

Other Treatments for Lower Urinary Tract Symptoms Suggestive of Benign Prostatic Hyperplasia: Self-management, Desmopressin and Phytotherapy

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ABSTRACT

A substantial number of men with lower urinary tract symptoms/benign prostatic hyperplasia (LUTS/BPH) who undergo watchful waiting or medical therapy still have bothersome symptoms. Other therapies, like self-management, the use of desmopressin and phytotherapy, may serve as adjuvant treatments for men with LUTS/BPH. Self-management refers to education and training of patients to learn the day-to-day management and control of their own symptoms. Recommendations for employing self-management for LUTS/BPH include: education and reassurance, lifestyle modification and behavioral changes. Nocturia, defined as the complaint that an individual wakes one or more times at night to pass urine, is one of the most bothersome symptoms for men with LUTS/BPH. Although the cause of nocturia is multi-factorial, some men with LUTS/BPH may receive benefit from the use of desmopressin. Clinical effects of desmopressin in decreasing nocturia have been confirmed by several drug trials but its use requires caution. Side effects like lower leg edema, headache and dizziness are not unusual from the use of desmopressin, and significant hyponatremia is present in about 5% of cases. Phytotherapy refers to using herbal supplements to treat ailments. Currently, a few herbal agents have been used either solely or conjointly to treat LUTS/BPH. Among the herbal agents, saw palmetto has been most frequently used for treating LUTS/BPH. In general, saw palmetto is well tolerated and patient compliance is usually good. However, its therapeutic effects on LUTS/BPH are not consistent among clinical trials. *Key Words:* lower urinary tract symptoms, benign prostatic hyperplasia, self-management, desmopressin, phytotherapy

INTRODUCTION

Current therapies for men with lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH) include watchful waiting (WW), medical therapy, minimally invasive procedures and surgical therapy [1]. WW is safe and appropriate for certain men with LUTS/BPH, yet high failure rates in following years are expected, especially in men with greater risk of disease progression [2,3]. Both medical and surgical therapies are effective in ameliorating LUTS but are not without side effects, which are of concern to many patients [4-8]. Besides the standard treatments, other therapies, like self-management of LUTS, the use of desmopressin and phytotherapy, have been suggested as useful for the treatment of LUTS/BPH.

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SELF-MANAGEMENT OF LUTS/BPH

WW is justified and widely used for men with mild to moderate LUTS that are not significantly bothersome. Though relatively safe, WW has an increasing possibility of treatment failure as time passes, manifesting as worsening of symptoms and quality of life (QoL), acute urinary retention and occurrence of certain complications of LUTS/BPH [2,3]. Men most likely to have disease progression during WW are those who have greater prostate specific antigen (PSA) levels, larger prostates, greater post-void residual urine amounts (for instance, more than 200 mL) and more severe symptoms [2,3]. To improve the outcome of WW, active surveillance, like application of self-management of LUTS, may be worth trying in some men with LUTS/BPH.

Self-management refers to education and training of patients to learn the day-to-day management and control of their own symptoms [9]. A consensus approach based on current evidence and clinical experience to create guidelines on self-management for LUTS/BPH has been accomplished [10]. Recommendations on employing self-management for LUTS/BPH include: education and reassurance, lifestyle modification and behavioral changes.

Education and reassurance are to provide information to men with LUTS/BPH about their conditions in order to reduce anxiety and to increase patients' participation in treatment decision-making [9,10]. Lifestyle modification comprises fluid management according to the frequency-volume chart, advice on alcohol or caffeine consumption, and adjustment of medication [9,10]. Behavioral interventions work mainly through bladder and toilet retraining [9,10]. For men with urgency and frequency, distraction techniques and pelvic floor squeezes to delay voiding may help. The interval between voidings can sometimes be effectively prolonged via bladder retraining. Men with the sensation of incomplete bladder emptying may try double voiding to reduce the post-void residual volume. Milking of the urethra, through perineal pressure, contraction of the pelvic floor muscles and leaning forward can expel urine left in the urethra after voiding, and work to resolve the problem of post-micturition dribble [9,10]. A recent pilot study has shown self-management interventions dramatically improved the LUTS of 25 men [11]. In this study, 25 newly diagnosed men attended a nurse-led self-management program. Symptom severity was assessed at baseline and at 8 weeks after entering the program. Results showed significant decreases in the International Prostate Symptom Score (IPSS) and the QoL score, and episodes of nocturia, urgency and frequency decreased significantly after finishing the program [11]. However, further randomized controlled trials are still needed to confirm the effects of self-management interventions for men with uncomplicated LUTS.

