

SMHS

Society for Men's Health (Singapore)

Better Prostate Health (BPH)



Society for Men's Health

A Simple Guideline for
Treatment of
Prostate Problems
in Primary Care



Society for Men's Health

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Statement of Intent

These guidelines are not intended to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge advances and patterns of care evolve.

The contents of this publication are guidelines to clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not ensure a successful outcome in every case. These guidelines should neither be construed as including all proper methods of care, nor exclude other acceptable methods of care. Each physician is ultimately responsible for the management of his/her unique patient, in the light of the clinical data presented by the patient and diagnostic and treatment options available.

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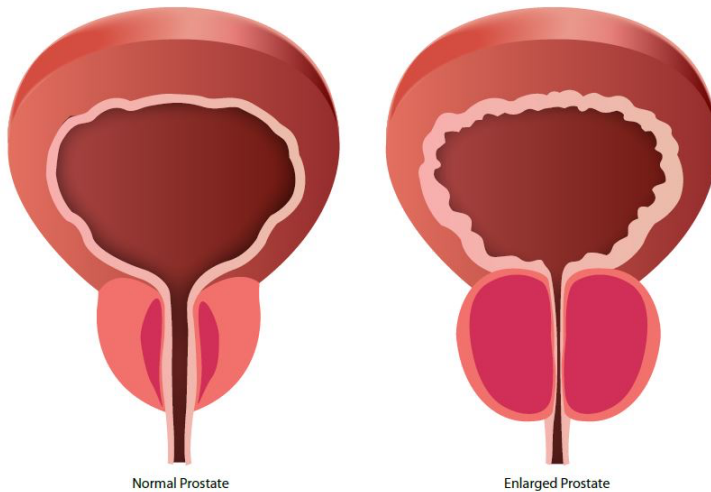
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INTRODUCTION

Benign prostatic hyperplasia (BPH) and **benign prostatic enlargement (BPE)** are one of the most common diseases in aging men which can lead to **lower urinary tract symptoms (LUTS)**. The relation between BPH, BPE and LUTS is complex, because not all men with BPE develop LUTS and not all men with LUTS have BPE. By definition, BPH implies a histological diagnosis, BPE means the anatomical enlargement of the prostate, and LUTS refers to the symptom complex that could arise as a result of prostatic enlargement. However, these 3 terms are used interchangeably in clinical practice.

Figure 1 – Left – normal prostate; Right – BPH causing bladder outlet obstruction



With a changing demographic profile and an increasingly aging population in almost all societies, it is inevitable that this disorder will become even more prevalent and a major challenge for all health care systems in the future.

EPIDEMIOLOGY AND AETIOLOGY

Aging

The prevalence of BPH rises markedly with increased age. Autopsy studies have observed a histological prevalence of 8%, 50%, and 80% in the 4th, 6th, and 9th decades of life, respectively¹. Observational studies from Europe, US, and Asia have also demonstrated older age to be a risk factor for clinical BPH onset and progression^{2,3,4}. Furthermore the prostate volume increases with age based on data from the Krimpen and Baltimore Longitudinal Study of Aging⁵ suggesting a prostate growth rate of 2.0% to 2.5% per year in older men^{6,7}. The continued growth of the prostate gland is a risk factor for LUTS progression and larger prostates are associated with BPE and increased risks of clinical BPH progression, urinary retention and need for prostate surgery.

Race

No clear patterns have emerged with respect to BPH risk and race. Observational studies comparing black, Asian and white men have produced variable results. Studies of black men in the US have observed an increased prostate transition zone and total volume compared with white men^{8,9}. Large analyses of the US Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial¹⁰ and the Health Professionals Follow-Up Study¹¹ observed no differences in clinical BPH risk between black and white men. Some data however have suggested a decreased risk of clinical BPH in Asian compared with white men.

Genetics

The evidence suggests a strong genetic component to BPH. A case control analysis¹², in which men less than 64 years underwent surgery for BPH, noted that male relatives and brothers had a 4-fold and 6-fold increase, respectively of age-specific risks for BPH surgery. These investigators further estimated that 50% of men less than 60 years undergoing surgery for BPH had a heritable form of disease. In a subsequent study, they observed that heritable disease was associated with larger prostate volume and younger age of onset compared with sporadic BPH¹³. These and other findings suggest an autosomal dominant pattern of inheritance¹⁴.

Lifestyle

It has increasingly been observed that modifiable lifestyle factors substantially influence the natural history of BPH.

Diet

There are some indications that both macronutrients and micronutrients may affect the risk of BPH¹⁵ although the patterns are inconsistent. For macronutrients, increased total energy intake, energy-adjusted total protein intake, red meat, fat, milk and dairy products, cereals, bread, poultry and starch all potentially increase the risks of clinical BPH and BPH surgery, while vegetables, fruits, polyunsaturated fatty acids, linoleic acid and vitamin D potentially decrease the risks of BPH^{16,17}. With respect to micronutrients, higher circulating concentrations of vitamin E, lycopene, selenium and carotene have been inversely associated with BPH. Zinc has been associated with both increased and decreased risk¹⁸.

Physical Activity

Increased physical activity and exercise have been consistently linked to decreased risks of BPH surgery, clinical BPH, histological BPH and LUTS¹⁹. A meta-analysis of 11 published studies²⁰ (n=43, 083 men) indicated that moderate to vigorous physical activity reduced the risk of BPH by as much as 25% relative to a sedentary lifestyle, with the magnitude of the protective effect increasing with higher levels of activity.

Alcohol

Like exercise, moderate alcohol intake also appears to be protective against multiple outcomes related to BPH. A meta-analysis²¹ of 19 published studies (n=120,091 men) observed up to a 35% decreased likelihood of BPH among men who drank daily.

