

Differences in Alpha Blocker Usage Among Enlarged Prostate Patients Receiving Combination Therapy with 5ARIs

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Prostate enlargement, also known as benign prostatic hyperplasia (BPH), is currently the fourth most prevalent diagnosed disorder in men 50 years of age and older.¹ The etiology of this disease has been linked to the hormone dihydrotestosterone (DHT) which promotes prostate growth.² An enlarged prostate (EP) can lead to bladder outlet obstruction and bothersome urinary symptoms (including hesitancy, urgency, frequent urination, nocturia, and inability to completely empty the bladder).³

Physicians often prescribe alpha blocker therapy to men who have bothersome urinary symptoms. Although alpha blockers are effective at providing prompt symptom improvement, they do not reduce prostate volume or lower the long-term risk of progression to acute urinary retention (AUR) or prostate-related surgery.⁴

5-Alpha reductase inhibitors (5ARIs) have been shown to reduce the size of the prostate and to decrease the rate of progression to AUR and prostate-related surgery.^{5,6} However, patients treated with 5ARIs may need to wait 3 to 6 months to experience significant symptom improvement; therefore, there is often a role for both alpha blockers and 5ARIs in men with bothersome symptoms who are also at risk for progression.⁷ In fact, the Medical Therapy of Prostatic Symptoms (MTOPS) study found that combination therapy with an alpha blocker and a 5ARI lowered the overall risk of BPH progression better than either drug alone,⁴ suggesting a possible synergistic effect when the drugs are used together. The American Urological Association recommends consideration of combination therapy with a 5ARI and an alpha blocker in men with urinary symptoms and a demonstrably EP.⁸

After several months of successful treatment with combination therapy, many clinicians choose to discontinue the use of alpha blockers. A placebo-controlled clinical trial has demonstrated that, in a majority of patients, alpha blockers can be discontinued after 6 months of combination therapy without significant loss of symptom control.⁷

There are currently two 5ARIs available for the treatment of EP, finasteride and dutasteride. Dutasteride blocks both the type-1 and type-2 5-alpha reductase isozymes, whereas finasteride blocks only

Abstract

Objective: The objective of this study was to directly assess the likelihood and timing of alpha blocker discontinuation in patients receiving combination therapy with dutasteride or finasteride plus an alpha blocker.

Methods: A retrospective analysis of the PharMetrics Integrated Medical and Pharmaceutical Database (Watertown, Mass) was conducted to assess differences in alpha blocker discontinuation rates for patients initiated on 5-alpha reductase inhibitor (5ARI) therapy. The database is nationally representative, encompassing more than 45 million patients from 85 managed healthcare plans. Male patients aged ≥ 50 years with a diagnosis of enlarged prostate (EP) who were receiving alpha blocker therapy and who began 5ARI treatment (dutasteride or finasteride) between January 1, 1999, and March 1, 2005, were included. Patients were studied for up to 12 months to evaluate the likelihood and timing of alpha blocker discontinuation.

Results: Overall, 56.7% of the patients remained on alpha blocker therapy for 6 months. At 1 year, more dutasteride patients had discontinued alpha blocker therapy (48.9% remained on alpha blocker) than finasteride patients (58.7% remained on alpha blocker). After controlling for background covariates, dutasteride patients were 19.9% more likely to discontinue alpha blocker therapy over 365 days.

Conclusion: Patients with EP who are taking an alpha blocker and 5ARI in combination for urinary symptom relief discontinue their alpha blocker 19.9% earlier when taking dutasteride than when taking finasteride. The ability to discontinue alpha blocker therapy earlier could reduce the costs of pharmacotherapy while continuing to provide an adequate level of symptom control and disease modification, which may result in cost savings to healthcare plans.

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the type-2 isozyme. As a result, dutasteride produces a greater reduction in serum DHT levels than finasteride, as demonstrated in a 24-week randomized trial in which serum DHT was reduced by 95% with dutasteride (0.5 mg/day) versus 71% with finasteride (5 mg/day).⁹ Dutasteride also has a longer half-life than finasteride.^{5,6} However, there have been no randomized head-to-head trials comparing clinical outcomes with the 2 drugs.

