# *Benign prostatic hyperplasia (BPH) management in the primary care setting*

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*Benign prostate hyperplasia (BPH) occurs in up to 50% of men by age 50, and the incidence increases with age. This common clinical problem is diagnosed by history, including the International Prostate Symptom Score (IPSS) questionnaire, and physical examination by digital rectal examination (DRE).*

*Initial management for BPH includes lifestyle modification, and smooth muscle relaxant alpha blocker therapy. Alpha blockers usually take effect quickly within 3-5 days, and have minimal side effects. Current commonly used alpha blockers include the selective alpha blockers tamsulosin (Flomax), alfusosin (Xatral), and silodosin (Rapaflo). For patients with larger prostates, the 5-alpha reductase inhibitor class (finasteride (Proscar) and dutasteride (Avodart)) work effectively to shrink prostate stroma resulting in improved voiding. The 5-ARI class of drugs, in addition to reducing prostate size, also reduce the need for future BPH-related surgery, and reduce the risk of future urinary retention. Drugs from the phosphodiesterase-5 (PDE-5) inhibitor class may now be considered for treating BPH. Once daily 5 mg tadalafil has been shown to improve BPH-related symptoms and is currently approved to treat patients with BPH.*

*Referral to a urologist can be considered for patients with a rising prostate-specific antigen (PSA), especially while on 5-ARI, failure of urinary symptom control despite maximal medical therapy, suspicion of prostate cancer, hematuria, recurrent urinary infections, urinary retention, or renal failure.*

*Currently the primary care physician is armed with multiple treatment options to effectively treat men with symptomatic BPH.*

**Key Words:** benign prostatic hyperplasia (BPH), pharmacotherapy, alpha blockers, 5-alpha reductase inhibitors, combination therapy, phosphodiesterase-5 inhibitors

## Introduction

Benign prostatic hyperplasia (BPH) is defined as the proliferation of prostatic stromal cells, which results in an enlarged prostate gland. As a result, the prostatic urethra is compressed, which restricts the flow of urine from the bladder. This interference with urine flow may cause uncomfortable symptoms such as frequency, urgency, nocturia, intermittency, decreased stream, and hesitancy, Figure 1. As BPH progresses, complications—such as the development of a urinary tract infection (UTI) or a bladder stone—may occur. In severe cases patients may develop urinary retention, kidney blockage (hydronephrosis), or renal failure.[1]

In this paper, which is aimed at guiding the primary care physician, we will summarize the epidemiology,

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incidence and clinical manifestations of BPH, and discuss how to diagnose and treat patients with BPH.

## Background

### *Incidence and epidemiology*

BPH is relatively common in men and symptoms can start as early as age 30. By the age of 50, up to 50% of men exhibit histologic evidence of BPH symptoms and these symptoms tend to increase with age.[2]

### *Clinical manifestations*

BPH symptoms are generally referred to as "lower urinary tract symptoms" or LUTS, and these can be subdivided into voiding symptoms and storage symptoms, as shown in Figure 1. Voiding symptoms include hesitancy, intermittency, straining, dribbling, and the decreased caliber of the urine stream. Storage symptoms include frequency, urgency, and nocturia. The severity of BPH can be measured by using the International Prostate Symptom Score (IPSS) questionnaire,[3] which includes seven questions about urinary symptoms and an eighth, quality-of-life (QOL) question that asks how much the patient is bothered by these symptoms. Although most symptoms can be attributed directly to the prostatic hyperplasia that constricts the flow of urine, about 30% of men have concurrent bladder detrusor overactivity, or overactive bladder (OAB). These men will therefore require therapy for OAB in addition to treatment for BPH.[4]

### *Cause*

Outflow obstruction from BPH is caused by increased prostate growth and large size, as well as by increased smooth muscle tone of the prostate.

