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REVIEW

Therapeutic options in the treatment of benign prostatic hyperplasia

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Abstract: Current theraputic options for the treatment of symptomatic benign prostatic hyperplasia (BPH) are reviewed. Therapeutic options for mild lower urinary tract symptoms (LUTS), as defined by the American Urological Association, are generally treated medically. Moderate to severe LUTS can be treated medically or with surgical therapy. Current medical and surgical treatments for LUTS secondary to BPH are reviewed and evolving treatments are explored.

Keywords: benign prostatic hyperplasia, prostatectomy, TURP

Introduction

Benign prostatic hyperplasia (BPH) is a pathologic process that contributes to the development of lower urinary tract symptoms (LUTS) in men. LUTS, arising from lower urinary tract dysfunction, are further subdivided into obstructive (urinary hesitancy, straining, weak stream, terminal dribbling, prolonged voiding, incomplete emptying) and irritative (urinary frequency, urgency, nocturia, urge incontinence, small voided volumes) symptoms. Autopsy series have shown that no men younger than 30 years of age have histologic evidence of BPH, while more than 50% of men greater than 60 years of age have histologic evidence of the disease.[1] The prevalence reaches almost 90% in the ninth decade.[1] While prostatic enlargement appears inevitable, it is believed that the LUTS and other sequelae of BPH are not just due to a mass effect, but also likely due to a combination of the prostatic enlargement and age-related detrusor dysfunction.[2]

Traditional management of BPH consisted of surgery or watchful waiting with treatment of complications if they arose. Medical therapy gained acceptance about two decades ago with the approval of alpha-adrenergic receptor antagonists and 5-alpha-reductase inhibitors for the treatment of symptomatic BPH. Alpha-adrenergic receptor antagonists were thought to treat the "dynamic" aspect of BPH by reducing sympathetically mediated tone of the bladder outlet and therefore decreasing resistance and improving urinary flow. 5-alpha-reductase inhibitors, on the other hand, were thought to treat the "static" aspect of BPH by reducing prostate volume and having a similar albeit delayed effect. They have also proven to be beneficial in the prevention of BPH progression, as measured by prostate volume, the risk of developing acute urinary retention, and the risk of having BPH-related surgery.[3] The use of an alpha-adrenergic receptor antagonist and a 5-alpha-reductase inhibitor as combination therapy seeks to provide symptomatic relief while preventing progression

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of BPH and has been validated by the Medical Therapy of Prostate Symptoms (MTOPS) trial.[4] Anti-cholinergic agents and phosphodiesterase-5 inhibitors have also recently shown efficacy in the management of LUTS.

Surgical therapy, despite being the mainstay of treatment for LUTS secondary to BPH in the past, is now considered second line therapy and is usually reserved for patients after a trial of medical therapy. The goal of surgical therapy is to "debulk" the prostate, effectively reducing resistance to urine flow. Surgical therapy ranges from office-based to same day surgery to inpatient surgery. Minimally invasive therapy, including transurethral microwave therapy (TUMT) and transurethral needle ablation of the prostate (TUNA), can be performed in an office setting and result in partially relieving symptoms secondary to BPH. Transurethral resection of the prostate (TURP), transurethral incision of the prostate (TUIP), and laser therapies are endoscopic therapies performed in an operating room that result in significant relief of LUTS in patients with BPH. Open prostatectomy is an open operative procedure reserved for patients with large volume prostates that also results in significant relief of LUTS.

Etiology of BPH

The etiology of BPH is multifactorial and not definitively established. Benign Prostatic Hyperplasia refers to stromal and glandular epithelial hyperplasia that occurs in the zone of the prostate that surrounds the urethra. This overgrowth is dependent mainly on androgens, particularly dihydrotestosterone (DHT).[5] 5-alpha-reductase is responsible for the conversion of testosterone to DHT, an androgen with five times the potency of testosterone for the androgen receptor. DHT binds to androgen receptor and the complex is primarily responsible for stimulation of growth factors that influence prostate cell division and growth and therefore maintain the balance between cell proliferation and cell death. Elevated levels of DHT, along with hypothesized hormonal imbalances, result in BPH.[2,5] The lack of prostate growth and resultant BPH or prostate cancer in male pseudohermaphrodites due to 5-alpha-reductase deficiency was first reported in 1974.[6,7] These observations were the rationale for the use of 5-alpha-reductase inhibitors in the treatment of BPH.

Prostate smooth muscle represents a significant volume of the gland[8] and its activity is mediated by the sympathetic nervous system.[9] Prostate smooth muscle tension has recently been shown to be mediated by alpha1-adenoreceptor receptor.[10] This is the rationale for the use of alpha-adrenergic receptor antagonists and more recently uroselective alpha-adrenergic receptor antagonists for the treatment of symptomatic BPH.

