Adherence to 5-Alpha Reductase Inhibitor Therapy For Benign Prostatic Hyperplasia
Clinical and Economic Outcomes

Stephen Gruschkus, PhD, MPH; Sara Poston, PharmD; Michael Eaddy, PharmD, PhD; and Sham Chaudhari, MS, PharmB

ABSTRACT

Objective: Our goal was to quantify relationships between adherence to 5-alpha reductase inhibitors (5-ARIs), the risk of acute urinary retention (AUR) and prostate surgery, and medical costs related to patients with benign prostatic hyperplasia (BPH).

Methods: Claims recorded over a period of 6.5 years in a nationwide managed care database were analyzed. We conducted time-to-event multivariate analysis to evaluate relationships between adherence (medication possession ratio [MPR] thresholds of 70% or higher, 75% or higher, and 80% or higher), persistence (length of therapy), and the risk of AUR and surgery. We compared mean monthly BPH-related medical costs in patients with MPRs at or above thresholds and those with MPRs below thresholds and determined changes in BPH-related costs associated with 30-day increments of therapy.

Results: In AUR analyses (N = 17,293), meeting or exceeding MPR thresholds was associated with a reduced likelihood of AUR for 70% (hazard ratio [HR], 0.380), 75% (HR, 0.613), and 80% (HR, 0.519) (P < 0.05 for all). In prostate surgery analyses (N = 17,739), the likelihood of surgery was reduced with MPR thresholds of 70% or above (HR, 0.294), 75% or above (HR, 0.542), and 80% or above (HR, 0.436) (P < 0.05 for all). A longer duration of therapy was associated with a reduced likelihood of AUR (HR, 0.860) and surgery (HR, 0.884) (P < 0.05 for both). In both populations, adherence and persistence were also associated with significantly decreased BPH-related medical costs.

Conclusion: In patients with BPH who received 5-ARI therapy, greater adherence and persistence were associated with significantly reduced risks of AUR and prostate surgery and with significantly lower medical costs. Maximizing adherence may enable patients to realize the potential long-term benefits of 5ARIs.

Key words: benign prostatic hyperplasia, 5-alpha reductase inhibitors, adherence, acute urinary retention, prostate surgery, pharmacoeconomics

INTRODUCTION

Benign prostatic hyperplasia (BPH) is very common in aging men, with an estimated prevalence exceeding 50% among those older than 60 years of age and as high as 80% by age 80. Although symptom relief remains a major goal of medical intervention, recent American Urological Association (AUA) guidelines highlight the importance of medical therapy to prevent disease progression and the need for surgery in high-risk patients.

As a result of the complex pathophysiology of BPH, multiple targets for therapy are available, allowing for medical options with varying mechanisms of action. The latest BPH treatment guidelines include two drug classes:

Alpha blockers (ABs) provide rapid improvement in urinary flow rate and symptoms but do not prevent progressive prostate enlargement. Examples of ABs include silodosin (Rapaflo, Watson) and tamsulosin (Flomax, Boehringer Ingelheim).

By contrast, 5-alpha reductase inhibitors (5-ARIs) shrink the prostate, reduce risks of acute urinary retention (AUR) and invasive procedures, and produce durable symptom improvement. However, the onset of symptom relief with 5-ARIs may take 3 to 6 months. Examples of 5-ARIs include dutasteride (Avodart, GlaxoSmithKline) and finasteride (Proscar, Merck).

Clinical trials have investigated the complementary benefits of these drug classes. Compared with monotherapy with either agent, combination 5-ARI/AB therapy has demonstrated reduced rates of clinical progression, lower risks of complications than with ABs alone, and improved quality of life for patients. A problem common with chronic pharmacotherapy is suboptimal adherence. Although data in BPH are limited, studies in the U.S. and Europe have found low adherence rates of 70% or less. In one study, nearly 25% of patients discontinued therapy early, citing persistent symptoms as a common reason. The 5-ARIs have shown in a reduced risk of AUR and surgery; however, nonadherence may have implications for development of these complications.

