

# Medical Therapy for Benign Prostatic Hyperplasia— Present and Future Impact

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## Abstract

The purpose of this manuscript is to provide clinicians, health plan decision makers, and policy makers with highlights of key findings pertaining to our current understanding of the condition of enlarged prostate (EP) from a managed care perspective. This includes a brief discussion regarding the prevalence and economic burden of EP, followed by a review of clinical characteristics and pathophysiology, with the final section on treatment approaches with a focus on pharmacologic options. This supplement is not intended to be a comprehensive review of EP, because many review articles on this subject are available elsewhere. This manuscript does, however, serve to introduce 3 additional manuscripts contained within this supplement.

The first article provides the readers with a real-world comparison of dutasteride and finasteride relative to acute urinary retention and surgery attenuation rates. The second article investigates differences in discontinuation rates of alpha blockers when used in combination with dutasteride or finasteride. The last article addresses the cost implications associated with dutasteride and finasteride therapy. All 3 articles represent data from a naturalistic, managed care population.

This supplement is intended to assist managed care formulary decision makers in evaluating key clinical and economic data which could help to differentiate dutasteride and finasteride. Although the information presented does not prove superiority of either product, it will answer some important questions and raise some important issues beyond ingredient cost.

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With the advent of the Medicare Modernization Act and the introduction of a drug benefit for eligible beneficiaries, health plans and policy makers are now realizing the need for potential shifts in disease management priorities. This is especially true for certain subsets of the population, such as elderly men. United States Census information suggests that from the year 2000 to 2020, the number of men older than the age of 64 will grow to nearly 9.3 million.<sup>1</sup> In a recent retrospective study of men 50 years of age and older in a managed care population, coronary artery disease, hyperlipidemia, hypertension, type 2 diabetes, osteoarthritis, and enlarged prostate (EP) were the most prevalent diagnoses (**Table 1**).<sup>2</sup> Perhaps the most surprising finding from this study was the inclusion of EP among the 5 most prevalent diseases. Although previously not on the “radar screen” for most health plans, EP may become one of the new priorities for disease management in this rapidly growing population of men currently or soon to be eligible for Medicare.

This supplement is not intended as a comprehensive review of EP, because this topic has been reviewed elsewhere.<sup>3-5</sup> Instead, our purpose is to provide clinicians, health plan decision makers, and policy makers with some key findings pertaining to our current understanding of this important condition from a managed care perspective. This includes a brief discussion of the prevalence and economic burden of EP, the clinical characteristics and pathophysiology, and treatment approaches with a focus on pharmacologic options.

## DISEASE PREVALENCE AND ECONOMIC BURDEN

Enlarged prostate or benign prostatic hyperplasia (BPH) is a chronic progressive urologic condition<sup>6</sup> which affects a significant number of the aging male population.<sup>7-10</sup> The prevalence of moderate-to-severe lower urinary tract symptoms (LUTS) is 26% in men aged 40 to 49 years and 46% in men aged 70 and older.<sup>7</sup> An estimated 1 in 4 men will seek medical care for management of symptomatic BPH by age 80.<sup>11-13</sup> Approximately 90% of men have histologic evidence of the disease by age 85.<sup>11</sup>

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The reported economic burden estimates of EP vary depending on the data sets studied. The incremental direct annual cost per patient associated with a diagnosis of EP has been estimated between \$1536 and \$2577 in 1999.<sup>7,14</sup> Data from the early 1990s estimate the cost of treatment to be \$4 billion annually.<sup>15</sup> In an analysis of privately insured men between the ages of 45 and 64 years, the estimated annual healthcare expenditure to treat BPH in this population was \$3.4 billion in 1999.<sup>14</sup> Finally, the Urologic Diseases in America BPH Project indicated that in the year 2000, the disease carried an economic burden of \$1.1 billion in direct annual healthcare expense in the United States, exclusive of outpatient pharmacotherapy costs.<sup>7</sup>

Since the late 1980s, pharmacologic therapy utilization has increased while more invasive surgical interventions have declined.<sup>7,16,17</sup> It is anticipated that treatment cost will continue to be adjusted as this trend continues. At the same time, population estimates provide a trajectory of increasing costs as the number of treatment-eligible men expands.

The economic burden should not overshadow the tremendous impact of EP on patients' quality of life. As severity of voiding symptoms increases, men experience a significant compromise in their overall well-being. For men with severe symptoms, the greatest impact appears to be on role limitations due to physical problems, energy/fatigue, role limitations due to emotional problems, and general perception of health.<sup>18</sup> These data support the importance of quality of life in the assessment of medical outcomes and treatment decisions with this condition.

