Alpha blocker monotherapy versus combination therapy with antimuscarinics in men with persistent LUTS refractory to alpha-adrenergic treatment: patterns of persistence

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Introduction: *Patients with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) often present with voiding and storage symptoms, which may require combination therapy with an alpha blocker and an antimuscarinic (AM). This study compared treatment persistence in LUTS/BPH patients on alpha blocker monotherapy with those using combination alpha blocker and AM therapy (AB/AM).*

Materials and methods: *Retrospective analysis of anonymized patient longitudinal prescription reimbursement claims data. All patients who had claims for any of four alpha blocker medications and six AM agents during an index period from April 1, 2011 to March 31, 2012 were included. For the combination therapy group, the effect of adherence with the AM medication on persistence to the alpha blocker was examined.*

Results: *Patients on AB/AM combination therapy remained on alpha blockers for longer than those on alpha blocker monotherapy ($p = 0.04$); 92.4% were persistent at 3 months versus 89.0%, and at 1 year 50.8% were persistent versus 49.6%, respectively. The highest number of days on therapy was reported for tamsulosin plus solifenacin. As confirmed by multivariate analysis, patients with the highest adherence to AM medication (≥ 80%) persisted on alpha blockers for longer than those with the lowest (< 50%) adherence ($p < 0.05$).*

Conclusions: *Patients taking an AM in combination with an alpha blocker showed greater persistence with alpha blocker treatment over a 1 year period. When an AM is combined with an alpha blocker in patients with LUTS/BPH, the additional medication burden does not have a negative impact on persistence and may even improve it.*

Key Words: benign prostatic hyperplasia, lower urinary tract symptoms, alpha adrenergic blockers, antimuscarinics, persistence

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Introduction

Benign prostatic hyperplasia (BPH) is a histologic description of enlarged glands and stroma within the prostate.[1] Obstruction of urine flow (bladder outlet obstruction, BOO) and increased smooth muscle tone at the bladder neck and in the prostatic capsule can be secondary to BPH.[2] The lower urinary tract symptoms (LUTS) commonly caused by BPH can be categorized as storage (urgency, daytime frequency, nocturia) or voiding (hesitancy, straining, dribbling) symptoms.[2] BPH is one of the most common age-related disorders

afflicting men, and histological evidence shows the presence of BPH in 50%-60% of men in their 60s.[3] A linear association indicating an increase of LUTS/BPH with age has been demonstrated.[4]

Alpha blockers are generally recognized as the first-line pharmacological therapy for treatment of LUTS/BPH.[5] They exert effects on smooth muscle tone within the prostate, bladder neck and prostatic capsule, relieving what is known as the "dynamic component" of BOO. They are most commonly recommended for men with moderate to severe LUTS which they find bothersome and who have a smaller prostate (< 30 cc).[6] Common agents in this class include alfuzosin, doxazosin, tamsulosin, terazosin and silodosin. Alpha blockers have a relatively rapid onset of action, within 3 to 5 days.[1]

A considerable proportion of men with LUTS/BPH have both voiding and storage symptoms.[2,7] In cases where LUTS/BPH patients find that storage symptoms persist after alpha blocker treatment, the addition of antimuscarinic (AM) therapy has been shown to be effective, safe and well tolerated.[5,8-12] The reported incidence of treatment-related adverse events with combination alpha blocker plus AM therapy (AB/AM) is low, with the most common events comprising mild to moderate dry mouth, constipation, and dyspepsia.[8,10,11] Serious adverse events are infrequent, but rare cases of acute urinary retention and small increases in post void residual volume have been reported with combination therapy.[8,10-12]

Irrespective of the evidence supporting long term therapy of LUTS/BPH with alpha blockers or with AM medications, many patients discontinue treatment early. Optimal management is often limited by poor rates of adherence.[13-16] This is not unique to BPH and suboptimal medication adherence has been reported across several different chronic conditions.[17]

Persistence, defined as "the duration of time from initiation to discontinuation of therapy," is frequently examined when evaluating medication use and includes an allowable grace period or gap between refills. This gap is based on drug properties and treatment situations and is often described as a fixed interval or by a variable interval such as 1.5, 2 or 3 times the days' supply of the prescription.[18]

