Therapeutic Treatment for
Benign Prostatic
Hyperplasia
Therapeutic Treatment for
Benign Prostatic Hyperplasia

Edited by
Roger S Kirby MA MD FRCS (Urol) FEBU
Visiting Professor of Urology
St. George's Hospital, London, UK

John D McConnell MD
Professor of Urology
University of Texas Southwestern Medical Center, Dallas, Texas, USA

John M Fitzpatrick MCh FRCSI FC Urol (SA) FRCSGlas FRCS
Consultant Urologist and Professor of Surgery
Mater Misericordiae Hospital, and University College Dublin, Dublin, Ireland

Claus G Roehrborn MD
Professor of Urology
University of Texas Southwestern Medical Center, Dallas, Texas, USA

Michael G Wyllie BSc PhD
Managing Director
Urodoc Limited, Herne Bay, UK

Peter Boyle PhD
Director
Division of Epidemiology and Biostatistics, European Institute of Oncology, Milan, Italy
# Contents

List of Contributors vii

1. Medical management – watchful waiting  
   P Hegarty, J M Fitzpatrick, R C Bruskewitz  
   1

2. The placebo effect in the treatment of benign prostatic hyperplasia  
   C G Roehrborn  
   11

3. Dutasteride in the treatment of the BPH patient  
   J D McConnell, C G Roehrborn  
   41

4. Finasteride in the treatment of benign prostatic hyperplasia  
   J D McConnell  
   53

5. Combination therapy in the treatment of BPH  
   C G Roehrborn  
   67

6. The differential effects of adrenoceptor antagonists on prostate tissue growth  
   N Kyprianou  
   83

7. Terazosin in the treatment of obstruction of the lower urinary tract  
   M K Brawer, J M Fitzpatrick  
   91

8. Doxazosin in the treatment of benign prostatic hyperplasia  
   R S Kirby  
   103

9. Alfuzosin  
   A Jardin  
   119

10. Tamsulosin  
    C R Chapple  
    139

11. Phytotherapeutic agents in the treatment of LUTS and BPH  
    K Dreikorn, J M Fitzpatrick  
    167

12. Uroselectivity revisited  
    K-E Andersson, M G Wyllie  
    185

Index 197
List of Contributors

Karl-Erik Andersson
Department of Clinical Pharmacology
Lund University Hospital
221 85 Lund, Sweden

Peter Boyle
Director, Division of Epidemiology and Biostatistics
European Institute of Oncology
via Ripamonte 435
20141 Milan, Italy

Michael K Brawer MD
Director of Northwest Prostate Institute
Northwest Hospital
Seattle, WA 98133, USA

Reginald C Bruskewitz MD
Professor of Surgery, Department of Surgery
Division of Urology
Clinical Science Center
600 Highland Avenue
Madison, WI 53792, USA

Christopher R Chapple MD FRCS(Urol) FEBU
Consultant Urological Surgeon
Department of Urology
Royal Hallamshire Hospital
Glossop Road
Sheffield S10 2JF, UK

Kurt Dreikorn
Urology Clinic
St. Jurgen Str.
28205 Bremen, Germany

John M Fitzpatrick MCh FRCSI FC Urol (SA) FRCSGlas FRCS
Consultant Urologist and Professor of Surgery
Mater Misericordiae Hospital and University College Dublin
47 Eccles Street
Dublin 7, Ireland

Paul Hegarty
University College Hospital
Galway, Ireland

Reginald C Bruskewitz MD
Professor of Surgery, Department of Surgery
Division of Urology
Clinical Science Center
600 Highland Avenue
Madison, WI 53792, USA

Alain Jardin MD
Chef du Service D’Urologie
Université Paris Sud
Centre Hospitalier de Bicêtre
Secteur P. Broca
78 rue Général Leclerc
94275 Le Kremlin-Bicêtre, Cedex, France

Roger S Kirby MA MD FRCS (Urol) FEBU
Professor of Urology
145 Harley Street
London W1G 6BJ, UK
Natasha Kyprianou MD PhD
Professor, Division of Urology
Department of Surgery
University of Kentucky Medical Center
800 Rose Street
Lexington, KY 40536, USA

Claus G Roehrborn MD
Professor and Chairman, Department of Urology
The University of Texas Southwestern Medical Center
5323 Harry Hines Boulevard, J8.142
Dallas, TX 75390-9110, USA

John D McConnell MD
Professor of Urology, Department of Urology
University of Texas Southwestern Medical Center
5323 Harry Hines Boulevard, B11.300
Dallas, TX 75390-9131, USA

Michael G Wyllie BSc, PhD
Managing Director
Urodoc Limited
Herne Bay, UK
INTRODUCTION

The spectrum of treatment options for benign prostatic hyperplasia (BPH) is matched by the spectrum of disease severity. New medications and minimally invasive modalities offer a greater range of choices to the urologist and the patient. This does not make treatment planning any easier. Despite these innovations the natural history of the condition with or without intervention is still unclear and can only be inferred from a number of studies. As BPH is rarely life-threatening, management is focused on quality of life. Provided it is safe to avoid surgery, watchful waiting (WW) can be offered to patients who are not bothered much by their symptoms.

WW is an active process of patient monitoring, which allows for change to medical or surgical intervention as required. The patient must understand that it is not a passive process and that compliance with follow-up appointments is essential. This chapter describes WW as an active treatment option.

The natural history of BPH appears to be one of waxing and waning. Only through knowing the natural history of the disease can we ascribe net benefit to any treatment. While the incidence of symptomatic BPH increases with age, it does not follow that the disease is not progressive in any one individual. Cohorts of untreated BPH are useful in describing the heterogeneity of the disease. As the studies have been carried out as the classification of the disease has evolved, it is difficult to compare results. Much of the work to date has compared WW to transurethral resection of the prostate (TURP), however the advent of novel medical and minimally invasive therapies has offered a 'middle ground', which must now be explored. Not only may these treatments improve symptoms, but there is also evidence that they may retard disease progression. The rate of TURP has dropped significantly with the introduction of \(\alpha\)-adrenergic antagonists and finasteride. This may reflect the lack of strong indications for TURP in the majority of patients, or indeed that these agents are in some way disease modifying. Although current guidelines recommend WW for patients with mild symptoms,\(^1\) or patients with more severe symptoms who are not bothered by them, medical management is also reducing the number of patients being assigned to WW, even for mildly symptomatic BPH.\(^2\) Large, randomized, controlled prospective trials using the American Urological Association (AUA) symptom score, urinary flow rates, and postvoid residual are necessary to allow valid comparison between the many treatments, including WW. Based on the available evidence, the indications for and logistics of WW are outlined.

Baltimore Longitudinal Study of Aging

A large epidemiological study by Arrighi et al. was published in 1991.\(^3\) A cohort of 1371 volunteers was followed from 1958 with physical
examination, digital rectal examination (DRE), and a self-administered questionnaire. Those with a history of prostate cancer or prostatectomy were excluded, leaving 1057 in the final analysis. The risk of prostatectomy increased with age. A man aged between 50 and 59 years had a 24% probability of undergoing prostatectomy in the subsequent 20 years. This risk increased to 39% for men over 60 years. Change in prostate size (determined on DRE) and obstructive symptoms increased the chance of prostatectomy.

The increase in prostatectomy rates with age in this cohort may not reflect progression of the disease as historical comparison is skewed by prevailing attitudes of practicing urologists. Transrectal ultrasonography would improve the sensitivity of measuring changes in prostate size.

**PROSPECTIVE STUDY OF PATIENTS WITH VOIDING SYMPTOMS**

Craigen et al. prospectively followed 251 patients with lower urinary tract symptoms (LUTS) for 4–6 years. Initially 39 patients had prostate cancer, 89 were in acute urinary retention, and 123 had prostatism. Of these 123 patients, 6.5% developed urinary retention and 39% required prostate surgery. Of the 67 patients who did not require surgery, 48% became symptom free. There was no difference in baseline symptoms, general health or age in those who did or did not require surgery.

This study was limited by its nonspecific urinary symptoms and patient selection. However, it illustrates that of patients who do not require surgery, symptoms resolve in 48% of cases. In a more recent study, of 50 patients with an International Prostate Symptom Score (I-PSS) score of less than 7, 81.2% were clinically stable at a mean follow-up of 17 months.

**NATURAL HISTORY OFUNTREATED ‘PROSTATISM’ OVER 5 YEARS**

Ball et al. described the 5-year follow-up of a cohort of 107 symptomatic patients for whom surgery was not indicated. Ten patients required surgery in the interim, two for acute retention and eight for worsening symptoms. Of the 97 untreated, 31 were subjectively improved, 50 unchanged, and 16 felt worse. This study included detailed urodynamic testing. The annual decrease in maximal flow rates of 1.2 ml/s was the same as that due to aging in the general population. Voiding pressure could safely remain above 70 cmH₂O, though it tended to fall over the 5-year period. On average, the ten patients who required surgery had lower initial flow rates and increased prostatic length of profilometry. All ten were classified as obstructed on pressure–flow studies. On review of the initial assessment parameters, it was not possible to predict those who would subsequently require surgery. The simplest and least invasive test, the urinary flow rate, was as good a screening parameter as any other. This study demonstrated the safety of WW over a 5-year period.

In an examination of the urodynamics of patients with bladder outlet obstruction (BOO) who underwent WW, it was possible to predict failure rate on the basis of obstruction grade, however. Treatment failure was defined as patients who did not wish to continue WW. Pressure–flow studies were conducted at baseline and again after 1 and 4 years. After 1 year, I-PSS had fallen at unchanged \( Q_{\text{max}} \) and postvoid residual (PVR), and this did not change at 4 years. LUTS severity and failure rate increased over time in patients with severe BOO. The results indicate that prediction of failure is possible, which may allow a more precise prognosis for
individual patients who prefer WW. The selection of patients for TURP, minimally invasive therapy, or WW on the basis of pressure–flow studies has also been shown to yield good symptomatic effects in terms of $Q_{\text{max}}$, PVR, and I-PSS with less risk of complications.¹

TURP WAITING LIST

Barham et al. reported in 1993 a study evaluating 118 patients on a waiting list for TURP.⁹ Surgery was indicated for symptoms of BPH in combination with an enlarged prostate on DRE. Patient mean age was 70 years (55–89 years), with a mean time on the waiting list of 3 years. Eleven of the original 118 patients were excluded because they had died, refused surgery, or had the procedure elsewhere, 107 patients were evaluated. Of these, 65% said symptoms were unchanged, 12% improved, and 22% deteriorated. Twenty-nine patients (27%) were kept on the waiting list for severe symptoms and a peak flow rate of less than 6 ml/s. The remaining 78 were re-evaluated. Of these, 51 (65%) were discharged from the waiting list due to mild symptoms, nine patients (12%) were kept under review for mild symptoms with objective evidence of severe obstruction (flow rate between 6 and 15 ml/s and residual volumes greater than 150 ml) and 18 (23%) stayed on the waiting list due to bothersome symptoms.

In summary, of the original 107 patients evaluated, 47 (44%) were kept on the waiting list, nine (8%) remained under review, and 51 (48%) were discharged. This study demonstrated the fluctuations in BPH symptoms. The authors concluded that patients will opt to avoid surgery if reassured of the natural history of BPH. Like other studies, this study is limited by its definition of symptoms and indications for surgery.

PROSPECTIVE TRIAL OF TURP VERSUS CONSERVATIVE MANAGEMENT

Kadow et al reported a randomized prospective trial of 38 patients with LUTS in 1988.¹⁰ Twenty-one patients were randomized to undergo TURP, and 17 WW. Patients were assessed by urodynamics and symptoms at baseline and 6 months after treatment.

Of the WW group, 56% of patients were either symptom free or improved, compared to 71% following TURP. Irritative symptoms decreased in both groups, with 79% of the TURP group and 50% of the WW group demonstrating improvement in detrusor instability on urodynamics. Peak flow increased from 8.5 to 19.0 ml/s in the TURP group, with little change in the WW group (9.8–11.2 ml/s). This demonstrates that, in a nonstratified group of patients, TURP is superior to WW in its urodynamic outcome and that with conservative management about half the patients improve over 6 months.

DEPARTMENT OF VETERANS’ AFFAIRS COOPERATIVE STUDY

The Department of Veterans’ Affairs (DVA) Cooperative Study compared TURP with WW in 556 men with moderate symptoms of BPH.¹¹ Symptoms were assessed using the Madsen symptom score and bother to patients was measured by a qualify of life score. Exclusion criteria were age less than 55, previous prostate surgery, bladder or prostate cancer, residual volume greater than 350 ml, or evidence of a neurogenic bladder; 280 patients were randomized to TURP and 276 to WW. Median age was 65, and there was no difference in the groups in their findings on examination, peak
flow, residual volume, serum creatinine, or urinalysis at baseline. The follow-up period was 3 years. Flow rates and residual volumes were measured every 6 months, whereas symptom scores and quality of life scores were repeated annually. All patients were advised about aggravating factors such as medication, coffee, and alcohol. Treatment failure was defined as any of the following: death, urinary retention, residual urine more than 350 ml, development of a bladder calculus, new-onset persistent incontinence, or a Madsen symptom score of more than 24, or more than 21 on two consecutive visits.

The values at baseline and after 3 years’ follow-up are listed in Table 1.1. The objective measurement of flow rate improved with TURP and was unchanged in the WW group. Postvoid residual volumes decreased to a greater extent in the TURP group over the WW cohort. Bother was ameliorated in both arms, however to a greater degree following TURP. General health and sexual performance remained stable in both groups. The treatment failures were greater in the WW group (17%) than in the TURP group (8%). Successful outcome with WW was more likely in those with high urinary flow rate, a low postvoid residual volume, and low bother score, whereas the only identifiable predictor of success in the TURP group was a high baseline bother score.

This study demonstrates that TURP achieves better objective and subjective outcomes than WW in patients with moderate symptoms of BPH. However, patients with minimal bother can be managed safely by WW, as 82% do not experience treatment failure.

WATCHFUL WAITING VERSUS MEDICAL THERAPY

The studies discussed so far have compared TURP to WW. A clinically more relevant question is the difference between medical management and WW. Direct comparison of outcomes of α-adrenergic blockade, finasteride, or WW showed improvement in symptoms and peak flow rates for all three approaches. However the actual degree of symptom

<table>
<thead>
<tr>
<th>Parameter</th>
<th>WW Baseline</th>
<th>WW 3-year follow-up</th>
<th>TURP Baseline</th>
<th>TURP 3-year follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak urinary flow rate (ml/s)*</td>
<td>12.3</td>
<td>12.7</td>
<td>11.6</td>
<td>17.8</td>
</tr>
<tr>
<td>Residual urine volume (ml)*</td>
<td>113</td>
<td>72</td>
<td>110</td>
<td>51</td>
</tr>
<tr>
<td>Symptom score (points)*</td>
<td>14.6</td>
<td>9.1</td>
<td>14.5</td>
<td>4.9</td>
</tr>
<tr>
<td>Bother from urinary difficulties (points)*</td>
<td>48.0</td>
<td>57.6</td>
<td>46.4</td>
<td>75.7</td>
</tr>
<tr>
<td>Sexual performance (points)</td>
<td>38.6</td>
<td>35.6</td>
<td>40.0</td>
<td>36.0</td>
</tr>
<tr>
<td>General well-being (points)</td>
<td>71.3</td>
<td>71.4</td>
<td>73.2</td>
<td>76.2</td>
</tr>
</tbody>
</table>

*Changes on transurethral resection of the prostate (TURP) significantly different (p < 0.01) from changes on watchful waiting (WW). †Scale ranges from 0 (most impaired) to 100 (least impaired). (Adapted from ref. 4 with permission.)
improvement was greatest for the $\alpha$-blockade group. In the Veterans' Affairs Cooperative Studies published by Lepor et al. in 1996, the degree of improvement in AUA symptom score and peak flow rates was greatest among those on an $\alpha$-adrenergic antagonist.

In an examination of the effect of a variety of BPH treatments on sexual function, finasteride, $\alpha$-blockers, and TURP were associated with levels of improvement and deterioration in sexual function similar to WW. Although surgical intervention has been more closely associated with negative sexual effects in the past, these findings suggest that other factors, such as age, may be more influential.

CURRENT TREATMENT PATTERNS GLOBALLY

The variation between countries on patterns of treatment was the subject of six articles in a European Urology supplement in 1999. The different approaches to treating patients are quite striking. In particular, phytotherapeutics command 40% of the market share in France and Germany. This is despite the lack of evidence of their efficacy over placebo. These papers also describe the widening range of physicians caring for men with BPH. This has occurred with the advent of medical management and the fall-off in the TURP rate occurring in most countries (except the UK). The prescribing of $\alpha$-adrenergic antagonists in combination with finasteride is still prevalent, and may increase following recent positive findings regarding the combination of doxazosin and finasteride; however, there is also evidence showing no benefit over $\alpha$-adrenergic antagonist alone. In a telephone survey of 502 American urologists, 20% said they favored medical management over WW in patients with only mild LUTS. Thus it is evident that in recent years medical management has reduced both the TURP and WW rates.

TREATMENT PREFERENCES

The influence of urologist preference is well described in a paper published in 1999 by Stoevelaar et al. The preferences of 39 urologists were evaluated in treating 670 consecutive patients, in 13 Dutch hospitals. The majority of patients (67.8%) belonged to the gray area for which, according to the study guidelines, management should be based on patient choice and urologist preference. Patients with high urinary flow rate, low residual volume, or mild irritative symptoms were more likely to undergo WW. Controlling for patient characteristics, the urologist’s preference could more than double the likelihood of surgery. The number of years’ experience also influenced treatment choice, in that younger urologists were less likely to recommend WW.

Patient preference should predominate in deciding treatment. However, since the advent of medical and minimally invasive therapies, this decision has become more difficult. When patients were shown an educational video program, those who had previously chosen an invasive therapy changed to a less invasive option. Based on AUA symptom scores, 35% of patients with severe symptoms preferred WW to medical or surgical intervention. This indicates that factors other than disease severity are important in the decision-making process.

INDICATIONS

When TURP was introduced over 70 years ago, the mortality and morbidity were high. The
procedure was reserved for life-threatening conditions such as hemorrhage, uremia and sepsis. With the gradual reduction in mortality, the indications for TURP have greatly expanded.\textsuperscript{31} The availability of medical and minimally invasive therapies has also altered indications for treatment.\textsuperscript{32–36}

**STRONG INDICATIONS FOR TREATMENT OR WATCHFUL WAITING**

The absolute indications for intervention are easy to define. Surgery is recommended for (1) refractory urinary retention, patients who have at least one trial without catheter with or without α-adrenergic blockade, (2) recurrent urinary tract infection caused by bacterial prostatitis, refractory to medical treatment, (3) bladder calculi, (4) renal insufficiency due to BOO, (5) severe hematuria from BPH. Other indications for TURP are relative. There is no strong indication for WW, however a strategy of WW is recommended for patients with mild symptoms of BPH.\textsuperscript{1}

**MODERATE INDICATIONS FOR TREATMENT OR WATCHFUL WAITING**

Management of patients with moderate symptoms of BPH is controversial. Such patients need to be informed of the current evidence regarding the available treatments, so that potential side-effects can be weighed against the natural history of the disease. Many patients, however, seek the opinion of a specialist, in which case it is appropriate to select the optimal treatment. This is based on clinical findings and a number of tests. For WW these include (1) the patient’s bother from urinary symptoms, (2) postvoid residual volume, and (3) uroflowmetry.

**Bother**

Two patients with the same AUA symptom score might be bothered by their symptoms to different degrees. Bother is ameliorated to a greater extent by TURP than by WW.\textsuperscript{11} The interference by the disease in the day-to-day activities of patients can be measured using the BPH impact index.\textsuperscript{37}

**Postvoid residual**

Patients with higher residual volumes fare less well with a WW strategy than with TURP.\textsuperscript{10} There is no strict cut-off volume at which intervention is recommended.

**Uroflowmetry**

Objective evidence of obstruction is gained with uroflowmetry, with the maximal flow rate being the best predictor of surgical outcome.\textsuperscript{38–40} Patients with a flow rate greater than 15 ml/s demonstrate poorer outcomes following TURP than those with maximal flow rates less than 15 ml/s.\textsuperscript{40,41}

**Conclusions**

Low bother score, high urinary flow rates, and low postvoid residual volumes favor management by WW, but the decision should not be based on these factors alone. The indications for WW versus other intervention are listed in Table 1.2.\textsuperscript{5}

**STRATEGY**

Patients being followed in a strategy of WW must understand that this is an active program. The patient’s symptoms and clinical course are monitored, usually on an annual basis. More (or less) frequent review periods have yet to be
defined by research. Patients should receive advice with regard to aggravating factors such as diuretic dose scheduling and coffee and alcohol consumption. On review, the patient should be asked about his satisfaction with this approach. Symptoms should be reassessed, along with physical examination and routine laboratory testing (serum creatinine, urinalysis). Repeat of uroflowmetry and residual urine measurement should be considered. Medical or surgical treatment can be offered to those who deteriorate or those substantially bothered by a lack of improvement. The WW program can be delivered in a shared care setting, provided the system is based on good information and mutual confidence.42

CONCLUSIONS

Urologists tend to measure outcome by means of symptom score and urinary flow rates. This is balanced against the side-effect profile of any treatment. A minor risk of even a serious side-effect such as incontinence is considered acceptable if the chance of success (as measured by symptom score or urinary flow) is high. From the patient’s aspect, the prime factor is whether the degree of bother is worth risking the morbidity of undergoing treatment. The risk of harm may outweigh the anticipated improvement.

Guidelines recently issued by the AUA recommend that patients with mild symptoms (AUA score ≤ 7), or moderate to severe symptoms who are not significantly bothered by them, be ‘treated’ with WW.

From the evidence in this chapter, it is appropriate to recommend WW for patients with mild symptoms. Patients with moderate or severe symptoms can be considered for WW, if their symptoms do not interfere with their activities of daily living. Large, prospective, randomized controlled studies of WW versus medical and surgical treatments are necessary to develop clearer indications for each modality. Further research is necessary to outline precise follow-up schedules, the need for repeated renal function tests, and how much postvoid residual is excessive. Allowing patients with BPH to

<table>
<thead>
<tr>
<th>Strength of indication</th>
<th>Watchful waiting</th>
<th>Therapeutic intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>Mild symptoms (AUA score ≤ 7)</td>
<td>Recurrent urinary retention (more than a single episode)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recurrent urinary tract infections</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recurrent gross hematuria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bladder stones</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal insufficiency due to BPH</td>
</tr>
<tr>
<td>Moderate</td>
<td>Moderate symptoms (AUA score ≥ 8 and ≤ 19) but not bothersome</td>
<td>Moderate to severe symptoms (AUA score ≥ 8) and bothersome (high BPH Impact Score)</td>
</tr>
<tr>
<td></td>
<td>(low BPH Impact Score)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Higher peak urinary flow rate (rate not specified)</td>
<td>High post-voiding residual and low peak urinary flow rate (volume and rate not specified)</td>
</tr>
<tr>
<td></td>
<td>Low post-void urinary residual (volume not specified)</td>
<td></td>
</tr>
</tbody>
</table>
participate in the decision process makes for better compliance and optimal care.

REFERENCES


The placebo effect in the treatment of benign prostatic hyperplasia

C G Roehrborn

‘The principal quality of a physician, as well as of a poet (for Apollo is the God of physics and poetry), is that of fine lying, or flattering the patient ... And it is doubtless as well for the patient to be cured by the working of his imagination, or a reliance upon the promise of his doctor, as by repeated doses of physics.’

‘Is it ethical to use a placebo? The answer to this question will depend, I suggest, upon whether there is already available an orthodox treatment of proven or accepted value. If there is such an orthodox treatment the question will hardly arise, for the doctor will wish to know whether a new treatment is more, or less, effective than the old, not that it is more effective than nothing.’

PLACEBO AND PLACEBO EFFECT: DEFINITIONS AND THEORETICAL CONSIDERATIONS

It has long been recognized by practicing physicians that procedures that offer patients reassurance or the expectation of help may lead to marked improvement in their clinical status, and many doctors believe that placebo intervention has an ethically acceptable place in clinical practice. The Latin-derived term ‘placebo’ originally appears in the Bible (placebo domino in regione vivorum, Psalm 116, Verse 9), where it may be literally translated as ‘I shall please’. This original meaning of please is still found in the first medical definition of the term in Hooper’s medical dictionary in the early nineteenth century: ‘quality ascribed to any drug prescribed to please the patient rather than being useful’. The first article dedicated to the placebo effect did not appear until 1945: ‘A note on placebo’ by Pepper. The potency of belief and expectation in affecting health is also underscored by such dramatic harmful effects as voodoo death, which in contrast can be referred to as a ‘nocebo’ (‘I shall harm’) effect.

In clinical context, placebo has come to denote a deceptive practice, a view that originates from the practice of singing vespers for pay. This negative connotation of placebo has come to dominate contemporary thinking due to the emergence of double-blind, placebo-controlled drug studies, in which the differentiation of effects due to the pharmacologic action of a compound from other unspecified effects is a primary consideration. Placebo effects are so omnipresent that if they are not controlled for in therapeutic studies, the findings are considered unreliable. Conditions in which placebo effects have been described include cough, mood changes, angina pectoris, headache, anxiety, hypertension, asthma, depression, lymphosarcoma, gastric motility, dermatitis, and pain from a variety of sources.

A prevalent view of placebo is that its use is mandatory in clinical trials, but unethical in clinical practice, a view that may be challenged on both accounts.

One of the most influential writers in the field of placebo research is Arthur K. Shapiro who offers the following definition:
A placebo is defined as any therapy or component of therapy that is deliberately used for its nonspecific, psychological, or psychophysiological effect, or that is used for its presumed specific effect, but is without specific activity for the conditions being treated. A placebo effect is defined as the psychological or psychophysiological effect produced by placebos.

Others have suggested definitions different from the one quoted above, or further deliberated on Shapiro’s theory. Grünbaum developed a diagram to illustrate his definition of placebo (Figure 2.1). If a therapeutic theory recommends a therapy ‘t’ for a condition, this treatment usually consists of a spectrum of factors, namely characteristic factors ‘F’ and incidental treatment factors ‘C’. These incidental treatment factors may be known or unknown. The patient’s life activities and functions are subdivided into two parts: the target disorder ‘D’, e.g. BPH, and other aspects of the patient’s life functions or health. The arrows in Figure 2.1 illustrate the possible causations (effects). The characteristic factors ‘F’ may have a positive or a negative effect on the target disorder (or it may have no effect whatsoever). Similarly, the factors ‘F’ may have similar influences, good or bad, on other aspects of the patient’s life, which are known as side-effects. The incidental treatment factors ‘C’ may have side-effects, but they may also affect the target disorder, in which case it is referred to as a placebo effect.

For example, let the target disorder be BPH and the therapeutic theory the administration of α-blocking drugs by a physician who evaluates the patient at regular intervals. The relaxation of the smooth muscle in the bladder neck and prostate positively affects the symptoms of BPH (nonplacebo effect), but it also causes side-effects, namely a lowering of the blood pressure (positive) and asthenia (negative). An incidental treatment factor is the dispensation of the drug by the physician. If he expresses his confidence in the medication it may result in a positive placebo effect, if he is neutral or makes a comment like: ‘We might try this for a while before we have to do something more serious’, it may result in a negative placebo effect. Obviously, the frequent visits to the physician’s office have an impact on the patient’s life functions as well by forcing him to make time for the visits, etc. (negative side-effect of incidental treatment factors).

Recent research has suggested that the dopaminergic reward mechanisms of the brain

![Figure 2.1 Illustration of a therapeutic theory used to clarify the definition of ‘placebo’. For further explanation see text. (Adapted from reference 10.)](image-url)
are responsible for mediating the placebo effect. Brody listed three possibilities to explain why a patient improves after a certain therapy is instituted:

- The patient got better due to the natural history of the condition in an organism with intact healing and recuperative powers.
- The patient got better due to the symbolic effect of the treatment, that is its impact on his or her imagination, beliefs, and/or emotions.
- The patient got better due to some specific or characteristic feature of the treatment that can be studied, isolated, and predicted within the context of contemporary medical theory.

A positive placebo effect (the second of the above list) is most likely to occur when three factors are present:

- The meaning of the illness experience for the patient is altered in a positive manner, given the patient’s belief system and world view.
- The patient is supported by a caring group.
- The patient’s sense of mastery or control over the illness is restored or enhanced.

This theory, emphasizing the importance of the patient’s belief system and his or her expectations, highlights the cultural dimension of the placebo phenomenon and the importance of cross-cultural studies in placebo research.

White et al. pointed out that there is no single placebo effect with a single mechanism and efficacy, but rather a multiplicity of effects with differential efficacy and mechanisms, and they provide a list of placebogenic variables or determinants of a placebo response (Table 2.1). Turner et al., in a review of the importance of the placebo effect in pain treatment and research, listed similar factors influencing the placebo response. Among the patients’ factors contributing to a

<table>
<thead>
<tr>
<th>Table 2.1 Biopsychosocial determinants of placebo response. (Reproduced with permission from White et al.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cultural context</td>
</tr>
<tr>
<td>Belief system</td>
</tr>
<tr>
<td>Faith</td>
</tr>
<tr>
<td>Environmental milieu</td>
</tr>
<tr>
<td>Instruction</td>
</tr>
<tr>
<td>Suggestion</td>
</tr>
<tr>
<td>Preparation characteristics</td>
</tr>
<tr>
<td>Doctor–patient relationship</td>
</tr>
<tr>
<td>Patient’s expectations and beliefs</td>
</tr>
<tr>
<td>Patient’s personality</td>
</tr>
<tr>
<td>Psychological state</td>
</tr>
<tr>
<td>Symptom severity</td>
</tr>
<tr>
<td>Discomfort severity</td>
</tr>
<tr>
<td>Anxiety and stress</td>
</tr>
<tr>
<td>Central evaluative processes</td>
</tr>
<tr>
<td>Cognitive processes</td>
</tr>
<tr>
<td>Cognitive schema</td>
</tr>
<tr>
<td>Self-schema</td>
</tr>
<tr>
<td>Self-control</td>
</tr>
<tr>
<td>Expectancy</td>
</tr>
<tr>
<td>Outcome expectancy</td>
</tr>
<tr>
<td>Efficacy expectations</td>
</tr>
<tr>
<td>Operant behavior</td>
</tr>
<tr>
<td>Symbolic processes</td>
</tr>
<tr>
<td>Imagination</td>
</tr>
<tr>
<td>Covert rehearsal</td>
</tr>
<tr>
<td>Emotions</td>
</tr>
<tr>
<td>Central nervous system influences upon physiology</td>
</tr>
<tr>
<td>Immune system</td>
</tr>
<tr>
<td>Stress mechanism</td>
</tr>
<tr>
<td>Endogenous opiates</td>
</tr>
<tr>
<td>Classical conditioning</td>
</tr>
<tr>
<td>Spontaneous remissions</td>
</tr>
</tbody>
</table>
high placebo response rate were anticipation and expectations, a positive attitude toward provider and treatment, anxiousness and compliance with the prescribed treatment. As an example for the latter, a randomized trial to evaluate the efficacy of a lipid-lowering drug in the therapy of coronary heart disease may be mentioned. Patients in the placebo arm were stratified by whether they took more or less than 80% of the placebo tablets. Even after controlling for 40 known or suspected risk factors, the noncompliers had a 57% higher 5-year mortality rate than the compliant patients. Either the placebo lowered mortality, or patients’ compliance related to other characteristics associated with mortality, which was not assessed in this study. Among the providers’ factors they listed warmth, friendliness, interest, sympathy, empathy, prestige, and, again, a positive attitude towards the patient and the treatment.

These considerations all address the issue of a ‘placebo treatment’ and the ‘placebo effect’ in the usually understood sense of a medical treatment with a drug. Placebo effects, however, are equally important to consider when the treatment consists of a procedure or surgical therapy. Instead of using an inactive preparation, a procedure or surgery is performed which is similar in all respects to the active procedure or surgery, but different in that the key aspect of the procedure, which is believed to convey the main therapeutic benefit, is omitted. Such procedures are referred to as ‘sham treatment’ and the incidental causes or effects as ‘sham effects’. Throughout this chapter, the term ‘placebo/sham’ will be used to indicate the pertinence of the observation to both medical (drug) treatments and procedural (surgical) interventions.

**RATIONALE FOR PLACEBO/SHAM CONTROLLED TRIALS**

The value of controlled clinical trials in the determination of the safety and effectiveness of a new intervention is largely undisputed. The US Food and Drug Administration (FDA) recognizes four types of comparative trials:

- **No treatment**, which involves a comparison of the results in comparable concurrent groups of treated and untreated patients. This type of control is utilized when objective measurements of effectiveness are available and placebo effect or spontaneous improvement of the condition is negligible.
- **Placebo control**, which involves a comparison of the results of a particular therapy with an inactive preparation or a sham procedure.
- **Active treatment control**, which involves a comparison of the results from the new intervention with those from a treatment known to be effective.
- **Historical control**, which involves comparison of the results from a new intervention with prior experience obtained in a comparable group of patients receiving no therapy or a known effective regimen.

The caveat listed in the first paragraph is of great relevance in BPH treatment trials. While better objective outcome measures are being developed and utilized, there is certainly a placebo effect and the natural history of the disease is such that spontaneous remissions are quite common. Thus, in clinical BPH research the only alternatives are placebo/sham-controlled trials, or active treatment-controlled trials. Active control trials might substitute for placebo-controlled trials (1) when there is reasonable certainty that a new treatment will be more effective than other agents known to
be effective; (2) when the effectiveness of the new treatment is self-evident; or (3) where the nature of the therapy or procedure is such that it is not possible to blind the patients or the observers. While the first two arguments rarely are true in BPH treatment trials, the third argument demands a closer look. Experience has shown that it is feasible to blind both patients and observers responsible for outcome assessment regarding the randomization in a trial comparing balloon dilatation of the prostate with a sham procedure (cystoscopy). As will be discussed below, blinding is also possible in treatment trials using microwave-induced heat and other minimally invasive treatments. Whether or not true blinding could be achieved in a trial comparing transurethral resection of the prostate (TURP) with a sham procedure is more questionable because of the need for catheterization, the bleeding, and the irrigation necessary following the TURP. Despite the absence of any such trial, TURP is currently considered the gold standard of BPH treatments, and, in fact, it serves occasionally as an active-treatment control for other invasive treatment modalities.

Despite the general acceptance of placebo/sham controls in medical research, others have warned against the ‘continuing unethical use of placebo controls’, stating that in many cases the use of placebo control groups is in direct violation of the Declaration of Helsinki. The Declaration states that:

‘The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.’

Thus, Rothman and Michels argue that the use of a placebo is unethical whenever there is a proven therapy available according to the Declaration of Helsinki. The two ethical counter arguments which can be made are the notion that withholding of active treatment may not lead to any harm on the part of the patient depending on the underlying condition, and second, that patients in fact give their informed consent, after being fully informed, to participate in a placebo/sham controlled trial.

In the field of clinical BPH research, the American Urological Association (AUA), the US FDA, and the World Health Organization (WHO) advocate rather strictly the use of placebo controls.

The AUA BPH Clinical Trials Subcommittee is currently preparing a blueprint for the design and reporting of clinical trials in BPH. It is noted that BPH is a disease characterized by a somewhat unpredictable natural history. A significant minority of patients experience stabilization of symptoms or actual improvement. Moreover, improvements in symptoms and uroflow are seen in patients treated with placebo. This makes a randomized, placebo- (or sham-) controlled design mandatory. New surgical technologies should be compared to standard surgical treatments, such as TURP or transurethral incision of prostate (TUIP), utilizing a randomized design. For BPH medical therapies and minimally invasive technologies, efficacy relative to placebo or sham must be established (J. D. McConnell, personal communication). The document furthermore stipulates that patients have to be blinded towards the assigned treatment, and that preferentially the treating physician should also be blinded (double-blind).

The FDA circulated a draft guidance for the clinical investigation of hyperthermia devices
used for the treatment of BPH. This document stipulates that the study protocol should include a randomized active control which best can be accomplished by a blinded, sham-treated control. The FDA specifically discusses the use of a watchful waiting control or historical controls, and expresses concern regarding both these suggestions. The watchful waiting control does not assess the placebo effect of repeated catheterization which is part of the heat treatment, and the historical TURP control group might not be well matched due to different selection criteria and evaluation methodologies. However, the use of an active, randomized, concurrent TURP control group is recommended to further enhance the evaluation of hyperthermia therapy. This draft guidance document has not yet been finalized, but it is widely used in the design of trials for hyperthermia devices or other minimally invasive treatment modalities (thermotherapy, transurethral needle ablation of the prostate (TUNA), high-intensity focused ultrasound (HIFU), etc.).

The International Consultation on BPH has published under the patronage of the WHO five consensus documents which address the standardization of the evaluation of treatment modalities. Similar recommendations were made in the proceedings from the 1991, 1993, 1995, and 1997 meetings. The 2000 consensus recommendations state that all new drugs and devices intended for the use in LUTS and BPH should undergo rigorous testing in phase III trials of at least 12 months’ duration in which they are compared with either standard treatments or placebo/sham treatments to document their efficacy.

Despite the ethical concerns voiced by some, in regards to BPH treatment trials there appears to be unanimity between physicians, industry, the government (FDA), and the WHO regarding the mandatory use of placebo/sham control groups, at least in those trials considered pivotal for a new treatment.

In November 2000 the National Center for Complementary and Alternative Medicine and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) convened a consensus conference in Bethesda, MD (USA) on the NIH campus regarding ‘The science of the placebo: towards an interdisciplinary research agenda’. The tremendous response and participation of researchers and clinicians from a wide variety of backgrounds highlighted the urgent need to improve our understanding of the placebo effect and its role in biomedical research.

PLACEBO EFFECTS IN OTHER FIELDS OF MEDICINE

Blackwell et al. chose the setting of a medical school class to demonstrate the range of possible placebo effects. Fifty-six second-year medical student volunteers were conditioned to expect either stimulative or sedative effects, but in fact all received placebo in either one or two blue or pink capsules, without knowing that in fact the number and color of the dispensed capsules differed between the volunteers. Following the ingestion of the study medication, 30% of participants reported drug-associated changes, which were severe in one or two of the participants. Two capsules produced more changes than one, and blue capsules were associated with more sedative effects than the pink capsules.

Physicians are powerful therapeutic agents, and their (placebo) influence can be felt to a greater or lesser degree at every consultation. In an unusual study, 200 patients with nonspecific symptoms but no definite diagnosis were selected
for one of four consultations: a positive consultation with therapy (thiamine hydrochloride 3 mg tablets) or without treatment, or a negative consultation with or without treatment. In a positive consultation the patient was given a firm diagnosis and told that he would be better in a few days. If no treatment was given, he was told he needed none. If treatment was given, he was told that the treatment would make him better with certainty. In a negative consultation the doctor stated that he could not be sure about the diagnosis, and that therefore no treatment was given (no treatment group), or that a treatment would be tried without assuring that it would help (treatment group). During the follow-up visit, 64% of patients in the positive consultation group got better versus 39% in the negative consultation group (p = 0.001). However, there was no significant difference between the treated (53%) and the not treated (50%) patients (p = 0.5). In this example the physician-related placebo effect was clearly stronger than the effect conveyed by the medication given.

The largest body of literature regarding placebo effects exists in the area of pain treatment. Turner et al. identified over 150 articles describing placebo effects in pain treatment and research. They found that placebo response rates vary greatly. Frequently they were found to be higher than the widely accepted one-third placebo response rate based on the classic article by Beecher. Placebos have time–effect curves, and peak, cumulative, and carry-over effects similar to those of active medications. A certain placebo-responder personality could not be identified, and the role of anxiety, expectations, and learning were emphasized. The authors concluded that placebo effects plus natural history and regression to the mean may result in high rates of good outcomes in pain treatment, which may be misattributed to specific treatment effects. The important role of the physician as administrator of the treatment for pain, be it active or placebo, was emphasized by Gracely et al. Dental patients were told that they would receive either a placebo, a narcotic analgesic, or a narcotic antagonist, and that this treatment might increase, decrease, or have no effect on their pain. The physicians administering the drugs knew, however, that one group of patients would receive either placebo or the narcotic antagonist but not the narcotic analgesic (group A), while another group would receive any one of the three agents (group B). Thus, the two groups of placebo-treated patients in groups A and B did only differ in the clinician’s knowledge of the range of possible double-blind treatments, including the knowledge that patients in the group A had no chance of receiving active pain medication. Nonetheless, the placebo-treated patients in group B had significantly less pain than those in group A. This experiment shows clearly that analgesia does not only depend on the action of the administered treatment, but also on the expectations of the patient and, most surprisingly, on those of the physician, who may influence the patient’s responsiveness by a subtle behavioral change. This phenomenon of expectation and anticipation of analgesia must be taken into account when designing a cross-over study, as the patient’s past experience of pain relief (i.e. during phase I of a cross-over trial) may influence his/her subsequent (i.e. during phase II of a cross-over trial) response to treatment.

Surgical procedures may also have a very strong placebo effect as described earlier by Beecher. A most striking and classic example is the history of internal mammary artery ligation for the treatment of angina pectoris, which was popular in the first half of the twentieth century.
as a means to increase blood flow to the coronary circulation. Beecher analyzed the early experience and divided the reports into those written by ‘enthusiasts’ versus ‘sceptics’. The former group found complete relief of chest pain in 71/213 patients (38%) while the latter in only 6/56 (10%).28 Cobb et al.29 and Diamond et al.30 performed a double-blind study (the cardiologist was blinded as to the procedure performed by the cardiac surgeon) of internal mammary artery ligation versus a sham procedure, namely skin incision only, and published remarkably similar results. Cobb et al. reported a 63% significant improvement and 34% decrease in the use of nitroglycerine in the ligation group versus a 56% improvement and 42% decrease in nitroglycerine use in the sham group. Diamond et al. reported a 100% improvement in both groups regarding exercise tolerance, nitroglycerine use, and angina pain. During the year after surgery, 69% of patients reported over 50% improvement in pain in the ligation group versus 100% who experienced greater than 50% improvement in the sham group. In a review, Johnson31 discussed the possible placebo effect of extracorporeal shock wave lithotripsy (ESWL) for gallstones. In a randomized trial comparing ESWL with open cholecystectomy the symptomatic response was similar in both groups but, surprisingly, the symptomatic response in the ESWL group was identical whether or not the stones had actually been cleared. Thus, the symptomatic response might at least partially be triggered by a placebo effect.

Comparatively little is known about the placebo effects on healthy volunteers in clinical pharmacology trials. Rosenzweig et al.27 reviewed adverse events reported during placebo administration in 109 double-blind, placebo-controlled studies involving 1228 volunteers. The overall incidence of adverse events was 19%, and complaints were more frequent after repeated dosing (28%) and in elderly subjects (26%). The most frequent adverse events were headache (7%), drowsiness (5%), and asthenia (4%). The overall incidence and distribution of adverse events also appeared to depend on the nature of the active investigational drug in the young volunteers in single-dose studies. The highest incidence for all adverse events was noted when the active drug had a central nervous system effect (16.7%). The incidence was lower when the active drug had miscellaneous effects (16.2%) or a cardiovascular system effect (6.1%).

**NATURAL HISTORY, WATCHFUL WAITING, VERSUS PLACEBO EFFECT**

The importance of placebo/sham-controlled trials in BPH research is emphasized by the highly variable natural history of the disease, and the tendency towards spontaneous improvement and regression documented in several watchful waiting studies, and, to a lesser degree in longitudinal studies of the natural history of the disease. While natural history studies refer to the longitudinal study of a cohort of men with signs and symptoms of BPH over time without any kind of treatment intervention, the watchful waiting studies usually entail at least a yearly follow-up visit with a ‘treating’ physician. According to the discussion above, this consultation may have a profound impact on the ‘natural history’ of the disease process depending on the attitude and behavior of the physician. It is probably reasonable to expect that at the end of each visit the physician would tell the patient that ‘he is doing well and does not need any [additional or active] treatment’, a statement that carries with it a considerable placebo effect. Even in a natural history study the mem-
bers of the study population have to be seen, interviewed, and examined at regular intervals, thus providing for the possibility of a placebo effect. Longitudinal natural history studies may provide nonetheless the best information about the ‘background activity’ of the disease process. Watchful waiting studies add at least one known and powerful placebo effect, and they carry with them the possibility of ‘treatment failure’ and conversion to a presumably more active treatment. Lastly, placebo/sham control groups add additional nonspecific effects and, thus, their outcomes theoretically should be superior to watchful waiting and natural history studies.

**Regression to the mean**

Placebo control arms differ in at least one other very important characteristic from natural history studies. In general, patients are selected to participate in studies based on inclusion/exclusion criteria, usually eliminating patients perceived to be less symptomatic, i.e. those with lower symptom scores and higher peak flow rates. By the principle of trial conduct, patients then repeat the symptom and flow rate assessment during and after therapy in both active and placebo groups. However, the same inclusion/exclusion criteria are not applied to those measurements. To determine the effect that the stringency of pretrial screening has on the outcome of placebo treatment, a cohort of 145 volunteers were invited to fill in the I-PSS score and perform a flow rate recording twice within a month without receiving any therapy or instructions whatsoever. Although many patients experienced either an increase or a decrease in both parameters, the mean values did not change significantly (I-PSS 12.1 vs 11.7 points, peak flow rate 17.7 vs 17.4 ml/s; not significant). However, when typical BPH trial conditions were applied and only those patients considered for analyses who had an I-PSS score above (>7, >10, >15) and a flow rate below a certain threshold (<15, <12, <10 ml/s), a unilateral regression to the mean took place, by which the ‘more’ symptomatic volunteers (i.e. patients) experienced still considerable natural variability on the occasion of the second assessment, but the net effect was towards ‘improvement’, i.e. lower scores and higher flow rates. For example, when only considering patients with I-PSS scores >10 points, the mean difference between first and second assessment was between 19.9 and 18.9 points or –1.1 (p < 0.05). Similarly, when only patients with a peak flow rate <12 ml/s were considered, the mean difference between the first and second assessments was 9.3 vs 10.9 ml/s or +1.6 ml/s (p < 0.01) (Tables 2.2 and 2.3). This experiment clearly illustrates that a unilateral regression to the mean induced and controlled by the stringency of the inclusion criteria can result in a significant ‘improvement’ in any parameter for which a threshold is set at the baseline screening. Such purely mathematical effect is probably at work in many if not all studies where the outcome parameters are measured using a numerical scale of some sort, and where baseline screening criteria are applied.

This effect, however, is by definition not at work in a longitudinal natural history study where no baseline inclusion criteria are applied, but rather all patients independent of the numerical value of the measured parameter are followed.

