The Economic Impact of Delaying 5-Alpha Reductase Inhibitor Therapy in Men Receiving Treatment for Symptomatic Benign Prostatic Hyperplasia

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Background: Pharmacologic treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia often includes alpha-blockers and 5-alpha reductase inhibitors. Many clinicians use alpha-blockers for rapid symptom control, later adding 5-alpha reductase inhibitors to modify long-term disease progression. Delaying the addition of these medications has been shown to result in reduced clinical outcomes. The economic impact of this practice has not been widely studied or reported to date.

Objective: The objective of this study was to assess the economic impact of delaying initiation of concomitant 5-alpha reductase inhibitor therapy (≥30 days) in patients receiving alpha-blockers for lower urinary tract symptoms.

Methods: Using 2 nationally representative databases (Integrated Health Care Information Solutions and PharMetrics), 2 retrospective analyses were conducted involving 2636 and 4260 men, respectively, aged ≥50 years treated for benign prostatic hyperplasia between 2000 and 2007. Economic outcomes (ie, the cost of therapy and the use of healthcare resources) were compared for adding 5-alpha reductase inhibitor therapy early (within <30 days of initiating an alpha-blocker) versus delaying these medications (≥30 days after initiating an alpha-blocker).

Results: In the Integrated Health Care Information Solutions analysis, patients in the early add-on therapy group (n = 1572) had lower benign prostatic hyperplasia–related medical costs in the posttreatment period than those in the delayed-therapy group (n = 1064), $349 versus $618 (P < .0001). Similar trends were seen in the PharMetrics analysis—the medical costs in the early add-on therapy group (n = 2604) and delayed group (n = 1656) were $344 versus $449, respectively (P < .001). Pharmacy costs were $1068 for the early-treatment cohort and $989 for the delayed-treatment cohort for the Integrated Health Care Information Solutions database, yielding total costs of $1417 and $1606, respectively, for a $189 savings per patient over the initial year of treatment (P < .0001). In the PharMetrics analysis, pharmacy costs were $1391 for the early-treatment cohort and $1237 for the delayed-treatment cohort, resulting in total cost of $1735 and $1686, respectively, yielding $59 in additional costs per patient annually for those treated early (P = .8645).

Conclusion: These results suggest that patients receiving 5-alpha reductase inhibitor therapy within 30 days after initiating alpha-blocker treatment have lower benign prostatic hyperplasia–related medical costs than those who start combination treatment later. The increase in pharmacy costs associated with early initiation of 5-alpha reductase inhibitor therapy resulted in total costs that were similar or significantly lower than those of delayed combination users.
Benign prostatic hyperplasia (BPH), also known as enlarged prostate, is a significant health problem among aging men. It affects approximately 50% of American men aged 51 to 60 years, 70% of men aged 61 to 70 years, and 90% of men aged 81 to 90 years. The burden of BPH on the US healthcare system is expected to grow even further as the population of men aged ≥65 years increases from 17 million in 2010 to approximately 30 million by 2030.

The clinical burden of BPH includes lower urinary tract symptoms, including frequency, urgency, nocturia, decreased or intermittent force of stream, and incomplete bladder emptying. Complications from BPH may include acute urinary retention (AUR), impaired bladder emptying, or the need for prostate surgery. Beyond the clinical burden imposed by BPH, the condition also carries a substantial economic burden.

Direct and indirect costs to the private sector related to BPH treatment are estimated to be $3.9 billion annually. In 2000, approximately 4.5 million individual visits were made to physician offices for a primary diagnosis of BPH, and an additional 3.5 million visits for a secondary diagnosis of BPH. The direct costs of medical services provided at hospital inpatient and outpatient settings, emergency departments, and physician offices to treat BPH in the United States in 2000 were estimated to be approximately $1.1 billion. Furthermore, the treatment of men with BPH places a significant burden on patients and their employers through direct medical costs and lost work time.