Natural history of BPH

BPH is a chronic, progressive condition that worsens with age. The natural history of BPH is progression in the majority of patients. This results in increased prostate size, worsening of symptoms, deterioration in urinary flow rate, increased risk of acute urinary retention, and increased risk of surgery for BPH.[11] Longitudinal studies have shown an increase of moderate to severe urinary symptoms from 13% in the fifth decade to 28% in the eighth decade.[12] An association between prostate size and urinary symptoms and flow rates has also been documented, with men developing diminishing flow rates with age.[13] Men in the sixth decade have an average flow rate of 20 to 21 mL/sec, whereas men in the eighth decade have an average flow rate of 13 to 15 mL/sec.[14] Men in their seventh decade with moderate LUTS had a 13% 10-year risk of developing acute urinary retention in longitudinal studies. Furthermore, men with prostate volumes greater than 20 mL and flow rate less than 12 mL/sec had a respective threefold and fourfold increased risk.[15] Along with the risk of acute urinary retention, the risk of undergoing BPH-related surgery also increases with age.[16] Estimated prostate growth rates increased by 1.6% per year in a large community based study.[16] Higher baseline prostate volume and elevated serum prostate-specific antigen (PSA) are associated with BPH progression.[3,16,17] This has led the AUA Practice Guidelines Committee to recommend a urinalysis, PSA, and completion of a validated symptom index in the initial evaluation of patients who seek medical attention due to symptomatic BPH.[11]

Overview of BPH therapy

Symptomatic relief is the most common reason men seek treatment for BPH and therefore the goal of therapy for BPH is usually relief of these LUTS.[11] LUTS symptoms are generally measured by using a validated, reproducible index that is designed to determine disease severity and determine response to therapy – the American Urological Association's Symptom Score (AUASS),[11] also adopted as the International Prostate Symptom Score (IPSS). Serial AUASS are particularly useful in following patients as they are treated with various forms of therapy. It should be noted that AUASS alone is not a reliable indicator of LUTS suggestive of BPH, but is a quantitative measure of LUTS after the diagnosis is made. Medical therapy is the mainstay for treatment of men suffering from mild to moderate LUTS. More invasive therapy is usually reserved for medical failures. There are, however, some clear indications for surgical therapy including acute urinary retention not responsive to a trial of alpha-adrenergic receptor antagonists,

recurrent bladder stones, azotemia, recurrent urinary tract infections, and intractable hematuria.[11]

Surgical therapy for BPH has traditionally been electrosurgical resection of the prostate (TURP) or open prostatectomy. These therapies are associated with excellent, durable results with acceptable morbidity.[11] Recent advances in laser prostatectomy have made this procedure comparable to the standard TURP, however long-term durability results are not available yet.[18,19] Because of decreased morbidity, laser prostatectomy can be performed effectively in patients who have failed medical therapy and are considered too high a risk for traditional surgical therapy.[20,21]

Minimally invasive surgical therapy, office-based therapies such as transurethral needle ablation of the prostate, transurethral microwave therapy, or interstitial laser coagulation, result in significant increases in maximum urinary flow rate (Qmax) and significant decreases in AUASS.[22] However, these types of therapies are associated with a significant re-treatment rate and their durability has not been adequately assessed.

Medical therapy

The initial form of therapy for BPH is medical, especially in patients with mild-moderate symptoms and no clear indication for surgical intervention.[11] Current accepted medical therapy consists of alpha-adrenergic receptor antagonists, 5-alpha-reductase inhibitors, or a combination.

Alpha-adrenergic receptor antagonists

Alpha-adrenergic receptor antagonists are the main class of agents used for medical therapy of symptomatic BPH. Their use is based on the hypothesis that BPH arises from bladder-outlet obstruction and a large proportion of cellular volume is made up of smooth muscle, whose tension is mediated by alpha-adrenergic receptors.[23] Four alpha-adrenergic receptor antagonists are currently approved to treat LUTS by the Food and Drug Administration (FDA) in the USA: terazosin (Hytrin®), doxazosin (Cardura®), tamsulosin (Flomax®), and alfuzosin (UroXatral®).

The alpha-adrenergic receptor antagonist terazosin has been used for the treatment of BPH since 1992 and was approved for such use in 1993 by the FDA. A multicenter trial of terazosin demonstrated the efficacy of alpha-adrenergic receptor antagonists with an approximately 6-point improvement in AUASS and 3 mL/sec improvement in maximum urinary flow rate (Qmax) after 1 year of therapy.[24] Subsequent multicenter trials with doxazosin demonstrated similar clinical results,[25,26] and the alpha-adrenergic receptor antagonists became the medical therapy of choice for BPH. Side effects of alpha-adrenergic receptor antagonist therapy (Table 1) can hinder compliance and consist mainly of dizziness, postural hypotension, asthenia, nasal congestion, gastrointestinal symptoms, headache, and occasionally retrograde ejaculation.[27] Dizziness and asthenia are the main reason for discontinuation of alpha-adrenergic receptor antagonists.