The purpose of our claims-based study was to quantify the relationships between 5-ARI adherence and persistence and the likelihood of AUR and prostate surgery, as well as corresponding BPH-related costs, among patients who were prescribed 5-ARIs for BPH.

METHODS
Study Design

We retrospectively analyzed medical and pharmacy claims recorded in the Integrated Healthcare Information Services (Ingenix) database. This nationally representative managed care database comprises more than 30 health plans and includes more than 25 million individuals. Data spanned the period from August 1, 2006, to July 31, 2012.

Disclosure: Dr. Gruschkus, Dr. Eaddy, and Mr. Chaudhari are employees of Xcenda, a consultant to GlaxoSmithKline, which sponsored the study in which the data from the manuscript were derived. Dr. Poston is an employee of GlaxoSmithKline.

Analyses were conducted to evaluate the relationships between adherence to 5-ARI therapy and AUR, prostate surgery, and BPH-related costs. We analyzed these outcomes separately using a model in which the length of treatment was truncated at 1 year for patients who had been treated for more than 1 year but who had not experienced an outcome.

**Patient Sample Selection**

Our study consisted of records from all patients with BPH (50 years of age or older at diagnosis), as indicated by the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) code on claims (i.e., 222.2x or 600.xx). Patients with a diagnosis of prostate cancer or bladder cancer were excluded from the study.

Patients were included if they met the following criteria: (1) 60 days or more of 5-ARI use during the observation period; (2) 6 months of more of continuous health plan enrollment before the first dispensing of 5-ARIs; (3) 6 months or more of continuous health plan enrollment following use of the first 5-ARI; and (4) no prostate surgery before use of the first 5-ARI. Baseline characteristics included:

1. age.
2. a previous occurrence of AUR.
3. the initial use of an AB before the first use of a 5-ARI.
4. the Charlson comorbidity index.
5. Thomson Medstat enlarged prostate (EP) stage. In this ICD-9-CM staging system, BPH alone is coded as 1.1; BPH plus urinary tract infection is coded as 1.2; and an ascending number of codes are used for BPH with bladder neck obstruction, hydronephrosis, or other complications. In our analysis, EP stage was dichotomous (1.2 or higher represented complicated EP; below 1.2 represented uncomplicated EP).
6. BPH-related costs.
7. occurrence of kidney, ureter, bladder, or unspecified urinary calculi (ICD-9-CM codes 592.0, 592.1, 592.9, or 594.1, respectively).
8. occurrence of hematuria (ICD-9-CM code 599.7).
9. visits to a urologist.

**Operational Terms and Study Outcomes**

The study period encompassed the 6.5 years from January 1, 2000 to June 30, 2006. For each patient, the first 5-ARI dispensing date was designated as the index date. Patients were those with an index date during the 5-year enrollment period (July 1, 2000–June 30, 2005) to enable analysis from 6 months prior to 12 months after the index date. The 6-month pre-index period described the baseline characteristics. The observation period extended from the index date to the earliest date of AUR (for the AUR analysis), prostate surgery (for the surgery analysis), the last 5-ARI dispensing, or 12 months.

Adherence was reflected by the medication possession ratio (MPR), defined as the total number of days of 5-ARI therapy, divided by the number of days from the first dispensed 5-ARI, to the last day covered by the last prescription. To evaluate the association between adherence and outcomes, we classified patients according to whether they met or surpassed MPR thresholds of 70%, 75%, and 80%.

We calculated persistence with therapy from the index date to the last day covered by the last prescription before discontinuation of therapy, which was defined by a lapse of 30 days or more without medication.

AUR was defined by ICD-9-CM code 599.6x, 788.20, or 788.29. Prostate surgery was defined by use of any of 26 Current Procedural Terminology, 4th edition (CPT-4) codes (Table 1).

