A Comparison of Varying α-Blockers and Other Pharmacotherapy Options for Lower Urinary Tract Symptoms

Christopher R. Chapple, MD

Department of Urology, Royal Hallamshire Hospital, Sheffield, UK

α_1-Adrenoceptor antagonists are now well established as the most common treatment for lower urinary tract symptoms (LUTS) suggestive of bladder outflow obstruction associated with benign prostatic hyperplasia. Both α_1-adrenoceptor antagonists and 5α-reductase inhibitors are accepted treatments for LUTS, but with finasteride this applies only to patients with clinically enlarged prostates, whereas α_1-adrenoceptor antagonists are considered to be appropriate treatment for all patients, irrespective of prostate size. Systematic analyses of placebo-controlled studies show that commonly used α_1-blockers are significantly superior to placebo in improving urinary flow and reducing symptoms. Efficacy of α-blockers appears to be well maintained over time, and there is no evidence of tolerance or tachyphylaxis to α_1-blockade after 6–12 months' usage. Direct comparative trials show that, in the short term, α_1-adrenoceptor antagonists are more effective than finasteride in reducing symptom score. For α_1-adrenoceptor antagonists, the most commonly reported adverse effects are dizziness, asthenia, postural hypotension, and syncope. Alfuzosin has a more pronounced effect on blood pressure than does tamsulosin, especially in elderly patients. Tamsulosin is well tolerated and has minimal effects on blood pressure; tamsulosin 0.4 mg has the lowest potential to reduce blood pressure and causes less symptomatic orthostatic hypotension than terazosin.
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Lower urinary tract symptoms (LUTS) suggestive of benign prostatic obstruction (BPO)—previously referred to as symptomatic benign prostatic hyperplasia (BPH)—are increasingly common in the aging male. Approximately 25% of men over 40 suffer from LUTS, and the prevalence of this condition rises with age.[1] Besides surgery and watchful waiting, medical therapies to treat LUTS

include α_1-adrenoceptor antagonists, finasteride, and phytotherapy.

Operative intervention is rather radical from the patient's perspective; not surprisingly, many patients feel reluctant to undergo surgery and prefer less invasive intervention, such as medical therapy. This trend has been encouraged not only by increased patient awareness of the availability of effective contemporary pharmacotherapy, but also by an increased awareness of the complications of surgery. In particular, it can be associated with significant morbidity, such as irreversible incontinence and loss of sexual function with subsequent impairment of a patient's quality of life. Therefore, pharmacotherapy, in particular using α_1-adrenoceptor antagonists, has, not surprisingly, become the most common course of therapy for symptomatic patients. Although both α_1-adrenoceptor antagonists and finasteride, a 5α-reductase inhibitor, are accepted treatments for LUTS, in the case of finasteride, this applies only to patients with clinically enlarged prostates (> 40 g) whereas α_1-adrenoceptor antagonists are considered to be appropriate treatment for all patients irrespective of prostate size.[2]

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In some European countries, plant extracts are also registered for the management of LUTS. Despite this, the World Health Organization does not recommend phytotherapy as an appropriate treatment for LUTS suggestive of BPO, mainly because too little information is available from well-designed clinical trials using placebo control, adequate follow-up, and sufficient numbers of patients to define the long-term efficacy and tolerability of plant extracts.[2]

α_1-Adrenoceptor antagonists are now well established as the most common treatment for LUTS suggestive of BPO, eg, bladder outflow obstruction (BOO) associated with BPH. The best available external evidence for the therapeutic decision to treat an individual patient with α_1-blockers and for the choice of a given drug within this class (prazosin, indoramin, doxazosin, terazosin, alfuzosin, tamsulosin) is provided by randomized controlled trials (RCTs), an important scientific tool to determine the efficacy and tolerability of a given treatment relative to placebo or other treatment forms. However, due to strict inclusion and exclusion criteria, the patient populations in RCTs may not be fully representative of those routinely consulting the physician. Moreover, participation in a formal study puts physician and patient in a situation where they may react differently from the way they would in real life. In contrast, in real-life practice (RLP) studies cannot determine treatment efficacy or tolerability in absolute terms, because they typically do not include a control group and are purely observational. On the other hand, they tend to be more representative of real treatment outcomes. Thus RCTs have high internal but less external validity, whereas RLP studies have less internal and greater external validity.