Adherence is defined as "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen."[18] Adherence is often measured in retrospective data analyses by calculating the Medication Possession Ratio (MPR), which is the gap between the number of days of medication supplied within the refill interval divided by the number of days in the refill interval.[19] Adherence studies typically define a patient as being adherent if an MPR of greater than 0.8 (or 80%) is observed.[13,20] In a study evaluating adherence and persistence to overactive bladder (OAB) medications, MPR was measured as the number of days of medication supplied divided by the number of days from the first prescription fill date to the date of the last prescription claim.[20] Therefore, a patient receiving a 90 day supply during a 120 day period would have an MPR of 0.75.

There have been few studies evaluating patient persistence or adherence to alpha blocker treatment for LUTS/BPH. Verhamme et al found that 26% of patients discontinued treatment early, with the median duration of treatment around 3 months, and adherence to alpha blocker therapy was 67%. Early discontinuers tended to have mainly voiding symptoms, were younger in age and had fewer comorbidities.[21] In a study by Nichol et al evaluating adherence over a 2 year time frame, patients on alpha blocker medication were considered non-adherent if their MPR was < 80%.[13] In this study, the mean adherence was less than 40%. Their research also showed that patients on a greater number of drugs before starting the BPH medication were less adherent to their BPH medications. However, a greater number of medications did not significantly impact time to BPH medication discontinuation. The authors suggested that a greater pill burden may impact adherence, but the type of medication or dosage may be more significant.

Poor patient persistence on AM therapy has been a challenge in the management of OAB. A review of almost 150 articles on persistence with, and adherence to, AM therapy revealed discontinuation rates ranging between 4%-31% in 12-week clinical trials, and 43%-83% in retrospective pharmacy claims studies.[22] Adherence (measured by MPR) was also low, with mean values ranging from 0.3 to 0.83. The review showed that at 1 year, 90% of patients in the claims studies had stopped taking their medication. In these studies, which included men and women and were not specific to patients with concurrent BPH, the most common reasons for discontinuation were side effects and not meeting treatment expectations. Patient-reported observational studies of OAB medication persistence and adherence were also explored in the review, offering insight into the patient experience. Similar findings of low persistence and poor adherence were reported.[23-25] Another review suggested that clinical effectiveness (i.e., the combination of treatment efficacy and tolerability) was associated with improved persistence.[14]

Observations in the clinical setting suggest that many patients with BPH/LUTS fail to continue their alpha blocker treatment beyond 3 months but to our knowledge, there are no studies evaluating persistence of male patients taking alpha blocker and

AM medications. The objective of this study was to analyze persistence of LUTS/BPH patients with voiding and storage symptoms who were on alpha blocker monotherapy compared to those patients using combination therapy (AB/AM). Secondary objectives were to evaluate which alpha blocker monotherapy and which AB/AM combinations were associated with the highest days on therapy (persistence), and to assess how adherence to AM medication influenced persistence to the index alpha blocker medication.

Materials and methods

A retrospective analysis of anonymized patient longitudinal claims data was obtained through the Ontario Public Drug Plan (OPDP) by IMS Brogan. This dataset comprises prescription claims coverage from the publicly administered drug plan in Ontario, Canada's most populous province. The robust dataset includes 2.5 million Ontarian claimants with 115 million prescriptions annually and has a 100% capture rate.

Four alpha blocker medications used for the treatment of LUTS/BPH were selected for this analysis: alfuzosin, doxazosin, tamsulosin, and terazosin. Silodosin was the only non-generic alpha blocker available in Canada at the time of this analysis, but it was excluded from the study as it was not available in the Ontario drug plan, with limited use access in Canada until February 2013. Antimuscarinic drugs that were included in this study, darifenacin hydrobromide, oxybutynin chloride, oxybutynin chloride XL, solifenacin succinate, tolterodine tartrate, tolterodine tartrate LA, and trospium chloride, are all fully covered by the OPDP.

