VA Pharmacy Benefits Management Strategic Healthcare Group
Medical Advisory Panel
Drug Class Review
Alpha$_1$ Adrenergic Blockers

This review was adapted from the VISN #12 P & T Review, written and edited by Elaine Furmaga, Pharm.D.

OBJECTIVE

1. To review the efficacy, safety, and administration of the currently available α_1 adrenergic blockers in the treatment of hypertension (HTN) and symptomatic benign prostatic hyperplasia (BPH).

Generic Name:	**Doxazosin**	**Prazosin**	**Terazosin**
Brand Name:	Cardura®	Minipress®	Hytrin®
Manufacturer:	Pfizer	Pfizer various generic	Abbott

2. To define selection criteria when contracting these agents for the Veterans Health Administration.

I. PHARMACOLOGY[1-4]

A. Hypertension

The α_1 adrenergic antagonists selectively block postsynaptic α_1-adrenergic receptors thereby decreasing peripheral vascular resistance and lowering arterial blood pressure.

B. Benign Prostatic Hyperplasia

Alpha$_1$ receptor blockade in hyperplastic prostatic tissue, prostatic capsule, and bladder neck decreases smooth muscle tone, thereby decreasing resistance to urinary flow. Two processes may be responsible for the symptoms associated with BPH. A mechanical obstruction of hyperplastic prostate tissue as well as a dynamic obstruction resulting from stimulation of alpha receptors in prostatic tissue (thereby increasing prostatic muscular tension) have been described.

II. INDICATIONS

The three alpha adrenergic blockers are approved by the Food and Drug Administration for the treatment of HTN.

A. Doxazosin

Doxazosin has an additional approved indication. It is indicated for the treatment of both the urinary outflow obstruction and obstructive and irritative symptoms associated with BPH.

B. Terazosin

Terazosin has an additional approved indication. It is indicated for the treatment of symptomatic BPH.

III. PHARMACOKINETICS[1,2]

Both doxazosin and prazosin are extensively metabolized in the liver, with prazosin converted to active metabolites. Several active metabolites of doxazosin have been identified with unknown pharmacokinetic properties. Doxazosin should be used with caution in patients with hepatic failure. Terazosin undergoes minimal hepatic first-pass metabolism, with almost all circulating drug in the parent form. Other pharmacokinetic properties are described in Table 1.

Table 1. Pharmacokinetics of alpha$_1$-antagonists[a]

DRUG	BIOAVAILABILTY (% oral dose)	HALF-LIFE (hours)	PROTEIN BINDING (%)	PEAK PLASMA LEVEL (hours)
Doxazosin	65	22	98	2-3
Prazosin	48-68	2-3	92-97	1-3
Terazosin	90	9-12	90-94	1-2

[a] Adapted from: Hebel SL ed. Drug Facts and Comparisons, St. Louis:Facts and Comparisons Inc., 1996163j-163q.

IV. SAFETY AND ADMINISTRATION

A. Adverse Effects [1,5-9]

The alpha adrenergic blockers are generally well-tolerated. Clinical trials evaluating the comparative efficacy and safety of the alpha adrenergic blockers were similar for all agents with a similar incidence of withdrawal. The percent of adverse effects for the three agents are listed in Table 2.

Table 2. Adverse effects associated with the alpha$_1$-antagonists

ADVERSE EVENT	DOXAZOSIN (%)	PRAZOSIN (%)	TERAZOSIN (%)
Postural hypotension	0.3-1	*	1.3
Palpitations	2	5.3	4.3
Nausea	3	4.9	4.4
Dyspnea	1	*	3.1
Nasal congestion	no report	*	5.9
Blurred vision	no report	*	1.6
Dizziness	19	10-20	19.3
Nervousness	2	*	2.3
Paresthesia	1	*	2.9
Somnolence	5	no report	5.4
Asthenia	1-12	7	11.3
Drowsiness	*	7.6	*
Sexual dysfunction	2	no report	< 1
Incontinence	1	*	no report
Pruritus/rash/sweating	1	*	1
Headache	14	7.8	16.2
Edema	4	*	< 1
Peripheral edema	no report	no report	5.5

