Criteria for Nonformulary Use of Clinically Uroselective Alpha$_1$-Adrenergic Blockers in VA Patients with Benign Prostatic Hyperplasia

VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient. The manufacturer's labeling should be consulted for detailed information when prescribing alfuzosin or tamsulosin.

Background

Of the available alpha$_1$-adrenergic blockers, doxazosin, prazosin, and terazosin are listed on the VA National Formulary (VANF). Alfuzosin and tamsulosin are considered clinically uroselective alpha$_1$-adrenergic blockers. Tamsulosin is reported to have a high affinity for the alpha$_{1A}$-adrenoreceptor (predominately in the stromal compartment of the prostate) whereas alfuzosin is considered a nonspecific alpha$_1$-adrenoreceptor antagonist, having a higher concentration in the prostate compared to plasma. Since receptor subtype affinity may not correlate with uroselectivity, it has been suggested that *clinical* uroselectivity (i.e., adverse effects) be used to differentiate between the alpha$_1$-adrenergic blockers. Alfuzosin and tamsulosin are not listed on the VANF but may be considered for use in patients with benign prostatic hyperplasia (BPH) under selected circumstances (see Recommendations below). All alpha$_1$-adrenergic blockers have been shown to improve lower urinary tract symptoms (LUTS) associated with BPH[1] (recommended doses for BPH are doxazosin 4 to 8mg qd, prazosin 2mg bid, terazosin 5 to 10mg qd; lower doses have also been effective) although the American Urological Association (AUA) guidelines state that there is insufficient data to support the use of prazosin in BPH. [1] There is no evidence that alfuzosin or tamsulosin provide any benefit in patients who have not responded to an adequate trial with a VANF alpha$_1$-adrenergic blocker.

Recommendations

It is unknown whether the clinically uroselective alpha$_1$-adrenergic blockers offer an advantage in patients at risk for falls. Based on meta-analyses by the AUA[2] that found alfuzosin and tamsulosin have less dizziness than terazosin but not doxazosin, patients considered at risk for falls, but who do not have evidence of postural hypotension, might preferentially be started on doxazosin rather than terazosin, at the discretion of providers (prazosin not included in meta-analyses). If the patient already has postural symptoms, or if postural symptoms develop, with or without evidence of hypotension, a clinically uroselective agent may be considered. Similarly, if the patient has other symptoms chronologically attributable to starting a VANF alpha$_1$-adrenergic blocker (including subsequent falls), consider a clinically uroselective agent (for additional information on prevention/risk of falls refer to: http://www.cdc.gov/ncipc/factsheets/falls.htm, http://www.americangeriatrics.org/products/positionpapers/Falls.pdf, http://vaww.ncps.med.va.gov/PPt/AggRev.html).

Criteria for Non-Formulary Use of Clinically Uroselective Alpha$_1$-Adrenergic Blockers in BPH
Consider if patient has or develops the following while on a VANF alpha$_1$-blocker[a]
↑ Significant symptomatic hypotension[b,c] ↑ Significant orthostatic[d] or postural hypotension symptoms on treatment, or at baseline ↑ Syncope or near syncope symptoms[e] ↑ Significant adverse event (consider ↓ dose or trial of alternate alpha$_1$-blocker)
Consider in patients with BPH and HTN in the following situations[f]
Hypertensive with LUTS/BPH ↑ Monotherapy with an alpha$_1$-blocker for HTN is not recommended, treat HTN with other antihypertensive agents as per VHA/DoD HTN guidelines[g]; add VANF alpha$_1$-blocker for LUTS, if symptomatic hypotension develops, adjust antihypertensive regimen before considering a clinically uroselective agent Normotensive on antihypertensive regimen ↑ Adjust antihypertensive treatment upon initiation of VANF alpha$_1$-blocker, if clinically appropriate[h]; if symptomatic ↓ BP despite adjustment of antihypertensive therapy, consider clinically uroselective agent

[a] Document ADE in medical record and forward ADE report to VISN and National PBM

[b] For patients with significant baseline hypotension (not receiving antihypertensive medication), use of an alpha$_1$-blocker should be at the clinician's discretion

[c] The change in blood pressure with terazosin has been found to be clinically insignificant in BPH patients who are either normotensive or have hypertension (HTN) that is well-controlled with pharmacologic agents[3]

[d] Defined as a ↓ SBP ≥ 20 mm Hg upon standing from the supine position, or a ↓ DBP > 10 mm Hg upon standing with DBP < 65 mm Hg, or an ↑ pulse of ≥ 20 bpm upon standing with a standing pulse ≥ 100 bpm

[e] Not related to inappropriate initiation of therapy

[f] Refer to *Statement on the Use of Alpha-Adrenergic Blockers in the Management of Patients with Hypertension*[4] at www.pbm.va.gov or http://vaww.pbm.va.gov

[g] Refer to *VHA/DoD Clinical Practice Guideline for Management of Hypertension in Primary Care* at www.pbm.va.gov or http://vaww.pbm.va.gov or http://www.oqp.med.va.gov/cpg/HTN04/HTN_GOL.htm

[h] Antihypertensive agents being used for indications other than HTN (e.g., heart failure, diabetic nephropathy, angina, cardiac arrhythmias, etc) may not be appropriate for modification

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Updated versions may be found at http://www.pbm.va.gov or http://vaww.pbm.va.gov

