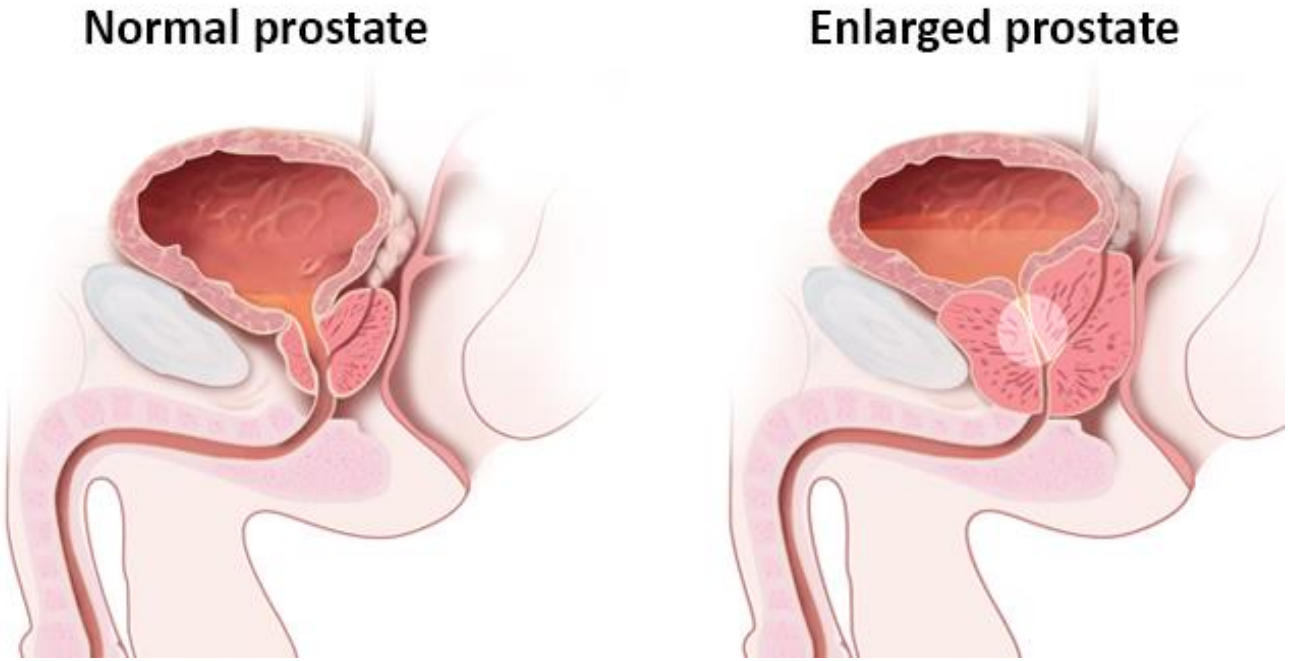
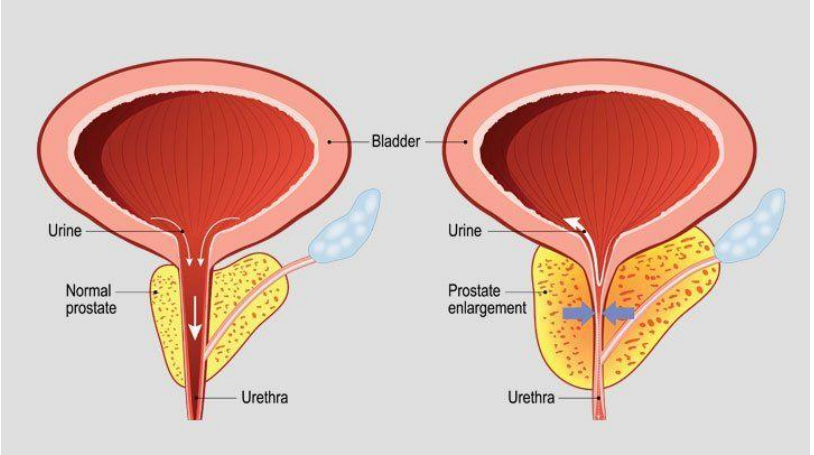


Benign Prostatic Hyperplasia

Introduction

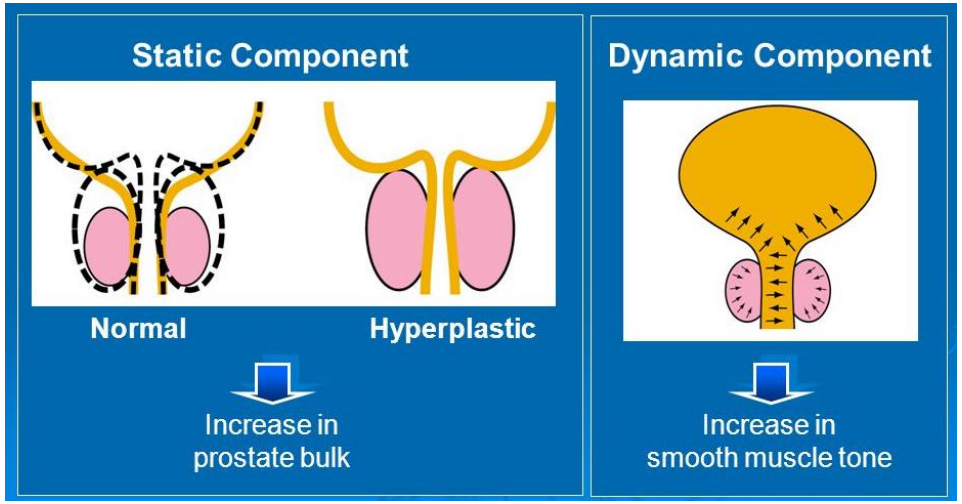
BPH is defined by the American Urological Association as "a histologic diagnosis that refers to *smooth muscle* and *epithelial cell* **proliferation** within the prostatic transition zone."

The histologic evidence of BPH may be prevalent in **~80%** of older males; however, only 60% at least age 60 years develop symptomatic disease.