Metabolic Syndrome

Obesity

Studies^{22,23} have consistently observed that increased adiposity is positively associated with prostate volume—the greater the amount of adiposity, the greater the prostate volume. Factors such as body weight, BMI, and waist circumference have all been positively associated with prostate volume in multiple different study populations^{24, 25}. In the Baltimore Longitudinal Study of Aging, each 1 kg/m² increase in BMI corresponded to a 0.41 mL increase in prostate volume and obese participants (BMI > 35 kg/m²) had a 3.5-fold increased risk of prostate enlargement compared to non-obese (BMI <25 kg/m²) participants. Epidemiological evidence also demonstrates that obesity increases the risks of BPH surgery, urinary symptom progression and initiation of BPH medical therapy^{26, 27}.

Diabetes and Disruptions in Glucose Homeostasis

Diabetes mellitus, increased serum insulin and elevated fasting plasma glucose have been associated with increased prostate size and increased risk of prostate enlargement, clinical BPH and BPH surgery^{28, 29}.

Lipids

There is relatively little data on potential associations between lipids and BPH. Some studies have shown positive associations while others did not find any association between them.

Erectile Dysfunction

There is overwhelming evidence to support that ED and LUTS are related^{30,31,32,33}. Common underlying pathophysiology between these two conditions has been hypothesized but there is no indication that one condition precedes the other³⁴.

Inflammation

It is likely that inflammation plays a role in the development and progression of BPH as shown by the strong links between BPH and histological inflammation in specimens obtained from prostate biopsies and BPH surgery³⁵. Furthermore inflammatory cytokines are over expressed in BPH tissues^{36, 37}. The underlying causes of prostatic inflammation remains unclear although there are several hypothesis, 1) response to tissue damage because of infection, 2) autoimmune response, 3) obesity and abdominal fat, because of excess production of inflammatory cytokines from adipose tissue.

Inflammation has been implicated as a primary stimulus for prostate carcinogenesis and it is possible that BPH represents a non-malignant pathway of unregulated prostate growth promoted by oxidative stress, inflammatory mediators and insulin growth factors.

Correspondingly, it would be reasonable to hypothesize, then, that inhibition of inflammatory pathways would potentially attenuate BPH risk. In the Olmsted cohort, men who reported daily non-steroidal anti-inflammatory drug (NSAID) or statin use had significantly decreased risks of both low urinary flow rate and prostate volume enlargement^{38, 39}. However, use of NSAIDS was not associated with decreased risk of clinical BPH in other large cohorts^{40, 41}.

As inflammation is thought to be involved in the pathogenesis of LUTS, the presence of inflammatory markers may be used as objective risk factors for LUTS. This was demonstrated by Choi et al⁴², who found significantly higher high-sensitivity C-reactive protein (hsCRP) levels in men with moderate to severe LUTS than in men with mild or no LUTS. However, in their study of men from a urology clinic, Chang et al did not find a relationship between hsCRP and LUTS, leaving the usefulness of hsCRP open to debate⁴³.

PRESENTATION

Middle Aged and Older Men with Lower Urinary Tract Symptoms (LUTS)

The most common presentation of BPH is of the men above approximately 50 years of age complaining of urinary symptoms. These symptoms complex is referred to as LUTS, and is divided into 2 components – the obstructive or voiding symptoms which is thought to arise as a direct result of anatomical obstruction caused by an enlarged prostate; and the irritative or storage symptoms which is thought to arise from the changes in the bladder properties. Obstructive symptoms are hesitancy, poor stream, straining, sense of incomplete void and intermittency. Irritative symptoms are frequency, urgency and nocturia.

The International Prostate Symptom Score (IPSS, Annex A) is a formal symptom inventory recommended for the objective assessment of symptoms at initial contact, for follow-up of symptom evolution for those on watchful waiting and for evaluation of response to treatment. This validated instrument is the best way to assess LUTS. Three categories of symptom severity were described using the IPSS: mild 0–7, moderate 8–19 and severe 20–35. Equally important within the IPSS is the global quality of life question, which assesses the impact or bother of LUTS on the patient. This will help guide the extent of intervention and treatment of the patient.

Generally, LUTS presents gradually, with a waxing and waning history, and increasing in severity slowly with time. As such, many patients might not notice or be bothered by the initial mild symptoms. Certain aggravating factors can worsen LUTS, so much so that it can lead to acute urinary retention (AUR). These include immobility, constipation and drugs like opioids (certain cough mixtures contain opioids). These factors, if reversible, should be treated first.

Men who are concerned about Prostate Cancer

Many asymptomatic patients are concerned whether they are suffering from prostate cancer. The severity of LUTS does not correlate with the likelihood of prostate cancer, and early prostate cancers can be asymptomatic.

For such patients, take a **family history**, especially that of male relatives like fathers or brothers, who have been diagnosed with prostate cancer at an early age (for example, less than 50 years of age). These patients may benefit from PSA testing at an earlier age.

Digital rectal examination needs to be performed and documented, especially the presence or absence of prostate nodules.

They will be keen for **PSA testing**, and the pros and cons of PSA testing need to be discussed with the patients before the performance of the test.

Young Men with Lower Urinary Tract Symptoms (LUTS)

Some young men in their 20s and 30s have LUTS, and this is unlikely due to BPH. Risk factors like sexually transmitted disease, urinary tract infections, recent instrumentations, drug intake will need to be elicited from these patients. After the exclusion of organic diseases, chronic prostatitis may be one of the causes of LUTS in young men. The symptoms of chronic prostatitis tend to be non-specific, and include suprapubic, perineal, testicular and/or lower back discomfort. It tends to have a waxing and waning history, with periods of recurrences and remissions. Persistence of symptoms may need specialist evaluation.

