Medical treatment of benign prostatic hyperplasia

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Benign prostatic hyperplasia (BPH) becomes increasingly common as men age. BPH can lead to urinary symptoms of increased frequency of urination, nocturia, urgency.

In patients with symptoms of benign prostatic hyperplasia (BPH) who do not have any discomfort from their symptoms and have no evidence of complications (such as bladder outlet obstruction, renal insufficiency, or recurrent infection), pharmacologic treatment may not be necessary .These patients may be monitored and advised regarding behavioral modification.

behavioral modifications

Avoiding fluids prior to bedtime or before going out

Reducing consumption of mild diuretics such as caffeine and alcohol

Men should also avoid medications that can exacerbate symptoms (eg,diuretics) or those that induce urinary retention

Indications for medical treatment

The decision to medically treat benign prostatic hyperplasia (BPH) balances the severity of the patient's symptoms with the potential side effects of therapy. Unless patients have developed bladder outlet obstruction, BPH only requires therapy if symptoms have a significant impact on a patient's quality of life

When to refer to urologist

there are several other situations in which patients should be referred to a urologist for evaluation prior to the initiation of medical therapy

Symptoms in the setting of autonomic or severe peripheral neuropathy

Symptoms following invasive treatment of the urethra or prostate

Abnormality in prostate exam

Age less 45 years

Presence of hematuria

Severe symptoms

Medications commonly used to treat lower urinary tract symptoms associated with benign prostatic hyperplasia (BPH) include:

Alpha-1-adrenergic antagonists

5-alpha-reductase inhibitors

Anticholinergic agents

Phosphodiesterase-5 inhibitors

Alpha-1-adrenergic antagonists provide immediate therapeutic benefits, while 5-alpha-reductase inhibitors require long-term treatment for efficacy. Patients who experience side effects, such as hypotension, with alpha1-adrenergic antagonists but still desire medical therapy for their BPH can be switched to 5-alpha-reductase inhibitors for monotherapy. Treatment with **5-alpha-reductase inhibitors requires 6 to 12 months** before symptom improvement.

Alternative options are available in specific populations of patients. **Anticholinergic agents** can be used in men who have predominately irritant symptoms, and **phosphodiesterase-5 inhibitors** are an option in men who also have **erectile dysfunction**.

In men with severe symptoms ,it may be reasonable to initiate therapy with a combination of an alpha-1-adrenergic antagonist and a 5-alpha-reductase inhibitor.

Alpha-1-adrenergic antagonists

We suggest treatment with an alpha-1-adrenergic antagonist for initial therapy of symptomatic BPH in most patients. Based on a meta-analysis, combining alpha-1-adrenergic antagonist with an anticholinergic did not improve outcomes more than alpha-1- adrenergic antagonist monotherapy did but increased adverse effects. Alpha-1-adrenergic antagonists are the most commonly prescribed medication for BPH .They act against the dynamic component of bladder outlet obstruction by relaxing smooth muscle in the bladder neck, prostate capsule, and prostatic urethra.

Terazosin, doxazosin, tamsulosin, alfuzosin, and silodosin are long-acting alpha-1-antagonists that have been approved by the US Food and Drug Administration (FDA) and are also available in Europe for treatment of the symptoms of BPH. Alpha-1-adrenergic antagonists improve symptoms of BPH. A meta-analysis of trials with alfuzosin, terazosin, doxazosin, or tamsulosin found that these drugs were more effective than placebo and that the efficacy of the drugs was similar.

Given the similar efficacy of all the approved alpha-1-adregergic antagonists, the choice of agent may be based on cost, side effects (particularly hypotension), and potential medication interactions (especially with phosphodiesterase-5 inhibitors).

Prazosin, a short-acting alpha-1- antagonist, is generally **not used for BPH** due to need for frequent dosing.

Terazosin and doxazosin generally need to be initiated at bedtime (to reduce postural lightheadedness soon after starting the medication), and the dose should be titrated up over several weeks.