Uroselectivity, the preferential action on the prostate and bladder with decreased LUTS while producing minimal side effects, has become a primary consideration when choosing an alpha-adrenergic receptor antagonist.[27] Tamsulosin, an alpha 1a and 1d subtype uroselective alpha-adrenergic receptor antagonist, was approved by the FDA in 1997 and has similar efficacy to terazosin and doxazosin.[28] It has significantly decreased cardiovascular side effects and has become the alpha-blocker of choice for most urologists. Long-term safety and efficacy has been established for tamsulosin via a 4-year open label extension trial that evaluated patients that had at least 2 years prior experience with the drug.[28] This study of 609 patients demonstrated that rapid improvements in AUA symptom index and maximum urinary flow rates were sustained throughout the maximum duration of the study – potentially 6 years. It also contained the longest follow-up for patients on any alpha-adrenergic receptor antagonist and demonstrated excellent safety and tolerability of tamsulosin. Alfuzosin, another uroselective agent, available in Europe for years, but recently approved by the FDA in the USA,[29] results in improvement of LUTS and flow rates that appear sustainable over time.[30]

Patients on alpha-adrenergic receptor antagonist therapy need to be monitored for the development of side effects, particularly on initiation of therapy. The non-uroselective

Table 1 Adverse events with alpha-adrenergic receptor antagonists (placebo rates in parenthesis)[27,50]

	Terazosin (%)	Alfuzosin OD (%)	Doxazosin (%)	Tamsulosin (%)
Dizziness	3–26 (3–7)	2.1–7.4 (1.3–2.9)	17–24 (4–6)	3–11 (0–5)
Hypotension	2–9 (0.5–1)	0.7–3.4 (0.0–3.4)	2.5–8.0 (0.0)	0.0 (0.5–1.0)
Ejaculatory disorders	0.0–1.4 (0.0–1.0)	0.0–0.6 (0.0–1.3)	0.0 (0.0)	1.0–26.0 (0.0–1.0)
Discontinuations	16–38 (8–17)	11 (6)	11–22 (4–23)	7–13 (9–11)

agents, terazosin and doxazosin, in particular need to be titrated to ensure that orthostatic hypotension does not develop.[27]

5-alpha-reductase inhibitors

The design and chemistry of 5-alpha-reductase inhibitors has been thoroughly studied and reviewed.[31] The most extensively studied are the 17b-substituted-4-azasteroids of which two (finasteride and dutasteride) are now approved for human use. The first of these to be approved for use by the FDA for treatment of BPH was finasteride, a potent competitive inhibitor of 5-alpha-reductase that shows no affinity for the androgen receptor.[32] This drug inhibits the type 2 isoenzyme of 5-alpha-reductase, which is present at high levels in the prostate. The principal North American study to evaluate efficacy was conducted by the Finasteride Study Group in 1992.[33] This study of 895 men revealed a small but significant improvement in symptoms and flow rate with finasteride over placebo. The study also noted an approximately 20% decrease in prostate volume after 1 year of treatment with finasteride. These results were confirmed by a subsequent European study.[34]

The definitive muticenter trial to examine the role of finasteride in the treatment of symptomatic BPH was performed by the Finasteride Long-Term Efficacy and Safety Study group (PLESS) and was reported in 1998.[3] This large double-blind, randomized, placebo-controlled trial studied 3040 men with moderate-to-severe urinary symptoms and enlarged prostate glands who were treated with 5 mg of finasteride daily or placebo for 4 years. At the end of the study, patients treated with finasteride had a significantly higher decrease in AUASS (2.6 vs 1.0) and increase in Qmax (1.9 mL/sec vs 0.2 mL/sec) compared to placebo. The prostate volume also decreased an average 18% in the finasteride group compared to an increase of 14% in the placebo group. The most significant finding in the study, however, related to the progression of BPH. The group of men treated with finasteride had a significantly lower risk of acute urinary retention (51% risk reduction) and the need for BPH-related surgery (55% risk reduction). The benefit of finasteride was evident at 4 months and continued throughout the trial. Long-term (7- to 8-year) experience with finasteride has been reported and revealed that long-term treatment with finasteride was well tolerated and resulted in durable symptom relief and improvement in prostate volume and urinary flow.[35]

