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Pharmacotherapy and herbal treatment of benign prostatic hyperplasia

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TABLE OF CONTENTS

1. Abstract
2. Introduction
3. Alpha-adrenergic receptor blockers
4. 5-Alpha-reductase Inhibitors
5. Combination therapy of α-blockers and 5-ARIs
6. Phytomedicines
7. Chinese herbal medicine
8. Combination therapy of Western medicine and Chinese herbal medicine
9. Phosphodiesterase-5 inhibitors
10. Anticholinergic Agents
11. Conclusions
12. Acknowledgements
13. References

1. ABSTRACT

Benign prostatic hyperplasia (BPH) is the most common tumor in aging men, and is associated with lower urinary tract symptoms (LUTS). Treatment options include watchful waiting, life-style modification, pharmacologic treatment, and surgery. Alpha-adrenergic receptor blockers (α-blockers) decrease LUTS and increase urinary flow rates in men with symptomatic BPH. 5-Alpha-reductase inhibitors (5-ARIs) decrease the production of dihydrotestosterone within the prostate, which results in decreased prostate volume. For patients with moderate to severe symptoms and a large prostate, combination therapy with α-blockers and 5-ARIs can further improve clinical efficacy of treatment. Numerous plant-based products (phytomedicines) are increasingly used as an alternative or complement the conventional medication. For some patients, phosphodiesterase-5 inhibitors (PDE5-Is) or antimuscarinic agents may be added. Here, we discuss the current pharmacotherapy of BPH.

2. INTRODUCTION

Benign prostatic hyperplasia (BPH), a histologic diagnosis that refers to smooth muscle and epithelial cell proliferation within the prostatic transition zone, is an almost universal occurrence in aging men and is probably the most common benign human neoplasm (1). The incidence of BPH increases with age. In men over 60 years of age, 50% are diagnosed with BPH, and 75% of men over the age of 70 have one or more symptoms attributable to BPH. Nearly all men develop microscopic BPH by the age of 90 years (2-4).

BPH manifests clinically with lower urinary tract symptoms (LUTS), which include urinary intermittency, frequency, straining, urgency, weak stream, incomplete emptying and nocturia. These symptoms are caused by disturbances in normal urine retention or voiding, which may be due to structural distortion and functional abnormality of the bladder neck, prostate, distal sphincter, or urethra (5, 6). However, these symptoms can be caused

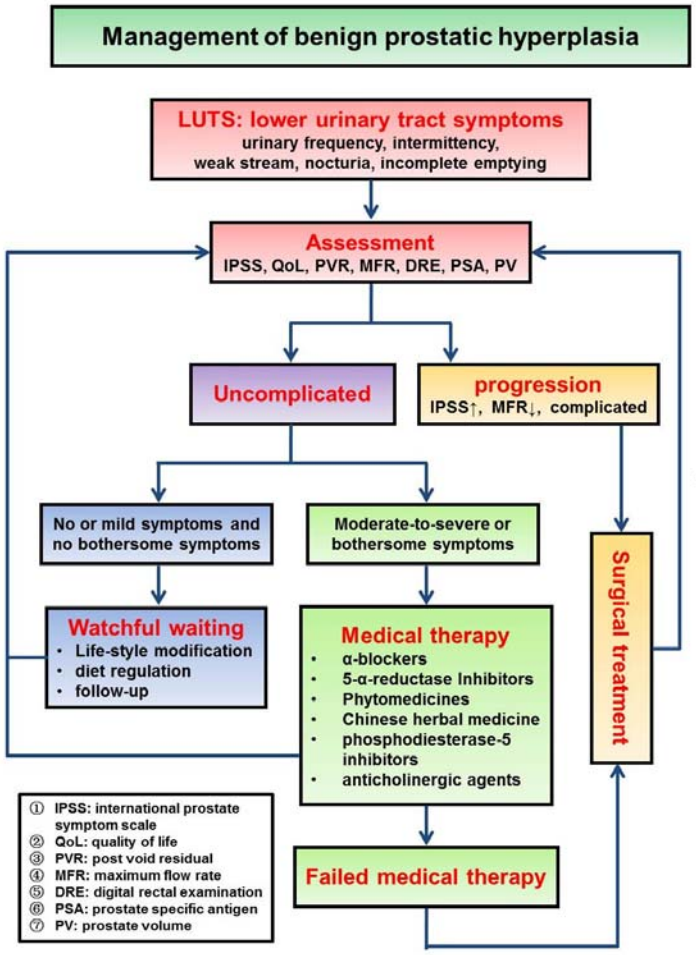

Figure 1. The current pharmacotherapy for the treatment of BPH.

by multiple conditions that include BPH as the most important and frequent cause, and the presence of these symptoms is not sufficient to make a diagnosis of BPH (7). BPH alone is rarely a life-threatening condition, but has a significant negative impact on quality of life (QoL) and causes a significant number of middle-aged to elderly men to seek treatment.

