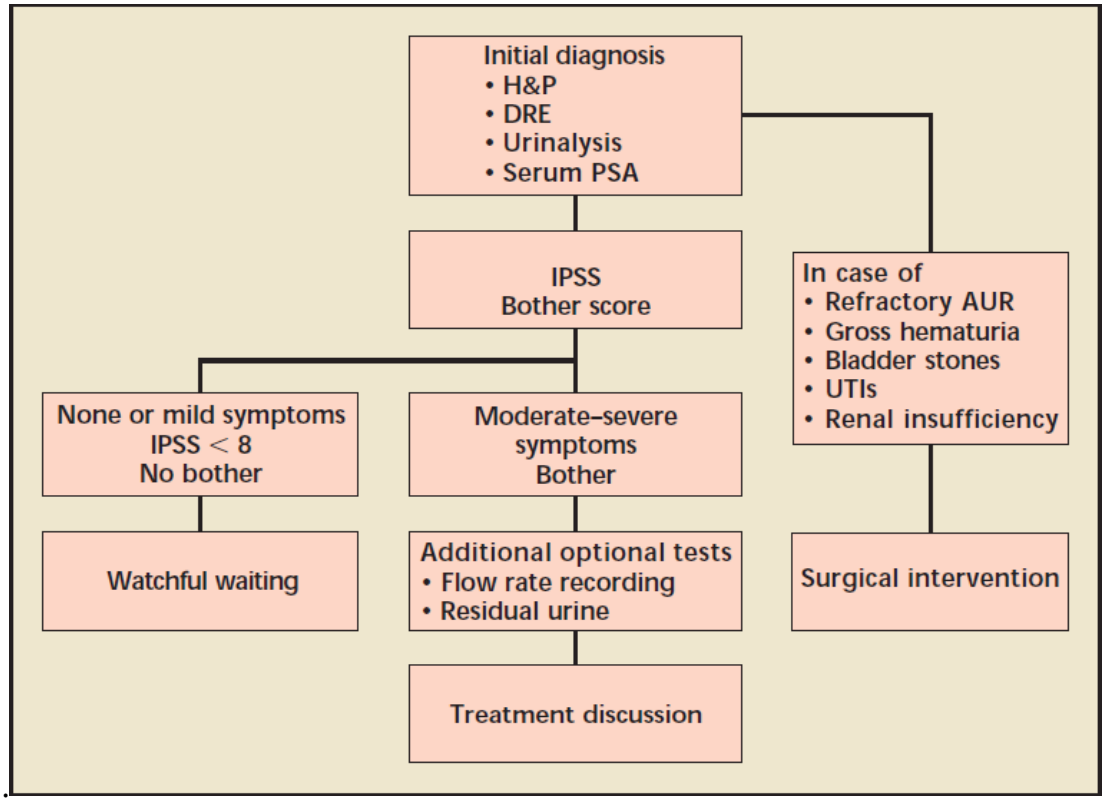

Figure 2. Guidelines for the evaluation of men with lower urinary tract symptoms and benign prostatic hyperplasia. H&P, history and physical examination; DRE, digital rectal examination; PSA, prostate-specific antigen; IPSS, International Prostate Symptom Score; AUR, acute urinary retention; UTI, urinary tract infection. Adapted from the American Urological Association Practice Guidelines Committee.10

Treatment Management of bladder and prostatic outlet obstruction involves administration of drugs that primarily target (i) the alfa1blocker to relax the smooth muscles and (ii) the 5alfa reductase enzyme inhibitor to block the intra-prostatic conversion of testosterone into dihydro-testosterone.

Many pharmacologic and surgical interventions have been approved for treating BPH, with the goals of improving patient symptoms and quality of life while slowing disease progression and reducing complications. Treatment decisions are based on the severity of the condition.

Watchful waiting for men with mild BPH symptoms (IPSS less than 8), watchful waiting is recommended. This includes yearly follow-up appointments with history and physical examination to determine the progression of the disorder and reevaluate treatment options. During this time period, various behavioral modifications, such as avoiding antihistamines,

reducing fluid intake in the evening and decreasing alcohol and caffeine consumption can provide symptom relief.

Men suffering from moderate to severe symptoms (IPSS of 8 and greater) may consider lifestyle changes, but will likely require pharmacologic treatment or surgery if pharmacologic

treatment fails. Patients on medication should be evaluated at least twice a year in the office to discuss the efficacy of the medication and potential dose adjustment. They also should

undergo DRE and PSA screening at least annually.