Current treatment options for BPH include watchful waiting, pharmacologic therapy, minimally invasive procedures, and prostate surgery. In most cases, first-line therapy is pharmacologic treatment with alpha-blockers and/or 5-alpha reductase inhibitors in men with bothersome lower urinary tract symptoms.

Alpha-blockers rapidly improve urinary symptoms but do not affect prostate size. In contrast, 5-alpha reductase inhibitors shrink the prostate and decrease the risk of progression to AUR and prostate surgery. There is typically a 4- to 6-month delay from the start of 5-alpha reductase inhibitor therapy to the onset of clinical improvement. Of note, although the American Urological Association (AUA) guidelines on management of BPH recognize the distinction of 5-alpha reductase inhibitors to reduce the incidence of AUR and surgeries compared with alpha-blockers, these guidelines do not offer a decision tree of when to advance which treatment in their diagnosis and treatment algorithm.

Previous studies have demonstrated that combining 5-alpha reductase inhibitor and alpha-blocker therapies is more effective at reducing the risk of overall clinical progression—defined as worsening in the AUA symptom score of 4 points or more, AUR, urinary incontinence, renal insufficiency, or recurrent urinary tract infection—than monotherapy with either agent alone. These results demonstrated significant differences in favor of combination therapy in men with bothersome symptoms of BPH at baseline and a confirmed enlarged prostate.

A recent study demonstrated that delaying 5-alpha reductase inhibitor therapy in men receiving an alpha-blocker was associated with an increased rate of clinical progression (defined as occurrence of AUR- or BPH-related surgery). Although that study documented the clinical consequences of delaying 5-alpha reductase inhibitor therapy, the economic impact was not investigated.

KEY POINTS

- Benign prostatic hyperplasia is associated with a significant economic burden, with direct and indirect private-sector costs estimated at $3.9 billion annually.
- The expected growth in the numbers of older men in the next 2 decades is bound to add to the clinical and economic burden of this condition, which affects a majority of men aged ≥70 years.
- The most common pharmacologic strategy is initiating alpha-blocker therapy and then adding 5-alpha reductase inhibitors. Previous studies show that delaying the addition of 5-alpha reductase inhibitors is negatively affecting clinical outcomes.
- This retrospective analysis is the first US-based study to distinctly quantify the real-world economic implications of 5-alpha reductase inhibitor timing by comparing the cost of adding 5-alpha reductase inhibitor therapy to alpha-blocker therapy early (≤30 days from initiating alpha-blocker therapy) and late (≥30 days) for men in a managed care population.
- Patients who had delayed 5-alpha reductase inhibitor therapy for >30 days incurred from $105 to $269 greater costs in months 6 through 12 than men who started combination therapy ≤30 days after initiating therapy with alpha-blockers.
men receiving alpha-blockers and early 5-alpha reductase inhibitor therapy versus delayed 5-alpha reductase inhibitor therapy in a managed care population.

Methods

Data Sources

Patients were identified from 2 databases—(1) the Integrated Health Care Information Solutions (IHCIS) National Managed Care Benchmark Database (Waltham, MA), containing medical, pharmacy, and enrollment data for more than 30 million lives, and (2) the PharMetrics Integrated Medical and Pharmaceutical Database, containing data from more than 90 different managed healthcare plans, encompassing more than 52 million lives.

Study Design

This analysis was an observational retrospective cohort study and included patients who were eligible for medical and pharmacy services within those 2 databases, using data from January 1, 2000, through December 31, 2007. This period allowed for a sufficient number of patients to be enrolled in the study based on the selection criteria.

The index date was defined as the date of the first fill for an alpha-blocker prescription. Patients had to be eligible for services at least 6 months before and 12 months after the index date. The 6-month preindex period (the preperiod) was used to assess the baseline characteristics of patients that might be associated with treatment initiation. The 5-month period after the index date was designated as the periperiod, for which outcomes were not assessed. The 7-month period after the periperiod was the time frame within which outcomes were assessed. The postindex period included the 12-month period after the index date, including the periperiod and the outcomes assessment period (Figure 1).

