Benign prostatic hyperplasia (BPH) is the most common benign neoplasm in American men. Autopsy findings have shown that 80% of men who live to the age of 80 years have microscopic BPH. Of these men, approximately 50% will develop urinary voiding symptoms or clinical BPH, and 50% of symptomatic patients will require treatment for the disease. Symptomatic BPH can begin in men in their fourth decade of life. Treatments available include watchful waiting, \( \alpha \)-adrenergic antagonists, finasteride, and surgery. Watchful waiting is indicated for patients with mild symptomatic BPH, surgery is indicated for patients with severe symptomatic BPH, and \( \alpha \)-adrenergic antagonists and finasteride are used for moderate to severe symptomatic BPH. Choosing the correct treatment depends on the severity of BPH; concurrent medical conditions of the patient; preference of the patient for or against surgical intervention; and comparative efficacy, onset of action, adverse effects, and cost of therapy. For elderly patients, the treatment must not interfere with concurrent medical therapy to minimize drug interactions.

The focus of this review is alfuzosin hydrochloride, a functionally uroselective \( \alpha \)-adrenergic antagonist indicated for the management of symptomatic BPH. Other commercially available \( \alpha \)-adrenergic antagonists in the United States include prazosin (Minipress, Pfizer), terazosin (Hytrin, Abbott Laboratories), doxazosin (Cardura, Pfizer), and tamsulosin (Flomax, Boehringer Ingelheim), all of which have been available for the same indication for some time. This review will compare alfuzosin with other \( \alpha \)-adrenergic antagonists for BPH.

### Prostate physiology and the role of \( \alpha \)-adrenergic receptors

A normal prostate gland comprises smooth muscle or stromal tissue and glandular tissue. The prostate...
produces some secretions that are included in the male ejaculate, and another secretion that may exert an antibacterial effect. Unlike a normal prostate, the prostate in patients with BPH contains a higher ratio of stromal to glandular tissue (5:1). The smooth muscle is innervated by α-adrenergic receptor stimulation α1 and α2. The outer prostatic capsule (outer shell), bladder neck (base), and proximal urethra also have a high concentration of α1-adrenergic receptors. Excessive stimulation of postsynaptic α1-adrenergic receptor stimulation causes the smooth muscle of the pro-state, prostatic capsule, bladder neck, and proximal urethra to contract, resulting in a decrease in the urethral lumen and obstructive voiding symptoms. This causes difficulty in urination, a decreased force of urinary stream, urinary hesitancy, straining to urination, a decreased force of urinary stream, and postvoid dribbling.

Chemistry

Alfuzosin, a 4-amino-2-piperazinyl quinazoline, is chemically related to prazosin. Its molecular formula is C19 H27 N5 O4 HCl and molecular weight is 425.9. It is highly soluble in water. Because of limited lipophilicity, it cannot easily penetrate the blood–brain barrier, as documented in experimental models using rats. Therefore, alfuzosin has a lower potential to cause dizziness, asthma, or somnolence than some of the other α1-adrenergic antagonists. Alfuzosin is commercially available in Europe under multiple brand names, including Xatral (Synthelabo), Benestan (Alonga), Dalfaz (Synthelabo), Mitoval (Schering), Urion (Zambon), and UroXatral (Synthelabo).

Pharmacology of α1-adrenergic antagonists

Three generations of α1-adrenergic antagonists have been used to treat BPH. First-generation agents (e.g., phenoxybenzamine) antagonize both prostatic and vascular α1-and α2-adrenergic receptors. As a result, first-generation agents cause many dose-related adverse effects, including first-dose syncope, orthostatic hypotension, reflex tachycardia, cardiac arrhythmias, nasal stuffiness, and retrograde ejaculation. In addition, phenoxybenzamine has been implicated as a mutagen. Because of these adverse effects, first-generation agents have been replaced by secondand third-generation agents in clinical practice.

Second-generation agents selectively and competitively antagonize α1-receptors but do not antagonize α2-receptors in typical therapeutic doses. They improve urinary voiding symptoms but cause less tachycardia and cardiac arrhythmias than first-generation agents. Second-generation agents include prazosin, terazosin, and doxazosin. Of these, prazosin has the shortest half-life, producing large differences between peak and trough serum prazosin levels after each dose. These differences have been associated with a higher frequency of orthostatic hypotension, dizziness, and syncope than that which occurs with terazosin and doxazosin. Compliance with prazosin therapy is a concern as it must be administered two or three times a day, whereas terazosin and doxazosin can be administered once or twice a day. However, all second-generation α1-adrenergic antagonists cause dose-related hypotensive adverse effects. To reduce the likelihood of these complications, physicians should (1) administer a subtherapeutic dose and slowly increase it to a full therapeutic maintenance dose over two to four weeks, (2) advise patients to take the first dose at bedtime to avoid first-dose syncope, (3) avoid combined use of any of these agents with other antihypertensive agents to reduce additive hypotensive adverse effects, and (4) use the lowest effective dose to treat BPH, as cardiovascular adverse effects are dose related. Other adverse effects of second-generation α1-adrenergic antagonists include asthenia and somnolence.