The main mediator of prostatic growth is dihydrotestosterone (DHT), a metabolite of testosterone that is formed in the prostate cell by the breakdown of testosterone. The enzyme 5-alpha reductase converts testosterone to DHT. This enzyme is the target of drug therapy—the 5-alpha reductase inhibitors (5-ARIs), such as finasteride and dutasteride—that aim to reduce the size of the prostate.-

### *Diagnosis*

The diagnosis of BPH is derived from the patient's medical history—including the IPSS questionnaire—and a physical examination of the prostate—that is, a digital rectal examination (DRE). Taking the patient's medical history should include taking a detailed analysis of voiding symptoms, Figure 1. The IPSS questionnaire quantifies each of seven

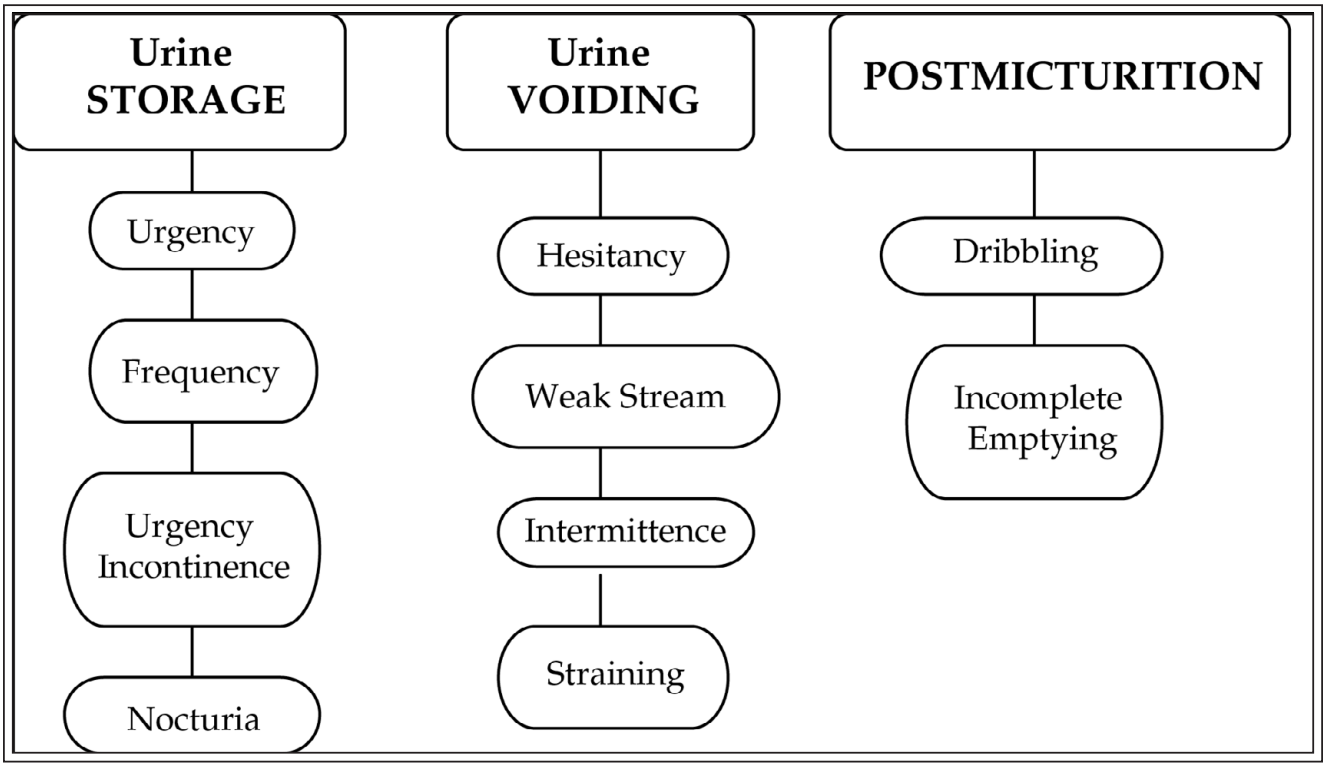


**Figure 1.** Symptoms of benign prostatic hyperplasia.

symptoms from a score of 0 (not at all) to 5 (almost always). The maximum IPSS is 35, and patients are classified as having severe symptoms if they have an IPSS of 20 to 35. After treatment is initiated, the IPSS questionnaire can be used to monitor response to therapy.