α_1-Adrenoceptor antagonists are considered to be appropriate treatment for all patients.

The present review discusses what we have learned from the many RCTs published in recent years, with reference finally to an ongoing study designed to document the use of α antagonists in real-life practice.

Randomized Controlled Trials with α_1-Blockers for Lower Urinary Tract Symptoms

RCTs evaluate the treatment benefit for LUTS in several ways: improvement of subjective symptoms, (quality of life) and improvement of objective function (flow rate, postvoid residual volume, urodynamics). Taking a longer-term perspective using a pragmatic noninterventional design, issues such as reduction of acute urinary retention rate, other BPH-related morbidity, and the avoidance of surgical intervention can be addressed.[3] Placebo-controlled trials are important to identify which part of the overall changes under treatment ("response") is actually attributable to active medication. They differentiate between medication-related and medication-independent changes of the study criteria over time (natural course of disease, improvement by intensified medical care resulting from participation in the trial, etc).

Comparison of α_1-Blockers to Placebo

The placebo response in LUTS is notoriously high: the Agency for Health Care Policy and Research (AHCPR) report estimated a mean probability of symptomatic improvement in open prostatectomy: 98%, transurethral resection of the prostate (TURP): 88%, transurethral incision of the prostate (TUIP): 80%, balloon dilatation: 57%, finasteride: 67%, α_1-blockade: 74%, watchful waiting: 42%, and placebo: 45%.[4]

Systematic analyses of placebo-controlled studies show that commonly used α_1-blockers (doxazosin, terazosin, alfuzosin, tamsulosin) are statistically significantly superior to placebo in improving urinary flow and reducing symptoms.[5] Active treatment is superior to placebo in terms of improving total symptom scores by about 30%–45%, with an additional benefit of 10%–20% above placebo. Similarly, the overall improvement in flow (Q_{max}) by 15%–30% is about 10 to 15 times greater than with placebo.

Symptom Improvement With α_1-Blockers

Although usually primarily evaluated in terms of total symptom score, symptomatic improvement can be shown to affect the specific components of filling (irritative) and voiding (obstructive) symptoms. As with other therapies, most would agree that the efficacy of α_1-blockade is more pronounced in those patients with more pronounced baseline symptomatology,[6] but the subject of the influence of baseline age on efficacy continues to be debated in the literature.

On the other hand, it should be emphasized that not all patients respond adequately to α_1-blockade; responder rates depend on the criteria used to define response and the eligibility criteria of the study sample (including baseline values). For example, with tamsulosin, single doses of 0.4 mg were reported to yield responder rates of 67% (placebo: 44%),[7] 66% (placebo: 49%),[8] 55% (placebo: 40%),[9] and 70% (placebo: 51%)[10] in terms of symptom improvement (≥ 25%) in shorter-term studies and 81% (placebo: 59%) in longer-term studies.[11] In contrast, Q_{max}-responder rates (≥ 30% increase) are notoriously lower in comparison: for instance, 32% (placebo: 20%)[8] and 31% (placebo: 21%).[10]

The efficacy of α-blockers appears to be well maintained over time, and there is no evidence of tolerance or tachyphylaxis to α_1 blockade after 6–12 months' usage.[3] This has been confirmed in open-label extension studies of placebo-controlled RCTs, which confirm maintained efficacy during longer-term use. The durability of tamsulosin, for example, has been maintained up to 6 years.

Active treatment is superior to placebo in terms of improving total symptom scores.

Comparison of α_1-Blockers to Finasteride

There have been four direct comparative trials between an α_1-adrenoceptor antagonist, finasteride, and their combination. The VA Cooperative study included 1229 patients randomized to placebo, finasteride, terazosin, or a combination of both drugs for 1 year,[11] whereas in the ALFIN study, 1051 patients were randomized to finasteride, alfuzosin sustained release, or a combination for 6 months.[12] The Prospective European Doxazosin and Combination Therapy (PREDICT) study randomized 1089 patients to placebo, finasteride, doxazosin, or a combination for 1 year.[13]

The Medical Therapy of Prostatic Symptoms Study (MTOPS) compared the effects of finasteride, doxazosin, and the combination of these two agents versus placebo in 3047 men who were followed for 4.5 years.[14] Key results from VA-COOP, ALFIN, PREDICT[15,16] and MTOPS are summarized in Table 1.