Alfuzosin is a second-generation α1-adrenergic antagonist. It competitively and selectively inhibits α1-adrenergic receptors in the prostatic stroma and capsule, bladder neck, and posterior urethra. Like the other agents in this group, alfuzosin was initially evaluated as an antihypertensive agent, although it is not currently approved or prescribed for this indication. It has a short half-life and requires twice- or thrice-daily administration when using the immediate-release (IR) formulation. Two extended-release (ER) formulations allow for once- or twice-daily administration. The ER formulations produce serum alfuzosin concentrations that simulate a continuous i.v. infusion of the drug, with small dif-
ferences between peak and trough serum concentrations over the dosing interval. This may partly explain why fewer cardiovascular adverse effects occur when using ER versus IR alfuzosin versus other second-generation α₁-adrenergic antagonists. Alfuzosin, considered to be functionally uroselective, relieves obstructive voiding symptoms in patients with BPH with less potential for causing significant reductions in systolic or diastolic blood pressure.13

Third-generation α₁-adrenergic antagonists are pharmacologically uroselective in that they are competitive antagonists for prostatic α₁A-receptors.16,17 Blockade of these receptors relaxes the smooth muscle of the prostate and bladder neck without blocking vascular receptors. Tamsulosin is currently the only third-generation uroselective α₁A-receptor α₁A-receptor commercially available in the United States. Pharmacologic studies have found that tamsulosin has a 40-fold greater affinity for α₁A-receptors than for other α₁-receptors.17,18 Tamsulosin has a low affinity for vascular α₁-receptors, which explains why hypotension is an uncommon adverse effect of tamsulosin therapy and why the drug has not been studied for use in hypertension.19 This pharmacologic uroselectivity for prostatic α₁A-receptors has multiple implications. Dosage adjustment is not necessary because first-dose syncope and hypotension do not occur. Patients can begin therapy with the usual daily maintenance dose and can take their tamsulosin dose at any time during the day, as opposed to taking doses at bedtime only. Also, the addition of tamsulosin to selected antihypertensive regimens (e.g., furosemide, enalapril, nifedipine, and atenolol) does not result in additive hypotension.20 Tamsulosin therefore is a good choice for patients who cannot tolerate hypotension (e.g., patients with poorly controlled angina or those at high risk of stroke), patients taking multiple antihypertensives, and instances in which dosage adjustment would be too complicated for the patient or would produce an unacceptable delay in the onset of symptom relief in patients with BPH.

Pharmacologic uroselectivity should be distinguished from functional or clinical uroselectivity. Functional uroselectivity is determined from intact animal models, and clinical uroselectivity is ascertained in normal volunteers or patients with BPH. A drug that exhibits functional or clinical uroselectivity displays a greater smooth muscle contractile effect on urethral or prostatic tissue than on blood vessels. Although not pharmacologically uroselective, alfuzosin has functional uroselectivity and, in some cases, clinical uroselectivity, as it can improve urinary voiding symptoms with a low potential for causing vascular adverse effects. This clinical uroselectivity has been reported with ER alfuzosin, which is administered once or twice daily.

Functional uroselectivity is not solely attributed to selective blockade of α₁A-receptors. Experimental studies have found that alfuzosin blocks a significant percentage of α₁A-, α₁B-, and α₁D-receptors. Alfuzosin’s uroselectivity may be due to its preferential binding to prostatic α₁A-receptors, as opposed to vascular α₁A-receptors, which has been demonstrated in intact anesthetized cat and rat models.21,22 In these studies, the ratio of the oral alfuzosin dose needed to reduce blood pressure by 20% to the dose that reduces urethral pressure by 50% was 11:1, a ratio indicative of the functional uroselectivity of alfuzosin.21

Pharmacokinetics

IR alfuzosin is rapidly and well absorbed after oral administration. The mean time to peak serum concentration of alfuzosin is 1.5 hours after an oral dose.23,24 Improved peak and mean urine flow rates have been documented within 1.5 hours of administration of an oral dose.25 Its oral bioavailability is 64%,26 and its absorption is not affected by food. Therefore, alfuzosin can be taken without regard to meals.

An ER formulation of alfuzosin, Geomatrix, was developed by Jagotec AG. The three-layered tablet includes a hydrophilic matrix core of active drug and two inert layers that control the rate of drug release from the core. This slows the dissolution of the drug in the matrix core and slows absorption of alfuzosin from the dosage form.27 The areas under the curve for the bioavailability of 10-mg ER formulations of alfuzosin were similar to those of IR 2.5-mg thrice daily and 5-mg twice daily alfuzosin tablets.28,29 Although direct comparison studies of 5-mg ER alfuzosin twice daily versus IR alfuzosin have not been conducted, such a study has been completed for 10-mg ER alfuzosin as a single daily dose versus 2.5-mg IR alfuzosin taken thrice daily. The latter formulations were found to be similar in clinical effectiveness.30

Alfuzosin has a serum half-life of five hours after oral administration. Alfuzosin has a linear pharmacokinetic profile over the dosing range of 1 to 5 mg, with no change in half-life despite an increase in the dose.23,26

The volume of distribution of alfuzosin is 2.5 L/kg, and 90% of each dose is protein bound. Because the volume of distribution of alfuzosin is lower in some elderly patients, the initial dose in these patients should be conservative, using the smallest effective daily dose.35

Alfuzosin undergoes extensive hepatic metabolism; however, its metabolism is not saturable. Only 11% of each dose is excreted by the kidneys as unchanged drug; 75–91% of alfuzosin metabolites are eliminated in feces and the rest is excreted in urine. Patients with liver failure should be started on the lowest daily dose and carefully monitored for adverse effects related to accumulation of the active drug. Dosage reduction may be necessary in these patients.
that emptying. It is important to note possibly as a result of improved bladder symptoms also improve, are relieved and in some cases irritating. Obstructive voiding symptoms include urinary frequency, and nocturia. The lower urinary tract symptoms if they have had long-term BPH with chronic bladder outlet obstruction and compensatory hypertrophy of the bladder neck and prostatic capsule, and bladder neck contractile function, the cause of irritative voiding symptoms.