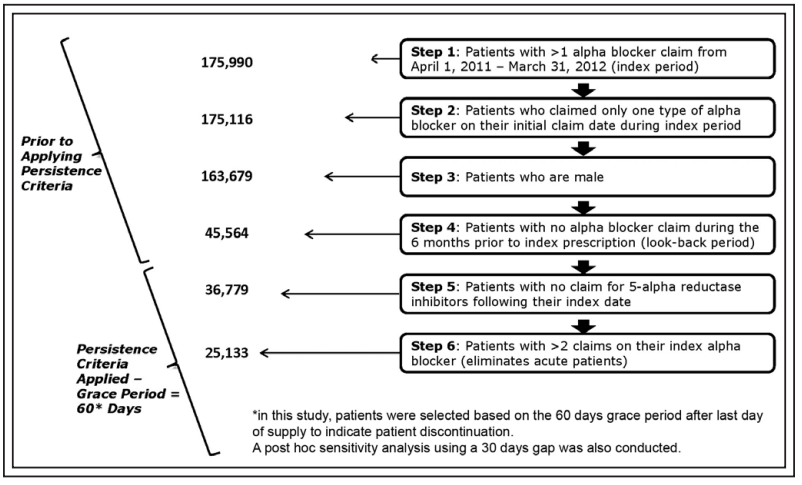

Figure 1. Study flow diagram indicating patient cohort size upon application of study inclusion and exclusion criteria.

The study period covered October 2010 to June 2013, and all patients who filled prescriptions for any of the four alpha blockers with or without AM medications during the index period from April 1, 2011 to March 31, 2012 were included in the analysis, Figure 1. This total cohort included all patients identified during the 12-month index period receiving a target alpha blocker medication. Prescriptions for non-BPH use were excluded, such as female patients. Although 5-alpha reductase inhibitors (5-ARIs) are also prescribed for BPH patients with enlarged prostates (i.e., > 30 cc),[6] patients using this class of medication alone or in combination with alpha blocker therapy were excluded from our analysis because of the difficulty in determining, through prescription claims analysis, the clinical reasons for initiation and/or discontinuation of the AB component of combination therapy.[26-28]

Only new to therapy patients were included in this study. All patients receiving a target alpha blocker medication during the study period but who had not filled a prescription for any alpha blocker medication in the 6 months prior to their first alpha blocker claim were considered "new to medication." These patients represent the final total cohort. A follow up period of 12 months from the index date allowed for observation of each patient to evaluate persistence and adherence to the medication. Patients were classified into two categories: 1) Alpha blocker only – those patients who started an alpha blocker medication and never added an AM and 2) AB/AM combination – those patients who started with AB/AM together, or added an AM at a later date within the observation period; patients must have had at least one prescription fill for the AM medication during the follow up period.

Several key persistence metrics for LUTS/BPH patients were analyzed. Persistence and adherence were evaluated in the 12-month follow up period. Persistence was defined by days on therapy with allowance for up to a 60-day gap between refills (i.e., 60 days after the last days' supply until the next prescription refill). If a patient lapsed on a drug for more than the grace period, then the patient was no longer considered persistent and their stop date was recorded as the date following their last day of supply. A post hoc sensitivity analysis was performed to determine if reducing the grace period gap to 30 days would have an effect on alpha blocker persistence. Adherence to AM therapy was defined by the

MPR, i.e., the proportion of days the patient took the prescribed AM while persistent on alpha blocker therapy during the observation period.[29]

A retention curve was plotted showing the percent of patients who remained on therapy over time. The average number of days on therapy was reported, as well as the number of days on therapy from initiation to stopping. The average number of days between the initial alpha blocker prescription fill and the first AM prescription fill was also estimated.

We wanted to examine whether the addition of an AM influenced the persistence (i.e., days on therapy) for the alpha blocker treatment. For patients on a combination of AB/AM medications, the impact of adding an AM on alpha blocker persistence was examined by measuring the AM MPR while on alpha blocker therapy. In this study, the AM MPR was calculated as the proportion of days patients took the prescribed AM medication while on alpha blocker therapy during the observation period. Adherence to the AM was classified as low if the proportion was < 50%, medium if 50%-80% and high if ≥ 80%. These categories were then examined to determine if low, medium or high AM adherence had an impact on alpha blocker persistence.