Pathophysiology

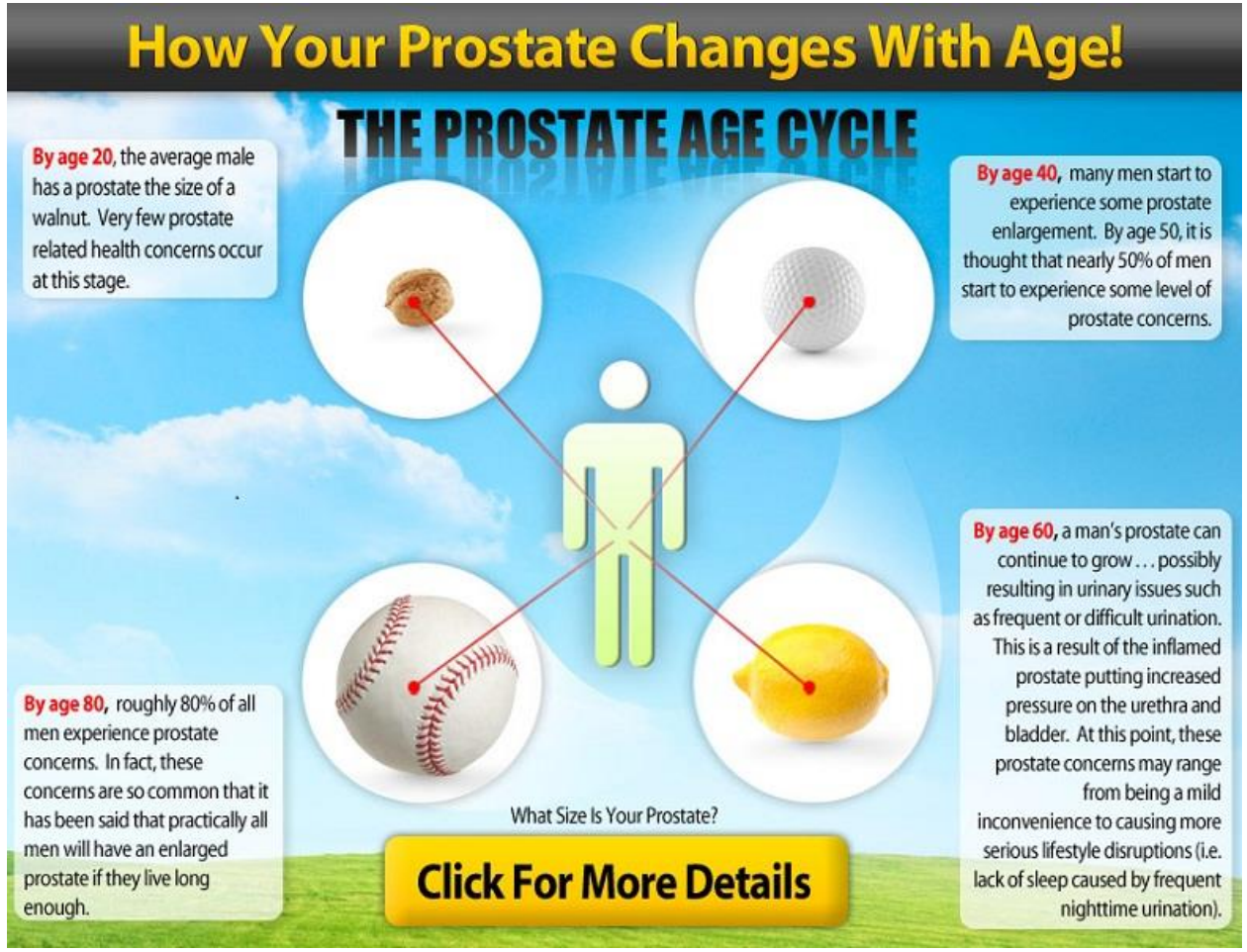
There is both a **static** and a **dynamic** component to prostate enlargement. The static component increases the *prostate size* by smooth muscle cell proliferation in the prostate stroma, whereas the dynamic component contributes to an enlarged prostate through an increase in *smooth muscle tone* in the prostate and bladder neck.



Pathophysiology

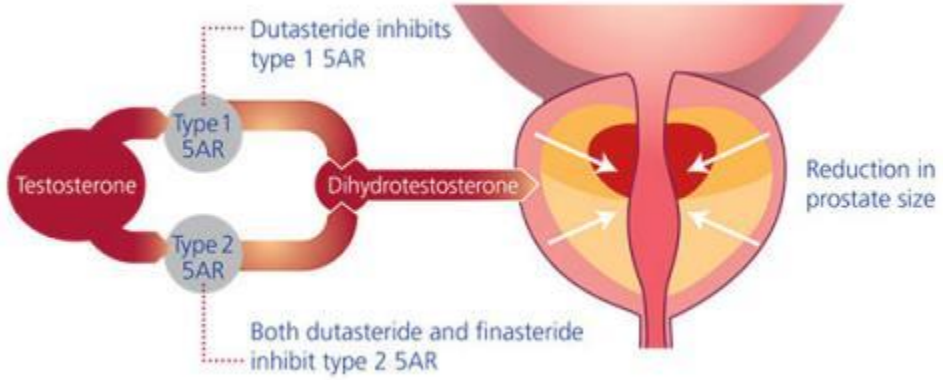
Static factors related to age and *androgen-induced prostate enlargement* cause **physical block** at the bladder neck and obstruct urinary flow.

After the *first growth* spurt at the time of **puberty** when prostate size starts to increase, a *second growth* spurt begins and continues **at age 40** and thereafter. During this phase, the prostate may enlarge up to quadruple the size and lead to symptomatic disease.



