# Pathophysiology of Benign Prostatic Hyperplasia: Insights From Medical Therapy for the Disease

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*The medical treatment of benign prostatic hyperplasia (BPH) has its roots in the early 1970s. During this era, the first clinical trials investigating α-blockade and androgen deprivation therapy were reported for men with clinical BPH. The observation that clinical BPH was improved following administration of both α-blockers and androgen deprivation therapy supported the evolving paradigm that clinical BPH resulted from dynamic and static pathways. During the past several decades, the evolution of α-blockers for the treatment of BPH has been impacted by innovations targeted to simplify the administration and improve tolerability while maintaining their effectiveness.*

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**Key words:** α-Adrenoceptors • α-Blockers • Benign prostatic hyperplasia • Bladder outlet obstruction • Lower urinary tract symptoms • Selectivity

The medical treatment of benign prostatic hyperplasia (BPH) has its roots in the early 1970s. During this era, the first clinical trials investigating α-blockade[1] and androgen deprivation therapy[2] were reported for men with clinical BPH. Although these preliminary studies enrolled a small number of subjects and did not use validated self-administered questionnaires and uroflowmetry to assess symptom improvement and relief of bladder outlet obstruction (BOO), they did yield evidence suggesting clinical benefit. The observation that clinical BPH was improved following administration of both α-blockers and androgen deprivation therapy supported the evolving paradigm that clinical BPH resulted from dynamic and static pathways.[3] In this paradigm of clinical BPH, the dynamic

component of BOO was mediated by the tension of prostate smooth muscle via α-adrenoceptors. The static component of BOO was attributed to the anatomic obstruction resulting from bulk enlargement of the prostate, which was under the regulation of androgens. Because the proliferative process of BPH involved both smooth muscle and epithelial hyperplasia,[4] it was reasonable to assume that both histologic elements contributed to the underlying pathophysiology of BOO and the disease.[5]

Beginning in the 1990s, the first multicenter, randomized, double-blind, placebo-controlled studies confirmed the clinical effectiveness of α-blockade[6] and androgen deprivation therapy[7] for the treatment of BPH. In these studies, α-blockade and androgen deprivation therapies were achieved using selective long-acting $\alpha_1$-blockers and 5α-reductase inhibitors (5ARIs), respectively. The agents represented a significant advancement over the drugs used in the early 1970s to achieve α-blockade and androgen deprivation, due primarily to better drug tolerance and ease of administration. The amelioration of side effects was a fundamental step forward because the pharmacologic improvement of quality of life via improvement of lower urinary tract symptoms (LUTS) mandated drugs with exceptionally favorable tolerability.

The Veterans Affairs (VA) Cooperative Trial[8] was the first study to compare the effectiveness of α-blockers, 5ARIs, the combination of these drugs, and placebo in a cohort of men with clinical BPH. The study demonstrated that effectiveness (symptom improvement and increase in peak urinary flow rate) was only observed in the α-blockade and combination arms. There were no significant differences in efficacy between placebo and the 5ARI groups or the α-blocker and combination groups. These studies were interpreted to show that in men designated as having clinical BPH, 5ARIs exhibit no effectiveness and simply act as a placebo. A second multicenter study using a different α-blocker confirmed the results of the VA Cooperative Trial.[9]

How does one resolve the apparent contradiction of the literature as it relates to 5ARIs? The answer is quite simple. All of the phase III BPH studies enrolled the subset of men with exceptionally large prostates, whereas the VA Cooperative Trial[8] and the Prospective European Doxazosin and Combination Therapy (PREDICT) trial[9] enrolled all men with clinical BPH. 5ARIs exhibit clinical effectiveness only in men with "large" prostates, which represents a relatively small subset of men classified as having clinical BPH; therefore, only those studies enrolling men with "large" prostates demonstrated the clinical effectiveness of 5ARIs.[10]

During the past 35 years, the evolution of α-blockers for the treatment of BPH has been impacted by innovations targeted to simplify the administration and improve tolerability while maintaining effectiveness.[11] This has been achieved primarily by the development of formulations with slow-release properties and new agents with unique selectivities for inhibition the 3 α-adrenoceptor subtypes. Phenoxybenzamine, the first α-blocker used for the treatment of BPH, was administered twice daily and caused severe side effects, including orthostatic hypotension.[1] Silodosin, the most recently US Food and Drug Administration (FDA)–approved α-blocker, is administered once daily and cardiovascular side effects are minimal.[12] The clinical implications of α-blocker selectivity is discussed in greater detail below.