Patients who remain symptomatic on a submaximal dose of an alphaadrenergic antagonist and are not experiencing adverse effects should have the dose increased

Side effects and interactions

Hypotension : The most important side effects of alpha-1-adrenergic antagonists are orthostatic hypotension and dizziness. Tamsulosin, alfuzosin, and silodosin have lower potential to cause hypotension and syncope than either terazosin or doxazosin .Tamsulosin may further have slightly less effect on blood pressure than alfuzosin .These differential effects on blood pressure by different alpha-1-antagonists may be due to their differential blocking of alpha-1 adrenoceptor subtype .Terazosin and doxazosin generally need to be initiated at bedtime (to reduce postural lightheadedness soon after starting the medication), and the dose should be titrated up over several weeks.

While the hypotensive effect can be useful in older men who have hypertension, careful blood pressure monitoring is required in all patients. In older adult men who are hypertensive but also experience orthostatic hypotension, tamsulosin may be a reasonable option. Alpha-1-adrenergic antagonists may increase the incidence of heart failure when used as monotherapy for hypertension.

Ejaculatory dysfunction: Tamsulosin and silodosin, in particular, can affect ejaculation .In one study, tamsulosin decreased mean ejaculate volume in more than 90 percent of patients, with 35 percent having no ejaculate; this problem was not observed with alfuzosin 10 mg.Silodosin produces retrograde ejaculation in approximately 28 percent of patients

Other common side effects include **headache, dizziness, and nasal congestion**.

interaction with phosphodiesterase-5 inhibitors

The hypotensive effects of terazosin and doxazosin can be potentiated by concomitant use of the phosphodiesterase (PDE)-5 inhibitors sildenafil or vardenafil. The risks with tadalafil are less clear. Tamsulosin at a dose of 0.4 mg/day does not appear to significantly potentiate the hypotensive effects of sildenafil

We advise men to separate the doses of alpha-1-adrenergic antagonists and PDE-5 inhibitors by at least four hours. In general, we use tamsulosin, alfuzosin, and silodosin in men who are also using PDE-5 inhibitors.

We suggest alpha-1-adrenergic antagonists as initial medical monotherapy for most patients with BPH. However, there may be some patients who do not tolerate these agents secondary to side effects but still desire to try medical therapy. 5-alpha-reductase inhibitors are an option in these patients .Alternatively, anticholinergic agents are an option in men who have predominately irritant symptoms, and PDE-5 inhibitors are an option in men who also have erectile dysfunction

Tamsolusin

Capsule: **0.4 mg once daily**. If response is inadequate after 2 to 4 weeks, may increase to **0.8 mg once daily**. If therapy is discontinued or interrupted for several days, restart with 0.4 mg once daily.

Controlled-release tablet :Initial and maximum dose: **0.4 mg once daily**

Administration

Adult Oral: Administer capsules 30 minutes after the same mealtime each day. Capsules should be swallowed whole; do not crush, chew, or open. The controlled-release tablet should be administered at the same time each day with or without food, and should be swallowed whole.

Dosing in renal impairment

No dose adjustment

Dosing in renal impairment

No dose adjustment

Terazosin

Oral: Initial: 1 mg at bedtime; thereafter, titrate upwards, if needed, over several weeks, balancing therapeutic benefit with terazosin-induced postural hypotension; most patients require 10 mg once daily; if no response after 4 to 6 weeks of 10 mg/day, may increase to 20 mg/day (maximum: 20 mg/day).

Administration: Adult Oral: Administer at the same time each day

No dose adjustment require in renal and hepatic impairment

5-alpha-reductase inhibitors

In patients who desire medical therapy but cannot tolerate alpha-1-adrenergic antagonists and do not have predominately irritant symptoms or concomitant erectile dysfunction, treatment with a 5-alpha-reductase inhibitor is reasonable. Patients should understand that treatment for 6 to 12 months is generally needed before prostate size is sufficiently reduced to improve symptoms.

5-alpha-reductase inhibitors are more effective in men with larger prostates. They act by reducing the size of the prostate gland and have demonstrated the potential for long-term reduction in prostate volume and need for prostate surgery. The type 2 form of 5-alpha-reductase catalyzes the conversion of testosterone to dihydrotestosterone in the prostate, hair follicles, and other androgen-sensitive tissues.