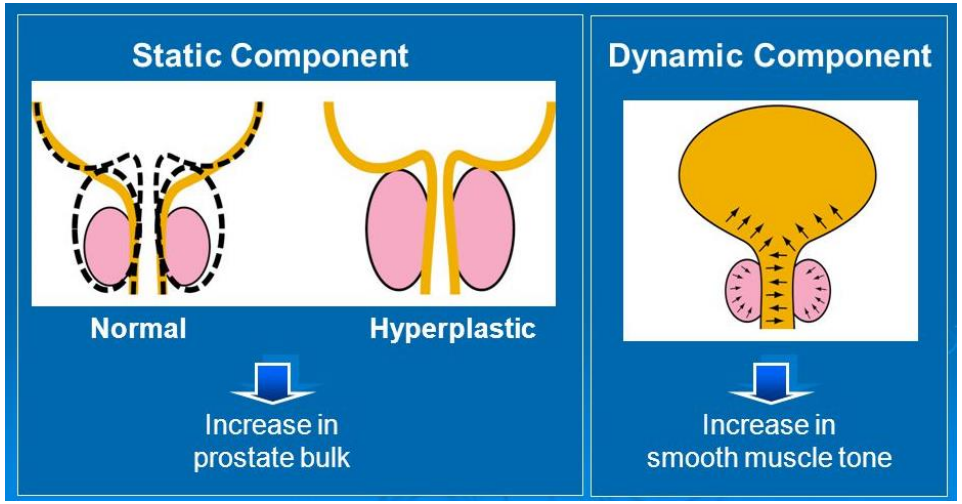
Pathophysiology

In the prostate, type II 5α-reductase enzyme converts *testosterone* into *dihydrotestosterone* (DHT), which is responsible for growth and enlargement of the prostate. Despite the age-related decline in testosterone level, **intraprostatic DHT** levels are maintained.



Pathophysiology

Dynamic factors relate to *exaggerated a-adrenergic tone* that leads to smooth muscle contraction, compression of the urethra, and reduced urinary bladder emptying. Normally, the ratio of stromal to epithelial tissue in the prostate is **2:1**, which is exaggerated to **5:1** in an *enlarged prostate*. Stromal tissue comprises **the α1-adrenergic receptors** that are stimulated as a result of the enlargement.



Clinical Presentation and Evaluation

Symptoms of BPH can be categorized as *obstructive* and *irritative* and are collectively referred to as lower urinary tract symptoms (LUTS).

- **Obstructive symptoms** are associated with *reduced bladder emptying* and result in straining to void, weak urine flow or stream, hesitancy, sensation of incomplete bladder emptying, and postvoid urinary dribbling.
- **Irritative symptoms** result from *long-standing bladder neck obstruction* and result in urgency, frequency, and nocturia.

Clinical Presentation and Evaluation

Approximately 17% to 20% of patients with symptomatic BPH suffer from **complications** including *acute urinary retention*, *suprapubic pain* from distended bladder, *recurrent urinary tract infections*, *hematuria*, *bladder stones*, *bladder diverticula*, and *renal failure*.

Patients with a prostate gland volume of **30 to 40 mL** or **PSA of ≥1.4 ng/mL** (μg/L) are especially more prone to **complications** of BPH.

Clinical Presentation and Evaluation

Acute urinary retention in BPH can occur as a result of increasing size of the prostate gland. Independent of gland size, **drugs** may precipitate acute urinary retention.

Drugs, such as alcohol, anticholinergic agents, α-adrenergic agents, and neuroleptics, have all been associated with acute urinary retention in males with BPH.

TABLE 1

Drugs That May Cause Urinary Retention

Class	Generic Name	Trade Name
Tricyclic Antidepressants	Amitriptyline Doxepin Protriptyline	Elavil Sinequan Vivactil
Antispasmodic	Phenobarbital Propantheline Oxybutynin	Donnatal Pro-Banthine Ditropan
Antipsychotic	Thioridazine Chlorpromazine	Mellaril Thorazine
Opiates	Morphine Codeine	
Sleep Medications	Diphenhydramine	Benadryl
Over-the-Counter Cold Remedies	Chlorpheniramine Maleate	Cold Formulas Comtrex Dristan Novahistine Ornade
Antiparkinsonism	Benztropine Mesylate	Cogentin

Clinical Presentation and Evaluation

To identify the most bothersome symptoms and select appropriate drug therapy, the patient's perception and severity of BPH should be evaluated using **validated instruments**.

The Multidisciplinary Measurements Committee of the American Urologic Association (AUA) also has published a urinary symptom index for BPH. The index is useful to assess the baseline severity of BPH, disease progression, and effectiveness of different therapies

AUA SYMPTOM SCORE (AUASS) AND QUALITY OF LIFE (QOL)

PATIENT NAME:_____ **DATE:**_____

(Circle One Number On Each Line)	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
Over the past month or so, how often have you had a sensation of not emptying your bladder completely after you finished urination?	0	1	2	3	4	5
During the past month or so, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5
During the past month or so, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
During the past month or so, how often have you found it difficult to postpone urination?	0	1	2	3	4	5
During the past month or so, how often have you had a weak urinary stream?	0	1	2	3	4	5
During the past month or so, how often have you had to push or strain to begin urination?	0	1	2	3	4	5
	None	1 Time	2 Times	3 Times	4 Times	5 or More Times
Over the past month, how many times per night did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0	1	2	3	4	5