## α-Adrenoceptors

In the early 1970s, α-adrenoceptors were further classified into $\alpha_1$ and $\alpha_2$ subtypes.[13] Both $\alpha_1$- and $\alpha_2$-adrenoceptors were subsequently identified in the prostate using radioligand binding techniques.[14,15] Prostatic $\alpha_1$-adrenoceptors were more predominant than $\alpha_2$-adrenoceptors and were observed to directly mediate the tension of prostate smooth muscle.[16] Localization studies revealed that the $\alpha_1$-adrenoceptors were associated primarily with prostatic smooth muscle, which is consistent with their mode of action.[17] Because the bladder neck also contained a high density of $\alpha_1$-adrenoceptors and the bladder body was essentially devoid of these receptors,[18] the composite clinical effect of α-blockers on micturition is to facilitate bladder emptying by reducing outlet resistance without diminishing detrusor contractility.

$\alpha_1$-Adrenoceptors were subsequently classified as $\alpha_{1A}$, $\alpha_{1B}$, and $\alpha_{1D}$ subtypes.[19] Using radioligand binding studies in transfected mouse tissue membranes expressing each of these individual receptor subtypes, $\alpha_{1A}$-adrenoceptors were shown to be the dominant subtype in the human prostate.[20] Immunohistochemical studies revealed that the $\alpha_{1A}$-adrenoceptor localized to the prostate smooth muscle.[21] A negligible density of $\alpha_{1B}$- and $\alpha_{1D}$-adrenoceptors were observed in the prostate. In vitro muscle isometric tension studies subsequently demonstrated that the

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$\alpha_{1A}$ subtype mediated prostate smooth muscle contraction.[20] Although different blood vessels express different proportions of the $\alpha_1$-adrenoceptor subtypes, the $\alpha_{1B}$ subtype is dominant in the vascular system.[22] These studies in the 1990s provided the rationale to develop highly selective $\alpha_{1A}$ antagonists for the treatment of BPH because efficacy of α-blockers was felt to be mediated by relaxing prostate smooth, whereas the side effects including orthostatic hypotension, asthenia, and dizziness were attributed to relaxation of blood vessels.[23]

Although all of the commercially available α-blockers have been consistently shown to improve LUTS and relieve BOO, the evidence linking commonality of mechanism for these outcomes is tenuous.[24] For example, men who experience the greatest symptom improvement on α-blockers do not exhibit the greatest improvement in BOO.[10] In addition, men with LUTS and no evidence of BOO experience improvement of their LUTS without changes in their BOO.[25] There is also evidence that dizziness and asthenia associated with administration of α-blockers are not attributable to effects on the vasculature,[26] indicating that a drug devoid of $\alpha_{1B}$ effects may not eliminate side effects in a meaningful way. These clinical observations question the wisdom of developing an $\alpha_{1A}$ subtype-selective antagonist for BPH that would only target relaxation of BOO.

There is increasing evidence that targets other than BOO are responsible for the clinical benefit of α-blockers on LUTS secondary to BPH (Figure 1). These targets include sensory afferents located within the bladder and spinal cord, which appear to be mediated by the $\alpha_{1D}$-adrenoceptor subtype.[27,28]

Collectively, these clinical observations suggest that an α-blocker with a unique profile for relative inhibition of the 3 α-adrenoceptor subtypes may also have unique clinical properties for the treatment of BPH.