Study Population

Men aged ≥50 years between January 1, 2000, and December 31, 2006, within the IHCIS and PharMetrics databases were eligible for study inclusion. The men had been diagnosed and treated for BPH with an alpha-blocker and a concomitant 5-alpha reductase inhibitor within 6 months of starting alpha-blocker therapy. Men were not included if they had been diagnosed with prostate or bladder cancer, used finasteride 1-mg tablets (for treatment of male-pattern baldness), had a history of prostate surgery, or used 5-alpha reductase inhibitor therapy before initiating alpha-blocker therapy. Inclusion and exclusion International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes are shown in Table 1 (page 158).

Outcomes

The primary outcome was total healthcare costs and utilization associated with BPH after initiation of treatment. All costs related to BPH, defined by the dollars charged on medical claims with a primary ICD-9-CM code of 222.2 or 600.xx during the postindex period, were calculated. However, because 5-alpha reductase inhibitors take 4 to 5 months to affect the prostate, it was assumed that BPH-related costs before this interval would not be avoided by 5-alpha reductase inhibitor therapy. Therefore, only BPH-related medical costs occurring after 150 days of therapy were evaluated (a 150-day “clean” period). BPH-related pharmacy costs were assessed over the entire 1-year follow-up, because patients must initiate therapy at day 1 to avoid all future costs. Therefore, this analysis included the incremental reduction in medical costs and utilization that are offset by the incremental increase in pharmacy costs.

Outcomes were compared between patients who started concomitant 5-alpha reductase inhibitor therapy within 30 days after initiation of alpha-blocker therapy (ie, early group) and those who started it after 30 days but within 180 days of alpha-blocker therapy (ie, delayed group). In the delayed group, outcomes were compared for every 30-day delay. Resource utilization costs (ie, cost
of BPH-related surgery and AUR events) were similarly compared between the early and delayed groups.

Component BPH-related healthcare costs were categorized as inpatient and outpatient and included outpatient hospitalizations, emergency department, physician, laboratory, and other ancillary costs.

**Statistical Analysis**

Ordinary least-squares regression models were used to estimate and compare mean healthcare costs and utilization between treatment cohorts, utilizing the following preindex baseline covariates: the presence of AUR, BPH stage, Charlson comorbidity index, age, number of unique diagnosis codes, number of unique non–BPH-related classes of prescriptions filled, and the presence of at least 1 urologist visit (specialty care).

For BPH stage (Table 2), each patient was categorized into 1 of the 7 disease-severity stages based on the presence of ICD-9-CM codes in the 6-month period before the index date. The Charlson comorbidity index was used to assess comorbidities. This index encompasses 19 medical conditions, each assigned a weight ranging from 1 to 6. The possible total scores range from 0 to 37; the higher the score, the more severe the burden of comorbidity.14

Differences in background covariates across treatment cohorts were assessed by t-test when data were continuous in nature, and with chi-square test when data were categorical. Analyses were conducted using SAS Version 9.1.3 (SAS Institute, Cary, NC) with an a priori significance level of $\alpha = .05$.

**Results**

A total of 2636 patients were identified from the IHCIS database and 4260 from the PharMetrics database. The early group (started on a 5-alpha reductase inhibitor within 30 days of an alpha-blocker initiation) comprised 59.6% of patients in the IHCIS database and 61.1% of those in the PharMetrics database. In the IHCIS delayed cohort, 30% of patients started 5-alpha reductase inhibitor therapy between 31 and 60 days, 21.3% between 61 and 90 days, 17.3% between 91 and 120 days, 15.3% between 121 and 150 days, and 16.1% between 151 and 180 days.

