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# Alpha-Adrenergic Receptor Antagonists in Older Patients With Benign Prostatic Hyperplasia: Issues and Potential Complications

Shari R. Fine, DO
Phillip Ginsberg, DO, JD

**Benign prostatic hyperplasia (BPH) is highly prevalent in men older than 50 years and is associated with a range of lower urinary tract symptoms that may have a negative impact on patient quality of life. Alpha$_1$-adrenergic receptor antagonists are the first-line of pharmacologic management for lower urinary tract symptoms associated with BPH. However, many patients take multiple medications that may exacerbate age-related orthostatic hypotension. Thus, clinicians should evaluate the treatment of these patients within the context of comorbidities. The present article discusses the role of non–subtype-selective and subtype-selective $\alpha_1$-adrenergic receptor antagonists in the clinical management of BPH. Safety and tolerability for both non–subtype-selective and subtype-selective $\alpha_1$-adrenergic receptor antagonists for patients with BPH are also reviewed.**

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Benign prostatic hyperplasia (BPH) is a highly prevalent disorder that affects more than 50% of men older than 50 years.[1] Incidence rates increase incrementally with age.[1] Benign prostatic hyperplasia is associated with obstructive and irritative lower urinary tract symptoms (LUTS), which may have a negative impact on patient quality of life. Lower urinary tract symptoms include urgency, frequency, nocturia, and weak urine stream. More serious complications of BPH include acute urinary retention, renal insufficiency, urinary tract infection, gross hematuria, bladder stones, and renal failure. Lack of or inadequate management of BPH may precipitate or worsen these conditions.[2-4]

Although the etiology of BPH has not been clearly defined, the disorder most likely involves age-related proliferation of stromal and glandular cells in the periurethral and transition zones of the prostate gland as well as long-term exposure of prostatic tissue to androgens.[5] The microscopic proliferative process that occurs in prostatic tissue may eventually result in an enlarged prostate, which may constrict the urethra and lead to bladder outlet obstruction. In addition, this process increases the smooth muscle tone of the prostate, which is also associated with urethral constriction and is mediated by $\alpha_1$-adrenergic receptors.[2]

For patients with BPH, the main medical options for relieving LUTS are (1) $\alpha_1$-adrenergic receptor antagonists (eg, alfuzosin, doxazosin, tamsulosin, terazosin) to reduce smooth muscle tone in the prostate and the bladder neck or (2) antiandrogen therapy with 5$\alpha$-reductase inhibitors (finasteride and dutasteride) to reduce prostate size.[2]

Because men in this age group are likely to have comorbidities (*Figure 1*),[1,6-8] clinicians should consider BPH within the context of coexisting medical conditions that may complicate clinical management. In fact, according to Harris et al,[8] 20.2% of men aged 60 to 74 years have diabetes, which is nearly twice the diabetes prevalence rate among men aged 50 to 59 years (12.9%). Similarly, the prevalence of cardiovascular disease (CVD) among men between the ages of 65 and 74 (65.2%) is almost twice that of men between the ages of 45 and 54 (34.2%).[7]

Physicians should also be aware of other issues associated with advancing age, such as orthostatic hypotension, syncope, and falls associated with reduced blood pressure (BP), that may complicate the treatment of older patients.[9] In addition, many older patients take multiple medications that may exacerbate age-related changes in the circulatory system.

## Benign Prostatic Hyperplasia in Context: The Aging Circulatory System

Orthostatic hypotension—defined as a decrease in systolic BP greater than or equal to 20 mm Hg or a reduction in diastolic BP greater than or equal to 10 mm Hg on changing from supine to erect posture—is associated with advancing age and is common even in otherwise healthy, unmedicated older individuals. The prevalence rate of orthostatic hypotension in this demographic group is estimated to be as high as 30%.[10] In an analysis of the medical records of patients older than 75 years who had entered a Veterans Affairs geriatric clinic, Poon and Braun[11] found that, of 342 patients, 189 (55%) had orthostatic hypotension. Falling, a risk associated with ortho-

From Christ Hospital in Jersey City (Dr Fine) and the Division of Urology at the Albert Einstein Medical Center in Philadelphia (Dr Ginsberg).