**Natural history of BPH**

The most informative natural history study to date is the Olmsted County study of urinary symptoms and health status among men, which has given us much information about prevalence and severity of urinary symptoms, bother, worry,
and embarrassment, quality of life due to symptoms, and the relationship between symptoms and other parameters such as flow rates, prostate volume, and prostate-specific antigen (PSA).33–41

With continued follow-up of this cohort, data have emerged regarding the longitudinal changes in symptoms and flow rate over time in this population-based study. Of 904 men reporting none to mild symptoms (AUASI 0–7 points) at baseline, 118 reported moderate to severe symptoms (AUASI > 7 points) at 18 months’, and 196 at 42 months’ follow-up.42 However, 47 men who had developed moderate to severe symptoms at 18 months, had none to mild symptoms at 42 months. At 42 months of follow-up an average increase in the I-PSS of 0.18 (95% confidence interval 0.13 to 0.24) points per year of follow-up was recorded. The average annual symptom

### TABLE 2.2

<table>
<thead>
<tr>
<th>Selection</th>
<th>Mean ± SD</th>
<th>Range</th>
<th>Mean difference 95% CI</th>
<th>t-Test</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>12.1 ± 8.8</td>
<td>0–32</td>
<td>-0.39</td>
<td></td>
<td>145</td>
</tr>
<tr>
<td></td>
<td>11.7 ± 9.0</td>
<td>0–32</td>
<td>-1.1 to 0.29</td>
<td>0.133</td>
<td>145</td>
</tr>
<tr>
<td>&gt; 7 at 1</td>
<td>17.8 ± 6.5</td>
<td>9 – 32</td>
<td>-0.97</td>
<td></td>
<td>88</td>
</tr>
<tr>
<td></td>
<td>16.8 ± 7.7</td>
<td>0–32</td>
<td>-2.0 to 0.08</td>
<td>0.035*</td>
<td>88</td>
</tr>
<tr>
<td>&gt; 10 at 1</td>
<td>19.9 ± 5.6</td>
<td>11–32</td>
<td>-1.1</td>
<td></td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>18.9 ± 6.9</td>
<td>0–32</td>
<td>-2.2 to 0.1</td>
<td>0.036*</td>
<td>70</td>
</tr>
<tr>
<td>&gt; 15 at 1</td>
<td>22.0 ± 4.6</td>
<td>16–32</td>
<td>-1.4</td>
<td></td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>20.6 ± 6.6</td>
<td>0–32</td>
<td>-2.8 to 0.01</td>
<td>0.026*</td>
<td>54</td>
</tr>
</tbody>
</table>

*p < 0.05.

### TABLE 2.3

<table>
<thead>
<tr>
<th>Selection</th>
<th>Mean ± SD</th>
<th>Range</th>
<th>Mean difference 95% CI</th>
<th>t-Test</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>17.7 ± 8.2</td>
<td>5.1–47.5</td>
<td>-0.18</td>
<td></td>
<td>145</td>
</tr>
<tr>
<td></td>
<td>17.4 ± 8.4</td>
<td>4.7–61.0</td>
<td>-1.2 to 0.82</td>
<td>0.36</td>
<td>145</td>
</tr>
<tr>
<td>&lt; 15 at 1</td>
<td>10.7 ± 2.5</td>
<td>5.1–14.6</td>
<td>1.5</td>
<td></td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>12.2 ± 4.6</td>
<td>4.7–25.5</td>
<td>0.47 to 2.6</td>
<td>0.002*</td>
<td>65</td>
</tr>
<tr>
<td>&lt; 12 at 1</td>
<td>9.3 ± 2.1</td>
<td>5.1–11.8</td>
<td>1.6</td>
<td></td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>10.9 ± 4.8</td>
<td>4.7–25.5</td>
<td>0.06 to 3.1</td>
<td>0.021*</td>
<td>40</td>
</tr>
<tr>
<td>&lt; 10 at 1</td>
<td>7.3 ± 1.6</td>
<td>5.1–9.9</td>
<td>1.7</td>
<td></td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>9.0 ± 3.7</td>
<td>4.7–17.4</td>
<td>0.4 to 3.8</td>
<td>0.05*</td>
<td>17</td>
</tr>
</tbody>
</table>

*p < 0.05.
score slope and variability in slope increased with patient age at baseline from a mean of 0.05 ± 1.06 (standard deviation) per year among men in their forties to 0.44 ± 1.35 per year for men in their sixties, and decreased to 0.14 ± 1.42 per year for men in their seventies.43 More recently, 92 months’ data showed an annual change of 0.34 points/year, with 31% of all men reporting at least a 3-point increase. The greatest annualized increase was observed in men in their sixties with 0.6 points/year.44

In addition, 6-year follow-up data on peak flow rate measurements in a subset of about 500 men showed a median peak urinary flow rate slope decrease of –2.1% per year (25th centile –4.0, 75th centile –0.6). Peak urinary flow rate declined more rapidly with decreasing baseline rate, and increasing baseline age, prostate volume, and symptom severity (all \( p = 0.001 \)). When the variables were simultaneously adjusted for each other, a rapid decline (negative slope 4.5% or greater per year) was more likely in men 70 years old or older and in those with a rate less than 10 ml/s at baseline compared to those 40 to 49 years old and those with a rate of 15 ml/s or greater, respectively. Prostate volume and symptom severity were not statistically significant predictors of a rapid decline in peak urinary flow rate when variables were considered simultaneously.45

Based on transrectal ultrasonography (TRUS), the growth of the prostate in the men aged 40–79 years was estimated to be about 0.6 ml per year or 6 ml per decade of life. However, prostate growth followed an exponential growth pattern, with a slope estimate of 0.4 ml per year for men aged 40–59 years at baseline and of 1.2 ml per year for those aged 60–79 years at baseline.46 An updated analysis revealed a median growth rate of about 1.9%/year independent of age and symptoms. However, a higher baseline serum PSA and larger prostate volume predicted greater annualized volume increases (Figure 2.2).47

Diokno et al.48 provided estimates of the prevalence, incidence, and remission of lower urinary tract symptoms in 803 community-dwelling men aged 60 years or older. The annual incidence of prostate surgery was 2.6% and 3.3% during years 1 and 2 of follow-up. The prevalence of at least one symptom was 35%, with annual incidence rates during years 1 and 2 of follow-up being 16.4% and 16.1%. Remission was also noted in that 22.9% of those having severe symptoms at baseline were asymptomatic at follow-up. Table 2.4 details the changes in symptom severity from one survey to the next. The tendency for fluctuation and spontaneous remission of symptoms as well as the regression to the mean become evident from an analysis of these data.

**Watchful waiting studies**

In the absence of other longitudinal natural history studies, several watchful waiting studies are available for review. Most of these studies have significant shortcomings. Inclusion and exclusion criteria are poorly defined, follow-up is loose, assessment instruments are either not defined or insufficient, and patient accounting is incomplete.

Five such studies, reported between 1919 and 1988 and totaling 456 patients with follow-up ranging from 3 to 6 years,49–53 were analyzed for the AHCPR BPH Guidelines.54 A change in symptom status was reported for all 456 patients, while none of the studies utilized a quantitative symptom severity scale. Data on urinary flow rate and residual urine were available for 223 and 197 patients, respectively. The peak urinary flow rate deteriorated in 66% and improved in 20%. Residual urine increased (35%), decreased (37%),
and remained unchanged (28%) in about the same number of all patients. The mean change in peak flow rate (in those patients for whom data are available) was 2.2 (from a mean of 9.0 to 11.2) ml/s or 24%, while the mean change in residual urine was +37 (from a mean of 115 to 152) ml or 32%. The data on symptom improvement were dichotomized (improved versus not improved). The probability for symptom improvement was then calculated using the confidence profile method (CPM) described by David Eddy55 (Figure 2.3). The mean probability for improvement in symptom severity was estimated to be 42.5% (90% CI 30.8 to 54.8), surprisingly similar to the probability for improvement noted in the placebo arms, and in a carefully designed, prospective study to be discussed below. It must, however, be recognized that, because of limitations of the dataset, the magnitude of the improvement cannot be estimated. In updated

![Figure 2.2](image-url)
guidelines for the management of BPH, published by the AUA, watchful waiting is recommended for patients with mild symptoms (AUA symptom score ≤ 7) or moderate to severe BPH in patients who are not bothered by their symptoms. Watchful waiting is therefore an appropriate early treatment strategy for most men with BPH.

A randomized study with a 3-year follow-up was reported comparing watchful waiting with TURP in 556 men with symptoms of BPH. Inclusion criteria included a Madsen–Iversen symptom score between 10 and 20 points (0–27 point scale), thus limiting the informational value of the watchful waiting arm of the study to patients with moderate lower urinary tract symptoms. There were 47 treatment failures (defined as death, recurrent infection, residual urine volume over 350 ml, development of bladder calculus, incontinence, a symptom score of 24 or higher, or a doubling of serum creatinine from baseline) in the watchful waiting arm (n = 276) versus 23 in the surgery arm (n = 280) over 3 years of follow-up (relative risk 0.48; 95% CI 0.3–0.77). Sixty-five (24%) men assigned to watchful waiting underwent surgery during follow-up, 20 of them for treatment failure. The majority of these men were classified as more bothered at baseline (Figure 2.4). It should be noted that about 40% of patients in this category experienced improvement in the degree of bother from urinary difficulties (Figure 2.4). The changes from baseline for the watchful waiting patients are shown in

**TABLE 2.4** Changes in status of obstruction severity from one survey to the next (adapted from reference 48). Patients who underwent prostatectomy in the preceding year were excluded from the next survey.

<table>
<thead>
<tr>
<th>Severity</th>
<th>Year</th>
<th>No</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Baseline</td>
<td>293</td>
<td>83.6</td>
<td>12.3</td>
<td>2.7</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>Year 1</td>
<td>223</td>
<td>83.9</td>
<td>9.0</td>
<td>2.2</td>
<td>4.9</td>
</tr>
<tr>
<td>Mild</td>
<td>Baseline</td>
<td>88</td>
<td>18.2</td>
<td>55.7</td>
<td>11.4</td>
<td>14.8</td>
</tr>
<tr>
<td></td>
<td>Year 1</td>
<td>84</td>
<td>33.3</td>
<td>52.4</td>
<td>8.3</td>
<td>6.0</td>
</tr>
<tr>
<td>Moderate</td>
<td>Baseline</td>
<td>38</td>
<td>7.9</td>
<td>31.6</td>
<td>26.3</td>
<td>34.2</td>
</tr>
<tr>
<td></td>
<td>Year 1</td>
<td>27</td>
<td>3.7</td>
<td>33.3</td>
<td>22.2</td>
<td>40.7</td>
</tr>
<tr>
<td>Severe</td>
<td>Baseline</td>
<td>35</td>
<td>22.9</td>
<td>17.1</td>
<td>11.4</td>
<td>48.6</td>
</tr>
<tr>
<td></td>
<td>Year 1</td>
<td>31</td>
<td>9.7</td>
<td>22.6</td>
<td>12.9</td>
<td>54.8</td>
</tr>
</tbody>
</table>
Table 2.5. It should be noted that the mean changes represented in almost all categories an improvement for those men who were followed in the assigned treatment arm (watchful waiting) over 3 years. The magnitude of the improvement, however, was less than that realized by surgery in almost all categories (\( p \) values in Table 2.5).

Furthermore, this analysis obviously excludes those men who were categorized as treatment failures, underwent surgery (cross-over), or were lost to follow-up.

Placebo arms of controlled medical treatment trials for BPH

For the AHCPR BPH guidelines, data on 1417 patients treated in 45 placebo arms of placebo-controlled trials were analyzed. Table 2.6 and Figure 2.3 allow a direct comparison between the watchful waiting and the placebo studies. A significant difference between the two treatment modalities cannot be identified for any of the

Table 2.5

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Baseline*</th>
<th>Follow-up**</th>
<th>Mean change ± SD</th>
<th>( p ) Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom Score (0–27)</td>
<td>14.6</td>
<td>9.1</td>
<td>–5.5 ± 5.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Residual urine (ml)</td>
<td>113</td>
<td>72</td>
<td>–41 ± 90</td>
<td>0.015</td>
</tr>
<tr>
<td>Peak flow rate (ml/s)</td>
<td>12.5</td>
<td>12.7</td>
<td>0.4 ± 9.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Bother from urinary difficulties‡</td>
<td>46.3</td>
<td>57.6</td>
<td>9.6 ± 29.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sexual performance‡</td>
<td>42.5</td>
<td>35.6</td>
<td>–3.2 ± 26.6</td>
<td>0.92</td>
</tr>
<tr>
<td>Activities of daily living‡</td>
<td>69.0</td>
<td>75.6</td>
<td>6.4 ± 30.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>General well-being‡</td>
<td>71.2</td>
<td>71.4</td>
<td>0.1 ± 28.3</td>
<td>0.217</td>
</tr>
<tr>
<td>Social activities‡</td>
<td>74.2</td>
<td>73.1</td>
<td>–1.7 ± 23.5</td>
<td>0.945</td>
</tr>
</tbody>
</table>

*\( n = 276 \); **only patients who were followed over 3 years excluding cross-overs, failures etc.; †for difference between treatment groups (surgery versus watchful waiting); ‡on a scale from 0 (greatest impairment) to 100 (least impairment).
examined parameters. However, several points deserve discussion. As opposed to the long-term follow-up in the watchful waiting studies, the placebo studies are part of short- to mid-term medical treatment trials ranging from 3 days to 52 weeks in duration (mean 13 weeks). In all these studies the patients are blinded as to the treatment arm, and thus have in most cases at least a 50 : 50 (or better in case of 2 : 1 or 3 : 1 randomization) chance of receiving active drug. Dropping out of such studies because of failure does not have the same ramification as it does in watchful waiting studies where the patients willingly assume a conservative treatment approach knowing that it might fail (i.e. they might fail and go on to active treatments). In contrast, in some placebo-controlled studies a promise—either tacit or openly—is made stating that following the conclusion of the trial the patient would be eligible for either ‘free’ active treatment or he would be ‘moved up’ on the surgical waiting list (this phenomenon is unique to those studies conducted in the UK). The inactive preparation given should theoretically add to the placebo effect and, thus, improve the outcome above those noted for watchful waiting studies. The probability for a patient to experience improvement, however, is estimated to be about 40% in the uncontrolled

### Table 2.6 Comparison of outcomes following watchful waiting and placebo treatment. (Adapted from reference 54.)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Watchful waiting</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients in database</td>
<td>456</td>
<td>1417</td>
</tr>
<tr>
<td>Peak flow rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probability for flow rate increase</td>
<td>19.7%</td>
<td>35.8%</td>
</tr>
<tr>
<td>Probability for no change in flow rate</td>
<td>14.2%</td>
<td>41.1%</td>
</tr>
<tr>
<td>Probability for flow rate decrease</td>
<td>66.1%</td>
<td>23.1%</td>
</tr>
<tr>
<td>Mean pretreatment flow rate (ml/s)</td>
<td>9.0</td>
<td>9.1</td>
</tr>
<tr>
<td>Mean posttreatment flow rate (ml/s)</td>
<td>11.2</td>
<td>9.7</td>
</tr>
<tr>
<td>Difference (ml/s)</td>
<td>+2.2</td>
<td>+0.6</td>
</tr>
<tr>
<td>Per cent change in peak flow rate</td>
<td>+24.4%</td>
<td>+6.6%</td>
</tr>
<tr>
<td>Residual urine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probability for decrease in residual urine</td>
<td>35.0%</td>
<td>38.0%</td>
</tr>
<tr>
<td>Probability for residual urine to remain unchanged</td>
<td>28.0%</td>
<td>26.1%</td>
</tr>
<tr>
<td>Probability for increase in residual urine</td>
<td>37.0%</td>
<td>35.9%</td>
</tr>
<tr>
<td>Mean pretreatment residual urine (ml)</td>
<td>115</td>
<td>87</td>
</tr>
<tr>
<td>Mean posttreatment residual urine (ml)</td>
<td>152</td>
<td>76</td>
</tr>
<tr>
<td>Difference (ml)</td>
<td>+37</td>
<td>−11</td>
</tr>
<tr>
<td>Per cent change in residual urine</td>
<td>+32.2%</td>
<td>−12.6%</td>
</tr>
<tr>
<td>Symptom improvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probability for symptom improvement</td>
<td>41.7%</td>
<td>41.7%</td>
</tr>
<tr>
<td>Probability for symptoms to remain unchanged</td>
<td>25.8%</td>
<td>53.5%</td>
</tr>
<tr>
<td>Probability for symptom worsening</td>
<td>32.4%</td>
<td>4.7%</td>
</tr>
<tr>
<td>Mean probability for symptom improvement*</td>
<td>41.7%</td>
<td>41.7%</td>
</tr>
<tr>
<td>90% Confidence interval for symptom improvement*</td>
<td>30.8 to 54.8%</td>
<td>26.3 to 65.1%</td>
</tr>
</tbody>
</table>

* Calculated by confidence profile method using hierarchical Bayes.55
watchful waiting studies, the randomized watchful waiting versus TURP study, and the combined placebo arms. The changes in peak flow rate and residual urine are similar, and similarly small, for these three groups as well (see Tables 2.5 and 2.6). Figure 2.5 shows a comparison of the percentage changes in peak flow rate and residual urine as well as the percentage of patients experiencing symptom improvement between various treatment modalities. It becomes evident that a 40% rate of patients reporting improvement and the minimal fluctuation of peak flow rate and residual urine represent the ‘placebo effect’ background against which the more substantial changes in these parameters achieved by active treatment modalities must be seen.

With the advent of symptom severity assessment tools or symptom scores it is possible to quantitatively describe the response of patients treated by a variety of treatment interventions including placebo and watchful waiting (see Chapter 1). Unfortunately, the different symptom-scoring instruments differ regarding their foot points (0 or different from 0), their scale, and occasionally even their direction (increasing or decreasing severity of symptoms with increasing score). While currently the AUASI or International Prostate Symptom Score (I–PSS), with its scale from 0 to 35 points, is the most widely utilized instrument, thus facilitating direct comparisons between studies, in the years past different scores with different scales were used. The only way to compare symptom improvement in different trials quantitatively in such cases is to rescale the individual scales to a 100% scale, and to express the changes as the drop in percentage symptom score from before to after treatment. Using this technique, seven placebo-
controlled trials were reanalyzed and compared to the most significant watchful waiting study (Figure 2.6). These seven trials enrolled between 11 and 267 subjects per arm, lasted from 4 to 24 weeks, and utilized an injectable steroid hormone (norprogesterone)\(^\text{64}\), a prolactin inhibitor (bromocriptine)\(^\text{65}\), an \(H_2\) blocker (cimetidine)\(^\text{66}\), an \(\alpha\)-blocker (alfuzosin)\(^\text{67}\), or candicin\(^\text{68–70}\) as the ‘active’ drug. Each study is represented by its active and the placebo arm side by side. Several points are noteworthy. The pretreatment symptom severity score expressed as percentage of achievable score on a 100% scale ranges from 35% to almost 60%, and the drop in symptom severity from 7% to 33% for the placebo arms. Moreover, the pre- to posttreatment symptom score range does not even overlap between some of the trials listed, indicating that vastly different patient populations were treated. Specifically addressing the three placebo-controlled, double-blinded trials using candicin as the active drug, the drops in symptom score were 9, 15, and 33% (placebo), and 6, 26, and 22% (candicin). With the exception of the bromocriptine trial, the baseline symptom severity was reasonably similar between the placebo and the active treatment arm, and in all such cases the placebo response closely matched the active drug response.

These observations allow several conclusions:

- There is a strong placebo response noted in medical treatment trials for BPH when quantitative symptom severity scores are used.
- The placebo response in medical treatment trials for BPH depends largely on the pre-treatment characteristics of the treated cohort.

**FIGURE 2.6** Improvements noted using a quantitative symptom score in seven placebo-controlled trials and a watchful waiting study. Due to the different scales used, all scores were rescaled to a 100% scale and the reported changes expressed as mean pretreatment and mean posttreatment per cent symptom score. The number above the vertical bar indicates the change noted following treatment (expressed as per cent).
• Even when the baseline symptom severity is similar between two trials (A and B), the response of the placebo group in trial A matches more closely its actively treated cohort than the placebo group in trial B.
• The latter fact indicates that factors other than the active drug or placebo are most responsible for the placebo effect.

These factors may include patient selection criteria (solicitation, advertising), design and duration of study, incentives offered to patients (financial or otherwise), conduct and attitude of treating physician or research coordinator (sympathetic versus unsympathetic, friendly versus unfriendly, positive versus negative), and other unrecognized factors. In fact, given the parallel changes in both treatment groups in most trials, the latter factors, which are provider factors, are more likely to be responsible than the previously mentioned patient factors.

It could be reasoned that placebo-treated patients enrolled with similar inclusion and exclusion criteria into clinical trials using the same class of active drugs might have a similar placebo response. A comparison of three \( \alpha_1 \)-receptor-blocker trials allows this hypothesis to be tested. Eighty-two patients were treated with doxazosin versus placebo over 16 weeks,\(^7\) 2064 patients with terazosin versus placebo over 52 weeks,\(^72\) and 296 patients with tamsulosin versus placebo over 12 weeks.\(^73\) In all three trials a different symptom score was used. In the doxazosin trial, the scale ranged from 0 to 30 points, in the terazosin trials from 0 to 35 points (AUASI), and in the tamsulosin trial from 0 to 27 (Boyarsky score). In Figure 2.7 all scores are rescaled to a 100% scale and the pre- and posttreatment mean scores are expressed as a percentage of the 100% scale. Although the pretreatment symptom severity is different in the three trials, the placebo

![FIGURE 2.7 Pre- and posttreatment mean symptom scores (upper and lower tickmark of vertical bar, respectively) rescaled to 100% for active-drug- and placebo-treated cohorts in three randomized \( \alpha \)-blocker trials (for details see text). The number at the bottom of the graph represents the per cent improvement achieved.](image-url)
responses are very similar, ranging from 8.1 to 10.6% on the 100% scale, roughly half of the active drug cohort in each trial.

Improvements in peak urinary flow rates are also similar between these three drug trials, ranging from 0.4 to 0.8 ml/s in the three placebo groups, despite the fact that the baseline mean peak flow rates are rather different (Figure 2.8). It should be noted that this improvement in peak flow rate is very similar to the mean changes noted in the combined placebo arm analysis of the AHCPR guidelines (0.6 ml/s) and the watchful waiting study (0.4 ml/s) by Wasson et al. The percentage improvement calculated for the combined placebo arms (6.6%) falls also in the range of improvements seen in these three α-blocker trials (3.8 to 8.3%).

Sham arms of controlled-device treatment trials for BPH

In recent years a multitude of minimally invasive device treatments for BPH have been developed and tested in randomized, sham-controlled, open, single-, or even double-blinded trials. While the majority of these trials compare various types of heat treatments (transrectal or transurethral hyperthermia or thermotherapy) with a sham treatment, one investigator compared balloon dilatation with ‘sham’ cystoscopy alone in a randomized, double-blinded trial involving 33 men with BPH. Blinding of the patients was effective in that an equal number of patients in each arm thought they had undergone balloon dilatation. After 3 months, 40% of balloon dilated patients noted marked improvement, while 27% noted no change. After cystoscopy, 63% had marked improvement and 12% no change. The changes in symptom score were significant at 3 months in both groups, while the peak urinary flow rate changes were not significant from baseline in either group (Table 2.7). Most importantly, there was no difference in the symptom score or peak flow rate data at 3 months between the ‘active’ and the ‘sham’ treatment. This study is widely used to support the notion that balloon dilatation has no role in the treatment of BPH, and is not better than placebo/sham treatment.

Figures 2.9 and 2.10 analyze the outcomes of the balloon dilatation versus cystoscopy trial, one multicenter trial using transrectal or transurethral hyperthermia in comparison with a sham control, and five transurethral microwave thermotherapy (TUMT) trials and their respective sham-control arms. The following observations can be made. The baseline or pretreatment mean symptom severity expressed as a percentage of total achievable severity (rescaled to 100%) is different from trial to trial. The mean improvements in symptom severity in the sham groups ranged from 5.2 to 15.6% (on a 100% scale), while the active thermotherapy-treated patients had improvements ranging from 27.0 to 37.8%, or in most cases twice the improvement compared to the sham control. The multicenter hyperthermia trial represents the exception, in that the actively treated cohort has an improvement similar to the sham control, which is well within the range of the other sham control trials. The changes in peak urinary flow rate follow a similar pattern (Figure 2.10). With the exception of TUMT trials 2 and 4, the changes in peak flow rate are either very modest improvements or deteriorations (0.5, 0.6, –0.2, –1.0 ml/s), while the active-treatment arms report substantial improvements, with the exception of the hyperthermia trial. The changes noted in the sham arms (and the largely ineffective hyperthermia treatment arm) are very similar to those observed after α-blocker therapy (see Figures 2.7 and 2.8). Both thermotherapy trial 5 and the terazosin trial
have similar entry criteria and baseline mean symptom severity. The improvements noted in the placebo and sham arms were 3.3 points (10.6%) and 2.6 points (6.4%), respectively, while in the active-treatment arms the improvements were 7.6 points (21.7%) and 12.1 points (34.6%), respectively.

**Placebo/sham effect and baseline symptom severity**

An area of considerable interest is the question to what degree the placebo/sham effect depends on the baseline status of the patients. This could pertain to baseline symptom severity, baseline bother,
quality of life, baseline flow rate, and all other imaginable parameters. Although very few investigators have thus far reported data stratified by baseline parameters, results from a multicenter, placebo-controlled, 12-month \(\alpha\)-blocker trial (terazosin) can be analyzed. Figure 2.11 shows the absolute and percentage improvement in AUA symptom score for the placebo- and drug-treated patients stratified in six strata by symptom severity. While the active drug-treated cohort has almost twice the improvement within each stratum, the placebo-treated patients had improvements ranging from 1.4 points (4.6%) to 7.5 points (21.4%). The placebo improvements for the entire placebo cohort were 3.3 points (10.6%).

A similar increase in the placebo effect with increasing baseline symptom severity has been reported for patients treated with finasteride in the phase III trials. It might be speculated that the baseline symptom severity may also affect the sham effect seen in device trials. This phenomenon might be due to increased expectations in patients with more severe baseline symptoms, or simply due to a regression to the mean.

**Natural history of disease progression in long-term placebo arms**

The distinction between placebo response in controlled studies versus the natural history of the disease itself observed in population-based studies becomes blurred when the placebo control is carried out over a period of time long enough to allow natural history changes to take place and

---

**FIGURE 2.9** Pre- and posttreatment (3 months) mean symptom scores (upper and lower tickmark of vertical bar) rescaled to 100% for active-treated and sham-treated patients in a multicenter hyperthermia trial, five transurethral microwave thermotherapy (TUMT) trials, and a balloon dilatation versus cystoscopy trial. The improvement in per cent is noted above the horizontal tickmark.
confound the situation. The Proscar Long Term Efficacy and Safety Study (PLESS) followed a cohort of over 3000 men with moderate symptoms and enlarged prostate glands randomized to treatment with finasteride 5 mg daily versus placebo over 4 years.\(^{82,83}\) While in most placebo arms of controlled trials lasting 12 months or less the combined placebo effect is maintained for the entire duration of the study, in this trial, both the mean symptom score and peak flow rate slowly drifted back to baseline after a typical initial placebo response, without quite reaching baseline levels, however.\(^{83}\)

The almost 1500 men in the placebo arm of this trial allowed for a detailed analysis of the placebo response and the subsequent natural history stratified by baseline parameters. By far the most powerful of these parameters proved to be unexpectedly the baseline serum PSA level. When stratifying the population by serum PSA into tertiles or thirds of patients with PSA levels from 0–1.3, 1.4–3.2, and 3.3–10 ng/ml, three distinctly different patterns emerged (Figure 2.12).\(^{82}\) While the initial placebo response in the lowest PSA tertile for both symptom and flow rate was maintained over the entire 4 years of follow-up, the middle tertile experienced a slow deterioration of symptoms back to baseline and in essence the natural history and progression of disease eliminated any flow rate gains. In the highest PSA tertile the symptom score increased steadily over time following an initial placebo response by –1.5 points. Over the subsequent years, the score increased by 0.5 points/year, bringing it at the end

![FIGURE 2.10](image-url)

**FIGURE 2.10** Pre- and posttreatment (3 months) mean peak urinary flow rates (lower and upper tickmark of vertical bar) for active-treated and sham-treated patients in a multicenter hyperthermia trial, five transurethral microwave thermotherapy (TUMT) trials, and a balloon dilatation versus cystoscopy trial. The changes in per cent are noted below the horizontal tickmark and the absolute improvement (deterioration) at the bottom of the graph.
of the study back to the original baseline level. The initial response in terms of flow rate improvement was completely negated by the progression/natural history after 2 years, and at the end of the study, this group of patients registered a net worsening of the flow rate by a mean of −1.0 ml/s (Figure 2.12b).

For the first time, the PLESS study and its placebo control group allowed the study of natural history and disease progression in a cohort selected for moderate symptoms and other evidence of disease (in contrast to a population-based study) on the background of the initial combined placebo responses.

**Relationship between placebo/sham effect and perception of improvement**

Barry et al. reported an important observation by assessing the relationship between changes in the AUASI and patients’ global rating of improvement in over 1200 men treated in a medical treatment trial for RPH. They noted that a mean decrease in AUASI of 3.1 points was associated with a slight improvement; however, this relationship was strictly dependent on the baseline AUASI (Figure 2.13). For patients to perceive a slight, moderate, or marked improvement, increasing drops in AUASI were required with increasing baseline symptom severity. In Figure 2.13 this relationship is illustrated graphically for slight, moderate, and marked improvement. The symbols indicate the improvement in AUASI noted in the already-mentioned α-blocker trial active-drug and placebo arms. It is evident, that for every symptom severity stratum, the improvement in the placebo arm fell roughly on the ‘slight’ improvement line, which is the minimum improvement noticeable to patients. Thus, for...
each baseline symptom severity level, patients treated with placebo would have a noticeable symptom improvement. However, the patients treated with active drug experienced in all strata analyzed at least a ‘moderate’ improvement.

**SUMMARY AND CONCLUSIONS**

The data discussed demonstrate rather convincingly that in both medical and minimally invasive-device treatment trials for BPH, a placebo/sham effect must be expected, in addition to a regression to the mean effect, the magnitude of which depends on the chosen thresholds for inclusion and exclusion (i.e. the more restrictive, the greater the effect). The combined regression to the mean and placebo/sham effect is surprisingly stable across different trials and different treatment modalities. About 40% of patients experience some unspecified degree of improvement, albeit marginal, in watchful waiting and placebo/sham control cohorts. Improvements in symptom severity scores range from 5 to 15%
THE PLACEBO EFFECT IN THE TREATMENT OF BENIGN PROSTATIC HYPERPLASIA

(about 2 to 5 points using the AUASI ranging from 0 to 35 points) for placebo/sham-treated cohorts, while changes in peak urinary flow rate are in general more modest, ranging from actual deterioration to improvements of 1.0 ml/s with few exceptions. The magnitude of this effect is similar to that seen in watchful waiting studies. Of great importance is the observation that the magnitude of the improvement correlates directly with the baseline symptom severity. Patients’ perception of improvement also correlates with baseline symptom severity and, in general, a larger drop in symptom score is associated with a global rating of a slight, moderate, or marked improvement with increasing baseline symptom score. In the limited datasets available the placebo effect for each symptom severity stratum is of a magnitude associated with a global perception of slight improvement.

The statement that treatment for BPH is associated with a ‘40% placebo/sham effect’ is clearly an inadequate oversimplification. More detailed and sophisticated analyses of responses in placebo/sham-treated cohorts of men with BPH are needed to further our understanding of the complex relationship between patients’ expectations, baseline symptom severity, bother, quality of life, nature and invasiveness of the active treatment arm, and the responses noted in regards to symptom, bother, quality of life, and indirect outcomes such as urinary flow rates. Only once a matrix of these responses and their predictors has been established will we be able to judge newly developed treatments for BPH against the backdrop of their associated placebo/sham effects.

FIGURE 2.13 Relationship between baseline (x-axis) symptom score and absolute changes in scores for subjects rating global improvement as slight, moderate, or marked (adapted from reference 85). The symbols indicate the absolute drops in symptom scores from baseline for patients treated in a placebo-controlled, 12-month α-blocker treatment trial stratified in six strata by baseline symptom severity (placebo = triangle; α-blocker = circle).
REFERENCES

1. Shaw P. The reflector: representing human affairs, as they are; and may be improved. 1750. Cited in: Drugs and Human Behavior. London: 1970
34. Guess H A, Chute C G, Garraway W M et al. Similar levels of urological symptoms have similar impact on Scottish and American men—although Scots report less symptoms. J Urol 1993; 150: 1701–1705


49. Clarke R. The prostate and the endocrines. 1919: 254–271


68. Abrams P H. A double-blind trial of the effects of candicidin on patients with benign prostatic hyper- 

69. Jensen KM, Madsen PO. Candicidin treatment of prostatism: a prospective double-blind placebo- 


hyperplasia in patients with mild to moderate essential hypertension: a double-blind, placebo- 

72. Roehrborn C G, Oesterling J E, Auerbach S et al. The Hytrin Community Assessment Trial study: a 
one-year study of terazosin versus placebo in the treatment of men with symptomatic benign prosta-

73. Abrams P, Schulman C C, Vaage S. Tamsulosin, a 
selective alpha 1c-adrenoceptor antagonist: a ran-
domized, controlled trial in patients with benign prostatic ‘obstruction’ (symptomatic BPH). The 

74. Lepor H, Sypherd D, Machi G et al. Randomized double-blind study comparing the effectiveness of 
balloon dilation of the prostate and cystoscopy for the treatment of symptomatic benign prostatic 

75. Abbou C C, Colombel M, Payan C et al. The effi-
cacity of microwave induced hyperthermia in the 
treatment of BPH: The Paris Public Hospitals’ 
experience. In: Kurth K H, Newling D W W (eds). Benign prostatic hyperplasia. Recent progress in 
clinical research and practice. New York: Wiley- 
Liss, 1994: 449–454

76. Ogden C W, Reddy P, Johnson H et al. Sham ver-
sus transurethral microwave thermotherapy in 
patients with symptoms of benign prostatic bladder 
outflow obstruction. Lancet 1993; 341: 14–17

77. Blute M L, Tomera K M, Hellerstein D K et al. Transurethral microwave thermotherapy for man-
gement of benign prostatic hyperplasia: results of the United States Prostatron Cooperative Study 
[see comments]. J Urol 1993; 150: 1591–1596

78. de la Rosette J J, de Wildt M J, Alivizatos G et al. Transurethral microwave thermotherapy (TUMT) 
in benign prostatic hyperplasia: placebo versus 
TUMT. Urology 1994; 44: 58–63

79. Bdesha A S, Bunce C J, Snell M E et al. A sham 
controlled trial of transurethral microwave therapy 
with subsequent treatment of the control group. J 
Urol 1994; 152: 453–458

80. Roehrborn CG, Oesterling JE, Auerbach S et al. 
Effectiveness and safety of terazosin versus placebo 
in the treatment of men with symptomatic benign 
prostatic hyperplasia in the HYCAT study. 
Urology 1996; 47: 159–168

81. Gormley G J, Stoner E, Bruskewitz R C et al. The 
effect of finasteride in men with benign prostatic 

82. Roehrborn C G, Boyle P, Bergner D et al. Serum 
prostate-specific antigen and prostate volume pre-
dict long-term changes in symptoms and flow rate: 
results of a four-year, randomized trial comparing 
finasteride versus placebo. PLESS Study Group. 
Urology 1999; 54: 662–669

83. McConnell J D, Bruskewitz R, Walsh P et al. The 
effect of finasteride on the risk of acute urinary 
retention and the need for surgical treatment 
among men with benign prostatic hyperplasia. 
Finasteride Long-Term Efficacy and Safety Study 

prostatic hyperplasia specific health status meas-
ures in clinical research: how much change in the 
American Urological Association symptom index 
and the benign prostatic hyperplasia impact index 
is perceptible to patients? [see comments]. J Urol 
1995; 154: 1770–1774

85. Barry M J, Williford W O, Chang Y C et al. BPH-
specific health status measures in clinical research: 
how much change in AUA symptom index and the 
BPH impact index is perceptible to patients? J Urol 
1995; 154: 1770–1774
INTRODUCTION

Benign prostatic hyperplasia (BPH) and the lower urinary tract symptoms (LUTS) associated with the condition are becoming increasingly prevalent as the Western male population ages and healthcare provision worldwide improves. The need for new and improved treatments for the condition is therefore ongoing and likely to increase.

BPH develops due to a combination of testicular androgens and aging. The main androgen present in the prostate is dihydrotestosterone (DHT). The role of DHT and the enzyme responsible for its reduction, 5α-reductase, in the development of BPH has long been established, and the clinical potential of inhibitors of the enzyme has been proven.

Limitations of inhibitors with a selective action on one of the isoforms of 5α-reductase have been described, however. Inhibition of both 5α-reductase isozymes has therefore been suggested as a means of increasing clinical response in terms of reducing prostate volume and thereby improving urinary symptoms and limiting risk of acute urinary retention (AUR) and BPH-related surgery.

The selective 5α-reductase type II inhibitor finasteride has been available for the treatment of BPH for over 10 years, and this is testament to its efficacy in reducing symptoms of the condition in patients over an extended period of time. However, dual inhibition of 5α-reductase has been predicted to expand and enhance response in both finasteride responders and nonresponders.

DEVELOPMENT OF BPH AND ROLE OF DHT

The prevalence of BPH increases in a linear fashion alongside age. At the age of 40, approximately 23% of men suffer from BPH, while 88% of men in their nineties are thought to have the condition.1 Androgen stimulation is necessary for the initial growth and development of the prostate and for the maintenance of its integrity, as well as the development of the obstructive urinary symptoms associated with BPH.2 Although the mechanisms underlying the development of BPH have not been fully established, testicular androgens, particularly DHT, are recognized as integral to the process. The influence of DHT in initial prostatic development has been determined, with the hormone found to be responsible for the embryonic differentiation of the prostate and the formation of external genitalia in the male.3 Fetal castration results in inhibited formation of the gland,4 and the continued role of testicular androgens in later life is evidenced by the lack of BPH development among men who have undergone castration prior to puberty.5

DHT, which is reduced by 5α-reductase from testosterone (Figure 3.1), has been identified as the predominant androgen contained in the prostate,6 and its permissive if not causative role...
in hyperplastic prostatic growth has been outlined in several studies.6,7

DHT binds to androgen receptors contained within the epithelium of the prostate.6,7 These receptors are upregulated during puberty, leading to increased androgen sensitivity and, although the receptors may also bind testosterone, DHT has much greater affinity, indicating that this hormone is the main driver of subsequent genetic modulation in the prostate.8 Although down-regulation of many androgen receptors occurs after puberty at other sites, this does not occur in the prostatic epithelium. Coupled with the fact that DHT levels remain constant after puberty, when testosterone levels fall, this explains the continued growth-promoting influence of DHT and the DHT–receptor complex in the prostate.

The formation of this complex stimulates the expression of a range of growth factor promoters, such as epidermal growth factor (EGF), basic fibroblast growth factor, keratinocyte growth factor (KGF), and insulin-like growth factor (IGF), leading to cellular proliferation,9,10 and inhibitors, such as transforming growth factor-β (TGF-β), which increases levels of apoptosis.11–13 Homeostasis is therefore achieved by the normally functioning prostate. Increased stimulation by DHT leads to increased expression of growth factor promoters and hyperplastic growth. Removal of the stimulus, through surgical or chemical means, leads to the opposite scenario, with a general move towards increased expression of cell growth inhibitors, such as TGF-β.

A lack of DHT, due to deficiency of the enzyme responsible for its formation from testosterone, i.e. 5α-reductase, has been identified in men with pseudohermaphroditism.14,15 The clinical and pathologic sequelae observed in these individuals provide further evidence of the role of androgens, specifically DHT, in the prostate. Men affected by 5α-reductase deficiency experience normal or partial virilization at puberty, due to the action of testosterone; however, the prostate itself remains underdeveloped, small, and unpalpable on digital rectal examination.

The normal development of the prostate, and its hyperplastic growth during BPH, are therefore predominantly attributed to the reduction of testosterone to DHT by 5α-reductase.

**5α-REDUCTASE**

The increased cell proliferation that takes place during hyperplastic prostatic growth mainly occurs in the stroma of the prostate and a strong

---

**FIGURE 3.1** Reduction of testosterone to dihydrotestosterone by 5α-reductase.
positive association of 5α-reductase activity with stroma and a negative correlation with epithelium has been recently identified.16

Two isoforms of the highly lipophilic enzyme 5α-reductase have been identified to date. These proteins are encoded by different genes, that for type I being located on chromosome 5 and that for type II on chromosome 2.17 The distribution of the 5α-reductase isoforms differs significantly, with type I predominating in the liver, scalp, and skin, with low levels found in the prostate, while type II mainly occurs in the prostate and other genital tissues and is found to a lesser extent elsewhere.2

The 5α-reductase deficiency observed in pseudohermaphroditic men involves type II 5α-reductase alone; type I 5α-reductase deficiency has not been identified to date in humans. In 5α-reductase deficient men, virilization at puberty is accompanied by increased expression of 5α-reductase type I in the skin,18 suggesting that DHT has paracrine effects, and that dual inhibition is necessary for complete control of the hormone. It may also explain why finasteride, which inhibits the action of type II 5α-reductase alone, only succeeds in reducing prostatic DHT by 85–90% and often fails to significantly reduce the urinary symptoms of BPH.19,20

THE NEED FOR A DUAL 5α-REDUCTASE INHIBITOR

The efficacy of the type II 5α-reductase inhibitor, finasteride, has been described in several short- and long-term clinical trials.21–25 Mainly through a reduction in prostate volume, the drug has been shown to significantly reduce risk of AUR and BPH-related surgery and improve urinary symptoms and peak urinary flow ($Q_{\text{max}}$) in both younger and older men, with positive consequences for quality of life scores. Since its launch in 1992, the drug has been used to treat millions of men worldwide, with good reported success in responders.

Stratification of the results of clinical trials has suggested that men with larger prostates are more likely to respond to finasteride therapy than those with smaller glands.20 A meta-analysis of six clinical trials indicated that significantly greater improvements in $Q_{\text{max}}$ and symptom score were experienced by men with prostates larger than 60 ml compared to those with prostates of 20 ml or smaller. The authors concluded that finasteride was most appropriate for men with prostates of 40 ml or greater. Severity of symptoms does not necessarily correlate with prostate volume, however,27 and the effects of a greater reduction in prostate volume than that seen with finasteride have yet to be determined.

It has been suggested that finasteride falls short of initial expectations due to the simultaneous occurrence of BPH with symptoms unrelated to prostatic growth,28 heterogeneity of the disease,29 and the effect of the increase in levels of testosterone as well as the influence of the DHT that continues to circulate despite 5α-reductase type II inhibition, i.e. that originating from type I reduction. Between 20 and 40% of baseline DHT remains in men treated with finasteride.30–32

The exact role of DHT reduced by type I 5α-reductase is not known and the level of entry of this protein to the prostate has not been established. Therefore, even though finasteride successfully reduces levels of DHT in the prostate, it can be postulated that systemic DHT maintains levels high enough to allow continued cell proliferation or negate the normal ongoing apoptosis of prostatic cells. On this basis, obstructive urinary symptoms may therefore persist, particularly in
men with smaller prostates. A dual inhibitor of both 5α-reductase isoforms, producing greater reductions in prostatic and circulating DHT, would reduce this possibility.

Over the last decade, the principle of 5α-reductase inhibition in terms of reducing prostate volume and thereby alleviating symptoms has been shown to have considerable clinical benefit; however, selective inhibition of one isozyme alone may limit the magnitude of the clinical response.

**PRECLINICAL DEVELOPMENT OF DUTASTERIDE**

The assumption that inhibition of both type I and type II 5α-reductase could improve the urinary symptoms of BPH over and above mono-inhibition with finasteride led to the development of the 6-azasteroid molecule 17β-N-(2,5-bis(trifluoromethyl) phenylcarbamoyl)-4-aza-5α-androst-1-en-3-one (dutasteride, Figure 3.2).

A range of dual 5α-reductase inhibitors was developed simultaneously; however, dutasteride was found to have a particularly high affinity for both 5α-reductase isozymes. In vitro, the compound was 60 times more powerful at inhibiting type I 5α-reductase and 10 times more powerful at inhibiting type II 5α-reductase than finasteride. Trials of the drug in humans revealed type I inhibition to be 100-fold higher and type II inhibition 3-fold higher than finasteride.35

Investigation of dutasteride’s mechanism of inhibition in rats revealed that the drug affects type I 5α-reductase differently to type II. The drug inhibits type I 5α-reductase in a classically competitive manner, forming a dissociable complex with this isozyme. In contrast, the inhibition of type II 5α-reductase is time-dependent. In this analysis, which compared the actions of finasteride and dutasteride in rats, the latter was found to be 20 times as powerful an inhibitor as finasteride of 5α-reductase type I, and 10 times as powerful with type II.

Previous studies in rats have indicated that finasteride acts as a dual inhibitor of 5α-reductase in these animals, so the beneficial effects of the drug may in fact be overestimated. However, this model allows the direct comparison of finasteride and dutasteride in terms of overall potency.

An additional animal study of dutasteride indicated that its half-life is considerably longer than that of finasteride. Examination of the pharmacokinetic and pharmacodynamic properties of dutasteride revealed a greater terminal half-life compared to finasteride, at 14 hours versus 1 hour in the rat, and 65 hours versus 4 hours in the dog. Total body clearance in the dog was found to be 0.5 mg/min per kg and volume of distribution was high, at 3 liters/kg. In man, a single dose was found to have a terminal half-life of around 240 hours. Levels of DHT were found to be reduced to a significantly greater level after a 10 mg dose of dutasteride compared to a 5 mg dose of finasteride.

The extended half-life of dutasteride, in addition to its dual-inhibitor nature and decreased
total body clearance, is considered to underpin the greater inherent potency of this drug compared to selective 5α-reductase inhibitors.38

**CLINICAL EXPERIENCE WITH DUTASTERIDE**

Clinical experience involving dutasteride is relatively limited due to its recent availability on the market, and comparison studies are lacking. What evidence there is, however, indicates that the drug consistently reduces prostate volume, improves urinary symptoms and $Q_{\text{max}}$, and reduces risk of AUR and BPH-related surgery.39

The pooled analysis of three phase III randomized, placebo-controlled studies of dutasteride, each lasting 24 months, has substantiated the potential of the drug in the treatment of LUTS in BPH patients.

A total of 4325 men aged over 50 with moderate to severe symptoms of BPH (American Urological Association symptom index (AUASI) ≥ 12, $Q_{\text{max}}$ ≤ 15 ml/s, prostate volume ≥ 30 ml, as measured using transurethral ultrasound) took part in the trials, which took place at 400 sites in 19 countries. After a 1-month placebo run-in period, participants were randomized to receive 0.5 mg dutasteride or placebo. Assessment, involving AUASI, $Q_{\text{max}}$, and PSA measurement, took place at 1, 3, 6, 12, 18, and 24 months and testosterone and DHT levels were measured at 12 and 24 months. Total prostate volume was assessed at regular intervals and transition zone volume was determined in two of the trials.

In total, 68% (2951) of participants completed the 24-month study period, with discontinuation rates similar between the active and placebo groups ($n = 657$ and $n = 717$, respectively). DHT levels fell by a mean of 90.2% in the active group compared to a mean increase of 9.6% in the placebo group (Figure 3.3).

Prostate volume fell significantly compared to placebo after just 1 month and this difference increased over the course of the study period.

Total prostate volume fell by a mean of 25.7% and transition zone volume by 20.4% from baseline in the active groups; AUASI fell by 4.5 points

![Figure 3.3](image-url) Changes in efficacy parameters at 24 months (expressed as a percentage change of baseline measurements, all changes for dutasteride are statistically significant ($p < 0.001$) versus placebo.)
compared to 2.3 points with placebo, reaching significance in the pooled results after 6 months; $Q_{\text{max}}$ increased by 2.2 ml/s compared to 0.6 ml/s with placebo, with a significant difference between active and placebo arms after 3 months; PSA increased by 15.8% in the placebo group and decreased by 52.4% with dutasteride.