## CLINICAL CHARACTERISTICS AND PATHOPHYSIOLOGY

The clinical impact of an EP is characterized by LUTS—including urinary frequency, urgency, nocturia, weak stream, hesitancy, and straining—with an increasing risk of clinical events, such as acute urinary retention (AUR) or surgery. Recent evidence suggests that the likelihood of AUR and/or surgery occurring within 1 year of initiating treatment is approximately 19%.<sup>19</sup>

The pathophysiology of EP includes both static and dynamic components. Abnormal and excessive nonmalignant growth of prostate tissue is a hall-

■ **Table 1. 10 Most Diagnosed Diseases for Men ≥50 Years**

Rank	Disease	Prevalence rate (%)
1	CAD and hyperlipidemia	51.3
2	Hypertension	45.2
3	Type 2 diabetes	17.5
4	Enlarged prostate	13.5
5	Osteoarthritis	13.3
6	Arrhythmias	8.8
7	Cataracts	8.6
8	GERD	8.4
9	Bursitis	8.0
10	Prostate cancer	7.8

CAD indicates coronary artery disease; GERD, gastroesophageal reflux disease.  
Source: Reference 2.

mark of the disease. Over time, the tissue growth starts impinging on the prostatic urethra and the bladder neck, leading to bladder outlet obstruction. This is the static component of prostatic hyperplasia. Continued exposure of the prostate to dihydrotestosterone (DHT) plays a central pathophysiologic role in this age-associated prostate growth and eventual hyperplasia. There is also an increase in the amount and tone of the smooth muscle within the prostate. Stimulation of alpha<sub>1</sub>-adrenergic receptors on the bladder neck, prostatic capsule, and stromal tissue results in constriction of the urethral lumen. This is the dynamic component of prostatic hyperplasia. Although other factors are involved in the pathophysiology of LUTS,<sup>20</sup> these 2 components provide a rationale for the 2 main pharmacologic approaches to BPH: alpha<sub>1</sub>-adrenergic antagonists (alpha<sub>1</sub> blockers) and 5-alpha reductase inhibitors (5ARIs).

## TREATMENT APPROACHES WITH A FOCUS ON PHARMACOLOGIC MANAGEMENT

Since the advent of effective medical therapy, the rate of surgical intervention for patients with symptomatic EP has progressively and substantially decreased. Once among the most commonly practiced surgical procedures, transurethral resection of

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the prostate is now performed much less frequently because of the availability of pharmacologic treatment options as well as minimally invasive procedures.<sup>7</sup>

Evidence-based practice guidelines for the therapeutic approach to EP were published by the American Urological Association (AUA) in 2003<sup>12</sup> and updated in 2006.<sup>13</sup> The classic treatment goals for EP are to reduce LUTS, arrest disease progression, and prevent complications.<sup>21</sup>

The AUA Symptom Index (AUASI) is used to categorize disease severity and aid in assessing treatment response.<sup>12,13</sup> The AUASI is a 7-item self-assessment questionnaire (identical to the 7 symptom items of the International Prostate Symptom Score [IPSS]) that focuses on LUTS. The 7 questions are answered on a scale of 0 to 5 based on the presence and frequency of the symptoms experienced by the patient during the preceding month. Total scores can range from 0 to 35. AUASI/IPSS scores  $\leq 7$  indicate mild disease, 8 to 19 moderate disease, and  $\geq 20$  severe disease.

Treatment approaches to EP include watchful waiting, pharmacologic intervention, minimally invasive therapies, and surgical options (Table 2). According to the AUA guidelines on BPH, a strategy of watchful waiting is appropriate in patients with mild symptoms of BPH (AUASI  $\leq 7$ ) and in patients with moderate or severe symptoms (AUASI  $> 7$ ) who are not bothered by their symptoms (ie, the symptoms do not interfere with daily activities).<sup>12,13</sup> Watchful waiting is also an option for patients with bothersome symptoms who have not yet developed complications (eg, AUR, recurrent infection, renal insufficiency); however, the risks and benefits of the various treatment options (including the risk of disease progression and complications with watchful waiting) should be discussed with these patients. Patients on watchful waiting are usually monitored annually.<sup>12,13</sup>

The AUA guidelines recommend that pharmacotherapeutic intervention should be considered in patients with bothersome symptoms and a score of  $\geq 8$  on the AUASI.<sup>12,13</sup> Pharmacologic therapies for

■ **Table 2.** Summary of Recent Guidelines for the Management of EP

LUTS severity	Prostate size	Bothersome symptoms	Complications	Treatment options
AUASI $\leq 7$				Watchful waiting
AUASI $\geq 8$	$\leq 30$ cc	No		Watchful waiting
		Yes		Watchful waiting Alpha blocker
	$> 30$ cc	No		Watchful waiting 5ARI
		Yes	No	Watchful waiting* Alpha blocker (monotherapy)* 5ARI Alpha blocker + 5ARI Minimally invasive therapy Surgical therapy
			Yes	Surgical therapy <sup>†</sup>