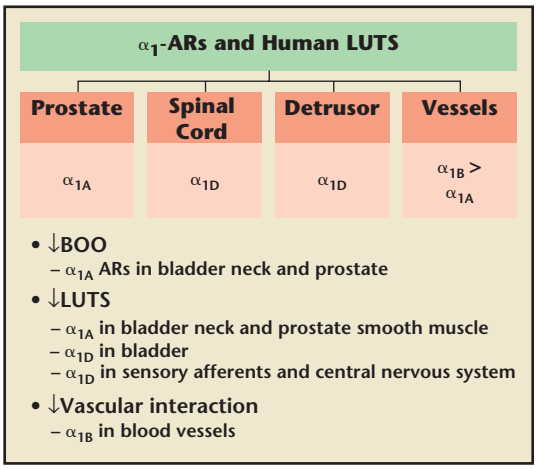


Figure 1. *New concepts in drug development of α-blockers. AR, androgen receptor; BOO, bladder outlet obstruction; LUTS, lower urinary tract symptoms. Data from Roehrborn CG and Schwinn DA[28] and Schwinn DA and Roehrborn CG.[19]*

## α-Adrenoceptor Selectivity

α-Adrenoceptor selectivity has been defined on the basis of pharmacologic, urologic, and clinical selectivity (Table 1). Pharmacologic selectivity is defined simply on the basis of binding affinities for the 3 subtypes of the $\alpha_1$-adrenoceptor. Uroselectivity has been defined using in vitro and in vivo methodologies. The in vitro methodology involves comparing the relative affinity of the α-blocker to inhibit prostate with vascular smooth muscle, whereas in vivo selectivity is based on relative potency for inhibiting prostatic urethral versus blood pressures. Clinical selectivity is based on the relative efficacy and side effects of the different agents. Ultimately, the only relevant selectivity is clinical selectivity. Uroselectivity presumes that efficacy and adverse events are mediated by prostate and vascular smooth muscle. If this were the case, this model would be superb for screening α-blockers respectively, which is not a valid assumption.

### *Pharmacologic Selectivity*

Tatemichi and colleagues[29] examined the pharmacologic selectivity of 3 different α-blockers—prazosin, tamsulosin, and silodosin—for the $\alpha_{1A}$-, $\alpha_{1B}$-, and $\alpha_{1D}$-adrenoceptors expressed in mouse LM (TK-) cells. The pKi values and relative selectivity for the $\alpha_1$ subtypes are shown in Table 2.

**Table 1**
**α-Adrenergic Selectivity of BPH Drugs**

| Study Type | Assessment |
|---|---|
| Pharmacologic | Receptor binding studies |
| Uroselectivity | Relative potency for inhibiting prostate vs vascular smooth muscle (in vitro studies) |
| Clinical | Efficacy vs adverse events in RCT |

BPH, benign prostatic hyperplasia; RCT, randomized, controlled trial.

**Table 2**
**Pharmacologic Selectivity: Receptor Binding Studies**

Human $\alpha_1$-Adrenergic Receptor Subtypes Expressed in the Mouse LM (TK-) Cell Line

| | pKi | | | Selectivity to $\alpha_{1A}$ | |
|---|---|---|---|---|---|
| | $\alpha_{1A}$ | $\alpha_{1B}$ | $\alpha_{1D}$ | Relative to $\alpha_{1B}$ | Relative to $\alpha_{1D}$ |
| Silodosin | 10.4 | 8.19 | 8.66 | 162 | 55 |
| Tamsulosin | 10.9 | 9.92 | 10.5 | 9.55 | 2.51 |
| Prazosin | 9.91 | 10.6 | 10.1 | .204 | .646 |

Ratio expressed as the relative concentration.
Data from Tatemichi S et al.[29]

**Table 3**
**Uroselectivity: Inhibition of Phenylephrine-Mediated Smooth Muscle Contraction**

| | $pA_2$ | | |
|---|---|---|---|
| Compound | $\alpha_{1A}$: Prostate | $\alpha_{1B}$: Mesenteric Artery | $\alpha_{1A}/\alpha_{1B}$ |
| Silodosin | 9.64 ± .12 | 7.47 ± .12 | .068 |
| Prazosin | 8.48 ± .04 | 9.15 ± .08 | 4.675 |
| Tamsulosin | 9.78 ± .09 | 9.36 ± .24 | .379 |