Physical examination of the prostate provides information about the prostate's size; any tenderness or "bogginess" suggests an infection, and any nodularity suggests possible prostate cancer. A prostate cancer nodule usually is hard and firm, and any asymmetry of each lobe of the prostate should be further evaluated. It is important to remember that current guidelines recommend that even men with a normal serum prostate-specific antigen (PSA) level should have an annual DRE. The age at which to start annual DRE and PSA is debatable, and ranges between 40 to 50 years of age, and sooner in high risk men. Some hard, nodular prostate cancers that do not produce PSA can only be identified by a DRE.

A PSA blood test can be used as a marker of BPH progression. A number of studies have shown that PSA can be a surrogate marker for prostate volume.[5] PSA can be elevated in prostate cancer, prostate infection, and BPH. It is important to remember that all prostate cells make PSA, so patients with BPH and large prostates will have higher PSA values than if they had normal-sized prostates. For this reason, PSA can be used as a marker for response to BPH treatment.

Urinalysis and culture tests are performed to rule out infection as a possible cause of urinary symptoms.

## Patient management

### *Lifestyle changes and herbal medicine*

Lifestyle modifications may help improve BPH-related symptoms. These include decreasing alcohol and caffeine consumption, decreasing fluids before bedtime to improve nocturia symptoms, and timed voiding.

One meta-analysis[6] suggested that the herbal medication saw palmetto may result in a small improvement in BPH-related symptoms, but more recent studies[7] have suggested the benefit is no better than placebo. Saw palmetto has minimal side effects, and it appears to be a harmless herbal remedy that may result in a slight benefit in a few patients.

## Pharmacotherapy

The two main classes of therapeutic agents used to treat BPH are the alpha blockers and the 5-alpha reductase inhibitors (5-ARIs).

### *Alpha blockers*

The alpha blockers, Table 1, work to relax the smooth muscle at the prostate and bladder neck by blocking alpha–1a receptors. By relaxing the smooth muscle at the prostate neck, the urinary channel is opened,

TABLE 1. **Alpha blockers for symptomatic benign prostatic hyperplasia (sBPH)**

| Name (Brand name) | Dose | Side effects/Notes |
|---|---|---|
| **Second generation** | | |
| Terazosin (Hytrin) | 1 mg-10 mg daily* | First dose syncope; dizziness; tachycardia; hypotension; headache; asthenia; rhinitis |
| Doxazosin (Cardura) | 1 mg-8 mg daily* | Same as above |
| **Third generation** | | |
| Alfuzosin (Xatral [Canada] Uroxatral [US]) | 10 mg daily with food | Dizziness; headache; minimal cardiovascular effect; less ejaculatory dysfunction than tamsulosin |
| Tamsulosin (Flomax CR, generic capsules) | Flomax CR: 0.4 mg daily (with or without food) Generic capsules: 0.4 mg-0.8 mg daily with food | Ejaculatory dysfunction; rhinitis |
| Silodosin (Rapaflo) | 8 mg daily; 4 mg daily with CrCl 30-50 mL/min | Well tolerated; minimal retrograde ejaculation and cardiovascular side effects |

*Dose titrated weekly to desired response, monitor blood pressure
CrCl = creatinine clearance

which allows a less constricted urinary flow. The alpha blockers have a quick onset of action, within 3 to 5 days. Once the medication is stopped, symptoms usually return to pre-treatment, baseline levels. There are five main alpha-blockers: two second-generation drugs—terazosin (Hytrin) and doxazosin (Cardura)[8]—and three third-generation drugs—tamsulosin (Flomax), alfuzosin (Xatral),[9] and silodosin (Rapaflo). Both terazosin and doxazosin require dose titration because of their anti-hypertensive properties. Tamsulosin, alfuzosin, and silodosin usually do not require dose titration and have fewer cardiovascular side effects.[10] All five agents are generally equally effective[11] and their side effects include light-headedness from orthostatic hypotension (5%-10% of patients), dizziness (5%-10%), weakness (5%), headache (5%), asthenia (5%-10%), nasal congestion (5%), and retrograde ejaculation (3%-10%).[7] Although alpha blockers improve urine flow quickly, they do not reduce prostate size, and as a result they do not reduce the risk of future urinary retention or the need for BPH-related surgery.[12] In patients with severe allergies to sulpha, an allergic reaction to tamsulosin has been reported, and therefore this drug should be avoided in such patients.