Add the score for each item above and write the TOTAL here: _____

Clinical Presentation and Evaluation

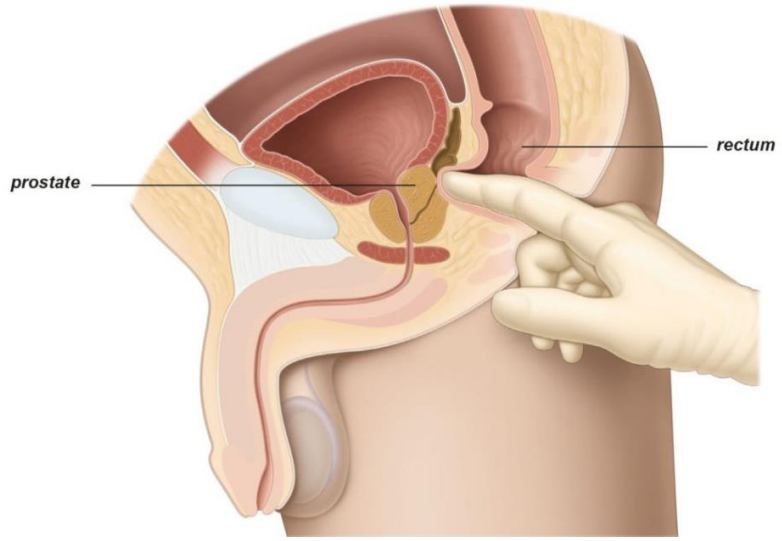
Categories of Benign Prostatic Hyperplasia Disease Severity Based on Symptoms and Signs

Disease Severity	AUA Symptom Score	Typical Symptoms and Signs
Mild	≤7	Asymptomatic Peak urinary flow rate <10 mL/second PVR urine volume >25–50 mL
Moderate	8–19	All of the abovementioned signs plus obstructive voiding symptoms and irritative voiding symptoms (signs of detrusor instability)
Severe	≥20	All of the abovementioned plus one or more complications of BPH

Additional Tests

- **Urinalysis**: Because patients with BPH also may have a *urinary tract infection*, a urinalysis with microscopic examination is essential.

- **Digital Rectal Examination**: The prostate examination should determine the *size*, *shape*, *consistency*, and *nodularity* of this gland. The digital rectal examination of a patient with BPH commonly finds asymmetry of the prostate, with one side being larger than the other. The presence of firm-to-hard nodules, irregularities, induration, or a stony, hard prostate suggests possible **prostate cancer**.



Additional Tests

- **Prostate-specific Antigen**: PSA *correlates* reasonably well, on average, with prostate weight owing to benign prostate glandular hyperplasia. Males **ages 40 years** and older with at least a **10-year life expectancy** have been encouraged to have an *annual measurement of serum PSA* and *a digital rectal examination* as a basic screen for prostate cancer and to monitor the growth of the prostate gland. PSA is **not necessary** for the *diagnosis* of BPH; however, it helps determine whether disease-modifying therapy options are indicated.

Lifestyle modifications

Lifestyle modifications and behavioral interventions are first-line treatments for all patients. These should be tailored to symptoms but generally include *avoiding fluids prior to bedtime* or *before going out*, reducing consumption of *mild diuretics* such as caffeine and alcohol, and *double voiding* to empty the bladder more completely.

Drug Therapy

The AUA recommends that **goals** of BPH management should include symptom improvement, as evidenced by a minimum of a *three-point decrease in the AUA-SI*, reducing the risk of complications, delaying the need for surgical intervention, and preventing progression of the disease.

Drug Therapy

Management of Benign Prostatic Hyperplasia

Disease Severity	AUA-SI Score	AUA Recommended Management
Mild	≤7	Watchful waiting Nonpharmacotherapy interventions Follow-up in 6–12 months
Moderate	8–19	Pharmacotherapy options to consider: 1. Small prostate, low PSA level: α_1-adrenergic antagonists 2. Large prostate, increased PSA level: α_1-adrenergic antagonists + 5α-reductase inhibitors 3. With erectile dysfunction: α_1-adrenergic antagonists, phosphodiesterase inhibitors, or both 4. With irritative symptoms: α_1-adrenergic antagonists + antimuscarinics, or + mirabegron
Severe	≥20	Minimally noninvasive surgery or prostatectomy if complications are present

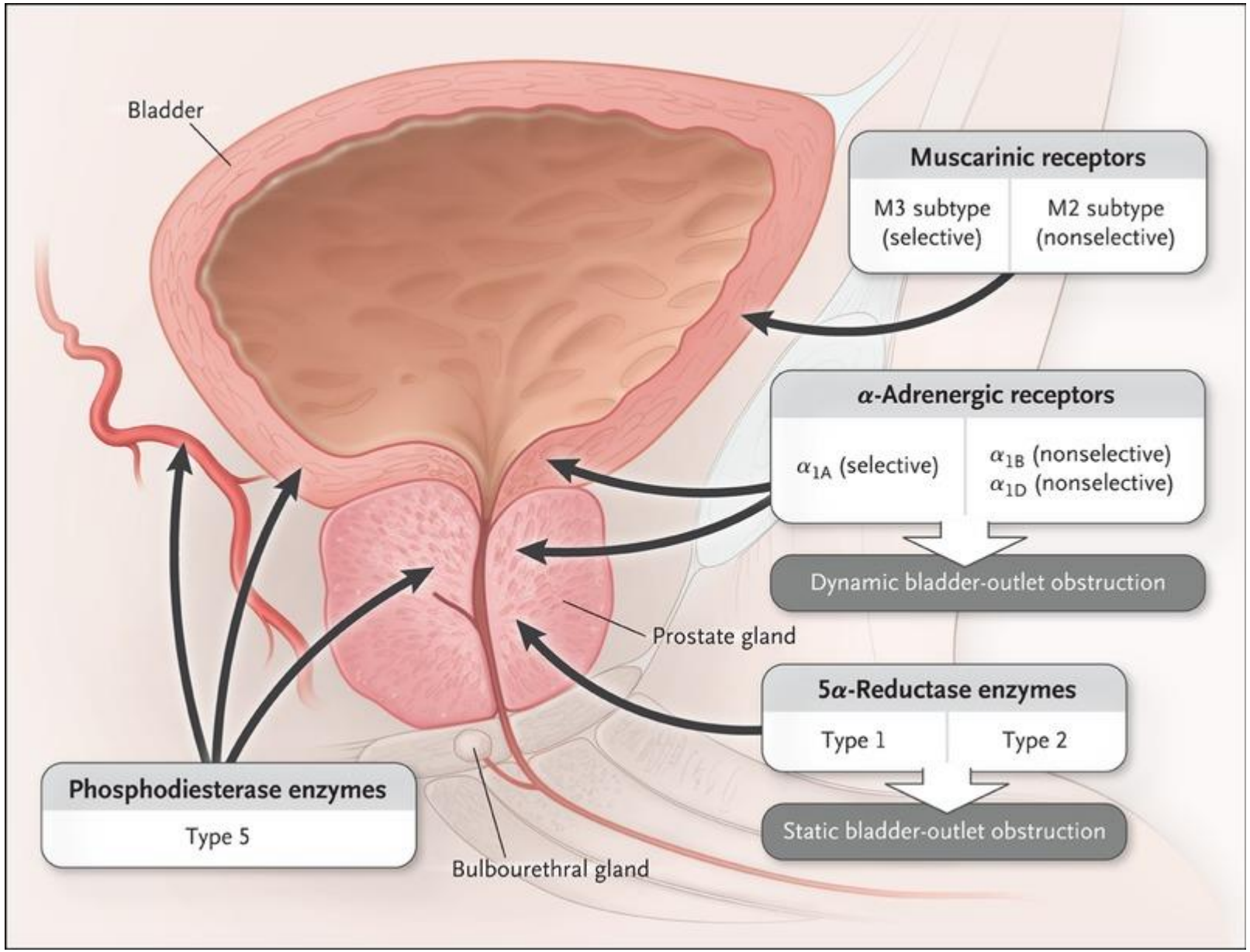
AUA, American Urological Association; AUA-SI, American Urological Association Symptom Index.