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Address correspondence to Shari R. Fine, DO, University of Medicine and Dentistry of the New Jersey School of Osteopathic Medicine, Department of Family Medicine, 324 Palisade Avenue, Jersey City, NJ 07307.
E-mail: sfine324@verizon.net

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■ **Hypertension**
- At ages 65 to 74, 63.6% of men have hypertension (ie, blood pressure ≥140/90 mm Hg).[7]
- At age 75 and older, this rate increases to 69.5% of men.[7]

■ **Diabetes**
- Approximately 21% of people older than 60 years have diabetes.[6]
- In 2005, approximately 600,000 people older than 60 years had a new diagnosis of diabetes.[7]

■ **Cardiovascular Disease**
- About 1 in 3 men aged 65 to 74 years have some form of CVD.[7]
- About 32% of deaths due to CVD occur in people aged younger than 75 years.[7]

**Figure 1.** *The risk of hypertension, diabetes, and cardiovascular disease (CVD) in patients aged 60 years and older.*

static hypotension, can be fatal and affects the older population at a high rate—approximately one-third of people older than 65 years who live at home and about one-half of nursing home residents fall at least once per year (*Figure* 2).[12]

Several age-related changes may predispose elderly patients to orthostatic hypotension and consequent risk of falls and related injuries. These changes include decreased cardiac output, vagal response, and maximum heart rate. In addition, vascular stiffening results in reduced vascular compliance and increased systolic pressure, while increased aortic impedance leads to decreased diastolic pressure. Diminished baroreflex activity results in abnormal regulation of blood pressure, which may also contribute to orthostatic hypotension. Hypertension and coronary artery disease may also contribute to orthostatic hypotension and are more likely to be present in older patients.[13-17]

The risk of hypotension and dizziness in elderly patients increases with the development of certain disease states and ameliorative pharmacotherapies.[18] For example, diuretics, commonly used to manage hypertension, are associated with hypovolemia and orthostatic hypotension.[19] Concomitant use of antihypertensives and sedatives, antipsychotics, hypoglycemics, or $\alpha_1$-adrenergic receptor antagonists in elderly patients may further decrease blood pressure and increase the risk of falls.[20] Therefore, physicians are encouraged to consider each patient's potential for treatment-related adverse events, such as dizziness or hypotension.

## Pharmacologic Treatment of Benign Prostatic Hyperplasia

Early stages of BPH may be treated by watchful waiting. Alpha-adrenergic receptor antagonists are the drugs of choice when pharmacologic therapy is indicated. There are three $\alpha_1$-adrenergic receptor subtypes. The $\alpha_{1A}$ subtype generally regulates smooth muscle tone in the prostate and bladder neck, whereas the $\alpha_{1B}$ subtype regulates BP via vascular smooth muscle contraction. The $\alpha_{1D}$ subtype is believed to be associated with bladder muscle contraction and sacral spinal cord innervation. It has been hypothesized that age-related changes in the distribution of vascular $\alpha_1$-adrenergic receptors may occur, with the greatest increase observed for the $\alpha_{1B}$-receptor subtype.[21,22] Terazosin, doxazosin, and alfuzosin are $\alpha_1$-adrenergic receptor antagonists that show equal affinity for all $\alpha_1$-receptor subtypes. Tamsulosin is selective for the $\alpha_{1A}$- and $\alpha_{1D}$-adrenergic receptors, while it shows less affinity for the $\alpha_{1B}$ subtype.[20,23]

The efficacy of these agents is comparable. However, some $\alpha_1$-adrenergic receptor antagonists (ie, terazosin, doxazosin) need to be titrated, and their full therapeutic doses are only achieved 2 to 4 weeks postinitiation.[24,25] Unlike other $\alpha_1$-adrenergic receptor antagonists, alfuzosin and tamsulosin do not require titration.[26,27] An 8-week, randomized, open-label comparative study[28] (N=1993) of tamsulosin (0.4 mg per day) and terazosin (titrated to 5 mg per day) demonstrated that subjects treated with tamsulosin had a statistically significant ($P<.001$) reduction of symptoms after 4 days of treatment when compared with subjects treated with terazosin. On day 4, terazosin had not yet reached maintenance dosing, as it was administered at 1 mg per day for the first 8 days of the trial.[28]

### *Non–Subtype-Selective $\alpha_1$-Adrenergic Receptor Antagonists*

Treatment-related adverse events are more likely to occur with some α-adrenergic receptor antagonists than others, especially in elderly patients.[30] Terazosin, doxazosin, and alfuzosin are long-acting, non–subtype-selective $\alpha_1$-adrenergic receptor antagonists. Originally marketed as antihypertensives, these medications may cause increased risk of hypotension or dizziness when administered at therapeutic levels.[4,25,29,30]