PHYSICAL EXAMINATION

Prior to starting BPH therapy, it is essential to perform a physical examination to check for distended bladder and to do a digital rectal examination (DRE). A **distended bladder** which would suggest chronic retention of urine and patient would be at risk for obstructive uropathy. Such a patient needs to be referred to an urologist. If the **DRE** is suspicious of prostate cancer, he should also be referred for specialist assessment.

A focused neurological examination to assess motor and sensory functions of the perineum and lower limbs is also recommended. The DRE is also useful to assess the anal tone and other pelvic pathology.

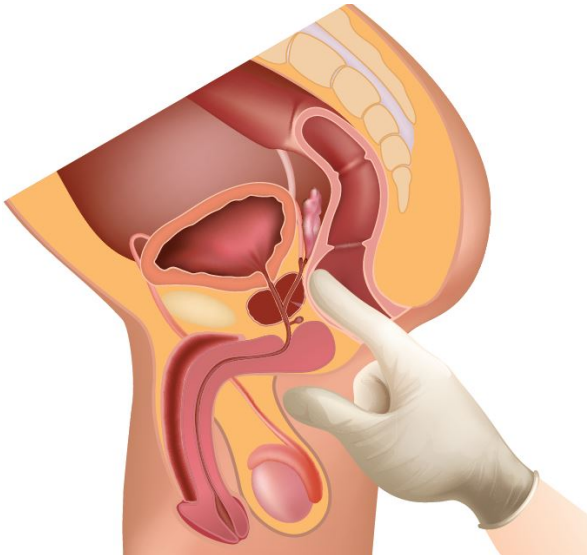


Figure 2 – Digital rectal examination

INVESTIGATION

Urinalysis (or urine labstick), PSA and serum creatinine are recommended for assessment of patients with BPH.

Recommended Investigations

Urinalysis

Although BPH is the most frequent cause of LUTS in men, they can also be caused, for example, by urinary tract infection or bladder cancer. Therefore, urinalysis is recommended during initial evaluation although there is little evidence in the literature to support this conclusion. Nevertheless, it is a useful screening tool for other potentially serious urological problems.

Prostate Specific Antigen

Testing of prostate specific antigen (PSA) should be offered to patients who have at least a 10 year life expectancy and for whom knowledge of the presence of prostate cancer would change management as well as those for whom PSA measurement may change the management of their voiding symptoms⁴⁴. This is because among patients without prostate cancer, serum PSA may also be a useful surrogate marker of prostate size and may also predict risk of BPH progression, such as the risks of either requiring surgery or developing acute urinary retention.

Generally speaking, PSA testing can be discussed for patients above the age of 50 years, and earlier if they have family history of relatives with prostate cancer at an early age.

| Pros | Cons |
|--|--|
| PSA testing can help detect prostate cancer early | Some prostate cancer is slow growing. Early detection can result in over detection of prostate cancer that might not affect the patient's life span. |
| Early detection of prostate cancer can lead to earlier treatment with better chance of cure. | Not all prostate cancer requires treatment and treatment of prostate cancer has risks and side effects. |
| Prostate cancer can be detected by a simple blood test (PSA) | An elevated PSA does not mean that patient has prostate cancer. Enlarged prostate and inflammation in the prostate gland can result in elevated PSA too. |
| A normal PSA helps to relieve anxiety about prostate cancer. | Some patients may have elevated PSA throughout their life without having prostate cancer, and it might induce more anxiety from repeated PSA testing. Transrectal ultrasound and biopsy of the prostate to diagnose prostate cancer also has certain risks associated with it. |
| Numbers of death from prostate cancer has declined with PSA testing. | The decline in the number of deaths may not be justified with the substantial cost and possible harm to the patient that arise from PSA testing. |

Table 1 – Pros and cons of PSA testing

Serum Creatinine

BPH may cause upper urinary tract dilatation and renal failure. In patients undergoing prostatectomy, 10% present with azotaemia; in those presenting with LUTS only, the incidence is lower. When renal impairment is present, however, diabetes and hypertension, and not BPH, are the most probable causes of creatinine elevation. Recent data of the MTOPS trial have shown that the risk of developing de novo renal failure in men with LUTS is minimal (<1%) suggesting that it is not necessary to control the serum creatinine if voiding remains compensated. As it is difficult to select those with renal insufficiency, it is probably cost effective to measure serum creatinine levels in all patients at initial evaluation.

Optional Investigations

When more facilities are available or when patients are referred to the urologist, they could undergo further testing.

Ultrasound

The ultrasound machine has become a common modality of imaging not only in specialist clinics, but also in the family practitioners' clinics. It is a useful adjunct in the assessment of LUTS as it provides real time information, relatively non invasive and with almost no risk to the patients. There are 2 ways that ultrasound of the urinary tract is performed, transabdominal and transrectal ultrasound. Transabdominal ultrasound provides quick assessment of the kidneys, bladder and prostate gland, and is especially useful and convenient as a bedside tool. Transrectal ultrasound is useful in providing detailed imaging of the prostate and is helpful in prostate biopsy; however, it is more invasive and uncomfortable for the patients.