Management of Bph-Luts

Common medications used to treat LUTS associated with BPH

Alpha 1 blockers -inhibit prostate smooth muscle contraction by blocking the alpha-1 receptor, thus relaxing the dynamic component of blockade decreasing resistance to urinary flow; Since the bladder body only has a negligible density of alpha-1 receptors while the bladder neck contains a substantial amount of alpha-1 receptors, alpha-1-blockers reduce bladder outlet resistance without impairing bladder emptying. Alpha-1 blockers. Also may regulate prostate growth by inducing apoptosis in both the epithelial and stromal smooth muscle cells without affecting the rate of cell proliferation. They are Terazosin Alfuzosin, Doxazosin **Silodosin**, Tamsulosin.

5 alpha reductase inhibitors -inhibit 5alpha-reductase, an isoenzyme that metabolizes testosterone to dihydrotestosterone (DHT) in the prostate gland, liver, and skin; blocking conversion of testosterone to DHT and reducing serum tissue DHT.They are Finesteride and Dutasteride.

Anticholinergic agent – relaxes bladder smooth muscle by reducing the muscarinic effect of acetylcholine on smooth muscle. They are Oxybutynin, **Fesoterodine,** Darifenacin, **Tolterodine Tartrate** Tolterodine, **Solifenacin,** Trospium.

Beta-3 adrenergic agonist -Increases bladder capacity by relaxing the bladder smooth muscle during the storage phase of the urinary bladder fill-void cycle**. ex. Mirabegron**

Phospodiesterase type 5 inhibitor - selectively inhibits PDE5 and increase cyclic guanosine monophosphate (cGMP). The smooth muscle cells of the prostate, bladder and surrounding vasculature contain PDE5; inhibiting PDE5and increasing cGMP levels in these tissues causes smooth muscle relaxation. ex. Tadalafil, **Sildenafil, Avanafil, Vardenafil**

Alpha-adrenergic receptor antagonists The mainstay of BPH treatment, these medications inhibit sympathetic adrenergic receptors, causing prostatic and bladder smooth muscle cell relaxation. The resultant reduced urethral constriction and improved urinary flow lessen obstructive BPH symptoms. Alpha-adrenergic receptor antagonists are further sub classified according to their extent of selectivity for certain alpha-1 receptors. Doxazosin, terazosin, and alfuzosin are considered nonselective, blocking all alpha-1 receptors equally; silodosin and tamsulosin are selective for alpha-1A receptors that are mainly located in the urogenital tract. Selective agents are associated with fewer systemic adverse reactions (such as hypotension, dizziness, and fatigue) than nonselective agents. Clinicians should avoid prescribing nonselective alpha-blockers to older adults because these drugs can cause orthostatic hypotension and syncope. However, a patient with BPH and hypertension may be a candidate for a nonselective agent because it would treat both conditions. Both types of alpha-adrenergic receptor antagonists cause clinically significant decreases in BPH symptoms after 1 week of therapy, as reflected by AUASI score decreases; however, 2 to 4 weeks of

treatment is recommended to achieve the full effect of the medication. The adverse events include dizziness, headache, asthenia, somnolence, postural hypotension, and abnormal ejaculation Alpha-adrenergic receptor antagonists should not be prescribed to patients planning to have cataract surgery due to the risk of floppy iris syndrome. Because this class of medications does not reduce prostate size, patients are still at risk for urinary retention, associated complications, and disease progression.

5-alpha-reductase inhibitors Another first-line drug option is a 5-alpha-reductase inhibitor, which blocks the conversion of testosterone to DHT, inhibiting prostatic hyperplasia, reducing prostate size, and slowing disease progression. Treatment with a 5-alpha-reductase inhibitor reduces urinary retention and the need for future BPH surgeries and should be started in patients with PSA levels greater than 1.5 ng/mL, as long as patients have no contraindications. Within 2 to 6 months, men taking 5-alpha-reductase inhibitors for BPH treatment should experience a 25% decrease in prostate size and an improvement in BPH symptoms. These drugs can be used as monotherapy or adjunct therapy to alpha-adrenergic receptor antagonists. Combination therapy is more successful than monotherapy but is associated with more adverse reactions.5*5-Alpha reductase inhibitors (5-ARI)*: Finesteride and Dutesteride are drugs in this group.The role of 5-ARI in BPH therapy stemmed from the discovery of the fact that congenital deficiency of the 5-Alfa 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.

Dose of Finesteride is 5mg and Dutasteride is 0.5mg per day orally. Both finasteride and Dutasteride 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%. 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-alfa reductase type-2 isoenzyme has shown that dutasteride is a more efficient inhibitor as compared to finasteride.

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 randomized clinical trials in men with symptomatic BPH ranges from 2.1% to 7.7%. Dutasteride has been shown to be well tolerated in several randomised controlled trials when administered on a long-term basis for the management of symptomatic BPH.

