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## Editorial

# Are All Alpha-Blockers Created the Same?

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In the next decade, the number of men who will consult for lower urinary tract symptoms (LUTS), often in connection with benign prostatic hyperplasia (BPH), will increase for two reasons: the population is aging and fewer and fewer men will consider LUTS as an inevitable mark of old age and accept this bothersome condition without seeking treatment. We should also expect continuity in the current management trend diminishing surgical intervention; medical therapy will take a more prominent role.

Contraction of the autonomically controlled prostate or bladder neck smooth muscle is postulated to be a significant modifiable functional component of BPH-mediated bladder neck obstruction. The predominance of  $\alpha_1$ -adrenergic receptors in the bladder neck or prostate (40 times the bladder concentration) helped focus interest on  $\alpha_1$ -adrenergic blocking agents in the treatment of symptomatic BPH. Presently,  $\alpha_1$ -adrenoreceptor antagonists ( $\alpha_1$ -blockers that include doxazosin, terazosin, tamsulosin, and alfuzosin) are common for treating BPH-related LUTS. They treat the dynamic component of BPH by blocking  $\alpha_1$ -receptor-mediated sympathetic stimulation to relax the smooth muscle in the prostate. All these agents produce their effects on voiding within hours of administration, regardless of prostate size, without altering serum prostate-specific antigen or volume.

Several double-blind, placebo-controlled studies that evaluated the efficacy of  $\alpha_1$ -blockers have been conducted in patients with symptomatic BPH. These studies focus on change in symptom score and peak flow rate. The absolute improvement in maximum

flow rate is greater than placebo, yet still relatively slight. As for AUA-SI, typically they provide a two- to four-point decrease over placebo. They are also associated with improvements in quality of life and BPH Impact Index (BII). Despite the subtype selectivity of tamsulosin for the  $\alpha_{1A}$ - and  $\alpha_{1D}$ - over that of the  $\alpha_{1B}$ -adrenergic receptor, there is no evidence that this conveys a clinical advantage for the treatment of symptoms.  $\alpha_1$ -blocker studies have recently undergone meta-analysis by the American Urological Association (AUA). The results have been summarized by Marberger et al. in their review article on the medical treatment of BPH [1] in the form of a table reproduced here as Table 1. In accordance with the results of this meta-analysis, the AUA guidelines conclude that the four  $\alpha_1$ -blockers examined provided equivalent benefits in improving symptoms and flow [2]. This was confirmed by a recent review from Djavan et al. that took these new data into account, including those from studies with new formulations [3]. Thus, practitioners have too much to choose from.

As there is no evidence for a significant superiority of one of these drugs, safety and tolerability become key issues. Although  $\alpha_1$ -blockers are generally safe, the withdrawal and adverse event data in short-term clinical trials were not negligible. Potential cardiovascular and other systemic effects of these drugs may limit their use alone and in particular with other vasoactive agents. Postural hypotension, dizziness, headache, syncope, anesthesia or fatigue, rhinitis, and abnormal ejaculation may complicate  $\alpha$ -adrenergic blocker administration. Discontinuation caused by adverse events

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**Table 1 – Extracted from Marberger et al. [1]**

	AUA/IPSS			Peak flow rate ( $Q_{max}$ )			QoL question score		BPH impact index	
	3–9 moths	10–16 months	>16 months	3–9 months	10–16 months	>16 months	3–9 months	10–16 months	3–9 months	>16 months
$\alpha$ -blockers										
Alfuzosin	–4.44			2.05			–1.10			
Doxazosin	–5.10	–5.63		3.11	2.98	1.90*	–1.25	–1.47	–2.00	–2.47
Tamsulosin	–4.63	–7.53*		1.85	1.86*		–1.43			
Terazosin	–6.22	–5.99		2.51	1.94	2.61*	–1.70*	–1.37	–1.45*	–2.09

Outcome parameters with  $\alpha_1$ -blockers: estimates of changes in symptom score and peak urinary flow rate [45].  
Reproduced from American Urological Association: AUA Guideline on the Management of Benign Prostatic Hyperplasia (BPH) (2003).  
Numbers without asterisks are based on RCT results with placebo controls.  
\*These numbers are based on single-arm analyses—no RCT data available.

is 4–10% for alfuzosin and tamsulosin—rates that are comparable with placebo. However, for terazosin and doxazosin, an additional 4–10% of patients withdraw because of adverse events [4].