Treatment goals of BPH are to improve bothersome symptoms, prevent symptom progression, enhance QoL, and reduce longer term complications (including acute urinary retention, urinary incontinence, recurrent urinary tract infections, renal insufficiency, and the need for surgery) (7-11). Treatment options include watchful waiting, life-style modification, pharmacologic treatments, and major surgical or minimally invasive surgical treatments. Treatment choices are primarily determined by how severe and bothersome the symptoms are and by patient preference for types of interventions based on their weighting of established effectiveness and adverse effects. For men with moderate or severe symptoms that do not improve satisfactorily with life-style management, drug treatments for BPH can be effective, with an average reduction in the international prostate symptom scale (IPSS) (range 0 to 35) of three to six points from baseline. A four point change in the IPSS corresponds to a noticeable difference in patients and is used to assess the clinical significance of interventions or symptom progression (12). On the basis of this criterion, approximately 60% of men will notice an improvement in their symptoms with drug treatment (7, 8, 13, 14).

BPH patients are increasingly exploring the use of medical treatments, such as alpha adrenergic blockers, 5-alpha reductase inhibitors (5ARIs) and phytomedicines, over the former gold standard surgical procedure, particularly due to the risk of mortality and long-term morbidity associated with surgical procedures. In addition to conventional medical management, the number of patients who choose phytotherapies (e.g., *Serenoa repens*, *Pygeum africanum*, pollen extracts and Chinese herbal medicine) as alternative or complementary treatments is increasing steadily around the world (15-18). This paper reviews current pharmacotherapy, including Western medicine (WM), phytomedicines and traditional Chinese medicine (TCM), for the treatment of BPH. (Figure 1)

3. ALPHA-ADRENERGIC RECEPTOR BLOCKERS

Alpha-adrenergic receptor blockers (α-blockers) were initially developed as antihypertensive agents. It has been proved that α-blockers may produce a decrease in muscle tone and inhibit smooth muscle contraction by blocking the adrenergic receptors which are abundant in the bladder neck, prostatic capsule and prostatic tissue itself (19, 20). A number of clinical trials and systematic reviews have evaluated the efficacy and safety of α-blockers in the treatment of BPH. An overview of 15 systematic reviews provided an up-to-date summary of evidence regarding the efficacy and safety of different α1-blockers for BPH (21). This overview provided important implications for both clinical practice and research. In randomized controlled clinical trials involving men with symptomatic BPH defined primarily by the presence of moderate-to-severe LUTS and in some studies by decreased urinary flow rates, α-blockers were more effective than 5-Alpha-reductase inhibitors (5-ARIs) in improving the IPSS (21-24).

All α-blockers have similar efficacy in improving symptoms and urinary flow rates, and their effect is generally maximal within a month after initiation of treatment. Adjustment to the highest dose without side effects is necessary for nonselective α-blockers. In most men who respond to an α-blocker and who tolerate it well initially, the drug continues to work and is well tolerated for many years. Alfuzosin, doxazosin, tamsulosin, terazosin, and silodosin are approved by the Food and Drug Administration (FDA) for the treatment of LUTS related to BPH in men.

Head to head trials of α-blockers are few, small, and have serious methodological limitations (7, 8, 25, 26). As a class, α-blockers are subdivided on the basis of their degree of selectivity for the α1-receptor subtype. Terazosin, doxazosin, and alfuzosin are nonselective (i.e., they block α1-receptor subtypes equally). The wide distribution of α1B and α1D receptors in vascular and central nervous system tissues explains their common side effects (e.g., hypotension, dizziness, and fatigue) (19). Terazosin and doxazosin require dose titration to minimize initial adverse effects (such as syncope and dizziness). Tamsulosin and silodosin block α1A-adrenergic receptors better than α1B-adrenergic receptors and are considered to be selective for the α1-receptor subtype, and are generally effective in the absence of obtrusive side-effects (27). Tamsulosin and alfuzosin do not require dose titration, but no convincing evidence exists that they cause fewer cardiovascular adverse effects, such as symptomatic hypotension, than other α-blockers (7, 8, 25, 26). Few data exist on the safety of α-blockers in men taking drugs for erectile dysfunction; however, there is no absolute contraindication to their concomitant use.