Similarly, in the PharMetrics analysis, 27.0% of patients in the delayed cohort started 5-alpha reductase inhibitor therapy between days 31 and 60, 22.6% between days 61 and 90, 20.1% between days 91 and 120, 16.2% between days 121 and 150, and 14.1% between days 151 and 180. In both databases, patients in the early cohort had more comorbidity during the preperiod (measured by the Charlson comorbidity index) and more severe disease (measured by BPH stage and the presence of AUR at baseline) than those in the delayed group (started on a 5-alpha reductase inhibitor on days 31-180 of an alpha-blocker) as shown in Table 3.

**Resource Utilization**

Naslund and colleagues previously reported that in the IHCIS database, patients in the late cohort were significantly more likely to have clinical progression (19.0% vs 11.2%, odds ratio [OR] = 1.857; $P < .0001$), significantly more likely to have AUR (13.2% vs 8.1%, OR = 1.709; $P < .0001$), and significantly more likely to have BPH-related surgery (9.5% vs 4.8%, OR = 2.083; $P < .0001$) compared with patients initiating 5-alpha reductase inhibitor therapy early.11 In the PharMetrics database, patients in the late cohort were significantly more likely to experience clinical progression (14.0% vs 10.2%, OR = 1.435; $P = .0002$), significantly more likely to have AUR (10.0% vs 7.0%, OR = 1.472; $P = .0006$), and more likely to have BPH-related surgery (6.3% vs 5.0%, OR = 1.282; $P = .0699$).

**BPH-Related Medical and Pharmacy Costs**

BPH-related medical costs were lower in each of the early groups compared with the delayed groups in both databases (Table 4). Furthermore, these costs were primarily composed of outpatient charges (Figure 2, page 160).

In the IHCIS database, every 30-day delay in starting 5-alpha reductase inhibitor therapy resulted in an average 25.1% increase in medical costs ($P < .0001$); in the PharMetrics database, every 30-day delay in starting 5-alpha reductase inhibitor therapy resulted in an average 13% increase in medical costs ($P < .0001$).

In the IHCIS analysis, pharmacy costs per person for the initial year of pharmacologic treatment of BPH were $1068 for the early cohort and $989 for the delayed
cohort, yielding total costs of $1417 for the early cohort and $1606 for the delayed cohort, or $189 per-patient savings ($P < .0001) for those in the early cohort over their initial year of treatment. In the PharMetrics analysis, pharmacy costs were $1391 for the early cohort and $1237 for the delayed cohort, meaning that total cost for the early cohort was $1735 and that for the delayed cohort was $1686, yielding $59 in additional costs per patient annually for those treated early ($P = .8645).

Discussion

The clinical benefits of combination therapy with 5-alpha reductase inhibitors and alpha-blockers for BPH have been established in clinical trials. The Medical Therapy of Prostatic Symptoms study demonstrated greater symptom improvement with the combination of an alpha-blocker plus a 5-alpha reductase inhibitor compared with an alpha-blocker or a 5-alpha reductase inhibitor as monotherapy, as well as reductions in AUR- and BPH-related surgery, which were similar to the 5-alpha reductase inhibitor monotherapy.10 The Combina
tion of Avodart and Tamsulosin study also showed greater reductions and improvement of symptoms with combination therapy versus either monotherapy.11,12