Drug Therapy

Comparison of Drug Classes for Benign Prostatic Hyperplasia Management

	α- AA	5α-RI	PDE-5Is	ACHs	β3-AA
Decreases Prostate Size	No	Yes	No	No	No
Halts Disease Progression	No	Yes	No	No	No
Peak Onset	1–6 weeks	3–6 months	4 weeks	1–2 weeks	2–8 weeks
Efficacy in Relieving Irritative Symptoms	++	++ (if enlarged prostate)	+	0	0
Frequency of Dosing	Once or twice a day	Once a day	Once a day	Varies	Once a day
Decreases PSA	No	Yes	No	No	No

ACH, anticholinergic; α-AA, α1-adrenergic receptor antagonist; 5α-RI, 5α-reductase inhibitor; β3-AA, beta-3 adrenergic agonist; PDE-5Is, phosphodiesterase type 5 inhibitor.


Bladder
Muscarinic receptors
M3 subtype (selective)
M2 subtype (nonselective)
α-Adrenergic receptors
α1A (selective)
α1B (nonselective)
α1D (nonselective)
Dynamic bladder-outlet obstruction
Prostate gland
5α-Reductase enzymes
Type 1
Type 2
Static bladder-outlet obstruction
Phosphodiesterase enzymes
Type 5
Bulbourethral gland

α1-adrenergic Antagonists

Alpha-adrenergic receptor blockers are used as *initial pharmacologic* agents in most patients with LUTS/BPH. Treatment effects are seen **within days**.

Bladder outlet obstruction (BOO) is primarily mediated by alpha-1 adrenergic receptors located on prostatic smooth muscle, which are *upregulated* in the stromal glandular hyperplasia seen in BPH. Blocking signaling through the alpha-adrenergic receptors leads to relaxation of the smooth muscle of the bladder neck and the prostatic urethra.

α1-adrenergic Antagonists

This drug class exerts its effects by targeting the dynamic factors and by *relaxing smooth muscle* in the bladder neck, prostate capsule, and prostatic urethra.

- **First-generation**: phenoxybenzamine
- **Second-generation nonselective α1-adrenergic antagonists**: prazosin, terazosin and doxazosin
- **Second-generation selective**: alfuzosin
- **Third-generation uroselective α1-A antagonists**: tamsulosin and silodosin.

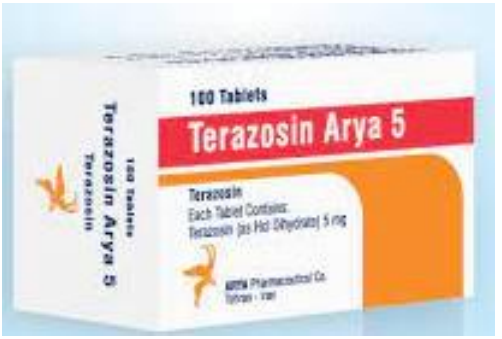
α1-adrenergic Antagonists

Prazosin is also a second-generation agent; however, owing to *multiple dosing frequency* and *higher risk factor for cardiovascular side effects*, it is <u>not recommended</u> for use per AUA guidelines.

α1-adrenergic Antagonists

Terazosin

- Started at 1 mg once daily at bedtime and titrated over several weeks to **5 to 10 mg** once daily
- *Orthostatic hypotension* may occur in the beginning days.
- In patients who *stop* their terazosin therapy *for ≥2 days*, therapy should be reinstituted cautiously to avoid the "first-dose" adverse effect of syncope.
- *Bedtime administration* may minimize orthostatic hypotension that is associated with the "first-dose" effect of these agents.



α1-adrenergic Antagonists

Tamsulosin

- *More specific* for the prostatic α1A-adrenergic and *less specific* for the vascular α1A-adrenergic receptors responsible for orthostatic hypotension.
- No need exists to *titrate* tamsulosin to the recommended daily dose range of 0.4 to 0.8 mg.
- Co-administration of tamsulosin with *antihypertensive agents* does not require dosage adjustment of the antihypertensives.
- Administer the dose of tamsulosin 30 minutes after the same meal daily.
- Renal dose adjustment is not required.
- Tamsulosin appears to reduce *mean ejaculatory volume* in 90% of patients.
- As with all α1-adrenergic receptor antagonists, tamsulosin *does not affect the PSA* and must be taken indefinitely to maintain its therapeutic effect.