In a safety analysis of six placebo-controlled trials, researchers found that terazosin-treated patients with BPH had a statistically significant ($P<.05$) increase in the incidence of dizziness and orthostatic hypotension than did patients treated with placebo. Adverse events were more common in terazosin-treated patients older than 65 years.[31] In another study, terazosin was associated with statistically significant ($P<.001$) decreases in systolic and diastolic BP in both normotensive and untreated hypertensive patients.[32] Similar observations have been reported for studies of doxazosin.[33] Alfuzosin (2.5 mg twice daily) has also been associated with vasodilatory adverse events, particularly for patients who are older than 75 years, have concomitant CVD, or receive treatment with antihypertensives or vasodilatory agents.[34] A once-daily formulation of alfuzosin (10 mg per day) was released in the United States in 2003. A clinical study[35] comparing the 2.5 mg thrice-daily formulation and the 10 mg once-daily formulation to placebo demonstrated that vasodilatory adverse

- In 2003, the unintentional fall death rate for men aged 65 years or older was 46.2 per 100,000, a rate 49% higher than that for women in the same age group.[52]
- In 2005, the rate of non-fatal fall-related injury for men aged 65 years or older was 3,674 per 100,000.[52]
- In 2003, the rate of hip fracture among men aged 65 years or older was 583.5 per 100,000.[52]

**Figure 2.** *Falls: a major cause of morbidity in older patients.*

events were more common for patients taking either of the alfuzosin formulations than those in the placebo arm. However, the incidence of vasodilatory adverse events was lower for patients receiving 10 mg of alfuzosin once per day than those receiving 2.5 mg of alfuzosin three times per day. Thus, while non–subtype-selective $\alpha_1$-adrenergic receptor antagonists are effective in the management of BPH, their use may be associated with dizziness and hypotension, which is likely related to their vasodilatory properties.[26,36,37]

### Subtype-Selective $\alpha_1$-Adrenergic Receptor Antagonists

Tamsulosin, which selectively antagonizes $\alpha_{1A}$- and $\alpha_{1D}$-adrenergic receptors while demonstrating little affinity for the $\alpha_{1B}$ subtype, was developed specifically for the treatment of LUTS associated with BPH.[23] Studies comparing tamsulosin with terazosin and doxazosin indicate that tamsulosin has greater affinity for prostatic rather than vascular $\alpha_1$-adrenergic receptors.[20,38] Tamsulosin may, therefore, be expected to produce few BP-related adverse effects.[19] In addition, clinical trials investigating the efficacy and safety of tamsulosin (0.4 mg per day) in the treatment of patients with BPH have reported symptom reduction, including significant improvements in urine flow, without clinically significant effects on BP or heart rate. A comparison of clinical trial results for available BPH drugs indicates that tamsulosin may not increase the incidence of orthostatic hypotension. In one study,[39] patients received either tamsulosin (0.4 mg per day) or placebo once daily. The incidence of treatment-emergent orthostatic hypotension and syncope was greater in the placebo group than in the tamsulosin group. These observations were independent of patient positioning (supine vs standing).

Similarly, Chapple et al[40] compared tamsulosin's safety and tolerability in patients younger than 65 years and those aged 65 years or older when treated with 0.4 mg of tamsulosin per day vs placebo. For the tamsulosin-treated group, the incidence of adverse events possibly associated with vasodilation was 8.4% for the younger group and 4.2% for the older cohort. A similar incidence rate was noted in the placebo-treated groups—7.5% for those younger than 65 years and 6% for older patients.[40] There were no statistically significant differences between placebo- and drug-treated groups for either age category, and changes in BP or pulse rate were minimal for both study groups.[40]

In an open-label extension study of the above trials evaluating the safety of tamsulosin for up to 3 years, 2.5% of patients cumulatively had treatment-emergent orthostatic hypotension, while 2.0% of patients had drug-related orthostatic hypotension.[41] In another open-label study that was extended up to 6 years, 1.3% of tamsulosin-treated subjects had orthostatic hypotension.[42]