A recent study found that a significantly greater percentage of dutasteride-treated patients experienced symptom improvement within 3 months compared with finasteride-treated patients.¹⁰ In terms of combination therapy, this may mean that clinicians could discontinue alpha blocker therapy earlier for patients treated with dutasteride, without affecting the symptom burden of the patient. Although this theoretical premise is plausible, no studies have directly compared the two 5ARIs with respect to alpha blocker discontinuation. The objective of this retrospective comparative study was to assess the likelihood and timing of successful alpha blocker discontinuation in patients receiving combination therapy with an alpha blocker plus dutasteride or finasteride.

METHODS

Data Source

The PharMetrics Integrated Medical and Pharmaceutical Database (Watertown, Mass) was used to assess differences in alpha blocker discontinuation rates for patients initiated on 5ARI therapy. The database is nationally representative, encompassing more than 45 million patients from 85 man-

aged healthcare plans. Data include inpatient and outpatient diagnoses as determined by *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* codes,¹¹ and procedures as determined by *Current Procedural Terminology 4 (CPT-4)* and Healthcare Common Procedure Coding System (HCPCS) formats, as well as prescription records. Dates of service and both paid and charged amounts are available for all services rendered.

Sample Selection

Male patients aged ≥ 50 years who began 5ARI treatment (dutasteride or finasteride, excluding dosage forms for male pattern baldness) between January 1, 1999, and March 1, 2005, were identified. The index date for each patient was defined as the first date of a 5ARI prescription within this period. Identified patients were required to have a diagnosis of prostatic enlargement due to BPH or benign neoplasms, based on *ICD-9-CM* codes, and to be continuously eligible for medical and pharmacy services for 6 months before and at least 12 months after their index dates. Patients were also required to have been receiving alpha blocker therapy on or before the index date, and for at least 45 days after the index date. Patients were excluded if they had an *ICD-9-CM* code for prostate or bladder cancer during the 18-month eligibility period; if they were less than 30% adherent to 5ARI therapy (measured by calculating a medication possession ratio over the follow-up period); or if they did not initiate alpha blocker therapy before or on the index date. **Table 1** lists all relevant inclusion and exclusion *ICD-9* codes.

Assessment of Alpha Blocker Discontinuation

Patients meeting selection criteria were studied for up to 12 months to evaluate the likelihood of discontinuing alpha blocker therapy. Time to alpha blocker discontinuation was measured from each patient's index date to the last alpha blocker prescription. If the last alpha blocker prescription was more than 365 days past index, the patient was assumed to be on therapy for 365 days.

Comorbidity Assessment

To assess comorbidities in the study population, the Charlson Comorbidity Index with Dartmouth-Manitoba and Deyo modification was utilized.^{12,13}

■ **Table 1.** Inclusion and Exclusion *ICD-9* Codes

Inclusion <i>ICD-9</i> codes	
Enlarged prostate	222.2, 600
Exclusion <i>ICD-9</i> codes	
Prostate cancer	185, 198.82, 233.4, 236.5, 239.5, V10.46
Bladder cancer	188, 198.1, 223.3, 233.7, 236.7, 239.4, V10.51

ICD-9 indicates *International Classification of Diseases, Ninth Revision*.

This index is based on 19 medical conditions, each assigned a weight ranging from 1 to 6. Possible total scores range from 0 to 37, with higher numbers representing a greater burden of comorbidity. In this study, Charlson Index scores were derived from ICD-9-CM diagnoses in the 6-month period before each patient's index date.

Staging of EP

The Thomson Medstat Disease Staging coding criteria were used to stage the severity of EP before the patient was placed on 5ARI therapy.¹⁴ This method is based on electronic screening and identification of a comprehensive map of ICD-9 diagnosis codes. The proprietary coding criteria, developed by physicians and medical records professionals employed by Thomson Medstat, have been widely used as a classification system for diagnostic categories—1 of 4 systems selected for dissemination with the Healthcare Cost and Utilization Project Nationwide Inpatient Sample. In the present study, each patient initiated on 5ARI therapy was placed into 1 of 7 disease stages based on the presence of ICD-9-CM codes in the 6-month period before the index date. The stages and corresponding ICD-9-CM criteria are presented in **Table 2**.