There are two 5-alpha-reductase inhibitors approved in the United States and Europe, finasteride and dutasteride

Administration

Finasteride can be initiated and maintained at 5 mg once daily. Dutasteride can be initiated and maintained at 0.5 mg once daily. In contrast to the alpha-1-adrenergic antagonists, 5-alpha-reductase inhibitors do not require titration.

Treatment for 6 to 12 months is generally needed before prostate size is sufficiently reduced to improve symptoms. Their ability to prevent acute urinary retention and reduction in need for surgery require chronic treatment for more than a year. If effective, such therapy is continued indefinitely in most patients with BPH as treatment discontinuation may lead to symptom relapse.

Concern regarding prostate cancer

The FDA recommends that before starting 5-alpha-reductase inhibitors for treatment of BPH, patients should be assessed for other urological conditions, including prostate cancer, due to the possible increased risk of high-grade prostate cancer . Prior to treatment, we evaluate patients with a digital rectal exam (DRE) and a serum prostate-specific antigen (PSA).

Side effects

Sexual dysfunction – The major side effects of 5-alpha-reductase inhibitors are decreased libido and ejaculatory or erectile dysfunction .A meta-analysis found that the risk of ejaculatory dysfunction was **similar** with finasteride and dutasteride.

Depression – There have been concerns by patients and regulatory agencies about possible adverse psychiatric effects of 5-alpha-reductase inhibitor therapy. Discontinuation of these medications may be appropriate if depression develops.

Product information for finasteride and dutasteride warns that pregnant **females should avoid touching the tablets.**

Finasteride

Administration

May be administered with or without meals. Pregnant women and females of childbearing potential should not touch or handle crushed or broken tablets.

No dose adjustment require in renal and hepatic impairment

Dutasteride

Administration

May be administered without regard to meals. Capsule should be swallowed whole; do not chew or open; contact with opened capsule can cause oropharyngeal irritation. Should not be touched or handled by women who are pregnant or may be pregnant.

No dose adjustment require in renal and hepatic impairment

Anticholinergic agents

Anticholinergic agents are an alternative monotherapy for patients with predominately irrelative symptoms (frequency, urgency, and incontinence) related to overactive bladder and without elevated post void residuals .They are also used in combination therapy with alpha-adrenergic agents for patients with persistent symptoms of BPH who have irrelative symptoms without elevated post void residuals.

Tolterodine, oxybutynin, darifenacin, solifenacin, fesoterodine and trospium are approved in the United States for overactive bladder.

Oxybutynin

Extended release: Note: Extended-release formulations are (or may be) preferred due to improved tolerability .Initial: **5 to 10 mg once daily**; adjust dose as needed and tolerated in 5 mg increments every 1 to ≥2 weeks .Maximum: 3**0 mg once daily.**

Immediate release: **5 mg 2 to 3 times daily**; adjust dose as needed and tolerated in 5 mg increments every 1 to ≥2 weeks .In patients with overactive bladder associated with neurodegenerative diseases, may consider initiation at 2.5 mg 2 to 3 times daily Maximum: 5 mg 4 times daily. Note: In patients with nocturia, some experts suggest a single daily dose of 2.5 to 5 mg at bedtime may be sufficient.

administration

Administer without regard to meals. Must be swallowed whole with liquid; do not crush, divide, or chew.

No dose adjustment require in renal and hepatic impairment

Tolterodine

Immediate release tablet: 2 mg twice daily; the dose may be lowered to 1 mg twice daily based on individual response and tolerability

Dosing adjustment in patients concurrently taking strong CYP3A4 inhibitors (eg, ketoconazole, clarithromycin, ritonavir): 1 mg twice daily

Extended release capsule: 4 mg once daily; dose may be lowered to 2 mg once daily based on individual response and tolerability

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ER capsule: Swallow whole; do not crush, chew, or open

Renal Impairment

Immediate release tablet: Significantly reduced renal function (studies conducted in patients with CrCl 10 to 30 mL/minute): 1 mg twice daily

Extended release capsule: CrCl 10 to 30 mL/minute: 2 mg once daily

Hepatic impairment

2mg once daily

Solifenacin

Initial: 5 mg once daily; if tolerated, may increase to 10 mg once daily.