Subgroup analysis of the PLESS data revealed that men in the finasteride treated arm had significantly less bother, activity interference, and worry due to urinary symptoms than the placebo group, with more pronounced differences in men with PSA levels greater than 1.4 ng/mL.[36] In fact, baseline serum PSA and prostate volume predicted long-term changes in symptoms and flow rate.[17] Patients with baseline serum PSA levels greater than 1.4 ng/mL and enlarged prostates had the best response to finasteride versus placebo. Age was not a factor in the efficacy of finasteride.[37] There was no impact on bone mineral density in men treated with finasteride.[38] The Finasteride Urodynamics Study Group evaluated pressure-flow parameters in men receiving finasteride for 2 years and found that men with prostate volumes greater than 40 mL continued to have decreases in detrusor pressure at Qmax throughout the course of the study.[39]

Dutasteride, a type 1 and type 2 5-alpha-reductase inhibitor, was approved for the treatment of BPH by the FDA in 2002. Dutasteride, because of dual inhibition of 5-alpha-reductase, results in a greater than 90% decrease in serum DHT levels.[40] Three parallel, multicenter, randomized, placebo-controlled trials of 24 months' duration have examined the safety and efficacy of dutasteride in men with BPH.[40] All three studies included men 50 years or older with a clinical diagnosis of BPH, a transrectal ultrasonography (TRUS) prostate volume greater than 30 mL, AUASS of 12 or more, and Qmax of 15 mL/sec or less. The pooled results of these trials showed a significantly lower AUASS for the dutasteride arm versus placebo (–4.5 vs –2.3), and significantly higher Qmax for the dutasteride arm vs placebo (2.2 mL/sec vs 0.6 mL/sec) at 24 months. The prostate volume decreased by approximately 25% at 2 years. These studies also confirmed the PLESS finding of decreased BPH progression in patients being treated with 5-alpha-reductase inhibitors. Risk reduction of acute urinary retention was 57% and the risk reduction of BPH-related surgery was 48% compared with placebo. These studies also evaluated the adverse events of dutasteride and found a small but significant increase in impotence, decreased libido, gynecomastia, and ejaculation disorder. Interestingly, only the rate of gynecomastia was significantly higher than placebo after 1 year of therapy. The PLESS trial noted similar adverse events with finasteride (Table 2).

Men started on 5-alpha-reductase inhibitor therapy should be counseled about the slow onset of action of this therapy (greater than 3 months) and about the side effects of the therapy. Table 2 lists the side effects, mainly sexual including decreased libido, impotence, ejaculatory disorder, and gynecomastia.[33,40] A breast examination should be performed periodically by the physician and

Table 2 Adverse events with 5-alpha-reductase inhibitors.[33,40]

	Finasteride (%)	Dutasteride (%)	Placebo (%)
Asthenia	2		3
Dizziness	5		5
GI symptoms	6		6
Headache	4		5
Hypotension	**4**		2
Nasal congestion	**9**		6
Ejaculatory disorders	**4**	**2**	1
Erectile dysfunction	**8**	**7**	4
Decreased libido	**5**	**4**	3
Gynecomastia	1	2	2

Notes: bold is significantly different from placebo $p < 0.05$.

the patient because of the risk of gynecomastia. The side effects tend to diminish after a period of time, a fact that should be made clear to patients. Consideration should be given to a transrectal ultrasound guided systematic biopsy of the prostate to rule out significant prostate cancer in those men with elevated PSAs. The PSA decreases by about 50% after a year of therapy from baseline with 5-alpha-reductase inhibitors – a fact that should be accounted for during yearly prostate cancer screening for men greater than age 50.[40] A reasonable rule-of-thumb for men who are candidates for prostate cancer screening and who have been on 5-alpha-reductase inhibitor monotherapy or combination therapy is to use a PSA cutoff level of 2.0 ng/mL to initiate further diagnostic workup for prostate cancer.

5-alpha-reductase inhibitor therapy may also play a role in the treatment of BPH-induced hematuria and an adjunct role in the surgical treatment of BPH. Recent studies demonstrate that 5-alpha-reductase inhibitors are effective in the treatment of BPH-induced hematuria,[41] probably through their effect on prostate microvessel density.[42] Multiple studies now support the role of short-term 5-alpha-reductase inhibitor monotherapy prior to definitive surgical resection in order to decrease hematuria during and after the procedure.[43,44]

5-alpha-reductase inhibitor and alpha-adrenergic receptor antagonist combination therapy

The role of finasteride as monotherapy and as part of combination therapy with terazosin was examined in 1996 by the Veterans Affairs Cooperative Studies Benign Prostatic Hyperplasia Study Group.[45] This double-blind, placebo-controlled study enrolled 1229 men and studied the effects of placebo, finasteride alone, terazosin alone, and finasteride and terazosin on men with respect to AUASS and Qmax for 1 year. The AUASS decreased by more than 3 points in the terazosin and combination arm but did not significantly change in the finasteride group compared with placebo. Similarly, the Qmax increased significantly in the terazosin and combination arms (1.3 and 1.8 mL/sec) but did not change in the finasteride arm when compared to placebo. The results of this study did not agree with 5-alpha-reductase inhibitor studies, perhaps because the average prostate size in the VA study was much smaller than in earlier trials.