α1-adrenergic Antagonists

Silodosin

- Silodosin has a strong affinity for prostatic tissue and is 20 times **more "uroselective"** than is tamsulosin.
- Silodosin is available as 4- and 8-mg capsules, and the recommended dose is *8 mg once daily*.
- The most common side effect of silodosin is *retrograde ejaculation*.

α1-adrenergic Antagonists

Side effects and interactions

- Most commonly reported adverse effects: hypotension, dizziness and rhinitis
- Agents with greater prostate selectivity (eg, tamsulosin, silodosin) have fewer systemic adverse effects but are associated with a higher frequency of retrograde or anejaculation

Phosphodiesterase-5 Inhibitor

PDE-5I use is associated with rare **adverse effects** including headache, flushing, dyspepsia, nasal congestion, back pain, myalgias, and sinusitis. There is an increased risk of *hypotension* in patients also using certain α-adrenergic antagonists.

Phosphodiesterase-5 Inhibitor

Tadalafil

- Selective PDE-5I
- It is FDA approved for use in males with BPH and ED at 5 mg/day dose.
- It should be taken at the same time every day *without regard to meals*.
- Evidence is **lacking** to support use of tadalafil in *combination* with α-adrenergic receptor antagonists and concurrent therapy may increase the risk of low blood pressure.
- Patients on antihypertensives, *nitrates*, or drinking 5 or more units of *alcohol* are also at increased risk for hypotension with tadalafil.

5α-reductase Inhibitors

The 5ARIs block one of the three isozymes of 5α-reductase and prevent the conversion of testosterone (T) to DHT. Such inhibition of 5α-reductase results in symptomatic relief in patients experiencing LUTS due to prostate enlargement; however, its *primary benefit* is **not acute** symptom management.

5α-reductase Inhibitors

The *larger the prostate*, the *bigger the impact* of this class of agents. **PSA** levels can be used as a proxy for prostate volume. Levels **below 1.5 ng/mL** indicate a prostate that is likely too small to benefit from this treatment.

5α-reductase Inhibitors

It is important to note that the *benefits of 5ARI* therapy may **not** be apparent for 6 to 12 months because the impact on prostate size and PSA levels takes months of therapy to be significant. Nonetheless, this drug class does **reduce or delay** the need for *invasive* management modalities including prostate surgery.

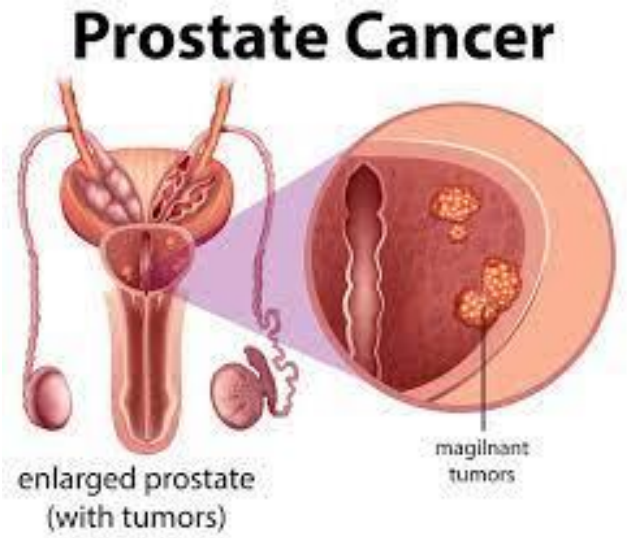
5α-reductase Inhibitors

A few *concerns* and ADRs associated with use of 5ARIs may limit their use. The most concerning ADR of 5ARIs is **sexual dysfunction**, including ED, decreased libido, ejaculatory dysfunction, gynecomastia, and breast tenderness. These ADRs are known to be *dose related* and reversible upon cessation of therapy.

The issue at hand is whether the *persistence* or *emergence* of dysfunction following drug cessation even exists. This putative adverse event has been coined "**post finasteride syndrome**" (PFS).

5α-reductase Inhibitors

A conflicting finding that 5ARIs can play a role in *reducing the risk of prostate cancer* has been challenged because of the lack of clear benefits; hence, prophylactic use of this drug class for this theoretical benefit is **not recommended**. Similarly, increased risk of high-grade tumors with concurrent use of 5ARIs also lacks support.



5α-reductase Inhibitors

To ensure that suppressed PSA levels are not mistaken as "normal" PSA levels in regard to prostate cancer monitoring, it is recommended to obtain *baseline* PSA before initiating 5ARI therapy. **Retest at 6 months** and consider that level the *new baseline*, and then continue monitoring for increases in levels thereafter compared to the new baseline level.

Alternatively, some experts recommend *multiplying PSA value by two* in patients receiving long-term (>3 months of continuous treatment) 5ARI therapy

5α-reductase Inhibitors

Nevertheless, patients receiving a 5ARI should have

(a) a *digital rectal examination* of their prostate periodically,
(b) the *PSA level* measured, and
(c) any *suspicious findings* investigated immediately.

Androgen suppression therapy is **not contraindicated** in BPH solely on the basis of its effect on serum PSA levels.

5α-reductase Inhibitors

Finasteride

- A *selective* 5ARI that specifically inhibits 5α-reductase type 2 isozyme.
- FDA approved for use in males with BPH **5-mg once-daily** dosing.
- Finasteride's efficacy in improving symptoms, urinary flow, and DHT levels in patients with enlarged prostates, especially those with prostates >40 g has been demonstrated in *several trials*.
- The efficacy and improvements from finasteride therapy were sustained for >4 years.