The results show that α_1-adrenoceptor antagonists are more effective than finasteride in reducing the symptom score.

A retrospective pooled analysis of several placebo-controlled studies

Table 1
Symptom Score Reduction From Baseline to Endpoint

Study	Placebo	α_1-Antagonist	Finasteride	Combination
VA-COOP[a]	-2.6	-6.1***	-3.2	-6.2***
ALFIN[b]	--	-6.3**	-5.2	-6.1*
PREDICT[c]	-5.7	-8.3*	-6.6	-8.5*
MTOPS[d]	-4.9	-6.6***	-5.6***	-7.4***

[a] Mean reduction in AUA symptom score at 52 weeks for placebo, tamsulosin, finasteride, tamsulosin + finasteride
[b] Mean reduction in IPSS score at 6 months for alfuzosin, finasteride, or alfuzosin + finasteride; *P* values versus finasteride (no placebo group included)
[c] Mean reduction in IPSS score at 52 weeks for placebo, doxazosin, finasteride, or doxazosin + finasteride
[d] Mean reduction in AUA score at 4.5 years for placebo, doxazosin, finasteride, or doxazosin + finasteride
*$P \leq .05$, **$P \leq .01$, ***$P \leq .001$ versus placebo, except as noted (ALFIN)

previously found that finasteride was more effective than placebo in patients with a large prostate volume (> 40 mL).[17] However, retrospective analysis of the VA Cooperative study showed that finasteride was no more effective than placebo even in patients with a prostate volume over 40 mL.[17] In those patients, finasteride improved Q_{max} significantly, but no difference was observed in relief of symptoms. Data from the PREDICT study also suggest that finasteride was no more efficacious than placebo when adjusting data for prostate size using surrogate measures such as prostate-specific antigen and digital rectal examination.[13] This supports the use of α_1-adrenoceptor antagonists as first-line agents in the medical treatment of LUTS. Furthermore, one of the main advantages of α_1-blockers is that their onset of action is prompt (within the first days of treatment) and the appropriateness of the chosen treatment option can be evaluated without delay, avoiding costly and ineffective long-term treatment, which can occur with finasteride.

α_1-Blockers as Antihypertensives

It has been suggested for a number of years that in patients with a combination of both BPH and hypertension, nonselective adrenoceptor subtype agents would be advantageous because both diseases could be treated with one drug. Although placebo-controlled studies do not indicate differences among the various α_1-blockers in terms of efficacy, they do suggest likely differences in terms of tolerability and ancillary cardiovascular effects. For α_1-adrenoceptor antagonists, the most commonly reported adverse events are dizziness, asthenia, postural hypotension, and syncope.

Doxazosin and terazosin have significant antihypertensive efficacy (vs placebo) and both have been shown to reduce elevated blood pressure more than placebo in hypertensive LUTS patients. In normotensive LUTS patients, their blood pressure–reducing effects are comparably smaller and usually reported as unlikely to be of clinical relevance. In contrast, with tamsulosin, the effects on blood pressure in both hypertensives and normotensives with LUTS are consistently not significantly different from placebo.[18] For alfuzosin, the profile is less conclusive: it was initially developed as an antihypertensive[19] and has been shown to reduce elevated blood pressure in hypertensives; on the other hand, alfuzosin is generally reported to have little effect on blood pressure in LUTS patients compared to placebo.

This distinction in terms of associated antihypertensive properties is relevant: antihypertensive α_1-blockers are generally not well tolerated and their capacity to reduce pathological blood pressure elevation is likely to result in an impairment of physiological blood pressure control ("homeostasis") in normotensives, resulting in orthostatic hypotension, dizziness, light-headedness, asthenia, etc.[20] Comparison of placebo-controlled RCTs endorses this: adverse events likely to relate to their cardiovascular properties were reported more frequently for antihypertensive α_1-blockers (such as doxazosin and terazosin) than with placebo.