Following the VA Cooperative study, a European study to evaluate the effect of combination therapy was undertaken. The PREDICT trial was a prospective, double-blind, placebo control trial that randomized 1095 men aged 50 to 80 years to treatment for 52 weeks with doxazosin, finasteride, the combination, and placebo.[46] Doxazosin was titrated to a maximum of 8 mg per day to maximize symptomatic improvement or urinary flow rate improvements without the development of hypotension. Finasteride was administered at the standard 5 mg daily dose. The discontinuation rates for doxazosin (28%), finasteride (31%), and combination (31%) were similar to placebo (28%). This 1-year study showed a significant improvement in the doxazosin and combination groups compared to placebo with respect to AUASS (−8.3 and −8.5 vs −5.7) and Qmax (3.6 mL/sec and 3.8 mL/sec vs 1.4 mL/s). Interestingly, this study did not show a difference in the finasteride group compared to placebo. This result was similar to and appeared to validate the results of the VA cooperative study. However, the limitations of the PREDICT trial are likely the same as that for the VA study – the average prostate size was small (36 mL) and the results were measured short term (1 year) compared to the PLESS and dutasteride monotherapy studies. The 4-year PLESS study and the 2-year dutasteride studies both showed significant improvements in AUASS and Qmax with 5-alpha-reductase monotherapy in contrast to the 1 year VA Cooperative and the PREDICT trial.

The definitive study for evaluation of combination therapy was sponsored by the National Institute of Health and initiated in 1995. The Medical Therapy of Prostate Symptoms (MTOPS) study was designed to evaluate the long-term efficacy of the alpha-adrenergic receptor antagonist doxazosin and the 5-alpha-reductase inhibitor finasteride, whether taken as monotherapy or in combination, in preventing or delaying the progression of BPH.[47] MTOPS randomized 3047 men at least 50 years of age with moderate

to severe symptoms of BPH based on AUASS who had no previous medical, surgical, or experimental interventions for BPH into one of four groups: doxazosin alone, finasteride alone, placebo, and the combination of finasteride and doxazosin. BPH related events (four-point rise in AUASS, creatinine rise attributed to BPH, acute urinary retention, recurrent urinary tract infection or urosepsis, and incontinence), incidence of BPH invasive therapy, change in Qmax, and change in AUASS were measured in each group. Initial results of the MTOPS study were presented in 2002 and the final results were published in 2004.[4] At 5 years, the rate of acute urinary retention and invasive surgery was significantly higher in the doxazosin and placebo groups compared to the finasteride and combination groups. Changes in AUASS and Qmax were highest in the combination group at year 4 (3.0 and 2.3 mL/sec difference between combination and placebo). The doxazosin group had slightly higher changes in AUASS and Qmax than the finasteride group (2.0 and 1.1 mL/sec versus 1.0 and 0.8 mL/sec), but both were significantly better than placebo. The investigators went further and evaluated whether any baseline parameter predicted BPH progression. In their analysis, an AUASS greater than 17 predicted BPH progression and increased rate of BPH-related therapy in all groups. PSA greater than 1.6 ng/mL predicted symptom and overall BPH progression in the doxazosin group, acute urinary retention in all groups, and BPH-related therapy in the doxazosin and combination groups but not in the finasteride group. A TRUS volume greater than 31 mL predicted acute urinary retention in the doxazosin and finasteride groups but not in the combination group. They concluded that baseline parameters are of most utility in predicting progression in the doxazosin group compared to the finasteride and combination groups. These results along with the PLESS results changed the paradigm for medical therapy. Two different goals of medical therapy are now apparent – treat the symptoms of BPH and prevent progression of BPH. Symptoms can be treated with alpha adrenergic receptor antagonists, long-term 5-alpha-reductase inhibitor therapy, or combination therapy whereas only 5-alpha-reductase inhibitors (as monotherapy or part of combination therapy) seem to prevent progression of BPH.