Intraoperative floppy iris syndrome was observed during cataract surgery in some patients who currently or previously were taking alpha blockers. Therefore, if cataract surgery is a possibility, consideration should be given to avoiding alpha blockers until after the surgery. The ophthalmologist should be informed if the patient has been on alpha blockers for as long as 6 to 9 months prior to any cataract intervention.

Silodosin (Rapaflo) is a super selective alpha blocker that has recently become available in Canada. This drug blocks alpha-1a receptors and, to a much lesser degree, alpha-1b and alpha-1d receptors. This heightened selectivity may result in fewer cardiovascular side effects, which are mainly regulated by alpha-1b receptors.[13] A number of studies have confirmed the safety of silodosin, especially in terms of cardiovascular safety. There are negligible effects on heart rate or ECG, including PR segment and QRS complex.[14] Side effects include upper respiratory tract infection (2%-19% of patients), diarrhea (2%-7%), dizziness (3%-5%), and orthostatic hypotension (3%). Alterations in ejaculatory function range from 5% to 28%, with a median of 20% of patients experiencing retrograde ejaculation. However, only about 2% of patients discontinued silodosin therapy based on ejaculatory dysfunction alone.[15]

A major study comparing silodosin versus tamsulosin was published in Europe[16] and involved 1228 patients randomized to tamsulosin versus silodosin versus placebo for 12 weeks. This study found no significant differences between tamsulosin and silodosin in terms of IPSS for storage or voiding symptoms, which suggests that both drugs are equally efficacious in the treatment of BPH. Two other studies[17,18] have suggested that silodosin may be more effective than tamsulosin, but in both these studies suboptimal dosing of tamsulosin (0.2 mg daily) was used as the comparator. Ejaculatory dysfunction was higher in the silodosin group (14.2%) versus the tamsulosin group (2.1%). Interestingly, patients with ejaculatory dysfunction had the highest efficacy with silodosin, suggesting that the presence of ejaculatory dysfunction can be used as a surrogate for efficacy.[19] Cardiovascular side effects were comparable for both groups, and although silodosin demonstrated a more favorable cardiovascular profile than tamsulosin, this difference was not statistically significant. Recent studies have suggested that silodosin may have a quicker onset of action than tamsulosin.[19]

Silodosin has recently been examined in men with chronic prostatitis/chronic pelvic pain syndrome.[20] In this study, equal numbers of 151 patients were randomized to silodosin 4 mg, silodosin 8 mg, and placebo. Compared to placebo, the 4 mg dose of silodosin was associated with a significant reduction in chronic prostatitis symptoms and an improved quality of life. There was no additional benefit from the 8 mg dose.

### *5-alpha reductase inhibitors*

The 5-ARIs, Table 2, inhibit the conversion of testosterone to DHT, the main mediator of BPH progression. This causes the prostate to decrease in size and slow the progress of prostate growth.[21,22] The onset of action with 5-ARIs is slower than with alpha blockers, and usually takes 4 to 6 months. The two main 5-ARIs are finasteride (Proscar)[23] and dutasteride (Avodart).[24] Finasteride inhibits the type 2, 5-alpha reductase isoenzyme, whereas dutasteride inhibits both type 1 and type 2 isoenzymes. With this dual blockade, dutasteride lowers DHT production in the prostate by over 90%, whereas finasteride lowers DHT by 70%.[1] As a result, dutasteride may have a faster onset of action than finasteride. The 5-ARI side effects include erectile dysfunction (ED, in 5%-8% of patients), ejaculatory dysfunction (1%-5%), decreased libido (5%), and, rarely, gynecomastia (1%). By shrinking the prostate, the 5-ARIs have been shown to improve BPH-related symptoms and to reduce the risk of future urinary retention and BPH–related surgery.[21]

