NPTC Drug Class Review: Alpha$_1$-receptor Blockers

Introduction

The purpose of this review is to support the IHS National P&T Committee in making recommendations for the IHS National Core Formulary (NCF) regarding the clinical effectiveness of the available alpha blocker agents. Alpha blockers can be divided into two classes based on affinity for sub-types of alpha receptors, alpha-1 and alpha-2 receptors. Except for some limited utility of the α_2-receptor blocker, yohimbine, in the treatment of male impotence, this class has little clinical utility and will not be reviewed here. The α_1-receptor blockers included are outlined in Table 1.

Table 1: Alpha-$_1$ Blockers

Drug	Usual Dosage (TDD)	Daily dosage frequency
Alfuzosin	10 mg	Once
Doxazosin	1-8 mg (BPH) 1-16 mg (HTN)	Once
Prazosin	2-20 mg	Twice-thrice
Tamsulosin	0.4-0.8 mg	Once
Terazosin	1-20 mg	Once-twice

FDA-Approved Indications and Off-Label Uses

The alpha$_1$-receptor blockers are FDA-approved for the treatment of essential hypertension and/or benign prostatic hypertrophy. Table 2 shows which agent carries which of these indications.

Table 2: Alpha$_1$-Receptor Blocker Approved Indications

Drug	HTN	Benign Prostatic Hypertrophy
Alfuzosin		Yes
Doxazosin	Yes	Yes
Prazosin	Yes	
Tamsulosin		Yes
Terazosin	Yes	Yes

Alpha blockers are clinically used in cases of chronic prostatitis/chronic pelvic pain syndrome. As well, theses agents are used to assist in the passage of urinary tract stones.[9]

Pharmacology, Dosing, and Administration

Alpha$_1$-receptor blockers selectively block the post-synaptic α_1-receptors, thereby reducing peripheral vascular resistance and lowering arterial blood pressure. They also block α_1-receptors in prostatic tissue, the prostate capsule, and the bladder neck leading to smooth muscle relaxation. However, there is growing evidence that the improvements of lower urinary tract symptoms are due to effects other than smooth muscle relaxation.[10] There are three sub-types of α_1-receptors, alpha$_{1A}$, alpha$_{1B}$, and alpha $_{1D}$. Seventy percent of the alpha receptors in the prostate are of the alpha$_{1A}$ subtype. Tamsulosin and alfuzosin show selectivity for this sub-type. These two agents are not indicated for treatment of hypertension. Prazosin has a short half-life of only 2-3 hours. The other agents in this class have half-lives of 9-22 hours.

Efficacy/Effectiveness

Hypertension

Alpha$_1$- receptor blockers are effective in reducing blood pressure and do so in a fashion comparable to most other antihypertensive drug classes.[1] These compounds are most effective in patients in the upright position, reducing systolic and diastolic pressures by 8%–10%. Alpha$_1$-receptor blockers incrementally reduce blood pressure when combined with most drug classes and are the only antihypertensive drug class to improve plasma lipid profiles.

Alpha$_1$-receptor blockers are recommended as third-line agents in the treatment of hypertension. This was based on the results of the alpha blocker arm of ALLHAT (Anti-hypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial) which assessed the hypertensive management of 42,000 patients. The alpha blocker arm was halted two years early because patients taking doxazosin were shown to be 25% more likely to have a major cardiovascular event than those taking chlorthalidone.[2] Alpha$_1$-receptor blockers may be preferential when the patient has more than one indication (both hypertension and BPH).[3,4]

Two comparative trials evaluated the relative efficacy of doxazosin vs. prazosin. 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.[5] In a second trial of 266 patients, participants received doxazosin 0.5 mg - 4mg 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.[6]

Doxazosin vs. terazosin given once daily was compared in trial of 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 < 90 mmHg). Most side effects were mild to moderate and were either transient or tolerated with continued treatment (30% doxazosin, 39% terazosin).[7]

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.[8]

Benign prostatic hypertrophy

Lower urinary tract symptoms associated with benign prostatic hypertrophy (BPH) occur in up to 70% of men over the age of 60 years. Alpha$_1$ receptor blockers have been used for the reduction of lower urinary tract symptoms in men who have symptomatic BPH.