The outcome date corresponded to the first medical encounter

---

**Table 1 Current Procedural Terminology Codes for Prostate Surgery Procedures**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>52450</td>
<td>Incision of prostate</td>
<td>55801</td>
<td>Removal of prostate, perineal</td>
</tr>
<tr>
<td>52510</td>
<td>Balloon dilation of prostatic urethra</td>
<td>55810</td>
<td>Radical removal of prostate</td>
</tr>
<tr>
<td>52601</td>
<td>Removal of prostate (TURP)</td>
<td>55812</td>
<td>Radical removal of prostate with biopsy</td>
</tr>
<tr>
<td>52612</td>
<td>Removal of prostate, first stage</td>
<td>55815</td>
<td>Radical removal of prostate with nodes</td>
</tr>
<tr>
<td>52614</td>
<td>Removal of prostate, second stage</td>
<td>55821</td>
<td>Removal of prostate, suprapubic</td>
</tr>
<tr>
<td>52620</td>
<td>Removal of prostate, residual</td>
<td>55831</td>
<td>Removal of prostate, retropubic</td>
</tr>
<tr>
<td>52630</td>
<td>Removal of prostate tissue regrowth</td>
<td>55840</td>
<td>Radical removal of prostate</td>
</tr>
<tr>
<td>52640</td>
<td>Relief of bladder neck contracture</td>
<td>55842</td>
<td>Radical removal of prostate with biopsy</td>
</tr>
<tr>
<td>52647</td>
<td>Prostate laser surgery non-contact</td>
<td>55845</td>
<td>Radical removal prostate with nodes</td>
</tr>
<tr>
<td>52648</td>
<td>Prostate laser surgery contact</td>
<td>55849</td>
<td>Needle/catheter placement of prostate</td>
</tr>
<tr>
<td>53850</td>
<td>Transurethral destruction of prostate tissue with microwave thermotherapy</td>
<td>55860</td>
<td>Exposure of prostate for radioactive substance</td>
</tr>
<tr>
<td>53852</td>
<td>Transurethral destruction of prostate tissue with radiofrequency thermotherapy</td>
<td>55865</td>
<td>Exposure of prostate for radioactive substance</td>
</tr>
<tr>
<td>53853</td>
<td>Transurethral destruction of prostate tissue with water-induced thermotherapy</td>
<td>55873</td>
<td>Cryosurgical ablation of prostate</td>
</tr>
</tbody>
</table>
for a given outcome.

BPH-related medical costs were defined as those associated with any claim having a primary ICD-9-CM code of 222.2 or 600.xx.

**Statistical Analysis**

For MPR and persistence analyses, we used multivariate Cox proportional hazards models to evaluate the likelihood of AUR or prostate surgery after controlling for baseline characteristics (see Patient Sample Selection earlier). In addition to hazard ratios (HRs) and associated 95% confidence intervals (CIs) for independent variables and covariates, survival distributions for policy-relevant levels of medication adherence were calculated to demonstrate the impact of varying degrees of adherence.

For MPR threshold analyses, we compared survival distributions for patients at or above each threshold value with those below the threshold. For persistence analyses, we calculated survival distributions for mean values of 30 days, 90 days, 150 days, 180 days, 240 days, 300 days, and 365 days.

For all analyses, patients who had a given outcome within 90 days of the index date were excluded. For instance, a patient who had AUR within 90 days of the index date was excluded from the AUR analysis but remained eligible for the surgery analysis. Patients who had surgery within 90 days were excluded from both the AUR and surgery analyses.

To evaluate the relationship between adherence and BPH-related medical costs, we calculated cost differences between patients who met or exceeded MPR thresholds and those who did not. To analyze persistence and costs, we evaluated costs by the number of months that the patient was receiving therapy. Differences in BPH-related medical costs were evaluated with a generalized linear model with a gamma distribution and log-link function. This method has the advantage of directly estimating adjusted log-transformed costs without the need for retransformation.