AUR occurred in less than half the number of dutasteride-treated patients compared to placebo (39 versus 90), representing a reduction in risk of 57% ($p = 0.001$). BPH-related surgery was performed in 47 and 89 patients, respectively, indicating a reduction in risk of 48% ($p = 0.001$) with dutasteride.

Adverse event rates were similar between groups, at 77% for dutasteride-treated patients and 75% in those receiving placebo. Drug-related adverse event rates were 14% and 19%, respectively, with sexual dysfunction being the most commonly reported in both groups (Figure 3.4). Prostate cancer was identified in 1.9% and 1.1% of the groups, respectively.

The results indicate that impressive clinical benefits are associated with dual 5α-reductase inhibition. Comparison of these results with those reported for other types of medical therapy for BPH indicates that the improvement in symptom score for dutasteride described here compares favorably with that reported for finasteride and many α-blockers. A review of the different medical treatments available for the management of BPH revealed symptom improvements compared to placebo of 9–40% for alfuzosin, 2–34% for terazosin, 3–19% for doxazosin, and 2–20% for tamsulosin. In the study described above, an improvement of 13% over placebo was observed, indicating similar results compared to these alternative therapies.

The decrease in risk of AUR and BPH-related surgery adds an additional dimension to the benefits of dutasteride; 23% of men surviving to 80 years are likely to suffer AUR and BPH-related surgery is needed in 29% of all men. The reduction in risk observed here is therefore extremely significant. Similar results have been shown for finasteride, indicating the influence of 5α-reductase inhibitors on this aspect of BPH.

![FIGURE 3.4](image-url) Sexual dysfunction adverse events: incidence (percentage of patients) over the entire study (2 years). Statistically significant for all disorders ($p < 0.001$), dutasteride versus placebo.
DUTASTERIDE IN THE TREATMENT OF THE BPH PATIENT

Direct clinical comparisons of dutasteride with finasteride are lacking, due to the recent release of the former drug. However, a phase II clinical trial, involving 399 BPH patients (mean age 62.6–65.6 across treatment group, mean prostate volume 41.9–47.3 ml) did compare a variety of doses of dutasteride (0.01, 0.05, 0.5, 2.5, and 5.0 mg) to 5 mg finasteride or placebo over a period of 24 weeks.44 A clear dose–response relationship was observed with dutasteride, with 98.4 ± 1.2% DHT reduction observed with the highest dose compared to a mean decrease of 70.8 ± 18.3% with 5.0 mg finasteride (Figure 3.5). Significantly greater decreases in DHT were observed at dutasteride doses of 0.5, 2.5 and 5.0 mg compared to both placebo (p = 0.001) and finasteride (p = 0.001). If, as thought, the reduction in DHT is the mechanism responsible for the improvement in symptoms seen with finasteride, it may be expected that a greater fall in DHT would be accompanied by greater improvements in symptomatology.

OTHER CONSIDERATIONS

Prostate-specific antigen

The reductions in prostate-specific antigen (PSA) levels observed with finasteride therapy have been mirrored in clinical trials of dutasteride,39 and it has been suggested that this may have implications for prostate cancer screening. However, in vivo studies have shown that complexed-to-total and free-to-total ratios remain constant with finasteride treatment, indicating that proportional reduction in all molecular forms of PSA occurs with 5α-reductase inhibition.45–47 If similar results are found for dutasteride, measurement of these PSA forms could potentially be used to screen for prostate cancer and the use of PSA in cancer screening would not be compromised.

In addition, investigation of PSA levels in men included in phase III trials of dutasteride revealed reductions in PSA of around 50%. Multiplication of these scores by 2 showed levels

![Figure 3.5](image-url) Comparative changes in serum DHT and testosterone following 24 weeks' treatment with dutasteride (0.5 mg), finasteride (5 mg), or placebo (serum DHT suppression significant for dutasteride versus finasteride, p < 0.001).
of PSA that were superimposable on curves observed at baseline, suggesting that this simple method could allow continued screening using total PSA levels. Again, free-to-total ratio did not change in these patients.

**Hematuria**

Finasteride and other anti-androgens have been shown to have potential clinical applications in the prevention of hematuria, possibly due to decreased expression of vascular endothelial growth factor (VEGF), which lowers microvessel density in the prostatic suburethra. It may be postulated that the decrease in VEGF will be greater following dutasteride treatment, indicating an even greater anti-hematuric effect; however, such aspects remain to be investigated.

**Combination therapy**

The combination of 5α-reductase inhibitors and α-blockers has recently been investigated, and the addition of doxazosin to 5α-reductase therapy was found to result in significantly greater benefits in terms of disease progression and symptom score than either treatment alone. The greater efficacy of dutasteride in terms of DHT reduction suggests that the combination of an α-blocker with this drug may hold even more promise. However, long-term, randomized, placebo-controlled trials are needed to investigate this theory.

**CONCLUSIONS**

The results of pharmacokinetic, pharmacodynamic, and clinical studies have indicated that dutasteride is the most powerful suppressor of DHT on the market. The drug effectively inhibits type II 5α-reductase activity to a greater extent than finasteride, with the additional benefit of completely inhibiting type I 5α-reductase. The net effect is a reduction in prostatic and circulating DHT to virtually zero. Greater reductions in prostate volume may therefore be expected with dual 5α-reductase inhibition than with selective inhibition, with positive clinical consequences with respect to urinary symptoms, AUR, BPH-related surgery risk and quality of life.

Dutasteride therefore builds on the well-documented long-term safety and tolerance of 5α-reductase inhibitors, but potentially could provide additional clinical benefit to that observed with finasteride due to more effective DHT suppression.

However, a direct comparison of finasteride and dutasteride is now needed to determine the relative clinical benefits of selective and dual isozyme inhibitors as monotherapy or in combination with other classes of drug.

**REFERENCES**

DUTASTERIDE IN THE TREATMENT OF THE BPH PATIENT


42. Boyle P. Some remarks on the epidemiology of acute urinary retention. Arch Ital Urol Nefrol Androl 1998; 70: 77–82


INTRODUCTION

The androgen dependency of the prostate is responsible both for the development of benign prostatic hyperplasia (BPH) in older men and the reduction in symptoms associated with finasteride therapy. Dihydrotestosterone (DHT), which is converted from testosterone by two 5α-reductase isozymes, accounts for around 90% of all intraprostatic androgens. Finasteride is an inhibitor of the type II isozyme of 5α-reductase, which effectively reduces testosterone conversion to DHT in the prostate and thereby improves the urinary symptoms associated with BPH.

The use of finasteride since its approval over a decade ago is supported by a wealth of clinical experience, with long-term studies indicating that the drug not only prevents acute urinary retention (AUR) but may delay the need for invasive therapy indefinitely or negate it altogether in responders.

It has been suggested that men with larger prostates are more likely to respond to treatment with finasteride than those with smaller glands. Reductions in libido and other sexual effects have also been reported in a minority of patients, and the reduction in prostate-specific antigen (PSA) levels may also have a bearing on the use of the drug. The clinical relevance of these assumptions will be examined in this chapter.

BPH affects the majority of older Western men and, as the age of the general population increases and improvements in healthcare provision occur in the developing world, the prevalence of this disease will grow. Pharmacologic treatments with a range of mechanisms of action are therefore desirable. Effective patient selection and the use of finasteride as monotherapy or in combination with other preparations also ensure the continued place of the drug in the armory of anti-BPH agents.

DHT AND 5α-REDUCTASE

The prostate is highly dependent on testicular androgens for its development and functional integrity. BPH develops in older men as a function of sensitivity to these testicular androgens, specifically DHT. Serum and prostatic DHT levels remain stable, unlike testosterone, which falls over time.

The role that androgens play in hyperplastic and normal prostatic growth is governed by the levels of DHT that bind to androgen receptors within the epithelium of the prostate. This complex plays a critical role in stimulating androgen-mediated prostatic growth. The characteristic reduction in androgen-dependent growth observed with aging in some other tissues does not occur in the prostate.

Testosterone is reduced to DHT through the action of 5α-reductase. Two forms of this enzyme have been identified: type I, which is found in greater proportions in the skin and liver, and type II, which is the predominant isozyme contained in the prostate.
The role of DHT and, by definition, the protein responsible for its reduction, in the development of BPH was determined following the identification of 5α-reductase deficiency in a group of individuals with pseudohermaphroditism. Virilization occurred at puberty in these individuals, although their prostates remained non-palpable, and male sexuality was in evidence alongside normal muscular composition. This, plus the observation that men with castrate levels of testosterone do not develop BPH and have very low levels of DHT, indicated that blockade of prostate-specific androgens could reduce the size of the prostate, thereby relieving obstructive urinary symptoms with limited adverse sexual or physical implications.

**THE DEVELOPMENT OF FINASTERIDE**

The above observations led to the development of synthetic 4-azasteroid α-reductase inhibitors. These agents were designed to reduce levels of type II 5α-reductase, the isozyme that predominates in the prostate (Figure 4.1).

One compound, N-(2-methyl-2-propyl)-3-oxo-4-aza-5-α-androst-1-ene-17-β-carboxamide (finasteride), was found to reduce levels of DHT in the canine prostate and reduce prostatic volume by up to 64%. Further studies showed that testosterone levels were unaffected by the drug, indicating that sexual function should be maintained.

As anticipated, intraprostatic testosterone levels were elevated, however, and serum and prostatic DHT were not completely inhibited, due to formation via the uninhibited type I 5α-reductase.

**MODE OF ACTION**

Finasteride, which reduces serum DHT by around 70% and prostatic DHT by 85–90% (Figure 4.2), is thought to act predominantly on the epithelium of the prostate, exerting its beneficial clinical effect by altering prostatic tissue composition and inhibiting cell proliferation.
24- to 30-month open-label extension study of finasteride in a group of 19 men whose prostates were assessed by magnetic resonance imaging (MRI) and biopsy revealed a reduction in symptoms, PSA, DHT, and prostate volume after 6 months. The percentage of prostate volume attributed to epithelium shrank significantly from 19.2% to 12.5% at intermediate follow-up and to 6.4% at long-term follow-up. Changes in the transforming growth factor beta (TGFβ) signaling system, in terms of upregulation of TGFβ signaling receptors and a subsequent increase in epithelial apoptosis, may be instrumental in this process.

The inhibition of prostatic cell proliferation has been demonstrated in several studies. Stromal and epithelial prostate cells from hyperplastic and normal glands treated in vitro with finasteride in the presence of labeled thymidine revealed that normal stromal cells incorporated more thymidine than epithelial cells. Finasteride treatment resulted in 80 ± 3% and 55 ± 10% thymidine incorporation in stromal and epithelial cells, respectively, while rates of 70 ± 4% and 74 ± 4% were observed in hyperplastic tissue. Measurement of 5α-reductase activity showed that type II activity was reduced 100-fold while type I activity was reduced 5-fold, demonstrating the selectivity of finasteride for the former isozyme. The incomplete inhibition of cell proliferation observed indicates the action of factors other than DHT in prostate cell proliferation, however.

Locally produced growth factors, such as basic fibroblast growth factor (bFGF), insulin-like growth factor (IGF), and keratinocyte growth factor (KGF), may also have an impact on prostatic enlargement, stimulating an increase in levels of mitosis in the prostatic stroma (Figure 4.3). Analysis of bFGF expression and that of fibroblast growth factor receptor types 1 and 2 (FGFR1, FGFR2) in finasteride-treated and untreated BPH patients revealed strong bFGF immunoreactivity in the stroma and weaker immunoreactivity in the epithelium of the untreated patients, and virtually no immunoreactivity in the epithelium and lower stromal immunoreactivity in finasteride-treated patients. This suggests that finasteride treatment leads to downregulation of bFGF activity, thereby limit-
ing the growth-stimulating action of this protein. Epidermal growth factor (EGF) appears to be unaffected by finasteride treatment, however, with only small changes observed in levels of TGF-α and EGF receptors after treatment, indicating a potential means of continued growth of androgen-independent basal prostatic epithelial cells.19

CLINICAL EXPERIENCE WITH FINASTERIDE

Finasteride was first launched in 1992 and is currently prescribed in developed countries worldwide. The duration of its clinical usage means that a range of long-term studies and meta-analyses are available as evidence of its safety and efficacy (Table 4.1). Men treated with 5 mg finasteride have been consistently shown to exhibit significant improvements in peak urinary flow ($Q_{\text{max}}$) and reductions in obstructive symptoms and prostatic volume in both older and younger men.20–28 Incidence of sexual dysfunction, in terms of lower libido, ejaculatory dysfunction, and impotence, is greater in men who receive the drug, although the majority of patients remain unaffected.

The Proscar (finasteride) Long-term Efficacy and Safety Study (PLESS) investigated the effects of finasteride relative to placebo over a 4-year period.22 Over 3000 men aged 45–78 with moderate to severe BPH were randomized to receive either 5 mg finasteride or placebo. Risk of acute urinary retention (AUR) or BPH-related surgery was significantly lower (~55–57% relative risk) in the finasteride group compared to placebo over the study period (Figure 4.4). Quasi-AUA symptom score improved in this group (3.3 versus 1.3 points) and prostate volume fell (~18% versus +14% for placebo). In 4 years, 6.6% of the placebo group experienced AUR compared to 2.8% of the finasteride group ($p = 0.001$).23 As a result of AUR, surgery was then performed in 75% of the former and 40% of the latter group ($p = 0.01$). Prostate volume and PSA level were powerful predictors of risk of AUR or BPH-related surgery in this patient group.27 Risk of AUR or surgery ranged from 8.9% to 22%, depending on prostate volume, and from 7.8% to 19.9% depending on PSA level.

In PLESS, only three drug-related side-effects occurred within the first year with an incidence of > 1%: impotence (8.1% versus placebo 3.7%); decreased libido (6.4% versus 3.4%), and decreased ejaculate volume (3.7% versus 0.8%). Further analysis of PLESS data showed that finasteride was effective and safe in both older (≥65 years) and younger (45–64 years) patients, with no additional risk of drug-related adverse events in the older cohort.24 Spine bone mineral density, for example, was unaffected by 4-year finasteride administration.29

Longer-term studies indicate that the efficacy of finasteride is durable and that, in responders, the drug negates the need for prostatic surgery altogether.25–27 Men prescribed open-label finasteride for a 7- to 8-year period ($n = 71$) after taking part in two short-term phase II trials were found to maintain the reductions in Boyarsky symptom score seen after 1 year over the following 6 years.25 Baseline DHT fell by 85% over the study period while serum PSA fell by 45%. Prostate volume fell by 25% from average baseline 61.2 g after 1 year and this was sustained after 7 years. Sexual side-effects (impotence, abnormal ejaculation, and low libido) occurred most often during the first year of extension and decreased over the extension period. Discontinuation due to such effects was 1.9% in year 1 and 0% after year 4. Likewise, only minor reductions in sexual
### TABLE 4.1 Long-term finasteride trials.

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration</th>
<th>Regimen</th>
<th>Reduction in AUR risk</th>
<th>Reduction in BPH-related surgery risk</th>
<th>Prostate volume</th>
<th>( Q_{\text{max}} )</th>
<th>Symptom score</th>
<th>Side-effects</th>
</tr>
</thead>
</table>
| Roehrborn et al.\textsuperscript{23} | 4 years  | 5 mg FIN/day or placebo | 57%                   | 55%                                   | -18%            | +1.9 ml/s       | -3.3          | ED 8.1%  
L LIB 6.4% 
EJD 3.7% |
| Vaughan et al.\textsuperscript{25} | 7–8 years| 5 mg FIN/day (or 10 mg 1st year) | —                     | —                                     | -25%            | +20%            | 1-year improvement maintained | 1st year, ED 6.4%  
L LIB 10.9%  
EJD 5.8% 
few new cases thereafter |
| Ekman et al.\textsuperscript{26} | 6 years  | 5 mg FIN/day          | —                     | —                                     | -21%            | +2.2 ml         | 30% improvement   | 0.6–1.7% drop-out to SD each year |
| Lam et al.\textsuperscript{27}   | 10 years | 5 mg FIN/day          | —                     | —                                     | —               | —               | 55.8% treatment success | Treatment duration not linked to side-effects |
| Boyle et al.\textsuperscript{33} | N/A meta-analysis | —                     | —                     | —                                     | —               | —               | 0.89–1.84 ml* + 1.8–2.8*   | —                      |

* Depending on prostate volume; larger prostates linked to greater improvement. ED, erectile dysfunction; FIN, finasteride; L LIB, lowered libido; EJD, ejaculatory dysfunction; SD, sexual dysfunction.
A 10-year follow-up study suggested that appropriately selected patients, often with larger prostates, could be effectively treated for BPH symptoms with finasteride over this extended time period. Of an original 43 patients who entered phase III 12-month double-blind trials, 41 completed the year and 30 continued to take the drug for a further 4 years. Twenty-two continued treatment for a further 10 years, indicating a 48.8% overall discontinuation rate, but only 26.7% between 5 and 10 years. In total, 24 (56%) were judged to be successfully treated over the 10-year follow-up. The majority of withdrawals due to treatment failure occurred in the first 1 or 2 years, suggesting continued therapeutic success in initial responders.

The adverse event profiles in the 1-year, placebo-controlled, phase III studies, the 5-year open extension study, and PLESS are similar. Overall, therefore, there is no evidence of increased side-effects with increased duration of treatment.

Adverse treatment effects are, by and large, limited to sexual dysfunction; however, few patients report such effects overall and superficial analysis would appear to indicate that numbers are similar across alternative treatment options (Figure 4.5). A study of 670 BPH patients treated with a range of medical and surgical options and watchful waiting (α = 90 (α-blocker 43, finasteride 47), 207, and 234, respectively involved assessment of sexual effects by questionnaire 9 months after surgery or the initiation of therapy. Libido, sexual activity, potency, and penile rigidity were determined. An improvement of between 7 and 14% was reported for libido for all treatments (α-blocker 3%, finasteride 8%) and deterioration in libido was reported by between 7 and 14% (α-blocker 14%, finasteride 8%) of all participants. Similar results were observed for sexual activity and erectile capacity; however, complete results for rigidity were not available for finasteride-treated patients.

A similar degree of improvement in urinary symptoms and quality of life has been reported in some studies of 5α-reductase inhibitors and α-blockers. For example, a randomized study of tamsulosin (0.2 mg) and finasteride (5 mg) showed both drugs to result in similar improvements in a group of Korean BPH patients.
(n = 205) after a period of 24 weeks. I-PSS, Q\textsubscript{max}, and quality of life improved in both groups with no significant difference between scores at endpoint; however, analysis at 4 weeks showed tamsulosin to have a swifter time to onset.\textsuperscript{31}

**COMBINATION STUDIES**

The different mode of action of 5α-reductase inhibitors and α-blockers has led to the assumption that a combination of both drug types may increase clinical improvement in BPH patients, due to the dual effects of inhibiting cell proliferation and altering the smooth muscle tone of the prostatic stroma and detrusor.

The most comprehensive evaluation of the clinical potential of combination therapy has been the Medical Therapy Of Prostatic Symptoms (MTOPS) study. This trial indicated that the combination of finasteride with doxazosin both slows the progression of BPH and reduces risk of AUR to a greater extent than either type of therapy alone.\textsuperscript{32} This study involved a total of 3047 BPH patients who received monotherapy, placebo, or combination therapy for an average of 5 years. Finasteride or doxazosin monotherapy brought about reductions in risk of disease progression of 34% and 39%, respectively, while combination therapy was associated with a 67% reduction in risk (Figure 4.6). AUR risk was cut by 79% in this group compared to 67% in the finasteride group and 31% in the doxazosin group. Reductions in risk of BPH surgery were 69%, 64%, and 8% relative to placebo in each group, respectively. No increase in side-effects was observed with combination treatment. The results suggest that enlargement of the prostate is slowed by finasteride while the symptoms of BPH are reduced by doxazosin. Interestingly, the combination of the two drugs reduces the risk of clinical progression even in...
men with only modest prostate enlargement (25–40 cc). 

Investigation of baseline characteristics and subsequent progression of the men in the MTOPS placebo group \((n = 737)\) indicated that easily obtainable measures, such as PSA level, \(Q_{\text{max}}\), postvoid residual urine, and prostate volume, correlate significantly with disease progression and the need for surgery. Such an approach may allow improved patient selection to ensure optimum clinical results.

Additional research has suggested that it may be possible to discontinue combination therapy after 1 year with no compromise in clinical benefit. A group of BPH patients \((n = 270)\) were prescribed 2, 4, or 8 mg doxazosin alongside 5 mg finasteride for a period of 3, 6, 9, or 12 months, after which the \(\alpha\)-blocker was discontinued. Of those who discontinued doxazosin at 12 months, 84\% of the 2 mg group, 85\% of the 4 mg group, and 87\% of the 8 mg group experienced no increase in AUA symptom score and reported no desire to resume taking doxazosin 1 month later.

In studies of generally shorter duration and reduced patient numbers the results with combinations have not been as conclusive. The addition of finasteride to terazosin in the Veterans’ Affairs Cooperative Studies BPH Study Group, which involved 1229 patients, conveyed no additional benefit compared to terazosin monotherapy after 1 year. The relatively low average prostate volume of the men involved in this study (36.2–38.4 ml) could explain the limited improvement observed in patients treated with finasteride alone, due to the correlation between gland size and clinical response observed in several studies. Pharmacokinetic interactions between finasteride and terazosin, but not doxazosin may also have a bearing on clinical response to different combination therapy regimens.

A 6-month trial of sustained-release alfuzosin (5 mg), finasteride (5 mg), or both drugs in 1051 men yielded similar findings to the VA Cooperative trial, with higher symptom improvement observed in patients who received \(\alpha\)-blockade or combination therapy. The short-term nature of this trial precludes any definitive conclusions, however.

An additional 1-year randomized placebo-controlled study involved 1007 men who received

![FIGURE 4.6 MTOPS—reductions in disease progression with combination treatment. AUR, acute urinary retention.](image-url)
finasteride (5 mg) or doxazosin (1–8 mg, titrated) monotherapy, combination therapy, or placebo. Results indicated no additional benefit of finasteride to doxazosin therapy.\(^{41}\) Again, mean prostate size was relatively small, at 36.3 g, which may explain the lack of observed efficacy of finasteride. No stratified analysis based on prostate volume was performed.

The role of prostate volume is illustrated by a further trial of finasteride, alfuzosin, or a combination of both in a group of 138 men with I-PSS \(>13\) and prostate volume of at least 60 ml. Overall, 96% of patients in the combination group showed improved \(Q_{\text{max}}\) and I-PSS, compared to 84% in the \(\alpha\)-blocker alone group and 74% in the finasteride group.\(^{42}\)

Meta-analysis of six randomized clinical trials involving finasteride (Table 4.2) provides further evidence of the role of prostate volume in response to therapy, with men with larger prostates showing particularly good response to treatment with finasteride.\(^{43,44}\) Over 2600 individuals were included in this study, which included all finasteride studies and phase III trials plus a number of other trials including the VA Cooperative Study. Men with prostates smaller than 20 g were less likely to show clinical improvement in quasi-I-PSS symptom score and \(Q_{\text{max}}\) compared to those with prostates larger than 60 g (1.8 versus 2.8 points and 0.89 ml versus 1.84 ml, respectively). Improvements were judged to become significant in men with prostates greater than 40 ml, i.e. 50% of the entire population, and the results indicate that prostate volume is a significant predictor of response to therapy.

**ADDITIONAL CONSIDERATIONS**

**Hematuria**

Hematuria, which often emerges secondary to BPH, is associated with significant morbidity, including anemia and clot retention. Recent research has shown that the condition may be successfully treated with finasteride and other anti-androgens.\(^{45-47}\) Although the exact mechanism is not understood, histochemical studies have suggested that this is due to decreased expression of vascular endothelial growth factor (VEGF) following finasteride treatment which, as a consequence, lowers microvessel density in the prostatic suburethra.\(^{48,49}\) Such mechanisms could explain the reduction in hematuria and

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (n)</th>
<th>Age (mean)</th>
<th>Prostate volume (mean ml)</th>
<th>Peak flow (mean ml)</th>
<th>Quasi-I-PSS (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gormley et al.(^{20})</td>
<td>567</td>
<td>64.1</td>
<td>59.9</td>
<td>9.6</td>
<td>12.1</td>
</tr>
<tr>
<td>The Finasteride Study Group(^{60})</td>
<td>447</td>
<td>65.5</td>
<td>48.1</td>
<td>8.9</td>
<td>11.8</td>
</tr>
<tr>
<td>Andersen et al.(^{40})</td>
<td>384</td>
<td>65.3</td>
<td>41.3</td>
<td>10.2</td>
<td>10.1</td>
</tr>
<tr>
<td>Lepor et al.(^{36})</td>
<td>601</td>
<td>65.7</td>
<td>37.5</td>
<td>10.4</td>
<td>13.4</td>
</tr>
<tr>
<td>Nickel et al.(^{62})</td>
<td>554</td>
<td>63.3</td>
<td>45.9</td>
<td>11.0</td>
<td>12.4</td>
</tr>
<tr>
<td>Bonilla et al.(^{63})</td>
<td>188</td>
<td>56.4</td>
<td>41.6</td>
<td>15.8</td>
<td>9.3</td>
</tr>
</tbody>
</table>
intraoperative blood loss observed when patients due to undergo transurethral resection of the prostate (TURP) receive finasteride treatment preoperatively.\textsuperscript{50,51}

Investigation of potential predictors of clinical response to finasteride treatment in patients with gross hematuria revealed that 94% responded to treatment and that 77% suffered no further bleeding while taking the drug.\textsuperscript{47} Treatment was effective in patients taking a range of anticoagulants. Recurrent but lower-grade bleeding and slower response time were identified in men with larger prostates. Men with smaller prostates and those who had undergone previous prostatectomy had more rapid responses to treatment (2.7 days in men with glands < 40 g versus 45 days in those with glands 100–150 g and 5.5 days in men who had undergone prostatectomy versus 18.6 days in those who had not).

\textbf{PSA}

PSA levels have been found to fall following application of finasteride to prostate cells treated in vitro with testosterone.\textsuperscript{52} In vivo studies have shown that plasma and serum complexed-to-total and free-to-total ratios remain constant with finasteride treatment, indicating that proportional reduction in all molecular forms of PSA occurs with finasteride treatment.\textsuperscript{53–55} Measurement of these PSA forms could potentially be used to screen for prostate cancer in men receiving finasteride, but this requires further investigation.\textsuperscript{55,56}

The effect of finasteride on overall PSA levels has implications for prostate cancer screening but may also impact upon actual risk of prostate cancer. A case–control study of the medication use in 639 men with prostate cancer and 659 tumor-free controls indicated that, after adjustment for confounders, finasteride has a protective role against prostate cancer while nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs) have no protective influence.\textsuperscript{57}

Further evidence of the potential preventative role of finasteride has been recently highlighted in a large-scale study of the incidence of prostate cancer among men aged \( \geq 55 \) years prescribed finasteride or placebo over 7 years.\textsuperscript{58} Men who received the active agent were significantly less likely to develop prostate cancer during the study than those prescribed placebo \((p = 0.001)\), although when cancer did develop in this group, it was more likely to be of a higher Gleason grade than in the placebo group. Whether the benefits of reduced likelihood of prostate cancer development and urinary symptoms outweigh the risks of higher-grade tumor development and sexual side-effects requires further investigation.

\textbf{CONCLUSIONS}

Patient perception of finasteride has been shown to be excellent. In a survey of French BPH patients, the primary preoccupations were reported as a reduced risk for urological complications and need for surgery, with improved symptoms and quality of life of secondary importance. These expectations were easily met by finasteride in the majority of cases, and 89% of participants reported good or extremely good improvement of symptoms, with very few tolerability issues.\textsuperscript{59}

The studies outlined here indicate that finasteride is an effective long-term treatment option for BPH. The benefit of finasteride over placebo has been repeatedly proven in well-designed large-scale clinical trials and comparison studies have shown the drug to be of similar efficacy in terms of AUR prevention and necessity for BPH surgery to \( \alpha \)-blockers in well-chosen patient groups. Men with larger prostates appear to ben-
efit particularly from finasteride therapy. Response to therapy has been shown to have exceptionally long duration in responders, exceeding 10 years in many cases. The data from the MTOPS study indicate that the drug has further potential when used in combination with α-blockers. On this basis, future treatment algorithms could include both a 5α-reductase inhibitor and α-receptor antagonist, depending on the initial clinical presentations.

The effects of finasteride on PSA level have been frequently documented; however, recent findings regarding the lack of effect of the drug on free-to-total PSA ratio may mean that suggestions that prostate cancer detection may be compromised can largely be dismissed. Further investigation of this aspect is required, however.

REFERENCES

17. Saez C, Gonzalez-Baena A C, Japon M A et al. Expression of basic fibroblast growth factor and its receptors FGFR1 and FGFR2 in human benign
33. Kaplan S, Roehrborn C, Lee M. The superior beneficial effect of combination therapy with doxazosin and finasteride versus either drug alone on clinical progression of benign prostatic hyperplasia in the MTOPS trial was not dependent on patients having prostatic enlargement at baseline. Eur Urol 2005; (Suppl) 4: 213 Abstract # 841


42. Loron O B, Pushkar’ Dlu, Rasner P I. [Comparative evaluation of the effectiveness and safety of combined drug therapy of patients with benign prostatic hyperplasia with finasteride and alfuzosine] [in Russian]. Urologiya 2002; 1: 19–22


Combination therapy in the treatment of BPH

C G Roehrborn

INTRODUCTION

Treatment for benign prostatic hyperplasia (BPH) in recent years has been characterized by a fall in the use of surgical procedures, mainly transurethral resection of the prostate (TURP), and a rise in the use of minimally invasive treatments and, particularly, medical therapy.1–3

Up to 90% of men in their eighties are estimated to suffer from BPH to some extent and prevalence of the disease is growing.4 Development of the associated symptomatology is androgen-dependent, and castration before or during puberty prevents its occurrence. Lower urinary tract symptoms (LUTS) secondary to BPH occur due to increased sensitivity to circulating androgens in the prostate. Increased cell proliferation, mainly in the transition zone of the prostate, occurs alongside a rise in the smooth muscle tone of both the prostate and bladder neck. Symptoms of reduced urinary flow and urinary retention, increased urinary frequency, and nocturia are particularly common.5

Pharmacologic therapies available for the treatment of LUTS include \(\alpha\)-adrenoceptor antagonists (\(\alpha\)-blockers), such as terazosin, doxazosin, alfuzosin, and tamsulosin, and the 5\(\alpha\)-reductase inhibitors, finasteride and dutasteride. Other strategies, such as plant-derived medication or watchful waiting, are applied to varying extents.

\(\alpha\)-blockers act on the \(\alpha\)-adrenoceptors of the prostate and bladder neck, thereby reducing the sympathetic nervous system controlled tone of the smooth muscle. Many placebo-controlled trials of \(\alpha\)-blockers have shown them to increase urinary flow and relieve irritative and obstructive symptoms, often within as little as 2 weeks of treatment.6–11

In contrast, 5\(\alpha\)-reductase inhibitors reduce the formation of dihydrotestosterone (DHT) from testosterone in the prostate and thereby increase rates of apoptosis and reduce rates of cell proliferation. Enlarged prostate glands therefore shrink, causing alleviation of BPH symptoms and urinary flow in the process,12–14 as proven by placebo-controlled trials.15–17 More recently, it has been shown that the risks of acute urinary retention (AUR) and BPH-related surgery are reduced in men receiving finasteride by 55% and 57%,15 respectively. However, symptom improvement may only be observed after up to 6 months of treatment15,16 and, indeed, it has been suggested that the clinical benefit is limited to men with larger prostates.16,18

The recent development of diverse formulations of pharmacologic therapies, such as the doxazosin gastrointestinal therapeutic system (GITS) and doxazosin XL, has increased patient and physician treatment choice.10 Further alterations in the pharmacokinetic profiles of available drugs are possible, however such avenues may be limited. In real terms we may have reached the limit of clinical benefit that can be achieved by monotherapy. Alternative pharmacologic treatment strategies for targeting BPH are therefore desirable.

Given the different mechanisms of action of \(\alpha\)-blockers and 5\(\alpha\)-reductase inhibitors, a
combination of each of the drug classes in a single drug regimen might logically be expected to convey cumulative benefit to BPH patients. Several large-scale studies have been performed in recent years to determine whether the administration of an α-blocker in combination with a 5α-reductase inhibitor leads to greater improvement in BPH symptoms than either one individually and whether the side-effects documented with each drug class occur with greater frequency in combination.

The following represents a summary of the salient findings from the most important combination studies that have been completed.

TERAZOSIN AND FINASTERIDE

VA Cooperative Study

The first large-scale trial established to examine the potential benefits of combining an α-blocker with a 5α-reductase inhibitor was the Veterans’ Affairs (VA) Cooperative Study. This multicenter trial compared the use of terazosin and finasteride individually and in combination.

The double-blind, placebo-controlled trial involved 1229 men (87% white, 11% black, 1% Asian/Pacific Islanders, 0.5% Native Americans) aged 45–80 suffering from symptomatic BPH. Baseline measures were obtained during an initial 1-month wash-out period and included American Urological Association (AUA) symptom score, peak urinary flow ($Q_{max}$), and volume of postvoid residual urine (PVR). Prostate-specific antigen (PSA) levels were recorded and transurethral ultrasound examination of the prostate was also performed.

Participants had an AUA symptom score of ≥8, $Q_{max}$ of 4–15 ml/s, minimal voided volume of 125 ml and PVR of < 300 ml. After the wash-out period, they were randomized to receive 5 mg finasteride, terazosin titrated to 10 mg, a combination of both drugs, or placebo for a period of 1 year.

Clinical evaluation, in terms of uroflowmetry, symptom score, PVR, and adverse effects, took place at 2, 4, 13, 26, 39, and 52 weeks. Transrectal ultrasound examination took place at the halfway point and on completion of the study. PSA was recorded at the end of the study period.

Drop-out rates were similar between groups after 1 year, although discontinuation due to adverse effects was less common in the placebo group ($p < 0.05$). Overall, men receiving terazosin either alone or in combination were more likely to suffer dizziness and men receiving finasteride alone or in combination were more likely to experience erectile dysfunction (ED) or lowered libido. Ejaculatory dysfunction was significantly more common in men receiving combination therapy. Compliance was similar between all four treatment groups, however.

Examination of symptom scores revealed that men receiving terazosin alone or in combination with finasteride had improved symptoms compared to both the finasteride and placebo groups ($p < 0.001$), with respective point reductions of 6.1, 6.2, 3.2, and 2.6 (Figure 5.1). Peak improvement levels were attained in the terazosin-exposed groups by 13 weeks and did not differ significantly between this point and completion of the study. The improvements in symptom score were accompanied by significant increases in $Q_{max}$ ($p < 0.001$ for terazosin and combination therapy compared to finasteride alone and placebo), which were greatest after 4 weeks. Mean increases in $Q_{max}$ at 52 weeks were 3.2, 2.7, 1.6, and 1.4 ml/s, respectively.

Significant reductions in prostatic volume were observed in the finasteride and combination
therapy groups (−61 ml and −70 ml, respectively) but no significant change was observed in this value in the other two groups. PSA was also significantly reduced in the finasteride and combination groups (p < 0.001) while increases were noted in men who received terazosin alone or placebo (p < 0.01).

The results of this study confirm previously documented evidence of the efficacy of terazosin, but they are not in agreement with studies indicating that finasteride reduces BPH symptoms and improves $Q_{\text{max}}$. The VA study suggests that reduction in smooth muscle tone by α-blockers is more likely to reduce symptoms of BPH than androgen suppression using 5α-reductase inhibitors. The role of prostate volume was not assessed in this trial, however.

Despite the lack of significant additional benefit with the addition of finasteride to terazosin therapy described in this trial, interactions between the two drugs have been documented. Rates of apoptosis and proliferation were determined from prostate samples obtained from 76 men who had been treated for BPH with terazosin, finasteride, or a combination of both. Both stromal and epithelial rates of apoptosis were significantly higher in the combination samples compared to monotherapy samples, although proliferation rates were similar. Upregulation of transforming growth factor (TGF) β1 was observed in the terazosin and combination therapy groups.

The cellular relationship between the two drugs remains unclear, however. An additional, retrospective, study of cell proliferation and apoptosis among men treated with doxazosin, terazosin, finasteride, or a combination of finasteride and one of the α-blockers indicated no increase in apoptotic index with addition of finasteride to the other agents.

A molecular relationship between the two drug classes was described in a comparison of the pharmacokinetic interactions between terazosin and finasteride and between doxazosin and finasteride. In this trial, the maximum plasma concentration and area under the plasma concentration–time curve from 0 to 24 hours of finasteride were significantly greater after coadministration.

**FIGURE 5.1** VA Cooperative Study: symptom improvement at 1 year according to treatment group. AUA, American Urological Association; $Q_{\text{max}}$, peak urinary flow.
The pharmacokinetic profile of terazosin was not altered, however. Whether this relationship is significant in terms of drug efficacy is as yet unknown.

ALFUZOSIN AND FINASTERIDE

**ALFIN study**

The α-blocker alfuzosin is a uroselective preparation that targets the α1-adrenoceptors of the prostate. Animal studies have shown alfuzosin to exert its effect at doses below the threshold of influence on the cardiovascular system. It does not require titration to its optimum dosage.

A 6-month evaluation of the effects of combining 5 mg twice-daily (sustained-release alfuzosin) with 5 mg once-daily finasteride (the ALFIN study) showed similar effects to the VA study described above. Again, the α-blocker was shown to improve symptoms of LUTS secondary to BPH to a greater extent alone or in combination compared to finasteride.

The ALFIN study involved 1051 BPH patients aged between 50 and 75 from 11 European countries. Participants had an International Prostate Symptom Score (I-PSS) > 7 and Qmax of between 5 and 15 ml/s. They underwent a 2-week wash-out period prior to randomization to alfuzosin, finasteride, or a combination of both.

Clinical assessment took place at baseline and then after 1, 3, and 6 months of therapy. I-PSS was recorded alongside uroflowmetry, blood pressure, and heart rate during these sessions, while prostate volume, measured using transurethral ultrasound, and PSA level were assessed at baseline and on completion of the study. Adverse events were reported throughout the entire trial.

All three patient groups were found to show improvement over the study period (Figure 5.2). Mean I-PSS fell by 6.3 points in the alfuzosin alone group, 6.1 in the combination group, and 5.2 in the finasteride alone group, but a significantly greater improvement in the alfuzosin and

![Graph showing reduction in I-PSS and increase in Qmax](image)

**FIGURE 5.2** ALFIN Study: symptom improvement at 6 months according to treatment group. I-PSS, International Prostate Symptom Score; Qmax, peak urinary flow.
Combination groups compared to finasteride was recorded ($p = 0.01$ and 0.03, respectively). Improvement of at least 50% was observed in 43, 42, and 33% of the men in each group, respectively.

$Q_{\text{max}}$ increased by similar degrees at 6 months (alfuzosin 1.8 ± 3.8 ml/s; combination 2.3 ± 4.7 ml/s; finasteride 1.8 ± 4.5 ml/s); however, at 3 months, men in the alfuzosin and combination groups had greater $Q_{\text{max}}$ than those in the finasteride alone group. Patients with a baseline $Q_{\text{max}}$ of < 10 ml/s had a significantly greater $Q_{\text{max}}$ at the end of the study period if they were treated with alfuzosin or combination therapy rather than finasteride alone, however ($p = 0.05$). Prostate volume and PSA level fell significantly in the finasteride and combination therapy groups, but no significant change was observed in men treated with alfuzosin alone.

Similar numbers of adverse events were observed in all patient groups; however, sexual dysfunction, in the form of erectile dysfunction (ED) and ejaculatory disorders, was more common among finasteride-treated patients. Levels of vasodilatory events, potentially linked to $\alpha$-blockade, were similar between all three groups, as was incidence of AUR. This is in accordance with previous reports of both drugs.15,32

The improvements observed with finasteride in this study are higher than those of the VA study, but are significantly lower than those seen with $\alpha$-blockade by alfuzosin. Patients were not selected or stratified according to prostate size and so the potential effects of this variable on outcome could not be analyzed.

A longer-term, but smaller-scale study indicated that the combination of alfuzosin and finasteride brought about greater improvements in I-PSS and urinary flow.33 One hundred and thirty-eight BPH patients with prostates $\geq 60$ ml and I–PSS > 13 were treated with alfuzosin, finasteride, or both for 3 years. Improved urinary flow and I-PSS results were observed in 84%, 74%, and 96% of patients, respectively. These findings have yet to be confirmed by larger-scale trials, however.

DOXAZOSIN AND FINASTERIDE

PREDICT

A large-scale, placebo-controlled study designed to evaluate the potential benefits of combining an $\alpha$-blocker with a 5$\alpha$-reductase inhibitor was conducted using the $\alpha_1$-selective adrenoceptor antagonist doxazosin in the Prospective European Doxazosin and Combination Therapy (PREDICT) Trial.34

The 1-year trial took place at 90 centers in Europe. Following a 2-week run-in period, 1095 men aged 50–80 with an I-PSS $\geq 12$ and $Q_{\text{max}}$ $\geq 5$ ml/s but $\leq 15$ ml/s in a total void of 150 ml or more, were randomized to receive doxazosin alone, finasteride alone, a combination of both drugs, or placebo for 52 weeks. Patients receiving doxazosin underwent a 10-week titration period, while the dose was increased from 1 mg to 8 mg on the basis of treatment response as judged by I–PSS and $Q_{\text{max}}$ as part of their regimen.

Participants were assessed at baseline for I–PSS and $Q_{\text{max}}$ and then at regular intervals (10, 14, 26, 39, and 52 weeks) throughout the study period. Blood pressure, heart rate, and adverse events were also recorded regularly over the 12-month period, while PSA, electrocardiography, and standard blood tests were performed at baseline and then again on conclusion of the trial. Prostate volume was estimated using DRE.

In total, 1007 patients were included in the intention to treat analysis. Mean doxazosin dose
was 6.4 mg/day in the monotherapy group and 6.1 mg/day in the combination group.

Men who received doxazosin alone or in combination had significantly improved I-PSS results compared to those who received finasteride alone (\( p \leq 0.0001 \)) or placebo (\( p < 0.01 \)), for both obstructive and irritative symptoms (Figure 5.3). Mean I-PSS improvements were \(-8.3, -8.5, -6.6,\) and \(-5.7\) points, respectively. No significant difference was observed between the doxazosin and combination groups or between the finasteride and placebo groups. Obstructive but not irritative symptoms improved with finasteride compared to placebo at endpoint (\( p < 0.05 \)).

Again, for \( Q_{\text{max}} \), a statistically significant improvement was observed in the doxazosin and combination groups (mean increases of 3.6 ml/s and 3.8 ml/s, respectively) compared to both placebo and finasteride alone (1.4 ml/s and 1.8 ml/s, respectively, both \( p \geq 0.0001 \)). No improvement above placebo was observed with finasteride treatment alone.

Discontinuation due to adverse events was similar between groups, however, side-effects differed according to treatment regimen. Participants treated with doxazosin alone or in combination were more likely to report asthenia, dizziness, and hypotension, while patients treated with finasteride and doxazosin in combination were more likely to suffer ED. No significant difference in ED was observed between the monotherapy groups.

The PREDICT study demonstrated that, in this patient group, doxazosin more effectively improves symptoms of BPH and urinary flow than finasteride alone or placebo. The findings confirm previous studies indicating the efficacy of doxazosin in the treatment of LUTS,\(^{35,37}\) and also reinforce the findings of the VA Study, calling into question the value of 5α-reductase inhibition in patients with smaller prostates.\(^{17,38,39}\)

**MTOPS**

The results of all three large-scale studies described above suggest that the role of 5α-reductase inhibitors as generalized monotherapy for LUTS may be somewhat limited, a finding at variance with some of the original studies on finasteride.\(^{15,16,23,24}\) An additional, longer-term

---

**FIGURE 5.3** PREDICT Study: symptom improvement at 1 year according to treatment group. I-PSS, International Prostate Symptom Score; \( Q_{\text{max}} \), peak urinary flow.
trial, which progressed in parallel to these studies, has generated important new information on both the clinical potential of 5α-reductase inhibitors as monotherapy and the potential of drug combinations.

The Medical Therapy of Prostatic Symptoms (MTOPS) trial, a prospective, randomized, double-blind, multicenter, placebo-controlled trial, was established to determine whether medical therapy can prevent or delay the progression of BPH in the long term. Further elucidation of the natural history of BPH, determining baseline factors associated with more rapid disease progression, was a secondary aim of the study.

In 18 academic centers across the US a total of 3 047 patients were recruited and randomized to receive doxazosin, finasteride, a combination of both, or placebo. Mean age of participants was 62.6 years, most were white (82.6%), with 8.8% black and 7.2% Hispanic participants. The inclusion/exclusion criteria allowed men with all prostate sizes to be enrolled, as long as the serum PSA was less than 10 ng/ml. This resulted in a wide distribution of prostate sizes and serum PSA values allowing for stratified analyses of subsets based on these criteria.

Disease progression was defined as a worsening of BPH symptoms according to the AUA symptom index (AUASI). Progression was deemed to have occurred in the case of one of the following: a 4-point rise in AUASI, confirmed by a second visit within 4 weeks; a 50% increase in creatinine relative to baseline levels; AUR; two or more urinary tract infections (UTIs) within 1 year or a single episode of urosepsis due to bladder outlet obstruction (BOO); socially unacceptable incontinence. The first occurrence of any of the above events indicated BPH progression. Progression as an endpoint represented a novel concept at the time of the initiation of the MTOPS study, although the PLESS study as well as the dutasteride studies later on utilized AUR and surgery as endpoints in their study design.

Entirely novel was the concept of utilizing a threshold to define symptom progression. Based on data from the VA Cooperative study, in which men perceived general improvement in their symptom status once the AUASI improved by more than 3 points, a threshold of 4 points was chosen — to be confirmed within 4 weeks — to indicate global subjective worsening of symptom status.

To assess the natural history of BPH, $Q_{\text{max}}$, prostate volume, sexual function, and quality of life were regularly recorded with respect to BPH symptoms. Transrectal ultrasound and DRE were used to evaluate prostate volume, the Sexual Function Inventory Questionnaire evaluated sexuality and the Short Form-36 Health Survey instrument recorded quality of life scores. Prostatic biopsies were obtained at baseline and at 5 years (or at primary endpoint) in 37% of study participants who volunteered to take part in a biopsy substudy.

Patients were randomized to receive 5 mg finasteride and doxazosin placebo, 5 mg finasteride and doxazosin titrated to up to 8 mg, titrated doxazosin and finasteride placebo, or two placebo drugs.

The results of the trial suggest that the combination of doxazosin and finasteride exerts a clinically relevant, positive effect on rates of disease progression (Figure 5.4). Men who received combination therapy were significantly less likely to experience BPH progression than those receiving either monotherapy or placebo, with risk reduction rates of 39% for doxazosin, 34% for finasteride, and 67% for combination therapy compared to placebo. Overall rates of BPH progression events are shown in Figure 5.5.
Invasive therapy and AUR risk were significantly reduced by finasteride and combination therapy (by 69 and 64%, and by 79 and 67%, respectively), while all treatment regimens (placebo, doxazosin, finasteride, and combination) brought about a significant improvement in AUA symptom score (4.0, 6.0, 5.0, and 7.0, respectively) and $Q_{\text{max}}$ (1.4, 2.5, 2.2, and 3.7 ml/s, respectively) at 4 years.

AUA symptom score and $Q_{\text{max}}$ improved significantly more in the combination therapy group compared to the monotherapy groups, while adverse events were similar to previously reported studies.