4. 5-ALPHA-REDUCTASE INHIBITORS

5-ARIs, which block the conversion of testosterone to its active metabolite, dihydrotestosterone, shrink the prostate and reduce further prostatic growth. The 5-ARIs are appropriate and effective treatment alternatives for men with LUTS secondary to BPH who have demonstrable prostate enlargement. It can be used to prevent progression of LUTS secondary to BPH and to reduce the risk of urinary retention and future prostate-related surgery. Pivotal phase III trials have shown that the preventive benefits of 5-ARIs are that they have excluded men with mild LUTS at screening (28-30). However, 5-ARIs should not be used in men with LUTS secondary to BPH without prostatic enlargement. A prostate size of more than 30 g, measured with the use of ultrasonography, and a prostate-specific antigen (PSA) level of more than 1.5 ng per milliliter are recommended as surrogate criteria for initiating therapy with 5-ARIs (31).

There are two FDA-approved 5-ARIs: finasteride and dutasteride (32-34). Finasteride (5 mg daily) inhibits the 5-AR type II isoenzyme leading to decreases in serum dihydrotestosterone levels by 70 to 90%, whereas dutasteride (0.5 mg daily) blocks both type I and II 5-AR isoenzymes, reducing dihydrotestosterone to levels that approach zero. Both agents have been shown in randomized, placebo-controlled trials to reduce prostate size by as much as 25% and to decrease LUTS over a period of 2 to 6 months, with total IPSS decreasing by 4 to 5 points in men with larger prostates (>30 g) (35). Comparisons of the two 5-ARIs are difficult due to differences in study design and variations in the definition of prostate enlargement. Only one direct comparison trial suggested that the clinical efficacy of finasteride and dutasteride is similar (36). Finasteride suppresses prostatic vascular endothelial growth factor. Prostate-related bleeding was found to respond to finasteride; bleeding was reduced or ceased completely and recurrent bleeding decreased (37, 38). Therefore, finasteride is an appropriate and effective treatment alternative in men with refractory hematuria presumably due to prostatic bleeding (i.e., after exclusion of any other causes of hematuria). A similar level of evidence concerning dutasteride was not reviewed; it is the expert opinion of the Panel that dutasteride likely functions in a similar fashion. A recent study assessed the role of dutasteride in preventing clinical progression of BPH in asymptomatic men with larger prostates and showed that dutasteride can significantly decrease the incidence of BPH clinical progression (39).

Side effects of both 5-ARIs include decreased libido, erectile dysfunction, decreased ejaculation, and gynecomastia (35, 40). Some trials assessing whether 5-ARIs could prevent prostate cancer demonstrated that treatment with either finasteride or dutasteride resulted in an absolute reduction in the risk of prostate cancer of up to 6 percentage points, but it was also associated with an increased risk of moderate-to-high-grade prostate cancer (Gleason score, ≥7) (40, 41). If prostate cancer is suspected or the PSA level begins to increase during therapy, the patient should be referred to a urologist (42). If PSA is measured with the aim of detecting prostate cancer, thresholds for “abnormal” values should be lowered because 5-ARIs can reduce PSA values by approximately 50% after 6 months of treatment (31, 40, 43).

5. COMBINATION THERAPY OF A-BLOCKERS AND 5-ARIS

Pivotal trials showed that combination therapy with α-blockers and 5-ARIs can halt the progression of

BPH in men with moderate to severe LUTS, with the greatest benefit noted in men with enlarged prostate volumes and / or high PSA. 5-ARIs have a direct impact on prostate size and have been shown to reduce retention even when used alone. However, better outcomes are achieved when 5-ARIs are combined with an α-blocker. The combination of an α-blocker and a 5-ARI has similar effects on QoL to that of an α-blocker alone in the first year and a half of treatment (28). The long-term effectiveness of combination therapy on symptom progression and the need for surgery depends on prostate size as assessed by digital rectal examination, ultrasonography or PSA level. For men with moderate to severe symptoms and a large prostate (>40 g) on digital rectal examination or ultrasonography or a baseline PSA level of >4 ng/ml, combination therapy can prevent approximately two episodes of clinical progression per 100 men per year over four years of treatment. Effectiveness was considerably less (or non-existent) in men with smaller prostates (24, 28).