*Reaction associated with the drug, unknown incidence

Due to the lack of well-controlled studies in pregnant women, these agents should be avoided during pregnancy (Category C) unless the use clearly outweighs the risk of potential harm to the fetus.[1]

Patients receiving doxazosin, prazosin, or terazosin should be monitored for postural hypotension and syncope, especially with the first few doses (referred to as "first-dose" effect). In order to minimize these symptoms, the initial dose should not exceed 1 mg and the patient should be instructed to administer the first dose at bedtime (prazosin, terazosin). Doses should be increased slowly until the desired therapeutic effect is achieved.[1]

Drug-drug interactions have been reported with the α_1 adrenergic blockers.[1,9-10] β-blockers may enhance hypotension associated with the first-dose of prazosin, although these findings are controversial. Concomitant administration of verapamil or nifedipine with prazosin may cause a greater hypotensive effect than with either drug alone. Caution should be used with concomitant use of terazosin and verapamil due to the possibility of significant hypotension. Indomethacin may decrease the antihypertensive action of prazosin, possibly via inhibition of prostaglandin synthesis.

B. Dosing[1]

Refer to Table 3.

Table 3. Recommended doses for the alpha$_1$-antagonists

DRUG	RECOMMENDED DOSE (mg/d)	DOSING FREQUENCY (times/d)	AVAILABILITY
Doxazosin	1-16 (HTN) 1-8 (BPH)	1	1 mg, 2 mg, 4 mg, 8 mg tablets
Prazosin	1-20 (HTN)	2-3	1 mg, 2 mg, 5 mg capsules
Terazosin	1-20 (HTN & BPH)	1-2	1 mg, 2 mg, 5 mg, 10 mg capsules[a]

[a] Tablets no longer available from manufacturer

V. CLINICAL TRIALS

The α_1 antagonists are all approved for the treatment of HTN. They have been recognized by the Fifth Report of the Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure (JNC V) as effective in reducing blood pressure. This class of antihypertensive is recommended as alternative or adjunctive therapy if the preferred initial therapy as recommended by the JNC V (diuretics or β-blockers) is contraindicated. The α_1 antagonists are the agents of choice in patients with more than one indication (HTN, BPH). They are effective as monotherapy or in combination with other antihypertensive agents. Efficacy is comparable for the three agents or when compared to other classes of antihypertensive medications.[5]

A. Hypertension

Only comparison trials were evaluated for this review.

1. Doxazosin versus prazosin

Torvik et al.[6] In a trial involving 172 patients, both agents significantly reduced mean blood pressure when compared to placebo (doxazosin 14.2/10.0 mmHg with $p < 0.05$, prazosin 12.0/10.4 mmHg with $p < 0.005$). Mean daily doses were 11.3 mg and 13.8 mg for doxazosin and prazosin, respectively. Adverse effects were similar in both groups.

Fukiyama et al.[7] A comparative trial of 266 patients receiving doxazosin 0.5 mg - 4 mg once daily doxazosin or prazosin 1.5 mg - 6 mg divided three times daily. Efficacy was comparable with 39.8% doxazosin patients and 42.7% of prazosin patients with normalized (< 150/90 mmHg) blood pressure. Efficacy was noted at a dose of 1.98 mg with doxazosin as compared to 3.82 mg with prazosin. Adverse effects were similar and occurred in 15.1% patients on doxazosin and 15.9% patients receiving prazosin. The incidence necessitating therapy withdrawal due to side effects were similar (5.6%) in each group.

2. Doxazosin versus terazosin

Hayduk et al.[8] The antihypertensive efficacy of doxazosin and terazosin given once daily was compared in 55 patients with mild to moderate hypertension. Mean dose of doxazosin 2.4 mg once-daily and terazosin 5.6 mg once-daily provided standing blood pressure reduction of 16.8/16.3 mmHg and 12.2/15.4 mmHg, respectively. Sixty-five percent doxazosin patients and 57% terazosin patients achieved normalized blood pressure (diastolic $\leq$ 90 mmHg). Most side effects were mild to moderate and were either transient or tolerated with continued treatment (30% doxazosin, 39% terazosin).