Furthermore, in normotensive patients, meta-analyses of placebo-controlled RCTs indicate an extra 5%–20% incidence of dizziness under treatment with terazosin or doxazosin (in addition to the 3%–10% seen with placebo)[21] versus an extra incidence of about 5% or less with alfuzosin and tamsulosin; the incidence of orthostatic hypotension in the RCTs with alfuzosin and tamsulosin was at placebo level (about 1%), whereas it was larger (2%–8%) under treatment with terazosin or doxazosin. In addition, discontinuation rates (due to adverse events) under treatment with terazosin or doxazosin were higher than in the placebo-control groups, whereas they were about the same as with placebo in the groups treated with alfuzosin and tamsulosin.

This study has raised a number of questions that cannot be answered at an interim analysis stage.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) is a large, randomized, double-blind study comparing the four antihypertensive drugs chlorthalidone, doxazosin, amlodipine and lisinopril, with a total of 42,448 recruited patients. The patients were men and women aged 55 years and older with hypertension plus an additional risk factor for coronary heart disease. At a median follow-up of 3.3 years in 9067 patients, the doxazosin limb of the study was discontinued because, compared with the chlorthalidone group, there was a 25% higher incidence of significant cardiovascular disease and twice the incidence of congestive heart failure.[22] Inevitably this study has raised a number of questions that cannot be answered at an interim analysis stage. Although α_1-adrenoceptor antagonists remain the best-validated first-line treatment for BPH, associated hypertension and cardiovascular diseases should be treated independently according to established guidelines. It is reassuring that selective α_1-blockers

without antihypertensive effects, such as tamsulosin, can be combined safely and efficaciously with suitable first-line antihypertensives.[18]

α_1-Blockers and Ejaculation Disorders

Disorders of ejaculation have been emphasized in this therapeutic area in recent years, as they are a common complication of the treatment of LUTS. The AHCPR report estimated a mean probability for retrograde ejaculation of 77.2%, 73.4%, 24.9%, and 6.2% for open prostatectomy, TURP, TUIP, and α_1-blockade, respectively.[23] α_1-Blockade in general carries a risk of causing retrograde ejaculation as a consequence of its pharmacological properties at the bladder neck and in prostatic smooth muscle and the vas deferens.

There is controversy about whether untoward effects on ejaculation are more frequent with tamsulosin. Indeed, tamsulosin has been found to be associated with an increased incidence of readily reversible retrograde ejaculation ("dry ejaculation" and/or cloudy urine on postcoital voiding); in both placebo-controlled RCTs and open extension follow-up studies,[24] incidence of retrograde or delayed ejaculation was 4.5%–10% for 0.4 mg tamsulosin versus 0%–1% for placebo. In studies with alfuzosin (either placebo-controlled or vs finasteride and terazosin), lower incidences were reported. However, a direct-comparative RCT between alfuzosin and tamsulosin showed no difference between the two drugs; they were associated with a comparable and only small increase in retrograde ejaculation.[25] In addition, abnormal ejaculation was not perceived as a major problem in the placebo-controlled RCTs with tamsulosin because it resulted in very few treatment discontinuations.

Modified-Release Formulations

Recently, modified-release formulations have been introduced with the intent to permit less frequent, ie, more convenient, dosing (alfuzosin–slow-release) or to improve overall tolerability (doxazosin). These modified-release formulations achieve a smoother time course of the plasma concentrations. The extent of bioavailability (AUC) of 5 mg and 10 mg modified-release formulations of alfuzosin was shown to be similar compared to the immediate-release 2.5 mg tablets.[26] However, there still are distinct pharmacokinetic differences, as shown by smoother peak-to-trough fluctuations and the lower peak concentrations, that might have therapeutic consequences.

These modified-release formulations achieve a smoother time course of the plasma concentrations.

For the 10 mg modified-release formulation (administered once daily), a placebo-controlled direct comparison with 2.5 mg t.i.d. has indeed been reported;[27] for the 5 mg modified-release formulation (administered twice daily), comparisons to placebo and finasteride but no direct comparisons with the 2.5 mg t.i.d. regimen have been published. With the doxazosin Gastro-Intestinal Therapeutic System (GITS), which has a bioavailability loss of about 40% versus the standard formulation,[28] comparative studies between GITS and the standard formulation were published for hypertension but not for LUTS.