Statistical analysis

For the univariate analysis, the distribution of days on therapy by covariates was evaluated for normal distribution with the Shapiro-Wilk, Kolmogorov-Smirnov, Cramér-von Mises, or Anderson-Darling test, as appropriate. For normally distributed data, independent t-tests, comparing all cohort mean days on therapy against a benchmark cohort of the alpha blocker monotherapy group, were used to determine whether the mean days on therapy were statistically different between cohorts. We also compared tamsulosin + solifenacin against other groups because tamsulosin is the most commonly used alpha blocker for BPH in this cohort and because previous studies have shown that solifenacin is associated with higher rates of persistence compared with other AM medications in patients with OAB.[16,30] Non-parametric tests were applied when distributions were not normal. The Wilcoxon-Mann-Whitney test was used to test the difference between two distributions. The Kruskal-Wallis one-way analysis of variance was used when more than two distributions were being compared. P values of < 0.05 were considered statistically significant for all analyses.

A multivariate analysis was conducted using Cox proportional hazards models (CPHM) to calculate the proportional hazard of the outcome according to age (< 65 or ≥ 65 years), index alpha blocker (tamsulosin, alfuzosin, doxazosin or terazosin), concomitant AM (none, tolterodine, darifenacin, oxybutynin, solifenacin, trospium or multiple AMs; patients could be taking any combination of AM medications; this category was omitted from the multivariate analysis because it could not be attributed which AM was started or switched), and adherence to AM therapy during the period of alpha blocker persistence (MPR < 50%, 50%-80% or ≥ 80%). Persistence curves were drawn to examine the distribution of duration of persistence. Patients who continued therapy beyond the 12-month observation period were censored at 12 months for all CPHM analyses.

Results

Medication use at baseline

A total of 175,990 patients using an alpha blocker medication were identified in the OPDP database during the specified time period. After applying the inclusion and exclusion criteria, there were 25,133 male patients who were new to medication, with no prescription fills for alpha blocker therapy in the look-back period and who were not taking any 5-ARI therapy, Figure 2. Among the four alpha blockers included in our analysis, tamsulosin use was highest (63%). Tolterodine was the most frequently used

Therapy	Naïve Patients
Alpha blocker only	23,868
Combo alpha blocker and AM	1,265
Total alpha blocker	25,133

Therapy	AB Used	Naïve Patients
Alpha blocker only	Alfuzosin	1,737
	Doxazosin	1,970
	Tamsulosin	15,048
	Terazosin	5,113

Therapy	AM Used	Naïve Patients
Combo alpha blocker and AM	Tolterodine	753
	Darifenacin	32
	Solifenacin	133
	Trospium	3*
	Oxybutynin	223
	Multiple AMs	119

*for compliance with IMS Brogan Privacy and Confidentiality policy, data groups with less than 6 patients/claims were masked at 3 and were excluded from reporting. AB = alpha blocker; AM = antimuscarinic

Figure 2. Summary of overall patient cohort, based on patient category and medication type.

AM medication. Among patients taking AB/AM combination therapy, 59% were using a combination of any alpha blocker medication plus tolterodine. Oxybutynin was the next most commonly used AM medication in combination with any alpha blocker (18%), followed by solifenacin (11%) and darifenacin (< 3%). Patients on trospium chloride (< 1%) in any combination, were excluded from our analysis.

Univariate analysis

We analyzed persistence with alpha blocker medication using a gap in therapy of 60 days to identify discontinuers. Patients on any AB/AM combination therapy remained on their alpha blocker longer than patients on alpha blocker therapy alone (p = 0.04; Figure 3). At 3 months, 92.4% of patients on AB/AM were still on their alpha blocker versus 89.0% of patients on an alpha blocker alone, and at 1 year, persistence rates fell to 50.8% and 49.6%, respectively. As shown in Figure 3, the persistence curves for the two groups showed the widest spread (greatest difference) during the period from 91 days to 240 days following initiation of therapy. A post hoc sensitivity analysis was conducted to assess persistence patterns using a stricter definition of persistence, i.e., a gap of 30 days. As expected, persistence was somewhat lower using this stricter definition; however, the pattern remained consistent with that of the standard 60 days' supply analysis, showing that combination AB/AM use was associated with higher persistence on alpha blocker therapy than on alpha blocker therapy alone (p = 0.004).