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%) . A longer duration of therapy with dutasteride (2 versus 4 years) has shown a greater sustained and continued symptom

improvement. 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.

Tadalafil This drug, mainly used to treat erectile dysfunction, is the phosphodiesterase-5 inhibitor approved for BPH treatment. Tadalafil causes smooth muscle relaxation of the detrusor muscle, prostate, and vascular cells of the urinary tract, and decreases prostatic and bladder hyperplasia. After 4 weeks of use, tadalafil improves lower urinary tract symptoms and quality of life and is an option for men suffering from concomitant BPH and erectile dysfunction.

Anticholinergic agents This class of medication has been approved as add-on therapy when alpha-adrenergic antagonists fail to control BPH symptoms. Anticholinergics block muscarinic receptors on the detrusor muscle and improve storage symptoms after fewer than 12 weeks of therapy. However, anticholinergics may exacerbate constipation, cognitive impairment, and dementia in older adults, and should be avoided or closely monitored if used in these patients.

Surgery Surgical treatment for BPH is indicated when medical treatment fails to elicit a sufficient response, when symptoms are severe, if there is concern for complications, or if the patient has renal failure, refractory gross hematuria, recurrent UTIs, or bladder stones. Recommended options include open surgery, transurethral resection of the prostate (TURP), and transurethral holmium laser enucleation of the prostate (HoLEP). Open surgery involves removing the prostatic adenoma from the adjacent prostate tissue. With the enlarged prostate

no longer compressing the urethra, voiding symptoms improve postoperatively. This procedure carries the risk of several complications including wound infection**,** hemorrhage,

UTI, and sepsis.

TURP is the gold standard for BPH treatment and is the most commonly performed procedure for men suffering from BPH. TURP is effective for improving BPH symptoms

but may cause complications such as hemorrhage, hyponatremia, and retrograde ejaculation. Bipolar TURP uses bipolar current and is a minimally invasive procedure associated with fewer complications and a shorter hospital stay. Because 0.9% sodium chloride solution can be used for irrigation instead of nonconducting glycine as in monopolar TURP, the procedure can be longer and complications are reduced.

HoLEP, another minimally invasive procedure, involves removal of the prostate adenoma by laser irradiation, and can be considered in men who do not qualify for TURP due to prostate size. Although HoLEP is a longer surgical procedure than TURP, it is less commonly associated with complications and requires a shorter hospital stay. Temporary and permanent urethral stents are also used to treat BPH in high-risk patients who are unable to undergo invasive surgery. The minimally invasive procedure involves endoscopic stent placement into the prostatic urethra, improving BPH symptoms and minimizing complications because of the smaller incision and reduced trauma to the surrounding tissue.

Botulinum toxin is another potential treatment option that has been explored but is not approved. Injecting the toxin into the prostate inhibits acetylcholine release, resulting in

smooth muscle paralysis and tissue atrophy. Acute inflammation is followed by scarring and shrinkage of the prostate.

Complications

Recurring urinary retention is a common complication of BPH. Men at greater risk for urinary retention are those with PSA levels above 1.6 ng/mL or prostate volumes over

31 mL. Other complications include bladder calculi as a result of urinary stasis and UTIs from increased postvoid residual urine. Macroscopic hematuria and renal failure have also been observed.

Patients also may develop sexual dysfunction as a result of pharmacologic or surgical interventions. Erectile dysfunction has been reported in patients taking 5-alpha-reductase inhibitors, and men taking these medications or alpha-adrenergic antagonists have reported ejaculatory dysfunction. Ejaculatory dysfunction also is a complication in 80% of men undergoing open surgery and 65% to 80% of men undergoing TURP.2

Discussion

An alfa-adrenergic blocker with 5-ARI is more beneficial and effective for the therapy of patients of LUTS with demonstrable enlargement of the prostate than with alfa-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 alfa-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. [22,23] 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. 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.[24]

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.[25,26]

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. [27,28]

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 alfa-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. [29,30]

Conclusions

About 15 years ago watchful waiting and surgery were the only two commonly practiced therapeutic options for LUTS and bladder outflow obstruction due to BPH. Today worldwide medication has emerged as the dominant front runner, and the rates of TURP/surgery for BPH have drastically declined. alfa-Blockers are here to stay, as they have persistently shown a rapid improvement in the BPH-related LUTS uroflow rates with minor side effects. Currently, tamsulosin and alfuzosin remain the most popularly prescribed alfa-blockers. Prolonged therapy with 5-alfa 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-alfa reductase inhibitor drug both in combination with alfa-blockers and in monotherapy for the larger and symptomatic BPH. Long-term therapy (48months) with 5ARIs 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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