The Forefront for Novel Therapeutic Agents Based on the Pathophysiology of Lower Urinary Tract Dysfunction: alpha-Blockers in the Treatment of Male Voiding Dysfunction - How Do They Work and Why Do They Differ in Tolerability?

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1. Introduction

Voiding dysfunction is common among elderly men and typically involves several lower urinary tract symptoms (LUTS) including voiding/obstructive symptoms such as weak stream, the feeling of incomplete emptying, hesitancy and intermittency as well as storage/irritative symptoms such as frequency, urgency, and nocturia. Typically, the presence of male voiding dysfunction has been attributed to the presence of benign prostatic hyperplasia (BPH). This has been based upon a pathophysiological model in which the histological diagnosis BPH leads to prostatic enlargement, which in turn causes bladder outlet obstruction (BOO). In this model, contraction of prostatic smooth muscle via $\alpha_1$-adrenoceptors may additionally contribute to BOO and hence LUTS. More recent data, however, question whether BPH and/or BOO is indeed the sole or at least major cause of LUTS in elderly males (1, 2).

Based upon such models, the treatment of LUTS suggestive of BPH has been based upon attempts to shrink the prostate either by surgical means (including minimally invasive approaches) and endocrine treatments such as 5α-reductase inhibitors. Alternatively $\alpha_1$-adrenoceptor antagonists ($\alpha$-blockers) have been used with the idea that they alleviate LUTS by reducing prostatic smooth muscle tone. Over the past decade, $\alpha$-blockers have become the mostly widely used rational therapeutic approach for LUTS suggestive of BPH (3). Internationally, these include the quinazolines alfuzosin, *Corresponding author. m.c.michel@amc.nl

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Abstract. $\alpha_1$-Adrenoceptor antagonists are the mainstay of medical treatment of male voiding dysfunction which typically is attributed to benign prostatic hyperplasia. While original concepts have assumed that they relieve voiding dysfunction by relaxing prostatic smooth muscle, newer data indicate that their therapeutic effects at least partly occur independent of prostatic relaxation, perhaps involving direct effects on blood vessels, urothelium, afferent nerves, and/or smooth muscle of the urinary bladder. The adverse event profiles differ among $\alpha_1$-adrenoceptor antagonists, with tamsulosin having a particularly good cardiovascular tolerability. While this was originally attributed to its selectivity for $\alpha_{1A}$-adrenoceptors, it appears that alfuzosin which lacks subtype-selectivity, has a very similar tolerability. In contrast, doxazosin and terazosin, which are chemically and pharmacologically more closely related to alfuzosin than to tamsulosin, appear to have more side effects attributable to the cardiovascular system. More recent data indicate that tolerability differences between $\alpha_1$-adrenoceptor antagonists may at least partly relate to pharmacokinetic rather than to pharmacodynamic differences. Taken together, these data emphasize the idea that concepts about drug efficacy and tolerability despite being highly plausible may not necessarily be true and always require thorough experimental testing.

Keywords: benign prostatic hyperplasia, alfuzosin, doxazosin, tamsulosin, terazosin, lower urinary tract
doxazosin, and terazosin and the non-quinazolines tamsulosin and, most recently, silodosin. Some other \( \alpha \)-blockers for the treatment of LUTS suggestive of BPH are available in some countries including naftopidil in Japan or indoramin in the UK. Several direct comparative studies as well as indirect comparisons between studies on individual drugs have indicated that all \( \alpha \)-blockers are similarly effective in treating LUTS when used in appropriate doses, but can differ quantitatively and perhaps even qualitatively in their tolerability (4). Against the background of an emerging shift in our pathophysiological understanding of LUTS in elderly males (2), this manuscript will review previous and emerging concepts regarding mechanisms underlying their efficacy as well as those involved in differential tolerability.