Optimal Dosing

The adequate comparison of data across different studies is difficult when evaluating both tolerability (differences in identifying and recording untoward events, adverse reactions, etc) and efficacy; direct comparison is needed to test such hypotheses. Such comparisons are often carried out without a simultaneous placebo-control, for instance to evaluate equivalence or superiority versus an already established reference treatment; this is a pitfall in some trials with short treatment courses or finasteride as active control. It should be remembered that parallel-group comparisons of different dose-levels may be confounded by dose-independent group effects. This is demonstrated in the dose-finding studies with tamsulosin: a dose of 0.4 mg administered once daily in the morning after breakfast is well established as the optimal dose level; there is little benefit in terms of increased efficacy obtained by increasing the dose above this level, and adverse events are more frequent at higher doses.[10] A small but distinct difference is seen between the doses of 0.4 and 0.8 mg in terms of efficacy after 12 weeks in these studies; this has been cited as proof that the dose level of 0.4 mg might be inappropriately low. Although tempting, this interpretation of the observed difference is erroneous, because it was related mainly to a dose-independent group effect: indeed, most of this difference between the groups was already present at the end of the first week of investigational treatment when both dose groups were still receiving the same dose of 0.4 mg.

For all direct comparisons, the selection of the dose is of critical importance: too low a dose might result in a better safety profile but could impair efficacy. Therefore arguments of differential tolerability, ie, clinical selectivity, should be

based on doses that yield comparable efficacy. A single daily dose of tamsulosin 0.4 mg is the optimal dose level in terms of both efficacy and tolerability. However, these are "average" findings; some patients might benefit from lower doses, others might take further benefit from higher doses without an undue increase in adverse events. Asian patients are most appropriately treated with lower doses of tamsulosin, 0.2 mg rather than 0.4 mg once daily.[29]

In a Korean study, a fixed dose of 0.2 mg tamsulosin (n = 39) was compared with step-up dosing with 1–5 mg terazosin (n = 33) in a direct, single-blind, parallel-group comparison, with endpoint evaluations after 4 and 8 weeks of treatment. At the endpoint evaluation, 51% and 45% of the patients treated with tamsulosin and terazosin were considered Q_{max} responders (> 20% improvement) and 74% and 79% were considered International Prostate Symptom Score (IPSS) responders (> 20% decrease); 72% and 67% of the patients were considered by the investigator to have at least moderately improved symptoms with tamsulosin and terazosin, respectively. Although there was no significant difference between endpoint and pretreatment baselines in terms of recumbent and standing blood pressure with tamsulosin, there was a statistically significant and clinically relevant hypotensive effect (relative to baseline) in those normotensive patients with LUTS under treatment with terazosin. Adverse reactions were most frequently dry mouth and dizziness, which, although they were usually mild and transient, were significantly higher in patients on terazosin (18 patients vs 1 on tamsulosin). The changes led to premature discontinuation of two patients on treatment with terazosin.[30]

Similarly, in Chinese patients, once-daily fixed doses of 0.2 mg tamsulosin (n = 105) and 2 mg terazosin (n = 107) were studied in a direct, single-blind, parallel-group comparison with endpoint evaluations after 4 weeks. The improvements in symptoms (IPSS, tamsulosin: from 21.5 ± 4.7 to 11.8 ± 4.5; terazosin: 21.8 ± 5.6 to 13.3 ± 5.3) and Q_{max} (tamsulosin: from 9.6 ± 2.8 to 13.2 ± 4.1; terazosin: 10.4 ± 2.6 to 13.6 ± 3.6 mL/sec) were comparable, but there were distinct differences in terms of cardiovascular effects and safety. Indeed, relative to baseline there was an average reduction of systolic/diastolic blood pressure of −22/−14.7 mm Hg with terazosin versus only −3.8/−2.1 mm Hg with tamsulosin. There were 13 and 50 adverse events, respectively, for which a causal relationship to the medication could not be excluded for the treatment with tamsulosin and terazosin; this related mainly to cardiovascular effects: dizziness (tamsulosin: 10; terazosin: 34), headache (tamsulosin: 0; terazosin: 3), palpitation (tamsulosin: 0; terazosin: 2), and severe hypotension requiring the subject's premature discontinuation (tamsulosin: 1; terazosin: 10).[31]

Parallel-group comparisons of different dose-levels may be confounded by dose-independent group effects.