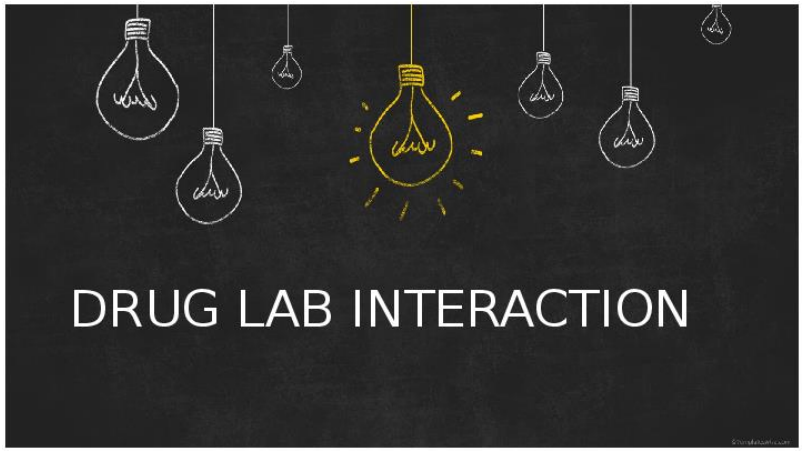
5α-reductase Inhibitors

Dutasteride

- A *nonselective* 5ARI that inhibits *both type 1 and 2* 5α-reductase isoenzymes.
- FDA approved for use in males with BPH at **0.5-mg once-daily** dosing.
- An advantage of dutasteride compared with finasteride is the additional inhibition of 5α-reductase (type 1) in the peripheral tissues, which produces a *further decline* in serum DHT.
- However, in a head-to-head trial of finasteride and dutasteride, **no significant difference** in prostate volume reduction and improvements in urine flow rates was found between the two drugs.

5α-reductase Inhibitors

Antiandrogen treatment of BPH could possibly adversely affect the **interpretation of the PSA** screening test *for prostate cancer*. Concern related to the utility of PSA levels as a marker for prostate cancer while a patient is on 5ARI therapy is legitimate because serum PSA levels are suppressed by ~50% with 5ARIs.



5α-reductase Inhibitors

Combination therapy

Certain patients with BPH may be appropriate candidates for combination therapy. For *quick symptomatic relief* of obstructive symptoms, **α1-adrenergic** receptor antagonists are first line and must be initiated. However, for symptomatic patients with an *enlarged prostate*, adding a **5ARI** is indicated.

5α-reductase Inhibitors

Even though 5ARIs may provide symptomatic relief, it could **take 6 to 12** months to improve symptoms. As a result, combination therapy is most appropriate for such patients.

A combination product of dutasteride 0.5 mg and tamsulosin hydrochloride 0.4 mg is commercially available.

Anticholinergics

For patients with LUTS related to **OAB**, the primary goal is to *decrease involuntary detrusor contractions*. Normal bladder contractions are primarily triggered by the neurotransmitter acetylcholine.

The human bladder has five cholinergic muscarinic receptor subtypes. The **M2** and **M3** types are found on *detrusor muscle*. Most smooth muscle contractions are mediated via the M3 type. Tolterodine, oxybutynin, and solifenacin are approved in the United States for OAB.

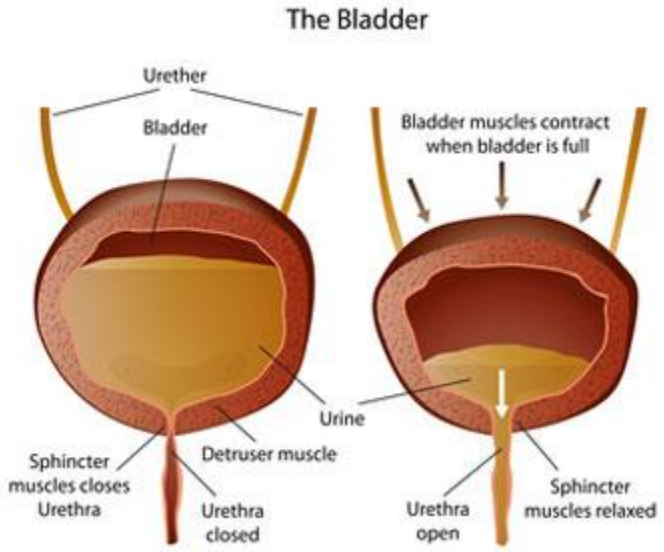
Anticholinergics

While anticholinergic monotherapy has been used for OAB symptoms, there can be some reluctance on the part of clinicians to use these agents alone in patients with BPH/LUTS due to the risk of **worsening postvoid residuals (PVRs) or retention.**

In the 2011 American Urological Association (AUA) BPH clinical guidelines, anticholinergic agents were considered *effective* treatment alternatives for the management of LUTS secondary to BPH in males without an elevated PVR urine and when LUTS are *predominantly irritative*.

Anticholinergics

The AUA panel recommended that, 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.