3. Prazosin versus terazosin

Deger G.[11] Twice-daily prazosin was compared to once-daily terazosin in 174 patients with mild to moderate HTN. Standing systolic blood pressure (SBP) decreased 9.4 mmHg and 8.4 mmHg while diastolic blood pressure (DBP) decreased 8.3 mmHg and 6.1 mmHg from baseline with terazosin and prazosin treatment patients, respectively. Doses ranged from 2 mg to 20 mg for each prescription with the majority of patients receiving 20 mg in each group.

B. Benign Prostatic Hyperplasia

Doxazosin and terazosin are indicated for the symptomatic treatment of BPH. This form of treatment is prescribed in patients who have symptoms that do not require surgery, or in patients who are poor surgical candidates. All three α_1 antagonists discussed in this review have been studied for their effects on bladder outlet obstruction.

Alterations in SBP and DBP appear to be selective in normotensive compared to hypertensive patients receiving α_1 adrenergic antagonists for the treatment of symptomatic BPH. SBP was reduced by 4 mmHg and 18 mmHg in normotensive and hypertensive patients, respectively treated with terazosin.[3] A blood pressure reduction of 5/4 mmHg and 19/10 mmHg was seen in normotensive and hypertensive patients, respectively treated with doxazosin.[12]

1. Doxazosin

Chapple et al.[13] Data of 122 patients with symptomatic BPH compared doxazosin 2 mg to 4 mg daily to placebo over 12 weeks. Treatment with doxazosin significantly increased mean urinary flow rates as compared to placebo ($p=0.04$). Significant improvement in hesitancy ($p=0.003$), impaired urinary stream ($p=0.019$), nocturia ($p=0.017$), and urgency ($p=0.041$) were seen compared to placebo as evaluated by questionnaire at the end of the study. The most frequent adverse effects were dizziness and headache which were reported in 8 and 6 events, respectively of 44 events reported in 25 patients. Drug discontinuation was thought to be related to doxazosin in one patient.

Holme et al.[14] Efficacy of doxazosin 4 mg daily in the treatment of symptomatic BPH was assessed at 9 and 29 weeks in 100 and 75 patients enrolled versus placebo, respectively. At 29 weeks the doxazosin group (n=41) demonstrated a significant improvement over placebo (n=34) in obstructive and irritative symptoms (both $p < 0.01$). Daytime frequency was significantly reduced compared to placebo ($p < 0.01$). A slight but significant improvement in maximum urinary flow rate was seen in patients treated with doxazosin ($p < 0.05$). Patient adverse events and tolerability were similar between the two groups.

2. Terazosin

Lepor et al.[15] Results of a multi center randomized double-blind placebo-controlled trial were reported in 237 patients receiving terazosin 2 mg, 5 mg, or 10 mg or placebo for 12 weeks. Peak and mean urinary flow rates and symptom scores were measured. Patients receiving terazosin 5 mg or 10 mg showed a significantly greater decrease in irritative and total symptom scores as compared to placebo. A statistically significant decrease in obstructive symptom score was also seen in the 10 mg treatment group. Patients receiving terazosin 10 mg exhibited a significantly greater increase in peak and mean urinary flow rates ($p=0.009$ and $p=0.005$, respectively). The improvements in these parameters appeared to be dose-related. Asthenia and dizziness were observed more frequently than placebo but were not statistically significant. Postural hypotension was increased compared to placebo at a statistical significance of $p < 0.05$ in the 5 mg treatment group.

Fabricius et al.[16] A 12 week randomized double-blind trial was conducted comparing terazosin 10 mg to placebo in 30 patients who initially responded to a 24 week single-blind treatment period following a 4 week placebo lead-in. Significant improvements in peak urine flow rates were seen in the treatment group compared to placebo ($p < 0.05$). Significant improvements in obstructive and irritative symptom scores were maintained during the double-blind phase. Twelve patients were evaluated for 2 years on terazosin 5 mg. Nine patients showed continued improvement in symptomatic BPH. Two of the 12 patients who were non-compliant with treatment underwent transurethral resection of the prostate and another dropped from the study. The most common side effects noted in the single-blind portion of the study were headache (10%), asthenia (5%), hypotension (3%), and dysuria (3%). Dose reduction or discontinuation due to side effects were not necessary.