Data from Murata S et al.[30]

**Table 4**
**Uroselectivity: Inhibition of Phenylephrine-Mediated Responses in Anesthetized Rats (n = 5-8)**

| | Urethral Pressure ($ID_{50}$) ($\mu\gamma$/kg) | Blood Pressure ($ED_{15}$) ($\mu\gamma$/kg) | Uroselectivity (BP/UP) |
|---|---|---|---|
| **Intravenous Injection** | | | |
| Silodosin | 1.4 | 12 | 8.6 |
| Tamsulosin | .67 | .70 | 1.0 |
| Prazosin | 4.8 | 1.4 | .3 |
| Terazosin | 49 | 7.3 | .15 |
| **Intraduodenal Injection** | | | |
| Silodosin | 54 | 870 | 16.1 |
| Tamsulosin | 19 | 61 | 3.2 |
| Prazosin | 48 | 24 | .5 |
| Terazosin | – | – | – |

BP, blood pressure; $ED_{15}$, dose required to reduce BP by 15%; $ID_{50}$, dose required to inhibit the increase in intraurethral pressure by 50%; UP, urethral pressure.
Data from Akiyama K et al.[31]

*Uroselectivity*

The uroselectivity of α-blockers, when defined using in vitro techniques, represents the relative affinity to inhibit phenylephrine-mediated contractions in fresh tissue preparations of prostate and vascular smooth muscle. The relative potency of prazosin, tamsulosin, and silodosin to inhibit prostatic and vascular smooth muscle is shown in Table 3.[30] In vivo techniques have also been used to define the uroselectivity of α-blockers by measuring inhibition of phenylephrine-mediated increases in intraurethral and blood pressure. Phenylephrine in this model may be injected via an intravenous or intraduodenal route. The relative potency of prazosin, tamsulosin, silodosin, and terazosin using these in vivo models is shown in Table 4.[31]

*Clinical Selectivity*

Clinical uroselectivity is defined in the clinical setting by comparing clinical outcomes relative to side effects. Silodosin's pharmacologic and urinary selectivities may explain its unique clinical properties. ■

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## Main Points

- Beginning in the 1990s, studies confirmed the clinical effectiveness of α-blockade and androgen deprivation therapy for the treatment of benign prostatic hyperplasia (BPH).
- During the past several decades, the evolution of α-blockers for the treatment of BPH has been impacted by innovations targeted to simplify their administration and improve tolerability while maintaining their effectiveness.
- Although all of the commercially available α-blockers have been consistently shown to improve lower urinary tract symptoms (LUTS) and relieve bladder outlet obstruction (BOO), the evidence linking commonality of mechanism for these outcomes is tenuous.
- The VA Cooperative study compared the effectiveness of α-blockers, 5α-reductase inhibitors, the combination of these drugs, and placebo in men with BPH. The study demonstrated that effectiveness (symptom improvement and increase in peak urinary flow rate) was only observed in the α-blockade and combination arms. The results of this study were confirmed in the subsequent PREDICT trial.
- In the early 1970s, the α-adrenoceptors were further classified into $\alpha_1$ and $\alpha_2$ subtypes. Both $\alpha_1$- and $\alpha_2$-adrenoceptors were subsequently identified in the prostate using radioligand binding techniques. Prostatic $\alpha_1$-adrenoceptors were more predominant than $\alpha_2$-adrenoceptors and were observed to directly mediate the tension of prostate smooth muscle.
- The composite clinical effect of α-blockers on micturition is to facilitate bladder emptying by reducing outlet resistance without diminishing detrusor contractility; however, there is increasing evidence that targets other than BOO are responsible for the clinical benefit of α-blockers on LUTS secondary to BPH.
- Clinical selectivity is based on the relative efficacy and side effects of the different agents; ultimately, the only relevant selectivity is clinical selectivity. Silodosin is the only α-blocker that has a unique selectivity profile that may have clinical implications.