Table 3 Demographic Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>IHCIS Early group (n = 1572)</th>
<th>IHCIS Delayed group (n = 1064)</th>
<th>P</th>
<th>PharMetrics Early group (n = 2604)</th>
<th>PharMetrics Delayed group (n = 1656)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>65.5</td>
<td>64.3</td>
<td>.0003</td>
<td>66.0</td>
<td>65.2</td>
<td>.1580</td>
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<tr>
<td>Charlson comorbidity index</td>
<td>1.04</td>
<td>0.77</td>
<td>&lt;.0001</td>
<td>0.99</td>
<td>0.84</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Count of comorbid diagnosis codes</td>
<td>9.4</td>
<td>8.2</td>
<td>&lt;.0001</td>
<td>9.0</td>
<td>8.5</td>
<td>.0003</td>
</tr>
<tr>
<td>Count of comorbid prescriptions filled</td>
<td>4.6</td>
<td>4.7</td>
<td>.7356</td>
<td>4.6</td>
<td>4.5</td>
<td>.4477</td>
</tr>
<tr>
<td>BPH stage</td>
<td>0.63</td>
<td>0.47</td>
<td>&lt;.0001</td>
<td>0.52</td>
<td>0.37</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>AUR, %</td>
<td>21.1</td>
<td>11.4</td>
<td>&lt;.0001</td>
<td>18.5</td>
<td>11.2</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Specialty care, %</td>
<td>20.8</td>
<td>20.1</td>
<td>.6676</td>
<td>55.1</td>
<td>39.6</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Preperiod BPH-related medical costs, $</td>
<td>192</td>
<td>103</td>
<td>.0002</td>
<td>408</td>
<td>136</td>
<td>.0009</td>
</tr>
</tbody>
</table>

AUR indicates acute urinary retention; BPH, benign prostatic hyperplasia; IHCIS, Integrated Health Care Information Solutions.

Table 4 Medical, Pharmacy, and Total Costs

<table>
<thead>
<tr>
<th>Cost</th>
<th>IHCIS Early group (n = 1572), $</th>
<th>IHCIS Delayed group (n = 1064), $</th>
<th>P</th>
<th>PharMetrics Early group (n = 2604), $</th>
<th>PharMetrics Delayed group (n = 1656), $</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical</td>
<td>349</td>
<td>618</td>
<td>&lt;.0001</td>
<td>344</td>
<td>449</td>
<td>&lt;.0001</td>
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<tr>
<td>Pharmacy</td>
<td>1068</td>
<td>989</td>
<td>.0006</td>
<td>1391</td>
<td>1237</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Total</td>
<td>1417</td>
<td>1606</td>
<td>&lt;.0001</td>
<td>1735</td>
<td>1686</td>
<td>.8645</td>
</tr>
</tbody>
</table>

IHCIS indicates Integrated Health Care Information Solutions.
because many patients are excluded from clinical trials if they fail to meet entry criteria, and patients who participate in clinical trials may not be representative of patients who present to a physician for treatment.

The recent managed care database study by Naslund and colleagues showed that in a real-world setting, a delay in treating a patient with a 5-alpha reductase inhibitor may increase the risk for BPH progression. The present study expands on this assessment by comparing the economic consequences associated with a delay in 5-alpha reductase inhibitor therapy.

The results of the current analysis indicate that a patient who received delayed 5-alpha reductase inhibitor therapy incurred from $105 to $269 more annually in BPH-related medical costs than a patient who received early combination therapy.

This finding is important, because it distinctly quantifies the real-world economic implications of 5-alpha reductase inhibitor timing. McDonald and colleagues also highlighted the cost-effectiveness of combined therapy by showing that the timing—early combination therapy—is a key factor for achieving optimal clinical benefit. This assessment is from a Canadian study based on clinical trial results; however, the results are similar to the findings of this present study.

In recent years, there has been a gradual shift in the management of chronic and progressive conditions from only symptomatic management to also managing the underlying disease to decrease the risk for long-term negative outcomes. This has been especially pertinent to the management of BPH, a chronic and progressive condition.

With these considerations in mind, the present study quantifies the incremental clinical and economic benefits of early combination medical therapy for BPH from a medical and pharmacy perspective. In the IHCIS analysis, even when adding in the additional pharmacy costs of early 5-alpha reductase inhibitor therapy, the study results favored early 5-alpha reductase inhibitor initiation, with a net difference ranging from a savings of $189 per patient to no significant differences between groups (P = .8645). Alternatively, in the PharMetrics analysis, the reduction in medical costs with early therapy was not entirely outweighed by the additional pharmacy spending for the early group ($49 higher total costs in the early group; P = .8645).