Alpha-1-adrenergic antagonists reduce excess α-adrenergic tone in the prostate gland, bladder neck, and urethra. Thus, smooth muscle relaxation of the bladder neck and urethra. This smooth muscle relaxation decreases the caliber of the urethra, the resistive force, and delay in voiding. Decreased bladder neck and urethra resistance results in less straining to void, incomplete voiding, or urinary stream intermittency. They may also complain of irritative voiding symptoms if they have had long-standing BPH with chronic bladder neck hypotrophy. Irritative voiding symptoms include urinary urgency, clothes wetting, increased daytime wetting, dysuria, increased daytime frequency, and nocturia. The usual improvement in peak urinary flow rate is 15–25%. Patients with more severe symptoms have a greater response to treatment than those with milder symptoms. Onset of action for these agents occurs within four to six weeks, but peak effect is reached in two to four months. Although drug treatment responses have been documented for up to four years, it delays disease progression and does not cure the patient of the disease.

Table 1. Pharmacokinetic Comparison of α₁-Adrenergic Antagonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral Bioavailability</th>
<th>Protein Binding</th>
<th>Excretion in Bile/Feces</th>
<th>Excretion in Urine</th>
<th>Serum Half-life</th>
<th>Time to Peak Serum Conc.</th>
<th>Take with Meals?</th>
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<td>92–97</td>
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<td>1–3</td>
<td>No</td>
</tr>
<tr>
<td>Terazosin</td>
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<td>60</td>
<td>40</td>
<td>9</td>
<td>1–2</td>
<td>Yes</td>
</tr>
<tr>
<td>Doxazosin</td>
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<td>90–94</td>
<td>63</td>
<td>9</td>
<td>11</td>
<td>1.5 (IR), 8 (ER)</td>
<td>No</td>
</tr>
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<td>Alfuzosin</td>
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<td>72–91</td>
<td>11</td>
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<td>&lt;10</td>
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<td>4–5</td>
<td>Yes</td>
</tr>
</tbody>
</table>

1IR = immediate release, ER = extended release. ER formulation soon to be available in the United States.
2Food delays time to achieve peak serum concentrations by two to three hours and decreases total amount of drug absorbed by 30%. Manufacturer recommends that tamsulosin be taken with meals regularly.
improving voiding symptoms and increasing urinary flow rate. However, the frequency of adverse effects differs among these drugs. The discontinuation rates and frequency of adverse cardiovascular effects, including first-dose syncope, orthostatic hypotension, and dizziness, are higher with terazosin, doxazosin, and IR alfuzosin, lower with ER alfuzosin, and least with tamsulosin. In addition, the highest rate of ejaculatory disorders has been reported with tamsulosin. In a direct comparison study with placebo, the frequency of drug-related ejaculation disorders with tamsulosin 0.4 mg daily and placebo was 4.5% and 0.5%, respectively. In a single direct comparison study, alfuzosin 2.5 mg administered thrice daily and tamsulosin 0.4 mg taken once daily caused 0% and 0.8% frequency of ejaculatory disorders, respectively.

Reports from many clinical trials have been published about using alfuzosin for the management of symptomatic BPH. Between 40% and 70% of patients with BPH who were treated with placebo have reported symptom relief. In addition, BPH symptoms have improved or stabilized in patients who have received no treatment, as found in one meta-analysis in which 38% of patients’ voiding symptoms had improved at 2.6 to 5.0 years follow-up despite not receiving any treatment for BPH. An excellent review of the published literature that summarizes the results of randomized controlled clinical trials with α1-adrenergic antagonists has been recently published. Tables 2 and 3 summarize some of these studies. The tables compare improvements in voiding symptoms as assessed using various standardized scoring systems and peak urinary flow rate (milliliters per minute) of alfuzosin versus placebo, which are consistent with those reported in various meta-analyses.

Alfuzosin studies. The effect of alfuzosin on postvoided residual urinary volume has been recently assessed in a meta-analysis of 11 double-blind controlled studies of 953 evaluable patients who received alfuzosin 2.5 mg thrice daily or ER alfuzosin 5 mg twice daily versus placebo for one to six months. At baseline, all patients had a postvoided residual urinary volume between 50 and 350 mL. Alfuzosin-treated patients had a significant decrease in postvoided residual urinary volume, greater than that seen with placebo (p < 0.01). The rate of acute urinary retention was less with alfuzosin than placebo (0.3% and 1.4%, respectively). Reduction in postvoided residual urinary volume is a direct extension of alfuzosin’s effect on the bladder neck and prostate to enhance bladder emptying. Additional clinical studies are needed to determine if alfuzosin can lower a patient’s risk for developing complications of BPH, including calculi, urinary tract infection, and renal failure.

Short-course two-day treatment with alfuzosin has been used as an interim measure following urethral catheterization for acute urinary retention to allow a successful trial without catheterization (TWOC). In these patients, a successful TWOC before surgical intervention could allow time for a full diagnostic workup and reduce the need for catheter reininsertion because of a repeated episode of acute urinary retention. In a study of 81 patients, 55% of patients treated with alfuzosin 5 mg twice daily, starting 24 hours before the TWOC and continuing for 24 hours after catheter removal, had a successful TWOC; 68% of patients with a successful TWOC did not have a second episode of acute urinary retention within the mean follow-up period of 7.2 months. However, 4 of 40 alfuzosin-treated patients had adverse effects, which was more than in the placebo group. These adverse effects included first-dose syncope, headache, dizziness, and arrhythmias.

Long-term therapy with alfuzosin. Alfuzosin produces durable treatment responses in patients with BPH. To date, the longest follow-up period has been three years. In that study, Lukacs et al. followed 2579 patients who were treated with 2.5 mg of alfuzosin three times a day. The percentage of patients requiring surgical intervention decreased or remained stable during the follow-up period, consistent with the belief that drug therapy may delay the development of BPH complications. Jardin et al. followed patients for 24–30 months and found that voiding symptoms and urinary flow rate improvements after long-term use were similar to those of shorter-term studies. Thus, the beneficial effects of alfuzosin are maintained with continued treatment.