Some potential problems of implementing the self-management

program for men with LUTS/BPH exist. The process requires several sessions to be completed and its success depends on the team work of the patients, physicians, nurses and co-workers. Though the program offers a chance of symptom improvement, the disease progress of LUTS/BPH is basically not altered.

DESMOPRESSIN FOR NOCTURIA DUE TO BPH

According to the definition of the International Continence Society (ICS), nocturia is the complaint that an individual wakes one or more times at night to pass urine [12]. Among LUTS, nocturia occurs frequently and can be the most bothersome symptom for many men [13, 14]. Etiology of nocturia is multi-factorial and cannot be explained on the basis of LUTS/BPH alone. Factors such as neuropathic bladder, reduced bladder capacity, sleep disturbance, psychiatric problems, medication effects (like taking diuretics late in the day), excessive fluid intake at night, poorly controlled diabetes mellitus, diabetes insipidus, heart failure (polyuria due to raised atrial natriuretic peptide, abbreviated as ANP, levels and an increased non-osmotic drive to thirst), hypercalcemia, dependent edema due to venous stasis or hypoalbuminemia are all possible causes of nocturia [15].

Nocturia clearly due to bladder outlet obstruction (BOO), overactive bladder (OAB) or other possible causative factors should be treated accordingly in the first instance. If bothersome nocturia is still present, the use of anti-diuretics can be considered. Before using anti-diuretics, a voiding diary or frequency-volume chart should be completed to show that the volume of urination during the night represents more than one third of the total daily urination volume (nocturnal polyuria) [15,16]. Arginine vasopressin is the natural anti-diuretic hormone and its serum concentration has a daily circadian variation [17]. It reaches its highest level of secretion during the night resulting in a decrease of urine secretion. The aging process causes the secretion of this hormone to diminish during the night and the renal response to desmopressin decreases [17,18]. Therefore, nocturia occurs more frequently in the elderly. Desmopressin is the only analog of vasopressin, and has been available for the treatment of enuresis and nocturia [16].

Several clinical trials have confirmed the effects of desmopressin in decreasing nocturia [19-21]. One phase III study applied a placebo or a tolerable dosage of 0.1 to 0.4 mg per day to randomized patients with nocturia for 10 to 12 months [21]. With the use of desmopressin, the mean number of nocturnal voids was decreased from 3 to 1.7, the total volume of urine decreased from 1500 to 900 mL and the mean duration of the first sleep period increased from 161 to 269 minutes. All the differences were statistically significant between the active treatment group and the placebo group. The number of patients describing nocturia as troublesome decreased from 70% at baseline to 33% at 12 months. Common side effects, including lower leg edema, headache and dizziness, occurred in about 5% of cases [21]. Significant hyponatremia, defined as a serum sodium concentration below 130 mmol/L, was present in about 5% of cases, mainly during the titration stage [21]. One meta-analysis study analyzed risk factors of hyponatremia from desmopressin treatment and showed that the risk of hyponatremia increased with age, lower serum sodium concentration at baseline, higher basal 24 hour urine volume per bodyweight and weight gain at time of minimum serum sodium concentration [22]. Elderly patients (> 65 years of age) with a baseline serum sodium concentration below the normal range were at very high risk [22].

The proper way to apply desmopressin to treat nocturia can be summarized as :(1) complete a frequency-volume chart to document the presence of nocturnal polyuria, (2) reduce fluid intake about 4 hours before bedtime, (3) start with 0.05 or 0.1 mg of desmopressin and slowly increase the dose, depending on the efficiency and tolerance, with a maximum dose of 0.4 mg, (4) carefully monitor side effects such as dizziness, nausea, vomiting, convulsions or weight gain, (5) measure the serum sodium concentration regularly, and (6) be cautious in treating patients above 65 years of age, especially if they have a low baseline serum sodium concentration [16].

PHYTOTHERAPY FOR LUTS/BPH

Phytotherapy refers to using herbal agents to treat ailments. Currently, a few herbal agents have been used worldwide for treating LUTS/BPH (Table 1). Although in most cases the validity of clinical effects of these products is not fully proven, phytotherapy is still well accepted by many men for treating their LUTS/BPH. The reasons for this include: patients' perception of phytotherapy as natural and safe, and the consideration of the positive results suggested by previous clinical trials. Among the herbal agents, saw palmetto, a product derived from the berry of the American dwarf palm tree, has been most frequently used for treating LUTS/BPH.