We conducted statistical analyses using procedures designed by the SAS Institute.

**RESULTS**

We initially identified 70,025 men. After we applied inclusion and exclusion criteria, 17,739 patients were qualified for the surgery analysis and 17,293 were included in the AUR analysis. Baseline characteristics are shown in Table 2. The mean age of the patients was approximately 66 years, and nearly 90% of patients had uncomplicated BPH. More than 91% had received alpha blockers (ABs) prior to study entry.

**Incidence of Outcomes**

Among the 17,293 patients in the AUR analysis, 3,727 (21.6%) experienced AUR. Of the 17,739 patients in the prostate surgery analysis, 812 (4.6%) underwent surgery during this period.

**Adherence and Outcomes**

**Mean Medication Possession Ratios and Thresholds**

The overall mean MPR threshold for patients in the AUR analysis was 69.0% (standard deviation [SD], 20.7; median, 74.0%; range, 16.4%–100%). Of these patients, 55.8% (n = 9,642) had MPRs of 70% or greater; 36.8% (n = 6,364) had MPR thresholds of 75% or greater; and 31.8% (n = 5,506) had MPR thresholds of 80% or greater.

The overall mean MPR threshold for patients in the surgery analysis was 69.6% (SD, 20.7; median, 74.0%, range, 16.4%–100%). In this group, 58.4% (n = 10,353) had MPR thresholds of 70% or higher; 37.4% (n = 6,632) had MPR thresholds of 75% or higher; and 32.6% (n = 5,786) had MPRs of 80% or higher.

**Acute Urinary Retention**

The proportion of patients with AUR differed between those with MPRs at or above the threshold and those with MPRs below the threshold. Among patients with MPR thresholds at

**Table 2 Baseline Sample Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Acute Urinary Retention (N = 17,293)</th>
<th>Prostate Surgery (N = 17,739)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall</td>
<td>MPR ≥70%</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65.8</td>
<td>66.1</td>
</tr>
<tr>
<td>Alpha blocker, prior*</td>
<td>91%</td>
<td>92%</td>
</tr>
<tr>
<td>Acute urinary retention, prior*</td>
<td>18%</td>
<td>18%</td>
</tr>
<tr>
<td>Charlson comorbidity index†</td>
<td>0.90</td>
<td>0.89</td>
</tr>
<tr>
<td>Complicated BPH‡</td>
<td>11%</td>
<td>11%</td>
</tr>
<tr>
<td>Hematuria*</td>
<td>17%</td>
<td>17%</td>
</tr>
<tr>
<td>Kidney/urinary/bladder stones*</td>
<td>4.5%</td>
<td>4.7%</td>
</tr>
<tr>
<td>Urologist visits†</td>
<td>56%</td>
<td>56%</td>
</tr>
<tr>
<td>BPH cost</td>
<td>$252</td>
<td>$252</td>
</tr>
</tbody>
</table>

BPH = benign prostatic hyperplasia; MPR = medication possession ratio.

* Dichotomous variable: 1 = yes; 0 = no.

† Ranges from 0 to 16 with higher values indicate more severe comorbidity status.

‡ Dichotomous variable: 1 = complicated enlarged prostate (defined as stage ≥1.2 per Medstat disease staging criteria); 0 = uncomplicated enlarged prostate.
70% or above, 16.5% (n = 1,587) experienced AUR during the assessment period, compared with 28.0% (n = 2,140) of those with MPR thresholds below 70%.

For the 75% and 80% thresholds, 18.5% of patients (n = 1,176) with MPRs of 75% or above had AUR, compared with 23.3% of those (n = 2,551) with MPRs of less than 75%, whereas 16.6% (n = 915) of patients with MPR thresholds of 80% or higher experienced AUR compared with 23.9% (n = 2,812) of those with MPRs below 80%.