In Europe, there is no reason to consider lower doses than those recommended on the basis of extensive regulatory review. Unfortunately there are few studies with a direct larger-scale comparison between the various α_1-blockers. One older study compared alfuzosin (2.5 mg t.i.d) with prazosin (2 mg b.i.d) for 3 weeks in a double-blind, randomized, parallel-group fashion. Both treatments had comparable efficacy and were well tolerated. Only eight adverse events were reported: in the prazosin group all were related to hypotension versus only one quarter of the adverse events seen in the alfuzosin group. Alfuzosin (2.5 mg b.i.d. increased to 2.5 mg t.i.d) was also compared directly with tamsulosin (fixed dose of 0.4 mg o.d.) in 256 patients with LUTS treated for 12 weeks according to a double-blind, double-dummy, parallel-group design. Both treatments were equally effective, with responder rates of 34% and 35%, respectively, for alfuzosin and tamsulosin in terms of Q_{max} (≥ 30% increase) and responder rates of 69% and 68%, respectively, in terms of the Boyarsky symptom score (≥ 25% improvement). Both treatments were well tolerated; alfuzosin had a small but statistically significantly larger effect on recumbent and standing blood pressure in comparison to tamsulosin.[32]

A double-blind, randomized study compared the potential of tamsulosin and terazosin to induce orthostatic hypotension during early-morning and nocturnal orthostatic stress testing in 50 normotensive elderly subjects (more than 50% had LUTS).[33] Tamsulosin and terazosin were administered for 15 days according to their recommended dosage regimens in daily practice: tamsulosin 0.4 mg once daily after breakfast without dose titration; terazosin dose-titrated from 1 to 5 mg once daily in the evening. The results showed that tamsulosin caused significantly less symptomatic orthostatic hypotension (4% of patients) than terazosin (36% of patients; P = .011). One patient with symptomatic orthostatic hypotension on tamsulosin had prestudy

vertigo, which was an exclusion criterion for the study.

A subgroup analysis of younger (< 65 years) and older (≥ 65 years) patients enrolled in two European phase III placebo-controlled trials[34] revealed that tamsulosin 0.4 mg once daily had comparable effects on blood pressure and was as well tolerated in both younger and older patients, compared with placebo.[35]

In three clinical interaction studies, tamsulosin was added to hypertensive patients controlled with the β-blocker atenolol, the angiotensin-converting enzyme inhibitor enalapril, or the calcium channel blocker nifedipine. The results confirmed that tamsulosin has no clinically significant additional effects on blood pressure nor increased potential for orthostatic hypotension in hypertensive patients treated with antihypertensive medication.[36]

In Europe, there is no reason to consider lower doses than those recommended on the basis of extensive regulatory review.

The TRIUMPH Project

LUTS due to BPH are likely to become an increasing burden for future health care budgets due to the high prevalence of this condition in the elderly and the aging population. Data on the cost-effectiveness of the available treatment options based on real-life practice will therefore be crucial. This information is currently largely lacking. The European Association of Urology has therefore endorsed the development of the TRIUMPH (Trans-European Research into the Use of Management Policies for LUTS suggestive of BPH in Primary Healthcare) project.[37] This project will evaluate how LUTS/BPH are currently managed in real-life practice in 6 European countries (France, Germany, Italy, the Netherlands, Poland, Spain, and the UK) and Australia and how this condition progresses over time in relation to initial treatment choice. The clinical data will be retrieved from continuous analysis of large computer-based patient files such as the General Practice Research Database (GPRD) in the UK and the Integrated Primary Care Information (IPCI) database in the Netherlands.

Results from the GPRD in the UK, including almost 80,000 new patients with LUTS/BPH followed between 1992 and 1999, show that prostatectomy rates have fallen and continue to fall, with a continuing increase in the use of medical treatments. Medical treatments are also used earlier and delay surgery compared with no treatment. Postponing surgery and low failure rates are most likely with finasteride, alfuzosin, and tamsulosin. ■