The practitioner can perform transabdominal ultrasound before and after the patient has voided. The practitioner should look for the following:

- 1) **Kidneys** for **hydronephrosis**. The presence of bilateral hydronephroses might suggest obstructive uropathy, which is a serious complication from BPH. Renal masses can sometimes be picked up incidentally on ultrasound, and should be referred for specialist assessment if detected. However, the primary purpose of ultrasound in LUTS evaluation is to detect hydronephrosis rather than to screen for renal masses. The incidence of renal masses in a LUTS population is not higher than in the general population.
- 2) **Bladder** for **post void residual urine (PVRU)**, a high value may indicate the degree of obstruction, and may suggest chronic retention of urine. PVRU can be calculated by measurement of the bladder height, width, and length obtained by transabdominal ultrasonography. This is a simple, accurate and non-invasive method. Because of the marked intra-individual variability of residual urine volume, the test should be repeated to improve precision, particularly if the first residual urine volume is significant. Large PVR volumes (>200ml) may indicate bladder dysfunction and predict a less favourable response to treatment. Automated "bladder scan" ultrasound machines, which measures and calculates the PVRU automatically, is commonly used in specialist clinics and wards as they are simple to use.

- 3) **Prostate for prostate volume and Intravesical Prostatic Protrusion (IPP)**. A small prostate volume does not mean that the patient is not obstructed from the prostate gland. Intravesical Prostatic Protrusion (IPP) refers to the degree of prostate enlargement indenting into the bladder. Studies⁴⁵ have shown that this is significantly correlated to bladder outlet obstruction.

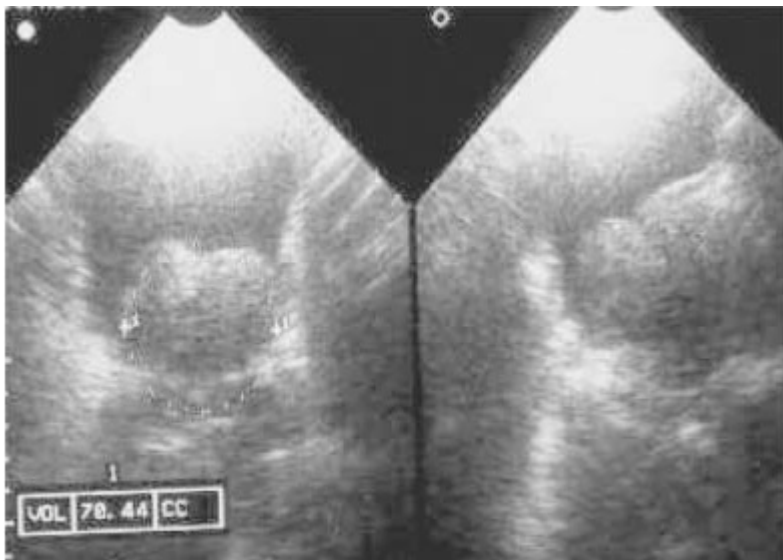


Figure 3 – Transabdominal ultrasound showing significant Intravesical Prostatic Protrusion (IPP)

Uroflowmetry

Uroflowmetry is recommended as a diagnostic test in the initial assessment of men with LUTS and should always be performed prior to prostatectomy. It is a simple, non-invasive test that can reveal abnormal voiding. Peak urinary flow (Q_{max}) is the best single measure to estimate the probability of a patient to be urodynamically obstructed, but a low Q_{max} does not distinguish between obstruction and decreased detrusor contractility. Because of the intra-individual variability and the volume dependency of the Q_{max} , at least 2 flow rates should be obtained, ideally both with a volume greater than 150 mL voided urine.

Voiding Charts

Voiding charts or diaries are simple to complete, cheap and can provide useful and objective information. The time and voided volume are recorded for each micturition during several 24-hour periods and help to identify patients with isolated nocturnal polyuria or excessive fluid intake, which are common in the aging male. There is no standard frequency volume chart available. However, recent data suggest that a 24-hour voiding chart is sufficient for the average patients and that longer time periods provide only little additional information.

Pressure Flow (Urodynamics) Studies

Non-invasive flow rates only determine the probability of benign prostatic obstruction, whereas pressure flow studies (pQs) can categorize the degree of obstruction and identify patients in whom a low flow rate may be due to a low-pressure detrusor contraction. Although pQs are the only means in diagnosing obstruction accurately, the debate continues as to their role in predicting treatment outcomes. The methodology for performing pQs is standardized and requires simultaneous recording of both intravesical and intra-abdominal pressure. Different nomograms exist with which to classify patients into categories of obstruction; the ICS (International Continence Society) nomogram has now been adopted as the standard nomogram. Although pQs are considered optional for the average patient, their use is recommended prior to prostatectomy under the following circumstances:

- 1) If the voided volume is <150ml or $Q_{max} >15\text{ml/s}$ prior surgical intervention particularly in the elderly to document the presence of BPO
- 2) Younger men (e.g. <50 years)
- 3) Elderly men (>80 years)
- 4) PVRU >300ml
- 5) Suspicion of neurogenic bladder dysfunction (e.g. Mb. Parkinson)
- 6) After radical pelvic surgery
- 7) Previous unsuccessful invasive treatment.

Cystoscopy

Cystoscopy is the standard procedure for endoscopic evaluation of the lower urinary tract. It can provide useful information as to the cause, size, and severity of obstruction, patency of the bladder neck, prostatic occlusion of the urethra, and estimated prostate size. Cystoscopy is recommended prior to surgical or minimal invasive therapy, particularly if treatment depends on prostate shape (e.g. median lobe) or size. In addition, Cystoscopy is indicated in men with a history of haematuria, urethral stricture, bladder cancer, or prior lower urinary tract surgery. However, cystoscopy is not indicated in the initial evaluation of the average patient without these risk factors or if watchful waiting or medical therapy is initiated.

TREATMENT

LUTS Secondary to BPH

The treatment of BPH depends on:

- How **symptomatic** the patient is?

IPSS is a good gauge on how symptomatic the patient is. Mild LUTS can be treated by watchful waiting.