At the 70%, 75%, and 80% MPR thresholds, rates of AUR over observation period days 90 to 365, after we controlled for baseline characteristics, were significantly lower among patients who met or exceeded the MPR threshold compared with those who did not (Figure 1). For all thresholds, survival curves for MPRs at or above the threshold and for those below the threshold were similar until approximately 130 to 140 days. By day 150, however, the curves began to diverge, and they remained divergent through the end of the observation period.

At all MPR thresholds, meeting or exceeding the threshold was associated with a significantly reduced likelihood of AUR (Table 3). For example, at MPR thresholds of 80% or greater, the likelihood of AUR was reduced by nearly half (HR, 0.519; 95% CI, 0.472–0.570; P < 0.05).

At all thresholds, among baseline variables, prior AUR was the strongest predictor for AUR for MPRs of 80% or higher (HR, 2.760; 95% CI, 2.523–3.019; P < 0.05), followed by complicated enlarged prostate (EP) for MPRs of 80% or higher (HR, 1.265; 95% CI, 1.132–1.414; P < 0.05). By contrast, previous AB therapy in all groups was associated with a modestly reduced risk of AUR for MPRs of 80% or greater (HR, 0.845; 95% CI, 0.742–0.964; P < 0.05).

**Prostate Surgery**

The proportion of patients who underwent surgery differed between those meeting or exceeding MPR thresholds and those not meeting MPR thresholds. Of patients with MPR thresholds of 70% or higher, 3.2% (n = 331) had surgery compared with 6.5% (n = 481) of those below this threshold.

For MPR thresholds of 75%, 3.7% of patients (n = 243) at or above the threshold had surgery compared with 5.1% of patients (n = 569) below this threshold.

For MPR thresholds of 80%, 3.2% of patients (n = 185) at or above the threshold had surgery compared with 5.3% of patients (n = 627) below this threshold.

For the MPR thresholds in Figure 2, adjusted rates of surgery were significantly lower among patients who met or exceeded the threshold than those who did not. As with AUR, for all thresholds, the survival curves for patients at or above thresholds and those below were similar until approximately 130 to

![Figure 1](image1.png) **Time to acute urinary retention (AUR) for 70% (A), 75% (B), and 80% (C) medication possession ratio (MPR) thresholds. Asterisk = P < 0.05.**

![Figure 2](image2.png) **Time to prostate surgery for 70% (A), 75% (B), and 80% (C) medication possession ratio (MPR) thresholds. Asterisk = P < 0.05.**

Vol. 37 No. 8 • August 2012 • P&T® 467
140 days; however, the curves began to diverge by day 150 and remained divergent through the end of the observation period.

At all MPR thresholds, meeting or exceeding the threshold was associated with a significantly reduced likelihood of surgery (Table 3). MPR thresholds of 80% or higher were associated with a 56% reduction in surgical risk (HR, 0.436; 95% CI, 0.333–0.570; P < 0.05).

Among baseline variables, the use of specialty care (i.e., a visit to a urologist) was the most important risk factor for surgery at all for MPR thresholds of 80% or higher (HR, 1.969; 95% CI, 1.528–2.537; P < 0.05), followed by complicated enlarged prostate for MPR thresholds of 80% or higher (HR, 1.390; 95% CI, 1.053–1.835; P < 0.05).

At all MPR thresholds, prior AB use was associated with a reduced risk of surgery for MPRs of 80% or higher (HR, 0.711; 95% CI, 0.511–0.990; P < 0.05).

### Persistence and Outcomes

The mean length of therapy was 276.8 days for patients in the AUR analysis (SD, 89.1 days; median, 291 days; range, 91–365 days). The mean length of therapy was 276.8 days for patients in the AUR analysis (SD, 89.1 days; median, 291 days; range, 91–365 days).
5-Alpha Reductase Inhibitors for Benign Prostatic Hyperplasia

days) and 289.5 days for patients in the surgery analysis (SD, 85.1 days; median, 328 days; range, 91–365 days). Adjusted AUR rates during observation days 90 to 365 decreased with an increasing duration of therapy.