2. Efficacy

Our classical concepts on the mode of action of \( \alpha \)-blockers in the treatment of male LUTS go back to observations of a noradrenaline-induced contraction of the mammalian prostate more than 90 years ago (5). Clinical data with the irreversible mixed \( \alpha \)-adrenoceptor antagonist phenoxybenzamine in the 1970s demonstrated that such drugs can alleviate male LUTS (6, 7). Clinical studies with the \( \alpha_1 \)-selective prazosin demonstrated that such beneficial effects are largely mediated by \( \alpha_1A \)-adrenoceptors (8), whereas concomitant in vitro studies demonstrated that catecholamine-induced contraction of the mammalian prostate was mediated predominantly if not exclusively by \( \alpha_1 \)-adrenoceptors (9, 10). After the discovery of the three \( \alpha_1 \)-adrenoceptor subtypes \( \alpha_{1A} \), \( \alpha_{1B} \), and \( \alpha_{1D} \) (11), it was found that the predominant subtype expressed in the human prostate is the \( \alpha_{1A} \)-adrenoceptor at the mRNA (12) and protein level (13), findings that were confirmed in numerous later studies (14). Most importantly, numerous studies with endogenously released neurotransmitter as well as exogenously applied agonists have demonstrated that contraction of the human prostate is mediated predominantly if not exclusively by \( \alpha_{1A} \)-adrenoceptors (14). An expansion of this model was findings that \( \alpha_{1A} \)-adrenoceptors in the prostate have a surprisingly low affinity for prazosin and other quinazolines (15), although such findings were more pronounced in the rabbit than in the human prostate (14). The \( \alpha_{1A} \)-adrenoceptors with a relatively low prazosin affinity were labelled \( \alpha_{1L} \)-receptors, but more later evidence indicates that they are not a separate subtype but rather a functional state of \( \alpha_{1A} \)-adrenoceptors (16). Based upon the prevailing pathophysiological models of male LUTS as well as these data on prostatic \( \alpha_{1A} \)-adrenoceptors, it was generally felt in the 1990s that \( \alpha \)-blockers improve male LUTS by preventing prostatic smooth muscle contraction and hereby reduce BOO and ultimately LUTS. This was a highly plausible model, as experimental induction of BOO in animals can cause not only voiding but also storage symptoms (17), whereas surgical relief of BOO in patients in many but not all cases improves storage symptoms (18).

This model implied that inhibition of the \( \alpha_{1A} \)-adrenoceptor would be sufficient to improve LUTS, whereas inhibition of other subtypes may not be necessary, but nevertheless contribute to side effects of such drugs. In this context it is noteworthy, that the quinazolines alfuzosin, doxazosin, and terazosin lack subtype-selectivity, whereas the non-quinazolines tamsulosin and, even more so, silodosin are \( \alpha_{1A} \)-selective (13, 19). Interestingly, the quinazolines also have lower affinity for the \( \alpha_{1L} \)-phenotype in the prostate, whereas the non-quinazolines do not discriminate the two states of the \( \alpha_{1A} \)-adrenoceptor (14).

However, both animal and clinical findings have questioned the model in which symptom relief by \( \alpha \)-blockers depends on prostatic smooth muscle relaxation. Firstly, storage symptoms such as non-voiding bladder contractions in animals induced by a partial ligation around the urethra were effectively inhibited by \( \alpha \)-blockers (20), although under such circumstances these drugs clearly could not improve bladder outlet obstruction. Secondly, a systematic review of urodynamic studies in men with LUTS suggestive of BPH demonstrated that \( \alpha \)-blockers as a class have only little effect on bladder outlet resistance (21). Moreover, we have recently demonstrated that improvements in voiding symptoms upon \( \alpha \)-blocker treatment show only a poor if any correlation with treatment-associated alterations in bladder outlet resistance (Fig. 1) (22). Taken together these findings strongly question whether relaxation of prostatic smooth muscle and hence reduction of BOO is the main mechanism by which \( \alpha \)-blockers improve male LUTS.

Of note, in cases of proven BOO, its reduction, for example, by surgical means, in most cases effectively reduces LUTS, but interestingly in many cases, LUTS, particularly storage LUTS, remain even after effective BOO reduction (23). Moreover, not all men with LUTS have enlarged prostates and/or BOO. Thus, LUTS as quantified, for example, by the International Prostate symptom score, correlate poorly if at all with prostate size even in very large cohorts of men (24). Taken together, these data indicate that male LUTS may have multiple causes of which BOO is only one. Similarly, the proven and undisputed male LUTS improvement by \( \alpha \)-blockers occurs at least in major parts independent of BOO obstruction and hence relaxation of prostatic smooth muscle. Nevertheless, the prostate is likely to
play some role in male LUTS and its susceptibility to treatment with α-blockers as this drug class appears ineffective against female voiding dysfunction (mainly storage symptoms) (25) despite a very consistent efficacy against male voiding dysfunction (4).