- What symptoms of LUTS the patient suffers from?

Whether the patient suffers from **obstructive** (or voiding) symptoms like hesitancy, poor stream, sense of incomplete void, terminal dribbling or intermittency; or **irritative** (or storage) symptoms like frequency, urgency or nocturia. For example, alpha blockers work well on both obstructive and irritative symptoms whereas antimuscarinics work well mainly on the irritative symptoms.

- The need to decrease the **progression** of BPH.

5 ARIs have been shown to decrease the progression of BPH. This is because they are able to reduce the prostate size in the long term.

- Whether there is associated **sexual dysfunction**.

Daily tadalafil is a FDA approved treatment for both LUTS and ED. Alpha blockers and 5 ARI have a small risk of sexual dysfunction.

Watchful Waiting

If LUTS is mild and does not bother patient that much, he can opt for watchful waiting. Sometimes, change in fluid habits like not drinking before bedtime can help reduce nocturia. Taking less of caffeinated drinks like coffee or tea may help to reduce frequency and urgency.

Medical Treatment

Alpha Blockers

Alpha (adrenergic) blockers act on the alpha adrenergic receptors in the prostate as well as the bladder. It offers rapid symptomatic relief from LUTS, both the obstructive as well as the irritative components. Because of this, alpha blockers are common initial treatment for LUTS. In a landmark study on the use of alpha blocker, at 3 months after starting terazosin, 40% of the patients exhibited 30% or greater improvement in peak flow rate. Symptom scores were also significantly improved.

| | Dosage | Remarks |
|------------|---|---|
| Terazosin | 1 mg ON may be increased gradually to 5 mg ON | Give first dose and subsequent doses at bedtime to decrease risk of syncope |
| Alfuzosin | 10 mg per day (extended release) | Take with the same meal every day |
| Doxazosin | 1 – 8 mg per day | Immediate-release: initially 1 mg per day; maintenance up to 8 mg per day. Extended-release: initially 4 mg per day with breakfast; up to 8 mg per day. The recommended titration interval is 3 to 4 weeks. |
| Tamsulosin | 0.4 mg per day | Most selective alpha blocker 8.4% chance of ejaculatory disorder |

Table 2 - Common Alpha blockers in Singapore

The main side effect of alpha blockers is hypotension and postural hypotension, as they may affect the alpha receptors within the smooth muscles of the vessel walls. Hypertensive patients tend to have more clinically significant decrease in blood pressure irrespective of their treatment⁴⁶. The newer selective alpha blockers have less effect on blood pressure, with the most selective alpha blocker being Tamsulosin. In any case,

patients who are being started on alpha blockers should be warned of this, as they tend to be elderly, and the giddiness resulting from the postural hypotension may result in falls with devastating consequences.

Some alpha blockers have a small chance of sexual side effects. For example, tamsulosin 0.4 mg has 8.4 % chance of ejaculatory disorder (diminished ejaculate and anejaculation)⁴⁷.

Other side effects include dizziness, asthenia and nasal congestion.

Despite the possible side effects, alpha blockers have proven to be an effective and generally safe treatment for LUTS.

5 Alpha Reductase Inhibitors

5 alpha reductase inhibitor blocks the enzyme 5 alpha reductase, which converts testosterone to dihydrotestosterone, which is responsible for prostate growth. As a result, 5ARIs can retard prostate growth and has been shown to decrease the size of the prostate when used long term. It has been found that patients treated with dutasteride had a 26.0% reduction in prostate volume versus an increase of 1.4% for placebo-treated patients at 2 years⁴⁸.

| | Dosage | Remarks |
|-------------|---------------|---|
| Finasteride | 5 mg OM | Dosage for LUTS is 5 mg OM Finasteride 1 mg OM is used for androgenic alopecia (male pattern baldness). Finasteride inhibits 5alpha-reductase isoenzymes type I |
| Dutasteride | 0.5 mg OM | Dutasteride inhibits 5alpha-reductase isoenzymes types I and II |

Table 3 - 5 alpha-reductase inhibitors

5ARIs do not give rapid symptomatic relief like alpha blockers. They will need to be used for several months before there are changes to the patients' symptoms. 5ARIs work best in larger prostate glands.

Combination therapy is the use of alpha blocker together with 5ARI. This has the advantage of rapid symptomatic relief from the alpha blocker, and the prostate size reducing effect from the 5ARI, leading to a more sustained decrease in LUTS. The CombAT study⁴⁹ showed that the combination therapy of dutasteride (5ARI) and tamsulosin (alpha blocker) decreased the relative risk of BPH clinical progression. Combination therapy decreased the risk of acute urinary retention and BPH related surgery as compared to the use of alpha blockers alone.

When patients are given 5ARI, their serum PSA will decrease in relation to the length of the 5ARI therapy. It will reduce PSA by about half after 6 months of therapy. There should be caution in interpreting PSA results in patients who are on 5ARI therapy.

The most common side effects were sexual dysfunction (ED, decreased libido, and ejaculation disorders) and gynaecomastia. The onset of most sexual side effects occurred within the first 6 months of therapy, and they tend to decrease with duration of treatment.