Of note, there was also a higher incidence of adverse events following combination therapy versus either agent as monotherapy (44, 45). Disadvantages of the combination therapy described above compared with an α-blocker alone include the need for treatment for more than a year before a difference in outcomes is usually noticed; the fact that most men will have no additional benefit; higher medication costs; and sexual side effects (from the 5-ARI), which occur in about four additional patients per 100. The decision on when to use combination therapy for LUTS is complex and should ideally be based on informed, shared decision making between patients and providers that incorporates the above information on benefits and harms for the urinary symptoms as well as prevention of prostate cancer.

6. PHYTOMEDICINES

Phytomedicines have gained widespread interest, probably due to a perceived reduction in side effects, and the desire to maintain control over treatment (46-48). BPH patients are increasingly exploring the use of complementary alternative medicine, particularly due to the risk of mortality and long-term morbidity associated with surgical procedures. Moreover, α-blockers and 5-ARIs may often have unpleasant and undesirable side effects. The incidence of prostate diseases is continually rising and the effects of the phytomedicines already tested provide relief, and are comparable to traditional forms of treatment. Only a few phytomedicines are available in the international market, however, locally-sourced medicinal plants play a key role in basic healthcare, particularly in rural areas due to their accessibility and affordability. However, the use of these phytomedicines is controversial as most of the studies have not been subjected to rigorous preclinical pharmacological testing and formal clinical trials. Moreover, the active ingredients and dosage of active medication is unknown, the quality is not publicly controlled, and the mechanism of action is unclear (49).

Numerous plant-based products (phytotherapy) are commonly used for self-treatment of LUTS and are prescribed in some African, European and Asian countries. Systematic reviews have suggested that both saw palmetto and *Pygeum africanum* provide modest improvement in urinary symptoms and flow (50-52). Saw palmetto, an extract of the berries of the dwarf palm tree, *S. repens* (family Arecaceae), is most widely used (53). The liposterolic extract contains β-sitosterol, which is chemically related to cholesterol and has inhibitory effects on 5α-reductase. Various additional mechanisms have also been suggested, including inhibition of binding of dihydrotestosterone to cytosolic androgen receptors in prostate cells and an anti-inflammatory effect. However, two recent high quality randomized trials found that saw palmetto even at increased doses was no more effective than placebo in men with BPH and moderate to severe symptoms (54, 55). Ongoing trials are assessing the long-term effectiveness and safety of varying doses of both saw palmetto and *Pygeum africanum*.

7. CHINESE HERBAL MEDICINE

Herbal products from Chinese herbal medicine (CHM) are considered to be a powerful new trend in the development of novel pharmaceuticals (56), and have gained increasing attention due to their extensive applications in the treatment of diseases. In Asian countries, especially China, CHM is commonly used as an alternative or complement to conventional medication and phytotherapy (16, 17, 57-59). Before the introduction of conventional medication and surgery to China, the Chinese had solely relied on CHM to treat BPH for more than three thousand years.

BPH is usually attributed to the TCM category of ‘Long-Bi’, which encompasses difficulty in urination, pain and fullness in the lower abdomen and obstructed urination. Its hyperplastic nature can be classified into the category of ‘Zheng Jia’ (tumor) of TCM. TCM believes that the Yang deficiency in the kidney and blood stasis are the main syndrome differentiations in ‘Long Bi’ and ‘Zheng Jia’. Many CHMs based on the rich experiences of Zheng differentiation are also effective in treating patients with BPH. Therefore, tonifying the Yang in the kidney and removing blood stasis are considered to be the major strategy in treating ‘Long Bi’ and ‘Zheng Jia’.

However, the clinical efficacy and safety of CHM in the treatment of BPH remain unclear. Although much of the classic literature, case series and trials have reported the clinical effects of different formulae of Chinese medicine, the therapeutic effects of CHM as a whole have not been evaluated. A recent systematic review of randomized controlled trials was carried out to compare the efficacy and adverse events of CHM, either as single or adjuvant use with WM, with placebo or WM for BPH (16). The outcome demonstrated that CHM was superior to WM in improving QoL, reducing prostate volume (PV) and maximum flow rate (MFR) in patients with BPH, although it was less effective in ameliorating the IPSS score when compared with WM. The frequency of adverse events in CHM was similar to that of placebo and less than that of WM. The evidence is too weak to support the efficacy of

CHM for BPH due to the poor methodological quality and small number of trials included. The commonly used herbs identified here should provide insights for future clinical practice and research. Larger randomized controlled trials of better quality are needed to truly evaluate the efficacy of CHM.