ER versus IR alfuzosin. ER alfuzosin is administered once or twice daily, enhances patient compliance, and is associated with fewer adverse cardiovascular effects than IR alfuzosin. Buzelin et al. found that ER alfuzosin 5 mg twice daily was similar to placebo in the rates of drug-induced adverse cardiovascular effects. However, in elderly and hypertensive patients, ER alfuzosin was associated with a higher cumulative frequency of asymptomatic orthostatic hypotension than placebo-treated patients. In another report, Buzelin et al. compared ER alfuzosin 5 mg twice daily with placebo. The number of patient dropouts due to adverse effects was similar between both groups. ER alfuzosin did not cause first-dose syncope in any patient, probably because the ER formulation produced little fluctuation in serum alfuzosin concentrations over the dosing interval and relatively stable serum concentrations were maintained between doses.

Van Kerrebroeck compared the efficacy and safety of 10 mg of ER alfuzosin given once daily without any dosage adjustment with 2.5 mg of IR alfuzosin thrice daily and placebo for three months, followed by an open-label extension period of up to
Table 2.
Comparison of Alfuzosin versus Placebo for Improving Mean Total Symptom Score in Patients with Benign Prostatic Hyperplasia

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Length of Study (mo)</th>
<th>Dosage (mg/day)</th>
<th>Mean Baseline Symptom Score</th>
<th>Change in Symptom Score</th>
<th>% Change in Symptom Score</th>
<th>Mean Baseline Symptom Score</th>
<th>Change in Symptom Score</th>
<th>% Change in Symptom Score</th>
<th>p</th>
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<tr>
<td>30a</td>
<td>447</td>
<td>3</td>
<td>10b</td>
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<td>234</td>
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<td>42, 43d</td>
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<td>10.7</td>
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<td>15.9</td>
<td>−3.4</td>
<td>−18</td>
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*American Urological Association Symptom Index.
*American Urological Association Symptom Index.
*Modified Boyarsky Symptom Scoring System.
*Danish Symptom Scoring System.
*Boyarsky Symptom Scoring System.
*Modified Boyarsky Symptom Scoring System.
*NS = not significant.
*Modified Boyarsky Symptom Scoring System.
*Dosing regimen: ER alfuzosin 5 mg twice a day.
*NA = not available; overall, 42% of alfuzosin-treated patients had improvement of >25% in Boyarsky Symptom Score versus 32% of placebo-treated patients (p = 0.002).

Table 3.
Comparison of Alfuzosin versus Placebo on Mean Peak Urinary Flow Rate (MPUFR) in Patients with Benign Prostatic Hyperplasia

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Length of Study (mo)</th>
<th>Dosage (mg/day)</th>
<th>Baseline MPUFR (mL/min)</th>
<th>Change in MPUFR (mL/min)</th>
<th>% Change in MPUFR</th>
<th>Baseline MPUFR (mL/min)</th>
<th>Change in MPUFR (mL/min)</th>
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<td>10</td>
<td>1.1</td>
<td>14</td>
<td>&lt;0.006</td>
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</table>

*Dosing regimens compared were extended-release (ER) alfuzosin 5 mg twice daily, immediate-release alfuzosin 2.5 mg three times daily, and placebo.
*NS = not significant.
*Dosing regimen: ER alfuzosin 10 mg once daily.
one year. The three-month treatment portion of the study found that both formulations were equally effective in increasing peak urinary flow rate and improving patients’ voiding symptom score and that both formulations were more effective than placebo. However, IR alfuzosin caused more vasodilatory adverse effects than the ER formulation (9.4% versus 3.4%), respectively. A greater percentage of patients treated with the IR drug discontinued treatment compared with those treated with the ER formulation (3.4% versus 1.4%, respectively).

Direct comparisons of alfuzosin with other α1-adrenergic antagonists

When compared with prazosin, IR alfuzosin had comparable efficacy and caused less cardiovascular adverse effects. Buzelin et al.55 compared the effects of alfuzosin with prazosin in 103 patients. IR alfuzosin 2.5 mg was administered three times a day. Prazosin was initiated in a step-up regimen of 1 mg daily on the first two days, 1 mg twice daily for the next five days, and then 2 mg twice daily beginning in the second week. Alfuzosin and prazosin produced similar increases in peak and mean urinary flow rates (26% and 28% and 30% and 27%, respectively) and in symptom score improvement (32% and 34%, respectively). However, alfuzosin caused less hypotension-related adverse effects than prazosin. Of the prazosin-treated patients, four experienced malaise, asthenia, and syncope. Only one patient receiving alfuzosin complained of dizziness; nausea and diplopia were reported in one and two patients, respectively.

When compared with tamsulosin, IR alfuzosin demonstrated comparable efficacy and caused a greater lowering of systolic and diastolic blood pressures. Buzelin et al.56 compared oral tamsulosin 0.4 mg once daily with oral alfuzosin 2.5 mg thrice daily for 12 weeks in 256 evaluable patients with BPH. Tamsulosin and alfuzosin were equally effective in increasing peak urinary flow rates (11.6 and 11.5 mL/sec, respectively) and improving Boyarsky scores (6.2 and 6.0, respectively). Tamsulosin caused fewer cardiovascular adverse effects. No significant change in blood pressure occurred in tamsulosin-treated patients, but a significant reduction in both standing and supine blood pressure (by 4–5 mm when compared to baseline) occurred in alfuzosin-treated patients (p < 0.05). The frequency of other adverse effects attributed to alfuzosin and tamsulosin (e.g., dizziness, headache, palpitation, tachycardia, postural hypotension, and syncope) was similar (10.5% and 9.2%, respectively). Both drugs also caused patients to have low but similar rates of erectile dysfunction.