Limitations

Any retrospective database analysis has inherent limitations, such as the influence of selection bias and limited generalizability. The methods in this study attempted to minimize selection bias by controlling for differences in background covariates. However, based on background covariates, patients initiating 5-alpha reductase inhibitor therapy earlier were in worse condition in terms of comorbidity and previous complications arising from BPH. Even with the increased severity, the analysis showed that the early treatment group had lower costs.

Also, the study population is comprised of patients enrolled in commercial plans; therefore, the results should not be generalized to other populations, such as Medicaid or Medicare enrollees. With the availability of generic finasteride, generic tamsulosin, and a branded fixed-dose combination of dutasteride and tamsulosin (Jalyn) in the US marketplace, decision makers should evaluate the anticipated pharmacy costs in relation to medical cost differences demonstrated in this study.

This study showed consistent reductions in medical costs with earlier dual pharmacologic therapy in 2 different databases. However, the medical spending represents only one half of the total spending, and the pharmacy spending represents the other half. This study demonstrates that differences that range from cost-savings to cost-neutrality can result in the total spending (ie, medical and pharmacy costs) when both components are considered. The pharmacy costs evaluated in this study, however, are limited to the costs of the batch of branded and generic agents available for treatment in the 5-alpha reductase inhibitor and alpha-blocker classes at the time of the analysis. The study conclusions are drawn on class-effect level; the effect of unique combinations of specific 5-alpha reductase inhibitors and alpha-blockers was not assessed in this study.

Treatment for BPH may be a lifelong proposition. The length of follow-up in the current study did not
examine the long-term economic outcomes of various treatment regimens. This is an area for future study.

Conclusion

Early combined therapy with an alpha-blocker and a 5-alpha reductase inhibitor results in direct medical cost-savings compared with alpha-blocker therapy followed with delayed (≥30 days) therapy with 5-alpha reductase inhibitors. The increase in pharmacy costs associated with early initiation of 5-alpha reductase inhibitor therapy resulted in total costs that were similar to or significantly lower than those of delayed combination users. The balance between lower medical spending related to fewer AUR- and prostate-related surgeries in men with BPH treated early with an alpha-blocker and a 5-alpha reductase inhibitor versus delayed addition of a 5-alpha reductase inhibitor to baseline alpha-blocker therapy, as well as the pharmacy spending for these medical treatments may attract increasing attention, especially with emerging generic medications and a new fixed-dose combination medication.

Acknowledgment

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Author Disclosure Statement

Dr Naslund is a Consultant and Speaker for GlaxoSmithKline; Drs Eaddy, Kruep, and Shah are Consultants for GlaxoSmithKline; Dr Hogue is a former employee of GlaxoSmithKline.

References

with enlarged prostates, initiating therapy with a combination medication is recommended.

In the present study, Naslund and colleagues suggest lower medical costs associated with the initiation of combination rather than single-agent therapy. Based on the available medical literature, combination therapy has a greater effect in men with severe symptoms and moderate-to-large prostates. From a drug benefit management perspective, it is difficult for a health plan or other payers to determine the optimal timing for using therapy with a single drug versus combination agents; optimal timing also does not warrant the payer's resources to place step-therapy edits, particularly for generic-based combination therapy.

**PATIENTS:** The question of initiating single- or combination-drug therapy for men with BPH should be mutually agreed on by the patient and the provider. It is a good thing for patients that a generic 5-alpha reductase inhibitor is available when an initial combination therapy is chosen, or when adequate response is not obtained with a generic alpha-antagonist that is used as an initial single-drug therapy. Even without prescription coverage, the combined monthly cost for tamsulosin or finasteride is less than $35. These are great options for patients that can be tried first, before embarking on brand-name therapies.


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