Patients discontinuing therapy at 30 days had 1-year AUR rates of 29.15%, whereas AUR rates were 22.15% for 90 days, 16.63% for 150 days, 14.36% for 180 days, 10.65% for 240 days, 7.86% for 300 days, and 5.77% for 1 year. Similarly, 1-year surgery rates decreased as the duration of therapy increased: 30 days, 4.58%; 90 days, 3.54%; 150 days, 2.73%; 180 days, 2.40%; 240 days, 1.85%; 300 days, 1.42%; and 1 year, 1.09%.

Persistence, categorized as an additional 30-day increment of treatment, was significantly associated with a reduced likelihood of AUR (HR, 0.860; 95% CI, 0.852–0.867) and surgery (HR, 0.884; 95% CI, 0.867–0.902) (P < 0.05 for both) (see Table 3). These data indicate that for every additional 30 days that a patient remained on 5-ARI therapy, the likelihood of AUR was reduced by 14% and the likelihood of surgery was reduced by 12%. With respect to associations of baseline variables with risk of AUR or surgery, results of the length of therapy analysis were similar to those of the MPR threshold analyses.

Adherence, Persistence, and Medical Costs

Adherence and Cost

In the AUR and surgery analysis populations, mean monthly BPH-related medical costs per patient were lower among patients who met or exceeded MPR thresholds than among those who did not for all three thresholds (Figure 3).

At the three MPR thresholds, meeting or exceeding the threshold was associated with significantly decreased monthly BPH-related costs after we adjusted for baseline characteristics. In the AUR population, MPRs of 80% or higher were associated with a reduction of approximately 24% in monthly costs (estimate, –0.241; 95% CI, –0.296 to –0.185).

In the surgery population, MPRs of 80% or higher were associated with a reduction of approximately 24% in monthly costs after we adjusted for baseline characteristics. Meeting any of three MPR threshold values was associated with significant and clinically meaningful reductions in the likelihood of complications in BPH. Meeting any of three MPR threshold values was associated with significant and clinically meaningful reductions in the likelihood of complications, as was continuation of therapy. Moreover, our study was the first to demonstrate that adherence and persistence were associated with reduced BPH-related medical costs.

The results underscore the importance of optimal compliance with therapy in patients receiving 5-ARIs in order to maximize the benefits of these medications. However, we could not definitively identify reasons for nonadherence. In an analysis of a population from the Netherlands with newly diagnosed lower urinary tract symptoms, among patients who stopped therapy early and

Persistence and Cost

Length of 5-ARI therapy was associated with significantly reduced mean monthly BPH-related costs per patient in the AUR analysis population (estimate, –0.0165; 95% CI, –0.024 to –0.0089) and surgery analysis population (estimate, –0.0188; 95% CI, –0.0264 to –0.0112) (P < 0.05 for both). Thus, every 30-day increase in length of therapy was associated with an almost 2% reduction in total BPH-related medical costs per month.

DISCUSSION

In our retrospective claims-based study, increased adherence and persistence in patients who received 5-ARIs were associated with a significantly reduced likelihood of AUR and prostate surgery, as well as decreased BPH-related health care costs, including AUR and surgery costs. Reduced rates of AUR and surgery among adherent patients emerged after about 5 months, consistent with the onset of activity of 5-ARIs. Several factors influenced outcomes and costs. Most prominent among these were previous AUR and complicated BPH, with reduced BPH-related medical costs. The results underscore the importance of optimal compliance with therapy in patients receiving 5-ARIs in order to maximize the benefits of these medications. However, we could not definitively identify reasons for nonadherence. In an analysis of a population from the Netherlands with newly diagnosed lower urinary tract symptoms, among patients who stopped therapy early and

Data on adherence and outcomes in BPH were initially reported by Nichol et al., who found that nonadherence over a 2-year period was associated with a significantly increased risk of a BPH-related procedure in their California Medicaid (Medi-Cal) population (odds ratio, 4.17; 95% CI, 2.56–6.79; P ≤ 0.0001). Our study was the first to be designed primarily to examine the influence of medication adherence on risk of complications in BPH. Meeting any of three MPR threshold values was associated with significant and clinically meaningful reductions in the likelihood of complications, as was continuation of therapy. Moreover, our study was the first to demonstrate that adherence and persistence were associated with reduced BPH-related medical costs.