Hofner et al.58 studied tamsulosin 0.4 mg daily, IR alfuzosin 2.5 mg thrice daily, and placebo in a subgroup of 830 patients with BPH. They found that abnormal ejaculation occurred more often in tamsulosin-treated patients than those receiving placebo (p = 0.045). However, the frequency of this adverse effect was similar and low in tamsulosin- and alfuzosin-treated patients (less than 1% and 0, respectively). Because only three patients in the study discontinued the study drug because of this, the investigators regarded this adverse effect as minor.

Effect of alfuzosin on quality of life

BPH is a disease of symptoms. Patients with moderate to severe BPH symptoms often change their daily activities to accommodate their voiding patterns. In one study, more than 15% of men who were at least 60 years of age reported that they needed to limit fluid intake before bedtime or long car rides.37 Also, such patients often needed to interrupt their daily activities because of frequent bathroom breaks. Although many patients can adjust to changes in their daily activities, others cannot, and their quality of life (QOL) decreases. Therefore, it is important to administer QOL assessments to patients with BPH. The World Health Organization59 and Agency for Health Care Policy and Research60 recommend using QOL assessments to nically measure a patient’s perception of impaired function in performing daily activities when assessing disease severity and treatment efficacy.

QOL assessments are questionnaires that patients can self-administer. Many different QOL questionnaires are used, and there is no agreement as to the best tool to use. QOL assessment tools for men with BPH vary with indices measured and scoring systems, making it somewhat confusing to analyze the literature in this area. Some include questions about a patient’s perception of his sexual performance. Sexuality is closely linked to QOL for men, yet this variable is difficult to measure. Independent of drug therapy, BPH may negatively affect a patient’s perception of sexual function, which in turn affects his overall evaluation of drug therapy.

Studies assessing QOL are not randomized, controlled clinical trials. Instead, prospective, nonexperimental, open-label, longitudinal, uncontrolled study designs are used to ensure a large enough patient sample to be representative of the typical patients receiving treatment for BPH. Often, the efficacy of the drug in these studies needs to be compared to historical controls. Because the patient dropout rate tends to be high—a 10% rate is common—it is somewhat difficult to evaluate results from these studies.

Nevertheless, such studies generally show that an improvement in QOL can be measured one to three months after alfuzosin treatment has begun. Thereafter, QOL assessments for BPH patients show continuous improvement over 12 months. Inter-
Combination therapy with finasteride

Alpha-1 adrenergic antagonists produce greater improvement in voiding symptoms and urinary flow rates than finasteride alone. No additive or synergistic effects have been proven when terazosin was used with finasteride.68

Similar to terazosin, alfuzosin is more effective than finasteride, and an alfuzosin–finasteride combination does not appear to be more effective than alfuzosin alone. Debruyne et al.69 conducted a multicenter, randomized study of 1051 patients with BPH. Patients received ER alfuzosin 5 mg twice daily, finasteride 5 mg daily, or both drugs for six months. Alfuzosin alone and alfuzosin–finasteride combination therapy significantly improved symptoms when compared with finasteride alone, as assessed with the International Prostate Symptom Score. Increases in peak urinary flow rates were greater with alfuzosin and alfuzosin–finasteride than with finasteride alone after one month of therapy, but after six months, peak urinary flow rates were similar among the three treatment groups. In patients with peak urinary flow rates less than 10 mL/sec, the mean increases in peak urinary flow rates were significantly higher with alfuzosin alone and with the alfuzosin–finasteride combination. Finasteride alone and in combination with alfuzosin significantly impaired sexual function; the frequency of erectile dysfunction and ejaculatory disorder increased. The number of postural symptoms was comparable and low in all treatment groups. Thus, in this clinical trial, alfuzosin was more effective than finasteride, and no additional benefit was observed when both drugs were combined.

Adverse effects

Alfuzosin was originally developed as an antihypertensive agent.23,24 Therefore, cardiovascular effects, such as hypotension, are intrinsic to this drug’s pharmacologic profile. However, these adverse reactions are dose related and reported more frequently with higher dosages (i.e., 10–20 mg/day).32,33 Since lower doses of alfuzosin are used for the treatment of BPH (i.e., 5–10 mg/day), the reported frequency of hypotension and dizziness is less in patients who receive alfuzosin for this indication.

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Table 4. Summary of Selected QOL Evaluations of Alfuzosin*

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th>Alfuzosin Dosage</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>57</td>
<td>Multicenter, observational (940)</td>
<td>2.5 mg thrice daily for 3 mo</td>
<td>At the end of the study, indices of QOL for mental health, general health, and activity were significantly improved (p &lt; 0.01 for all). The activity index showed the greatest improvement (p &lt; 0.01). The mental health and general health indices showed less improvement.</td>
</tr>
<tr>
<td>64</td>
<td>Multicenter, open Phase IV, observational (2767)</td>
<td>5 mg twice daily for 60 days</td>
<td>60% of patients had improvement in voiding symptoms as assessed by the IPSS system, which was associated with a significant improvement in QOL (p &lt; 0.001).</td>
</tr>
<tr>
<td>65</td>
<td>Prospective, open label, nonrandomized (2442)</td>
<td>2.5 mg thrice daily or 5 mg twice daily for 12 mo</td>
<td>BPHRQL profile improved continuously from baseline up to 12 mo with greater improvement over time. At each observation (3, 6, 9, and 12 mo), QOL was better than baseline (p &lt; 0.05). Patient’s perception of BPH-specific interferences with daily activities improved more than the overall sense of well-being or patient’s perceptions of sexual function.</td>
</tr>
<tr>
<td>66</td>
<td>Open outcome, prospective (4621)</td>
<td>2.5 mg thrice daily for 12 mo</td>
<td>Improvement in HRQL status over a 12-mo period, particularly in those with moderate or severe nocturia and daytime frequency at baseline (p &lt; 0.001). Sexuality score improvement was age related with most significant improvement in patients less than 70 years old (p = 0.0001). Greatest improvement was in physical–functional status (p &lt; 0.001). Less improvement seen in mental health and social life (p &lt; 0.0001).</td>
</tr>
<tr>
<td>67</td>
<td>Open label, uncontrolled, observational (990)</td>
<td>2.5 mg thrice daily for 6 mo</td>
<td>Improved mental health, general health, and ability to participate in daily activities documented at day 28. Further improvement documented at day 84. Improvement more marked in patients with severe symptoms at the start of treatment. For mental health and general health, significant improvements observed (p &lt; 0.001 for both). Activity improvement increased the most (p &lt; 0.01).</td>
</tr>
</tbody>
</table>