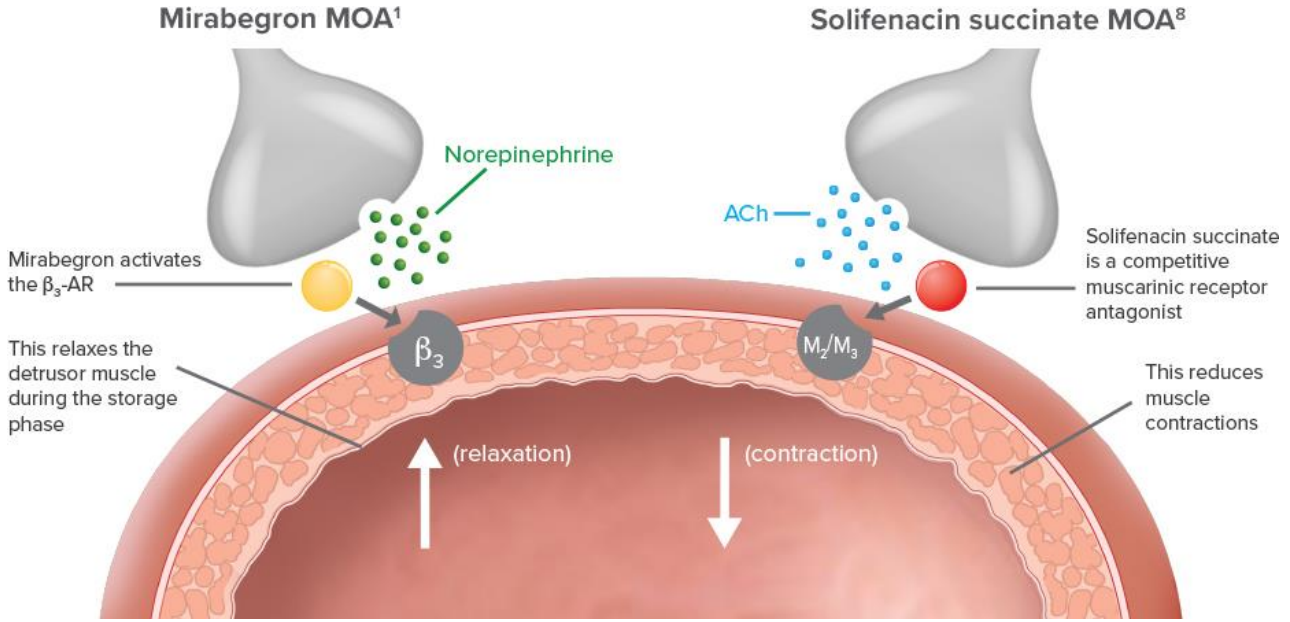


Beta3-adrenoceptor Agonists

Mirabegron is a first-in-class *beta3-adrenoceptor agonist* that is available and effective for treatment of **LUTS** related to **OAB**. The initial dose is 25 mg per day. The effect is evaluated in six weeks. Patients with little or no response on 25 mg can increase to 50 mg if they are tolerating the drug.

Beta3-adrenoceptor Agonists

This agent **do not** raise the same concern for *urinary retention* as do the anticholinergic medications. Mirabegron activates beta-3 adrenergic receptors in the bladder resulting in relaxation of the detrusor smooth muscle during the urine storage phase, thus **increasing bladder capacity.**



Medications other than alpha-1-receptor antagonists used to treat lower urinary tract symptoms due to benign prostatic hyperplasia (BPH)

Pharmacologic class	Medication	Initial dose	Titration interval	Maximum dose
Phosphodiesterase-5 (PDE-5) inhibitor*	Tadalafil (Cialis)	5 mg daily	None	5 mg daily
5-alpha-reductase inhibitors (5-ARIs)¶	Finasteride (Proscar)	5 mg daily	None	5 mg daily
	Dutasteride (Avodart)	0.5 mg daily	None	0.5 mg daily
Beta-3 adrenergic agonists	Mirabegron (Myrbetriq)	25 mg daily	May increase dose as needed and tolerated after ≥4 weeks	50 mg daily
	Vibegron (Gemtesa)	75 mg daily	None	75 mg daily
Anticholinergic agents△	Fesoterodine (Toviaz)	4 mg daily	May increase dose as needed and tolerated after ≥2 weeks	8 mg daily
	Tolterodine IR (Detrol)	1 to 2 mg twice daily	None	2 mg twice daily
	Tolterodine ER (Detrol LA)	2 to 4 mg daily		4 mg twice daily
	Oxybutynin IR (Ditropan◇)	5 mg 2 to 3 times daily	May increase dose as needed and tolerated in 5 mg increments every 1 to ≥2 weeks	5 mg 4 times daily
	Oxybutynin ER (Ditropan XL)	5 to 10 mg daily		30 mg daily
	Darifenacin (Enablex)	7.5 mg daily	May increase dose as needed and tolerated after ≥2 weeks	15 mg daily
	Solifenacin (Vesicare)	5 mg daily		10 mg daily
	Trospium IR (Sanctura◇)	20 mg twice daily (once daily if >75 years old)	None	20 mg twice daily
	Trospium ER (Sanctura XR◇)	60 mg daily		60 mg daily

Nonprescription Treatments

Two agents, saw palmetto and pygeum, have been promoted for the treatment of BPH.

Saw palmetto is an herbal product obtained from the fruit of the *Serenoa repens* tree with antiandrogen activity.

Nonprescription Treatments

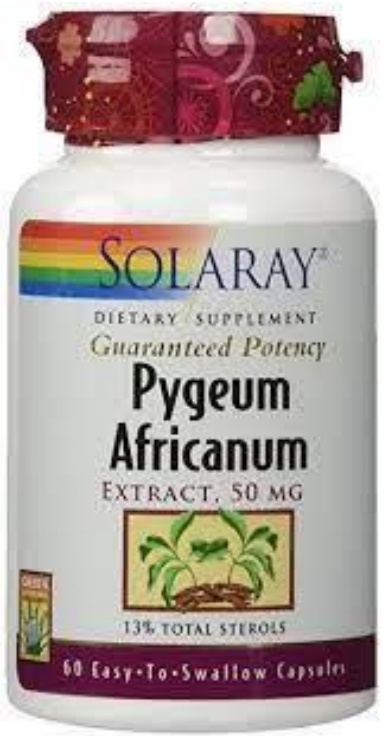
Several trials have shown that it significantly improves BPH symptoms to a degree *similar to that of finasteride*.

However, a 2012 meta-analysis of 32 randomized trials **failed to detect a difference** in urinary symptom improvement even with *triple the usual dose* of saw palmetto compared to placebo. The dose most often studied is 320 mg a day in one or two divided doses.

Nonprescription Treatments

Pygeum (*Pygeum africanum* bark extract) has been observed to moderately reduce urinary symptoms associated with enlargement of the prostate gland at a dose **of 75 to 200 mg/day**.

Herbal products *may be tried* by males with mild symptoms that would usually be managed by watchful waiting; however, the use of complementary and alternative medicines for BPH is **not currently recommended** by the AUA guidelines.



Nonpharmacologic Treatment

Transurethral Resection of the Prostate

TURP provides significant relief of BPH symptoms in 86%, 83%, 75%, and 75% of patients at 3 months, 1 year, 3 years, and 7 years, respectively.

The TURP is considered the **gold standard** for the treatment of BPH and is used in 90% of patients with symptoms of residual urine or acute urinary retention. As a result, surgical alternatives are always compared with the outcome studies of TURP.