The results underscore the importance of optimal compliance with therapy in patients receiving 5-ARIs in order to maximize the benefits of these medications. However, we could not definitively identify reasons for nonadherence. In an analysis of a population from the Netherlands with newly diagnosed lower urinary tract symptoms, among patients who stopped therapy early and

Figure 3 Monthly BPH-related medical costs by medication possession ratio (MPR) threshold values. AUR = acute urinary retention; BPH = benign prostatic hyperplasia.
whose reasons could be ascertained, adverse events, persistent symptoms, and perceived resolution of symptoms were cited with similar frequency. In the Medi-Cal analysis, factors associated with nonadherence included total number of pre-existing medications and the absence of add-on BPH therapy. Patients starting with ABs were less likely to augment therapy by adding a second agent compared with patients who initially received a 5-ARI. Of note, AB therapy, when initiated prior to 5-ARI therapy, was also associated with reduced risks of AUR and surgery. Given the efficacy of ABs in improving symptoms and the lack of effect in slowing the progression of prostate enlargement, the risk reductions seen may reflect improved adherence to 5-ARIs owing to satisfactory symptom control through AB therapy. Patient perception of the benefit of medication is recognized as an important determinant of adherence. Lack of early response to therapy may be at least as important in premature discontinuation of therapy as side effects are. If a lack of immediate symptom improvement leads to reduced adherence to 5-ARI monotherapy, it would be expected that combination therapy with ABs might alleviate this problem and thus encourage adherence.

Future studies should evaluate whether a fixed-dose combination (a 5-ARI plus an AB) single tablet improves adherence for BPH patients. In studies of other populations with chronic disease (e.g., hypertension or diabetes), fixed-dose combinations have consistently been shown to encourage adherence.

**STUDY LIMITATIONS**

Limitations of our study include those common to retrospective claims-based analyses. Dispensed prescription claims served as a proxy for adherence and persistence, and it was not possible to ascertain the degree to which patients took the drug prescribed for them. Thus, actual adherence might be lower than indicated by the MPRs. However, we aimed to determine the influence of relative improvements in adherence on BPH outcomes, not to quantify absolute adherence rates. Our reported MPRs were consistent with those previously described in other studies.

Although our analysis included covariates on demographics, disease and medical history, comorbidities, and health care utilization, data were not available for other potentially confounding factors (e.g., symptom severity, prostate volume, and prostate-specific antigen levels). For example, persistence of symptoms that were severe at baseline might precipitate confusion of patients having AUR and surgery occurring less than 90 days after treatment initiation aimed to minimize the confounding influence of such baseline factors. Although it is assumed that the delayed onset of 5-ARI clinical activity contributes to nonadherence and discontinuation of therapy, it was beyond the scope of our study to ascertain reasons for or to identify risk factors for discontinuation.

Finally, our conclusions were drawn on the class-effect level. The effect of unique pairings of specific 5-ARIs and ABs should be assessed in future studies.

**CONCLUSION**

In our analysis of patients with BPH who received 5-ARIs, greater adherence (indicated by the medication possession ratio) and persistence (indicated by the time to discontinuation of therapy) were associated with significantly reduced risks of acute urinary retention and prostate surgery. The timing of risk reduction for these complications coincided with the known onset of clinical activity of 5-ARIs. Greater adherence and persistence were also associated with significant reductions in BPH-related medical costs. These data support interventions to maximize adherence to 5-ARI therapy so that patients may realize the potential benefits of long-term treatment with these agents.

**References**