In the early 21st century, 5-alpha-reductase therapy is used to prevent progression of BPH, and is a viable alternative to alpha blockers or combination therapy for the treatment of symptoms. Table 3 summarizes data from multiple clinical trials that evaluated use of 5-alpha-reductase inhibitors as monotherapy or as part of combination therapy. The PLESS and MTOPS trials, along with recent data on dutasteride, clearly show that therapy with a 5-alpha-reductase inhibitor decreases the risk of acute urinary retention and BPH-related surgery.[3,4,40] These trials also confirm that BPH progression is related to baseline PSA, with values greater than 1.4–1.6 ng/mL leading to significantly greater risk of BPH-related events.[3,4] Baseline prostate size has similar implications. Prostate volumes greater than 30 to 40 mL are also associated with significantly higher rates of BPH-related events.[3,4] The improvement in AUASS and Qmax with 5-alpha-reductase inhibitors is significantly different from placebo.[3,4,40] Open label extensions of early trials show that the results of finasteride are durable without increases in adverse events at 6 to 10 years.[35,48,49] Prior to release of MTOPS data, alpha adrenergic receptor antagonists seemed to have a greater impact on improvement in Qmax and AUASS.[24–26,50] However, results of the MTOPS trial clearly show that the combination of alpha adrenergic receptor antagonists and 5-alpha-reductase inhibitors has the greatest impact on Qmax

Table 3 Summary of large North American studies that evaluated the role of 5-alpha-reductase inhibitor monotherapy and combination therapy with 5-alpha-reductase inhibitors and alpha-adrenergic receptor antagonists[3,4,33,40,45]

	Finasteride study group	VA coop (5ARI)	VA coop (comb)	PLESS	MTOPS (5ARI)	MTOPS (comb)	Dutasteride multicenter
Year published	1992	1996	1996	1998	2004	2004	2002
Follow-up (years)	1	1	1	4	5	5	2
Number of patients	895	243	254	1384	768	786	1510
Mean prostate volume		36.2	37.2	54	36.9	36.4	55
Change in AUASS	decreased	NS	3.6	2	1	3	2.2
Change in Qmax	1.6	NS	1.8	1.7	0.8	2.3	1.6
RR in AUR	NR	NR	NR	57	68	81	57
RR in BPH surgery	NR	NR	NR	55	64	67	48

Abbreviations: AUASS, American Urological Association's Symptom Score; AUR, acute urinary retention; BPH, benign prostatic hyperplasia; NS, not significant; NR, not reported.

and AUASS.[4] Therefore, it is reasonable to use combination therapy on most men, and reserve 5-alpha-reductase monotherapy for those men that cannot tolerate alpha-adrenergic receptor antagonists because of side effects, those that are unwilling to pay for two medications, or those men with large volume prostates or elevated PSA who are at a high risk of progression without LUTS. The MTOPS data demonstrates that the improvements in Qmax and AUASS achieved by 5-alpha-reductase inhibitor and alpha-adrenergic receptor antagonist combination therapy are significantly greater than either alone. If combination therapy cannot be tolerated, improvements by 5-alpha-reductase inhibitor monotherapy approach those that are achieved by alpha-adrenergic receptor antagonist monotherapy, although the time to achieve these results is longer.

Anticholinergic therapy

Newer classes of pharmacologic agents have recently been used to treat LUTS secondary to BPH. LUTS due to BPH often coexists with LUTS due to overactive bladder (OAB), and the most common pharmacologic agents for the treatment of OAB symptoms are anticholinergics. This fact has led to multiple studies evaluating the efficacy of anticholinergics for the treatment of LUTS secondary to BPH. Tolterodine extended release was shown to be of benefit in men that could not tolerate alpha blockers. In a prospective trial of 43 patients, treatment with tolterodine extended release significantly reduced AUASS by 6.1 points 6 months after initiation of therapy[51] and also resulted in significant improvement in maximum flow rate and post-void residual urine. A subsequent randomized trial compared tolterodine ER, tamsulosin, placebo, and combination.[52] This study determined that tamsulosin alone and the combination of tamsulosin and tolterodine ER resulted in significant improvent in IPSS compared to the other two groups. However, with respect to IPSS QOL score, the combination of tamsulosin and tolterodine ER was significantly better than either drug alone or placebo. This may be due to patients that suffer from incontinence due to BPH and are not reliably captured by the IPSS, but are capture by the IPSS QOL score. Interestingly, despite a high rate of dry mouth (27% in the combination group), adverse events were low in all groups, and urinary retention only occurred in 0.7% of the patients treated with toterodine ER, alone or in combination. Anticholinergic agents may be a useful adjunt to alpha blocker therapy in patients that suffer from irritative symptoms[53] or have small volume prostates.[54]

Phosphodiesterase inhibitors

Another class of medications that has shown improvement in LUTS secondary to BPH is phosphodiesterase-5 inhibitors, used currently in the treatment of erectile dysfunction. A recent study showed significant improvement in LUTS secondary to BPH in patients that received sildenafil and alfuzosin over patients that received alfuzosin alone.[55] All three of the PDE5 inhibitors available in the US, sildenafil,[55] vardenafil,[56] and tadalafil,[57] appear to be effective in the treatment of LUTS secondary to BPH. The use of phosphodiesterase-5 inhibitors in not without controversy, however, given the fact that short-active phosphodiesterase inhibitors such as sildenafil need to dosed separate from alpha-blockers such as tamsulosin because of potential hypotensive effects.