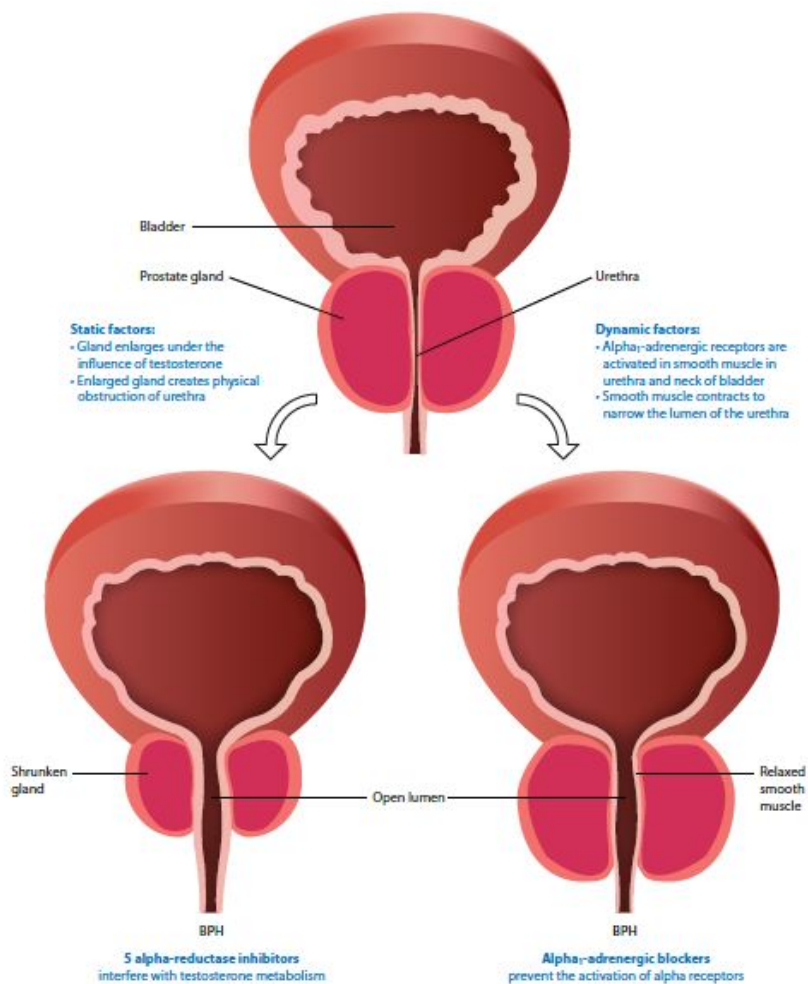


Figure 4 – Actions of 5 alpha-reductase inhibitors and alpha₁-adrenergic blockers

Phosphodiesterase Type V Inhibitors

PDE5i has traditionally been used for the treatment of Erectile Dysfunction (ED). However, many studies have shown that it also helps to alleviate LUTS in patients. As many elderly patients have both ED and LUTS, PDE5i offers the treatment of both symptoms using a single drug. Tadalafil 5 mg daily has been approved by FDA for the treatment of both LUTS and ED. Earlier studies⁵⁰ have shown that Tadalafil significantly improves symptoms in patients with LUTS, and more recent studies⁵¹ show that it gives rise to a small but statistically significant improvement in flow rate.

In addition, when patients are put on daily Tadalafil 5mg, they have improvement in erectile function, with the advantage of not having the pressure for timing of medication intake prior to sexual intercourse.

The most common side effects are headache and back pain, which tend to be mild to moderate in severity.

Antimuscarinics

Antimuscarinics work mainly on the muscarinic receptors in the bladder, decreasing the bladder sensitivity and contractility. This helps to decrease the irritative symptoms of LUTS, namely, frequency, urgency and nocturia.

| | Dosage | Remarks |
|-------------|---|--|
| Oxybutynin | 5 mg BD to QDS | Also has direct antispasmodic effect on smooth muscles |
| Tolterodine | 2 mg BD 4 mg once daily (extended release) | Has selectivity for urinary bladder over salivary glands – less incidence of dry mouth |
| Solifenacin | 5 to 10 mg once daily | |

Table 4 - Antimuscarinic Drugs

However, as it affects the contractility of the bladder, it can increase the risk of urinary retention.

Combination therapy of alpha blockers and antimuscarinics has been shown to be effective and safe ⁵². However, prior to starting patients on antimuscarinic, it is essential that patient do not have high residual urine, which might manifest as a distended bladder.

The most common side effect of antimuscarinics is dry mouth, which is also the most common cause of discontinuation of the medication. Other side effects include blurred vision and constipation⁵³.

Phytotherapy

Phytotherapy, like saw palmetto, has gained in popularity with patients wanting an over the counter herbal medication. Many studies attesting to its efficacy tend to be small, retrospective or with flaws in their methodologies. One of the larger randomized controlled trials showed that the efficacy of phytotherapy is no different from that of a placebo⁵⁴.

Dietary Advice

The role of diet in altering the natural history of BPH has not been conclusively proven. Nevertheless, fluid advice like not drinking before bed time, and reducing the intake of caffeinated beverages⁵⁵ help to decrease irritative symptoms of frequency, urgency and nocturia.

Surgery

Surgery can be considered for patients with severe LUTS, LUTS refractory to medical therapy, and complications from BPH (obstructive uropathy, bladder stones, recurrent urinary tract infection, refractory haematuria). These patients can be referred to the Urologist who can advise further regarding about the various modalities of treatment available.

The traditional surgery for prostate is TURP (Transurethral Resection of Prostate). It is a safe and effective surgery, but has the side effects of retrograde ejaculation amongst others. Other surgeries that mimic the open prostatectomy, like HoLEP (Holmium Laser Enucleation of Prostate), TUEP (Transurethral Enucleation of Prostate) offer more complete removal of the prostatic adenoma.

Due to the possible risks and side effects of TURP, Minimally invasive surgical techniques (MIST) have been developed and aim to preserve a man's sexual function while dealing with the bothersome BPH-LUTS. MIST are not to completely replace the surgeries like TURP or prostatic enucleation techniques mentioned above. MIST should be considered the bridging procedures between medical and surgical procedures. Current available MIST in Singapore (at the time of print) include prostatic urethral lift (UroLift), convective water vapour energy therapy (Rezum) and thermolatilation (Prolieve).