Adverse Drug Events

Adverse Drug Event[a]	Tamsulosin 0.4mg	Tamsulosin 0.8mg	Placebo	Alfuzosin 10mg	Placebo
Dizziness	14.9%	17.1%	10.1%	5.7%	2.8%
Headache	19.3%	21.1%	20.1%	3.0%	1.8%
Abnormal ejaculation	8.4%	18.1%	0.2%	0.6%	NA
Symptomatic postural hypotension	0.2%	0.4%	0%	0.4%	0%
Syncope	0.2%	0.4%	0.6%	0.2%	0%

[a] Patients should be instructed to avoid situations where injury may result if syncope occurs upon initiation of therapy

Unpublished data comparing alfuzosin 10mg to tamsulosin 0.4mg report dizziness: placebo 3.9%, alfuzosin 5.8%, tamsulosin 1.9%; syncope: placebo 0%, alfuzosin 0%, tamsulosin 0.6%; hypotension: placebo 0%, alfuzosin 0%, tamsulosin 0.6%; impotence: placebo 0%, alfuzosin 1.3%, tamsulosin 4.4%; ejaculation failure: placebo 0%, alfuzosin 1.3%, tamsulosin 1.3%; ejaculation disorder: placebo 0%, alfuzosin 0%, tamsulosin 1.9% (ALFOTAM results available at http://www.fda.gov/cder/foi/nda/2003/21-287_Uroxatral_Medr_P2.pdf)

Contraindications

Alfuzosin

(refer to National PBM Drug Monograph for Alfuzosin at www.pbm.va.gov or http://vaww.pbm.va.gov)

- *Potent CYP3A4 inhibitors*: Alfuzosin is principally metabolized by the CYP3A4 enzyme and should not be administered with potent CYP3A4 inhibitors including ketoconazole, itraconazole, and ritonavir.
- *Hepatic insufficiency*: Alfuzosin should not be prescribed in patients with moderate to severe hepatic insufficiency.

Alfuzosin and tamsulosin are contraindicated in patients who are known to be hypersensitive to each agent or their components, respectively.

Concomitant Administration of Alpha-Blockers with PDE5 Inhibitors[a]

PDE5 Inhibitor	Drug Interaction	Precautions
Sildenafil	Symptomatic hypotension with sildenafil 50mg or 100mg plus an alpha-blocker (doxazosin 4mg); sildenafil 25mg with doxazosin 4mg reduced SBP and DBP 7 mm Hg	Sildenafil 50mg or 100mg should not be taken within 4 hours of an alpha-blocker; 25mg may be taken at any time
Tadalafil	Significant augmentation of BP lowering effect with concomitant administration of tadalafil 20mg plus doxazosin 8mg; significant hypotension (standing SBP < 85 mm Hg and/or decrease SBP > 30 mm Hg from baseline) with concomitant tadalafil 20mg and doxazosin 8mg as well as 12hrs post doxazosin; no clinically significant BP changes with tadalafil 10mg or 20mg administered 2 hrs after tamsulosin 0.4mg	Patients should be on a stable dose of their alpha-blocker or tadalafil prior to administration of the other agent; start with the lowest recommended dose and titrate based on response and tolerability
Vardenafil	Significant hypotension (standing SBP < 85 mm Hg and/or decrease SBP > 30 mm Hg from baseline) with concomitant administration of vardenafil 5mg and terazosin 5mg or 10mg or tamsulosin 0.4mg, or tamsulosin 0.4mg administered 6hrs post vardenafil; no hypotension noted with terazosin administered 6hrs post dose. One report of decrease SBP > 30 mm Hg from baseline in another study with concomitant administration of vardenafil 10mg or 20mg with tamsulosin 0.4mg or 0.8mg. Simultaneous dosing of vardenafil 10mg or 20mg resulted in a standing SBP < 85 mm Hg and/or decrease SBP > 30 mm Hg from baseline more frequently than when vardenafil and terazosin 10mg were dosed to separate T_{max} by 6hrs; dizziness was reported with simultaneous T_{max} administration of vardenafil 10mg or 20ng and tamsulosin 0.4mg, but not when dosed to separate T_{max} by6 hrs	Patients should be on a stable dose of their alpha-blocker or vardenafil prior to administration of the other agent; start with the lowest recommended dose and titrate based on response and tolerability

[a] Unknown if recommendations apply to patients on an alpha-blocker in combination with other antihypertensive medications and a PDE5 inhibitor

Dosing

Alpha$_1$-blocker	Dosing
Alfuzosin (10mg extended-release tablet)	10mg qd[a] (with food, immediately after the same meal each day)
Tamsulosin (0.4mg capsule)	0.4mg qd[a,b] (30 min after the same meal each day)

[a] Should be swallowed whole and not opened, chewed, or crushed.
[b] Two to four weeks may be necessary before patient response can be assessed. An increase in dose has not been found to be consistently more effective, however manufacturer information and AUA guidelines state the dose may be increased to 0.8mg once daily. If the dose is increased, the patient should be reassessed and the dose decreased or discontinued if inadequate response since higher doses are associated with increased side effects.

References

[1] AUA Practice Guidelines Committee. AUA guideline on management of benign prostatic hyperplasia (2003). Chapter 1: diagnosis and treatment recommendations. J Urol 2003;170:530-47.
[2] AUA Guidelines. Management of BPH (2003). Chapter 3: Results of the treatment outcome analyses. URL: http://www.auanet.org/timssnet/products/guidelines/main_reports/bph_management/chpat_3_appendix.pdf. Available from Internet. Accessed 2003 Nov 13.
[3] Lowe FC, Olson PJ, Padley RJ. Effects of terazosin therapy on blood pressure in men with benign prostatic hyperplasia concurrently treated with other antihypertensive medications. Urology 1999;54:81-5.
[4]The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2000;283:1967-75.