In addition to indicating the potential benefits of combination therapy, MTOPS provided important data regarding the natural history of untreated BPH and the prediction of BPH patients who will respond most effectively to medical treatment45–47 (Figure 5.6). While the patients receiving finasteride alone or in combination experienced the expected decrease in prostate volume, patients on placebo or doxazosin alone experienced an increase in prostate volume.
from a baseline of 34.0 ml by 9.3 (30.3%) (placebo) and from 36.4 ml by 9.9 (31.4%) (doxazosin), respectively. Stratified by PSA quartiles, total prostate volume in both placebo- and doxazosin-treated patients increased from 4.9 ml (24.9%) to 16.2 ml (34.5%) from the lowest to the highest quartile for an annualized growth of 1.1 to 3.6 ml/year. These findings suggest that doxazosin despite its apoptotic effect does not interfere with the natural growth tendency of the prostate gland, and that baseline PSA is a useful predictor of future prostate growth in men with LUTS and BPH.

Examination of baseline measures and the disease outcomes of 737 patients treated with placebo revealed that PSA, $Q_{\text{max}}$, PVR, and prostate volume at baseline correlated with clinical progression of the disease and the need for BPH-related surgery ($p = 0.03$ to $< 0.001$). Age was linked to clinical progression ($p < 0.001$) and AUA symptom score correlated with need for surgery ($p = 0.002$). Baseline PSA and prostate volume correlated with risk of AUR ($p = 0.03$–0.003). Risk of progression, BPH-related surgery, and AUR increased alongside levels of serum PSA.

In medically treated patients, however, baseline values were variably predictive of BPH outcome. In doxazosin-treated patients, for example, PSA, $Q_{\text{max}}$, and prostate volume were predictive of outcome; however, this was not true of patients treated with finasteride alone or combined therapy. The number needed to be treated (NNT) to prevent a case of BPH progression as defined in MTOPS in the overall population was 8.4 for the combination therapy group, and 13.7 and 15.0, respectively, for the doxazosin- and finasteride-treated patients. For those men treated with combination therapy who had a baseline PSA of $> 4.0$ ng/ml, however, the NNT was 4.7, and for those with a prostate volume over 40 ml it was 4.9, suggesting that in fact combination therapy becomes an economically viable option in patients at higher risk for progression (unpublished MTOPS data, personal communication Dr Claus Roehrborn).

The link between sexual dysfunction and severity of LUTS was also confirmed by the

**FIGURE 5.6** MTOPS Study: prediction of future risk of BPH clinical progression, BPH-related invasive surgery, and acute urinary retention from baseline prostate-specific antigen (PSA) measures in placebo-treated patients.
MTOPS data. A correlation was observed between LUTS and five domains of sexual dysfunction (libido, sexual function, ejaculatory function, the patient’s assessment of his sexual problems, and overall satisfaction). In addition, men with larger prostates were more likely to have low libido, low overall sexual functioning, reduced ejaculatory function, and greater sexual problems.

ADDITIONAL COMBINATION STUDIES

Anticholinergic plus α-blocker

The anticholinergic agent tolterodine is used for the treatment of incontinence related to detrusor instability, while the α-blocker tamsulosin is commonly used for the treatment of BOO. Patients may present with concomitant BOO and detrusor instability. Investigation of the efficacy of a combination of 2 mg tolterodine twice daily and 0.4 mg tamsulosin once daily was performed to determine whether patient quality of life improved as a result.

Fifty patients took part in the study, and all initially received tamsulosin for 1 week. After this point, the patients were randomized to continue with this regimen or to receive tolterodine in addition to tamsulosin. Baseline urodynamics and quality of life were recorded and these measures were repeated after 3 months of treatment.

Quality of life scores were found to increase significantly in patients who received combination therapy (p = 0.0003), while no increase was observed in patients who received tamsulosin alone. In addition, a significant difference in maximum detrusor pressure and unstable contraction pressure was observed in the combination group. Qmax and volume at first contraction improved significantly in both groups and no AUR was reported. The results suggest that this combination is a safe and effective treatment option for this patient group.

Combined ‘natural’ products

The role of plant-derived therapy in the treatment of BPH has been, and still is, considered controversial, and the combination of products such as Serenoa repens, β-sitosterol, and Pygeum africanum is even more debatable.

One trial comparing a combination of cernitin, Serenoa repens, β-sitosterol, and vitamin E to placebo indicated potential benefits for patients receiving the active agents. In total, 127 BPH patients with a Qmax of 5–15 ml/s took part in the study and were randomized to receive either the combined therapy or placebo for 3 months. AUASI, Qmax, PSA, and PVR were assessed at baseline and on conclusion of the trial.

Significant reductions in nocturia (p < 0.001) and daytime frequency (p < 0.04) were observed in the active arm of the study compared to the placebo group. Average score on AUASI also improved in this group compared to placebo (p < 0.014). No difference in PSA, Qmax, or PVR was observed and no serious side-effects were reported.

The combination of phytotherapy with conventional pharmacotherapy has not been fully investigated to date; however, a 3-month trial of tamsulosin, cernitin, or a combination of the two revealed significant improvements in I-PSS in all three groups, but improved Qmax and average urinary flow only in the tamsulosin and combination groups.

DISCUSSION

Several large-scale studies have indicated that the combination of an α-blocker with a 5α-reductase inhibitor does not add any clinically significant
value to α-blockade alone. However, the larger and longer-term MTOPS study would appear to be at variance with these findings (Table 5.1). In this trial, participants were followed up for 4.5 years on average and those who were involved in the pilot phase were followed up for an average of 6 years. This is considerably longer than previous trials of combination therapy for BPH. The VA and PREDICT studies had a duration of 1 year, while the ALFIN study lasted just 6 months.

Although earlier trials indicated no benefit over and above α-blockade with the addition of finasteride treatment, the evidence provided by MTOPS has shown that combination therapy may be appropriate for many patients, particularly those with larger glands and higher baseline serum PSA values. This observation is reflected in the recently published AUA Guidelines on the Management of BPH state, on the basis of panel consensus, that the combination of an α-blocker and a 5α-reductase inhibitor may be appropriate in LUTS patients with demonstrable enlargement of the prostate.

Any reduction in risk of AUR and BPH-related surgery associated with combination therapy described in the MTOPS study should be weighed up against cost and other factors on an individual basis, however. The panel stated that those most likely to benefit are men at greatest risk of disease progression, i.e. those with larger prostates and higher PSA levels. Although the best-tested combination to date is doxazosin and finasteride, and the safety of other combinations has not been fully assessed, the panel assumes that any combination of these drug classes would lead to a similar degree of clinical benefit.

Additional factors should also be considered in the combination therapy debate. Cost issues are of primary importance, as dual therapy is obviously more expensive than monotherapy alone. It has been suggested that dual therapy need not be continued indefinitely, however, which may have a bearing on associated costs.

Baldwin et al. found that BPH patients treated initially with finasteride plus an α-blocker tolerated discontinuation of combination therapy after 1 year with no compromise in clinical benefit. A group of BPH patients (n = 270) were prescribed 2, 4, or 8 mg doxazosin alongside 5 mg finasteride for a period of 3, 6, 9, or 12 months, after which doxazosin was discontinued. Of those who discontinued combination therapy at 12 months, 84% of the 2 mg group, 85% of the 4 mg group, and 87% of the 8 mg group experienced no increase in AUA symptom score and reported no desire to resume taking doxazosin 1 month later. Similarly high tolerance levels were reported in patients with BOO and moderately enlarged prostates who discontinued combination therapy after 9 months.

Other factors, such as the difference in the effects of 5α-reductase inhibitors and α-blockers on PSA levels, and the recently discovered relationship between the use of finasteride and a reduction in risk of prostate cancer, may also influence the use of combination therapy.

It has been suggested that prostate volume influences the outcome of patients treated with finasteride, and that men with larger prostates will benefit more from treatment with 5α-reductase inhibitors. The VA, ALFIN, and PREDICT studies all included BPH patients with relatively small prostates (36.2–38.4 ml, mean 41.2 ml, and mean 36.3 g, respectively). Men with larger glands may therefore benefit more from combination treatment than those with smaller glands, who might be better treated with an α-blocker alone. The ongoing subset stratification
TABLE 5.1  Comparison of large-scale combination studies of BPH treatments.

<table>
<thead>
<tr>
<th>Duration</th>
<th>Mean age</th>
<th>Mean baseline prostate volume (ml)</th>
<th>n</th>
<th>Regimen (daily dose)</th>
<th>Symptom score* % improvement</th>
<th>Qmax % improvement</th>
<th>Prostate volume % change</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA Cooperative Study⁶ 1 year 65 36.2–38.4 305</td>
<td>Terazosin (10 mg) 38</td>
<td>26</td>
<td>+1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>310 Finasteride (5 mg) 20</td>
<td>15</td>
<td>–17</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>309 Combination 39</td>
<td>31</td>
<td>–19</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>305 Placebo 16</td>
<td>13</td>
<td>+1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALFIN³¹ 6 months 63 41.2 358</td>
<td>Alfuzosin (10 mg) 41</td>
<td>19</td>
<td>–0.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>344 Finasteride (5 mg) 36</td>
<td>18</td>
<td>–11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>349 Combination 39</td>
<td>23</td>
<td>–12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PREDICT³⁴ 1 year 63 36.3 g 275</td>
<td>Doxazosin (&lt; 8 mg) 49</td>
<td>35</td>
<td>—</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>264 Finasteride (5 mg) 39</td>
<td>18</td>
<td>—</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>286 Combination 49</td>
<td>37</td>
<td>—</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>270 Placebo 33</td>
<td>10</td>
<td>—</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTOPS⁴⁴ 4 years 62 31.0 756</td>
<td>Doxazosin (4/8 mg) 35</td>
<td>24</td>
<td>+18</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>768 Finasteride (5 mg) 30</td>
<td>21</td>
<td>–16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>786 Combination 41</td>
<td>35</td>
<td>–13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>737 Placebo 24</td>
<td>13</td>
<td>+18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Evaluation tools: for VA, PREDICT, and MTOPS = American Urological Association symptom score; for ALFIN = International Prostate Symptom Score.
of the MTOPS data may provide further insight into this area.

CONCLUSIONS

The reduction in frequency of TURP for the treatment of BPH and the rise in use of medical therapy suggest high levels of patient and physician satisfaction with pharmacologic options. However, future advances in available drug preparations may be limited. Dual therapy, involving preparations from different drug classes, may represent a further potential avenue for medical BPH therapy.

The efficacy of the \( \alpha \)-blockers doxazosin, terazosin, alfuzosin, and tamsulosin and the 5\( \alpha \)-reductase inhibitors finasteride and dutasteride has been proven in many large, well-controlled clinical trials. However, the combination of the two drug classes has produced variable clinical results. Until recently, the benefits that might logically be expected from therapy targeting two separate elements of BPH pathology—namely, prostatic enlargement and an increase in smooth muscle tone—had not been described in larger-scale studies.

The results of the MTOPS trial, however, indicate that symptomatic improvements in BPH occur to a greater extent in men receiving doxazosin and finasteride in combination compared to either agent alone. Disease progression, as assessed mainly by a four-point rise in the AUASI, was significantly less likely in patients in the combination group, while AUR and BPH surgery were also less common in this group.

The strength of the findings has led to the inclusion of recommendations for combination therapy in suitable patients in the AUA BPH management guidelines. Further trials assessing the safety and efficacy of other types of \( \alpha \)-blocker and 5\( \alpha \)-reductase inhibitor in combination may be expected to follow.

The value of different types of combination therapy, involving plant-derived preparations or the use of anticholinergics for example, remains to be determined.

REFERENCES


27. Erdogru T, Ciftcioglu M A, Emreoglu I et al. Apoptotic and proliferative index after alpha-1-adrenoceptor antagonist and/or finasteride treat-
Combination therapy in the treatment of BPH


INTRODUCTION

Benign prostatic hyperplasia (BPH) is the most frequently diagnosed neoplastic disease in the aging male, affecting approximately 85% of all men over 50 years of age. By the ninth decade of life, 50% of all American men require treatment for symptomatic relief of the lower urinary tract symptoms (LUTS) associated with BPH. Clinically, BPH is characterized by prostatic enlargement and the accompanying symptoms of progressive bladder outlet obstruction.

Histologically, BPH can present as hyperplasia in both the stromal and glandular components of the gland and arises in the periurethral and transition zones. It has been hypothesized that this abnormal proliferation arises because of the ability of the prostate stroma to retain an embryonic growth potential that is ‘reawakened’ in the aging gland. Although aging and the presence of a functional testis have become established as major factors causally related to the development of the disease, the molecular processes involved in the pathogenesis of BPH remain poorly understood.

In this chapter we review some recent clinical data that may provide additional insight into the pathophysiology of BPH and facilitate the development of more effective pharmacologic therapy.

MEDICAL MANAGEMENT OF BPH: A HISTORICAL PERSPECTIVE

The development of LUTS secondary to prostatic enlargement is thought to be caused by static (mechanical) and dynamic components of urethral restriction. The mechanical component arises from the physical obstruction of urinary outflow caused by urethral constriction, induced by the mass of the enlarged gland. The dynamic component is related to the variations in smooth muscle tone in the fibromuscular stroma, prostate capsule, and bladder neck. Treatment modalities therefore aim either to reduce the mechanical obstruction, or to induce relaxation of the periurethral prostatic smooth muscle.

A critical level of androgen is required to maintain the benign growth pattern and androgen deprivation results in significant involution of the glandular epithelial component of the prostate, without affecting stromal growth. Androgen ablation/deprivation undoubtedly leads to a favorable ‘therapeutic’ response in canine BPH, a species where the bulk of the hyperplasia is androgen-dependent epithelial proliferation. In man, however, the maximal therapeutic effect of androgen deprivation appears to be limited by both the substantial stromal component of the proliferation and by intrinsic resistance of stromal cells to androgen modulation.

Given that at least 40% of the cellular volume of the enlarged prostate is composed of stromal smooth muscle, it is not surprising that pharmacologic intervention at this level has proved highly successful. In this context, $\alpha_1$-adrenoceptor antagonists ($\alpha$-blockers) are widely used to produce acute symptomatic relief. The classic belief is that $\alpha$-blockers reduce the tone of the prostate smooth muscle and thereby inhibit the dynamic component of the obstruction. The pharmacol-
ogy of α-blockers is described in detail elsewhere.\textsuperscript{11} The following represents a summary of the key features.

Periurethral smooth muscle tone, and therefore urethral resistance, varies according to the degree of sympathetic nervous system activation of the α\textsubscript{1} adrenoceptors in the prostate and prostate capsule.\textsuperscript{12,13} Therefore, pharmacologic blockade of the α\textsubscript{1} adrenoceptors would reduce the actions of noradrenaline (the endogenous neurotransmitter), resulting in tissue relaxation. This provided the impetus for the development of several α\textsubscript{1}-blockers and has resulted in widespread use of this class of drugs as first-line intervention in BPH.

Currently, four native α\textsubscript{1}-adrenoceptor subtypes—α\textsubscript{1A}, α\textsubscript{1B}, α\textsubscript{1D}, and α\textsubscript{1L)—have been identified and are known to be located in the prostate.\textsuperscript{11} The best correlation between prostate tissue contraction and binding with any α\textsubscript{1}-adrenoceptor recognition site is with the α\textsubscript{1A} subtype.\textsuperscript{14,15} Many investigators consider this evidence to be consistent with a primary role of this adrenoceptor subtype in the control of prostate tone and urethral resistance. However, when considering the treatment of BPH symptoms, extraprostatic actions of α\textsubscript{1}-blockers must also be taken into account\textsuperscript{11}. In particular, α\textsubscript{1}-adrenoceptors in the bladder and bladder neck,\textsuperscript{16,17} and spinal cord,\textsuperscript{18,19} and on efferent pathways\textsuperscript{19,20} may make an important contribution to the overall improvements in urodynamic and symptom profiles that are observed shortly after the onset of therapy.

Although the immediate and short-term therapeutic benefit of α-blockers is believed to arise from the prostatic and extraprostatic physiologic actions listed above, it has become apparent that in the long term other factors or loci may make an equally important contribution.\textsuperscript{5}

### THE α-BLOCKER PARADOX

Consistent with their actions as α-blockers on periurethral stromal smooth muscle, the acute clinical benefit of terazosin and doxazosin in BPH is well documented\textsuperscript{22}.

In the early days of use in the management of BPH, there was a general expectation that α-blockers might serve as clinical ‘sticking plaster’ in the face of ongoing glandular hyperplasia; tachyphylaxis (tolerance) to the drug action was anticipated. Although this may undoubtedly occur in individual patients, the effects of doxazosin and terazosin in BPH have been maintained (Figure 6.1), in some cases for up to 7 years,\textsuperscript{22–24} a period over which the prostate mass would be expected to increase by up to 50\textperthousand.\textsuperscript{1} The equivalent long-term data for doxazosin similarly show no overall evidence of tachyphylaxis. On the assumption that the increase in prostate bulk (the static component of obstruction) would result in a corresponding increase in urethra resistance, considerable diminution in benefit might be anticipated over an equivalent time period.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure6_1.png}
\caption{Long-term terazosin efficacy data. Data were generated in open-label uncontrolled clinical trials. From 1 month onwards all points were significantly different from baseline and there was no evidence of tachyphylaxis.}
\end{figure}
Several clinical papers now offer a partial explanation of the well-documented, but unexpected longevity of the α-blocker response. These were retrospective, placebo-controlled studies involving a total of 134 BPH patients and were designed to determine the effects of α-blockers on apoptosis and the interrelationship with symptom improvement. Importantly, each patient acted as his own control: LUTS and histochromed parameters were measured at baseline and at one other time point in the study after the patient had been assigned to either placebo or α-blocker.

In three other studies, cell proliferation and apoptosis were evaluated in BPH patients, who comprised an untreated control group and two cohorts treated with either terazosin or doxazosin at doses designed to provide symptom relief. The treatment period varied from 1 week to 3 years. Terazosin was used at 1–10 mg/day and doxazosin at 2–8 mg/day. Proliferation and apoptosis of the stromal and epithelial cell components of the prostate, obtained by initial biopsy or at prostatectomy, were quantified by Ki 67 immunostaining and TUNEL (terminal transferase UTP-end labeling) assay, respectively.

Both terazosin and doxazosin induced epithelial and stromal cell apoptosis within the first month of treatment (Figure 6.2) when compared with the untreated controls ($p < 0.05$). The marked induction of stromal apoptosis was paralleled by significant decreases in smooth muscle α-actin expression (Figure 6.3). This loss of prostate smooth muscle cells correlated with the morphologic stromal regression (measured by trichrome staining) and improvement in BPH symptoms. Proliferation was relatively unaffected by both drugs.

The data indicate that there is a significant induction of apoptosis in the prostate epithelium and stroma in response to terazosin and doxazosin (over the normal therapeutic dose range). Compared with the untreated controls, terazosin induced epithelial and stromal cellular apoptosis.

**FIGURE 6.2** Effect of terazosin on prostate apoptosis in patients with BPH. The apoptotic index of glandular epithelial (■) and stromal (■) smooth muscle cells in biopsy sections is expressed as mean percentage of TUNEL–positive cells/total number of cells after various periods of terazosin therapy (1–10 mg/day). (Adapted from Chon et al.)

**FIGURE 6.3** Effect of terazosin on stromal smooth muscle α-actin expression. The bars represent the quantitative evaluation of smooth muscle α-actin immunoreactivity in prostate sections from BPH patients treated with terazosin (1–10 mg/day). (Adapted from Chon et al.)
within the first month of treatment, which correlated with morphologic stromal regression and the improvement in LUTS. There was no effect on cell proliferation. The data indicate that terazosin induced apoptosis in the glandular epithelium and stroma but has no effect on the cellular dynamics of normal (i.e. nonBPH) tissue.\textsuperscript{22,23}

There is an excellent correlation between the degree of apoptosis and improvement of symptoms (Figure 6.4). One interpretation of these phenomena is that α-blockers can affect abnormal prostate growth such as that observed in BPH and potential prostate carcinoma. This could reflect a direct effect on cellular dynamics or may arise secondary to an action on cellular proliferative factors. As in the case of the vasculature, androgenic and estrogenic factors alter the expression of α1-adrenoceptors in prostate tissue.\textsuperscript{28,29} Catecholamines have been shown to have proliferative (promitogenic) action in several vascular tissues.\textsuperscript{30} Should this translate to the prostate, the observed effects could merely reflect the drug-induced attenuation of endogenous catecholamines. A model of the potential intervention points for terazosin is shown in Figure 6.5.

The most obvious explanation of the proapoptotic phenomenon is that this is directly related to blockade of α1-adrenoceptor subtypes. A good correlation is known to exist between activity at the α1A subtype and prostate smooth muscle contraction.\textsuperscript{11} However, prostate tissue contains other α1-adrenoceptor subtypes (α1A and α1B) and it is tempting to speculate that an action at one of these could underpin the cellular effects of the α-blockers. It is likely that an action additional to blockade of the proliferative effects of endogenous catecholamines, and independent of α-adrenoceptors, is involved.\textsuperscript{5,10}

The clinical evidence for a proapoptotic action of doxazosin and terazosin is supported by cell biology and in vivo animal experiments.\textsuperscript{31,32} In a mouse prostatic reconstruction model, α-blockers had a proapoptotic action and reduced oncogene-induced growth hormone without affecting normal cellular growth patterns\textsuperscript{11}. This proapoptotic effect does not appear to be restricted to the mouse, at least in vitro; a similar profile of activity is observed in cancer cell lines\textsuperscript{33–35} at drug concentrations similar to those found therapeutically.\textsuperscript{33} The effect was apparent in both hormone-dependent and hormone-independent cell lines,\textsuperscript{32,34} and as such could indicate a potential beneficial effect in prostate carcinoma, in addition to prevention of BPH/LUTS. Intriguingly, these actions are not found with tamsulosin.\textsuperscript{34} Tamsulosin is a sulfonamide that is structurally dissimilar to the quinazoline α-adrenoceptor antagonists (Figure 6.6). This indicates that the proapoptotic actions are not a class effect, and are independent of the α1-adrenoceptor.\textsuperscript{5,32,34}

The effects of terazosin on prostatic apoptosis may also help in the interpretation of clinical data generated by the Veterans’ Affairs study\textsuperscript{36} and the PREDICT study\textsuperscript{37} using a combination of finasteride with terazosin and doxazosin, respectively.
These studies showed that the combination of finasteride and an \( \alpha \)-blocker does not provide any therapeutic benefit within the first 2 years over terazosin alone, at least with respect to symptom improvement. Potentially, doxazosin and terazosin in their own right can affect prostate growth by inducing both epithelial and stromal apoptosis; by comparison, the anti-androgenic effect of finasteride is likely to be restricted to induction only of glandular epithelial apoptosis.\(^{38}\)

Thus, it could be argued that the apoptosis-inducing profile of quinazolines provides the molecular basis for the inability of finasteride to enhance the therapeutic effect of doxazosin and/or terazosin therapy in the short to medium term.

However, considering the multifactorial pathogenesis, there is logic in the use of therapies that target different cellular components. The combination of a 5\( \alpha \)-reductase inhibitor with a quinazoline-type \( \alpha \)-blocker should potentially combine the clinical benefit resulting from the anti-growth effects of androgen deprivation-induced apoptosis in the epithelium with the apoptosis induced by the quinazolines in the stroma. In the long-term MTOPS study over 7 years such synergy was observed.\(^{24}\) At least with respect...
to delaying clinical progression, the combination was more effective than either component. Intriguingly, doxazosin alone was found to delay progression only over the first 3 years or so. Thus the long-term data are consistent with the data in the combination studies described above, of 2 years’ duration.\textsuperscript{36,37}

**SUMMARY**

There is now considerable evidence that \( \alpha \)-blockers have a proapoptotic effect in prostate tissue. Although such an action may not underlie the short-term therapeutic benefit observed with these agents, it could make an important contribution to the longer-term durability of the response. The proapoptotic effect of doxazosin and terazosin in both stromal and epithelial components could offer an explanation of the inability of finasteride (which has effects on epithelial components) to augment the response of these \( \alpha \)-blockers in clinical studies of up to 2 years’ duration. The finding that tamsulosin does not have these properties raises the possibility that the proapoptotic action is not a class effect, and may be independent of the \( \alpha_1 \)-adrenoceptor.

**REFERENCES**

18. Ishizuka O, Persson K, Mattiasson A et al. Micturition in conscious rats with and without out-
ADRENOCEPTOR ANTAGONIST EFFECTS ON PROSTATE TISSUE GROWTH

let obstruction: role of spinal \( \alpha_1 \)-adrenoceptors. Br J Pharmacol 1996; 117: 962–966


INTRODUCTION

The treatment of the lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) with $\alpha$-adrenoceptor antagonists (blockers) has evolved considerably since the pioneering clinical work of Marco Caine\(^1\) using phenoxybenzamine. Initially, only two types of $\alpha$-adrenoceptors ($\alpha_1$ and $\alpha_2$) were identified. Phenoxybenzamine has antagonist activity at both $\alpha_1$- and $\alpha_2$-adrenoceptors and is therefore a nonselective antagonist. Subsequently, it was found that prostate tissue contraction relied primarily on activation of the $\alpha_1$-adrenoceptor.\(^2\)

This led to the development and clinical evaluation of the prototype selective $\alpha_1$-adrenoceptor antagonist, prazosin, in an attempt to reduce the side-effects associated with phenoxybenzamine.

The proposed mechanism for the efficacy of selective $\alpha_1$-blockade in BPH is via relaxation of prostate smooth muscle. It therefore follows that the magnitude of the clinical response to selective $\alpha_1$-blockade in BPH should be related directly to the proportion of the hyperplasia that is smooth muscle. Shapiro et al.\(^3\) evaluated the relationship between the percentage area density of prostate smooth muscle and the clinical response to the selective long-acting $\alpha_1$-antagonist, terazosin. Before starting terazosin therapy, prostate biopsy specimens were obtained from 26 men. The dose of terazosin was titrated to 5 mg, provided that serious adverse events were not observed. The percentage area density of smooth muscle in the biopsy specimens was quantified using double immunoenzymatic staining and color-assisted computer image analysis. A direct relationship between the increase in peak urinary flow rate ($Q_{\text{max}}$) and the percentage area density of smooth muscle was observed. This correlation strongly supports the hypothesis that a component of the development of bladder outlet obstruction is mediated by an increase in prostate smooth muscle tone. Certainly the classical belief is that $\alpha$-antagonists act by reducing the tone of the prostate smooth muscle, decreasing urethral resistance, and thereby the dynamic component of the obstruction.\(^4,5\) However, increasingly this is being challenged and it is probable that extraprostatic actions of $\alpha$-antagonists are of considerable importance.\(^6\)

Although bladder outlet obstruction in aging men is often mediated by prostate smooth muscle proliferation, there is increasing evidence that the severity of urinary symptoms is not exclusively the result of bladder outlet obstruction. The correlation between symptom severity captured by the American Urological Association (AUA) symptom index and $Q_{\text{max}}$ is poor\(^7\) and, unlike $Q_{\text{max}}$, the density of prostate smooth muscle is not directly correlated with symptom severity.\(^3\) These observations suggest that urinary symptoms in the aging male are probably multifactorial. It is also conceivable that symptom improvement in men with prostatism is achieved via nonprostate smooth muscle events mediated by the $\alpha_1$-adrenoceptor.
Our understanding of adrenoceptor pharmacology has increased considerably. Four native α₁-adrenoceptor subtypes have now been identified and are known to be located in the prostate: the α₁A, α₁B, and α₁D subtypes are high-affinity receptors for prazosin; the α₁L is a low-affinity receptor. The evolution of this nomenclature has been confusing and has changed over the last few years, as reviewed by Bylund et al. The best correlation between prostate tissue contraction and binding with any of the α₁-adrenoceptor recognition sites is with the α₁A subtype (Figure 7.1). On the basis of this and other evidence, many investigators consider that the α₁A subtype within the periurethral stroma is the prime determinant of prostatic tone. However, the extraprostatic actions of α₁-antagonists may make important contributions to the overall urodynamic and symptom score that is observed soon after therapy is initiated.

Considerably less is known about the role of the prostate α₁B and α₁D subtypes. However, these could be linked to the effects of terazosin on glandular growth and apoptosis (see Chapter 10), described in more detail below.

The α₁-antagonists that have been used clinically in the treatment of LUTS/BPH can be subgrouped according to their selectivity for different receptor subtypes and their pharmacokinetic half-lives. Phenoxybenzamine is a non-selective α₁-antagonist with equal affinity for α₁- and α₂-adrenoceptors. Drugs with selectivity for the α₁-adrenoceptor, including prazosin, alfuzosin, indoramin, terazosin, doxazosin, and tamsulosin, were subsequently developed. The primary advantage of these selective α₁-antagonists is that the incidence and severity of adverse events is significantly less than with the nonselective α-blocker, phenoxybenzamine. There is no evidence from in vitro or whole-animal experiments that any of the established agents is selective for any one α₁-adrenoceptor subtype (Figure 7.2), or possesses any degree of clinical uroselectivity as defined by the α-blocker subcommittee of the International Consultation on BPH.
As a class, \( \alpha \)-adrenoceptor antagonists have been shown to be safe and effective in the treatment of obstruction-related LUTS. Obstructive and irritative symptoms are improved, and changes in urinary flow and residual volume are consistent with a reduction in urethral resistance. Prazosin has been used in this context for several years, but its clinical use is limited by its dosing regimen and the orthostatic hypotension that follows rapid absorption. Terazosin was the first selective \( \alpha \)-antagonist specifically developed to overcome these shortcomings. It has similar affinity for the \( \alpha_{1A} \), \( \alpha_{1B} \), and \( \alpha_{1D} \)-adrenoceptor subtypes (Figure 7.2), and is therefore considered to have a balanced profile. In addition, terazosin can be distinguished from prazosin on the basis of physicochemical differences that result in a more gradual onset of action and a much longer plasma half-life (16 hours compared with about 3 hours).

In this chapter we review the clinical data on terazosin and discuss how the balanced action of terazosin across the three high-affinity \( \alpha \)-adrenoceptor subtypes translates into potential clinical advantages for patient, primary-care physician, and urologist alike.

### HISTORIC BACKGROUND

Terazosin is a potent quinazoline \( \alpha \)-adrenoceptor antagonist that is extremely selective for the \( \alpha_1 \) versus the \( \alpha_2 \) subtype. There is little evidence from isolated-tissue studies or whole-animal experiments that terazosin has higher affinity for any one of the \( \alpha \)-adrenoceptor subtypes. The plasma half-life (16 hours) is consistent with once-daily dosing. The contribution of metabolites to the overall profile of terazosin is unknown.

### SAFETY AND EFFICACY IN THE MANAGEMENT OF BPH

#### Short-term efficacy

At least 11 double-blind placebo-controlled studies in patients with BPH/LUTS have been completed, and a rigorous meta-analysis of the findings has been reported. The data from a large (285 patients) representative study are shown in Figure 7.3. Statistically significant decreases from baseline were observed for obstructive, irritative, and total symptom scores, for all terazosin groups; the higher doses produced statistically significant improvements over placebo, with up to 70% of patients achieving more than a 30% improvement in symptom scores. Changes in symptoms were mirrored by dose-related improvements in peak and mean urinary flow (Figure 7.4).

The LUTS symptoms associated with BPH were also improved to a statistically significant extent in most of the studies included in the meta-analysis. Irrespective of the different symptom
scores used in these studies, consistently greater responses were recorded in patients treated with terazosin than in those receiving placebo and, when assessed, the degree of symptom bothersomeness was reduced significantly. The usual effective dose was either 2 mg or 5 mg per day, although additional benefits were observed in some patients with doses up to 10 mg per day.

The beneficial effects of terazosin on irritative and obstructive symptoms and urinary flow are seen within the first few weeks of treatment, often before the dose of terazosin has been titrated to its optimum (Figure 7.4). This has considerable clinical implications, in that patients may be more likely to comply with treatment if they experience an early improvement in symptoms.

Systematic reviews of the effectiveness of terazosin in the treatment of LUTS have confirmed that the drug is superior to both placebo and finasteride.\(^\text{15,17,18}\) In these analyses, terazosin treatment was associated with increases in peak flow of 1.4 ml/s compared to placebo and with an average reduction in symptom score of 2.2 points beyond that observed with placebo.

**Long-term efficacy**

Any treatment for LUTS/BPH must achieve a durable clinical response in order to assume a meaningful role in patient management. The durability of the terazosin response has been reported in one open-label study of almost 500 men over a 4-year period.\(^\text{19}\) In this study, terazosin was started at 1 mg per day and the dose was titrated upwards at the investigators’ discretion, to a maximum of 20 mg per day. The primary efficacy variables were $Q_{\text{max}}$ and Boyarsky symptom score. At the follow-up visits, $Q_{\text{max}}$ was significantly higher than baseline; a 30% improvement over the course of the follow-up was observed in 40–59% of patients. Similarly, the irritative, obstructive, and total Boyarsky symptom scores were significantly lower than at baseline at all follow-up intervals (Figure 7.5); 30% or
greater improvement was noted in 62–77% of patients.

A similar durability of response was observed in another long-term study involving over 1200 patients in whom the response to terazosin was compared with that of placebo, finasteride (a 5α-reductase inhibitor), and a combination of finasteride plus terazosin (Figure 7.6).20 In this study, finasteride and placebo were equally effective, producing only marginal improvements in symptoms. By contrast, terazosin and the combination therapy were significantly more effective; terazosin alone reduced the AUA symptom score by 6 units and increased $Q_{\text{max}}$ by 3.6 ml/s. Thus, improvements in symptoms and urinary flow were equivalent to those observed in the shorter double-blind studies described above.

These data certainly refute the expectations of earlier years that α1-antagonists may only provide temporary benefit in BPH/LUTS. In the face of ongoing glandular proliferation, it was anticipated that tachyphylaxis (tolerance) would occur. However, the long-term data show that the effect of terazosin in BPH is maintained over a 5-year period, over which time the prostatic mass would be expected to increase by up to 50%.21 On the basis that the increased prostatic bulk would result in a corresponding increase in urethral resistance, considerable diminution of benefit could have been expected over this time course. Two clinical studies (described in more detail below) suggest that the unanticipated longevity of the response could be due to induction of apoptosis within the prostate (see Chapter 10).11,22

**Safety profile**

The clinical database for terazosin in the treatment of LUTS/BPH and hypertension extends to more than 3 billion patient days and shows that the drug is well tolerated. In double-blind studies in BPH, overall 15% of terazosin-treated patients discontinued therapy, compared with 9% of placebo recipients (representing only a 6% reduction in compliance compared with placebo). The most frequently reported side-effects in both groups were dizziness, vertigo, headache, and fatigue; cardiovascular events such as postural hypotension were infrequent. Most side-effects...
were mild in severity and did not warrant treatment or discontinuation of therapy.

Terazosin was equally well tolerated over much longer periods. In the long-term study described above,21 the incidence of adverse events was similar to that observed in the initial double-blind studies.

Overall, the side-effect profile of terazosin at doses that are fully effective in providing relief of LUTS/BPH appears to be characteristic of the class.13

OVERALL CLINICAL PROFILE

Effects on blood pressure

The role of $\alpha_1$-adrenoceptors in the control of the hemodynamic baseline is of potential clinical consequence to both normotensive and hypertensive BPH patients. Epidemiologic studies have shown that up to 40% of men with BPH have hypertension (controlled or uncontrolled).

Although (as described above) there is some consensus that the $\alpha_{1A}$-adrenoceptor is the prime determinant of prostate tissue contraction, much less is known about the subtype involved in cardiovascular regulation. Perhaps not surprisingly, as blood pressure is the algebraic summation of many cardiac and vascular processes, the "blood pressure receptor subtype" has not been identified.6 Although there may be differential distributions within the vasculature, all three subtypes ($\alpha_{1A}$, $\alpha_{1B}$, and $\alpha_{1D}$) are ubiquitous.8,21 On this basis it can be assumed that these three subtypes are involved in cardiovascular homeostasis and that effective blood pressure control will therefore occur only with a balanced $\alpha_1$-adrenoceptor antagonist, such as terazosin. Equally, a "uroselective" antagonist will not provide effective blood pressure control in the many LUTS/BPH patients who also have hypertension.

It is well documented that the changes in blood pressure observed with $\alpha_1$-blockers are highly dependent on the hemodynamic baseline. Terazosin lowers blood pressure when the sympathetic tone is high, for example in BPH/LUTS patients with hypertension (Figure 7.7),17,24 but has much less effect on resistance vessels in normotensive patients, in whom only clinically insignificant changes in blood pressure are observed (Figure 7.7).17,24,25 Terazosin has no effect on the hemodynamic baseline, irrespective of whether the BPH/LUTS patients are physiologically normotensive or are stabilized on hypertensive therapy.24,25

Overall, therefore, the potential antihypertensive effect of terazosin could be of considerable advantage to the relatively high proportion (40%) of BPH/LUTS patients who have uncontrolled or poorly controlled hypertension. Similarly, the long-term effects of terazosin in normotensive patients are of little clinical concern, although the potential to produce first-dose postural hypotension must always be considered.

FIGURE 7.7 Effect of terazosin on blood pressure in (a) hypertensive and (b) normotensive patients. Data show blood pressure at baseline (■) and after treatment (●). (Adapted from reference 17.)
Tamsulosin does not appear to lower blood pressure consistently or markedly in hypertensive patients.\textsuperscript{26} This profile is claimed to arise from the intrinsic ‘uroselectivity’ of the drug; however, this claim has been disputed,\textsuperscript{6} and the ‘uroselectivity’ may simply reflect incomplete $\alpha$-blockade at the dose used in clinical practice (0.4 mg).\textsuperscript{27}

**Cardiovascular risk factors**

Most of the risk factors for hypertension are common to congestive heart failure and atherosclerosis.\textsuperscript{28} Particularly relevant are an abnormal lipid profile and abnormal insulin resistance/glucose tolerance. The metabolic effects of terazosin and other antihypertensive agents have been reviewed by Pool.\textsuperscript{28,29} Terazosin has potentially beneficial actions on several of the risk factors (abnormal lipids, fibrinolysis, platelet aggregation) that could have important implications in the prevention of hypertension, coronary heart disease (CHD), and atherosclerosis.\textsuperscript{30–32}

Extensive studies of almost 17,000 hypertensive patients in primary care and community facilities suggest that the blood-pressure-lowering actions of terazosin, coupled with its beneficial effects on associated cardiovascular risk factors, should significantly reduce CHD.\textsuperscript{30} On the basis of the Framingham model,\textsuperscript{31} a reduction in the incidence of CHD of approximately 20% would be predicted from these changes in CHD risk factors. However, the recent results from the ALLHAT study,\textsuperscript{34} and the conclusions of JNC-7,\textsuperscript{35} indicate that terazosin and other $\alpha$-blockers should not be considered as front-line monotherapy in the treatment of cardiovascular disease. However, bearing in mind that many BPH/LUTS patients have several associated cardiovascular risk factors, these data provide support for the use of terazosin in any holistic approach to the management of the BPH/LUTS patient as a whole.

**Effects on the urogenital tract**

The clinical improvement in BPH/LUTS observed with any $\alpha$-antagonist depends on a variety of actions within the urogenital tract.\textsuperscript{5,12} Although actions on prostate smooth muscle undoubtedly contribute to these effects, it is important to remember that there is no direct correlation between changes in urethral resistance and flow rates on the one hand and symptom improvement on the other. Furthermore, it should be remembered that patients usually present because of symptoms and bothersomeness, not because of reduced urinary flow. Thus, the extraprostatic actions of terazosin on the bladder, bladder neck, spinal cord, and efferent pathways\textsuperscript{6,36} may be just as important as the changes induced in periurethral prostate smooth muscle tone.

**Effects on glandular growth**

Although (as described above) the immediate and short-term therapeutic benefits of $\alpha$-antagonists undoubtedly arise from direct and indirect actions on prostate smooth muscle, it is becoming apparent that other factors are important in the long term.

In the early days of the use of $\alpha$-blockers in BPH/LUTS, tachyphylaxis (tolerance) to the drug was expected, and, because of the continued glandular hyperplasia, it was thought that $\alpha$-antagonists might act only as clinical ‘sticking plasters’, with the effect reducing with time. Clearly, long-term studies with terazosin (Figure 7.5) show a durability of response beyond the original expectations.
The findings of at least two recent clinical studies may offer some insight into this apparently paradoxical longevity of response with terazosin.\textsuperscript{11,20,37} In one study cell proliferation and apoptosis were evaluated in BPH patients who either received no treatment (control group) or were treated with terazosin at the normal clinical dose range (1–10 mg); the treatment period was between 1 week and 3 years. Compared with the untreated controls, terazosin induced epithelial and stromal cellular apoptosis within the first month of treatment (Figure 7.8), and there was a parallel increase in the expression of smooth muscle $\alpha$-actin. The loss of prostate smooth muscle cells correlated with morphologic stromal regression and the improvement in LUTS. There was no effect on cell proliferation. The data indicate that terazosin treatment (over the normal dose range) results in a substantial induction of apoptosis in the glandular epithelium and stroma. However, there was no effect on the cellular dynamics of normal (i.e. nonBPH) tissue. One potential interpretation is that terazosin can affect abnormal prostate growth, such as that observed in BPH or prostate carcinoma. Theoretically this could account for the durability of the response to terazosin in long-term studies.

The effects of terazosin on prostate apoptosis may also help in the interpretation of the clinical data generated in the Veterans’ Affairs study (Figure 7.6).\textsuperscript{20} This study showed that the combination of finasteride and terazosin did not provide any therapeutic benefit over terazosin alone, at least with respect to symptom improvement. Terazosin potentially affects prostate growth by inducing apoptosis in both epithelial and stromal components. Should this be the case, it is perhaps not surprising that finasteride (which affects only epithelial tissue) cannot augment the response to terazosin. However, further clinical evaluation of this hypothesis is required. The overall profile of terazosin and the possibility that the induction of apoptosis is independent of the $\alpha_1$-adrenoceptor and is not a class effect is explored in Chapter 30.

**CONCLUSIONS**

Terazosin has a balanced pharmacologic action across the three high-affinity receptor subtypes of the $\alpha_1$-adrenoceptor, which is reflected clinically in the drug’s utility in the holistic approach to the management of the patient with BPH/LUTS. At the level of the prostate, the potent action of terazosin on the $\alpha_{1A}$-adrenoceptor subtype undoubtedly accounts for the rapid changes seen in urinary flow rate and voiding pressure, secondary to changes in urethral resistance. However, in addition to these prostatic actions, the extraprostatic actions of terazosin on the bladder, bladder neck,
and higher centers also contribute to the significant changes in symptoms and bothersomeness.

In addition there is increasing evidence that terazosin may have an additional action on apoptosis within prostate tissue. Intriguingly, this action, which could underpin the durability of the clinical benefit seen with terazosin, may not involve an action at adrenoceptors and may not be a class effect.

Terazosin produces clinically beneficial reductions in blood pressure in patients with BPH/LUTS who are also hypertensive, via actions at all three high-affinity $\alpha_1$-adrenoceptor subtypes. However, in patients who are normotensive or whose hypertension is controlled, only minor, clinically insignificant reductions in blood pressure are observed. Terazosin also has beneficial effects on several cardiovascular risk factors (e.g. lipid profiles, glucose metabolism) which, when coupled with the blood-pressure-lowering effect seen in hypertensive BPH patients, could translate into a reduction in CHD risk.

In addition to the balanced pharmacologic action across all three high-affinity $\alpha_1$-adrenoceptor subtypes, the physicochemical properties of terazosin offer considerable advantages over most other $\alpha$-antagonists. Terazosin has a long plasma half-life, which makes it suitable for once-daily administration. The relatively slow absorption and gradual onset of action associated with this long plasma half-life underpin the reduced propensity for postural effects and general side-effects. Importantly, the pharmacokinetics are unchanged in the elderly or in patients with renal failure.

Terazosin is well tolerated in both old and young patients. Most side-effects are mild or moderate and do not require treatment or discontinuation of therapy.

Overall, therefore, terazosin has a desirable clinical profile for the treatment of BPH/LUTS. Any theoretic advantage that could be achieved with a genuinely ‘uroselective’ agent will ultimately have to be weighed against the deficits of such therapy with respect to the treatment of the whole patient.

REFERENCES


29. Shinori H, Gotoh E, Ito T et al. Long-term therapy with terazosin may improve glucose and lipid


INTRODUCTION

The treatment with $\alpha_1$-adrenoceptor antagonists of the benign prostatic hyperplasia (BPH) symptom complex associated with obstruction of the lower urinary tract has evolved substantially from the original observations of Caine with phenoxybenzamine. Initially, only two types of $\alpha$-adrenoceptor ($\alpha_1$ and $\alpha_2$) were identified. Phenoxybenzamine, an antagonist at both $\alpha$-adrenoceptors, was classified as a nonselective $\alpha$-adrenoceptor antagonist. Subsequently, the prime determinant of periurethral smooth muscle tone was found to be the $\alpha_1$-adrenoceptor, which led to the clinical evaluation of the first $\alpha_1$-selective antagonist, prazosin, in an attempt to improve the side-effect profile of phenoxybenzamine. Understanding has increased further, to an extent where three major subtypes of the $\alpha_1$-adrenoceptor have been cloned and characterized, namely $\alpha_{1A}$, $\alpha_{1B}$, and $\alpha_{1D}$. A fourth receptor subtype, the $\alpha_{1L}$-adrenoceptor, has also been defined pharmacologically, but neither fully characterized nor cloned. The evolution of the nomenclature, which has been confusing and has undergone change over the last few years, is described in a review by Bylund et al.2

As a class, $\alpha_1$-adrenoceptor antagonists are well tolerated and effective in the treatment of obstruction-related lower urinary tract symptoms.3 Both obstructive and irritative symptoms are improved, and there are changes in urinary flow and residual volume consistent with a reduction in urethral resistance. Prazosin has been used in this context for several years, but its therapeutic potential has been limited owing to the dosing regimen and the side-effects associated with the rapidity of onset of action. Doxazosin, a selective $\alpha_1$-adrenoceptor antagonist, was developed to overcome these shortcomings. It has similar affinity for all $\alpha_1$-adrenoceptor subtypes and, therefore, can be considered to have a balanced pharmacologic profile.4 In addition, doxazosin can be distinguished from prazosin on the basis of physicochemical differences, which result in a more gradual onset of action and an extended plasma half-life (22 hours), consistent with utility as a once-a-day agent (Figure 8.1).5,6 Doxazosin has had a wide exposure in BPH and hypertensive patients, and also in the high proportion of patients with concomitant disease.7

FIGURE 28.1 Onset of action of doxazosin (● mean dose 0.95 mg i.v.) and prazosin (○ mean dose 1 mg i.v.): effect on standing systolic blood pressure (BP). (From Elliot et al.,5 with permission.)
This chapter reviews the available data on doxazosin, and analyzes whether the balanced action of doxazosin on \( \alpha_1 \)-adrenoceptor subtypes translates into clinical advantages for patient, primary-care physician, and urologist, alike.