In a Cochrane Review from 2002, tamsulosin provided a small to moderate improvement in urinary symptoms and flow compared to men receiving placebo in men with BPH. Effectiveness was similar to other alpha antagonists and increased only slightly with higher doses. [11]

In a Cochrane Review from 2000, the available evidence suggests that terazosin improves urinary symptoms and flow measures associated with BPH. Effectiveness is superior to placebo or finasteride, similar to other alpha-blockers but less than transurethral microwave therapy. Adverse effects were generally mild but more frequent than other alpha-blockers and associated with between a two-to-four fold increase in treatment discontinuation.[12]

Doxazosin was shown to be superior to placebo in two trials involving 122 and 175 patients, respectively. Doxazosin showed statistically lower rates of hesitancy, impaired urinary stream, nocturia, and urgency with increases in urinary flow rates.[13, 14]

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 ($p< 0.01$).[15] 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.[16]

Doxazosin and terazosin were evaluated in 43 men with symptomatic prostatism. Patients were randomized to either terazosin 5 mg every morning, terazosin 5 mg every evening, doxazosin 4 mg every morning, or doxazosin 4 mg every evening 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 ($p< 0.05$).[17]

Safety / Tolerability

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. Dose escalation of an α_1-receptor blocker can trigger renal Na^+ retention, and the ensuing volume expansion can attenuate its blood pressure-lowering effect. Orthostatic hypotension can occur with these compounds, particularly when a patient is volume-contracted. Common side effects include dizziness, headache, and fatigue. 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.[18] Alfuzosin and tamsulosin do not require titration.

Table 3: Alpha$_1$-Receptor Blocker Adverse Effects

Adverse effect	Terazosin		Doxazosin		Tamsulosin			Alfuzosin	
	Terazosin	Placebo	Doxazosin	Placebo	0.4 mg	0.8 mg	Placebo	Alfuzosin	Placebo
Asthenia/fatigue	7.4%	3.3%	8.0%	1.7%	7.8%	8.5%	5.5%	2.7%	1.8%
Postural hypotension	3.9%	0.8%	1.7%	0.0%					
Dizziness	9.1%	4.2%	15.6%	9.0%	14.9%	17.1%	10.1%	5.7%	2.8%
Somnolence	3.6%	1.9%							
Nasal congestion/rhinitis	1.9%	0.0%							
Impotence	1.6%	0.6%							
Edema			2.7%	0.7%					
Dyspnea			2.6%	0.3%					
Abnormal ejaculation					8.4%	18.1%	0.2%		
Libido decrease					1.0%	2.0%	1.2%		
Amblyopia					0.2%	2.0%	0.4%		
URI								3.0%	0.6%
Headache			14%					3.0%	1.8%

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Conclusions

All the alpha$_1$-receptor blockers that are FDA approved for the treatment of hypertension are equally effective for the treatment of hypertension. However, these agents should not be used as first-line treatment for the disorder.

Four long-acting alpha$_1$ blockers are approved by the Food and Drug Administration for treatment of symptomatic LUTS/BPH: terazosin, doxazosin, tamsulosin, and alfuzosin. When comparing them, it is imperative to recognize that both efficacy and tolerability are dose dependent. The ability of the 0.4 mg tamsulosin dose to achieve a clinically significant effect without the requirement for dose titration represented a unique advantage over the other approved alpha blockers, but this convenience came at the expense of ejaculatory dysfunction. The American Urological Association Guidelines Committee concluded that alfuzosin has comparable clinical efficacy to tamsulosin and the other approved alpha blockers but does not cause ejaculatory dysfunction.[19]

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