\*May be considered in absence of complications,<sup>12,13</sup> but not recommended for patients with risk factors for progression—ie, EP ( $> 30$  cc) and/or high PSA ( $> 1.4$  ng/mL).<sup>22</sup>

<sup>†</sup>In patients with AUR, who have not failed an attempt at catheter removal, an alpha blocker before catheter removal is an additional option. However, surgery is recommended for patients with renal insufficiency due to BPH, and for patients with other BPH complications (eg, recurrent urinary tract infections, recurrent gross hematuria, bladder stones) that are refractory to other treatments. Patients who are not surgical candidates may be treated with intermittent catheterization, an indwelling catheter, or a stent.<sup>12,13</sup>

EP indicates enlarged prostate; LUTS, lower urinary tract symptoms; AUASI, American Urological Association Symptom Index; 5ARI, 5-alpha reductase inhibitor; PSA, prostate-specific antigen; AUR, acute urinary retention; BPH, benign prostatic hyperplasia.

Sources: References 12, 13, 22.

symptomatic BPH include  $\alpha_1$  blockers and 5ARIs; however, 5ARIs are appropriate only when there is evidence of prostate enlargement. Patients with prostate enlargement and nonbothersome symptoms also may be offered 5ARI therapy to prevent disease progression.<sup>12,13</sup> Prostate enlargement has been defined as a prostate volume >30 cc.<sup>22</sup>

$\alpha_1$  blockers target smooth muscle receptors in the fibromuscular stroma of the prostate and bladder neck,<sup>20</sup> relaxing the smooth muscle fibers at the bladder outlet and making it easier for the patient to urinate. These agents include 2 therapies now available generically (doxazosin and terazosin) and 2 branded drugs, Flomax® (tamsulosin) and Uroxatral® (alfuzosin). Prazosin is not approved by the US Food and Drug Administration for treatment of BPH.

The 1997 AUA Gallup survey indicated that  $\alpha$  blockers are the most frequently used pharmacologic intervention for BPH. According to the survey,  $\alpha$  blockers are prescribed for 88% and 69% of moderately symptomatic patients with prostate volumes  $\leq 40$  cc and  $>40$  cc, respectively.<sup>23</sup> However, although  $\alpha$  blockers work effectively to rapidly relieve bladder symptoms, they are considered purely symptom-modifying therapy rather than disease-modifying therapy. They do not reduce prostate size and, therefore, do not prevent disease progression or reduce the long-term risks of AUR and the need for invasive treatment.<sup>24</sup>

$\alpha$  blockers are generally well tolerated. Class side effects include orthostatic hypotension, dizziness, tiredness, ejaculation problems, and nasal congestion.<sup>12,13</sup> There are, however, differences in the adverse-effect profiles among the various  $\alpha$  blockers. Alfuzosin (especially the XL formulation) and tamsulosin (especially the 0.4-mg/day dose) are better tolerated than doxazosin and terazosin.<sup>25</sup> Tamsulosin is the least likely to cause vasodilatory side effects, and the most likely to cause abnormal ejaculation.<sup>25</sup>

There are 2 marketed 5ARIs, finasteride (Proscar®, now also available generically) and dutasteride (Avodart®). Their main pharmacologic action is inhibition of 5- $\alpha$  reductase, the intraprostatic enzyme that converts testosterone and androstenedione to DHT.<sup>26,27</sup> This decreases DHT concentrations within the prostate tissue, resulting in a reduction in prostate size. Compared

with placebo, the 5ARIs produce significant reduction in prostate volume and improvement in symptom scores as well as significant decreases in AUR and surgical intervention rates.<sup>28-30</sup>

Combination treatment with an  $\alpha$  blocker and a 5ARI is emerging as the medical treatment of choice for patients with LUTS who have EP (>40 g) glands as suggested in the 2003 AUA treatment guidelines.<sup>12,13</sup> The  $\alpha$  blocker component of the combination therapy provides early symptom control, while the 5ARI component addresses disease progression leading to long-term symptom control.