Several additional modes of action have been proposed including effects of α-blockers on receptors in the spinal cord and/or the bladder. While α₁-adrenoceptors in the central nervous system including the spinal cord can contribute to the regulation of lower urinary tract function, their role in beneficial α-blocker effects is difficult to reconcile with the observation that several drugs of this class, for example, alfuzosin or tamsulosin, show only little penetration of the blood-brain-barrier (26, 27), but nevertheless are similarly effective as other representatives of this drug class (4). The concept of bladder α₁-adrenoceptors playing a role in the treatment of male LUTS is questioned by their low expression density in the healthy bladder of several mammalian species including humans (14). On the other hand, bladder α₁-adrenoceptors undergo regulation upon BOO (28) and may become functionally important under such conditions (Fig. 2) (29). Thus, it remains to be established where the α₁-adrenoceptors mediating LUTS relief in men are located. Of note, a possible location in the bladder does not necessarily imply those on detrusor smooth muscle cells but may equally involve those in lower urinary tract blood vessels (30), the urothelium, and/or afferent nerves (31), possibilities which have been tested experimentally to a limited extent only.

To make matters even more complex, it should be noted that male LUTS may have multiple causes. Specifically, there is no a priori reason why the overactive bladder symptom complex, which shares symptoms, particularly storage symptoms, with LUTS suggestive of BPH should not exist in men. Indeed a recent clinical study using inclusion criteria of classical BPH as well as overactive bladder studies has found that surprisingly few men respond well to either α-blockers or muscarinic receptor antagonists when given in isolation, whereas good responses were seen to combination treatment (32). Accordingly, a range of recent studies has shown that male LUTS resistant to α-blocker monotherapy respond well upon addition of a muscarinic receptor antagonist (33).
3. Tolerability

When used at adequate doses (alfuzosin at 10 mg, doxazosin at 4 – 8 mg, tamsulosin at 0.4 mg, or terazosin at 5 – 10 mg, all per day), all α-blockers are similarly effective in reducing male LUTS based on several direct comparative studies as well as on many indirect comparisons between individual placebo-controlled studies (4). However, they appear to differ in tolerability profiles with doxazosin and terazosin apparently having more side effects than alfuzosin and tamsulosin (4). Such differences can largely be explained by differential effects on the cardiovascular system. While small differences in cardiovascular effects may exist between alfuzosin and tamsulosin, which can be detected by dedicated clinical pharmacology studies (34) or in large meta-analyses (35), their overall cardiovascular profile is very similar (36).

Originally it had been assumed that the very good cardiovascular tolerability of tamsulosin (37) was explained by its relative selectivity for α1A-adrenoceptors. This was based upon the idea that the vasculature expresses all three α1-adrenoceptor subtypes (38) and that specifically in the elderly, the relative role of the α1B-adrenoceptor increases (39). While this does not exclude cardiovascular side effects mediated by α1A-adrenoceptors, it makes them less likely than with drugs blocking all three α1-adrenoceptor subtypes. However, two types of experimental and clinical findings have challenged this concept. Firstly, particularly in resistance vessels, α1A-adrenoceptors can be functionally important, both in experimental animals (30, 40, 41) and in humans (42). Secondly, alfuzosin, similarly to the other quinazolines doxazosin and terazosin, lacks selectivity for the α1A-adrenoceptors (13), but with regard to cardiovascular tolerability is much closer to tamsulosin than to the other quinazolines (35). These findings have stimulated a search for additional reasons why alfuzosin and tamsulosin may have fewer cardiovascular side effects than doxazosin and terazosin.

The two lines of evidence which have emerged from such studies both relate to pharmacokinetic properties of these drugs. Firstly, for alfuzosin (43), doxazosin (44), and tamsulosin (45), multiple pharmaceutical formulations have been developed and those with a smoother pharmacokinetic profile tend to have fewer adverse effects, although such differences typically did not reach statistical significance in phase III studies. However, dedicated clinical pharmacology studies have shown that the novel OCAS formulation of tamsulosin has fewer cardiovascular effects than the previously used formulation (46, 47). Of note, in all cases, the trend for fewer side effects by the formulations with smoother pharmacokinetic profiles did not occur at the expense of therapeutic efficacy against LUTS.