*QOL = quality of life, HRQL = health-related quality of life, BPHRQL = benign prostatic hyperplasia (BPH)-related quality of life.
Patients treated with IR alfuzosin have less hypotension and dizziness when compared to patients treated with prazosin. The frequency of hypotension and dizziness with alfuzosin is similar to that with terazosin and doxazosin. Also, the improved pharmacokinetic profile of ER alfuzosin should cause less cardiovascular adverse effects than the IR formulation, although ER alfuzosin has been associated with these adverse effects. Van Kerrebroeck et al. showed that ER alfuzosin 10 mg once daily produced vasodilatory adverse effects in 6.3% of treated patients, whereas IR 2.5 mg p.o. thrice daily caused the same adverse effects in 9.4% of patients. When compared with tamsulosin, IR alfuzosin causes more cardiovascular adverse effects.

The cardiovascular effects of alfuzosin are the most common adverse effects of the drug. In a placebo-controlled study, vasodilatory adverse effects were reported by 8.4% of patients receiving alfuzosin 2.5 mg thrice daily, compared with 3.8% of patients receiving placebo. In one multicenter study of 13,389 patients, two thirds of adverse events leading to discontinuation of therapy were due to peripheral vasodilation. These usually occur during the first two weeks of treatment and are readily reversible after discontinuing the drug. The clinical presentation of these adverse effects includes dizziness, orthostatic hypotension, reflex tachycardia, headache, and asthenia. Rare occurrences of first-dose syncope have been reported.

Alfuzosin has also been linked with chest pain and myocardial infarction, although a cause–effect relationship has not been elucidated. Alfuzosin may be similar to other α-blockers in that it may enhance the risk of major cardiovascular events in some hypertensive patients.

Alfuzosin’s cardiovascular effects appear to be dose related. After single doses of 1.25 and 2.5 mg of alfuzosin were administered to patients with BPH, an asymptomatic lowering of blood pressure occurred in two patients who received the 1.25-mg dose and five patients who received the 2.5-mg dose. Patients given the 2.5-mg dose also had a reflex increase in heart rate by 5 beats/min. In a study of healthy volunteers who received 1, 2.5, 5, and 10 mg of alfuzosin, significant decreases in systolic and diastolic blood pressure occurred in patients receiving the 5-mg dose.

It has been suggested that patients over age 75, patients who are taking medications for cardiovascular diseases, and patients with preexisting hypertension are more sensitive to the blood-pressure-lowering effects of α-adrenergic antagonists. In a large postmarketing surveillance study of patients taking alfuzosin 2.5 mg thrice daily, an overall 3.2% withdrawal rate due to cardiovascular problems was reported. Patients over age 75 with concomitant cardiovascular diseases and those taking cardiovascular medications had a 1.5-fold higher withdrawal rate than patients younger than 60 years. However, this has not been consistently observed across other studies. In an open-label, observational study of 4018 Spanish outpatients, age had no significant effects on drug efficacy or frequency of adverse effects. The patients were not evenly subdivided into various age groups, and only 458 patients (11%) were over 75 years old. Subgroup analysis found that patients age 67 and older had a higher overall frequency of adverse effects and withdrawal rate than did patients less than 67 years of age (30.1% versus 14.1%, respectively).

Alpha-1 adrenergic antagonists have been associated with ejaculation disorders, including retrograde ejaculation, reduced ejaculation volume, and absence of ejaculate, in 4–11% of patients. Ejaculation disorders occur more frequently with tamsulosin than with placebo. In an excellent review of the literature comparing the adverse effects of α-adrenergic antagonists, tamsulosin caused abnormal ejaculation in 3–14% of patients in various studies, compared with 0–1% of placebo-treated patients. Hofner et al. reported similar findings. These adverse effects occur because α1-adrenergic antagonists relax the bladder neck, allowing semen to flow into the bladder during ejaculation. As a result, patients complain of decreased ejaculate volume or dry sex. These effects are reversible when the drug is discontinued. They are not life-threatening problems and rarely cause discontinuation of treatment.