Renal Impairment

CrCl ≥30 mL/minute: There are no dosage adjustments provided in the manufacturer's labeling; use with caution

Hepatic Impairment

Mild impairment (Child-Pugh class A): No dosage adjustment necessary; use with caution. Moderate impairment

(Child-Pugh class B): Maximum dose: 5 mg/day. Severe impairment

(Child-Pugh class C): Use is not recommended.

Oral: Administer tablet with water without regard to food. Swallow whole. Do not crush or chew.

Missed dose: Administer as soon as possible as long as ≤12 hours have passed. If >12 hours have passed, skip dose and administer next dose at usual time.

Phosphodiesterase-5 inhibitors

It is reasonable to consider treatment with PDE-5 inhibitors in patients who have erectile dysfunction and mild or moderate symptoms of BPH.

I n the United States, tadalafil is approved by the FDA for use in BPH. Daily dosing of tadalafil should not be prescribed in men with a creatinine clearance less 30 ml/min .

Dosing: 5 mg once daily. Note: When tadalafil is used with finasteride to initiate BPH therapy, the recommended duration of therapy is ≤26 weeks.

Decreased efficacy of tadalafil in older men was found in a pooled analysis of 12 phase II-III randomized trials.

Renal impairment

CrCl ≥51 mL/minute: No dosage adjustment

CrCl 30 to 50 mL/minute: Initial: 2.5 mg once daily; maximum: 5 mg once daily

clearance less 30 ml/min not recommended

Hepatic impairment

Mild to moderate hepatic impairment (Child-Pugh class A or B): Use with caution; the use of tadalafil for once-daily use has not been extensively evaluated in patients with hepatic impairment. Severe hepatic impairment (Child-Pugh class C): Use is not recommended.

COMBINATION THERAPY

Alpha-1-adrenergic antagonist and 5-alpha-reductase inhibitor

In patients with severe symptoms of BPH hose who are known to have a large prostate (>40 mL), and/or in those who do not get an adequate response to maximal dose monotherapy with an alpha-adrenergic antagonist, we suggest combination treatment with an alpha-adrenergic antagonist and a 5-alpha-reductase inhibitor

Short-term therapy with combined alpha-adrenergic antagonist and 5-alpha-reductase inhibitor therapy appears to be superior to either agent alone in men with BPH and larger prostate glands ,but not in men with only moderate BPH

Alpha-1-adrenergic antagonist and anticholinergic

we suggest combination treatment with an alpha-1-adrenergic antagonists and an anticholinergic agent In patients with severe symptoms of BPH .

HERBAL THERAPIES — Data concerning efficacy of herbal therapies for benign prostatic hyperplasia (BPH) are conficting. Until additional studies of herbals are performed, we suggest not using these agents for the treatment of BPH. Herbal therapies for BPH are commonly used in Europe. No herbal therapies have been approved by the US Food and Drug Administration (FDA) for this purpose, although many men likely try these treatments. There is a substantial placebo efect associated with herbal therapy, as there is for most drugs used to treat BPH. Additionally, concerns regarding standardization remain, particularly in the United States.

HERBAL THERAPIES

Data concerning efficacy of herbal therapies for benign prostatic hyperplasia (BPH) are conflicting. Until additional studies of herbals are performed, we suggest not using these agents for the treatment of BPH. Herbal therapies for BPH are commonly used in Europe. No herbal therapies have been approved by the US Food and Drug Administration (FDA) for this purpose, although many men likely try these treatments. There is a substantial placebo effect associated with herbal therapy, as there is for most drugs used to treat BPH. Additionally, concerns regarding standardization remain, particularly in the United States.

While there is some evidence evaluating herbal therapies for BPH, questions regarding safety and efficacy

Saw palmetto – Saw palmetto is widely used for treatment of BPH, but there are few data to support its efficacy

Beta-sitosterol – A 2011 systematic review of four randomized trials concluded that while evidence suggests that the plant extract beta-sitosterol improved symptoms in men with BPH, the long-term efectiveness and safety were not known

Cernilton

Pygeum africanum

Thanks Attentions