\( \alpha_1 \)-ADRENOCEPTOR HETEROGENEITY

To understand the clinical profile of doxazosin it is necessary to consider briefly the pathophysiologic roles of \( \alpha_1 \)-adrenoceptor subtypes. A comprehensive review of the literature is not within the scope of this chapter, but the salient features are summarized below. For a more detailed review of the potential role of the different \( \alpha_1 \)-adrenoceptor subtypes throughout the urogenital, cardiovascular, and central nervous system, consult Kirby et al.\(^8\)

All three high-affinity \( \alpha_1 \)-adrenoceptor subtypes \( \alpha_{1A}, \alpha_{1B}, \) and \( \alpha_{1D} \) are present in the prostate. The \( \alpha_1 \)-receptor predominates, in both hyperplastic and normal prostate tissue, and its presence is correlated with the prostatic contractile response.\(^9\)–\(^11\) \( \alpha \)-Blockers were first thought to relieve the symptoms of BPH by inhibiting the \( \alpha_{1A} \)-adrenoceptors of the prostatic smooth muscle. Any associated side-effects were assumed to be mediated via \( \alpha_1 \)-adrenoceptors in the vasculature. However, more recent evidence suggests that both the efficacy and tolerability of \( \alpha \)-blockers in BPH may have a centrally mediated component.\(^8\) The \( \alpha_{1D} \)-receptor subtype, for example, is predominant in CNS structures involved with micturition. Side-effects such as asthenia and dizziness may be due to a central rather than a vascular effect. As such, although an \( \alpha_1 \)-adrenoceptor subtype probably cannot preferentially be targeted as a treatment for BPH, reducing activity at the \( \alpha_{1B} \) subtype may reduce cardiovascular complications.\(^8\)

SAFETY AND EFFICACY OF DOXAZOSIN IN BPH TREATMENT

**Short-term efficacy**

A number of double-blind, placebo-controlled clinical studies of doxazosin in patients with BPH have been completed, and reported in the literature.\(^12\)–\(^19\) Patients enrolled in the studies have been men aged between 50 and 80 years with clinical evidence of BPH and maximum flow rates below 15 ml/s. In general, patients receiving treatment with other \( \alpha_1 \)-adrenoceptor antagonists, and patients with urinary tract infections or other serious illnesses, were excluded from these studies. A wash-out phase of at least 1 week was followed by a double-blind treatment period of between 1 and 6 months. Patients were randomized either to doxazosin (at an initial dose of 1 mg/day and increased sequentially according to protocol) or to placebo. Both normotensive and hypertensive patients were included in these studies.

Treatment with doxazosin increased both maximum and average urinary flow rates in almost all studies. The changes achieved statistical significance compared with placebo in the majority of patients. Doxazosin also produced a consistently reduced residual urine volume, albeit small and variable, compared with placebo. BPH-associated symptoms were also improved to a statistically significant extent in the majority of studies. Irrespective of the different symptom scores used in these studies, consistently greater responses were recorded in patients treated with doxazosin than in those given placebo.
In the studies reported above, the beneficial effects of doxazosin on symptoms and uroflow were seen within the first few weeks of treatment, often before doxazosin had been titrated to the optimum dose (Figure 8.2). This has important clinical implications, in that patients may be encouraged to continue to comply with treatment if they experience an early improvement in symptoms.

Doxazosin has a beneficial effect on symptoms and urinary flow rates, irrespective of the baseline severity of disease. In a pooled analysis of three of the double-blind, placebo-controlled studies reported above, doxazosin was seen to produce a significantly greater improvement compared to placebo in peak urinary flow rate, symptom severity, and symptom bother.20 Stratification by severity of symptoms at baseline demonstrated that the greatest improvement with doxazosin was seen in patients with the most severe symptoms \( (p = 0.0001) \); age did not impact on the capacity to benefit from treatment. Thus, it can be concluded that treatment with doxazosin is effective in patients with mild, moderate, and severe BPH, not just those with only mild or moderate symptoms.

Pooled analysis also allowed a more in-depth assessment of urodynamic changes with doxazosin versus placebo.21 Doxazosin significantly improved free urinary flow rate versus placebo, and reduced detrusor pressure, leading to a decreased voiding time and increased voided volume. Urethral resistance was also reduced with doxazosin.

While the majority of studies have been concluded in men between 50 and 80 years of age, the efficacy and safety of \( \alpha_1 \)-adrenoceptor antagonists has also been investigated in men over the age of 80 years.22 In a study of doxazosin and terazosin, both agents were seen to produce a significant increase in peak urinary flow rate and a significant improvement in American Urological Association (AUA) symptom score. Importantly, doxazosin or terazosin could be introduced for the treatment of BPH in patients who were already receiving antihypertensive treatment.

**FIGURE 8.2** Effect of doxazosin (—) versus placebo (---) on (a) symptom score and (b) peak uroflow. Asterisks indicate significant differences from placebo \( (*p < 0.005) \); dagger indicates significant difference from baseline \( (\dagger p < 0.05) \). (From Fawzy et al.,14 with permission.)
Long-term efficacy
The longest double-blind study with doxazosin was conducted by Holme et al.,\textsuperscript{15} with a duration of 29 weeks. This study demonstrated that efficacy was maintained throughout the treatment period. These double-blind data are supported by data from an open-label extension study of patients who completed three of the double-blind, placebo-controlled studies listed above.\textsuperscript{23} A total of 450 men entered the long-term study, and data are available for up to 48 months of follow-up. Results show that doxazosin, over the course of 4 years, produces a clinically and statistically significant increase in maximum and average urinary flow rate (Figure 8.3), as well as a clinically and statistically significant improvement in total, obstructive, and irritative BPH symptoms (Figure 8.4).

In a further analysis of only those patients with concurrent hypertension and BPH, treatment with doxazosin over 48 months resulted in a sustained improvement in the severity and bothersomeness of BPH symptoms, and an increase in maximum urinary flow rate.\textsuperscript{24} There was also a significant and sustained reduction in diastolic blood pressure.

The efficacy and tolerability of doxazosin in combination with finasteride has also been evaluated in the Prospective European Doxazosin and Combination therapy (PREDICT) trial.\textsuperscript{25} In this study of 1095 men, doxazosin was effective in improving symptoms and flow and was more effective that finasteride or placebo. Addition of finasteride did not provide further benefit to that observed with doxazosin alone. Therefore, overall the results were similar to combination studies involving other $\alpha$-blockers.\textsuperscript{26}

The PREDICT study and the Medical Therapy of Prostatic Symptoms (MTOPS)\textsuperscript{27} study have also provided further evidence of the durability of the response to doxazosin with little evidence of tachyphylaxis.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure8_3.png}
\caption{Maximum urinary flow rates ($Q_{\text{max}}$) during the 4-year open-label extension study with doxazosin. Decreased patient numbers at successive time points are not because patients withdrew from the study, but primarily because patients were enrolled as they completed each double-blind study, which spanned many months. Asterisks indicate $p < 0.0001$ versus baseline. (From Lepor et al.,\textsuperscript{23} with permission.)}
\end{figure}
Safety profile

The clinical database for doxazosin in the treatment of hypertension extends to more than 3 billion patient days. Data from studies of doxazosin in BPH have shown consistently that the compound is equally well tolerated in patients with this condition and, intriguingly, perhaps is even better tolerated in normotensive than in hypertensive patients.

In a pooled analysis of seven double-blind, placebo-controlled studies, doxazosin was well tolerated in normotensive and hypertensive patients with BPH.28 In general, older patients (≥65 years) treated with doxazosin experienced fewer adverse events than younger patients (42% versus 47%), although the difference was not statistically significant. A similar incidence of adverse events was seen in the placebo group (38% compared with 44%). The most commonly reported adverse events in all groups were dizziness, headache, fatigue, and dyspnea. The majority of adverse events were mild and did not require discontinuation of treatment.

The good tolerability profile of doxazosin has also been seen with long-term treatment.23 In the 4-year, long-term extension study, almost 90% of adverse events were mild or moderate in severity. The tolerability profile of doxazosin was very similar to that seen in short-term studies, the most frequently reported adverse events being dizziness, headache, and fatigue. Doxazosin was similarly well tolerated by normotensive and hypertensive patients with BPH. The incidence of adverse events with doxazosin did not increase over time. In fact, a reverse Kaplan–Meier plot of patient withdrawals from therapy during long-term treatment illustrates a leveling-off of discontinuations after the first few months. Approximately half of those patients who discon-
continued therapy with doxazosin due to adverse events did so within the first 9 months of therapy (Figure 8.5).

TREATMENT OF THE WHOLE PATIENT

Effects on blood pressure control

The involvement of $\alpha_1$-adrenoceptor subtypes in cardiovascular control is of prime importance in normotensive and hypertensive patients. Not surprisingly, as blood pressure regulation is the algebraic sum of many cardiac and vascular processes, the ‘blood pressure subtype’ of the $\alpha_1$-adrenoceptor has not been identified. Although there may be differential distributions within the vasculature, and distribution may be species and vessel dependent, all subtypes appear to play a role in the contractile response of vascular tissue.\(^8,9,30\)

The human $\alpha_{1A}$-adrenoceptor appears to be the predominant $\alpha_1$-adrenoceptor subtype in arterial smooth muscle, but this does not mean that it necessarily controls systemic blood pressure and orthostasis. It is more reasonable to assume that cardiovascular homeostasis depends on all subtypes, and effective blood pressure control will be achieved only with a balanced $\alpha_1$-adrenoceptor antagonist. Equally, a prostate-selective antagonist may be incapable of providing effective blood pressure control in BPH patients with associated hypertension.

It is well documented that the blood pressure-lowering effects of $\alpha_1$-adrenoceptor antagonists are highly dependent on the hemodynamic baseline. Doxazosin lowers blood pressure when sympathetic drive is high, for example in hypertension. In contrast, doxazosin has less effect on resistance vessel tone in normotensive patients, and clinically insignificant changes in blood pressure are observed (Figure 8.6).\(^{31,12}\) Interestingly, there is no effect on the hemodynamic baseline, irrespective of whether BPH patients are physiologically normotensive or are stabilized on antihypertensive therapy.\(^{31}\)

Hypertension and BPH are often encountered concomitantly in primary care practice. It is important, therefore, that an agent used to treat BPH can be used effectively and safely in patients

![FIGURE 8.5 Reverse Kaplan–Meier plot of discontinuations from long-term doxazosin therapy because of adverse events (upper curve) or inadequate clinical response (lower curve). (From Lepor et al.,\(^{23}\) with permission.)](image-url)
receiving additional antihypertensive treatment. The Hypertension and BPH Intervention Study (HABIT) evaluated the efficacy and safety of doxazosin in patients with concomitant hypertension and BPH, in a community-based setting. There were four groups in the study: patients treated with antihypertensives who were well controlled; patients treated and poorly controlled; untreated, hypertensive patients; and untreated normotensive patients. Treatment with doxazosin was effective in all groups of patients; there was significant improvement in symptom scores as well as BPH-specific indices of health status (p < 0.0001). A clinically important and beneficial reduction in blood pressure was seen only in patients who had an elevated blood pressure at baseline, and was evident in both younger (45–64 years) and older (≥65 years) patients. The incidence of treatment-related adverse events was similar across all groups, ranging from 30 to 37%. The majority were mild or moderate in severity, the most frequent being dizziness, fatigue, somnolence, and headache.

**Cardiovascular risk factors**

Many of the risk factors for hypertension are common to congenital heart failure and atherosclerosis. Particularly relevant are an aberrant lipid profile and insulin resistance/glucose intolerance. The effects of doxazosin compared with other quinazolines and other antihypertensive agents have been extensively reviewed by Pool. Clearly, doxazosin offers a number of benefits in this respect. In the Treatment of Mild Hypertension Study (TOMHS), doxazosin, in contrast to other antihypertensive agents, produced sustained reductions over a 48-month period in total and low-density lipoprotein (LDL) cholesterol and triglycerides, and increases in high-density lipoprotein (HDL) cholesterol and HDL: total cholesterol ratios.

Although understanding of the effect of α-blockers on serum lipid profile is incomplete, Pool has identified several in vitro loci that could account for the clinical observations. Increases in LDL-receptor activity and lipoprotein lipase activity, and decreases in intracellular LDL synthesis and cholesterol absorption, have been observed in the presence of these drugs. A single α₁-adrenoceptor subtype has not been linked to these effects. Indeed, studies of doxazosin metabolites indicate that a component of the drug’s actions may arise from a direct action on signal transduction, independent of the α₁-adrenoceptor.

In the context of cardiovascular risk factors, catecholamines are involved in smooth muscle...
proliferation in the vasculature via an $\alpha_1$-adrenoceptor mechanism.\textsuperscript{38,39} $\alpha_1$-Adrenoceptor-antagonist attenuation of a proliferative vascular response could have important implications in the prevention of hypertension, coronary heart disease (CHD), and atherosclerosis. Doxazosin has also been shown to have a favorable effect on other cardiovascular risk factors, including increased fibrinolysis, inhibition of platelet aggregation, attenuation of the adverse hemodynamic and hemostatic effects of smoking, and regression of left ventricular hypertrophy.\textsuperscript{34,35}

Extensive studies of almost 5000 hypertensive patients in general practice show a beneficial effect of doxazosin in significantly reducing CHD.\textsuperscript{40} On the basis of the Framingham Study equation,\textsuperscript{41} an approximate 20% reduction in CHD incidence would be predicted to result from these changes in CHD risk factors. In the Hypertension and Lipid Trial (HALT), a study enrolling over 800 patients with hypertension in a clinical practice setting, treatment with doxazosin produced a significant reduction in mean total cholesterol levels, LDL cholesterol, and triglycerides; levels of HDL cholesterol were essentially unchanged. In previously untreated patients, these doxazosin-induced changes in serum lipid profile, together with a significant reduction in blood pressure, resulted in a reduction in mean 5-year coronary disease risk of 15%.\textsuperscript{42} The effects of doxazosin on predicted coronary disease risk are in contrast to other antihypertensive agents, e.g. $\beta$-blockers. In a 5-year comparison of doxazosin and the $\beta$-blocker atenolol, doxazosin significantly reduced the predicted 10-year risk of CHD by approximately 12%, whereas atenolol had essentially no effect (0.2% increase). While both agents were effective antihypertensives, and both were well tolerated, only doxazosin had favorable effects on the serum lipid profile.\textsuperscript{41}

More recently, the Antihypertensive Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was completed.\textsuperscript{44} Although the interpretation of data has created considerable debate, careful analysis confirms that it does not affect the management of BPH patients with doxazosin.\textsuperscript{45}

Thus, the beneficial effects of doxazosin on cardiovascular risk further support the use of a balanced agent in the treatment of the BPH patient as a whole.

**Sexual function**

For several years there has been indirect evidence that doxazosin has a positive effect in males with erectile dysfunction (ED). In the 4-year TOMHS study,\textsuperscript{36,46} a much reduced incidence of ED was reported in the doxazosin group compared with placebo (Figure 8.7). In contrast, other antihypertensive agents (e.g. diuretics) appeared to increase the incidence. Throughout the duration of the study, erection problems disappeared in 88% of men randomized to doxazosin, compared with 55% of men in all other groups combined. More recently, in an Italian multicenter study in BPH patients, doxazosin was found to improve erectile function, independent of any improvement in LUTS.\textsuperscript{47} The positive effect is consistent with the well-documented role of $\alpha_1$-adrenoceptors in the control of corpus cavernosal tone\textsuperscript{48} and the clinical benefit observed with intracavernosal injection of $\alpha_1$-adrenoceptor antagonists.

Although doxazosin may not necessarily represent effective monotherapy for ED per se, there is some suggestion that it could form part of a combination strategy in the management of ED refractory to other agents. In one study of men with moderate to severe ED, oral doxazosin improved the response to intracavernosal alprostadil injection. There was an 18% improve-
ment in International Index of Erectile Function (IIEF) with alprostadil alone, compared with a 52% improvement over 12 weeks with the addition of doxazosin ($p < 0.01^{49}$). More recently, evidence of synergy with sildenafil has also been reported.\(^{50}\)

Overall, given the high degree of co-morbid ED in LUTS,\(^{51}\) the impact of therapy (negative or positive) should be an important component of the decision-making process.

Other contributing factors to the clinical profile of BPH

When considering the urogenital tract it is important to remember the potential contribution from extraprostatic actions to the overall clinical profile of BPH.\(^{48}\) There is no direct correlation between flow rates and urethral resistance and the observed improvement in symptoms. Furthermore, it should be remembered that patients generally present because of symptoms and bothersomeness, not because of a reduced urinary flow. Thus, the extraprostatic actions that have been observed with doxazosin on the bladder,\(^{48}\) spinal cord,\(^{52}\) and efferent pathways\(^{53}\) may be just as important as changes induced in periurethral stromal tone.

Several studies have shown that certain α\(_1\)-adrenoceptor antagonists may regulate prostate growth by inducing apoptosis in the epithelial and stromal cells.\(^{54}\) Over the clinical dose range, within the first month of treatment both doxazosin and terazosin produced a significant induction of apoptosis in prostate biopsies compared to untreated controls. This was paralleled by a loss of prostatic smooth muscle and an improvement in BPH symptomatology.\(^{55}\) This effect, not found with tamsulosin,\(^{54,56}\) is considered to be confined to quinazoline-derived α\(_1\)-antagonists and may indeed be independent of an action on the α\(_1\)-adrenoceptor.\(^{54}\)

Potentially such an action could account for the long-term clinical durability of the response to doxazosin in BPH patients.
DOXAZOSIN: THE NEW GITS FORMULATION

A new formulation of doxazosin, the doxazosin gastrointestinal therapeutic system (GITS), has been developed to enhance the pharmacokinetic profile of the drug. It employs controlled-release technology to allow more gradual drug delivery with the first dose, and precise, sustained serum levels with long-term, once-daily administration. It is as effective and well tolerated as the standard formulation. For example, in a study of patients with mild hypertension, both doxazosin standard and doxazosin GITS produced significant reductions in blood pressure compared to placebo ($p < 0.001$). The most commonly reported side-effects were headaches, dizziness, and asthenia. The GITS formulation appears to eliminate the need for doxazosin dose titration in most patients.

In a combined analysis of two randomized, double-blind studies in hypertension, approximately 60% of patients achieved goal blood pressure response at the 4 mg starting dose. The simplified dosing regimen is likely to result in fewer office visits for patients.

Studies with doxazosin GITS have also been carried out in patients with BPH. Results have shown that doxazosin GITS provides effective relief from the signs and symptoms of BPH, with an efficacy comparable to that of the standard formulation. In a combined analysis of two double-blind, placebo-controlled studies, a similar increase in urinary flow rate and a similar improvement in symptoms were seen with doxazosin GITS and doxazosin standard (Figure 8.8).

Intriguingly, in a ‘gold standard’ double-blind study, the doxazosin GITS (4 mg, 8 mg) was

![Figure 8.8](image_url)

**FIGURE 8.8** Effect of doxazosin gastrointestinal therapeutic system (GITS) (●), doxazosin standard (○), and placebo (□) on (a) total International Prostate Symptom Score (I-PSS) and (b) maximum urinary flow rate. (From Kirby et al., with permission.)
found to be more effective than tamsulosin (0.4 mg, 0.8 mg) in improving LUTS symptoms. This could represent the first evidence from a carefully controlled study that \( \alpha \)-blockers may have different effects.

**CONCLUSIONS**

Doxazosin has a balanced pharmacologic action at all subtypes of the \( \alpha_1 \)-adrenoceptor, which is reflected clinically in a beneficial effect on the whole patient. It improves both symptoms and measures of urinary flow in the patient with BPH, as well as producing clinically important blood pressure reductions in BPH patients with hypertension. It is likely that an action on all adrenoceptor subtypes is required to produce this profile. In subjects with physiologic or drug-controlled normotension, only minor, clinically insignificant changes in blood pressure are observed.

Doxazosin appears to have a beneficial effect on several risk factors (e.g., lipid profile, glucose metabolism) associated with hypertension, CHD, and atherosclerosis. The \( \alpha_1 \)-adrenoceptor subtype involved has not been identified, and there may be a contribution from receptor-independent events.

In addition to these pharmacologic actions, the physiochemical properties of the drug offer considerable advantages. In particular, doxazosin, compared with other \( \alpha_1 \)-adrenoceptor antagonists, has a long plasma half-life consistent with once-daily dosing. The associated gradual onset of action also underpins the reduced propensity for side-effects. Importantly, the pharmacokinetics are unchanged in the elderly and in renal failure. The new GITS formulation extends the established benefits of standard doxazosin therapy. Doxazosin GITS has an efficacy and tolerability profile similar to that of the standard formulation, with the additional advantages of an enhanced pharmacokinetic profile and simplified dosing regimen.

Doxazosin is very well tolerated in both old and young patients. Most adverse events are mild or moderate in severity and do not require discontinuation of therapy. There is no suggestion of a deleterious impact on sexual function—in fact, there is evidence of a positive effect of doxazosin on erectile dysfunction.

Overall, the balanced action of doxazosin on \( \alpha_1 \)-adrenoceptor subtypes is associated with a highly desirable clinical profile for the BPH patient. Any advantages arising from a genuinely prostate-selective antagonist will ultimately have

**TABLE 8.1** Incidence of adverse events in patients with BPH treated with doxazosin GITS, doxazosin standard, and placebo. (Adapted from Kirby et al.59)

<table>
<thead>
<tr>
<th></th>
<th>Doxazosin GITS (%)</th>
<th>Doxazosin standard (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( n = 666 )</td>
<td>41.1</td>
<td>53.6</td>
<td>39.1</td>
</tr>
<tr>
<td>( n = 651 )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All adverse events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment-related adverse events</td>
<td>16.1</td>
<td>25.3</td>
<td>7.7</td>
</tr>
<tr>
<td>Discontinuations due to treatment-related adverse events</td>
<td>3.3</td>
<td>4.8</td>
<td>0.6</td>
</tr>
</tbody>
</table>

GITS, gastrointestinal therapeutic system.
to be weighed against the deficits of such therapy in the treatment of the whole patient.\textsuperscript{64}

REFERENCES


INTRODUCTION

Alfuzosin, a quinazoline derivative, acts as a selective antagonist of $\alpha_1$-adrenoceptor-mediated contraction of bladder neck, proximal urethral, and prostatic smooth muscle. Bladder outlet resistance resulting from benign prostatic hyperplasia (BPH) is consequently reduced. Alfuzosin is approved in Europe for the treatment of symptomatic BPH.

PHARMACOLOGIC PROFILE OF ALFUZOSIN AT $\alpha_1$-ADRENOCEPTOR SUBTYPES

The human prostatic smooth muscle contains high densities of $\alpha_1$-adrenoceptors.\(^1,2\) Several $\alpha_1$-adrenoceptor subtypes have been identified and their heterogeneity revealed both pharmacologically and by molecular cloning.\(^3,4\) The three $\alpha_1$-adrenoceptor subtypes with high affinity for prazosin (grouped under the $\alpha_{1H}$ heading), so far identified, i.e. $\alpha_{1A}$-, $\alpha_{1B}$-, and $\alpha_{1D}$-adrenoceptors, have been cloned (\(\alpha_{1a}, \alpha_{1b},\) and \(\alpha_{1d}\)). Another adrenoceptor subtype has been identified and is characterized by a low affinity for prazosin and for that reason entitled $\alpha_{1L}$.\(^5,7,8\) Table 9.1 summarizes the affinity for the three cloned $\alpha_1$-adrenoceptors of the major $\alpha_1$-adrenoceptor antagonists available today. As shown with doxazosin, terazosin, and prazosin, alfuzosin has no distinct selectivity for any of the receptor subtypes. Uroselectivity has been shown to result from the pharmacodynamic properties of agents without specificity for any particular subtype, however.\(^9\) In addition, uroselectivity does not appear to be related to receptor subtype affinity.\(^10\)

**AFFINTY OF ALFUZOSIN FOR $\alpha_1$-ADRENOCEPTORS IN THE HUMAN PROSTATE**

The cranial region of the human prostatic adenoma possesses high affinity $[^{3}H]$-prazosin binding sites.\(^11,12\) These sites display the pharmacologic characteristics of $\alpha_1$-adrenoceptors. As shown in Table 9.2, $[^{3}H]$-prazosin binding is potently displaced by alfuzosin and phentolamine, with IC\(_{50}\) values in the low nanomolar range, while the $\alpha_2$-adrenoceptor antagonists idazoxan and yohimbine, and the $\beta$-adrenoceptor antagonist propranolol, only affect $[^{3}H]$-prazosin binding with IC\(_{50}\) values in the micromolar range. Thus, alfuzosin

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\alpha_{1a}$</th>
<th>$\alpha_{1b}$</th>
<th>$\alpha_{1d}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfuzosin</td>
<td>8.20</td>
<td>8.53</td>
<td>8.40</td>
</tr>
<tr>
<td>Doxazosin</td>
<td>8.56</td>
<td>8.98</td>
<td>8.78</td>
</tr>
<tr>
<td>Prazosin</td>
<td>9.70</td>
<td>9.60</td>
<td>9.50</td>
</tr>
<tr>
<td>Tamsulosin</td>
<td>9.70</td>
<td>8.90</td>
<td>9.80</td>
</tr>
<tr>
<td>Terazosin</td>
<td>8.16</td>
<td>8.71</td>
<td>8.46</td>
</tr>
<tr>
<td>5-ME-Urapidil</td>
<td>8.68</td>
<td>6.76</td>
<td>7.91</td>
</tr>
</tbody>
</table>

Adapted from Forray C et al.\(^5\) and Kenny et al.\(^7\)
shows high affinity for $\alpha_1$-adrenoceptors in the human prostate, which represents the pharmacologic target in BPH. In support of this view, it has been reported that alfuzosin-displaceable $[\text{125I}]$-HEAT (iodo-4-hydroxyphenyl-ethyl-amino-methyl-tetralone) binding sites, which have the pharmacologic characteristics of $\alpha_1$-adrenoceptors, are exclusively associated with muscular stroma of the prostate and are markedly elevated in sections from prostatic adenomas as compared with nonhypertrophic tissue.\(^{13}\)

As far as $\alpha_1$-adrenoceptor subtypes are concerned, Faure et al.\(^{14}\) have shown that the human prostate expresses at the level of the apex, base, periurethral, and lateral lobe, mRNA transcripts corresponding to $\alpha_1a$-, $\alpha_1b$-, and $\alpha_1d$-adrenoceptors. In addition, these authors have shown that a reconstituted partial sequence (349 amino acids) of the human prostatic $\alpha_1\alpha$-adrenoceptor shares 94% identity with the bovine brain $\alpha_1a$-adrenoceptor, and that this receptor represents the predominant $\alpha_1$-adrenoceptor subtype in this tissue.

### FUNCTIONAL UROSELECTIVITY OF ALFUZOSIN

#### Effects on elevated urethral and blood pressure

Inhibition of urethral responses to stimulation of hypogastric sympathetic nerves in the cat is considered to represent an animal model of the dynamic sympathetic constriction of urethral smooth muscle, which is regarded as a contributory factor in the obstructive disorders which characterize BPH.\(^{15}\) On the other hand, $\alpha_1$-adrenoceptor antagonist reduction of blood pressure in spontaneously hypertensive rats is accepted as a model to assess antihypertensive drugs acting at receptors physiologically stimulated by an increased sympathetic tone. Thus a relationship between the ability of alfuzosin to inhibit sympathetically mediated increases in urethral tone in the cat and sympathetically mediated hypertension in the spontaneously hypertensive rat can be considered as a relevant way to evaluate the therapeutic margin in BPH with respect to unwanted vascular effects (e.g. orthostatic hypotension).\(^{15}\)

Studies conducted in the anesthetized cat and in conscious spontaneously hypertensive rats confirm the $\alpha_1$-antagonist properties of alfuzosin. The compound produces a dose-related as well as a complete and prolonged inhibition of the rise in urethral pressure resulting from postganglionic stimulation of hypogastric sympathetic nerves in the cat. As shown in Table 9.3, alfuzosin decreases the urethral resistance induced by hypogastric nerve stimulation in the cat at doses 11 times lower than those which reduce blood pressure in spontaneously hypertensive rats.\(^{15}\)

#### Effects on normal urethral and arterial blood pressure

In recent years, attempts have been made to evaluate, in the same animal, the respective effects of $\alpha_1$-adrenoceptor antagonists on prostatic tissue

### TABLE 9.2 Affinity of alfuzosin for $\alpha_1$-adrenoceptors in cranial human prostatic adenoma labeled with $\text{[3H]prazosin.}$

<table>
<thead>
<tr>
<th>Drug</th>
<th>IC\textsubscript{50} * (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfuzosin</td>
<td>0.035 ± 0.008</td>
</tr>
<tr>
<td>Phenoxybenzamine</td>
<td>0.038 ± 0.016</td>
</tr>
<tr>
<td>Idazoxan</td>
<td>3.5 ± 1.0</td>
</tr>
<tr>
<td>Yohimbine</td>
<td>6.0 ± 2.0</td>
</tr>
<tr>
<td>Propranolol</td>
<td>37 ± 9</td>
</tr>
</tbody>
</table>

*IC\textsubscript{50} values represent drug concentrations producing 50% inhibition of specific $\text{[3H]prazosin binding. Values are taken from Pimoule et al.}^{11}$ and Lefevre-Borg et al.\(^{12}\)
compared to side-effects, most particularly the effects on blood pressure. In the most recently developed model, which allows the simultaneous measurement of urethral and arterial pressures in conscious male rats, a direct estimation of the functional uroselectivity of alfuzosin was performed. At clinically relevant doses (10–30 µg/kg, intravenous route), alfuzosin decreased urethral pressure without noticeable effects on blood pressure (Figure 9.1). In a comparative investigation, using the same experimental model, the functional uroselectivity of alfuzosin has been shown to be superior to that of other α₁-adrenoceptor antagonists. These results are further evidence that functional uroselectivity may be achieved in the absence of pharmacologic selectivity for one of the α₁-adrenoceptor subtypes.

TISSUE DISTRIBUTION

The role of tissue distribution of α₁-adrenoceptor antagonists and its possible effect on functional uroselectivity has been less rigorously examined. However, a direct measurement of plasma and prostate distribution of alfuzosin, related to measurement of its pharmacologic activity on arterial blood pressure and urethral pressure, has brought new and useful information. One hour following oral administration of 10 mg/kg of alfuzosin

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose producing a 50% reduction in urethral pressure (ID₅₀ UP) (mg/kg, id)</th>
<th>Dose producing a 20% reduction in arterial blood pressure (ID₂₀ AP) (mg/kg, po)</th>
<th>Uroselectivity ratio (ID₂₀ AP/ID₅₀ UP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfuzosin</td>
<td>0.36</td>
<td>4.0</td>
<td>11</td>
</tr>
<tr>
<td>Terazosin</td>
<td>0.12</td>
<td>0.42</td>
<td>3.5</td>
</tr>
<tr>
<td>Prazosin</td>
<td>0.12</td>
<td>0.13</td>
<td>1</td>
</tr>
</tbody>
</table>

TABLE 9.3 Effects of alfuzosin on urethral pressure (UP) in the cat and on mean arterial blood pressure (AP) in the spontaneously hypertensive rat.

The doses of each compound producing a 50% reduction in urethral pressure (UP₅₀) in anesthetized cats and a 20% reduction in blood pressure (UP₂₀) in spontaneously hypertensive rats are shown. Values are taken from Lefevre-Borg et al.¹⁵

FIGURE 9.1 Effect of alfuzosin (triangle) compared with vehicle control (circle) on an increase in urethral pressure in the anesthetized cat. Doses of alfuzosin correspond to cumulative i.v. bolus administration of the drug. Increased urethral pressure was elicited by electrical stimulation of sympathetic hypogastric nerves. (From ref. 5 with permission.)
in rats, plasma and prostate levels, respectively, reached 88.0 ng/ml and 335 ng/ml, leading to a prostate/plasma concentration ratio of 3.8. At 6 hours, the plasma concentration decreased to 20 ng/ml, whereas prostatic tissue concentration was still about nine times higher than plasma concentration. Moreover, in the same study, an index of the antagonistic activity of alfuzosin against phenylephrine-induced urethral contractions was directly correlated with prostatic tissue concentrations. This study, by demonstrating that alfuzosin concentrates in the prostate at levels 4–9-fold above the plasma levels, may thus provide a basis for its preferential activity in the lower urinary tract compared to vascular effects. High prostatic diffusion of alfuzosin has also been observed in orally treated patients.19

Conclusions

In conclusion, alfuzosin is a potent selective $\alpha_1$-adrenoceptor antagonist which displays functional uroselectivity in animal models. These pharmacologic properties lend support to the theory that alfuzosin alleviates the dynamic component of urinary obstruction attributable to sympathetic tone in BPH. These pharmacologic properties are likely to underlie the clinical profile of alfuzosin.

PHARMACOKINETIC PROPERTIES

The pharmacokinetics of alfuzosin are linear and nonsaturable. Absorption of the immediate release (IR) formulation of alfuzosin is relatively rapid, with a maximum plasma concentration occurring after a mean of 1.5 hours. Its bioavailability is 64%, with a negligible effect of concomitant administration of food on its absorption. Alfuzosin is approximately 90% protein bound in plasma. It is extensively metabolized by the liver and the metabolites are inactive. Its main route of elimination is fecal. The mean plasma elimination half-life of IR alfuzosin is 4.8 hours. Because of this pharmacokinetic profile, the IR of alfuzosin has to be administered three times daily (7.5 mg/day). The slow release (SR) formulation of alfuzosin (5 mg daily), currently available in Europe, has been developed in order to improve compliance with the treatment by reducing the number of daily doses from three to two. The relative bioavailability of this formulation is 15% lower than for the IR formulation of alfuzosin. The time to reach the peak is longer, approximately 3 hours instead of 1.5 hours, confirming that the absorption is delayed as well as its apparent elimination half-life, which is 8 hours. The usual recommended daily dose is 5 mg twice daily, i.e. 10 mg/day. This higher daily dosage compares with the usual daily dose of 7.5 mg for the IR formulation, compensating for the relative loss of bioavailability.

A once-daily formulation of alfuzosin is now available and, although the absorption characteristics are different from the IR and SR formulations, the metabolism of the drug is similar.20,21 Inactive barrier layers ensure that the active element is released over 20 hours. The dissolution rate is almost constant between 2 and 12 hours and the area under the plasma concentration–time curve is similar over 24 hours to that observed for 2.5 mg thrice-daily and 5 mg twice-daily formulations. The plasma elimination half-life of the prolonged-release 10 mg formulation was 9.1 hours compared to 7 hours for the IR formulation.19 The pharmacokinetic properties of 10 mg alfuzosin once-daily were not significantly different in patients with renal impairment or in older adults compared to the IR formulation.22,23

The overall pharmacokinetic profile of alfuzosin is not significantly changed in patients with
renal insufficiency, in contrast to what is observed in patients with hepatic insufficiency, where dosage modifications appear to be necessary.

**PHARMACODYNAMIC EFFECTS IN HUMANS**

**Urodynamic effects**

Intravenous alfuzosin significantly reduced high urethral pressure arising from neurologic causes. One hundred and sixty-three patients with neurogenic bladder disease (NBD) and a mean maximal urethral pressure of 108 cmH₂O were included in a randomized, double-blind, placebo-controlled study assessing the effect of a single i.v. injection of alfuzosin (0.5, 1, or 2 mg) or placebo. Alfuzosin significantly and dose-dependently decreased urethral pressure, with a mean decrease of 44% for the 2 mg dose.²⁴ A single i.v. test dose of 5 mg alfuzosin had previously been used to determine which patients with spinal cord injury (n = 21) were likely to benefit from alfuzosin therapy. Response was assessed in terms of change in micturition, residual urine, and posterior urethral pressure and diameter.²⁵ Furthermore, in a placebo-controlled study conducted in 66 patients with NBD, this decrease was maintained with oral alfuzosin for 12 weeks and associated with a significant improvement of voiding symptoms (–45%) and residual urine volume (–39%) compared with placebo.²⁶ These actions appear to be correlated with the α₁-adrenoceptor antagonism produced by alfuzosin.

In patients with BPH, orally administered IR alfuzosin significantly and dose-dependently increased urinary flow rates from the first dose.²⁷ At 90 minutes after a single alfuzosin dose, peak flow rate (PFR) was significantly increased by 23 and 34% with 1.25 and 2.5 mg, respectively, compared with placebo in 93 patients with initial PFR values of less than 15 ml/s. In patients with PFR values of less than 10 ml/s (n = 47), mean increases in PFR with 1.25 or 2.5 mg alfuzosin or placebo were even greater: 26, 55, and 17%, respectively.²² Similar results were observed with SR alfuzosin. At 180 minutes after a single SR alfuzosin dose, PFR was significantly increased by 29 and 36% with 3 and 5 mg doses compared with placebo (+17%) in elderly patients (≥65 years) with initial PFR values of less than 15 ml/s.²⁸

The 30% increase in flow rates, which is the rate of improvement expected with α₁-blocker therapy in patients with BPH, is maintained after multiple-dose administration of alfuzosin.²⁸⁻³² Furthermore, this is of the same order of magnitude as that of prazosin 4 mg per day³³,³⁴ and tamsulosin 0.4 mg per day.³¹ In those patients with an increase in PFR of at least 25% (i.e. 45–50% of patients), the mean increase with alfuzosin is approximately 5 ml/s.

Residual urine volume is a parameter reflecting not only the decrease in urinary flow resistance, but also the bladder contractility which may show wide intra-individual variability between serial examinations.³⁵ Alfuzosin has been shown to decrease significantly the volume of residual urine by 38% after 6 months of treatment compared with 9% in placebo recipients.²⁹

A pooled analysis of 11 double-blind, placebo-controlled trials involving 1470 LUTS patients showed that immediate- and sustained-release alfuzosin effectively reduced postvoid residual urine volume.³⁶ Significant differences were observed between patients treated with alfuzosin and those who received placebo. The analysis showed that acute urinary retention (AUR) was more common in men with residual urine greater than 100 ml. Patients receiving alfuzosin were less likely to suffer AUR than those receiving placebo.
Several more complex urodynamic assessments have been carried out in patients under alfuzosin treatment. In a 3-month, double-blind, placebo-controlled study performed in 31 patients with urodynamically proven bladder outflow obstruction treated with alfuzosin, there was a significant increase in the volume that produced a strong desire to void, which reflected the increase of bladder capacity. A pressure–flow, placebo-controlled study carried out in 52 patients with BPH treated with alfuzosin (7.5 mg/day for 4 weeks followed by a 5–8-week single-blind extension) showed that alfuzosin significantly decreases detrusor pressure compared with placebo (opening pressure, −39%; pressure at maximum flow, −30%; and maximum pressure, −29%; \( p < 0.05 \) for all parameters). These improvements gradually increased up to 12 weeks.

It can be concluded that the urodynamic effect of alfuzosin is characterized by a decrease in urethral pressure of about 45%, an increase in flow rate in patients with BPH of 30%, i.e. the expected benefit from \( \alpha_1 \)-blocker therapy in BPH, and a beneficial effect on bladder capacity and pressure.

**Hemodynamic effects**

At doses used in the treatment of BPH, as would be predicted from the uroselectivity described above, alfuzosin produces only minor changes in blood pressure. After single oral doses of IR alfuzosin (1.25 mg (\( n = 31 \)) and 2.5 mg (\( n = 31 \)) administered to BPH patients, mean supine and standing systolic and diastolic blood pressures were not significantly changed by alfuzosin compared with placebo. The effects of SR alfuzosin on supine blood pressure following medium term administration are likewise minimal, as shown in a large placebo-controlled study conducted on 390 patients who received SR alfuzosin 10 mg per day or placebo for 3 months. The mean reductions in systolic and diastolic blood pressures did not differ statistically from those observed with placebo in the whole population as well as in the subgroups of normotensive and hypertensive patients. Similar results were observed in a large 6-month double-blind study comparing SR alfuzosin (5 mg once daily), and the combination of both: mean changes in blood pressure were comparable in the three treatment groups (Figure 9.2).

However, supine blood pressure effects do not entirely represent the potential risk associated with \( \alpha_1 \)-blockers, which is mainly related to orthostatic changes in blood pressure, particularly in the elderly and/or hypertensive patients.

![Figure 9.2](image-url)
Thus, in order to address this potential risk specifically in patients receiving SR alfuzosin, a combined analysis of two clinical studies conducted with SR alfuzosin (10 mg/day) was performed with special attention to orthostatic blood pressure changes during the first month of treatment. Blood pressure was measured at peak plasma concentrations. Asymptomatic orthostatic hypotension (AOH) was defined as a decrease in systolic blood pressure of at least 20 mmHg when standing. The cumulative incidence of AOH was slightly more frequent with alfuzosin than with placebo, but the difference was not statistically significant. SR alfuzosin moderately increased the incidence of AOH in elderly and hypertensive patients, during the first month of treatment. This effect was transient and was not associated with an increased incidence of related adverse events (i.e. postural side-effects) in this subgroup of frail patients. In addition, orthostatic blood pressure changes were assessed in the large ($n = 1051$ patients) 6-month study comparing SR alfuzosin (5 mg twice daily), finasteride (5 mg once a day (od)) and the combination of both. The incidence of AOH was comparable in the three treatment groups, regardless of age or pre-existing hypertension (Figure 9.3).

**THERAPEUTIC POTENTIAL**

More than 33 000 BPH patients have been evaluated in reported European clinical studies assessing the efficacy and/or safety of alfuzosin or the improvement in quality of life after administration of alfuzosin. These studies were conducted with the IR formulation of alfuzosin (7.5 to 10 mg per day given in three divided doses), the SR for-
mulation (SR alfuzosin 5 mg bid), and, more recently, the once-a-day formulation (alfuzosin 10 mg od) for the treatment of symptomatic BPH.

**Clinical efficacy**

Jardin et al. reported the efficacy of alfuzosin in a large multicenter placebo-controlled study of 518 patients with symptoms of BPH who received either alfuzosin 7.5 or 10 mg/day or placebo for 6 months. Patients were evaluated using the Boyarsky symptom scoring system, urinary flow rates, and postvoid residual urine volume. Obstructive and irritative symptoms, assessed according to the Boyarsky scale, improved significantly in the alfuzosin group compared with the placebo group \((p = 0.004)\). Fewer patients in the alfuzosin group than in the placebo group dropped out due to lack of efficacy \((6.8 \text{ vs } 14.6\%, \ p = 0.0004)\) and the prevalence of spontaneous acute urine retention (AUR) was lower in the alfuzosin group \((0.4\% \text{ vs } 2.6\%, \ p = 0.04)\). By 6 months, mean urinary flow rates had increased \((p < 0.05)\) and residual volume had decreased \((p < 0.017)\) in the alfuzosin group. Clinical improvement with alfuzosin could be maintained for up to 30 months, as observed in noncomparative extensions of the original 6-month study \(^{42,43}\) (Figure 9.4).

In a 3-month placebo-controlled study with the SR formulation of alfuzosin (5 mg bid) in 390 men, patients reported a clinically relevant and statistically significant improvement of their systolic and diastolic blood pressure (BP) in a 3-month study of placebo ( ) vs. slow release (SR) alfuzosin 10 mg/day ( ) in 390 patients with BPH: (a) changes from baseline in supine BP; (b) changes in upright minus supine BP. (Unpublished data.)

**FIGURE 9.4** Systolic and diastolic blood pressure (BP) in a 3-month study of placebo ( ) vs. slow release (SR) alfuzosin 10 mg/day ( ) in 390 patients with BPH: (a) changes from baseline in supine BP; (b) changes in upright minus supine BP. (Unpublished data.)
urinary symptoms in comparison with placebo (Figure 9.5). A clinical improvement in LUTS was observed whatever their initial severity, with an overall improvement in total I-PSS score of 30% as a mean. The clinical efficacy was observed from the first month. Maximum flow rate increased significantly with SR alfuzosin (+2.4 ml/s, i.e. +29%) compared with placebo (+1.1 ml/s, i.e. +14%, \( p = 0.006 \)). Residual urine was also significantly reduced with SR alfuzosin. In those patients with baseline \( Q_{\text{max}} \leq 12 \text{ ml/s} \) and I-PSS score \( \geq 13 \), the total I-PSS score decreased by 6.7 points (36%) (comparison versus placebo: \( p = 0.002 \)) (Table 9.4).

The efficacy of the once-daily formulation, administered at a dose of 10 mg per day without initial titration, has been compared to that of the IR formulation (2.5 mg thrice daily) and placebo in a 3-month study which involved 436 patients: symptomatic improvement with the od formulation was significantly higher than placebo and similar to that of the IR formulation, with I-PSS improvements of 6.9 points in the od group and 6.4 points in the 2.5 mg tid group (\( p = 0.002 \) and 0.02 vs placebo, respectively). The bothersomeness of these symptoms, assessed using the quality of life index, was also significantly improved with both formulations compared with placebo (Table 9.5) (the ALFORTI study\(^4\)). Following treatment with alfuzosin od, \( Q_{\text{max}} \) (measured at trough plasma levels) also significantly increased in comparison with placebo (mean SD values: 10.

![Figure 9.5](image)

**FIGURE 9.5** Total BPH symptom score improvement with alfuzosin: maintenance of symptomatic efficacy in the long term. Part 1: 6-month placebo-controlled study (circle; \( n = 251 \)); part 2: 1-year open extension (triangle; \( n = 131 \)); part 3: 1-year (additional) open extension (square; \( n = 50 \)). \(* p < 0.05 \) vs baseline. (Data from refs 29, 42, and 43 with permission.)
In a 9-month, non-blinded extension of this study, the long-term efficacy of 10 mg od alfuzosin was assessed over 12 months. In total, 311 of the original 436 patients took part in the extension phase. At the start of the extension phase, mean I-PSS was 10.9 and did not change over the subsequent 9 months, with mean I-PSS 9.3 at endpoint. Significant improvements were observed in patients who had originally received placebo as part of the double-blind study ($p = 0.0001$). Peak flow, which was 11.5 ml/s at month 3, remained at its improved rate at month 12 ($p = 0.0001$ compared to baseline).

In addition, the 10 mg od formulation has been compared to 15 mg od over 3 months. As in the ALFORTI study, the ALFUS study included a wash-out period of 1 month before

### TABLE 9.4

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SR alfuzosin 10 mg/day</th>
<th>Placebo</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-PSS score†</td>
<td>n = 104</td>
<td>n = 110</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>17.8 (3.9)</td>
<td>18.3 (4.1)</td>
<td>0.13</td>
</tr>
<tr>
<td>Final</td>
<td>11.2 (6.5)</td>
<td>14.4 (6.5)</td>
<td></td>
</tr>
<tr>
<td>Change vs baseline</td>
<td>−6.7 (−36%)</td>
<td>−4.0 (−22%)</td>
<td>0.002</td>
</tr>
<tr>
<td>$Q_{\text{max}}$ (ml/s)†</td>
<td>n = 91</td>
<td>n = 91</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>9.3 (2.1)</td>
<td>8.9 (2.2)</td>
<td>0.13</td>
</tr>
<tr>
<td>Final</td>
<td>12.5 (5.1)</td>
<td>10.1 (3.8)</td>
<td></td>
</tr>
<tr>
<td>Change vs baseline</td>
<td>+3.2 (+39%)</td>
<td>+1.1 (+16%)</td>
<td>0.0006</td>
</tr>
<tr>
<td>% Patients with $Q_{\text{max}}$ change &gt;30%</td>
<td>53</td>
<td>26</td>
<td></td>
</tr>
</tbody>
</table>

*Adapted from Buzelin et al.\(^{30}\); †intergroup comparison; ‡mean (SD). SR, slow release.

