Alfuzosin, Silodosin, Tamsulosin/Clinically Uroselective Alpha$_1$-Adrenergic Blockers: Recommendations for Use
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The product information should be consulted for detailed prescribing information.

Issue
Is there a preference to using a clinically uroselective alpha$_1$-adrenergic blocker over a non-uroselective alpha$_1$-adrenergic blocker for the management of lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH).

Background
Of the available non-uroselective alpha$_1$-adrenergic blockers, doxazosin, prazosin, and terazosin are listed on the VA National Formulary (VANF); alfuzosin, silodosin, and tamsulosin are considered clinically uroselective alpha$_1$-blockers , of which tamsulosin is available on the VANF for use in patients with LUTS due to BPH.

Summary of Clinical Evidence[1-6]
All alpha$_1$-blockers have been shown to improve LUTS associated with BPH (recommended doses for BPH are doxazosin 4 to 8mg once daily, prazosin 2mg twice daily, terazosin 5 to 10mg once daily; lower doses have also been effective) although the American Urological Association (AUA) guidelines for BPH state there are insufficient data to support the use of prazosin in BPH. There is no evidence that alfuzosin, silodosin, or tamsulosin provide benefit in patients who have not responded to an adequate trial with a non-uroselective alpha$_1$-blocker.

It is unknown whether the clinically uroselective alpha$_1$-blockers offer an advantage in patients who are at risk for falls. Based on meta-analyses by the AUA, alfuzosin and tamsulosin were found to have significantly less dizziness than terazosin but not doxazosin. In addition, the change in blood pressure with doxazosin or terazosin has been found to be clinically insignificant in patients with BPH who are either normotensive or have hypertension (HTN) that is well-controlled with pharmacologic agents.

Issues for Consideration
- Due to the risk for symptomatic postural hypotension, dizziness, or syncope with any of the alpha$_1$-blockers, patients should be instructed to avoid situations where injury may result if syncope occurs upon initiation of therapy. In addition, patients should be queried as to whether they experienced a fall while on treatment
- Ejaculatory disorders have been reported with silodosin and tamsulosin
- Tamsulosin has rarely been associated with priapism and patients should be informed as to the seriousness of this condition
- Since doses of tamsulosin greater than 0.4mg have not been found to be consistently more effective and may result in increased adverse effects (e.g., dizziness, orthostatic hypotension, abnormal ejaculation), it is recommended that patients prescribed doses greater than 0.4mg daily be reevaluated for efficacy and tolerability, and the dose lowered if appropriate
- Due to the potential for significant hypotension with concomitant administration of an alpha$_1$-blocker and PDE5 inhibitor (e.g., vardenafil), patients should be on a stable dose of their alpha$_1$-blocker or PDE5 inhibitor prior to administration of the other agent; start with the lowest recommended dose and titrate based on response and tolerability. In addition, it is recommended that simultaneous administration be avoided to reduce the potential for hypotension
- During cataract surgery, the occurrence of Intraoperative Floppy Iris Syndrome (IFIS) has been observed in some patients receiving or previously treated with an alpha$_1$-blocker. Product information for alfuzosin, silodosin, and tamsulosin includes a recommendation that ophthalmologists should be aware of those patients receiving treatment with an alpha$_1$-blocker in order to prepare for potential surgical modifications that may be required
- Alfuzosin is contraindicated in patients with moderate or severe hepatic insufficiency; silodosin is contraindicated in patients with severe hepatic insufficiency
- Silodosin should not be used in patients with severe kidney impairment (e.g., CrCl < 30 mL/min)
- Alfuzosin and silodosin should not be used with strong CYP3A4 inhibitors

Recommendations
Selection of an alpha$_1$-blocker for the management of LUTS associated with BPH should take into consideration efficacy, tolerability, and cost. Given the comparable efficacy and current lower price, a VANF non-uroselective alpha$_1$-blocker should initially be considered in the management of symptomatic LUTS due to BPH. Patients considered at risk for falls, but who do not have evidence of postural hypotension, might preferentially be started on doxazosin rather than terazosin; or a VANF clinically uroselective alpha$_1$-blocker could be selected, at the discretion of the provider. Some patients experiencing side effects (especially syncope) from a non-uroselective alpha$_1$-blocker may not be good candidates to take a clinically uroselective agent as orthostasis and other class side effects may also be seen with these agents.

Initiation with a VANF clinically uroselective alpha$_1$-blocker may also be considered in the following:
- Patients with conditions that do not allow adequate time for titration with a non-uroselective alpha$_1$-blocker (e.g., urinary stone passage, acute urinary retention, for bothersome LUTS immediately following brachytherapy of prostate)

- Symptomatic hypotension, orthostatic[a] or postural hypotension, or syncope or near syncope while on a non-uroselective alpha$_1$-blocker[b]
- Significant adverse event attributed to a non-uroselective alpha$_1$-blocker after consideration of decrease in dose or trial of alternate non-uroselective alpha$_1$-blocker
- Baseline significant orthostatic[a] or postural hypotension symptoms prior to treatment with a non-uroselective alpha$_1$-blocker
- Patients with concomitant HTN and BPH who are being treated with antihypertensive therapy in addition to a non-uroselective alpha$_1$-blocker, who develop symptomatic hypotension (despite adjustment of the VANF non-uroselective alpha$_1$-blocker or antihypertensive therapy) or who develop inadequate control of LUTS after adjustment of the non-uroselective alpha$_1$-blocker to avoid hypotension

[a] Defined as a decrease in SBP $\geq$ 20 mm Hg upon standing from the supine position, or a decrease in DBP > 10 mm Hg upon standing with DBP < 65 mm Hg, or an increase pulse of $\geq$ 20 bpm upon standing with a standing pulse $\geq$ 100 bpm
[b] As noted previously, some patients experiencing side effects (especially syncope) from a non-uroselective alpha$_1$-blocker may not be good candidates to take a clinically uroselective agent as orthostasis and other class side effects may also be seen with these agents

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.(Update in Progress)
[2] AUA Guidelines. Management of BPH (2003). Chapter 3: Results of the treatment outcome analyses. URL: http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines/main-reports/bph-management/chapt_3_appendix.pdf Available from Internet. Accessed 2010 Sep 28.
[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.
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[5] Kaplan SA, Meade-D'Alisera P, Quinones S, Soldo KA. Doxazosin in physiologically and pharmacologically normortensive men with benign prostatic hyperplasia. Urology 1995;46:512-7.
[6] Guthrie RM, Siegel RL, for the Hypertension and BPH Intervention Trial (HABIT) Multicenter Study Group. A multicenter, community-based study of doxazosin in the treatment of concomitant hypertension and symptomatic benign prostatic hyperplasia: The Hypertension and BPH Intervention Trial (HABIT). Clin Ther 1999;21:1732-48.

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