MIST are day surgical procedures that can be performed under moderate sedation. Sexual function can be preserved with MIST but the patients have to be counseled with regards to retreatment rates, degree of preservation of sexual function as well as the need for post-procedural placement of urethral catheter.

| | Mechanism of action | Erectile function | Ejaculatory function | Retreatment rates |
|----------|--|-------------------|---------------------------------------|---------------------------------------|
| UroLift | Prostatic lateral compression | No ED | No ejaculatory dysfunction | 13.6% in 5 years 56,57,58,59,60,61 |
| Rezum | Convective water vapour energy therapy | No or minimal ED | 1.5-2.9% decreased ejaculatory volume | 4.4% in 4 years ^{62, 63} |
| Prolieve | Thermodilatation | 3.3% | 3.1% | 14.2% in 5 years ⁶⁴ |

Prostate Cancer

PSA testing can be offered to patients who are above the age of 50 years and above the age of 40 years if the patient has family history (male relatives with history of early onset prostate cancer). If the PSA is high, there is a higher probability of prostate cancer, but there are other non malignant causes of raised PSA like BPH and prostatitis. The patients should be referred to the Urologist for assessment of prostate cancer if his PSA is high.

Chronic Prostatitis

Many younger men have vague perineal, suprapubic or scrotal discomfort, which may or may not be associated with lower urinary tract symptoms. This usually occurs for a prolonged period of time with periods of recurrences and remissions. This discomfort is very disturbing to the patients. Typically, physical examination, urinalysis and urine cultures are all normal. These men suffer from a symptom complex generally described as chronic prostatitis⁵⁶, though the aetiology of this condition is not entirely clear.

Various empirical treatments have been offered for chronic prostatitis, including antibiotics, analgesia and alpha blockers, usually for a prolonged period of time from weeks to months. Patients do get better with such treatments but many do recur after that.

The best approach to the treatment of chronic prostatitis, other than medications, is counseling the patient on the waxing and waning nature of the symptoms, and the reassurance that there is no serious underlying disease in his urinary system after appropriate investigations.

FAQ

An elderly patient comes in with typical symptoms of LUTS, but when I do a DRE, his prostate appears to be small, is his LUTS still due to BPH?

The size of the prostate may not correlate with the patient's LUTS. A small prostate can be very symptomatic and a large prostate may not have appreciable effects on patient's symptoms and flow rate. The configuration of prostate is important too. A small prostate can have a configuration whereby it has a significant Intravesical Prostatic Protrusion (IPP), by which there is growth of prostate indenting into the bladder⁵⁷. This is best appreciated through ultrasound. Prostate with significant IPP tends to be very symptomatic with poor objective flow rates. This patient can still be treated with alpha blockers first, but if there is no appreciable change to his symptoms, he should be referred to a urologist for further assessment, and patients with significant IPP are typically best served by surgery.

If a patient has severe LUTS, does it mean that he has a higher chance of cancer?

No. The severity of LUTS is not related to the risk of prostate cancer.

If a patient has a large prostate on DRE, does it mean that he has a higher chance of cancer?

No. The size of the prostate gland is not related to the risk of prostate cancer. As benign prostatic cells produce PSA as well as prostate cancer, a larger benign prostate gland may give a higher value of PSA, as opposed to a smaller prostate gland.

If the patient has LUTS and ED, can he be given both alpha blockers and PDE5i together?

A patient with LUTS and ED can be treated with daily Tadalafil 5 mg (low dose), which has been approved by the FDA. Nevertheless, some patients prefer to have daily alpha blockers and on demand PDE5i, especially if their sexual intercourse tends to be infrequent. All the PDE5i have registered caution when used together with alpha blockers, as there are small additive effects of lowering blood pressure when both drugs are taken together. This may lead to increased incidence of orthostatic hypotension. The patients should be advised to look out for symptoms of orthostatic hypertension, space out the alpha blocker and PDE5i by 4 to 6 hrs, and be well hydrated prior to taking the drugs.

A patient has been taking saw palmetto (phytotherapy) for his LUTS; can he take alpha blockers together with saw palmetto?

The evidence for the use of phytotherapy in the treatment of LUTS tends to be from small scale studies with weak methodologies. However, it should be safe for him to take both saw palmetto and alpha blockers. Combination of saw palmetto with 5ARI, PDE5i or antimuscarinic are also not contraindicated.

Is there any drug that can prevent prostate cancer?

The jury is still out for a drug that prevents prostate cancer. In the Prostate Cancer Prevention Trial (PCPT), a 5ARI, finasteride, was given to patients, it was found that although finasteride reduced the risk of prostate cancer by about one third, high-grade prostate cancer was more common in the finasteride group than in the placebo group. After 18 years of follow-up, there was no significant between-group difference in the rates of overall survival or survival after the diagnosis of prostate cancer.⁵⁸

CASE STUDIES

Case 1

Mr A, a 60 years old gentleman, had moderate LUTS. Physical examination showed no distended bladder and digital rectal examination showed a smooth prostate gland with no nodules. Urine labstick was normal and PSA was 2.1 ng/ml.

Because of his moderate symptoms, he was started on a course of Alfuzosin XL 10 mg (**alpha blocker**).

On follow up, his symptoms have improved, especially his urinary stream and he has less intermittency. However, he was still bothered by urgency, which led to urge incontinence sometimes when he failed to reach the toilet in time, as well as nocturia of 4 times per night.