Alpha blockers do not affect PSA and have no effect on prostate cancer risk. However, the 5-ARIs lower PSA by 50% after 6 months on therapy.[25] For example,

TABLE 2. **5-alpha reductase inhibitor (5-ARI) medications for symptomatic benign prostatic hyperplasia (sBPH)**

| Name (Brand name) | Dose | Half-life | Mechanism | Side effects/Notes |
|---|---|---|---|---|
| Finasteride (Proscar) | 5 mg daily | 6-8 hours | Inhibits type II 5-AR* | Decreased libido; sexual dysfunction; gynecomastia |
| Dutasteride (Avodart) | 0.5 mg daily | 3-5 weeks | Inhibits types I and II 5-AR* | Same as above |
| Dutasteride/ Tamsulosin (Jalyn) | 0.5 mg dutasteride & 0.4 mg tamsulosin combination daily | 9-13 hours (tamsulosin), 3-5 weeks (dutasteride) | Combination 5-ARI and alpha blocker | See dutasteride and tamsulosin |

*5-AR = 5-alpha reductase

if a patient's PSA is 8 ng/mL prior to the initiation of a 5-ARI, then after 4 to 6 months of therapy, the PSA should be in the 4 ng/mL range. While continuing on 5-ARI the PSA value should stay around this level. If the PSA rises on 5-ARI then a referral to a urologist is mandatory to exclude the development of new prostate cancer. While the patient is receiving a 5-ARI, the prostate should be checked with an annual DRE.

Controversy still exists about the increased risk of developing high grade prostate cancer in patients taking a 5-ARI such as finasteride or dutasteride. Health Canada and the US Food and Drug Administration (FDA) issued a label change for finasteride and dutasteride to include new safety information about the possible increased risk of being diagnosed with high grade prostate cancer while on these agents, based on analysis of data from the Prostate Cancer Prevention Trial (PCPT)[26] and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial.[27] Some experts have suggested that the increased risk of high grade prostate cancer may be an artifact resulting from the interpretation of prostate biopsies in these studies. Current recommendations are to exclude prostate cancer in BPH patients (based on PSA and DRE) prior to initiating 5-alpha reductase inhibitors for BPH.

## *Combination therapy*

Studies have shown the benefit of combination therapy with 5-ARIs and alpha blockers.[25] The benefit is greatest in patients with large prostates, where the 5-ARI shrinks the prostate and the alpha blocker relaxes the smooth muscle of the prostate providing combination benefits. For patients with smaller prostates, alpha blockers alone may be sufficient to alleviate urinary symptoms. Two landmark studies examined combination therapy for BPH:

***MTOPS:*** The Medical Therapy of Prostate Symptoms (MTOPS) study was a landmark trial comparing monotherapy with an alpha blocker (doxazosin) or a 5-ARI (finasteride [Proscar]) versus combination therapy (doxazosin and finasteride) for BPH.[28] This study randomized patients into four treatment groups: an alpha blocker (doxazosin) alone, a 5-ARI (finasteride) alone, combination therapy, and placebo.[28] Combination therapy provided the most effective increase in flow rate, improvement in symptom scores, reduction in risk of acute urinary retention, and reduction in the need for surgery. Prostate volume decreased in patients who received finasteride alone, and in patients who were treated with finasteride plus an alpha blocker. Patients who were treated with an alpha blocker alone or with placebo had an increased prostate volume over time, and they did not have a reduced need for future BPH-related surgery or a reduced risk of developing acute urinary retention.