Botulinum toxin A

Injection of botulinum toxin A into the prostate is a novel treatment for LUTS secondary to BPH. This treatment, applied through trans-perineal injection of 100 units of botulinum toxin into each lobe of the prostate under trans-rectal guidance, was subjected to a randomized control trial, first reported in 2003.[58] In this trial 30 patients showed significant improvement in IPSS (65% decrease) and serum PSA (51% decrease) compared to controls, who had injections of saline without botulinum toxin A, at a median follow-up of 19.6 months. Subsequent long term follow-up of 77 patients up to 30 months has shown similar results – significant reduction in IPSS (approximately 50% lower), significant improvement in maximum flow rate (approximately 70% higher), and significant reduction in serum PSA values (approximately 50% lower).[59] Importantly, no adverse events were noted.

Surgical therapy

Surgical therapy remains a mainstay for treatment of LUTS secondary to BPH, refractory to medical therapy. As noted earlier, there are a host of surgical procedures available. Current practice is to offer minimally invasive surgery to patients who do not want or are unfit for a more involved operation. Endoscopic surgery is the gold standard for treatment of LUTS secondary to BPH, with open surgery reserved for those patients with large glands or those that need concomitant procedures.

Minimally invasive surgery

Multiple BPH therapies, including water-based thermotherapy and interstitial laser coagulation, have been touted as being

minimally invasive. Currently accepted forms of minimally invasive surgery are TUMT and TUNA. In the USA, FDA approved TUMT therapies are Thematrx TMX-2000™, Prostatron®, Targis®, Cooled ThermoCath®, CoreTherm®, and Prolieve®.[60] TUMT is an office-based procedure that uses a catheter based system containing a microwave antenna for energy delivery. It has evolved from the original low-power to the current high-power treatments. In general, TUMT is considered safer than standard endoscopic therapies for LUTS secondary to BPH such as TURP, with lower rates of hematuria, urinary tract infection, erectile dysfunction, ejaculatory problems, urethral strictures, urinary incontinence, and blood transfusion. TUMT decreases IPSS by 24% to 87%, and increases maximum urinary flow rate by approximately 50%. While these results are better than medical therapy, TUMT is associated with rates of invasive retreatment as high as 66% at 5 years.[61] In addition, TUMT therapy in contraindicated in patients with adverse anatomy (such as the presence of a significant prostatic intra-vesical component) and is not recommended for patients in urinary retention.

TUNA is an office-based therapy, first introduced in 1993, that relies on delivering energy via a radiofrequency generator, an optical transurethral device and monopolar catheters that allow selective necrosis of tissue.[62] Similar to TUMT, TUNA likewise is safer than TURP but with less efficacy. The only FDA approved TUNA system in the USA is Prostiva™.

Endoscopic therapy

Electrosurgical transurethral resection of the prostate

TURP is a transurethral endoscopic procedure that relies on electrosurgical resection of prostate adenoma, followed by removal of "prostate chips" from the bladder with an aqueous evacuator.[63] It has been performed since early in the last century, and has evolved to be the procedure of choice for surgical treatment of LUTS secondary to BPH and is often called the gold standard surgical treatment for BPH/LUTS. While TURP is known to be efficacious for the treatment of LUTS secondary to BPH, it is associated with reasonably high rates of complications, including hematuria, reoperation, dilutional hyponatremia, and the need for blood transfusion.[64] Advances in optics and energy generation/delivery systems have decreased complications significantly in modern times.[65] However, the number of TURPs performed in the USA continues to decrease yearly, perhaps because of the perception of increased morbidity.[66]

Transurethral electro-vaporization of the prostate evolved from the electrosurgical TURP to limit morbidity, particularly hematuria and blood transfusions.[67] Subsequent meta-analysis has shown this modality to be comparative to TURP.[68] Electrovaporization, however, does require higher energy sources and therefore has not been adopted by the general urology community.