The use of CHM as monotherapy and adjuvant therapy was diversified in the formula composition and dosage of the included studies. Such a large difference in herbal combinations may be due to the complexity of TCM diagnosis and the personal experiences of practitioners. Based on the symptoms and signs of individual patients, TCM practitioners would classify them into different syndrome differentiations (Zheng in Chinese) and prescribe herbal formulas accordingly (60). Some complementary herbs would be added if necessary. Therefore, even trials with exactly the same CHM formulas and dosages may not simulate the usual practice of TCM, thus proving the efficacy of a particular formula is impossible.

Compound medicines of Chinese herbal formulae are most commonly used for the treatment of BPH. The herbal formulae used are prepared in decoctions, capsules, tablets and pills. Rou Gui (*Cortex cinnamomi*) is the most frequently used herb, likely because it is thought to be able to tonify the Yang in the kidney by TCM practitioners. Huang Qi (*Radix astragali*) is the second most commonly used herb, and is believed to be a strong Qi tonifying herb. The herbs of Chuan Shan Jia (*Manis pentadactyla* L.), E Shu (*Rhizoma curcumae*) and Wang Bu Liu Xing (*Semen vaccariae*) are considered to be blood circulation enhancers and blood stasis removers. Because TCM believes that Qi is the driving force of blood circulation, Qi deficiency will lead to blood stasis. Therefore, these herbs can be used to restore the driving force for blood circulation and hence remove the stasis. Shu Di Huang (*Radix rehmanniae perparata*) and Shan Zhu Yu (*Fructus corni*) are the third and fourth most commonly used herbs, respectively, and are considered to be able to tonify the Ying in the kidney. According to TCM theory, developing a Yang deficiency in the kidney is a long-term process that is usually initiated by a Ying deficiency in the kidney. Ying is also another vital element for controlling kidney function, and its deficiency would cause other types of symptoms. Because the Ying and Yang in the kidney are mutually dependent, both should be tonified for a better outcome. Fu Ling (*Poria cortex*), Huang Bo (*Cortex phellodendri*) and Ze Xie (*Rhizoma alismatis*) are considered to have the ability to remove dampness and to clear heat in the lower part of body, which is considered another important syndrome differentiation in 'Long Bi' and is associated with urinary tract infection in BPH patients.

In addition to the TCM theory, some pharmacological studies have provided scientific evidence on the possible mechanisms of the most commonly used herbs in BPH. These herbs were found to diminish prostate size in rats by increasing the expression of inducible nitric oxide synthase in the prostate gland, hence inducing cell apoptosis. *Radix astragali* was found to possess a moderate diuretic effect. *Radix astragali*, *Manis pentadactyla* L. and *Rhizoma curcumae* were able to improve hematological rheology. *Semen vaccariae* was found to have anti-tumor activity, and *Cortex phellodendri* was found to possess anti-bacterial and anti-viral effects.

8. COMBINATION THERAPY OF WESTERN MEDICATION AND CHINESE HERBAL MEDICINE

Some randomized controlled trials have compared the symptomatic effects in patients with BPH treated by two therapeutic approaches, WM and CHM (17). However, WM and CHM both have advantages and disadvantages. Combination therapy with WM (e.g., α-blockers, 5-ARIs) and CHM may be an ideal treatment method for BPH. One study compared the adjuvant use of CHM and WM with WM alone. It was found that CHM plus tamsulosin (0.2 mg, per day) was superior to tamsulosin (0.2 mg per day) alone in reducing the post-treatment TCM symptom score (mean difference: -7.9, 95% CI: -9.75 to -6.05, $P<0.0001$). There were no differences in the improvements in IPSS, PV, MFR or residual urine between the two groups ($P>0.05$). After performing sensitivity analyses for all comparisons, the results for all outcomes remained robust. Larger randomized controlled trials of better quality are needed to truly evaluate the combined efficacy of WM and CHM.