### TABLE 9.5

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo $(n = 154)$</th>
<th>Alfuzosin 10 mg od $(n = 143)$</th>
<th>Alfuzosin 2.5 mg tid $(n = 150)$</th>
<th>$p$*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-PSS score†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>17.7 (4.1)</td>
<td>17.3 (3.5)</td>
<td>16.8 (3.7)</td>
<td>0.13</td>
</tr>
<tr>
<td>Change vs. baseline†</td>
<td>−4.9 (5.9)</td>
<td>−6.9 (4.9)</td>
<td>−6.4 (5.6)</td>
<td>0.005</td>
</tr>
<tr>
<td>% of patients with a clearance of at least 50%</td>
<td>26</td>
<td>37</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Quality of life index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline†</td>
<td>3.3 (1.0)</td>
<td>3.3 (1.0)</td>
<td>3.3 (0.9)</td>
<td>0.96</td>
</tr>
<tr>
<td>Change vs. baseline†</td>
<td>−0.6 (1.2)</td>
<td>−0.1 (1.1)</td>
<td>−1.1 (1.1)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*Intergroup comparison; †mean (SD). Data from van Kerrebroeck et al.\(^{44}\)

+2.3 (3.6) ml/s and +1.6 (3.2) ml/s, respectively; $p = 0.03$, demonstrating the therapeutic coverage over a 24-hour period.

+2.3 (3.6) ml/s and +1.6 (3.2) ml/s, respectively; $p = 0.03$, demonstrating the therapeutic coverage over a 24-hour period.
treatment with nontitrated alfuzosin or placebo. I-PSS, uroflowmetry, and quality of life were assessed at baseline and then regularly throughout the studies. The men who took part in the trial were aged 50 or over, had a history of LUTS suggestive of BPH, an I-PSS of 13 or greater, a peak flow of 5–12 ml/s, a voided volume of 150 ml or greater, and a PVR volume of 350 ml or less.

Patients were stratified in each study according to whether they were < 65 or ≥ 65 and also according to blood pressure (< 90 or ≥ 90 mmHg). The primary efficacy outcome was mean change in I-PSS.

The 3-month trial indicated that 15 mg od alfuzosin and 10 mg od both improved I-PSS significantly compared to placebo. In the ALFUS study, endpoint I-PSS scores improved from baseline by 3.6 points in the 10 mg od group and 3.4 points in the 15 mg od group (p = 0.001 and 0.004, respectively). As in the ALFORTI study, improvements were observed in the I-PSS filling and voiding subscores.

Peak urinary flow increased by 1.7 ml/s (17%, p = 0.0004) in the 10 mg od group and by 0.9 ml/s (10%) in the 15 mg od group.

Quality of life is now becoming accepted as an important criterion in the evaluation of treatments for BPH. Results from a study involving over 7000 outpatients treated with alfuzosin for 3 months in general practice showed quality of life scores to improve by 43% and to correlate significantly with symptom scores. These symptomatic and quality of life improvements were maintained in those patients who continued the treatment for 2 years (> 4500) and 3 years (> 3200). In this population, the rate of spontaneous AUR and of prostate surgery was low, respectively 0.3% and 3.7%, confirming the beneficial effect of alfuzosin on the risk of AUR demonstrated in the medium term.

In the ALFUS and ALFORTI trials, quality of life scores were significantly better in the active treatment groups compared to placebo. In the ALFORTI trial, the quality of life index fell by 33%, 30%, and 18% in the 10 mg od, 2.5 mg tid, and placebo groups, respectively (p = 0.0008 and 0.005 for the active groups vs placebo, respectively). In the ALFUS study, quality of life index improved by 18% in both active groups compared to 8% with placebo (p = 0.002 vs placebo). The extension of the ALFORTI trial saw an improvement from 2.3 at month 3 to 2.1 at endpoint (35% improvement from baseline).

The potential additive benefit of combining the α1-blocker alfuzosin and the 5α1-reductase inhibitor finasteride was assessed in a European, randomized double-blind, multicenter trial which involved 1051 patients with lower urinary tract symptoms associated with BPH. Patients treated with SR alfuzosin 5 mg twice daily without dose titration, finasteride (5 mg once daily, or both drugs for 6 months. Symptomatic improvement was significantly higher from the first month of treatment with SR alfuzosin, alone or in combination; mean changes in I-PSS versus baseline at endpoint were –6.3 and –6.1, respectively, compared with –5.2 with finasteride alone (SR alfuzosin vs finasteride, p = 0.01; combination vs finasteride p = 0.03). More than 40% of patients who received alfuzosin alone or in combination with finasteride had a 50% reduction of their urinary symptoms (Figure 9.6). In the overall population, increases in Qmax were greater with SR alfuzosin and the combination compared with finasteride alone after 1 month of therapy, but changes at endpoint were similar in the three treatment groups. In those 47% of patients likely to be obstructed
(baseline $Q_{\text{max}} < 10 \text{ ml/s}$), however, mean increases in $Q_{\text{max}}$ were significantly higher with SR alfuzosin, alone or in combination, whatever the visit. Thus, in this 6-month trial, SR alfuzosin was more effective than finasteride, with no additional benefit in combining both groups.

As described above, in symptomatic BPH patients, alfuzosin reduces the residual urine volume and in the medium term the incidence of AUR. This beneficial effect on bladder emptying is also confirmed by the low rate of AUR observed in long-term treatment. Moreover, alfuzosin has also been demonstrated to be useful in the management of AUR. Alfuzosin (5 mg bid) administered for 2 consecutive days in patients suffering from AUR secondary to BPH significantly increased the chance of voiding after removal of the catheter in comparison with placebo. These results were confirmed at the completion of the study: 22 out of 40 (55%) of patients treated with alfuzosin voided successfully in comparison with 12 out of 41 (29%) who received the placebo.

Overall, alfuzosin has been found to produce symptomatic improvement in patients suffering from moderate BPH, i.e. a 25% improvement in two-thirds of treated patients and a 50% improvement in one-third, with a favorable impact on quality of life. The increase in flow rate was 30%, and residual urine volume may be decreased by

![Graph showing maintenance in the long term (up to 6 months) of at least 25% improvement in BPH symptoms (circles, obstructive scores; squares, irritative scores; triangles, total scores) in patients given alfuzosin or placebo.](image)

**FIGURE 9.6** Maintenance in the long term (up to 6 months) of at least 25% improvement in BPH symptoms (circles, obstructive scores; squares, irritative scores; triangles, total scores) in patients given alfuzosin or placebo.
40%. The relief is prompt, more pronounced than with finasteride, and can be maintained over 3 years. In the medium term, alfuzosin reduced the incidence of AUR and, in long-term treatment, it is associated with a low incidence of AUR and prostate surgery.

**Side-effects and tolerance**

Oral IR alfuzosin (7.5–10 mg/day) is generally well tolerated in clinical studies of up to 30 months’ duration. The overall incidence of side-effects with alfuzosin appears to be similar to that seen with placebo, and the incidence of postural side-effects potentially related to the pharmacodynamic properties of alfuzosin appears to be lower than that with prazosin (up to 2 mg bid) and similar to that observed with the SR formulation of tamsulosin 0.4 mg od. Reported adverse effects with alfuzosin are usually transitory: the majority occur within the first 4 weeks of treatment and resolve spontaneously after drug withdrawal. Furthermore, both the SR and the od formulations of alfuzosin are at least as well tolerated as the immediate formulation.

In the 6-month placebo-controlled study, the overall incidence of adverse events was similar in alfuzosin-treated patients (36%) and in the placebo group (36%), with a similar rate of drop-out for adverse events (10 and 9%, respectively). In addition, the number of patients reporting at least one vasodilatation-related adverse effect was also similar in alfuzosin and placebo groups (11 and 10%, respectively). A lower incidence of impotence with alfuzosin (< 1%) compared with placebo (3%) may reflect the beneficial effect of α₁-adrenoceptor antagonists in this condition (Table 9.6). Alfuzosin appears to be well tolerated in the long term, which is of particular interest because BPH patients are likely to require long-term treatment.

In support of these data were the results of a noncomparative, nonblinded, multicenter post-marketing general practice survey, involving over 13 000 evaluable BPH patients who received alfuzosin 2.5 mg three times daily for 3 months. This study showed that the overall discontinuation rate was low (3.7%) and that two-thirds of patients’ withdrawals due to side-effects were caused by vasodilatation-related adverse events: vertigo/dizziness (1.4%), malaise (0.6%), postural hypotension (0.6%), and headache (0.4%). Most of these side-effects occurred during the first week of treatment and in fewer than 0.3% of patients after the first dose. As expected, postural side-effects were more common in the elderly and in patients receiving concomitant antihypertensive treatment. In this survey, which was extended up to 3 years, the incidence of side-effects leading to

<table>
<thead>
<tr>
<th>Table 9.6</th>
<th>Adverse effects reported by patients with benign prostatic hyperplasia during 6 months’ treatment with alfuzosin 7.5–10 mg/day (n = 251) or placebo (n = 267). (Adapted from Jardin et al.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse effect</td>
<td>Alfuzosin recipients (%)</td>
</tr>
<tr>
<td>Vasodilatory adverse effects</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>7.2</td>
</tr>
<tr>
<td>Headache</td>
<td>6.4</td>
</tr>
<tr>
<td>Postural hypotension</td>
<td>1.9</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>1.6</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>1.6</td>
</tr>
<tr>
<td>Other adverse effects</td>
<td></td>
</tr>
<tr>
<td>Skin rash</td>
<td>4.4</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>4.4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2.8</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.6</td>
</tr>
<tr>
<td>Asthenia</td>
<td>2.0</td>
</tr>
<tr>
<td>Chest pain</td>
<td>2.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.6</td>
</tr>
<tr>
<td>Bad taste</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Impotence</td>
<td>&lt; 1</td>
</tr>
</tbody>
</table>
drug discontinuation was 2.3% and 4.2% during the 1-year and 3-year survey, respectively.48–50,53 These figures confirm the good safety profile in long-term administration. Alfuzosin was better tolerated than prazosin in terms of postural symptoms in patients with BPH.33,34 The IR formulation of alfuzosin (2.5 mg tid) was as well tolerated as the marketed formulation of tamsulosin (0.4 mg od) in a 12-week study conducted in BPH.31 Decreases in supine and standing blood pressure were slightly greater in patients receiving alfuzosin than with tamsulosin. However, these changes were not associated with an increased incidence of side-effects, confirming that they were not clinically relevant. The number of drop-outs for adverse events was twice as low with alfuzosin than with tamsulosin (4% and 8%, respectively). The incidence of postural hypotension was low, i.e. 1% with alfuzosin and 3% with tamsulosin.

The safety profile of SR alfuzosin was specifically addressed in a pooled analysis of two placebo-controlled studies involving 588 patients (292 receiving SR alfuzosin 5 mg twice daily and 296 a placebo).41 Fifty-one per cent of the patients were ≥65 years of age and 43% had associated cardiovascular disease including hypertension and/or were receiving concomitant antihypertensive drugs. SR alfuzosin administered without initial titration was very well tolerated, with an overall incidence of adverse events similar to that of placebo (18.5% and 15.8% of patients, respectively) and an overall incidence of withdrawal from therapy for adverse events lower than that of placebo (3.4% and 5.7%, respectively). Adverse events potentially related to vasodilatation were infrequent with SR alfuzosin (the same incidence as with placebo, i.e. 2.7% of patients) and these adverse events occurred mainly during the first month of alfuzosin treatment.

The safety profile of SR alfuzosin was also compared to that of a standard dose of finasteride (5 mg od) and the combination of both drugs.32 The incidence of postural symptoms was not increased in those patients who received alfuzosin (Table 9.7). Conversely, impotence and ejaculatory disorders were significantly more frequent with finasteride, alone or in combination, than with alfuzosin alone. No ejaculatory disorders were reported with alfuzosin monotherapy.

The safety profile of the od SR formulation of alfuzosin assessed in the ALFORTI study was also very satisfactory. Alfuzosin od 10 mg was administered without dose titration. No first-day effect was observed. The incidence of adverse events related to vasodilatation was low (dizziness/vertigo 2.8%, headache 1.4%, malaise 1.4%, asymptomatic hypotension 0.7%). No case of syncope was recorded. In addition, no sexual dysfunction was observed.44
ALFUZOSIN 133

double-blind phase. Discontinuation due to adverse effects occurred in 5.6% of patients; vasodilatory effects were reported by 4.4% of patients, but were not due to first-day or age effects. Hypertensive patients reported more vasodilatory-related effects. No clinically relevant changes in systolic or diastolic blood pressure occurred (–2.6 and –2.8 mmHg compared to baseline, respectively). Nonclinically relevant orthostatic hypotension affected 2.8% of patients and risk was low in patients with mild and moderate renal impairment. Only 0.6% of patients reported ejaculatory disorders.

Apart from the intrinsic functional uroselectivity of alfuzosin, the low incidence of postural events observed with the new formulation of alfuzosin could be related to its pharmacokinetic properties, i.e. delayed peak plasma concentrations due to both a slowing and a prolongation of the rate of release of the active drug. The lack of CNS-related side-effects such as asthenia or somnolence could also be related to its low brain barrier penetration. Overall, consistent with the good tolerability of the drug, alfuzosin is not associated with impairment of sexual function.

**TABLE 9.7** Comparative safety profile of alfuzosin (slow release (SR) 5 mg twice daily), finasteride (5 mg once daily), and the combination of both drugs: incidence of adverse effects.

<table>
<thead>
<tr>
<th></th>
<th>Alfuzosin (n = 358)</th>
<th>Finasteride (n = 344)</th>
<th>Combination (n = 349)</th>
<th>Intergroup p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasodilatory events (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vertigo/dizziness</td>
<td>1.7</td>
<td>1.2</td>
<td>2.3</td>
<td>NS</td>
</tr>
<tr>
<td>Headache</td>
<td>2.0</td>
<td>1.2</td>
<td>1.4</td>
<td>NS</td>
</tr>
<tr>
<td>Postural hypotension/hypotension</td>
<td>0.6</td>
<td>0.9</td>
<td>0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Malaise</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Sexual disorders (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impotence</td>
<td>2.2</td>
<td>6.7</td>
<td>7.4</td>
<td>&lt; 0.002</td>
</tr>
<tr>
<td>Ejaculation failure</td>
<td>0.0</td>
<td>1.5</td>
<td>0.9</td>
<td>0.04</td>
</tr>
<tr>
<td>Decreased libido</td>
<td>0.6</td>
<td>1.7</td>
<td>2.0</td>
<td>NS</td>
</tr>
<tr>
<td>Others (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>0.0</td>
<td>0.3</td>
<td>0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Asthenia/fatigue</td>
<td>1.1</td>
<td>0.6</td>
<td>0.0</td>
<td>NS</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.0</td>
<td>0.3</td>
<td>0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Acute urinary retention</td>
<td>0.6</td>
<td>0.3</td>
<td>0.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data from Debruyne et al.32

PLACE OF ALFUZOSIN IN THERAPY

Although it is unlikely that a drug would abolish both the static and dynamic components of BPH as effectively as surgery, pharmacologic approaches to the symptomatic treatment of BPH have attracted increasing interest and have become the mainstay of patient management. α1-Blockers such as alfuzosin54 and 5α-reductase inhibitors55 are now considered first-line therapy for BPH. 5α-Reductase inhibitors can reduce the size of the prostate, but may take months to have such an effect and in the overall study population,
the magnitude of benefit is relatively modest. The potential benefits of the combination of alfuzosin and finasteride have yet to be demonstrated in the medium term.

The potential clinical advantage of alfuzosin over some other \( \alpha_1 \)-adrenoceptor antagonists is that it selectively blocks contraction mediated by \( \alpha_1 \)-adrenoceptors in the genitourinary tract compared to its action on receptors in the vasculature. Therefore, as described above, alfuzosin may be effective in BPH at doses that produce minimal adverse effects related to vascular \( \alpha_1 \) blockade, especially postural symptoms. In addition, the incidence of CNS-related adverse events (i.e. asthenia, somnolence) is not markedly increased with alfuzosin compared to placebo and no deleterious effects on sexual function have been reported. With increased realization of the importance of maintained sexual function in older adults, this factor is likely to be of significant value to BPH patients. Both the SR and IR formulations of alfuzosin offer patient-friendly daily dosings. These are convenient for the normal routine of daily life, as once-a-day and twice-a-day regimens are associated with better compliance (73 and 70%, respectively) than are thrice-daily regimens (52%). There is new evidence regarding the od formulation, indicating that it is as effective as SR and IR formulations, with fewer vasodilatory effects.

The beneficial effect of alfuzosin as an adjuvant treatment of AUR is promising, as is the reported low incidence of AUR in patients treated in the medium and long term with alfuzosin. Although the predictive criteria of those patients with BPH who are likely to respond to \( \alpha_1 \)-blockers have not yet been identified, the \( \alpha_1 \)-blocker alfuzosin is a first-line and safe agent in patients with symptomatic BPH.

**ACKNOWLEDGMENTS**

The author would like to thank S. Arbilla, M. C. Delauche and D. Martin for their fruitful collaboration in the writing of this chapter.

**REFERENCES**

5. Ford A P D W, Arredondo N F, Blue D R Jr et al. RS-17053 (N-[2-(2-cyclopropylmethoxyphenoxyl)ethyl]-5-chloro-\( \alpha \),\( \alpha \)-dimethyl-1H-indole-3-ethamine hydrochloride), a selective \( \alpha_1 \)-adrenoceptor antagonist, displays low affinity for functional \( \alpha_1 \)-adrenoceptors in human prostate: implications for adrenoceptor classification. Eur J Pharmacol 1996; 49: 209–215
8. Van Der Graaf P H, Deplanne V, Duquenne C et al. The $\alpha_{1A}$-adrenoceptor is not involved in phenylephrine-mediated contractions of rabbit isolated prostate. Eur Urol 1996; 30/52: 51


15. Lefevre-Borg F, Lechaire J, O’Connor S E. In vivo uroselectivity of alfuzosin compared to prazosin and terazosin. Br J Pharmacol 1992; 106; 84P


17. Martin D J, Lluel P, Guillet E et al. Comparative $\alpha_{1}$-adrenoceptor subtype selectivity and functional uroselectivity of $\alpha_{1}$-adrenoceptor antagonists. J Pharmacol Exp Ther 1997; 282: 228–235


INTRODUCTION

Introduction to α₁-adrenoceptor antagonists

α₁-Adrenoceptor antagonists were originally developed for the treatment of hypertension. Blockade of postsynaptic α₁-adrenoceptors in the blood vessels by these agents results in vasodilatation. As a consequence, the peripheral vascular resistance and blood pressure are reduced. Examples of α₁-adrenoceptor antagonists that have been developed for and/or are still used for the treatment of hypertension are alfuzosin, doxazosin, prazosin, and terazosin.

In 1976, Caine et al. proposed a hypothesis for the use of α₁-adrenoceptor antagonists in lower urinary tract symptoms (LUTS) suggestive of benign prostatic obstruction (BPO), also referred to as symptomatic benign prostatic hyperplasia (BPH).¹ By inhibiting the effect of noradrenaline—the neurotransmitter of the sympathetic nervous system—at α₁-adrenoceptors in the bladder neck, prostatic urethra, and prostate capsule and stroma, α₁-adrenoceptor antagonists reduce the dynamic component of BPH.¹–³ Today, α₁-adrenoceptor antagonists are one of the most widely used medical therapies for this condition.³–⁵ They improve symptoms and urinary flow quickly (within a few weeks) and have a favorable clinical response in about 70% of patients. Total symptom score is in general improved by 30–40% and maximum urinary flow rate (Q max) is increased by 16–25%.³–⁴

The 5α-reductase inhibitor (5αRI) finasteride is another medical treatment option for LUTS suggestive of BPH accepted by the 4th and 5th International Consultations on BPH.⁶,⁷ It reduces the prostatic mass and therefore the mechanical or static component of BPH. Several direct comparative studies between α₁-adrenoceptor antagonists and finasteride have been published or presented.⁸–¹⁰ The initial trial demonstrated superior efficacy of α₁-adrenoceptor antagonists over finasteride in terms of improvement in BPH symptoms and peak flows. More recently, the MTOPS study has demonstrated greater efficacy for a combination of α₁-adrenoceptor antagonist + 5αRI, although the extrapolation of these findings to clinical practice still remains the subject of debate¹¹. Comparison of an alternative 5αRI, dutasteride, to α₁-adrenoceptor suggests that there are no major therapeutic differences.

There is evidence that the efficacy of α₁-adrenoceptor antagonists is independent of prostate size at baseline.¹² Finasteride in contrast across the whole spectrum of patients has modest efficacy compared with placebo and is most effective in patients with an enlarged prostate (> 40 g).⁶,¹³

Finally, α₁-adrenoceptor antagonists work much faster (within a few weeks) than finasteride (up to 6 months) and, in contrast to 5αRIs are not associated with erectile dysfunction or loss in sexual interest and do not reduce prostate-specific antigen (PSA).¹⁴ These facts together will reinforce the use of α₁-adrenoceptor antagonists as first-choice medical therapy for LUTS suggestive of BPH. The most important drawback of the classical α₁-adrenoceptor antagonists remains,
however, adverse events attributed to the blood pressure-lowering potential such as dizziness, orthostatic hypotension, and syncope. In addition, in order to reduce the occurrence of the first dose effect (i.e., excessive blood pressure reduction with subsequent symptomatic orthostatic hypotension), they are recommended to be initiated at a low, subtherapeutic dose with gradual titration to the optimal therapeutic dose.

Introduction to tamsulosin

Tamsulosin hydrochloride (YM-617) has been specifically developed by the Yamanouchi Pharmaceutical Company for the treatment of LUTS suggestive of BPH. The chemical structure of tamsulosin, a methoxybenzenesulfonamide, differs from that of the other clinically available short-acting (alfluzosin and prazosin) and long-acting (doxazosin and terazosin) \( \alpha_1 \)-adrenoceptor antagonists which are quinazoline derivatives.15 This may have consequences for drug–receptor interaction.

In the late 1980s and the 1990s, it became clear that part from \( \alpha_1 \)- and \( \alpha_2 \)-adrenoceptors, there exist several subtypes of the \( \alpha_1 \)-adrenoceptor. The International Union of Pharmacology (IUPHAR) has accepted the existence of three \( \alpha_1 \)-adrenoceptor subtypes (with high affinity for prazosin): \( \alpha_{1A} \), \( \alpha_{1D} \), and \( \alpha_{1D'} \) (quoted in lower case when referring to the cloned entities).16 Another \( \alpha_1 \)-adrenoceptor subtype has been described pharmacologically, which is a low-affinity prazosin adrenoceptor, termed \( \alpha_{1L} \).12 Although the molecular identity of this fourth \( \alpha_1 \)-adrenoceptor subtype is not fully established, recent evidence suggests that the \( \alpha_{1L} \) subtype may represent a particular conformational state of the \( \alpha_1 \)-adrenoceptor.17 It has been demonstrated that the \( \alpha_{1A} \) and \( \alpha_{1L} \)-adrenoceptor subtypes are the predominant functional \( \alpha_1 \)-adrenoceptors in the human prostate.17–22 Research indicates that \( \alpha_1 \)-adrenoceptors in the human detrusor are of the \( \alpha_{1D} \) and to a lesser extent of the \( \alpha_{1A} \) subtypes and it has been suggested that inhibition of these subtypes leads to improvement of irritative symptoms by \( \alpha_1 \)-adrenoceptor antagonists.23 It is not complete clear which subtype is involved in blood pressure regulation in humans, since receptor binding and molecular biological techniques do not provide consistent data on this matter.24–26 However, clinical pharmacology studies with doxazosin, terazosin, and tamsulosin suggest that \( \alpha_{1A} \)-adrenoceptors are more prominently involved in vasoconstriction than \( \alpha_1 \)-adrenoceptors.27,28

At present, tamsulosin is the only clinically available \( \alpha_1 \)-adrenoceptor antagonist that displays selectivity for \( \alpha_{1A} \)- and, to a slightly lesser extent, \( \alpha_{1D'} \) over \( \alpha_{1D} \)-adrenoceptors.29–31 In addition, tamsulosin has 12 times greater affinity for \( \alpha_1 \)-adrenoceptors in the human prostate than in the aorta in contrast to prazosin which has similar affinity for those in the prostate and aorta.32 This can be referred to as receptor pharmacologic uroselectivity.33 Other available \( \alpha_1 \)-adrenoceptor antagonists (alfluzosin, doxazosin, prazosin, and terazosin) do not display selectivity for any of the \( \alpha_1 \)-adrenoceptor subtypes.29–31

Tamsulosin hydrochloride is available worldwide as a modified-release formulation. Due to the long half-life (about 10–13 hours in elderly subjects), tamsulosin can be classified as a long-acting \( \alpha_1 \)-adrenoceptor antagonist that can be taken once daily (after a meal). In Japan it was introduced by Yamanouchi in 1993 under the tradename Harnal®. In Europe it was first introduced in The Netherlands in 1995 and has since been marketed in most countries by Yamanouchi Europe (tradenames Omnic®, Omic®, Omix®, and Flomax®) and/or Boehringer Ingelheim (Alna®, Pradil®, Josir®, or Urolosin®).
TAMSULOSIN 141

Tamsulosin is also available in many Latin American countries (Flomax® and Secotex®) and was approved by the FDA in the US in 1997 (Flomax®).

PHYSIOLOGIC UROSELECTIVITY

Physiologically, an α1-adrenoceptor antagonist can be considered uroselective if it inhibits to a lesser extent than other α1-adrenoceptor antagonists the α1-adrenoceptors in the vascular system. Considerable species differences for tissue distribution and functionality of α1-adrenoceptor subtypes exist. Therefore, α1-adrenoceptor antagonists can only be differentiated from a physiological uroselectivity point of view based on results obtained in human beings.

Two such experimental studies have been performed with tamsulosin and a hemodynamically active α1-adrenoceptor antagonist to evaluate the inhibition of phenylephrine or cold-induced vasoconstriction.27,28 One placebo-controlled trial compared a single dose of tamsulosin (modified-release formulation) 0.2 mg and doxazosin 1 mg in eight Japanese healthy subjects in a cross-over design.27 The other placebo-controlled trial compared equi-effective single doses of tamsulosin (modified release) 0.4 mg with terazosin 5 mg in ten healthy Caucasian volunteers in a cross-over setting.28 Figure 10.1a shows that the number of patients who had an increase in diastolic blood pressure of 7.6 mmHg after phenylephrine infusion was reduced to a lesser extent in tamsulosin-treated than in terazosin-treated patients. In addition, the inhibition of phenylephrine-induced increases in diastolic blood pressure relative to placebo was less with tamsulosin than terazosin (Figure 10.1b).

There is evidence from in vivo studies in human volunteers that tamsulosin causes less inhibition of vasoconstriction and therefore has lower affinity for vascular α1-adrenoceptors than doxazosin and terazosin.27,28

CLINICAL UROSELECTIVITY

Clinical uroselectivity has been defined as ‘desired effects on obstruction and LUTS related to adverse events’ in patients with LUTS suggestive of BPH.33 This implies that the α1-adrenoceptor antagonist should have at least comparable efficacy to other α1-adrenoceptor antagonists with an improved side-effect profile (i.e. lower potential to induce excessive blood pressure reductions with subsequent dizziness, symptomatic orthostatic hypotension, and syncope).

Japanese clinical placebo-controlled data

A randomized, double-blind, placebo-controlled, parallel-group, phase II, dose-ranging study was performed in 270 Japanese patients with LUTS suggestive of BPH, using 0.1, 0.2, or 0.4 mg tamsulosin once daily for 4 weeks, after a 2-week placebo run-in period.34

The Qmax for the placebo, 0.2 mg, and 0.4 mg groups improved by 1.4 ml/s (15%), 4.0 ml/s (44%), and 3.6 ml/s (35%), respectively (nonsignificant vs placebo; Table 10.1). With respect to average urinary flow rate (Qave), there were statistically significant differences between 0.2 and 0.4 mg tamsulosin once daily (increases of 26% and 41%, respectively) and placebo (decrease of 4%). In addition, global subjective improvement was similar in the 0.2 mg and the 0.4 mg dosing groups and significantly better in comparison with placebo (p < 0.01). Approximately 80% of patients
reported that their condition had (slightly, moderately, or markedly) improved.

Tamsulosin was very well tolerated. Neither orthostatic hypotension nor a significant decrease in blood pressure were observed.

In conclusion, both 0.2 and 0.4 mg tamsulosin once daily are effective and well-tolerated dosages in the treatment of Japanese patients with LUTS suggestive of BPH. Tamsulosin 0.2 mg is the recommended dose in Japan.

**European clinical placebo-controlled data**

A randomized, double-blind, placebo-controlled, parallel group, *phase II dose-ranging* study was performed in the UK. After a 3-week placebo run-in period, 126 patients with LUTS due to
BPH \((Q_{\text{max}} < 15 \text{ ml/s for a voided volume > 100 ml; urethral resistance: detrusor pressure (P_{\text{det}}) at Q_{\text{max}} (P_{\text{det}} \cdot Q_{\text{max}}) / Q_{\text{max}}^2 \geq 0.5)}\) were randomized to placebo or tamsulosin (0.2, 0.4, or 0.6 mg) once daily for 4 weeks. Efficacy was evaluated by free-flow and pressure–flow parameters and by a modified Boyarsky symptom score (eight symptoms to be rated from 0 to 5; total score range 0–40).

Table 10.1 and Figure 10.2a show that both the 0.4 and 0.6 mg dose increased mean \(Q_{\text{max}}\) (2.2 ml/s or 22.6% and 1.8 ml/s or 20.2%, respectively) statistically significantly compared with placebo (–0.1 ml/s or –0.9%, \(p < 0.05\)). The 0.4 mg dose produced the greatest decrease in mean \(P_{\text{det}} / Q_{\text{max}}\) (–26.6 cmH\(_2\)O or –28.2%) compared with an increase of 4.9 cmH\(_2\)O (+5.7%) with placebo (Figure 10.2b). The decrease in mean total symptom score was comparable for the 0.4 (–29 or –17.7%) and 0.6 mg dose (–4.4 or –28.2%) and was superior to the decrease in the placebo group (–2.9 or –17.7%: Table 10.2 and Figure 10.2c). The difference versus placebo did not reach statistical significance, probably due to the small sample size and the relatively short duration of treatment (4 weeks). The percentage of patients who experienced slight or much improvement in their condition was also greatest in the 0.4 mg group (Figure 10.2d).

It can be concluded that optimal improvement in all efficacy parameters was achieved with the 0.4 mg dose of tamsulosin. This dose was also well tolerated and did not induce statistically significantly greater blood pressure changes during the first 8 hours after the first dose. Therefore, the 0.4 mg dose was further evaluated in phase III clinical trials in Europe.

Two multinational, multicenter, double-blind, randomized, placebo-controlled phase III studies were performed in Europe. The Boyarsky symptom score was used to assess the effect on LUTS (nine symptoms, each to be rated from 0 to 3; total score range 0–27). Both studies enrolled more than 300 patients with mild–moderate LUTS (total Boyarsky score > 6) suggestive of BPH (free flow \(Q_{\text{max}}\) 4–12 ml/s for a voided volume ≥120 ml). They were randomized to 12 weeks of treatment with placebo or tamsulosin 0.4 mg once daily in a 1:2 ratio (after a 2-week placebo run-in period). As the design, assessments, and results (Tables 10.1. and 10.2) of both studies were comparable, a meta-analysis that involved 193 placebo and 381 tamsulosin patients was carried out.

Tamsulosin increased mean peak flow \(Q_{\text{max}}\) by 1.6 ml/s (16%). Although there was a considerable placebo-effect (0.6 ml/s or 6%), the difference was statistically significant (\(p = 0.002\); see Table 10.1). The same applied for the percentage of patients with a clinically significant improvement in \(Q_{\text{max}}\) (defined as an increase from baseline of ≥ 30%): 32% of tamsulosin- and 20% of placebo-treated patients (\(p = 0.003\)). Mean total Boyarsky symptom score was decreased to a statistically significant extent in the tamsulosin (–3.3 or –35.1%) versus the placebo group (–2.4 or –25.5%, \(p = 0.002\)). The same applied for the decrease in total voiding (\(p = 0.008\)) and filling (\(p = 0.017\)) scores. A decrease in total Boyarsky symptom score from baseline ≥ 25% was considered to be a clinically significant response. This was achieved in 66% of patients in the tamsulosin and 49% of patients in the placebo group (\(p < 0.001\)).

Tamsulosin has a fast onset of action. The increase in mean \(Q_{\text{max}}\) was already apparent and optimal compared with placebo at the first assessment after 4 weeks of treatment with tamsulosin 0.4 mg (Figure 10.3a). Although improvements in total Boyarsky symptom score were apparent and significant over placebo at the first assessment at
<table>
<thead>
<tr>
<th>First author</th>
<th>Duration (weeks)</th>
<th>Dose (mg)</th>
<th>Baseline</th>
<th>End-point</th>
<th>Change</th>
<th>Change (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kawabe</td>
<td>4</td>
<td>0.2</td>
<td>9.1</td>
<td>13.1</td>
<td>4.0</td>
<td>44</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>0.4</td>
<td>10.4</td>
<td>3.6</td>
<td>35</td>
<td>13</td>
<td>10.9</td>
<td>NS</td>
</tr>
<tr>
<td>Abrams</td>
<td>34</td>
<td>0.2</td>
<td>9.6</td>
<td>10.7</td>
<td>1.1</td>
<td>13</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>0.4</td>
<td>9.8</td>
<td>2.2</td>
<td>23</td>
<td>13</td>
<td>10.9</td>
<td>NS</td>
</tr>
<tr>
<td>Abrams</td>
<td>37</td>
<td>0.4</td>
<td>10.7</td>
<td>12.0</td>
<td>1.4</td>
<td>13</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>0.4</td>
<td>10.2</td>
<td>1.8</td>
<td>16</td>
<td>13</td>
<td>10.4</td>
<td>NS</td>
</tr>
<tr>
<td>Chapple</td>
<td>38</td>
<td>0.4</td>
<td>10.2</td>
<td>12.0</td>
<td>1.4</td>
<td>13</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>0.6</td>
<td>10.9</td>
<td>1.8</td>
<td>20</td>
<td>13</td>
<td>10.4</td>
<td>4</td>
</tr>
<tr>
<td>Lepor</td>
<td>43</td>
<td>0.4</td>
<td>9.8</td>
<td>—</td>
<td>1.6</td>
<td>10.4</td>
<td>0.028</td>
</tr>
<tr>
<td></td>
<td>0.8</td>
<td>9.6</td>
<td>—</td>
<td>1.8</td>
<td>13</td>
<td>10.4</td>
<td>0.002</td>
</tr>
<tr>
<td>Narayan</td>
<td>44</td>
<td>0.4</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>0.8</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>NS</td>
</tr>
<tr>
<td>Lepor</td>
<td>46</td>
<td>0.4</td>
<td>9.5</td>
<td>—</td>
<td>1.7</td>
<td>10.4</td>
<td>0.064</td>
</tr>
<tr>
<td></td>
<td>0.8</td>
<td>9.5</td>
<td>—</td>
<td>2.1</td>
<td>18</td>
<td>9.9</td>
<td>0.007</td>
</tr>
</tbody>
</table>
4 weeks, the symptom score continued to improve for the last 8 weeks of the trial when the effect was (nearly) optimal (Figure 10.3b). At 4 weeks, about 70% of the total effect seen after 12 weeks was achieved.

Tamsulosin 0.4 mg was very well tolerated. It had minimal effects on blood pressure. In comparison with placebo there were no clinically significant changes in supine or standing systolic or diastolic blood pressure at end-point. Except for the change in standing diastolic blood pressure (−2.5 mmHg), the differences were also not statistically significant (Table 10.3). Approximately 20% of patients were hypertensive. In both the normotensive and hypertensive subgroups, tamsulosin 0.4 mg did not affect blood pressure to a clinically significantly greater extent than placebo. The decrease in standing diastolic blood pressure in normotensive patients was statistically significantly greater than in the placebo group but the reduction was minimal (−0.8 mmHg; \( p = 0.049 \); Table 10.4).

In addition, tamsulosin did not induce more adverse events than placebo, be it treatment emergent adverse events (36% vs 32%, \( p = 0.290 \)) or possibly/probably drug-related adverse events according to the investigator (13% vs 12%, \( p = 0.802 \)). The same applied for the percentage

![Figure 10.2](image-url)
### TABLE 10.2 Effect of placebo or tamsulosin on mean total symptom score in placebo-controlled studies in Japan, Europe, and the US.

<table>
<thead>
<tr>
<th>First author (symptom score)</th>
<th>Duration (weeks)</th>
<th>Dose (mg)</th>
<th>Baseline</th>
<th>End-point</th>
<th>Change</th>
<th>Change (%)</th>
<th>Baseline</th>
<th>Change</th>
<th>Change (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrams (modified)</td>
<td>35</td>
<td>0.2</td>
<td>16.9</td>
<td>13.6</td>
<td>-3.4</td>
<td>-20</td>
<td>16.7</td>
<td>-2.9</td>
<td>-18</td>
<td>NS</td>
</tr>
<tr>
<td>Abrams</td>
<td>37</td>
<td>0.4</td>
<td>14.9</td>
<td>10.2</td>
<td>-4.1</td>
<td>-29</td>
<td>16.7</td>
<td>-2.9</td>
<td>-18</td>
<td>NS</td>
</tr>
<tr>
<td>Abrams (I-PSS)</td>
<td>42</td>
<td>0.4</td>
<td>17.7</td>
<td>-8.8</td>
<td>-50</td>
<td>-36</td>
<td>17.4</td>
<td>-4.7</td>
<td>-27</td>
<td>≤ 0.01</td>
</tr>
<tr>
<td>Lepor (I-PSS)</td>
<td>43</td>
<td>0.4</td>
<td>19.8</td>
<td>-9.4</td>
<td>-48</td>
<td>-42</td>
<td>19.6</td>
<td>-5.5</td>
<td>-28</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Narayan (I-PSS)</td>
<td>44</td>
<td>0.8</td>
<td>19.9</td>
<td>-9.6</td>
<td>-48</td>
<td>-5.8</td>
<td>20.0</td>
<td>-6.5</td>
<td>-34</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Note: I-PSS indicates International Prostate Symptom Score.
of patients that discontinued due to adverse events (4.5% vs 3.6%). Adverse events commonly attributed to hemodynamically active $\alpha_1$-adrenoceptor antagonists such as dizziness, orthostatic hypotension, and syncope occurred at a comparable incidence in the tamsulosin and placebo groups (Table 10.5). This also applied for other adverse events associated with $\alpha_1$-adrenoceptor antagonists (asthenia, somnolence, rhinitis/nasal congestion). The only adverse event that was reported by significantly more tamsulosin than placebo patients was abnormal ejaculation (4.5% vs 1%, $p = 0.045$). This adverse event was, however, very well tolerated by the patients, because few tamsulosin patients (0.8%) withdrew from the study for this reason. Other sexual function-
related adverse events (impotence and decreased libido) were reported to the same extent in the tamsulosin and placebo groups (Table 10.5).41

Another randomized, double-blind, placebo-controlled phase IV, 12-week study has been performed with tamsulosin 0.4 mg once daily in European patients with LUTS (I-PSS ≥ 13) suggestive of BPH (Q\textsubscript{max} < 12 ml/s): ESPIRIT (European Standardized Pressure Flow Investigation Trial).42 In a subset of this trial (n = 193), the effects on pressure–flow parameters were studied in particular. Tamsulosin produced statistically significant decreases in P\textsubscript{det}Q\textsubscript{max} (–7.2 cmH\textsubscript{2}O or –10%) compared with placebo (+2.0 cmH\textsubscript{2}O or +3%; p = 0.038: Table 10.6).

**Effects on pressure–flow**

Q\textsubscript{max} and the Abrams–Griffiths (AG) number (P\textsubscript{det}Q\textsubscript{max} – [2 × Q\textsubscript{max}]) were also significantly improved in the tamsulosin-treated compared with the placebo-

---

### TABLE 10.3 Change in mean systolic and diastolic blood pressure (SBP/DBP) at end-point with placebo or tamsulosin 0.4 mg in meta-analysis of two European phase III placebo-controlled studies: all patients.38

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 189)</th>
<th>Tamsulosin (n = 373)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Supine SBP (mmHg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>144.3</td>
<td>143.1</td>
</tr>
<tr>
<td>Change</td>
<td>–3.5</td>
<td>–3.1</td>
</tr>
<tr>
<td><strong>Supine DBP (mmHg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>85.4</td>
<td>85.4</td>
</tr>
<tr>
<td>Change</td>
<td>–0.9</td>
<td>–1.6</td>
</tr>
<tr>
<td><strong>Standing SBP (mmHg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>142.9</td>
<td>141.8</td>
</tr>
<tr>
<td>Change</td>
<td>–1.7</td>
<td>–3.3</td>
</tr>
<tr>
<td><strong>Standing DBP (mmHg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>86.4</td>
<td>86.8</td>
</tr>
<tr>
<td>Change</td>
<td>–0.4</td>
<td>–2.5*</td>
</tr>
</tbody>
</table>

*p = 0.018 vs placebo.

### TABLE 10.4 Change in mean systolic and diastolic blood pressure (SBP/DBP) at end-point with placebo or tamsulosin 0.4 mg in meta-analysis of two European phase III placebo-controlled studies: normotensive and hypertensive patients.38

<table>
<thead>
<tr>
<th></th>
<th>Normotension</th>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n = 150)</td>
<td>Tamsulosin (n = 294)</td>
</tr>
<tr>
<td><strong>Supine SBP (mmHg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>139.7</td>
<td>137.8</td>
</tr>
<tr>
<td>Change</td>
<td>–2.5</td>
<td>–2.0</td>
</tr>
<tr>
<td><strong>Supine DBP (mmHg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>81.4</td>
<td>81.1</td>
</tr>
<tr>
<td>Change</td>
<td>+1.0</td>
<td>+0.4</td>
</tr>
<tr>
<td><strong>Standing SBP (mmHg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>138.7</td>
<td>137.4</td>
</tr>
<tr>
<td>Change</td>
<td>–0.6</td>
<td>–2.5</td>
</tr>
<tr>
<td><strong>Standing DBP (mmHg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>83.0</td>
<td>83.1</td>
</tr>
<tr>
<td>Change</td>
<td>+1.0</td>
<td>–0.8*</td>
</tr>
</tbody>
</table>

*p = 0.049 vs placebo.
treated patients. The AG number was reduced by 10.3 (−19%) on tamsulosin and increased by 1.2 (2%) on placebo (p = 0.014). Clinical improvement in total I-PSS occurred within 1 week with continuing improvement up to 12 weeks (decrease 8.8 or −50% vs −4.7 (−27%) with placebo; p ≤ 0.01).

It can be concluded that tamsulosin 0.4 mg once daily is the optimal dose for European patients with LUTS suggestion of BPH. It has a rapid onset of action: \( Q_{\text{max}} \) is maximally increased at the first assessment after 4 weeks and total symptom score within 1 week. It is extremely well tolerated, even without the need for dose titration. It has no clinically significant effect on blood pressure in normotensive or hypertensive patients and no increased potential to induce symptomatic orthostatic hypotension compared with placebo. Abnormal ejaculation is the only adverse event that occurs to a greater extent than with placebo.

**US clinical placebo-controlled data**

Two randomized, double-blind, *placebo-controlled phase III* short-term (13-week) studies were performed in the US with tamsulosin 0.4 mg or 0.8 mg once daily.\(^{43,44}\) The American Urological Association (AUA) symptom index, which is identical to the International Prostate

---

**TABLE 10.5** Incidence of adverse events (AEs) with placebo or tamsulosin 0.4 mg in the meta-analysis of the two European placebo-controlled phase III studies.\(^{38,41}\)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 193)</th>
<th>Tamsulosin (n = 381)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>61 (32)</td>
<td>137 (36)</td>
</tr>
<tr>
<td>Any drug-related* AE</td>
<td>24 (12)</td>
<td>50 (13)</td>
</tr>
<tr>
<td>Discontinued due to adverse events</td>
<td>7 (3.6)</td>
<td>17 (4.5)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6 (3.1)</td>
<td>13 (3.4)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (2.1)</td>
<td>8 (2.1)</td>
</tr>
<tr>
<td>Tachycardia/palpitation</td>
<td>3 (1.6)</td>
<td>5 (1.3)</td>
</tr>
<tr>
<td>Postural hypotension</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Syncope</td>
<td>1 (0.5)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>2 (1.0)</td>
<td>4 (1.0)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>2 (1.0)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Rhinitis (nasal congestion)</td>
<td>1 (0.5)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Abnormal ejaculation</td>
<td>2 (1.0)</td>
<td>17 (4.5)</td>
</tr>
<tr>
<td>Impotence</td>
<td>3 (1.6)</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>Libido decreased</td>
<td>0 (0)</td>
<td>4 (1.0)</td>
</tr>
<tr>
<td>Discontinued due to sexual function-related adverse events</td>
<td>1 (0.5)</td>
<td>3 (0.8)</td>
</tr>
</tbody>
</table>

*Possibly or probably drug-related according to the investigator; \( p = 0.045 \) vs placebo.

---

**TABLE 10.6** Effect on pressure–flow parameters and total I-PSS after 12 weeks of therapy with tamsulosin 0.4 mg or placebo in the European ESPRIT study.\(^{42}\)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 54)</th>
<th>Tamsulosin (n = 106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( P_{\text{det}}O_{\text{max}} ) (cmH(_2)O)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>68.0</td>
<td>69.2</td>
</tr>
<tr>
<td>Change (%) at 12 weeks</td>
<td>2.0 (3%)</td>
<td>−7.2 (−10%)**</td>
</tr>
<tr>
<td>Pressure flow ( Q_{\text{max}} ) (ml/s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>6.4</td>
<td>7.1</td>
</tr>
<tr>
<td>Change (%) at 12 weeks</td>
<td>0.4 (6%)</td>
<td>1.5 (21%)†</td>
</tr>
<tr>
<td>AG number</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>55.2</td>
<td>55.1</td>
</tr>
<tr>
<td>Change</td>
<td>1.2 (2%)</td>
<td>−10.3 (−19%)†</td>
</tr>
<tr>
<td>Total I-PSS score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>17.4</td>
<td>17.7</td>
</tr>
<tr>
<td>Change</td>
<td>−4.7 (−27%)</td>
<td>−8.8 (−50%)**</td>
</tr>
</tbody>
</table>

\( n = 193 \) instead of 160 for total I-PSS. \( *p = 0.038; \)
\( †p = 0.002; \) \( ‡p = 0.014; \) \( **p ≤ 0.01. \)
Symptom Score (I-PSS), was used in these studies to assess the effect on LUTS (seven symptoms, each to be rated from 0 to 5; total score range 0–35). In each study, approximately 750 patients with moderate–severe LUTS (total I-PSS ≥ 13) suggestive of BPH ($Q_{\text{max}}$ 4–15 ml/s) were randomized to one of the three groups after a placebo run-in of 4 weeks. There were four primary efficacy parameters in each study (at end-point): (a) mean change in total I-PSS, (b) mean change in $Q_{\text{max}}$, (c) number of symptom score responders (decrease total I-PSS ≥ 25%), and (d) number of $Q_{\text{max}}$ responders (increase $Q_{\text{max}}$ ≥ 30%).

**FIGURE 10.4** Percentage of (a) $Q_{\text{max}}$ responders and (b) total symptom score responders at end-point in the placebo and tamsulosin groups of two short-term US studies: study 1 and study 2.
In both studies, tamsulosin 0.4 mg and 0.8 mg once daily were statistically significantly superior to placebo (see Tables 10.1 and 10.2, and Figure 10.4a and b). The only parameter that did not reach but approached statistical significance over placebo in the 0.4 mg group ($p = 0.064$) was mean $Q_{\text{max}}$ (measured at through plasma concentration) in one of the studies. Tamsulosin 0.4 mg and 0.8 mg had comparable efficacy in both studies, only the change in total I-PSS at end-point was greater in the 0.8 mg than in the 0.4 mg group ($p = 0.020$). However, the difference between the two treatment groups was already partly apparent after 1 week of therapy when both the

![Figure 10.5](image-url)

**Figure 10.5** Effect of tamsulosin (0.4 or 0.8 mg) and placebo on (a) mean $Q_{\text{max}}$ and (b) mean total I-PSS score over time in one of the US short-term studies. 