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Main Points

- The efficacy of α_1-blockers in relieving symptoms, improving quality of life and augmenting urinary flow in patients with lower urinary tract symptoms is clear from currently reported studies.
- Improvement involves both filling (irritative) and voiding (obstructive) symptoms, occurs promptly, is well maintained over time, and is independent of prostate size and baseline prostate-specific antigen.
- There is no evidence of relevant differences between the different α_1-blockers in terms of efficacy, and all α_1-blockers can be accepted as appropriately efficacious at the presently recommended doses.
- All α_1-adrenoceptor antagonists have similar efficacy in the treatment of lower urinary tract symptoms suggestive of benign prostatic obstruction, but they differ in their potential to lower blood pressure and induce related adverse events such as symptomatic orthostatic hypotension.
- Most α_1-adrenoceptor antagonists affect blood pressure by design; sustained release alfuzosin and tamsulosin have the lowest propensity to cause side effects.
- Tamsulosin is easy to use as it does not require dose titration and can be taken once a day.
- Alfuzosin has a more pronounced effect on blood pressure than does tamsulosin, especially in elderly patients, and it is more often discontinued because of adverse vasodilatory events in patients over 75 years with lower urinary tract symptoms, who are receiving therapy for concomitant cardiovascular disease(s).
- In elderly patients and the majority of patients with cardiovascular comorbidity or comedication, tamsulosin is well tolerated and has minimal effects on blood pressure; tamsulosin 0.4 mg has the lowest potential to reduce blood pressure and causes less symptomatic orthostatic hypotension than terazosin.

Editor's Summary of Meeting Presentation

Dr. Lepor opened the discussion stating that all α-blockers appear very similar in terms of efficacy as measured by symptom scores and flow rates, whereas there are differences regarding the adverse event (AE) profiles. The development of slow release formulation of alfuzosin and doxazosin both administered now without dose titration as a once-a-day formulation, in fact, may suggest that the formulation of the drug and pharmacokinetics play a more significant role in terms of safety profiles than the chemical compounds themselves. This provocative assumption would imply that selectivity to the α_{1A} receptor versus the (vascular) α_{1B} receptor may be less important than the way in which the drug is administered.

Dr. Lowe agreed with the basic statement and suggested tolerability of the older, titratable α-blockers might even be better when taken postprandial without dose titration. Although it is unlikely that such a trial will be carried out using the traditionally titratable α-blockers, it is clear that the future and the market place belong to the once-a-day and the slow release formulations, which do not require titration.

Dr. Lepor suggested that the ideal tamsulosin formulation might be a slow release 0.8 mg tablet that could be taken without the need of titration and satisfy the need and desire for optimized efficacy. This remark was triggered by a brief discussion of the most commonly used tamsulosin dosage. According to market information, no more than 20% of prescribing physicians offer their patients tamsulosin 0.8 mg in the form of 0.4 mg b.i.d. One reason clearly is the doubling of the cost associated with such regimen, as Dr. Lepor pointed out. The absence of well-designed and -executed direct comparator trials was noted by the panel, as all trials comparing two or more α-blockers with each other suffer from small patient numbers, inappropriate dosing schemes, poor randomization or blinding, and all are very short in duration. To truly compare both efficacy and (more importantly) safety of different α-blockers, appropriately powered direct comparator trials are needed to assure that all patients are enrolled under the same inclusion and exclusion criteria, follow the same trial design, and have the same intensity of follow-up. The justification for such a trial becomes more urgent when different drugs for the same indication have seemingly similar efficacy but different AE profiles, which may be real or just the result of different trial design and follow-up.

The last discussion topic was brought up by Dr. Lepor, regarding the various "superselective" α_{1A} receptor blockers and their failure in early clinical studies. Such drugs were developed by Roche Pharmaceuticals, Merck Sharp and Dohme, as well as Abbott Laboratories. The Roche compound apparently induced improvements in flow rate—consistent with the α_{1A}-blockade—but had no impact on symptoms. This dataset was never published, but suggest that other mechanisms than smooth muscle relaxation via α_{1A} receptors must be involved in symptom improvement. The Abbott drug, fiduxosin, had both α_{1A} and α_{1D} activity, but liver toxicity prevented its clinical development. Finally, the Merck Sharp and Dohme compound was found inferior or at least not superior to tamsulosin in a direct comparator trial, despite a 1000-fold increase in selectivity, also suggesting that increased selectivity does not necessarily increase efficacy in terms of symptoms or flow rate. The desire to publish such negative trials was expressed by the entire faculty, as the knowledge gained would greatly increase our understanding of the mechanisms of action of α-blockers overall.