It is unclear whether tamsulosin causes more ejaculatory problems than does alfuzosin. Hofner et al. described three separate studies with 830 patients: two studies compared tamsulosin 0.4 mg daily versus placebo and the other study compared alfuzosin 2.5 mg thrice daily with tamsulosin 0.4 mg daily over 12 weeks. In the first comparison trials, tamsulosin-treated patients reported abnormal ejaculation more frequently than placebo-treated patients ($p < 0.045$). In the second trial, less than 1% of tamsulosin-treated patients and no alfuzosin-treated patients reported ejaculation disorders. Patients receiving tamsulosin had a significantly higher overall sexual function score than those receiving placebo ($p < 0.05$). No difference in drug-related adverse effects occurred when comparing alfuzosin with tamsulosin. For the tamsulosin group, drug-related impotence, decreased libido, and abnormal ejaculation occurred in 2.3%, 0.0%, and 0.8% of patients, respectively. In alfuzosin-treated patients, these adverse effects occurred in 0.8%, 0.0%, and 0.0% of patients. Differences between these drugs’ adverse effects were not significant. No other published reports describe ejaculation disorders attributable to alfuzosin therapy. In fact, Lukacs et al. followed more than 7000 alfuzosin-treated patients over three years, none of whom reported ejaculation disorders related to alfuzosin.
Alpha-1 adrenergic antagonists cause less erectile dysfunction (impotence) than do other antihypertensives, perhaps because the vasodilatory effects of \( \alpha_1 \)-adrenergic antagonists can enhance the filling of the corpora cavernosa and promote penile erection.77

One case of alfuzosin-associated dermatomyositis has been reported. The patient developed severe muscle weakness and tenderness, swelling of the upper arms, an erythematous rash and edema over the malar area and nose bridge, erythematous plaques over the finger joints, and purpura in the periungal area.78 In addition, the patient had elevated levels of hepatic transaminases, lactate dehydrogenase, creatine kinase, and aldolase. This reaction occurred one year after the start of treatment with alfuzosin. The dosage was not reported. After discontinuing alfuzosin and starting prednisone 1 mg/kg/day, the patient's symptoms disappeared over the ensuing month. However, no cause-effect relationship was established. A subsequent letter to the editor questioned whether alfuzosin caused this, as opposed to an undiagnosed neoplastic condition in the patient.79

Zabala et al.80 described one patient with severe, acute, mixed cholestatic and heptocellular-type hepatitis that was probably induced by alfuzosin. The patient was a 63-year-old male who had been taking alfuzosin 5 mg twice daily for nine months before being admitted to the hospital for jaundice. He was also taking amiloride for hypertension. Laboratory tests revealed significantly elevated levels of hepatic transaminases, total bilirubin, and alkaline phosphatase and a prolonged prothrombin time, (four times the control value). His platelet count was 93 \( \times \) 10\(^6\). Alfuzosin therapy was stopped and laboratory test values returned to near normal over the next six weeks, resulting in rapid correction of the problem.

Other uncommon adverse effects of alfuzosin therapy include nausea, vomiting, diarrhea, skin rash, dry mouth, and asthenia.23 Alfuzosin may have a low potential to cause central nervous system adverse effects because it poorly penetrates the blood-brain barrier in animal models.10,72

Apoptosis (programmed cell death) in prostate cancer cells has been observed in vitro with \( \alpha \)-adrenergic antagonists. This could be potentially beneficial in decreasing prostate volume. However, the clinical importance of this finding is unknown.31

Alfuzosin is contraindicated in patients with a hypersensitivity to alfuzosin or other quinazolones. Alfuzosin should be used cautiously in patients who are predisposed to hypotension, including patients with severe coronary artery disease, those taking multiple antihypertensive agents, those with severe volume depletion, patients with severe cardiac arrhythmias, or those with severe orthostatic hypotension. It should be used cautiously in patients undergoing general anesthesia, as hypotension has been reported with the combination. Caution is also warranted when alfuzosin is used in patients with severe hepatic failure, as alfuzosin may accumulate.

Drug interactions

Similar to other \( \alpha_1 \)-adrenergic antagonists, alfuzosin is metabolized by the hepatic microsomal enzyme system. Therefore, enzyme inhibitors and stimulators affect its metabolism. Both cimetidine and diltiazem slow hepatic metabolism of alfuzosin and increase serum levels of diltiazem.79 Alfuzosin has been shown to reduce the bioavailability of oral diltiazem and cause hypotension when the combination is used. The clinical importance of these interactions has not been elucidated.

Alfuzosin does not appear to interact with warfarin, digoxin, hydrochlorothiazide, or atenolol.23,81 Caution is recommended when alfuzosin is given to patients taking other antihypertensives (e.g., angiotensin-converting-enzyme inhibitors, \( \beta \)-adrenergic antagonists, calcium-channel blockers) and ethanol. This is because alfuzosin shares many of the pharmacologic effects of older \( \alpha_1 \)-adrenergic antagonists. Additive hypotensive effects have been previously reported with prazosin in combination with these drugs. Therefore, if using alfuzosin in patients taking antihypertensives, the lowest effective dose of alfuzosin should be used.82,83

Current packaging labeling for sildenafil includes a caution to avoid taking it within four hours of an \( \alpha \)-adrenergic antagonist to avoid a systemic hypotensive reaction as a result of the combination. Whether FDA will require such labeling for ER alfuzosin is unknown at this time.

Dosage and administration

The dosage of IR alfuzosin hydrochloride ranges from 2.5 mg p.o. thrice daily to a maximum of 10–12 mg/day. Frequent daily administration is required because of alfuzosin’s short serum half-life.

There are two ER formulations of alfuzosin hydrochloride. One formulation can be prescribed as a 10-mg tablet once daily and the other as a 5-mg tablet twice daily. Neither formulation requires dosage titration. Both ER formulations produce less cardiovascular adverse effects than the IR formulation and other second-generation \( \alpha \)-adrenergic antagonists. The adverse effect profile of these ER formulations is similar to placebo.84

FDA is currently reviewing the once-a-day ER preparation for release onto the commercial market.

Common dosing regimens for various \( \alpha_1 \)-adrenergic antagonists are summarized in Table 5.