His fluid drinking habits were examined, and he admitted to drinking tea throughout the day, and a glass of water before bedtime. He was advised to decrease his tea intake and **change the habit** of water drinking before bedtime. However, he was keen for medication. After assessment that he did not have chronic retention of urine (by making sure that he did not have a distended bladder), the **antimuscarinic** medicine, Tolterodine 2 mg bd was added.

On subsequent visits, his episodes of urgency, urge incontinence were less, and nocturia decreased from 4 to 2 times, which he found tolerable. He was okay with his symptoms and was happy to continue with his two medications of alpha blocker (Alfuzosin) and antimuscarinic (Tolterodine).

Case 2

Mr B, a 52 years old gentleman, had moderate LUTS and has erectile dysfunction, and is keen for treatment of both conditions. Physical examination showed no distended bladder and digital rectal examination showed a smooth prostate gland with no nodules. External genitalia were normal. Urine labstick and PSA were normal. He has normal libido and sexual intercourse frequency ranges from 1 to 2 times per week, and each time, though he can initiate erection, found it unsatisfactory in stiffness and duration.

His options include:

- PDE5i only - **Daily tadalafil** 5 mg.
- **Alpha blockers** (daily) and **on demand PDE5i** – any of the PDE5i can be used (sildenafil, vardenafil, tadalafil). Do note that if tadalafil is used, its dosage should be 20 mg. As both alpha blockers and PDE5i can lower blood pressure, the patient should be advised to take them at least 4 hours apart from each other and be well hydrated.

Choice will depend on his sexual intercourse frequency, cost considerations, efficacy and side effects.

Case 3

Mr C, a 57 years old gentleman, had mild LUTS, and was on phytotherapy (saw palmetto). He read about prostate cancer and was worried that he may suffer from it because he had LUTS. Physical examination performed showed that he had no distended bladder and his prostate was smooth with no nodules.

He was **counseled** on and agreed to **PSA testing**, and it came back at 3.9 ng/ml (normal range 0 – 4.0 ng/ml). He was told that a normal PSA does not mean that he does not have prostate cancer, though clinically significant prostate cancer would be very rare. As prostate cancer tend to progress slowly (as opposed to other cancers), he was offered PSA testing in a year's time.

He was however anxious about his result, and requested a repeat test in 6 months' time. 6 months later, his PSA had risen to 4.5 ng/ml. This was not associated with any symptoms suggestive of urinary tract infections.

He was referred to an Urologist for further assessment for prostate cancer, and the Urologist would be counseling him on the option of **prostate biopsy** to look for prostate cancer.

Case 4

Mr D, a 54 years old gentleman, had moderate to severe LUTS. Physical examination reviewed no distended bladder. On digital rectal examination, his prostate was noted to be smooth but severely enlarged. Urine labstick was normal, and PSA was normal at 3.5 ng/ml (normal range 0 – 4 ng/ml).

As the patient was very symptomatic with a clinically enlarged prostate, he was offered combination therapy of tamsulosin 0.4 mg OM and dutasteride 0.5 mg OM. Tamsulosin (**alpha blocker**) would help to relieve his symptoms rapidly, and dutasteride (**5ARI**) would help to decrease the size of the prostate, and therefore the clinical progression, as well as the risks of acute urinary retention and BPH related surgery.

On follow up appointment at 6 months' time, it was noted that he had significant improvement of symptoms. His PSA was also noted to be lower at 3.3 ng/ml. Dutasteride had the effect of **lowering PSA**.

On his next follow up appointment at 1 year's time, it was noted that he had an increase of PSA to 3.8 ng/ml. Though this level of PSA seemed to be within the normal range of 0 – 4 ng/ml, however, it is considered to be elevated in view that he had been on chronic 5ARI therapy. He was referred to an Urologist for further assessment.

ANNEX A - INTERNATIONAL PROSTATE SYMPTOM SCORE (IPSS)⁵⁹

| | Not at all | Less than 1 time in 5 | Less than half the time | About half the time | More than half the time | Almost always | Your score |
|---|------------|-----------------------|-------------------------|---------------------|-------------------------|---------------|------------|
| Incomplete Emptying Over the past month, how often have you had a sensation of not emptying your bladder completely after you finish urinating? | 0 | 1 | 2 | 3 | 4 | 5 | |
| Frequency Over the past month, how often have you had to urinate again less than two hours after you finished urinating? | 0 | 1 | 2 | 3 | 4 | 5 | |
| Intermittency Over the past month, how often have you found you stopped and started again several times when you urinated? | 0 | 1 | 2 | 3 | 4 | 5 | |
| Urgency Over the last month, how difficult have you found it to postpone urination? | 0 | 1 | 2 | 3 | 4 | 5 | |
| Weak Stream Over the past month, how often have you had a weak urinary stream? | 0 | 1 | 2 | 3 | 4 | 5 | |
| Straining Over the past month, how often have you had to push or strain to begin urination? | 0 | 1 | 2 | 3 | 4 | 5 | |
| Nocturia Over the past month, many times did you most typically get up to urinate from the time you went to bed until the time you got up in the morning? | 0 | 1 | 2 | 3 | 4 | ≥5 | |

| | |
|-------------------------|--|
| Total IPSS Score | |
|-------------------------|--|

| Quality of Life due to Urinary Symptoms | Delighted | Pleased | Mostly satisfied | Mixed – about equally satisfied and dissatisfied | Mostly dissatisfied | Unhappy | Terrible |
|--|-----------|---------|------------------|--|---------------------|---------|----------|
| If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that? | 0 | 1 | 2 | 3 | 4 | 5 | 6 |

Total score: 0-7 Mildly symptomatic, 8-19 Moderately symptomatic, 20-35 Severely symptomatic.

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