Additionally, patients having hematuria (ICD-9-CM code 599.7) and/or bladder stones (ICD-9-CM codes 592.0, 592.1, 592.9, and 594.1) in the 6-month pre-period were identified, because these outcomes may also be indicative of disease severity.

Analysis of Outcomes

The likelihood and timing of alpha blocker discontinuation were assessed via survival analysis techniques. Time to discontinuation was modeled as a function of age, Charlson Comorbidity Index score, Thomson Medstat stage, number of alpha blocker prescription days before the index date, number of office visits related to EP, use of urological specialty care, use of uroselective alpha blockers, initiating treatment before 2003, and presence of hematuria and bladder stones, because all of these variables may be relevant severity indices for EP or confounders for alpha blocker discontinuation. Univariate analyses of frequencies and means were performed to describe the demographic characteristics of the study population. When appropriate, chi-square tests were used to compare differences in

■ **Table 2.** Thomson Medstat Staging Criteria for Enlarged Prostate

Stage	Description	ICD-9-CM codes
1.1	Benign prostatic hypertrophy	222.2, 600.xx
1.2	with urinary tract infection	Stage 1.1 + 599.0
2.1	with bladder outlet obstruction	Stage 1.1 + 593.5, 596.0, 599.6
2.2	with hydronephrosis	Stage 1.1 + 591.xx
3.1	with renal failure	Stage 1.1 + 584.xx, 586.xx
3.2	with sepsis	Stage 1.1 + 038.xx
3.3	with shock	Stage 1.1 + 785.50, 785.59

Source: Reference 14.
ICD-9-CM indicates *International Classification of Diseases, Ninth Revision, Clinical Modification*.

dichotomous variables and *t*-tests were used to compare differences in continuous variables.

RESULTS

Population Overview

A total of 2443 men ≥ 50 years of age met the study's inclusion criteria; of these, 81.4% (1989 patients) had begun alpha blocker treatment before initiating 5ARI therapy, while 18.6% (454 patients) had begun both an alpha blocker and a 5ARI on the index date. The mean age of the study population was 62.8 years. Approximately 90% (2216) of the men were classified as having stage 1 prostate enlargement (ie, without bladder outlet obstruction, hydronephrosis, renal failure, sepsis, or shock). The mean Charlson Comorbidity Index score was 0.9, indicating a low level of comorbidity.

Dutasteride patients ($n = 503$) were an average of 3 years younger ($P = .0711$) than finasteride patients ($n = 1940$). Charlson Comorbidity Index scores, disease severity stage, the proportion of patients who initiated alpha blocker therapy before the 5ARI, and the mean duration of alpha blocker therapy before initiating the 5ARI were equivalent across both cohorts. Demographics of the study population are summarized in **Table 3**.

Alpha Blocker Utilization

Overall, 56.7% of the patients remained on alpha blocker therapy for 6 months; however, more finasteride than dutasteride patients remained on alpha blocker therapy at 1 year (58.7% vs 48.9%,

■ **Table 3.** Demographics of Study Population (N = 2443)

	Overall (N = 2443)	Dutasteride (n = 503)	Finasteride (n = 1940)
Age group, years, n (%)			
50-55	421 (17.2)	103 (20.5)	318 (16.4)
56-64	1378 (56.4)	346 (68.8)	1032 (53.2)
65 and older	644 (26.4)	54 (10.7)	590 (30.4)
Enlarged prostate stage, n (%)			
1	2216 (90.7)	453 (90.1)	1763 (90.9)
2	132 (5.4)	24 (4.8)	108 (5.6)
3+	95 (3.9)	26 (5.2)	69 (3.6)
Age, mean (SD)			
	62.8 (9.0)	60.1 (6.8)	63.5 (9.4)
Charlson rating, mean (SD)			
	0.9 (1.6)	0.8 (1.6)	0.9 (1.6)
Timing of alpha blocker treatment			
Pre-index period, n (%)	1989 (81.4)	403 (80.1)	1586 (81.8)
Same day, n (%)	454 (18.6)	100 (19.9)	354 (18.2)
Duration of alpha blocker treatment in pre-period			
Number of days, mean	90.0	85.6	91.2
SD indicates standard deviation.			