TAMSULOSIN 151
patients in the 0.4 and 0.8 mg groups had received 0.4 mg (Figure 10.5b). This shows that the greater effect of the 0.8 mg dose with regard to change in total I-PSS at end-point was probably caused by a difference in response between treatment/patient groups and not by a difference in response to tamsulosin dose.

Tamsulosin 0.4 mg had a very fast onset of action in both studies. In one of the studies, $Q_{\text{max}}$ was measured 4–8 hours after intake of the first dose. At that time point, $Q_{\text{max}}$ was already significantly and maximally increased compared with placebo (Figure 10.5a). In addition, the difference in improvement in total I-PSS score between tamsulosin and placebo was significant at the first assessment after 1 week (Figure 10.5b). The symptom score continued to improve up to 13 weeks when the optimal effect on LUTS was achieved. At week 1, approximately 50% of the total reduction was observed.

Tamsulosin 0.4 mg and 0.8 mg had no clinically significant effects on blood pressure, either in normotensive or (controlled or uncontrolled) hypertensive patients. Multiple and rigorous orthostatic stress testing was performed at every visit in both studies. Despite this, the number of patients that developed symptomatic orthostatic hypotension with tamsulosin 0.4 mg or 0.8 mg in both studies was comparable to that with placebo: 1 (0.2%), 2 (0.4%), and 0 (0%), respectively. Other symptoms of orthostatic hypotension reported during the multiple and rigorous orthostatic stress tests (such as dizziness, lightheadedness, and faintness/syncope) were also included in the adverse events listing (Table 10.7). The only adverse event that was reported consistently and significantly more frequently with the 0.4 mg dose in both studies was abnormal ejaculation (6% and 11%) vs <1% with placebo. The occurrence of this adverse event was dose-dependent as

| TABLE 10.7 | Incidence of adverse events with placebo, tamsulosin 0.4 mg or tamsulosin 0.8 mg in the two US placebo-controlled, short-term (13-week), phase III studies. Data in parentheses are percentages. |
|------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
|            | Study 1*                                         | Study 2*                                         | Study 1*                                         | Study 2*                                         | Study 1*                                         | Study 2*                                         |
|            | Placebo ($n = 254$)                              | Tamsulosin 0.4 mg ($n = 254$)                    | Tamsulosin 0.8 mg ($n = 248$)                    | Placebo ($n = 259$)                              | Tamsulosin 0.4 mg ($n = 248$)                    | Tamsulosin 0.8 mg ($n = 244$)                    |
| Any AE     | 151 (59)                                        | 165 (65)                                        | 180 (73)                                        | 181 (76)                                        | 194 (78)                                        | 188 (77)                                        |
| Discontinued due to adverse events | 22 (9)                                          | 18 (7)                                          | 31 (13)                                         | 20 (8)                                          | 22 (9)                                          | 30 (12)                                         |
| Dizziness  | 13 (5)                                          | 25 (10)                                         | 28 (11)*                                       | 37 (15)                                        | 50 (20)                                         | 56 (23)*                                       |
| Orthostatic hypotension | 0 (0)                                          | 1 (0.4)                                         | 2 (0.8)                                         | 0 (0)                                          | 0 (0)                                          | 0 (0)                                          |
| Asthenia   | 5 (2)                                           | 12 (5)                                          | 13 (5)                                          | 22 (9)                                         | 27 (11)                                         | 29 (12)                                         |
| Headache   | 46 (18)                                         | 48 (19)                                         | 45 (18)                                         | 53 (22)                                        | 49 (20)                                         | 59 (24)                                         |
| Rhinitis   | 14 (6)                                          | 31 (12)*                                        | 37 (15)*                                       | 26 (11)                                        | 35 (14)                                         | 50 (20)*                                       |
| Abnormal ejaculation | 0 (0)                                          | 15 (6)*                                          | 44 (18)*                                       | 1 (< 1)                                        | 27 (11)*                                        | 45 (18) *†                                     |

*Significant vs placebo; †significant vs 0.4 mg.
it was reported by significantly more patients on 0.8 mg (18%) than 0.4 mg in both studies. The reporting of other adverse events such as dizziness, rhinitis/nasal congestion, and somnolence also increased with the higher tamsulosin dose and they were experienced by significantly more patients on tamsulosin 0.8 mg than placebo. Discontinuation due to adverse events occurred in about 8% of patients in both the placebo and tamsulosin 0.4 mg groups and in 12–13% of patients on 0.8 mg.43,44

A total of 418 patients who completed one of the 13-week placebo-controlled US studies43 continued with a 40-week, placebo-controlled extension study in which they remained on the same double-blind medication as in the short-term study.46

The efficacy and good tolerability of tamsulosin (0.4 mg and 0.8 mg) in comparison with placebo was sustained during the 40-week extension phase. Both tamsulosin doses had comparable efficacy (Figure 10.6). The number of patients

![Figure 10.6](image-url)

**Figure 10.6** Change in (a) mean $Q_{\text{max}}$ and (b) mean total I-PSS score after 53 weeks of treatment with placebo or tamsulosin (0.4 mg or 0.8 mg) once daily in a long-term US study.46
that discontinued due to adverse events remained low and comparable in the placebo (6%) and tamsulosin 0.4 mg (5%) groups. A total of 16% of patients on 0.8 mg discontinued due to adverse events.

It can be concluded that tamsulosin 0.4 mg is the optimal dose in the treatment in American patients with LUTS suggestive of BPH with a very good safety profile. It has a fast onset of action with significant improvements in $Q_{\text{max}}$ within 24 hours and a symptomatic score within 1 week. It does not lower blood pressure to a clinically significant extent, even in uncontrolled hypertensives. It has no increased potential for symptomatic orthostatic hypotension compared with placebo, even when administered without dose titration and when exposed to multiple and rigorous orthostatic stress testing. Only abnormal ejaculation occurred consistently and significantly more often with tamsulosin 0.4 mg than placebo. Therefore, 0.4 mg is the recommended tamsulosin dosage in the US. If patients fail to respond after 2–4 weeks, the dose may be increased to 0.8 mg.

**Long-term open-label extension studies**

All patients (be it tamsulosin- or placebo-treated) who completed the two European placebo-controlled phase III studies could be enrolled in a long-term extension study with open-label tamsulosin for up to 4 years. In an interim analysis, 355 patients were treated with tamsulosin for up to 3 years. The significant improvements in $Q_{\text{max}}$, total Boyarsky symptom score, $Q_{\text{max}}$ responders, and symptom score responders observed in the 12-week placebo-controlled studies were sustained for up to 3 years in the patients who remained in the study. The increase in mean $Q_{\text{max}}$ from baseline ranged from 0.7 to 1.8 ml/s ($p < 0.05$) and remained between 11.5 and 12 ml/s throughout the follow-up period (Figure 10.7a). Total Boyarsky symptom score was improved from baseline by 3.7 to 4.1 (or −39% to −44%: $p < 0.001$) (Figure 10.7b). The percentage of patients having a clinically significant response was also sustained: about 30% for $Q_{\text{max}}$ and between 70 and 80% for symptom score responders (Figure 10.8a and b). Tamsulosin also remained very well tolerated. A total of 27% of patients had possibly/probably drug-related adverse events over the entire 3-year period and dizziness and abnormal ejaculation were still the most common side-effects (occurring in ≤6% of patients). Similar results were seen in a meta-analysis of the extension of the placebo-controlled studies and an alfuzosin comparative study (see later) which involved 516 patients followed for up to 3 years.

In the US, a total of 955 patients received open-label therapy with tamsulosin for up to 2 years with sustained efficacy and safety. The range for improvements from baseline were 1.4 to 2.5 ml/s for $Q_{\text{max}}$, −5.9 to −10.4 for total I-PSS, 32–44% for $Q_{\text{max}}$ responders, and 58–83% for symptom score responders. A further long-term US trial involved 609 BPH patients treated with tamsulosin for 6 years. Participants received a maintenance dose of 0.4 or 0.8 mg/day. The improvements in AUA symptom index and $Q_{\text{max}}$ were maintained throughout the study period, with good levels of tolerance. Orthostatic hypotension was observed in only 1.3% of the group.

It can be concluded that the favorable efficacy/safety ratio of tamsulosin is sustained in approximately 1500 patients with LUTS suggestive of BPH receiving open-label tamsulosin for up to 3 years in Europe or the US.
Direct comparative clinical studies vs other \( \alpha_1 \)-adrenoceptor antagonists

Three direct comparative clinical studies have been performed.\(^{51-53} \) One was a European phase III, double-blind, randomized, comparative study between alfuzosin (2.5 mg twice daily for 2 weeks and 2.5 mg three times daily for 10 weeks) and tamsulosin (0.4 mg once daily after breakfast throughout). It involved 256 patients with LUTS (total Boyarsky score > 6) suggestive of BPH (\( Q_{\text{max}} \) 4–12 ml/s).\(^{51} \) The other single-blind, randomized trial compared terazosin (dose titrated from 1 to 5 mg once daily) and tamsulosin (0.2 mg once daily throughout) for 8 weeks in 98 Korean patients with LUTS (total I-PSS \( \geq \) 8) suggestive

---

**FIGURE 10.7** Effect of tamsulosin over time on (a) mean \( Q_{\text{max}} \) and (b) mean total Boyarsky symptom score in patients followed for up to 3 years in an extension of the two European placebo-controlled studies.\(^{47} \)
The results show that tamsulosin had comparable efficacy to both alfuzosin and terazosin. They all increased $Q_{\text{max}}$ by 1.6–2.1 ml/s (16–22%: Figure 10.9a) and reduced total symptom score by 36–40% (Figure 10.9b). Both tamsulosin and alfuzosin were very well tolerated. The incidence of abnormal ejaculation was also comparable in both groups (one patient with tamsulosin and none with alfuzosin). Terazosin was, however, associated with significantly more drug-related adverse events (37% of patients) than tamsulosin (2% of patients; $p = 0.001$). In particular, dry mouth (16% vs 0%)}
and dizziness (12% vs 0%) were reported more frequently with terazosin. None of the patients on tamsulosin or terazosin experienced (drug-related) abnormal ejaculation. Alfuzosin and terazosin produces significant decreases in blood pressure compared with baseline whereas this was not the case with tamsulosin (Figure 10.10). In addition, the blood pressure reductions with alfuzosin were statistically significantly greater than those with tamsulosin, especially in elderly patients.\textsuperscript{51}

\textbf{FIGURE 10.9} Percentage improvement in (a) total symptom score and (b) $Q_{\text{max}}$ in two direct comparative clinical trials between tamsulosin and alfuzosin\textsuperscript{51} or tamsulosin and terazosin.\textsuperscript{52}
A third 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). Tamsulosin and terazosin were administered for 15 days according to their recommended dosage regimen 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 show that tamsulosin caused significantly
less symptomatic orthostatic hypotension (4% of patients) than terazosin (36% of patients; \( p = 0.011 \); Figure 10.11). The patient with symptomatic orthostatic hypotension on tamsulosin had pre-study vertigo, which was an exclusion criterion for the study.

It can be concluded that \( \alpha_1 \)-adrenoceptor antagonists have similar efficacy in the treatment of LUTS suggestive of BPH. It is their potential to lower blood pressure and produce cardiovascular-related adverse events such as symptomatic orthostatic hypotension that differentiates between \( \alpha_1 \)-adrenoceptor antagonists.\(^3,4\) Tamsulosin 0.4 mg has the lowest potential to reduce blood pressure and causes less symptomatic orthostatic hypotension than terazosin. This may be clinically important as orthostatic hypotension and syncope are risk factors for falling. Falls are the sixth largest cause of death in the elderly and the cost of fall-related fractures in the elderly amounts to US $10 billion/year.\(^\text{54} \) Tamsulosin, furthermore, is easy to use as it does not require dose titration and can be taken once a day.

**Tolerability in elderly patients and patients with co-morbidity or co-medication**

Tamsulosin has been repeatedly shown to be well tolerated.\(^\text{51-53,55} \) A subgroup analysis of younger (<65 years) and older (\( \geq 65 \) years) patients enrolled in the two European phase III placebo-controlled trials\(^\text{38} \) 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.\(^\text{56} \)

In two observational surveys, in which almost 20,000 German patients with LUTS suggestive of BPH received tamsulosin 0.4 mg once daily for 4 or 12 weeks, approximately 40–50% of patients had concomitant hypertension, other cardiovascular (CV) diseases, or diabetes.\(^\text{57} \) It appeared that overall about 95% of patients rated the global tolerability of tamsulosin as good or very good. Concomitant hypertension, other CV diseases, or diabetes had only a minor effect on global tolerability, which became significant due to the large patient numbers. It was still rated as good or very
good in more than 90% and 95% of cases in the two surveys. A multivariate analysis showed that hypertension did not contribute to changes in global tolerability. Diabetes and other CV diseases contributed significantly. This may be due to the reduced quality of life associated with these conditions and the large patient numbers and may therefore not be clinically significant for the majority of these patients. Many patients in these trials also took concomitant CV medication.
(diuretics, β-blockers, angiotensin-converting enzyme (ACE) inhibitors, or calcium antagonists). Global tolerability in these patients remained good to very good in 95% of patients and the CV co-medication did not contribute to changes in global tolerability in a multivariate analysis. Blood pressure changes in patients with co-morbidity or co-medication were minimal and comparable to those reported for tamsulosin and placebo in placebo-controlled trials. In patients with co-morbidity or co-medication, additional blood pressure reductions were not more than 2 mmHg. This did not significantly contribute to blood pressure changes in a multivariate analysis.

In three clinical interaction studies, tamsulosin was administered to the hypertensive patients controlled with the β-blocker atenolol, the ACE inhibitor enalapril, or the calcium antagonist nifedipine. The results confirm that tamsulosin has no clinically significant additional effects on blood pressure or an increased potential to produce orthostatic hypotension in hypertensive patients treated with antihypertensive medication.58

It can be concluded that in such elderly patients and the majority of patients with cardiovascular co-morbidity or co-medication, tamsulosin is well tolerated and has minimal effects on blood pressure.

USE IN PATIENTS PRETREATED WITH OTHER MEDICAL THERAPY

In two large German observational surveys, patients pretreated with other medical therapies, such as phytotherapy, finasteride, or other α1-adrenoceptor antagonists, were asked to rate the global efficacy and tolerability of tamsulosin in comparison with their previous treatment (i.e. worse, similar, better).59 It appeared that relative to patients pretreated with other α1-adrenoceptor antagonists, the global efficacy of tamsulosin was perceived better than that of previous treatment in about 25% of phytotherapy- and 15% of finasteride-pretreated patients (Figure 10.12a). Relative to previous treatment with phytotherapy, the global tolerability of tamsulosin was perceived better than that of previous treatment in about 25% of other α1-adrenoceptor antagonists and 13% of finasteride pretreated patients (Figure 10.12b).

META-ANALYSIS

In addition to the two meta-analyses mentioned previously38,41 two systematic reviews of tamsulosin in the treatment of BPH have been performed in recent years.60,61 The latest of these included 14 studies with a total of 4122 participants, mean age 64, with moderate LUTS. Patients were treated with a range of doses of tamsulosin per day. The weighted mean difference (WMD) for mean change in Boyarsky symptom score from baseline showed a 12% improvement with 0.4 mg/day and a 16% improvement with 0.8 mg/day, relative to placebo. Improvements in \( Q_{\text{max}} \) were 1.1 ml/s for both dosages. Lower doses of tamsulosin (0.2–0.4 mg/day) were found to be as effective as alternative α-antagonists.

Rates of adverse events, which were generally mild, included dizziness, rhinitis, and abnormal ejaculation. These increased in a dose-dependent manner, with discontinuations due to such effects similar to placebo at the 0.2 mg/day dose, but increasing to 16% with 0.8 mg/day. Efficacy increased only slightly with higher doses.
ANCILLARY PROPERTIES

Effect on PSA

In contrast to finasteride, which reduces mean PSA plasma levels by 50%, tamsulosin (0.4 or 0.8 mg once daily), in comparison with placebo, had no clinically significant effect on PSA plasma levels, either in the phase III placebo-controlled European54 (Figure 10.13) or US studies.43,44

Effect on lipids

Modest positive effects on lipid plasma levels have been described in hypertensive patients treated with hemodynamically active α1-adrenoceptor antagonists. In one of the US placebo-controlled studies, tamsulosin also reduced serum triglyceride levels by 9% compared with < 1% on placebo.44

SUMMARY

α1-Adrenoceptor antagonists have superior efficacy over finasteride and phytotherapy (at least in the short term), work independent of prostate size, are not associated with erectile dysfunction, and do not affect PSA plasma levels. Therefore, they are a very good first-choice medical therapy for patients with LUTS suggestive of BPH. The major disadvantages of the classical α1-adrenoceptor antagonists that were originally developed for hypertension (prazosin, doxazosin, terazosin, and alfuzosin) are their blood pressure-lowering potential with subsequent risk of (first-dose) orthostatic hypotension and associated need for dose titration. The reduction of the occurrence of orthostatic hypotension is clinically important because it is one of the risk factors for falling. Falls may lead to major injuries such as fractures and are the sixth leading cause of death in the elderly.

Tamsulosin is an α1-adrenoceptor antagonist that displays selectivity for α1A- and α1D-adrenoceptors. In human volunteers, tamsulosin (modified-release formulation) caused less inhibition of experimentally induced vasoconstriction than hemodynamically active α1-adrenoceptor antagonists such as doxazosin and terazosin and it was
therefore specifically developed to treat LUTS suggestive of BPH. It is available in Japan, most European countries, many Latin American countries, and the US. The recommended dosage for Caucasian patients is 0.4 mg once daily (after a meal). Tamsulosin 0.4 mg can be administered as its therapeutic dose from the start of therapy with no need for dose titration. As such it has superior efficacy to placebo and is as effective as other $\alpha_1$-adrenoceptor antagonists such as alfuzosin and terazosin. It has, however, a negligible potential for blood pressure lowering compared with other $\alpha_1$-adrenoceptor antagonists such as alfuzosin and terazosin, and induces less symptomatic orthostatic hypotension than terazosin. The only adverse event that was reported consistently and significantly more often with tamsulosin 0.4 mg than placebo was abnormal ejaculation. There was no difference in reporting of abnormal ejaculation on tamsulosin, alfuzosin, or terazosin in comparative trials. The very good tolerability and minimal effects on blood pressure of tamsulosin are maintained in elderly patients and the vast majority of patients with cardiovascular comorbidity and co-medication. The global efficacy of tamsulosin 0.4 mg was perceived better than that of previous treatment with finasteride or phytotherapy. The global tolerability was perceived better than that of previous treatment with other $\alpha_1$-adrenoceptor antagonists or finasteride. Tamsulosin 0.4 mg once daily is therefore a very good first-choice medical therapy for Caucasian patients with LUTS suggestive of BPH.

REFERENCES


29. Foglar R, Shibata K, Horie K et al. Use of recombinant α₁-adrenoceptors to characterize subtype...


INTRODUCTION

The spectrum of synthetic pharmaceutical treatment options for patients presenting with lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH) has expanded considerably over the last decade and this has been accompanied by an increase in the use of plant-derived therapies. At the same time, a worldwide decrease in classical operative procedures has been reported, with rates of transurethral resection of the prostate (TURP) and open prostatectomy falling by up to 50% in some countries.3

While there is at least some agreement concerning the scientific rationale and indications for the use of α-adrenoceptor blockers and 5α-reductase inhibitors, the role of phytotherapeutic agents in the treatment of LUTS and BPH has traditionally been less clear and has been continuously debated.4–22 The use of plant extracts is long established in France and Germany, and so products containing extracts of *Serenoa repens* and *Pygeum africanum*, among others, have a market share of up to 50% of all preparations used for the treatment of symptomatic BPH. In these countries, plant extracts are prescribable drugs, their costs being totally or partly reimbursed by the healthcare system, in contrast to the UK, for example, where they are neither approved nor reimbursed.23

In the US, plant-derived medications are sold as nonreimbursable nonprescription dietary supplements, mostly in natural health food stores. Some preparations which are available by prescription only in Europe, such as the lipidosterolic extract of *Serenoa repens* (LSESe) Permixon®, are not available at all in the US. In 2000, US sales of dietary supplements were reported to have reached $17.1 billion,24 and around $1.5 billion are reportedly spent on the self-medication of LUTS.25

According to some US urologists, 50–90% of newly referred patients with LUTS secondary to BPH have already tried or are using some form of alternative or complementary medication at the time of their presentation.13–15,26 The suggestion that ‘natural agents’, commonly supposed to be without side-effects, might be as efficacious as synthetic and chemical products, seems attractive for patients who prefer such an approach.17,26 We as treating physicians have to face this development. This widespread and increasing patient preference, however, has to be balanced against the need for increased awareness of the importance and necessity to select treatment options on evidence-based rationales.27,28

ORIGIN OF PLANT EXTRACTS

In Europe alone, more than 100 botanic preparations are available for the treatment of LUTS secondary to BPH.5,6,29 Although extracts from more than 30 different plants are being used for these products, the most popular phytotherapeutic agents originate from the roots, seeds, barks, or fruits of the plants listed in Table 11.1.
THERAPEUTIC TREATMENT FOR BENIGN PROSTATIC HYPERPLASIA

Some preparations are produced from a single plant, others contain extracts from two or more sources. The extraction procedures differ from company to company. Therefore, the composition and components of one individual product may be significantly different to those of another manufacturer, even if the product originates from the same plant(s). As a consequence, the results of basic research studies or clinical trials involving a specific product cannot automatically be applied to another preparation.

Several active components of plant extracts have been identified (Table 11.2). However, whether these elements represent all the most active and important elements of the preparations for the beneficial in vitro and in vivo effects described (Table 11.3) is still not known.\textsuperscript{6,8–12,29,30}

The precise mechanism of action of many products has also yet to be elucidated, although antiestrogenic and proapoptotic effects have been reported for some preparations, alongside inhibition of 5α-reductase activity.\textsuperscript{31,32}

As the extraction methods of products derived from the same source could lead to differing levels of efficacy, bioavailability, and pharmacodynamics, it has been recommended that individual products be evaluated separately.\textsuperscript{29} In addition, both synthetic and natural products should be subjected to identical analytic, biological, and clinical evaluations.

### PHYTOTHERAPEUTIC COMPOUNDS

**Serenoa repens**

The extracts from the berries of the American dwarf palm (\textit{Serenoa repens}, saw palmetto, \textit{Sabal serrulata}) are the most popular plant-based
products used in the treatment of symptomatic BPH.\textsuperscript{4–6,13–16,29} In Germany alone, more than 30 different products contain \textit{Serenoa repens},\textsuperscript{6,29} while numerous similar products are also available in the US. Many of them contain extracts from other plants (\textit{Pygeum africuum}, pumpkin seeds, etc.) and minerals, such as zinc. The different extracts contain mainly free and esterified fatty acids, phytosterols, and long-chain alcohols. More recently, free fatty acids have been proposed to be the active components of \textit{Serenoa repens} extracts, primarily responsible for their beneficial effects on the prostate. On this basis the precise composition could critically influence both biological and clinical activity.

The most extensively investigated preparation is Permixon, an n-hexane LSESr and a complex mixture of free fatty acids, phytosterols, aliphatic alcohols, and various polyphenolic compounds.\textsuperscript{6,29,33} A number of potential mechanisms of action have been attributed to Permixon, including anti-androgenic and anti-inflammatory activity, inhibition of cell proliferation, and promotion of apoptosis.\textsuperscript{31,33–38}

The action of Permixon is now considered to be predominantly attributable to uncompetitive 5α-reductase type I and type II inhibition, resulting in lower levels of dihydrotestosterone (DHT) formation from testosterone in the prostate.\textsuperscript{31,39} Although Rhodes et al.,\textsuperscript{40} in 1993, did not

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Extract</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibition of 5α-reductase I and II activity</td>
<td>\textit{Serenoa repens, Secale cereale, cactus flower}</td>
</tr>
<tr>
<td>Anti-estrogenic effect</td>
<td>\textit{Serenoa repens, Pygeum africuum}</td>
</tr>
<tr>
<td>Anti-androgenic effect</td>
<td>\textit{Serenoa repens, Cucurbita pepo}</td>
</tr>
<tr>
<td>Anti-inflammatory effect</td>
<td>\textit{Serenoa repens, β-sitosterol, Pygeum africuum, Cucurbita pepo}</td>
</tr>
<tr>
<td>Induction of apoptosis</td>
<td>\textit{β-Sitosterol, Serenoa repens}</td>
</tr>
<tr>
<td>Interference with prostaglandin metabolism</td>
<td>\textit{β-Sitosterol, Pygeum africuum}</td>
</tr>
<tr>
<td>Inhibition of phospholipase A2 and 5-lipoxygenase enzymes</td>
<td>\textit{β-Sitosterol}</td>
</tr>
<tr>
<td>Suppression of prostate cell metabolism and growth</td>
<td>\textit{Urtica dioica, Serenoa repens}</td>
</tr>
<tr>
<td>Inhibition of proliferative growth factors</td>
<td>\textit{Urtica dioica}</td>
</tr>
<tr>
<td>Decrease of sex hormone-binding globulin</td>
<td>\textit{Pygeum africuum}</td>
</tr>
<tr>
<td>Protection/strengthening of detrusor muscle</td>
<td>\textit{Pygeum africuum}</td>
</tr>
<tr>
<td>Alteration of cholesterol metabolism</td>
<td>\textit{Pygeum africuum}</td>
</tr>
<tr>
<td>Free radical scavengers/membrane stabilization</td>
<td>\textit{Cactus flower}</td>
</tr>
<tr>
<td>Inhibition of aromatase activity</td>
<td>\textit{Urtica dioica, Serenoa repens}</td>
</tr>
<tr>
<td>Reduction of prostatic urethral resistance</td>
<td>\textit{Secale cereale}</td>
</tr>
<tr>
<td>Action on α-adrenergic receptors</td>
<td>\textit{Secale cereale, Serenoa repens}</td>
</tr>
</tbody>
</table>
subscribe to this, the theory that Permixon is an effective inhibitor of 5α-reductase type I and type II has been substantiated by in vitro studies by Bayne et al. In a specially developed clinically relevant model, 5 days’ treatment of co-cultured human prostate cells with 10 µg/ml Permixon resulted in significant inhibition of 5α-reductase type I and type II; the dose utilized was estimated to correspond to the concentration reached in plasma and prostate at the recommended clinical dose.

The hypothesis promulgated is that lauric and myristic acid, which comprise a subfraction of the free fatty acids contained in the preparation, modulate the cell-membrane environment in a way that reduces the activity of the nuclear membrane-bound 5α-reductase. The observation that no decrease of prostate-specific antigen (PSA) is observed in vivo is explained by the assumption that Permixon, in contrast to finasteride, does not interfere with PSA production and has little or no effect on other androgen-dependent processes which rely on the binding of androgens to their receptor. Subsequent studies also suggested that Permixon specifically decreases cell proliferation and increases the apoptotic index of the prostatic stromal and epithelial cells. Studies involving alternative sources of Serenoa repens have suggested that it has anti-estrogenic or anti-inflammatory effects.

Lower levels of DHT and higher levels of testosterone have been identified in the prostates of Permixon-treated BPH patients; however, superficially at variance with an action as a 5α-reductase inhibitor, no significant effect on serum levels of PSA and prostate volume has been demonstrated in several studies. Indeed, the data on several potential mechanisms of action of Serenoa repens are often confusing and contradictory and many of the effects described have only been demonstrated in vitro, often with considerably higher dosages of the extract than are recommended for clinical treatment.

The commonly recommended dose of Serenoa repens is 320 mg daily, often divided into two doses. A dose of 160 mg Permixon twice daily seems to be as efficacious as two capsules of 160 mg once daily. Aside from occasional gastrointestinal discomforts, no significant side-effects have been reported with the extract, in contrast to most other medical or surgical approaches.

The numerous published clinical trials involving Serenoa repens extracts have been critically reviewed by a committee during the 4th (1997) and 5th (2000) International Consultations on BPH, and in two articles by one of the committee members. These Consultations recommended that extracts of Serenoa repens produced by different manufacturers be evaluated separately and regarded as discrete entities, due to variance between products associated with different extraction processes and other factors. They also highlighted the need for placebo-controlled trials of such products, as are conducted for traditional synthetic pharmaceuticals.

Although it is accepted that uncontrolled trials and comparative trials without placebo controls are of only limited value in the quantification of the clinical efficacy of Serenoa repens in the treatment of LUTS and BPH, several trials involving the extract have taken place that indicate that significant improvements in LUTS symptomatology occur. However, the results are dependent on the product (and presumably the composition).

A recent long-term trial examined the efficacy of twice-daily Permixon (160 mg) in 130 BPH patients over 2 years. Prostatic symptoms were assessed using validated instruments such as the
International Prostate Symptom Score (I-PSS) and sexual function using the Male Sexual Function (MSF-4) questionnaire. PSA, peak urinary flow ($Q_{\text{max}}$), and quality of life were also evaluated every 6 months. Significant improvements were observed for I-PSS, $Q_{\text{max}}$, and quality of life, while prostate size fell by 5.9 ml by the end of the study period. MSF-4 scores rose significantly in the second year of treatment and total PSA and hormonal levels did not change.

A further, longer-term study of Permixon in men with mild to moderate BPH ($n = 26$) revealed that twice-daily administration of 320 mg of the drug decreased mean I-PSS by $8.8 \pm 0.18$, increased $Q_{\text{max}}$ by $4.13 \pm 0.51$ ml/s on average, and improved quality of life after 5 years, providing further evidence of the long-term efficacy of the drug.

It has been suggested that a ‘placebo effect’ may contribute to the improvements observed in men receiving some extracts of *Serenoa repens*. In a study of 50 men with LUTS, who were treated for 6 months with a *Serenoa repens* preparation, a significant improvement in I-PSS from 19.5 to 12.5 was noted ($p = 0.001$). No significant changes in PSA levels or improvement in $Q_{\text{max}}$, postvoid residual volume (PVR), bladder capacity, or detrusor pressure at peak urinary flow rate were observed, however. The authors accept that this subjective improvement in voiding symptoms that occurred without demonstrable objective change in any of the measure urodynamic parameters may be attributable in part to the placebo effect and conclude that further studies, including placebo-controlled trials, are needed.

Other studies have suggested that the benefit does not only arise from a placebo effect. A trial excluding patients who had previously responded to placebo medication revealed that, when treated with Permixon, these nonresponders showed significant reductions in both daytime and nocturnal urinary frequency and improvement in $Q_{\text{max}}$.

Some data have proven inconclusive. Thus, although it was shown in the 30-day study described above that dysuria, daytime frequency, nocturia, and $Q_{\text{max}}$ were all significantly improved in Permixon-treated patients compared with baseline values and placebo-treated patients, the study did not show any real perceived clinically relevant benefit of the drug over placebo by the patients or their physicians. When the patients and physicians were asked to assess the global efficacy of the treatment at the end of the trial, the rates of satisfaction were 68% and 47%, respectively, for the placebo group versus 71% and 57%, respectively, for the *Serenoa repens*-treated patients. The short-term nature of this trial limits the interpretation of the data.

In an attempt to quantify the benefit more precisely, double-blind randomized clinical trials have been undertaken on some *Serenoa repens*-containing products. In a 6-month, double-blind, randomized comparative trial with finasteride in 1098 patients, the efficacy of Permixon was found to be equivalent to that of the $5\alpha$-reductase inhibitor. The decrease in I-PSS was 37% and 39% and the increase in $Q_{\text{max}}$ was 2.7 ml/s (25%) and 3.2 ml/s (30%) in the *Serenoa repens* and finasteride groups, respectively. Greater drug-related side-effects, particularly in terms of lowered libido and increased erectile dysfunction were observed in the finasteride group.

Unfortunately, this study did not include a placebo group and the volumes of the prostates were rather small (baseline volumes 43 ml and 44 ml, respectively, for the two groups). As we know today, the effect of finasteride may be limited in small prostates. Therefore, in analogy to the VA study, the comparison between *Serenoa repens* and finasteride in this study might simply
show equivalency of both agents to placebo, although Hamdy et al. postulated that prostatic volume does not correlate with the efficacy of treatment using either finasteride or phytotherapy.\textsuperscript{51}

Comparison of \textit{Serenoa repens} to ‘conventional’ therapy is not limited to finasteride, however. A comparison of the \(\alpha\)-blocker tamsulosin to Permixon took place over a period of 12 months and involved 811 BPH patients from 11 different countries.\textsuperscript{54} I-PSS fell by 4.4 in each group and \(Q_{\text{max}}\) also improved to a similar extent. A second trial, involving alfuzosin and Permixon, also revealed the latter drug to be equally effective for the treatment of urinary symptoms. Sixty-three men with mild to moderate BPH who did not respond to placebo were randomized to receive either 320 mg Permixon daily or 2.5 mg alfuzosin three times a day for 3 weeks.\textsuperscript{55} Symptom scores improved significantly from baseline with no significant difference between treatment groups.

Overall, therefore, Permixon has been shown to produce clinical efficacy equivalent to that observed with both \(\alpha\)-blockers and finasteride; this would tend to indicate that the action of Permixon does not arise from a placebo effect alone.

\textbf{Phytosterols/\(\beta\)-sitosterol}

Although \(\beta\)-sitosterol and various other phytosterols are contained in many plant extracts used for the treatment of symptomatic BPH, some manufacturers presume that \(\beta\)-sitosterol is the major active component and therefore classify their preparation by the content of this element. Most preparations available derive from the species \textit{Hypoxis rooperi}, \textit{Pinus}, or \textit{Picea}.

\(\beta\)-Sitosterol is claimed to be both a cyclo-oxygenase and a lipoxygenase inhibitor, interfering with prostaglandin metabolism and thereby exerting anti-inflammatory effects.\textsuperscript{30} A stimulatory effect on transforming growth factor (TGF\(\beta\)), which induces apoptosis, and translocation protein kinase \(C\alpha\) has also been discussed.\textsuperscript{6,56,57}

In a German study the \(\beta\)-sitosterol preparation Harzol\textsuperscript{®} was evaluated in a 6-month, double-blind, placebo-controlled study of 200 patients.\textsuperscript{56,58} While the placebo group showed only mild improvements, statistically significant improvements were noted for I-PSS, quality of life, \(Q_{\text{max}}\), and PVR in the \(\beta\)-sitosterol-treated patients who received 20 mg of the product, three times daily. The I-PSS improved by 2.3 points for placebo and 7.4 for \(\beta\)-sitosterol; \(Q_{\text{max}}\) increased by 1.1 ml/s for placebo and 5.2 ml/s for the test group. Follow-up observations (up to 18 months) have shown that those patients who continued treatment and even those who stopped the medication maintained their benefit, while placebo-treated patients improved with a similar response once started on \(\beta\)-sitosterol.\textsuperscript{56}

Another preparation, also containing mainly \(\beta\)-sitosterol (Azuprostat\textsuperscript{®}, 65 mg twice daily) was evaluated in a 6-month, randomized, placebo-controlled trial of 177 patients.\textsuperscript{59} The magnitude of the statistically significant improvement in this study was great: the I-PSS improved by 2.8 in the placebo group compared to 8.2 in the treatment group and \(Q_{\text{max}}\) increased by 4.4 ml/s and 8.8 ml/s, respectively. The results of both studies with phytosterols, although exciting, await confirmation by other groups.

\textbf{African plum tree}

Extracts from the bark of the African plum tree (\textit{Pygeum africanum}) are widely used in France and the US. Almost all basic research and clinical studies have been performed with the product Tadenan\textsuperscript{®}.\textsuperscript{6,15,16} The chloroform extract contains
phytosterols, short-chain (lauric and myristic) and unsaturated long-chain (oleic and linolic) fatty acids.

The extract is thought to inhibit fibroblast proliferation and to exert an anti-inflammatory and anti-estrogenic effect. 6,60,61 Eleven constituents have been identified in the crude extract, including high levels of myristic acid, which is thought to affect membrane fluidity directly and to reduce the contact between propagating free radicals and unsaturated lipid substances, thereby slowing the process of hydrolysis and membrane degradation. 61 Moreover, in a rabbit model, the agent is thought to protect the bladder musculature from contractile dysfunction caused by outlet obstruction, improving bladder ultrastructure, bladder compliance, and contractile responses. 62–67

According to Levin et al. 65 and Hass et al., 61 obstruction induces ischemic muscular membrane damage, which might be caused by lipid peroxidation. High levels of myristic acid found in the Pygeum extract may make the bladder cell membranes less susceptible to lipid peroxidation and thereby exert their protective effect on the bladder. However, in the experimental studies demonstrating this effect, highly supraclinical doses were used. Therefore, the applicability of these findings to clinical BPH remains questionable. Although there are numerous open and short-term placebo-controlled studies suggesting clinical efficacy, 68–70 the trials do not meet the guidelines recommended by the International Consultation conferences. 6

Breza et al. 71 reported a multicenter open-label trial involving 85 patients, treated over 2 months with Tadenan, followed by 1 month without treatment. Improvement in I-PSS was 40%, reduction of nocturia 32%, improvement of quality of life 31%, and increase in $Q_{\text{max}}$ 19%, without any reduction of prostate volume. Significantly, the improvements were maintained during the 1-month no-treatment phase. Overall, the data are not conclusive, however, and longer-term data are not available.

**Stinging nettle**

Extracts from the roots of the stinging nettle (Urtica dioica) are widely used in Germany. They contain a complex mixture of water- and alcohol-soluble compounds, including lectins, phenols, and sterols. 5,6,30

Whether the suggested modes of action, which include inhibition of prostatic growth factor interaction, suppression of prostatic cell metabolism and modulation of the binding of sex hormone-binding globulin, have any relevance in clinical BPH is uncertain. Studies performed more than 10 years ago are inconclusive because of small patient numbers and short trial duration. 72,73 In a randomized, placebo-controlled, 3-month study of 41 patients, a liquid preparation showed superiority over placebo, but was not marketed because its taste was not accepted by patients. 74

Extracts of stinging nettle are often combined with one or more alternative plant-derived therapy, as discussed later in the chapter.

**Rye grass pollen extract**

A product deriving from the pollen of some selected plants growing in southern Sweden is marketed as a registered pharmaceutical (Cernilton®) in some European countries, Japan, Korea, and Argentina. The extract consists of a water- and fat-soluble fraction combined into a tablet or capsule.

In vitro studies suggest that pollen extracts exert an effect on $\alpha$-adrenergic receptors, relax
the sphincteric musculature, increase prostatic and serum zinc levels, and 5α-reductase activity. Moreover, the growth of immortal cancer cell lines was inhibited and in rats atrophy of the prostatic lobes was observed.

In a German 3-month, multicenter, double-blind, placebo-controlled study of 103 patients, nocturia and diurnal frequency were significantly reduced by 69 and 66%, respectively, in the treatment group, compared to 37% and 44% in the placebo group. A 6-month, double-blind, placebo-controlled study of 60 patients reported an overall significant symptomatic improvement of 69% in the pollen extract group compared to 29% in the placebo group.

In a comparative trial of 89 patients over 4 months with a *Pygeum africanum* extract (Tadenan), the pollen extract showed better results with regard to improvement of irritative and obstructive symptom scores, *Q*<sub>max</sub>, and residual urine. However, comparison of Cernilton to tamsulosin and a combination of both revealed the combination and tamsulosin alone to be more effective than Cernilton alone.

**Pumpkin seeds**

Extracts from pumpkin seeds (*Cucurbita pepo*) are used to treat symptomatic BPH in several countries, such as Germany. The seeds contain a sweet-tasting, oily substance, mainly composed of linolic acid, Δ5 and Δ7 sterols, tocopherol, selenium, magnesium, and carotenoid. The extract is thought to have an anti-androgenic and anti-phlogistic action.

A randomized, placebo-controlled, double-blind trial of 476 men with BPH showed a significantly greater reduction in I-PSS (−6.8) compared to the placebo group (−5.6) over a period of 12 months. The other parameters (*Q*<sub>max</sub>, quality of life, prostate volume, PVR) did not change in either of the groups, however.

**Cactus flower extracts**

Cactus flower extract, known as opuntia, is included in the British herbal pharmacopoeia as indicated for prostatic hypertrophy and is a commonly used herbal remedy for BPH in Israel.

Aqueous and organic solvent extracts of dried cactus flower powder have been described as having a broad spectrum of activity, including inhibition of both type I and type II 5α-reductase activity and inhibition of aromatase and antioxidant activity. The authors postulate that as cactus flower has simultaneous 5α-reductase and aromatase inhibitory activity it possesses a uniquely dual advantage in the treatment of BPH; however, there are no reports of any controlled clinical trials with cactus flower products.

**COMBINATION PRODUCTS**

Although there is no scientific evidence showing that the efficacy of phytotherapeutic preparations is enhanced by the combination of extracts from several plants, many companies offer mixtures of plant extracts, claiming that the possible effects demonstrated for extracts from individual plants may be additive in combination products.

In a 3-month, randomized, double-blind study of 53 patients given extracts from pumpkin seeds and *Serenoa repens*, urinary flow rates, mic- turition time, residual urine, frequency of mic- turition, and a subjective assessment of the treatment effect were all significantly improved while the changes in the placebo group were not.

A combination product of *Serenoa repens* and stinging nettle (Prostagutt® forte) was used in a randomized, placebo-controlled study of 40
patients (6-month double-blind treatment phase followed by 6 months of open treatment). Greater improvement in both I-PSS and $Q_{\text{max}}$ was observed with treatment than with placebo: I-PSS decreased from 18.6 to 11.1 in the treatment group during the 6 months of double-blind treatment, compared to a decrease from 19 to 17.6 ($p = 0.002$) with placebo. During the open-label extension phase, the initially placebo-treated patients decreased in I-PSS from 17.6 to 13.3 and the treatment group continued to improve from 11.1 to 9.8. $Q_{\text{max}}$ increased by 2.3 ml/s over the first phase in the verum group and by an additional 1.15 ml/s over the open-label second 6-month phase, while an increase of only 0.45 ml/s was observed in the placebo group over the initial placebo phase with a 2 ml/s increase during the subsequent active treatment phase.83

The same preparation was also compared with finasteride in 489 patients randomized and observed for 48 weeks.84 There was a statistically significant improvement in each group, with a drop in I-PSS from 11.3 to 6.5 for the patients treated with the plant extract, compared with a decrease from 12.6 to 6.9 in finasteride-treated patients. $Q_{\text{max}}$ increased by 1.9 ml/s in the plant extract group and 2.7 ml/s in the finasteride group; however, there was no statistical significance between the treatment groups. Prostate volume and PSA decreased in the finasteride group only. The mean baseline prostate volume was 42 ml in the plant extract group versus 44 ml in the finasteride group.

META-ANALYSES OF PHYTOTHERAPEUTIC AGENTS

If adequate (gold-standard) randomized, placebo-controlled studies are lacking, confirmation of efficacy of a drug is often sought through meta-analysis. There are some potential limitations in this approach, however, as it has been shown that the agreement between meta-analyses and subsequent large clinical trials can be discordant. Meta-analyses have a positive predictive value of 68% and a negative predictive value of 67%.85 This means that up to one-third of meta-analyses may not accurately predict subsequent clinical trial results. Further, when the studies pooled in a meta-analysis are of poor quality, the meta-analysis itself can be compromised and the impact of the conclusions diluted. Overall, however, there is an increasingly widespread use of meta-analyses in the health-care environment.

Several meta-analyses involving plant-derived BPH treatments have been published, four on *Serenoa repens* extracts,86–89 two on β-sitosterols,90,91 one on *Pygeum africanum*,92 and two on rye grass pollen (Cernilton).93,94 In general, the meta-analyses support the hypothesis that phytotherapeutic agents are beneficial in the treatment of LUTS in BPH patients.

In the original meta-analysis published by Wilt et al.86 on *Serenoa repens*, 18 randomized studies were included, involving 2939 men with BPH. The mean weighted difference in comparison to placebo was an improvement in symptom score of 1.41 points, an increase in $Q_{\text{max}}$ of 1.93 ml/s and a reduction in nocturia episodes of 0.76 per night. A follow-up analysis conducted 4 years later, with an additional three trials and a total of 3139 patients, revealed quantitatively and qualitatively similar results.57 Overall, urinary symptom score fell by 1.41 points (range 0–19), nocturia rates fell by 0.76/night, and $Q_{\text{max}}$ increased by 1.86 ml/s.

Despite the benefit observed in these analyses, the inclusion of products from 11 different manufacturers obtained by different extraction
processes partially compromised the interpretation of the data and thereby potential extrapolation to general clinical use.

On the basis of the evidence, it was therefore concluded that *Serenoa repens* improves urologic symptoms and flow parameters, but that further clinical profiling is needed. In particular, the clinical activity of individual standardized preparations should be determined.

It has been emphasized by an expert committee at the ICUD BPH Consultations, and even recently by Wilt himself, that comparison between various manufacturers’ preparations of the same plant extract is problematic. Data analysis can be hindered because of variations in the extraction processes, absence of precise analytical information on composition, lack of certainty that the same supposedly active component(s) of the extract are included in the final product, and variability in batch preparation. Moreover, only one of the 18 studies included in the first meta-analysis by Wilt et al. fulfilled the three main criteria of being placebo-controlled, utilizing standard symptom score evaluations, and being of at least 3 months’ duration.

In an attempt to address some of the issues raised in previous analyses, another meta-analysis on a single *Serenoa repens* product (Permixon) was published by Boyle et al. Eleven placebo-controlled randomized trials and two open-label trials were pooled. Eleven trials had information regarding $Q_{\text{max}}$ and nocturia. The additional Permixon effect, beyond that observed on placebo, on $Q_{\text{max}}$ was 1.87 ml/s and the additional effect on nocturia was a decrease of 0.55 episodes per night. A further meta-analysis conducted by the same team of all contemporary published data available on Permixon involved a further 1963 men from four randomized studies. The additional data allowed examination of the effect of Permixon on I-PSS and revealed that, in addition to improving peak flow (2.28 ± 0.29 above placebo) and nocturia (1.01 ± 0.13 above placebo), the drug caused a significant fall in I-PSS (–4.7 ± 0.41). Such changes are at least as great as those described in equivalent meta-analyses for terazosin and finasteride (Figure 11.1).

Wilt et al. also published a review of β-sitosterol studies, including four double-blind trials of 519 men, with a duration of 4–26 weeks. The weighted mean difference (WMD) of β-sitosterol versus placebo was –4.9 points on the I-PSS (35% improvement versus placebo) in two studies. When a study which did not show pure β-sitosterol-β-D-glucoside to be superior to placebo was excluded, the WMD for the $Q_{\text{max}}$ was 5.13 ml/s (53% improvement). The authors state that β-sitosterols improve symptom scores by 35%, $Q_{\text{max}}$ by 34%, and reduced PVR by 24%. Nevertheless, the necessity of additional studies of sufficient size and duration, with known concentrations of β-sitosterol, is emphasized in order to assess the long-term efficacy of β-sitosterols and their ability to prevent complications from BPH. Three different preparations were used in the four studies, and as it is uncertain whether the doses are comparable, no definite conclusions can be drawn from this review.