To confirm the hypothesis that receptor selectivity allows fewer vasodilatory adverse events, a direct comparative study of terazosin (titrated to 5 mg once daily) and tamsulosin (0.4 mg once daily) was conducted on ambulatory BP using nocturnal orthostatic stress testing in 50 elderly normotensive patients with LUTS. Symptomatic hypotensive orthostatic stress occurred more frequently in the terazosin-treated group than in those who received tamsulosin.[37]

Data from tamsulosin trials demonstrate that coadministration of tamsulosin with nifedipine, enalapril, or atenolol—cardiovascular drugs frequently prescribed for hypertension or heart failure—produced no clinically significant differences in BP and pulse rate and did not increase adverse effects.[27,43] Therefore, for patients with cardiovascular comorbidities, the use of tamsulosin for the clinical management of BPH may be a safer choice than the non–subtype-selective $\alpha_1$-adrenergic receptor antagonists.

Adverse events observed in studies of tamsulosin efficacy and safety include dizziness, which occurred in 10% of patients enrolled in six US and European trials, as well as cephaligia and rhinitis.[27]

### Concomitant Medications and Conditions

Medical comorbidities are common among older patients. Approximately 25% to 30% of all men older than 60 years have concomitant hypertension and BPH.[1] It is possible that elderly patients with CVD may have unfavorable reactions to medications used in the management of BPH. For example, commonly prescribed medications for patients diagnosed with CVD (eg, diltiazem) may increase plasma levels of a given $\alpha_1$-adrenergic receptor antagonist by inhibiting cytochrome enzymes, resulting in an increased risk of hypotension.[26] In addition, medications used to manage BPH may cause adverse effects in comorbid patients. For example, blood levels of certain $\alpha_1$-adrenergic receptor antagonists may increase with moderate hepatic insufficiency or renal insufficiency.[26] Thus, it is important to consider the potential for interactions when prescribing a pharmacologic agent for the management of BPH in a patient who either has a comorbid condition, is taking concomitant medications, or both.

Erectile dysfunction (ED) is increasingly prevalent with advancing age and is often associated with a perception of reduced quality of life.[44] Epidemiologic studies indicate that older men with ED are likely to have concomitant diabetes and CVD, including hypertension.[45] Vascular disease is thought to

be the most common organic etiology of ED.[45] Pharmacologic therapies for ED (eg, sildenafil, vardenafil, and tadalafil) are selective inhibitors of cyclic guanosine monophosphate-specific phosphodiesterase type 5.[46-48] Currently, there are precautions in the prescribing information for phosphodiesterase type 5 inhibitors about concomitant use with $\alpha_1$-adrenergic receptor antagonists.[46-48] In a clinical pharmacology study,[48] the simultaneous administration of tadalafil 20 mg and tamsulosin 0.4 mg produced no statistically significant decrease in BP.

In some patients treated with $\alpha_1$-adrenergic receptor antagonists, a surgical condition known as intraoperative floppy iris syndrome has been observed during phacoemulsification cataract surgery.[49] This syndrome is characterized by a flaccid iris that billows in response to ordinary irrigation currents, progressive pupil constriction despite preoperative dilation with standard dilatory drugs, and potential prolapse of the iris toward the phacoemulsification incisions.[49] The cause of this syndrome is unknown,[49] and, until it is better understood, surgeons should ask patients undergoing cataract surgery if they have taken $\alpha_1$-adrenergic receptor antagonists.[50] If necessary, the surgeon should be prepared to modify his or her surgical technique. The benefit of stopping $\alpha_1$-adrenergic receptor antagonist therapy before cataract surgery has not been established.[50]

## Conclusion

Benign prostatic hyperplasia is a highly prevalent condition in older men and often occurs in combination with a number of other serious diseases, such as diabetes and CVD. Non–subtype-selective $\alpha_1$-adrenergic receptor antagonists used in the management of BPH may block $\alpha_1$-adrenergic receptors in the vasculature, which may in turn precipitate hypotension, dizziness, syncope, falls, and subsequent morbidity and mortality.[51] As many elderly patients with BPH may take multiple medications that, in combination, may also exacerbate age-related hypotension, appropriate drug selection is particularly important.

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*[The body] is not a biological apartment house with separate floors and no intercommunicating doors. It is a commune—an interrelated group of body organs and systems sharing in the common rights and property of a biological community.*

George W. Northup, DO
*Osteopathic Medicine: An American Reformation (3rd ed) (1987)*