The second line of evidence relates to potential selective tissue partitioning of both alfuzosin and tamsulosin. Thus, at time points of trough plasma concentrations during chronic treatment, alfuzosin concentrations within the prostate were about twice as high as those in plasma (48). In a similar study design, even greater drug enrichment in the prostate as compared to plasma was observed in tamsulosin-treated patients (49). For tamsulosin, this concept has been confirmed in dog studies that actually have shown that its effects on urethral pressures correlate much better with prostatic than with plasma concentrations (50). Whether this enrichment in prostatic tissue is unique for alfuzosin and tamsulosin is unclear as similar studies have not been reported for other α-blockers. Taken together, these data indicate that selectivity for α1A-adrenoceptors may contribute to a good cardiovascular tolerability, as also evidenced by a similar good tolerability of the even more α1A-selective silodosin (51).

However, additional factors such as smooth pharmacokinetics and partitioning in target tissues apparently also contribute to overall tolerability to a major and possibly even greater extent. While adverse effects attributable to the cardiovascular system are a main limitation to the tolerability, two other adverse effects that may be controlled by factors other than the above deserve separate consideration. It has already been recognized in early clinical studies with tamsulosin that this drug may cause abnormal ejaculation more often than placebo, particularly when exceeding a dose of 0.4 mg/day (52). Such abnormal ejaculation was originally classified as retrograde ejaculation based upon the above concepts that α-blockers would cause a major reduction of bladder outlet resistance. However, more recent studies demonstrated that the abnormal ejaculation actually is a relative anejaculation (53). While such abnormal ejaculation has been observed less frequently in placebo-controlled studies with the various quinazolines (52), the differences in incidence apparently are too small to be consistently detectable in direct comparative clinical studies (54, 55). On the other hand, abnormal ejaculation apparently occurs even more frequently with silodosin than with tamsulosin (51, 56). As silodosin has greater selectivity for α1A vs. other α1-adrenoceptor subtypes than tamsulosin (57), it appears that this may be an adverse event specifically related to α1A-adrenoceptor selectivity. Abnormal ejaculation, which can be physiologically linked to reduced vas deferens motility, can also be observed in α1A-adrenoceptor knock-out mice (58), but overall α1-adrenoceptor blockade in mice, that is, a triple knock-out of all three subtypes causes greater impairment of ejaculation than selective loss of α1A-
adrenoceptors, a situation at odds with the clinical data in humans (59). While it remains to be resolved why in patients selective blockade of $\alpha_{1A}$-adrenoceptors causes a greater tendency for abnormal ejaculation than overall $\alpha_1$-adrenoceptor antagonism, it needs to be considered that this adverse event is not treatment limiting in most patients and if anything associated with a greater treatment efficacy (52).

Finally, an adverse event needs to be discussed which has only been reported after many years of use of $\alpha$-blockers in the treatment of LUTS suggestive of BPH. Thus, in 2005, two ophthalmologists reported that patients on $\alpha$-blocker treatment for BPH could experience a complication during cataract surgery that they named “intraoperative floppy iris syndrome” (IFIS) (60). While this complication did not put patients at risk, it made the procedure technically more challenging. Meanwhile several other reports have confirmed these initial observations. Interestingly, IFIS has been reported more frequently with tamsulosin than with other $\alpha$-blockers, but it remains unclear whether this is due to a specific property of tamsulosin or rather to its much more widespread clinical use. While studies in rabbits indicate that the ratio between doses causing urethral relaxation (a proxy for their therapeutic effects in LUTS patients) and those causing pupillary dilation (a proxy for IFIS) are very similar across all various $\alpha$-blockers (61), recent clinical data suggest that a specific but as yet uncharacterized property of tamsulosin may also contribute to its potential to cause IFIS (62). Further studies will be required to resolve the mechanism underlying the occurrence of IFIS during cataract surgery.

### 4. Conclusions

The above data demonstrate that the original concepts of mechanisms underlying the efficacy and tolerability of $\alpha$-blockers used in the treatment of LUTS suggestive of BPH, despite being highly plausible, have proven to be only partly correct at best. While novel concepts are emerging, they have not been thoroughly tested at present. In a broader picture, these findings remind us that there is an important difference between what we accept to be true based on plausibility and what we actually have proven to be true.

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