respectively). The survival curve is shown in the **Figure**. After controlling for background covariates, dutasteride patients were 19.9% more likely to discontinue alpha blocker therapy over 365 days, meaning that at any time point, dutasteride patients discontinued alpha blocker therapy 19.9% faster than finasteride patients. The percentages of patients remaining on alpha blocker therapy at specific 30-day intervals are presented in **Table 4**.

The Cox proportional hazards model controlled for age, Charlson Comorbidity Index score, Thomson Medstat stage, number of alpha blocker prescriptions days before the index date, number of office visits related to EP, use of urological specialty care, use of uroselective alpha blockers, index year, and presence of hematuria and bladder stones. Results from the Cox regression model for days to alpha blocker discontinuation are presented in **Table 5**.

Discussion

The purpose of this study was to assess the likelihood and timing of alpha blocker discontinuation in patients initiating combination therapy with

dutasteride or finasteride plus an alpha blocker. The results indicate that the rate of alpha blocker discontinuation was 19.9% greater among the dutasteride patients compared with the finasteride patients. Although it is not possible to determine causality in a retrospective database assessment, the results of this study raise the possibility that patients receiving dutasteride may have faster symptom improvement than finasteride patients, allowing them to discontinue alpha blocker therapy earlier. This premise is supported by a study by Hagerty et al, in which 86% more dutasteride patients had some symptom improvement within 3 months when compared with finasteride patients.¹⁰ The more rapid symptom improvement may be due to dutasteride's improved (50% greater) suppression of serum DHT compared with finasteride.^{9,15} Because DHT is the primary hormone responsible for prostate growth, one may surmise that greater DHT suppression could lead to faster prostate volume reduction and symptom improvement; however, this hypothesis has yet to be confirmed.

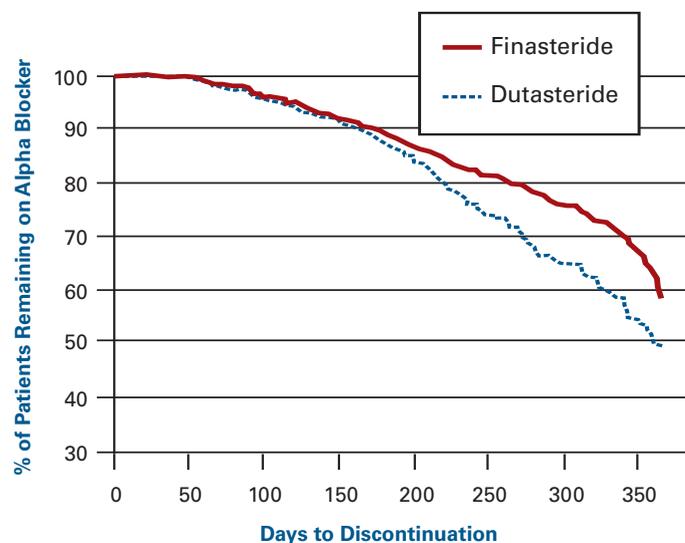
In the present study, discontinuation curves separate substantially after 5 to 6 months of treatment.

This supports work by Barkin et al, who found that alpha blocker therapy can be successfully discontinued in the majority of patients after 6 months of combination therapy with dutasteride without diminishing the level of symptom control achieved with combination therapy.⁷ In contrast, a study by Baldwin et al found that with finasteride, alpha blocker therapy could not be discontinued earlier than 9 months without affecting symptom control.¹⁶ Putting these 2 studies together, the 3-month difference suggests that alpha blocker therapy in dutasteride patients can be stopped 25% earlier (over 1 year), which supports the 19.9% faster discontinuation rate in the present analysis.