Saline bipolar transurethral resection of the prostate is a further evolution of electrosurgical TURP.[69] It consists of similar transurethral equipment as TURP; however, it relies on bipolar current with both electrodes within the cystoscope and therefore can be used with saline as the irrigant. This decreases the risk of dilutional hyponatremia and allows the operator to perform the procedure for a longer period of time. Multiple randomized control trials have shown similar efficacy to TURP.[70] Some have touted this procedure as a useful adjunct to resident training because of the fact that saline is used as an irrigant decreasing the risk of dilutional hyponatremia – which increases with operative time in standard TURP.[71]

A limited version of the electrosurgical TURP is the TUIP, which is designed to limit rates of retrograde ejaculation, particularly for younger men interested in fertility. TUIP consists of deep unilateral or bilateral incisions through the base of the prostate from bladder neck to the veru montanum. A unilateral incision in on either side of midline (5 or 7 o'clock position as viewed through the cystoscope), whereas a bilateral incision is on both sides. TUIP is indicated for patients with small volume prostate glands (less than 30 mL), and those interested in preserving antegrade ejaculation. The risk of retrograde ejaculation is markedly diminished with a TUIP as compared to a TURP with rates around 20% for bilateral TUIP.[72]

Transurethral laser procedures

Laser procedures for LUTS secondary to BPH have been available since the mid 1990s. The neodymium-based visual laser ablation of the prostate procedure was a endoscopic procedure which relied on using a 980 nm neodymium laser which essentially cause coagulation necrosis of the underlying tissue.[73] This procedure proved efficacious in the long term, but had significant short-term morbidity, particularly retreatment or urinary retention with the need for a urethral catheter for a prolonged period of time.[74] Because of the significant short term urinary morbidity and the advent of more efficacious laser procedures, this procedure has been generally abandoned by practicing urologists.

Two other laser technologies based on the Holmium laser and the Greenlight laser are currently used for the treatment

of symptomatic BPH. The holmium laser was first used for LUTS secondary to BPH as an ablative procedure, also known as Holmium laser ablation of the prostate (HoLAP).[75] This procedure consists of visually ablating prostate tissue with a 1032 nm Holmium laser using a near-contact technique. HoLAP is efficacious as compared to TURP with reasonable long-term results, decreased morbidity, but at the cost of higher operative times.[76] Holmium laser enucleation of the prostate (HoLEP) is a procedure which consists of using an end-firing fiber to aim the holmium laser beam at the interface between the surgical capsule and the prostate adenoma and enucleating the prostate adenoma by separating it from the peripheral zone.[77] This technique is somewhat difficult to master, but once mastered results are excellent.[78] In fact, its efficacy is comparable to open prostatectomy in large glands and TURP in smaller glands with decreased morbidity.[79]

The Greenlight laser vaporization of the prostate is the newest laser procedure for treatment of LUTS secondary to BPH. It consists of using a 532 nm potassium tytanyl phosphate/greenlight laser in non-contact mode to ablate prostate tissue.[80] Greenlight laser vaporization of the prostate has been shown to be as effective as TURP with decreased morbidity in a host of patient populations.[81,82] Because it is extremely hemostatic and uses saline as the irrigant, there is very little risk of significant bleeding or dilutional hyponatremia, making this modality ideal for high-risk patients.[83,84] Laser procedures for the prostate have increased dramatically since the widespread adoption of the high-power Greenlight laser vaporization of the prostate around 2002, and now account for approximately 30% of surgical procedures for BPH.[85]

Open prostatectomy

Open (or "simple") prostatectomy is an open surgical procedure that consists of enucleating the prostate adenoma through a transvesical, suprapubic route or a trans-prostate, retropubic route.[86] This operation is the most efficacious for patients with large volume prostate glands. However, it is associated with significant blood loss, prolonged hospital stay, and increased morbidity as compared to TURP or laser procedures. Typically, in the age of advanced endoscopic surgery, open prostatectomy is reserved for patients fit for open surgery with large volume glands and the need for concomitant procedures, such as removal of large bladder stones or the need for a bladder diverticulectomy.

Conclusion

Theraputic options for treatment of LUTS secondary to BPH are varied. Once other causes of LUTS have been eliminated, it is reasonable to treat mild to moderate LUTS with medical therapy. Initial medical therapy consists of alpha blockers, 5-alpha-reductase inhibitors, or a combination. Additional classes of pharmacologic agents appear to have efficacy for LUTS, including anti-cholinergic agents and phosphodiesterase inhibitors, and may be included in the pharmacologic armamentarium in the future, but are not as of yet considered standard of care. Surgical therapy is an option for patients that are unable to tolerate medical therapy or for whom medical therapy is not efficacious. Traditional surgical therapy consists of TURP, which is still considered the gold standard. Laser procedures, particularly Greenlight laser vaporization of the prostate or Holmium laser ablation/enucleation of the prostate, are being used more often with similar results as TURP and decreased complications. Open surgery for LUTS secondary to BPH is reserved for patients with very large symptomatic prostate glands or those with concomitant pathology such as large bladder stones or symptomatic bladder diverticula.

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