3. Prazosin

Although not FDA approved for the treatment of symptomatic BPH, prazosin has been studied for the management of symptoms associated with this condition with favorable results.

Hedlund et al.[17] A double-blind crossover study of 20 men with benign prostatic obstruction showed a significant improvement in obstructive symptoms ($p < 0.05$) on prazosin 4 mg daily. Maximum and average flow rates also significantly improved ($p < 0.01$). Dizziness was noted in 1 patient treated with prazosin.

Kirby et al.[18] Results of 55 patients with prostatic obstruction who participated in a double-blind placebo-controlled parallel study of prazosin showed a significant increase in mean maximum flow rates ($p < 0.005$). Patients on prazosin experienced a statistically significant decrease in urinary frequency compared to placebo ($p < 0.01$) as measured by patient voiding diary. Side effects were similar with prazosin 2 mg twice daily versus placebo.

4. Doxazosin versus terazosin

Kaplan SA et al.[19] Doxazosin and terazosin were evaluated in 43 men with symptomatic prostatism. Patients were randomized to either terazosin 5 mg every morning (QAM), terazosin 5 mg every evening (QPM), doxazosin 4 mg QAM, or doxazosin 4 mg QPM in this open-label, parallel, pilot study. Mean peak uroflow rate significantly increased by 3.0, 3.1, 2.8, and 3.1 ml/second in the terazosin 5 mg QAM, terazosin 5 mg QPM, doxazosin 4 mg QAM, and doxazosin 4 mg QPM groups, respectively when compared to baseline ($p < 0.05$). Mean decrease in Boyarsky symptom scores were similar and were significant when compared to baseline for all treatment groups ($p < 0.05$). Eight patients were removed from the study due to adverse effects. Eighty-seven percent of these adverse events occurred in patients who received the medication in the morning and 13% in those who took the medication in the evening. The difference in occurrence of adverse events in the morning versus the evening groups was statistically significant ($p< 0.05$).

C. Additional Properties[1,5,20-22]

Many hypertensive patients have concomitant hyperlipidemia which can increase coronary heart disease (CHD) risk. Some antihypertensive agents have been associated with adverse effects on the lipid profile. On the other hand, favorable trends in mean serum total cholesterol, high-density and low-density lipoprotein cholesterol, and triglyceride levels have been seen in patients receiving the α_1 adrenergic antagonists. Trials have varied in percent change and statistical significance. The clinical significance of these effects on the lipid profile and decreasing the risk of CHD is unknown at this time.

VI. CONCLUSIONS

A. Efficacy/Outcomes

- All available α_1 adrenergic blockers are effective for the management of essential HTN
- Doxazosin and terazosin are approved for the management of symptomatic BPH, and both are efficacious for this indication
- Due to the limited number of comparative trials, equivalent effective doses are difficult to determine

B. Safety/Administration

- Adverse effects may be more prevalent upon initiation of therapy due to the potential for postural hypotension or "first-dose" syncope
- “First-dose” syncope is a dose-related phenomenon which can be reduced by initiating therapy with the lowest possible dose
- Although the pharmacokinetic profiles of the available agents differ, which alters their safety and administration , they are all generally well-tolerated
- A longer elimination half-life allows for once daily dosing which may enhance compliance

D. Pharmacy Factors/VA Population

- Scored tablets may be split to decrease the cost, although the patient's ability to split these tablets would need to be assessed on an individual basis, and cannot be assumed for the entire VA population
- The cost of switching patients to another drug in the class (additional clinic visits) needs to be taken into consideration especially since there is not sufficient literature for recommendations on a dosage conversion
- The manufacturer can only recommend that patients be started at the lowest possible dose and re-titrated to avoid possible first-dose syncope

E. Cost

- Of the three α_1 adrenergic antagonists, prazosin is significantly less expensive due to its availability as a generic product

VII. RECOMMENDATIONS

1. Prazosin should be included on the Veterans Health Administration National Drug Formulary, due to the cost savings associated with its generic availability. The availability of other agents generically must also be taken into consideration.