MacDonald et al. published a review of four old studies with the rye pollen extract Cernilton. Two placebo-controlled and two comparative trials involving 444 men were included. None of the studies would have fulfilled the quality criteria of the recommendations of the International Consultation, because of short trial duration, insufficient and incomplete outcome data, and no controls in two studies. The conclusion of the review was that Cernilton is well tolerated and modestly improves subjective urologic symptoms. Cernilton was not shown to improve urinary flow
compared with placebo. The most important conclusion, however, could be anticipated by looking at the studies included, namely, that randomized, placebo-controlled studies are needed to evaluate the clinical effectiveness and safety of Cernilton and its ability to prevent complications from BPH.

After a critical evaluation of the four published meta-analyses available at the time, the expert committee (‘Other Medical Therapies’) of the 5th International Consultation on BPH (Paris, 2000) came to the following conclusions:

Although there is uniformity in the results of these meta-analyses to suggest clinical efficacy of phytotherapeutic products, it is the opinion of the committee that the hypothesis and claim of phytotherapies to be beneficial in the management of LUTS/BPH can not be confirmed conclusively without large, appropriately randomised clinical trials of adequate duration that meet the GCP Guidelines resp. recommendations of the International Consultation on BPH.

On this basis the more recent analyses by Boyle et al. would appear to indicate that, of the products evaluated, only Permixon would come close to satisfying these criteria.

**CONCLUSIONS**

While there has always been at least basic consensus on the rationale and indications for α-blockers and finasteride in the treatment of LUTS secondary to BPH, there has been much controversy concerning the place and efficacy of plant extracts in these patients. As clinical evidence gathers, at least for some preparations, this picture is slowly changing, however. As evidence of their efficacy, plant-derived agents have been used for many years, especially in some European countries, and
their use is increasing in the US, where a 100% rise in the sale of botanic products has been noted since 1994. Moreover, there is an increasing trend of patients and even physicians in many countries to turn away from chemical and synthetic drugs to ‘natural’ preparations and paramedical forms of therapy. Additionally, an increasing number of patients prefer self-medication and treatment, which is supported by the marketing strategies of companies producing such products.

On the other hand, the medical profession is increasingly aware of the importance of the need to make treatment selections on the basis of good evidence of benefit: risk from carefully controlled clinical trials.\(^{27,28}\) For novel therapies, potentially this may lead to conflicts when guidelines are established according to the principles of evidence-based medicine.

It is astonishing that, although a tremendous amount of literature concerning the use of phytotherapy in LUTS and BPH exists, many important questions remain at least partially unanswered:

- Which are the active components of the preparations?
- How do they exert their claimed effects?
- What is their bioavailability?
- Is there a dose dependency?
- How can the products be standardized and compared?

The International Consultations on BPH have repeatedly called for phytotherapeutic preparations to be subjected to the same critical evaluations which are applied to the treatment of LUTS and BPH with drugs designed by medicinal chemists, such as \(\alpha\)-blockers and 5\(\alpha\)-reductase inhibitors.\(^{6,8,11,29,97}\) Only a few companies have so far taken up this challenge. Reasons for others not having done this might include that the costs of such evaluations would be difficult to recoup because these products are not patentable.

Overall, it can reasonably be concluded that phytotherapeutic products are generally well tolerated and, in some countries, less expensive than \(\alpha\)-blockers and 5\(\alpha\)-reductase inhibitors. Although both objective and subjective clinical improvements have been shown in carefully controlled clinical trials, these evaluations have been restricted to only a few products/brands and have yet to be mirrored with the majority of plant-based preparations.

It is pertinent to note that most plant extracts are complex mixtures and a product from one company is, in real terms, unique, as the extraction procedures differ from producer to producer and the exact compositions of the preparations may vary between batches. In the majority of cases they are also only partly chemically defined. Therefore, the products of the different companies may not be comparable with regard to the components contributing to the overall biological and clinical profile, even if the extracts originate from the same plant. As a consequence, meta-analyses containing extracts from different companies are only of limited use in evaluation of the efficacy of plant extracts, even if the products stem from the same species.

In addition, it may be assumed that an extract from one type of plant has different mechanisms of action, efficacy, bioavailability, and pharmacodynamics, compared to an extract from another plant species. For this reason, meta-analyses which include studies with products from different companies and different plant species may carry a substantial risk of ‘inborn errors’ if general conclusions are drawn. Further, meta-analytical data from one brand will not be directly translatable to another with a different composition.
In conclusion, as long as the components of plant extracts are not chemically defined or standardized for all products, separate scientific studies have to be performed with each extract/mixture in order to assess its individual efficacy. If the principles of evidence-based medicine are applied to the evaluation of the current data on phytotherapeutic agents in the treatment of LUTS and BPH, clear-cut evidence for their efficacy until recently has been difficult to establish. Although there is increasing evidence of efficacy for some products this is not true of all extracts by any means. More proof is needed for other plant-based medications, particularly if the prescription costs are to be reimbursed by the public health care system.

If patients buy phytotherapeutic agents because of their preferences for 'natural' products as dietary supplements at their own expense they should not be discouraged because they will, at least, enjoy a placebo effect. However, it must be stressed that a sole symptom relief may mask the progression of a disease.

Uncontrolled studies with low patient numbers and of short duration, not performed according to accepted standards and guidelines, are of questionable value. Likewise, meta-analyses are only acceptable if the quality of the studies included is assessed and shown to be appropriate. Due to the widely controversial and partly insufficient 'hard' data about the efficacy of phytotherapy for the treatment of symptomatic BPH, the International Consultations on BPH were reluctant to recommend phytotherapy as a therapeutic option. The same opinion was developed by an expert committee which established the guidelines for the German urologists according to the principles of evidence-based medicine. More evidence has become available, from gold-standard clinical trials and rigorous meta-analysis, however, suggesting that a review of the role of phytotherapy in the management of the BPH is required.

REFERENCES


finasteride in the treatment of benign prostatic hyperplasia: a randomized international study of 1,089 patients. Prostate 1996; 29: 231–240


53. Hamdy F C, Chopin D K, Authié D et al. Prostatic volume does not correlate with efficacy of treatment for mild to moderate benign prostatic hyperplasia using either finasteride or phytotherapy. 4th International consultation on BPH, Paris 1997; abstract 77


BACKGROUND

The two major components of lower urinary tract symptoms (LUTS)—voiding (obstructive) and storage (irritative) symptoms—associated with benign prostatic hyperplasia (BPH) have traditionally been linked directly or indirectly to pathophysiologic changes in the prostate.1 Voiding symptoms have been attributed to two facets of prostate function: the physical mass of the enlarged gland (the static component) and the tone of the smooth muscle of the prostate stroma (the dynamic component).2 Storage symptoms, however, have been more closely associated with bladder dysfunction produced secondary to the increased outflow resistance, arising from prostate-dependent urethral obstruction. The precise interrelationship between morphologic BPH, bladder outflow obstruction, and profile of symptoms produced is, however, unclear3 and there are several paradoxes. In particular, both voiding and storage symptoms are common in women.3,4 Furthermore, many patients who have undergone prostatectomy to relieve obstruction still experience persistent storage symptoms. Several studies have also now shown that there is little or no correlation between drug-induced changes in flow and symptom improvement5,6. The use of LUTS as a clinical descriptor is a neutral way to describe the symptoms, and makes no assumption about their link to the prostate.

On the basis of our knowledge of the control of periurethral, stromal prostate smooth muscle tone it is logical to assume that prostate α-adrenoceptors should be responsible for at least part of the LUTS associated with BPH (Figure 12.1). However, the welldocumented beneficial effects

![Sympathetic innervation of the human prostate showing the location of α₁- and α₂-adrenoceptors.](image)

FIGURE 12.1  Sympathetic innervation of the human prostate showing the location of $\alpha_1$- and $\alpha_2$-adrenoceptors.
of $\alpha_1$-adrenoceptor antagonists on the symptoms of BPH\(^7\)-\(^{11}\) occur even in the absence of outflow obstruction. This indicates that extraprostatic $\alpha_1$-adrenoceptors may also be fundamentally involved in the pathogenesis of LUTS.\(^9\) The lack of correlation between $\alpha$-antagonist-induced improvements in urine flow and symptom improvement\(^6\),\(^12\) could also be explained on the basis of an action via extraprostatic $\alpha_1$-adrenoceptors (Figure 12.1).

The extraprostatic $\alpha_1$-adrenoceptors may be located in the bladder, ganglia, and nerves innervating the lower urinary tract and at spinal or supraspinal levels within the central nervous system. Indeed, there is evidence for involvement of $\alpha_1$-adrenoceptors in the spinal control of both sympathetic and somatic (filling), as well as parasympathetic (voiding), efferent activity of the lower urinary tract.\(^10\),\(^13\)

In approximately 10% of patients, the use of $\alpha_1$-adrenoceptor antagonists in common clinical use (alfuzosin, doxazosin, tamsulosin, terazosin) has been limited by side-effects, particularly dizziness, headache, asthenia, nasal congestion, and orthostatic hypotension, that may be attributed to action on nonprostatic $\alpha_1$-adrenoceptors. It is likely that most of the common side-effects are characteristic of a direct action on the vasculature. To circumvent these side-effects, the pharmaceutical industry has attempted to find $\alpha_1$-adrenoceptor antagonists that are selective for the prostate $\alpha_1$-adrenoceptors. The underlying assumption is that these should be ‘uroselective’ agents. It should be noted, however, that the definition of uroselectivity is ambiguous because the criteria were not established at the outset. Not surprisingly, therefore, the term has been used in various contexts which are often confusing and contradictory. In this chapter we attempt to put some degree of definition on the criteria to be used in the definitive designation of a drug as uroselective as it relates to management of the patient with LUTS/BPH.

In theory, the selectivity of drugs can be defined using a variety of parameters, including pharmacologic or physiologic uroselectivity, or may be defined from a clinical perspective.\(^9\),\(^14\) Ultimately, however, only clinical uroselectivity is relevant to patient and physician.

**PHARMACOLOGIC UROSELECTIVITY**

$\alpha_1$-Adrenoceptors

Multiple $\alpha_1$-adrenoceptor subtypes have been identified,\(^15\)-\(^17\) and may offer the opportunity to target the prostate selectively. Receptor cloning and pharmacologic studies of the human prostate have revealed the existence of both high-affinity ($\alpha_{1A}, \alpha_{1B}$, and $\alpha_{1D}$) and low-affinity ($\alpha_{1L}$) receptors for prazosin.

$\alpha_1$-Adrenoceptors in the prostate

Nerves that contain adrenergic, cholinergic, and nonadrenergic, noncholinergic neurotransmitters or mediator-producing enzymes supply the smooth muscles of the prostate capsule and the trabecular tissue around the ducts.\(^18\),\(^19\) The adrenergic nerves are considered to be responsible for prostate smooth muscle tone by releasing noradrenaline, which stimulates contraction via $\alpha$-adrenoceptors.\(^20\) Although both $\alpha_1$- and $\alpha_2$-adrenoceptors can be identified in the human prostate, the contractile effects of noradrenaline are mediated primarily by $\alpha_1$-adrenoceptors.\(^10\)

All three high-affinity $\alpha_1$-adrenoceptor subtypes have been identified in prostate stromal tissue using molecular techniques. The $\alpha_{1A}$ subtype predominates, representing 60–85% of the
α1-adrenoceptor population. However, the α1-adrenoceptor subtype responsible for prostatic smooth muscle contraction has not been established unequivocally, although it is likely to be closely related to the α1A-adrenoceptor.

α1-Adrenoceptors in the urethra

Urodynamic studies in humans have suggested that up to about 50% of intraurethral pressure is maintained by stimulation of α-adrenoceptors, as judged from results obtained with α1-adrenoceptor antagonists.21,22 In human male urethral smooth muscle, functional and receptor-binding studies have suggested that the predominating postjunctional α-adrenoceptor is α1.23,24 Using RNase protection assays and in situ hybridization, Nasu et al.25 quantified and studied the distribution of α1-adrenoceptor subtypes in the human proximal urethra. They found (in both males and females) that mRNA for the α1a subtype was predominant; the ratio of mRNA for α1a, α1b, α1d in the male urethra was 100:0:0. Fukasawa et al.26 found that in man the α1L-adrenoceptor subtype was more prominent in the male urethra than in the prostate.

α1-Adrenoceptors in the bladder

In detrusor muscle from most species, including humans, β-adrenoceptors, which mediate relaxation, normally dominate over α-adrenoceptors, which mediate contraction; the normal response to noradrenaline is β-adrenoceptor-mediated relaxation. However, this may change in outflow obstruction. Perlberg and Caine27 assessed the response to noradrenaline in the hypertrophic bladder and found that, in strips taken from hypertrophic bladders, noradrenaline caused α-adrenoceptor-mediated contraction in almost one-quarter of patients. This change was also reflected in the symptoms: patients whose bladders responded to noradrenaline by contracting had symptoms of bladder overactivity. This observation suggests that a change in the response to noradrenaline may play a role in producing both obstructive and irritative symptoms. However, Smith and Chapple28 studied α1-adrenoceptor function in strips from obstructed bladders and found that only five of 72 strips responded to phenylephrine; these results are not in agreement with the view that α-adrenoceptor stimulation during storage contributes to bladder contraction and thereby to symptoms. Most probably, the balance between β- and α-adrenoceptor functions in the bladder changes in BPH, but it is not known what this really means for the pathophysiology of LUTS, particularly storage symptoms.

The predominating postjunctional α-adrenoceptor subtype in the human lower urinary tract seems to be α1; however, the number of α1-adrenoceptors in the detrusor is very low.29 In normal human isolated detrusor muscle, drugs that selectively stimulate isolated α-adrenoceptors, particularly those acting on α1-adrenoceptors, produce a small and variable contractile effect.23 It is not clear which α1-adrenoceptor subtype predominates in the detrusor, trigone, and bladder base.

Walden et al.30 reported a predominance of α1a-adrenoceptor mRNA in the human bladder dome, trigone and bladder base. This contrasts with the findings of Malloy et al.,31 who found that among the high-affinity receptors for prazosin, only α1a- and α1d-adrenoceptor mRNA was expressed in the human bladder. The total α1-adrenoceptor expression was low (6.3 ± 1.0 femtomol/mg), but was highly reproducible. The relationship between the different subtypes was 66% α1d and 34% α1a; α1a was not
expressed. This is in contrast to findings in the human prostate. The fact that drugs that act selectively on prostate $\alpha_1$-adrenoceptors may have little effect on LUTS could, in theory, be explained if they did not block the $\alpha_1$-adrenoceptors ($\alpha_{1D}$) of the bladder. Considering the doubtful functional importance of the bladder $\alpha_1$-adrenoceptors, this mechanism seems unlikely, but cannot be discounted completely.

$\alpha_1$-Adrenoceptors in peripheral and central nervous system structures (Figure 12.2)

In animal experiments, facilitatory $\alpha_1$-adrenoceptors have been identified in ganglia and on cholinergic terminals in the bladder. An effect of $\alpha_1$-adrenoceptor antagonists at the ganglionic and/or prejunctional level, leading to a decrease in acetylcholine release, is also possible.

Descending spinal pathways involved in micturition include noradrenaline-containing projections from the locus coeruleus. From the locus coeruleus, the noradrenergic neurones supply sympathetic and parasympathetic nuclei in the lumbosacral spinal cord. Bladder activation through these bulbospinal noradrenergic pathways may well involve excitatory $\alpha_1$-adrenoceptors. Thus, in the anesthetized cat, electrical stimulation of the locus coeruleus induced bladder contractions that were antagonized by intrathecal administration of prazosin. In addition, destruction of noradrenergic cell bodies in the locus coeruleus by microinjection of 6-hydroxydopamine produced a hypoactive bladder, which could be partly reversed by intrathecal injection of prazosin or phentolamine in cats, depressed the external urethral sphincter activity, and reduced reflex firing in pudendal nerve efferent pathways by a presumed central site of action. In the conscious cat, however, Downie et al. found that the intrathecal prazosin did not alter the micturition reflex. The reasons for these apparently conflicting results are unclear, but most of the evidence supports a key central role for central $\alpha_1$-adrenoceptors.

![Figure 12.2](image_url)
In the central nervous system, facilitatory α₁-adrenoceptors, tonically active in both the sympathetic and somatic neural control of the lower urinary tract, were identified in the cat. Intrathecal doxazosin decreased micturition pressure, both in normal rats and in animals with postobstructive bladder hypertrophy. The effect was much more pronounced in the animals with hypertrophied/overactive bladders. Doxazosin did not markedly affect the frequency or amplitude of the unstable contractions observed in rats with obstructed bladders. It was suggested that doxazosin may have an action at the level of the spinal cord and ganglia, thereby reducing activity in the parasympathetic nerves to the bladder, and that this effect was more pronounced in rats with bladder hypertrophy than in normal rats.

Urodynamic studies revealed that spontaneously hypertensive rats (SHRs) have pronounced bladder overactivity. These animals also have an increased noradrenergic bladder innervation and an increased voiding frequency. Whereas the control rats (Wistar Kyoto rats) have a regular contraction frequency during continuous cystometry, the SHRs show both micturition and nonmicturition contractions. To investigate whether the peripheral adrenergic system was involved in the pathogenesis of the bladder overactivity, SHRs were treated with 6-hydroxydopamine in order to destroy the noradrenergic nerves chemically. Under these conditions, bladder overactivity was maintained (as demonstrated by continuous cystometry). Furthermore, α₁-adrenoceptor antagonists, injected intra-arterially near the bladder, did not abolish the bladder overactivity. On the other hand, when given intrathecally, the same dose of α₁-adrenoceptor antagonist normalized micturition. Although the relevance of these findings to man is not known, it is probable that spinal α₁-adrenoceptors may contribute to the overall clinical improvement in LUTS seen with α₁-adrenoceptor antagonists.

The neuronal localization of α₁-adrenoceptor subtypes (α₁a, α₁b, α₁d) in the human spinal cord was investigated. In situ hybridization studies revealed that α₁-adrenoceptor mRNA was present in ventral gray matter only (ventral > dorsal; sacral > lumbar = thoracic > cervical). Signaling cell bodies were detected in anterior horn motor neurones at all levels, in the dorsal nucleus of Clark, and in intermediolateral columns in cervical enlargement, in thoracic and lumbar spinal cord regions, and in the parasympathetic nucleus in the sacral spinal cord. Although all three high-affinity α₁-adrenoceptor subtypes were present throughout the human spinal cord, α₁d-adrenoceptor mRNA predominated. Whether this has any clinical significance in the treatment of LUTS remains to be established. It is pertinent, however, to note that the distribution of α₁-adrenoceptor mRNA subtypes in the rat spinal cord is different from that in humans; this should be borne in mind when discussing the clinical relevance of data obtained in rats.

Overall, there is good evidence in several species that α₁-adrenoceptors at spinal and supraspinal levels can profoundly influence the micturition reflex. The possibility that they may contribute to the overall clinical improvement in LUTS cannot be discounted.

α₁-Adrenoceptors in the cardiovascular system

The involvement of α₁-adrenoceptor subtypes in vascular control is of particular relevance to any discussion of uroselectivity. Species- and vessel-dependent α₁A, α₁B, α₁D, and α₁L-adrenoceptors all seem to subserve the contractile response in vascular tissue. On this basis, one could assume that cardiovascular homeostasis depends on all of the different subtypes, albeit to varying
extents. Equally, no one $\alpha_1$-adrenoceptor subtype can be considered to be the ‘blood pressure adrenoceptor’.

**Summary of pharmacologic uroselectivity**

There is good evidence to suggest that an agent selective for the $\alpha_{1A}$-adrenoceptor subtype will influence periurethral smooth muscle tone, urethral resistance, and thereby urinary flow. However, there is some degree of uncertainty as to whether the use of $\alpha_{1A}$-adrenoceptor antagonists would improve symptoms. Indeed, should an extraprostatic action on the other subtypes be required to optimize symptom improvement, an $\alpha_{1A}$-adrenoceptor-selective antagonist may have lower efficacy than existing agents. Equally, a selective action at $\alpha_{1A}$-adrenoceptors may not necessarily translate into a reduction in cardiovascular side-effects. Thus, although several agents with considerable pharmacologic ($\alpha_{1A}$-adrenoceptor) ‘uroselectivity’ have been synthesized, there is no guarantee that this will translate into clinical benefit.

**PHYSIOLOGIC UROSELECTIVITY**

Obviously the response in the whole animal and, indeed, in man represents an integrated response that is much more complicated than can be predicted from analysis at the pharmacologic or receptor level in isolation. In the whole animal, homeostatic mechanisms tend to counteract

### Table 12.1 Binding affinities (pK$_I$) for compounds at cloned human $\alpha_1$-adrenoceptors.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\alpha_{1A}$</th>
<th>$\alpha_{1B}$</th>
<th>$\alpha_{1D}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMY 7378</td>
<td>6.2 ± 0.10</td>
<td>6.7 ± 0.11</td>
<td>8.2 ± 0.10</td>
</tr>
<tr>
<td>Prazosin</td>
<td>9.7 ± 0.20</td>
<td>9.6 ± 0.14</td>
<td>9.5 ± 0.10</td>
</tr>
<tr>
<td>Doxazosin</td>
<td>8.5 ± 0.20</td>
<td>9.0 ± 0.20</td>
<td>8.4 ± 0.12</td>
</tr>
<tr>
<td>WB 4101</td>
<td>9.3 ± 0.10</td>
<td>8.2 ± 0.16</td>
<td>9.2 ± 0.06</td>
</tr>
<tr>
<td>5-Methylurapidil</td>
<td>8.5 ± 0.09</td>
<td>6.8 ± 0.13</td>
<td>7.8 ± 0.09</td>
</tr>
<tr>
<td>Tamsulosin</td>
<td>10.3 ± 0.21</td>
<td>9.5 ± 0.17</td>
<td>10.1 ± 0.22</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>8.1 ± 0.09</td>
<td>7.1 ± 0.15</td>
<td>7.8 ± 0.03</td>
</tr>
<tr>
<td>SNAP 1069</td>
<td>7.8 ± 0.19</td>
<td>7.6 ± 0.18</td>
<td>6.8 ± 0.20</td>
</tr>
<tr>
<td>Indoramin</td>
<td>8.3 ± 0.03</td>
<td>8.0 ± 0.12</td>
<td>7.3 ± 0.15</td>
</tr>
<tr>
<td>Alfuzosin</td>
<td>8.0 ± 0.20</td>
<td>8.0 ± 0.13</td>
<td>8.5 ± 0.07</td>
</tr>
<tr>
<td>Spiperone</td>
<td>7.6 ± 0.12</td>
<td>8.5 ± 0.16</td>
<td>8.1 ± 0.03</td>
</tr>
<tr>
<td>Terazosin</td>
<td>8.6 ± 0.22</td>
<td>8.7 ± 0.08</td>
<td>8.3 ± 0.13</td>
</tr>
</tbody>
</table>

Affinities were determined by displacement of 0.2 nM [$^3$H]prazosin from rat-1 fibroblasts stably expressing cloned $\alpha_1$-adrenoceptor subtypes by 12 concentrations of competing drug. Values represent mean ± SEM for three to five separate determinations. Hill slopes for displacement curves were not significantly different from unity. (Data from reference 67 with permission.)
many of the effects produced by any drug, particularly under normal conditions. However, in disease or in situations of abnormal pathophysiology, homeostatic compensation may have occurred to the maximum extent. Thus, the response to the drug under these conditions may be substantially different—either exaggerated or attenuated.

In terms of LUTS and in the context of uroselectivity, an agent that decreases outflow resistance without affecting the blood pressure would obviously be of considerable interest. Many groups have reported that $\alpha_1$-adrenoceptor antagonists decrease urethral resistance in animal models. Indeed, such animal models are used routinely within the pharmaceutical industry to determine the relative potency and selectivity of $\alpha_1$-adrenoceptor antagonists for prostate function over other parameters such as blood-pressure lowering. The rank order of potency of the effects of various $\alpha_1$-adrenoceptor antagonists on urethral pressure has been defined in several animal models, and has then been related to blood pressure changes in the same animal. The ratio of these effects could therefore be considered as a potential index of uroselectivity. Although such models may have some predictive value, they also have limitations, and the results may be both species- and assay-dependent. Thus, results obtained in one animal species may differ from those obtained in another, and it has not been established which animal model is the most predictive of effects in humans.

Side-effects that may be dose limiting clinically are not always cardiovascular (or directly related to hemodynamic changes), but may arise from the central nervous system, for example drowsiness and dizziness. Also, because such effects cannot always be studied in animals, animal models may not adequately predict benefit–risk profiles or provide a reliable index of clinical uroselectivity as it would impact on patient management. The use of animal models has, however, produced encouraging results. All established agents—alfuzosin, doxazosin, prazosin, tamsulosin, and terazosin—affect urethral pressure in animals over the same dose range that produces vascular effects (see Table 12.1 and Figure 12.3). The relative lack of uroselectivity seen in whole-animal studies is entirely consistent with the receptor-binding profile of these $\alpha_1$-adrenoceptor antagonists (i.e. the pharmacologic ‘uroselectivity’, as defined by the selectivity for the $\alpha_{1A}$-adrenoceptor subtype over the other subtypes) (Figure 12.3). Thus, none of these agents can be considered to demonstrate significant physiologic uroselectivity in the whole animal. Although it is possible to carry out similar evaluations in man, ultimately we need to define clinical uroselectivity.

**CLINICAL UROSELECTIVITY**

A clinically relevant definition of uroselectivity can be made only in relation to man. It is known that $\alpha_1$-adrenoceptor antagonists have more pronounced effects on blood pressure in hypertensive patients than in normotensive patients. For example, it is well documented that doxazosin and terazosin effectively reduce blood pressure in hypertensive BPH patients but have only relatively modest effects in normotensive men (Figure 12.4). Assuming that this occurs at doses that affect urinary flow, both drugs could be considered to demonstrate clinical uroselectivity, at least in normotensive BPH patients. Ironically, however, using this definition neither agent would be classified as uroselective in hypertensive BPH patients. The blood pressure-lowering effect is of
benefit in the large number of BPH patients who are hypertensive. Thus, in theory, a drug could affect blood pressure in a hypertensive subject before it has any noticeable effects on the urethra (i.e. the drug has no uroselectivity or indeed has vascular selectivity). The same drug may reduce outflow resistance in a normotensive patient but without having any effects on blood pressure (i.e. the drug is uroselective in this situation). The situation is complicated further by the fact that pharmacokinetic properties may contribute to apparent differences between drugs in the effects on different organ systems.

In the context of managing patients with BPH, it is therefore both obvious and essential to have an all-encompassing but precise definition of clinical uroselectivity. This has to take into account the fact that the clinical endpoints of outflow obstruction (as defined urodynamically) and LUTS, and adverse effects may vary independently. Thus, uroselectivity (as for any clinical therapeutic index) may be defined by describing the ratio between the dose required for the desired therapeutic action and the dose that produces side-effects. Such a definition of uroselectivity is the one recommended in 1995 by the Fourth International Consultation on Benign Prostatic Hyperplasia: ‘desired effects on obstruction and lower urinary tract symptoms related to adverse effects’.\(^9\) It should be noted that clinical uroselectivity defined in this way is not an all-or-nothing phenomenon but is merely a qualitative descriptor.

The clinical definition should be borne in mind when considering the profiles described for the \(\alpha_1\)-adrenoceptor antagonists. It is obvious that, although animal studies have greatly increased our understanding of the control of the lower urinary tract, they may be of relatively little value in the prediction of clinical uroselectivity.

**FIGURE 12.3** (a) Selectivity profile of doxazosin (Dox), terazosin (Ter), alfuzosin (Alf), tamsulosin (Tam), and 5-methylurapidil (5-MU) for the cloned \(\alpha_{1A}, \alpha_{1B}\), and \(\alpha_{1D}\)-adrenoceptor subtypes. 5-MU is the only compound that shows selectivity for the cloned human \(\alpha_{1A}\)-adrenoceptor. (b) Selectivity profile of the same compounds in the anesthetized dog. All compounds are equi-active on prostate pressure and blood pressure, except the \(\alpha_{1A}\)-selective 5-MU, which is about 30-fold prostate selective.
A drug may be uroselective in the sense that it has a preference for the $\alpha$-adrenoceptors in the prostate, or that in an animal model it can affect the prostate and urethra without affecting blood pressure, for example. There are $\alpha_1$-adrenoceptors in the urethra, trigone, detrusor, spinal cord, supraspinal structures, and peripheral ganglia, the contributions of which to the symptoms of BPH remain unknown, and whose subtypes have not been determined. Thus, such a definition of uroselectivity may not be meaningful from a clinical point of view. A clinically meaningful definition of uroselectivity can be made only with respect to findings in man, and considers desired effects on obstruction and LUTS relative to adverse effects. Clinical uroselectivity can be used as a guideline for selecting drugs for the management of BPH that are cost-effective and safe, and which can improve the individual patient's quality of life. It is possible, however, that the pharmaceutical industry may have exhausted both the pharmacologic and pharmacokinetic options for achieving uroselectivity.

**REFERENCES**

5. Lepor H, Machi G. Comparison of the AUA symptom index in unselected males and females between 55 and 79 years of age. Urology 1993; 42: 36–40


32. Nasu K, Moriyama N, Kawabe K et al. Quantification and distribution of alpha₁-adreno-


74. Wyllie M G. Uroselectivity; end of the road? BJU Int 2003; 92: 141–142
Index

<table>
<thead>
<tr>
<th>Adrenoceptors</th>
<th>185–91</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtypes</td>
<td>92, 93, 103–4</td>
</tr>
<tr>
<td>Adrenoceptor antagonists</td>
<td>91–2</td>
</tr>
<tr>
<td>Apoptosis induction</td>
<td>85–6</td>
</tr>
<tr>
<td>Blood pressure effects</td>
<td>193</td>
</tr>
<tr>
<td>Differential effects on prostate tissue growth</td>
<td>83–9</td>
</tr>
<tr>
<td>Physiologic uroselectivity</td>
<td>190–1, 192–3</td>
</tr>
<tr>
<td>Serum lipids</td>
<td>109</td>
</tr>
<tr>
<td>vs watchful waiting</td>
<td>4–5</td>
</tr>
<tr>
<td>African plum tree <em>(Pygeum africanum)</em></td>
<td>172–3</td>
</tr>
<tr>
<td>ALFIN study</td>
<td>70–1, 77–8</td>
</tr>
<tr>
<td>ALFORTI study, alfuzosin</td>
<td>128–9, 132</td>
</tr>
<tr>
<td>ALFUS study, alfuzosin</td>
<td>129</td>
</tr>
<tr>
<td>Alfuzosin</td>
<td>119–37</td>
</tr>
<tr>
<td>Acute urinary retention</td>
<td>123</td>
</tr>
<tr>
<td>Alpha-adrenoceptor affinity</td>
<td>119–20</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>120, 122–4</td>
</tr>
<tr>
<td>vs tamsulosin</td>
<td>157–8</td>
</tr>
<tr>
<td>Clinical studies</td>
<td>125–31</td>
</tr>
<tr>
<td>ALFORTI</td>
<td>128–9, 132</td>
</tr>
<tr>
<td>ALFUS</td>
<td>129</td>
</tr>
<tr>
<td>Combination therapy, finasteride</td>
<td>129, 131, 133</td>
</tr>
<tr>
<td>Efficacy</td>
<td>126–34</td>
</tr>
<tr>
<td>vs placebo</td>
<td>27, 46</td>
</tr>
<tr>
<td>Formulation, comparisons</td>
<td>122</td>
</tr>
<tr>
<td>Hemodynamic effects</td>
<td>124–5</td>
</tr>
<tr>
<td>Pharmacodynamic effects</td>
<td>122–3</td>
</tr>
<tr>
<td>Pharmacokinetic properties</td>
<td>122</td>
</tr>
<tr>
<td>Pharmacologic profile</td>
<td>119</td>
</tr>
<tr>
<td>Prostate/plasma concentrations</td>
<td>122</td>
</tr>
<tr>
<td>Safety and adverse events</td>
<td>132, 133</td>
</tr>
<tr>
<td>Therapeutic applications</td>
<td>133–4</td>
</tr>
<tr>
<td>Urodynamic effects</td>
<td>123</td>
</tr>
<tr>
<td>Urethral pressure</td>
<td>121</td>
</tr>
<tr>
<td>vs tamsulosin</td>
<td>157–8</td>
</tr>
<tr>
<td>ALLHAT <em>(Antihypertensive Lipid-Lowering Treatment to Prevent Heart Attack Trial)</em></td>
<td>110</td>
</tr>
<tr>
<td>Alpha-1 adrenoceptors</td>
<td></td>
</tr>
<tr>
<td>Binding affinities</td>
<td>186, 190</td>
</tr>
<tr>
<td>In bladder</td>
<td>187–8</td>
</tr>
<tr>
<td>In cardiovascular system</td>
<td>189–90</td>
</tr>
<tr>
<td>Contractile role</td>
<td>186</td>
</tr>
<tr>
<td>and LUTS</td>
<td>93</td>
</tr>
<tr>
<td>In peripheral and CNS structures</td>
<td>188–9</td>
</tr>
<tr>
<td>Pharmacologic uroselectivity</td>
<td>186–90</td>
</tr>
<tr>
<td>In prostate</td>
<td>186–7</td>
</tr>
<tr>
<td>Subtypes</td>
<td>84</td>
</tr>
<tr>
<td>In urethra</td>
<td>187</td>
</tr>
<tr>
<td>Alpha-adrenoceptor antagonists</td>
<td>91–2</td>
</tr>
<tr>
<td>With 5-alpha reductase inhibitor, MTOPS trial</td>
<td>76–7</td>
</tr>
<tr>
<td>Apoptosis</td>
<td>85–6</td>
</tr>
<tr>
<td>See also alfuzosin; doxazosin; tamsulosin: terazocin</td>
<td></td>
</tr>
<tr>
<td>5-alpha-reductase (5-AR)</td>
<td>42–3</td>
</tr>
<tr>
<td>Deficiency, pseudohermaphroditism</td>
<td>4, 43</td>
</tr>
<tr>
<td>Types I and II</td>
<td>43</td>
</tr>
<tr>
<td>Type II see finasteride</td>
<td></td>
</tr>
<tr>
<td>5-alpha-reductase inhibitors (5-ARI)</td>
<td></td>
</tr>
<tr>
<td>And alpha-blockers</td>
<td>48</td>
</tr>
<tr>
<td>Combination therapy</td>
<td>48</td>
</tr>
<tr>
<td>DHT</td>
<td>41–2</td>
</tr>
<tr>
<td>DHT reduction</td>
<td>47</td>
</tr>
<tr>
<td>Dual isoforms</td>
<td>43–4, 46</td>
</tr>
<tr>
<td>Phytotherapeutic agents</td>
<td>178</td>
</tr>
<tr>
<td>See also dutasteride; finasteride</td>
<td></td>
</tr>
</tbody>
</table>
American dwarf palm (*Serenoa repens*) 76, 168–72
American Urological Association (AUA)
AUASI scale 26, 73
bother score 6, 24
combination therapy guidelines 77
watchful waiting treatment guidelines 5–7
androgen ablation/deprivation 83
angina, surgical procedures, placebo effects 17–18
apoptosis, alpha-adrenoceptor antagonists 85–6
balloon dilatation vs cystoscopy, placebo/sham controlled trials 29–33
Baltimore longitudinal study of aging, watchful waiting 1–2
bladder
alpha-1 adrenoceptors 187–8
smooth muscle, alpha-blockers 83
bladder outlet obstruction (BOO) 185
tolterodine/tamsulosin combination therapy 76
watchful waiting 2
blood pressure effects
adrenoceptor antagonists 193
alfuzosin 122–4, 120
doxazosin 108–9
tamsulosin 148
vs alfuzosin 157–8, 158
vs terazosin 157–8
terazosin 96, 99
BMY-7378, binding affinities 190
bother score 6, 24
Boyarsky symptom scores 145, 147, 154
BPH (benign prostatic hyperplasia)
historical perspective 83–6
natural history, placebo effects 18–34
treatment preferences 5
bromocriptine, efficacy, vs placebo 27
cactus flower extracts 174
candicin, efficacy, vs placebo 27
cardiovascular system, alpha-1 adrenoceptors 189–90
cernitin, combination therapy 76
cimetidine, efficacy, vs placebo 27
combination studies
ALFIN study 70–1
MTOPS trial 72–6
phytotherapy 76
Veterans’ Affairs (VA) Cooperative Study 68–70
confidence profile method (CPM), symptom improvement 22
controlled clinical trials, placebo/sham effect 14–16
coronary heart disease (CHD), doxazosin 109–10
*Cucurbita pepo* (pumpkin) 174
cystoscopy vs balloon dilatation, placebo/sham controlled trials 29–33

Declaration of Helsinki, rationale for
placebo/sham controlled trials 15
detrusor overactivity (DO),
tolterodine/tamsulosin combination therapy 76
DHT (dihydrotestosterone)
5-alpha-reductase inhibitors (5-ARI) 47
BPH development 41–2
dual inhibition, dutasteride treatment 44
formation 42
doxazosin 103–17
affinity for adrenoceptor subtypes 93
ALLHAT trial 110
antihypertensive effects 108–9
binding affinities 190
efficacy 46
with finasteride 5
GITS formulation 112–13
adverse events 113
HABIT 109
HALT 110
MTOPS 59, 72–6, 77–8, 106
PREDICT 71–2, 77–8, 106
prostate apoptosis effect 85–6
safety and efficacy
adverse events 107–8
long-term 84–5, 106
safety profile 107
short-term 104–5
sexual dysfunction 110–11
TOMHS 109
uroselectivity 192
drugs, meta-analyses 61, 161
dutasteride 41–51
adverse events 46
clinical experience 45–7
combination studies 48
preclinical development 44–5
and PSA (prostate-specific antigen) 45, 47–8
structure 44
vs dutasteride 47–8
ESPIRIT (European Standardized Pressure Flow Investigation Trial) 148–9
FDA, rationale for placebo/sham controlled trials 14–15
finasteride 53–66
adverse events 58
ALFIN study 70–1, 77–8
clinical studies 56–9
combination studies 59–61
with alfuzosin 129, 131, 133
with alpha-adrenoceptors 5
with doxazosin 5
terazosin, interactions 60
development 54
DHT and 5-alpha-reductase 53–4
hematuria prevention 48, 61
meta-analysis 61
mode of action 54
MTOPS study 59–60, 72–6, 77–8
PREDICT study 71–2, 77–8, 106
PSA effects 62
safety profile 133
structure 54
VA Cooperative Study 60
vs dutasteride 47–8
France and Germany, phytotherapeutic agents 5
growth factors
DHT-receptor complex 42
and finasteride 55
3H-prazosin, binding sites 120
HABIT (Hypertension and BPH Intervention study), doxazosin evaluation 109
HALT (Hypertension and Lipid Trial), doxazosin 110
hematuria prevention, finasteride treatment 48, 61
hermaphroditism, pseudohermaphroditism, 5-AR deficiency 43
hyperplasia, adrenoceptor antagonist differential effects 83–7
hypertension, TOMHS 109
hyperthermia devices see TUMT
hypotension, tamsulosin 147, 149, 159, 161
Hypoxis rooperi (South African star grass) 168
124I-HEAT, binding sites 120
I-PSS (International Prostate Symptom Score) 26
tamsulosin 149, 150–2
indoramin
binding affinities 190
efficacy, and potency 92
Ki 67 immunostaining 85
lipids, alpha-blocker effects 109–10
LUTS (lower urinary tract symptoms)
  alpha-adrenoceptor antagonist therapy 93
dutasteride treatment 45
effects of alpha-1 adrenoceptors 93
terazosin therapy 91–6
watchful waiting prospective study 3
5-methylurapidil
  affinity for adrenoceptor subtypes 93
  binding affinities 190
micturition reflex 188
MTOPS (Medical Therapy of Prostatic Symptoms) trial 59–60, 72–6, 77–8
doxtazosin 106
norprogesterone, efficacy, vs placebo 2, 27
Olmsted County Study of Urinary Symptoms and Health Status Among Men 19–21
orthostatic hypotension, tamsulosin 147, 149, 159, 161
pain treatment, placebo effects 17
  patients
  monitoring see watchful waiting
  treatment preferences 5
peripheral NS, alpha-1 adrenoceptors 188–9
phenoxybenzamine 103
phentolamine, binding affinities 190
phytotherapeutic agents 167–84
  5-alpha-reductase inhibition 168–9
  active constituents 168
  combination preparations 174–5
  combination therapy 76
France and Germany 5
  meta-analyses 175–7
  mode of action 169
  origin 167–8
  phytosterols/beta-sitosterol 172
  *Picea* (spruce) 168
  *Pinus* (pine) 168
placebo/sham effect 11–39
  balloon dilatation vs cystoscopy studies 29–33
  biopsychosocial determinants 13
  controlled trials, cystoscopy vs balloon dilatation 29–33
  definitions and theoretical considerations 11–13
  ethical considerations 15
  hyperthermia treatment studies 15–16, 29–32
  improvement perception 33–4
  long-term natural history of disease progression 31–3
  medical treatment studies 24–9
  natural history studies 18–34, 31–3
  regression to mean 19
  watchful waiting studies 21–4
Olmsted County study 19–21
pain control 17
phytotherapeutic agents, *Serenoa repens* 170
quantitative symptom scores 30–3
surgical procedure studies 17–18
therapeutic theory 12
watchful waiting studies 21–4
plants, phytotherapeutic agents 167–84
PLESS (Proscar Long-term Efficacy and Safety Study) 32–3, 56–8
postvoid residual urine (PVR), treatment
  indications 6
prazosin
  binding affinities 190
  efficacy, and potency 92
  *[^H]-prazosin, binding sites 120
PREDICT (Prospective European Doxazosin and Combination Therapy) study 71–2, 77–8
finasteride 106
terazosin 86–7
prostate, innervation 185
prostatic growth/development
  cell proliferation control 86–7
  finasteride 54–6
  growth rate (40–79 y) 21
prostatic size/volume
  doxazosin 111
  dutasteride 45, 77
  finasteride 56, 61, 77
  terazosin growth effects 97–8
prostatism, watchful waiting over 5 years 2–3
PSA (prostate-specific antigen)
  dutasteride treatment 45, 47–8
  and finasteride 62
pseudohermaphroditism, deficiency of 5-alpha-reductase 43
pumpkin (Cucurbita pepo) 174
Pygeum africanum 172–3
rye (Secale cereale) 168, 173
  meta-analyses 175–7
Sabal serrulata (saw palmetto) see Serenoa repens
Secale cereale (rye) 168, 173
Serenoa repens (American dwarf palm) 168–72
  cernitin, beta-sitosterol and vitamin E
    combination therapy 76
    combination therapy 174–5
    meta-analyses 175
sexual function/dysfunction
  doxazosin 110–11
  dutasteride 46
  ejaculation abnormalities 147, 147–9
  MTOPS data 75–6
  tamsulosin 147–8
beta-sitosterol
  meta-analysis 175–7
  phytotherapeutic agents 172
Serenoa repens, cernitin and vitamin E
  combination therapy 76
smooth muscle, alpha-blockers 83
SNAP 1069
  binding affinities 190
  efficacy, and potency 92
South African star grass (Hypoxis rooperi) 168
spiperone, binding affinities 190
spruce (Picea) 168
stinging nettle (Urtica dioica) 173
surgical procedures
  placebo effects 17–18
  risk, MTOPS data 72–6
symptom improvement, confidence profile
  method (CPM) 22
tamsulosin 139–70
  adverse events 149
  affinity for adrenoceptor subtypes 93
  ancillary properties 162
  binding affinities 190
  blood pressure effects 148
  chemical structure 87
  clinical studies
    direct comparative studies 155–9
    European phase II 142–3
    European phase III 143, 147
    European phase IV 148
    Japanese phase II 141–2, 144
    long-term 154–5
    US phase III 149–52
  co-medication 159–60
  dosages and formulations 140–1, 158–9
  efficacy and tolerability 46, 146, 159–61, 160
  vs placebo 28
  elderly patients 159–60
  ESPIRIT 148–9
  meta-analysis 161
  onset of action 143, 152
  previous treatment comparisons 161
tolterodine combination therapy 76
uroselectivity 192
vs alfuzosin, blood pressure effects 157–8
vs terazosin, blood pressure effects 157–8
terazosin 91–101
affinity for adrenoceptor subtypes 93
binding affinities 190
blood pressure effects 96, 193
cardiovascular risk factors 97
chemical structure 87
effects on urogenital tract 97
efficacy 46
long-term 84–5, 93–4
and potency 92
short-term 93
vs placebo 28
finasteride interactions 60
historic background 92
LUT obstruction 91–2
prostate apoptosis effect 85–6
prostate gland growth 97–8
safety profile 95–6
uroselectivity 192
VA Cooperative Study 60

Testosterone
dutasteride treatment 47
formation of DHT 42
tolterodine, tamsulosin combination therapy 76
TOMHS (Treatment of Mild Hypertension Study), doxazosin evaluation 109–11
TUMT (transurethral microwave thermotherapy)
efficacy, vs sham control 29
placebo/sham controlled trials 15–16, 29–32
TUNEL assay 85
TURP (transurethral resection of prostate) 1
indications 4, 5–6
vs conservative management 3
WW, waiting list 3

Urethra, alpha-1 adrenoceptors 187
urethral pressure, alfuzosin 120–1
urinary flow rate $Q_{\text{max}}$
and density of smooth muscle 91
ESPRIT study 148–9
treatment indications 6
urinary retention, acute
alfuzosin 123
MTOPS data 74, 75
urinary tract symptoms see LUTS
urodynamic studies, doxazosin 104–5
urologists, treatment preferences 5
uroselectivity 185–96
clinical, defined 191
pharmacologic 186–90
physiologic 190–1, 192–3
summary 190

Urtica dioica (stinging nettle) 173

Veterans’ Affairs (VA) Cooperative Study 3–4
baseline and 3-year follow-up 3–4
terazosin 86–7
terazosin vs finasteride 60, 68–70
vitamin E, beta-sitosterol, Serenoa repens and cernitin combination therapy 76

Watchful waiting (WW, patient monitoring) 1–9
placebo/sham effect 21–4
strategy 6–7
treatment indications 6
vs medical therapy 6–7
vs placebo, comparison of outcomes 25
WB-4101, binding affinities 190
WHO, on placebo/sham control groups 16

YM-617 see tamsulosin
TEXTBOOK OF 
BENIGN PROSTATIC HYPERPLASIA

Since publication of the first edition of the Textbook of Benign Prostatic Hyperplasia, major advances have been made in the diagnosis and treatment of this very common condition. Medical therapy in particular has moved dramatically with the clinical trials of 5 alpha-reductase inhibitors and alpha blockers and the development of combination therapy. Surgical options have expanded with the introduction of safe and effective new minimally invasive techniques. New guidelines for treatment have been developed to aid decision making.

The Textbook of Benign Prostatic Hyperplasia has been extensively revised and updated to include all of the most recent and significant developments in the field. It continues to provide essential reference and a valuable resource for primary care physicians, urologists and all those interested in prostatic diseases.

Related titles

The Scientific Basis of Urology, 2nd Edition
Edited by AR Mundy, JM Fitzpatrick, DE Neal and NJR George
ISBN 1-901865-13-4

Disorders of the Prostate
Edited by Fouad K Habib
ISBN 1-84184-140-4

Basic and Advanced Techniques in Prostate Brachytherapy
Edited by A Dicker, G Merrick, L Gomella, R Valicenti and F Waterman
ISBN 1-84184-298

Benign Prostatic Hyperplasia
Edited by Paul D Miller, Ian Eardley and Steven A Kaplan
ISBN 1-85317-534-X