9. PHOSPHODIESTERASE-5 INHIBITORS

Phosphodiesterase-5 inhibitors (PDE5-Is), initially approved for the treatment of erectile dysfunction, may also improve LUTS. The PDE5 isoenzymes are highly expressed in the lower urinary tract including prostatic tissue, particularly in the transition zone, bladder detrusor, and vascular smooth-muscle cells relating to the urinary tract (61). *In vitro* assays have demonstrated that PDE5-Is regulate cyclic guanosine monophosphate (cGMP) degradation and enhance the nitric oxide/cGMP signaling pathway to relax human smooth muscle strips in the prostate, bladder, and lower urinary tract arteries. In animals characterized by ischemia/hypoxia of the genitourinary tract, treatment with PDE5-Is increase bladder and prostate tissue oxygenation. PDE5-Is have been shown to reduce nonvoiding contractions and bladder afferent nerve firing in decerebrate spinal cord-injured rats, and to reduce mechanosensitive afferent activities in both Aδ- and C-fibers in an irritated or overextended bladder model (62).

Only tadalafil has received FDA approval for the treatment of urinary symptoms. In a randomized, placebo-controlled trial involving men with LUTS for at least 6 months, a 5-mg dose of tadalafil resulted in an average decrease in the AUASI score of 2.8 points at 6 weeks and 3.8 points at 12 weeks (63). Efficacy was shown as early as 4 weeks (64, 65). Common side effects are usually transient but may occur with a delayed onset.

10. ANTICHOLINERGIC AGENTS

Antimuscarinic agents inhibit muscarinic receptors in the detrusor muscle, thereby decreasing the overactive-bladder component of LUTS. Several antimuscarinic agents have been approved for voiding

dysfunction: darifenacin, solifenacin, trospium chloride, oxybutynin, tolterodine, and fesoterodine. Four randomized trials evaluating the use of tolterodine as monotherapy or in combination with an alpha blocker in men with LUTS/BPH were identified (66-69). Although these trials do not sufficiently demonstrate the efficacy or effectiveness of tolterodine, the Panel concluded that the use of anticholinergics may benefit some patients who have predominantly storage symptoms.

Anticholinergic agents are appropriate and effective treatment alternatives for the management of LUTS secondary to BPH in men without elevated post void residual (PVR) urine and when LUTS are predominantly irritative (70). Prior to initiation of anticholinergic therapy, baseline PVR urine should be assessed. Anticholinergics should be used with caution in patients with a PVR greater than 250 to 300 ml.

11. CONCLUSIONS

BPH is the most common condition in aging men, and is associated with LUTS. Treatment options include watchful waiting, life-style modification, pharmacologic treatments, and surgery. Alpha-blockers decrease LUTS and increase urinary flow rates in men with symptomatic BPH, but do not reduce the long-term risk of urinary retention or the need for surgical intervention. 5-ARIs decrease the production of dihydrotestosterone within the prostate, which results in decreased PV, increased peak urinary flow rate, improvement of symptoms, decreased risk of acute urinary retention, and the need for surgical intervention. For patients with moderate to severe symptoms and a large prostate, the combination therapy of α-blockers and 5-ARIs can further improve clinical efficacy. Numerous plant-based products (phytomedicines) and CHM are increasingly used as an alternative or complement to conventional medication. The combination therapy of WM and CHM may be an ideal treatment method for BPH. If the patient also has erectile dysfunction for which he desires treatment, PDE5-Is should be prescribed, since these agents can address both problems. Alternatively, an antimuscarinic agent might be added, as trial data show a greater reduction in storage symptoms with combination antimuscarinic and alpha-blocker therapy as compared with alpha-blocker monotherapy.

For complicated cases or for patients with clinically significant LUTS whose response to pharmacotherapy is deemed to be inadequate, surgical treatment is recommended. For patients who are not interested in therapy, watchful waiting and life-style modification are recommended to monitor the patient for progression of LUTS and urinary retention.

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Abbreviations: BPH, benign prostatic hyperplasia; LUTS, lower urinary tract symptoms; QoL, quality of life; IPSS, international prostate symptom scale; α-blockers, Alpha adrenergic receptor blockers; FDA, Food and Drug Administration; CHM, Chinese herbal medicine; WM, Western medicine; TCM, traditional Chinese medicine; 5-ARIs, 5-Alpha-reductase Inhibitors; PSA, prostate-specific antigen; MFR, maximum flow rate; PV, prostate volume; PDE5-Is, Phosphodiesterase-5 inhibitors; cGMP, cyclic guanosine monophosphate; PVR, post void residual

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