Place in therapy

Drug therapy for BPH can be categorized into two groups: agents that interfere with testosterone’s stimulatory effect on prostate enlargement and agents that relax prostatic
BPH85,86a

physicians prescribe an 

verse effects, potential for drug in-

convenience of the dosing regimen, ad-

therapy, onset of action, conveni-

or patient-perceived effectiveness of 

moderate to severe BPH, the choice of 

teride, a 5-

adrenergic antagonists relax prosta-

smooth muscle, but do not reduce prosta-

teride.33,59 These benefits outweigh the more frequent cardiovascular adverse effects of α₁-adrenergic antagonists when compared with finasteride. Alpha-1 adrenergic antagonists are also the first-line treatment for moderate to severe BPH in patients whose prostate is less than 40 g in size. Finasteride has been found to be useful in patients with significantly enlarged prostates (more than 40 g in size).87

Drug therapy for BPH should begin with a single agent, most likely an α₁-adrenergic antagonist. Adding finasteride to a failing α₁-adrenergic antagonist regimen offers no benefit, except possibly in patients with prostates at least 40–50 g in size.86 If patients do not respond to treatment with an α₁-adrenergic antagonist, surgery is recommended.

Patients should be informed that symptom improvement will continue only as long as the drug is continued.33 This applies to both finasteride and α₁-adrenergic antagonists. When used to treat severe BPH, α₁-adrenergic antagonists should be viewed as interim treatment only (i.e., they may control symptoms and delay the eventual need for surgical intervention). It is unclear if such drug therapy halts BPH progression. Thus, despite continuation of treat-

ment, BPH may progress and the patient may require another form of treatment (e.g., surgery).

All α₁-adrenergic antagonists are equally effective in treating the voiding symptoms of BPH and in improving a patient’s quality of life.5 However, they do differ in their poten-
tial to cause adverse effects. Approximately 10–12% of patients discontinue second-generation α₁-
adrenergic antagonists because of cardiovascular adverse effects; there-
fore, agents less likely to produce ad-
verse effects would be advantageous in selected patients.88,89 Of the α₁-
adrenergic antagonists available on the U.S. market, tamsulosin is the least likely to cause hypotension and other cardiovascular adverse effects and is the preferred agent for patients with poorly controlled angina, pa-
tients with serious cardiac arrhyth-

mias, patients with reduced circulat-
ing volume, and patients taking multiple antihypertensives.35,90 It is un-
known whether the once-a-day al-
fuzosin formulation has a cardiovas-
cular adverse effect profile similar to that of tamsulosin.

It is estimated that 30–50% of pa-
tients with BPH have essential hy-

tension.91,92 Souverein et al.93 con-
ducted an epidemiologic study of 6249 patients with BPH who had recently started taking α₁-adrenergic antagonists. According to the results, cardiovascular diseases (e.g., heart diseases, acute myocardial infarction, angina pectoris, arrhythmias, congestive heart failure, and cerebrovascular accidents) were twice as common among these patients than age-
matched population controls. Patients with hypertension who are beginning treatment with α₁-adrenergic antagonists may be more likely to experi-
ence cardiovascular adverse effects, since they may be taking antihyper-
tensive medications. For such pa-
tients, it was once thought that second-generation α₁-adrenergic an-
tagonists might be good choices as they are effective antihypertensives

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Oral Dosing Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prazosin</td>
<td>1 mg at bedtime to start. Increase dose to 2, 5, or 10 mg/day at 3–10-day intervals. Usual maintenance dose 2–10 mg daily in two or three divided doses.</td>
</tr>
<tr>
<td>Terazosin</td>
<td>1 mg at bedtime to start. Increase dose to 2, 5, or 10 mg/day at 3–10-day intervals. Usual maintenance dose 5–10 mg once daily. Up to 20 mg daily has been used.</td>
</tr>
<tr>
<td>Doxazosin</td>
<td>1 mg at bedtime to start. Increase to 2, 4, or 8 mg daily at 3–10-day intervals. Usual maintenance dose 2–8 mg once daily. Up to 12 mg daily has been used.</td>
</tr>
<tr>
<td>Alfuzosin</td>
<td>IR: 2.5 mg three times a day, up to 10 mg a day in three divided doses. In patients older than 65 years of age or those with hypertension, start with 2.5 mg twice daily. Increase dose to a maximum of 10 mg/day based on patient’s response to treatment.32</td>
</tr>
<tr>
<td>Tamsulosin</td>
<td>ER: 0.4–0.8 mg daily. Start with 0.4 mg once daily.</td>
</tr>
</tbody>
</table>

*BPH = benign prostatic hyperplasia, IR = immediate release, ER = extended release.
and may ameliorate the symptoms of BPH. However, clinical opinion does not support the use of one α₁-adrenergic antagonist to treat both BPH and hypertension if the patient is already responding well to an existing antihypertensive regimen for a variety of reasons: (1) additive hypertensive adverse effects of combination therapy are unpredictable, (2) the U.S. Joint National Committee on the Detection and Evaluation of High Blood Pressure does not support the use of α₁-adrenergic antagonists as first-line treatment for essential hypertension,94 (3) urologists treating BPH are uncomfortable modifying the antihypertensive drug therapy of patients, which was likely initiated by another physician, and (4) discontinuation of some antihypertensives (when starting an α₁-adrenergic antagonist) can result in rebound hypertension. In patients with moderate to severe BPH and essential hypertension who are being treated with one or more antihypertensive agents, it is more convenient for physicians to choose a treatment for BPH which will not interfere with the other medications taken by the patient. Presently, tamsulosin is the most commonly used α₁-adrenergic antagonist in these patients.

Conclusion
IR alfuzosin is similar to all other second-generation α₁-adrenergic antagonists in mechanism, clinical efficacy, and adverse effects. No dosage titration is needed for ER alfuzosin, and its onset of peak action is within days of the start of treatment.

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Alfuzosin hydrochloride

Clinical Reviews


CLINICAL REVIEWS

Alfuzosin hydrochloride


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