Alpha 1-blockers are associated with a similar incidence of sexual adverse events compared with placebo. Tamsulosin appears to be an exception, with an incidence of retrograde or delayed ejaculation of 4.5–10% versus 0–1% for placebo [1]. No study reported ejaculatory dysfunction in men treated with alfuzosin [5], an adverse event occasionally linked to the use of tamsulosin and, to a lesser extent, to terazosin and doxazosin.

The most common adverse events observed with  $\alpha_1$ -blockers at a significantly higher frequency than placebo are dizziness and postural hypotension, although again there may be differences between individual agents in this class [3]. The incidence of postural hypotension with doxazosin was 4.4% in MTOPS [6] and 5.8% in PREDICT [7], with rates of dizziness of 4.8% and 15.6%, respectively. Other vasodilatory adverse events such as syncope were infrequent.

No published studies directly compare alfuzosin XL 10 mg and tamsulosin oral controlled absorption system (OCAS) 0.4 mg. However, Nordling recently published a study that evaluated the efficacy and safety of two doses (10 and 15 mg) of alfuzosin once daily and tamsulosin (0.4 mg) once daily, compared with placebo, in men with BPH [8]. Alfuzosin 10 mg and tamsulosin 0.4 mg significantly improved urinary symptoms and  $Q_{max}$  compared to placebo. The authors found no significant difference between the Alfuzosin 10 mg, tamsulosin 0.4 mg, and placebo groups as regards changes in blood pressure. Incidence of dizziness was 6% with alfuzosin 10 mg, 2% with tamsulosin 0.4 mg, and 4% with placebo.

In this issue of *European Urology*, researchers have tested directly whether tamsulosin OCAS 0.4 mg may have fewer cardiovascular effects than alfuzo-

sin XL 10 mg in two clinical pharmacology studies [9]. The data were obtained from two selected populations, both made up of healthy, volunteer males: in the first study 18 young men (18–45 years) and in the second study 40 men 60 or older. Their conclusion was that the former provides a better cardiovascular safety profile than the latter. The primary objective in the first study was to compare the drugs' ability to inhibit the increases in diastolic blood pressure and total peripheral resistance following graded infusion of the  $\alpha$ -blockers agonist phenylephrine. In the second study the primary objective was to measure the response to orthostatic stress testing.

The information obtained is certainly valuable. However, neither setting reflects the clinical reality. The latter is characterized by a different age range, a significant proportion of patients with cardiovascular comorbidity or vasodilating comedication. Furthermore, the correlation between the pathophysiological surrogate criteria used and the occurrence of clinical problems is not obvious. This explains why other similar studies that used different methods and judgment criteria could reach different conclusions. Nieminen et al. [10] recently published the results of a study that compared in detail the effects of alfuzosin and tamsulosin on the cardiovascular responses to passive orthostasis. They concluded that both alfuzosin and tamsulosin have clear cardiovascular effects, which are most striking in their influences on systemic vascular resistance and cardiac output. However, the alfuzosin and tamsulosin groups did not significantly differ from each other in terms of any parameter.

The authors of this article are difficult to follow when they state that the RCT is not the optimal instrument to assess the real risk of orthostasis when patients receive an  $\alpha$ -blocker. RCTs, provided appropriate inclusion criteria, allow an assessment over a long period of patients with different ages,

comorbidities, lifestyle (or as the authors stated, conditions that stress the cardiovascular system, such as posture change, exercising, taking a hot bath/sauna or a heavy meal), sodium intake, and many other yet unknown points, all of which should be well balanced in the different study arms thanks to randomisation. Moreover, considering a single item among the adverse effects does not reflect the general tolerance of a drug. This is often better achieved by examining the overall withdrawal rate in a clinical trial.

Thus, a clinical phase III study that compares in a "real-life" population cardiovascular safety of tamsulosin OCAS 0.4 mg and alfuzosin XL 10 mg with clinical endpoints would have been more conclusive. To date, I believe the jury is still out and practitioners still have too much to choose from.

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