2. A long-acting agent should also be available, and the decision should be based on the efficacy, outcomes, safety and administration (including pharmacokinetics) of the available agents.

3. The availability of starter packs for re-titration needs to be considered since there is not sufficient literature for recommendations on a dosage conversion.

REFERENCES

1. Olin BR, ed. Drug Facts and Comparisons, 50th ed. St. Louis, MO: A Wolters Kluwer Co. Alpha$_1$-Adrenergic Blockers. 1996:163j-163q.

2. Luther RR. New perspectives on selective alpha$_1$ blockade. Am J Hypertens 1989;2:729-735.

3. Osterling JE. Benign prostatic hyperplasia: Medical and minimally invasive treatment options. NEJM 1995;332:99-109.

4. Caine M. The present role of alpha adrenergic blockers in the treatment of benign prostatic hypertrophy. J Urol 1986;136:1-4.

5. The Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. The Fifth Report of the National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V). Arch Intern Med 1993;153:154-183.

6. Torvik D, Madsbu HP. Multicentre 12-week double-blind comparison of doxazosin, prazosin and placebo in patients with mild to moderate essential hypertension. Br J Clin Pharmacol 1986;21:S69-75.

7. Fukiyama K, Omae T, Iimura O et al. A double-blind comparative study of doxazosin and prazosin in the treatment of essential hypertension. Am Heart J 1991;121:317-322.

8. Hayduk K, Schneider HT. Antihypertensive effects of doxazosin in systemic hypertension and comparison with terazosin. Am J Cardiol 1987;59:G95-98.

9. Stanaszek WF, Kellerman D, Brogden RN et al. Prazosin update: A review of its pharmacological properties and therapeutic use in hypertension and congestive heart failure. Drugs 1983;25:339-384.

10. Abbott Laboratories. Terazosin hydrochloride prescribing information. North Chicago, IL, 1994.

11. Deger G. Comparison of the safety and efficacy of once-daily terazosin versus twice-daily prazosin for the treatment of mild to moderate hypertension. Am J Med 1986;80(suppl 5B):62-67.

12. Kirby RS. Doxazosin in benign prostatic hyperplasia: Effects on blood pressure and urinary flow in normotensive and hypertensive men. Urol 1995;46:182-186.

13. Chapple CR, Carter P, Christmas TJ et al. A three month double-blind study of doxazosin as treatment for benign bladder outlet obstruction. Br J Urol 1994;74:50-56.

14. Holme JB, Christensen MM, Rasmussen PC, et al. 29-week doxazosin treatment in patients with symptomatic benign prostatic hyperplasia. Scand J Urol Nephrol 1994;28:77-82.

15. Lepor H, Auerbach S, Puras-Baez A et al. A randomized, placebo-controlled multi center study of

the efficacy and safety of terazosin in the treatment of benign prostatic hyperplasia. J Urol 1992;148:1467-1474.

16. Fabricius PG, Hannaford JM. Placebo-controlled study of terazosin in the treatment of benign prostatic hyperplasia with 2-year follow-up. Br J Urol 1992;70(Suppl 1):10-16.

17. Hedlund H, Anderson KE, Ek A. Effects of prazosin in patients with benign prostatic obstruction. J Urol 1983;130:275-278.

18. Kirby RS, Coppinger SWC, Corcoran MO et al. Prazosin in the treatment of prostatic obstruction. Br J Urol 1987;60:136-142.

19. Kaplan SA, Soldo KA, Olsson CA. Terazosin and doxazosin in normotensive men with symptomatic prostatism: A pilot study to determine the effect of dosing regimen on efficacy and safety. Eur Urol 1995;28:223-228.

20. Deger G. Effects of terazosin on serum lipids. Am J Med 1986;80(suppl 5B):82-85.

21. Macphee GJA, Curzio J, Farish E, Reid JL, Elliott HL. Placebo-controlled trial of doxazosin in management of patients with hypertension and hypercholesterolemia. J Cardiovasc Pharmacol 1992;20:429-433.

22. Babamoto KS, Hirokawa WT. Doxazosin: A new α_1-adrenergic antagonist. Clin Pharm 1992;11:415-427.