The Medical Therapy of Prostatic Symptoms (MTOPS) trial, which enrolled patients between 1993 and 1998, provides the most definitive data supporting dual therapy.<sup>24</sup> The study objective was to evaluate whether an  $\alpha$  blocker (doxazosin) or a 5ARI (finasteride), alone or in combination, would impact disease progression. Although all active therapies provided significant symptom score improvements and reduced the risk of overall clinical progression (defined as an increase of  $\geq 4$  points on the AUASI, AUR, urinary incontinence, renal insufficiency, or recurrent urinary tract infection), the risk reduction associated with dual therapy (66%) was significantly greater compared with either agent alone (39% doxazosin, 34% finasteride). The long-term risks of AUR and invasive therapy were significantly reduced by finasteride alone or in combination with doxazosin, but not by doxazosin alone.

As mentioned previously, symptom control occurs at 1 to 2 weeks with  $\alpha$  blocker therapy compared with 3 to 6 months with 5ARIs. This understanding led several authors to investigate the impact on symptom control of  $\alpha$  blocker withdrawal after initial combination treatment. In a study conducted by Baldwin et al,<sup>31</sup> 272 men with prostate glands >40 g and with AUA scores >20 were treated with a 5ARI (finasteride) and an  $\alpha$  blocker (doxazosin) in combination. Doxazosin was discontinued at 3, 6, 9, or 12 months, while continuing finasteride, and patients were re-evaluated 1 month after  $\alpha$  blocker discontinuation. Symptom control was most likely to be maintained in patients who discontinued doxazosin at month 9 or 12; the authors concluded that  $\alpha$  blocker therapy could be successfully discontinued

at 9 months or later in patients initially treated with doxazosin and finasteride.

A second study was conducted utilizing dutasteride in combination with the alpha blocker tamsulosin.<sup>32</sup> This multinational, multicenter trial included 327 men with moderate-to-severe symptoms (IPSS  $\geq 12$ ) and prostate volumes  $\geq 30$  cc. Patients underwent 24 weeks of combined therapy, followed by a 12-week double-blind phase in which they were randomly assigned to continued dual therapy or dutasteride monotherapy plus an alpha blocker placebo. The primary end point was the percentage of patients experiencing improvement or no change in symptoms between weeks 24 and 30. Overall, 77% of participants who had alpha blocker therapy withdrawn reported feeling the same or better at week 30 than they did at week 24 compared with 91% of those who continued dual therapy. In the alpha blocker discontinuation group, 84% of those with IPSS  $< 20$  at baseline had no deterioration in symptom control compared with 57.5% of those with IPSS  $\geq 20$  at baseline. The authors concluded that in a majority of patients treated with combination therapy (dutasteride and tamsulosin), the alpha blocker can be successfully discontinued after 6 months of combination treatment, but that patients with severe symptoms may benefit from longer-term combination treatment.

Differences between these 2 studies in the timing of successful alpha blocker discontinuation may be explained by the characteristics of dutasteride versus finasteride. Both 5ARIs work by inhibiting 5-alpha reductase; however, dutasteride inhibits both the type-1 and type-2 isozymes of 5-alpha reductase, whereas finasteride inhibits only type 2. Consistent with these distinct mechanisms, suppression of serum DHT has been shown to be significantly greater with dutasteride than with finasteride.<sup>33</sup> Furthermore, a recent nonrandomized comparative study demonstrated that a significantly greater percentage of dutasteride-treated patients experienced symptom improvement at 3 months compared with finasteride-treated patients.<sup>34</sup>

These data may indicate that earlier symptom control allows for earlier alpha blocker withdrawal in patients receiving combination therapy with dutasteride versus finasteride. Moreover, based on serum DHT results, it has been hypothesized that

more prostate volume reduction may occur with dutasteride, and that this could translate to lower AUR and surgery rates.

Beyond traditional treatment approaches with alpha blockers and/or 5ARIs, new concepts in medical therapy are emerging to include use of an alpha blocker together with an antimuscarinic agent to help men suffering from irritative or storage symptoms.<sup>35</sup> In addition, the use of phosphodiesterase type 5 inhibitors are being explored in the medical therapy of BPH.<sup>36</sup>

This supplement is intended to assist managed care formulary decision makers in evaluating key clinical and economic data which could differentiate dutasteride and finasteride. The following 3 analyses used data from a naturalistic, managed care environment to answer some important practical questions and raise some important issues beyond drug cost.

The first article in the series is a real-world comparison of dutasteride and finasteride with respect to AUR and surgery attenuation rates. The second article investigates differences in time to discontinuation of alpha blockers when these agents are initially used in combination with dutasteride or finasteride. The final article in the series evaluates economic differences in medical cost between patients initiating 5ARI therapy.

Efforts focused on optimizing the use of our current knowledge in the management of EP will likely result in improved outcomes and potential reduction in healthcare resource utilization. In the years ahead, the expected growth of the older male population will continue to place a spotlight on this men's health issue for managed care organizations and healthcare providers, especially considering new Medicare Part D drug benefit changes.

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