For managed care decision makers, the results of this study may have important economic implications. The ability to discontinue alpha blocker therapy earlier could reduce the costs of pharmacotherapy while continuing to provide an adequate level of symptom control and disease modification. Now that finasteride has become generically available, it is important for managed care decision makers to explore the economic differences between the two 5ARIs in terms of both 5ARI and concomitant alpha blocker acquisition costs.

There are several limitations with this study. First, patients initiating finasteride therapy before 2003 were included in this analysis even though dutasteride was not available at this time. The analysis controlled for a timing and uroselective alpha blocker use bias by including a covariate that represented the index date of the patients and the type of alpha blocker prescribed. Additionally, a post-hoc sensitivity analysis was conducted to ensure the robustness of the results, stratifying the analysis from 2003 forward. The stratification provided a parameter estimate that was similar to that of the original analysis (hazard ratio, 1.201; 95% confidence interval, 1.002, 1.439; $P = .048$). Also, patients were not required to be 100% adherent with alpha blocker therapy. Time to alpha blocker discontinuation was defined as the time between initiating a 5ARI and the last alpha blocker prescription within the patient's follow-up. During this time period, patients could have stopped and restarted alpha blocker therapy several times in unsuccessful attempts at discontinuation. Although patients were not required to be 100% adherent, this type of pharmacotherapy pattern is reflective of

■ **Figure. Alpha Blocker Survival Analysis**



real-world scenarios, and may increase the external validity of the findings. Second, the exact reasons for alpha blocker discontinuation are not known; discontinuation may be for a result of reasons other than symptom control. Third, the results do not quantify the level of symptom control that was established within each cohort. Finally, the data for analysis in this study were obtained from a managed

■ **Table 4. Percentages of Patients Remaining on Alpha Blocker Therapy**

Day of alpha blocker discontinuation	Finasteride (%)	Dutasteride (%)
1	100.0	100.0
30	100.0	100.0
60	99.1	98.9
90	97.6	96.2
120	94.7	94.1
150	92.0	91.0
180	89.0	87.4
210	85.9	82.2
240	82.1	75.6
270	79.3	70.8
300	75.5	64.5
330	71.6	59.2
365	58.7	48.9

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■ **Table 5.** Cox Regression Model Results—Days Until First Alpha Blocker Discontinuation

Model term	Point estimate (95% CI)	P value
Dutasteride	1.199 (1.002, 1.436)	.0479
Age	1.004 (0.996, 1.012)	.3212
Alpha blocker before 5ARI start date	1.333 (1.066, 1.665)	.01115
Number of office visits related to EP	1.053 (1.009, 1.098)	.0172
Charlson comorbidity rating	0.959 (0.916, 1.005)	.0812
EP stage 2 or more	1.026 (0.855, 1.232)	.7882
Urologist specialty care visit	0.611 (0.525, 0.710)	<.0001
Number of alpha blocker days before 5ARI start date	0.995 (0.994, 0.997)	<.0001
Use of uroselective alpha blocker	1.498 (1.276, 1.759)	<.0001
Index before 2003	1.024 (0.866, 1.210)	.7840
Presence of hematuria	0.927 (0.753, 1.141)	.4746
Presence of bladder stones	1.089 (0.790, 1.502)	.6031

5ARI indicates 5-alpha reductase inhibitor; CI, confidence interval; EP, enlarged prostate.

care database and may not be generalizable to other populations (eg, patients receiving care through publicly funded sources).

Even with these limitations, this study provides evidence that patients receiving combination medical therapy for BPH are likely to discontinue alpha blocker therapy at an earlier time when taking dutasteride than when taking finasteride.

CONCLUSION

BPH patients who are taking an alpha blocker and 5ARI in combination for urinary symptom relief discontinue their alpha blockers 20% earlier when taking dutasteride than when taking finasteride, which may result in cost savings to health-care plans.

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