A number of different mechanisms of action of saw palmetto in men with BPH have been proposed, including antiandrogenic effects, antiestrogenic effects, androgen receptor blockade, growth factor inhibition, α -receptor blockade and others [23-29]. However, it is most commonly believed that saw palmetto works as a naturally occurring 5- α reductase inhibitor [28,29].

Most older clinical studies of saw palmetto had certain kinds of flaws, like small numbers of patients, too short treatment intervals, lack of placebo, not using standard objective measures of treatment results and so on [30-33]. In recent years, however, an increasing number of well-performed studies have been completed that have focused on treating men with LUTS/BPH with saw palmetto.

Gerber et al conducted a randomized, double-blind, placebo-controlled trial of saw palmetto in 85 men with moderately severe LUTS for 6 months [34]. At the end of the study, the mean symptom score decreased significantly in the saw palmetto group compared with the placebo group (-4.4 vs 2.2, $p = 0.038$). However, improvement of the QoL score and the peak urinary flow rate were not significantly different between the two groups. Carraro et al reported their results of comparing saw palmetto and finasteride in treating 1,098 men with moderate BPH symptoms [35]. At the end of 26 weeks, both saw palmetto and finasteride had decreased the IPSS (-37% and -39%, respectively),

Table 1. Commonly used herbal agents for LUTS/BPH

Common Name	Species Name
Saw palmetto (fruit)	<i>Serenoa repens</i>
African plum (bark)	<i>Pygeum africanum</i>
Purple coneflower	<i>Echinacea purpurea</i>
Pumpkin (seeds)	<i>Cucurbitae peponis</i>
Rye (pollen)	<i>Secale cereale</i>
South African star grass (root)	<i>Hypoxis rooperi</i>
Stinging nettle (root)	<i>Urtica dioica</i>

improved the QoL score (by 38% and 41%, respectively) and increased the peak urinary flow rate (+2.7 mL/s and +3.2 mL/s, respectively). Both drugs were well tolerated with no significant side effects. Patients on finasteride reported significantly more sexual dysfunction. The use of saw palmetto resulted in a 6% decrease in prostate volume (compared with 18% in the group receiving finasteride) and did not change the mean PSA level significantly. Another double-blind, randomized trial was conducted to compare the efficacy of saw palmetto and tamsulosin [36]. Seven hundred and four men with LUTS/BPH were randomized to receive either drug for 12 months. The two drugs decreased the IPSS significantly and equally. The increase in the peak urinary flow rate was similar in both treatment groups (1.8 mL/s for saw palmetto and 1.9 mL/s for tamsulosin). Both drugs were well tolerated, although ejaculation disorders were more frequently reported by patients taking tamsulosin.

On the other hand, a few studies have failed to confirm the clinical effects of saw palmetto for treating BPH/LUTS. In one randomized, placebo-controlled trial that recruited 100 men with moderate LUTS, Willetts et al did not find any significant improvement from the use of saw palmetto when compared with placebo [37]. Nevertheless, their results had bias. The duration of treatment was very short (only 3 months) and might not have been long enough for saw palmetto to exert its maximal effects. Recently, another double-blind trial was completed [38]. Two hundred and twenty five men with moderate to severe symptoms of BPH were randomized to one year of treatment with saw palmetto extract (160 mg twice a day) or placebo. No significant difference between the saw palmetto and placebo groups was noted during the one year study regarding change in the IPSS, maximal urinary flow rate, prostate size, post-void residual volume, QoL or serum PSA level. The incidence of side effects was similar in the two groups.

In general, saw palmetto is well tolerated, serious adverse events are extremely uncommon and patient compliance is usually good [34-39]. However, its clinical effects on LUTS/BPH are not consistent among drug trials [34-39]. When men with LUTS/BPH inquire about professional opinions on phytotherapy, immediate discouragement might provide no help and make them turn to other resources, which are sometimes detrimental. It may be better to state that herbal supplementation for LUTS/BPH is usually safe, takes longer periods (at least 3 months) to work and is only effective in a proportion of men.

CONCLUSIONS

A self-management program provides men with LUTS/BPH with a chance of reducing symptom severity in a safe way but it takes certain efforts to implement such a program. Desmopressin has been shown to be effective in treating nocturnal polyuria. Caution must be taken when using desmopressin since serious side effects may occur. Phytotherapy has been widely used for the treatment of LUTS/BPH. It is generally safe but its effectiveness is still controversial.

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