***CombAT:*** The Combination of Avodart and Tamsulosin (CombAT) study was designed to examine whether the combination of dutasteride and tamsulosin was more effective than monotherapy alone for improving symptoms for men who had BPH, or to prevent the progression of BPH. The 4 year results and the 2 year results showed that there was an improvement in the quality of life and an improvement in symptom scores in men with proven, enlarged prostates that were larger than 30 cc. There was also a 66% relative risk reduction in the onset of acute urinary retention or the need for surgery in the combination arm compared to the active treatment with tamsulosin.[29] With improvement on combination therapy, in most cases men were able to stop taking the alpha blocker after 6 to 9 months.[29] After stopping the alpha blocker most of the men were still able to maintain a fairly good, symptom-free response. Jalyn, a single-capsule combination of dutasteride 0.5 mg and tamsulosin 0.4 mg was approved for use in men with symptomatic BPH based on the study results from the CombAT trial.

## Single-agent treatment of BPH and erectile dysfunction

Erectile dysfunction (ED) and BPH often coexist in aging men.[30,31] BPH not only causes prostatic obstruction and bladder neck contraction, it may also alter smooth muscle relaxation, reduce blood flow, and reduce the function of nerves and endothelium.[32] Phosphodiesterase-5 (PDE-5) promotes smooth muscle contraction; therefore, PDE-5 inhibitors may have a role in smooth muscle relaxation in BPH and may provide symptom relief. Recent studies of oral PDE-5 inhibitors—including tadalafil (Cialis), vardenafil (Levitra), and sildenafil (Viagra)—have demonstrated significant improvements of LUTS in patients with BPH.[33-37] A dosage of 5 mg tadalafil/day significantly improved IPSS compared to placebo,[38] with improvement onset occurring within 2 weeks. Although urodynamic profiles were not significantly improved with daily tadalafil, patients' symptom scores improved. Side effects included headache, back pain, facial flushing, dyspepsia, and nasopharyngitis. In Canada, 5 mg daily tadalafil (Cialis) was approved for the treatment of BPH and ED, as of June 2012.

## Surgical therapy

If patients continue to be bothered by their urinary symptoms despite medical therapy, the next options include minimally invasive surgical therapies. The most common surgical procedure for BPH is transurethral resection of the prostate (TURP). This involves removing the prostatic urethra and "coring" the prostate, which creates a channel for the patient to void through. Risks from this surgery include bleeding (with a risk of blood transfusion), permanent sexual side effects (such as retrograde ejaculation and less commonly, ED), UTIs, and, rarely, urinary incontinence. Numerous energy sources have been studied and used for TURP. These include cautery, holmium laser (holmium laser enucleation of the prostate [HoLEP], or holmium laser ablation of the prostate [HoLAP]), Nd-YAG visual laser-assisted prostatectomy (VLAP), GreenLight laser (potassium-titanyl-phosphate [KTP]), and photoselective vaporization (PVP). In general, TURP is the gold standard for surgical management of BPH.

## Guidelines and algorithms

The Canadian Urological Association (CUA) guidelines for the management of BPH[39] are available on the CUA website.

## Reasons for referral to a urologist

Once treatment for BPH has been initiated, a referral to a urologist would be indicated in the following instances:

- Rising PSA, especially while on a 5-ARI such as finasteride or dutasteride
- Failure of urinary symptom control despite combination therapy
- Suspicion of prostate cancer, from a prostate exam and/or elevation in serum PSA levels
- Hematuria (microscopic or gross)
- Recurrent UTIs
- Urinary retention
- Renal insufficiency or renal failure from obstruction

## Summary

The standard therapy for managing a patient with BPH is initiating an alpha blocker with a quick onset of action, between 3 to 5 days. Selective alpha blockers include tamsulosin, alfuzosin, and more recently, silodosin. For patients with larger prostates, the addition of a 5-ARI such as finasteride or dutasteride may be considered, to reduce prostate volume, reduce the risk of acute urinary retention, and decrease the risk of future prostate-related surgery. After 6 to 9 months of combination therapy with an alpha blocker and a 5-ARI, consideration can be given to stopping the alpha blocker. In addition to treating patients with BPH with drugs from the 5-ARI class and the alpha blocker class, drugs from the PDE-5 inhibitor class may now be considered for treating BPH. Once daily tadalafil 5 mg has been shown to improve BPH-related symptoms and is a current treatment option for BPH patients.

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