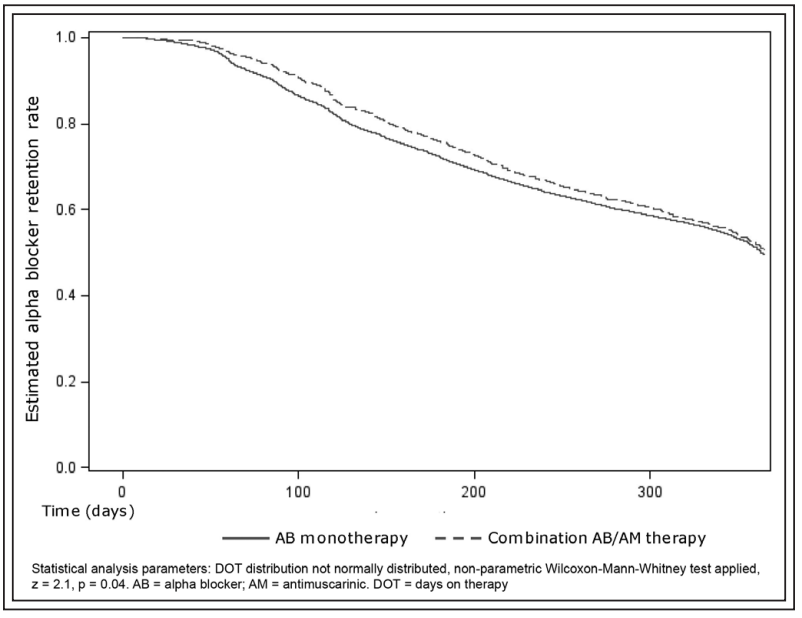

Figure 3. Estimated alpha blocker retention rates in patients on alpha blocker monotherapy versus AB/AM combination therapy.

The univariate analysis showed a statistically significant difference in persistence on alpha blocker therapy between patients who took different types of alpha blocker monotherapy (p = 0.02, Kruskal-Wallis test). Persistence was highest for alfuzosin followed by tamsulosin, doxazosin and terazosin. Analysis of specific pairings amongst monotherapy patients showed that persistence was statistically significantly higher for patients on alfuzosin versus terazosin monotherapy (p < 0.05; multiple pairwise comparisons), with 25% of patients on terazosin discontinuing therapy before 156 days, versus 25% of patients on alfuzosin discontinuing before 182 days. This was the only statistically significant difference between specific alpha blocker monotherapies. There was no statistically significant difference in persistence to alpha blocker therapy between patients taking tamsulosin versus any other alpha blocker monotherapy.

Analyzing specific combinations of alpha blocker and AM medications, only patients on tamsulosin-based combination AB/AM therapy showed a statistically significant difference in persistence between different AM combinations (p = 0.0001; Wilcoxon-Mann-Whitney test). Tolterodine was the most commonly used AM with tamsulosin. Of the tamsulosin-based AM combination therapies, patients on solifenacin were, numerically, the most persistent (darifenacin was excluded from the multiple comparisons test due to low sample size). Multiple comparison tests amongst patients on a combination of tamsulosin plus an AM showed that patients on tamsulosin + solifenacin had significantly higher persistence than those on tamsulosin + oxybutynin (p < 0.05; multiple pairwise comparisons), but not compared to any other specific combinations of tamsulosin + AM. Descriptively, at 3 months persistence rates were 98.0% versus 93.1% for tamsulosin + solifenacin and tamsulosin + oxybutynin, respectively, and at 1 year persistence rates were 60.4% versus 44.4%.

Effect of AM medication adherence on persistence to alpha blocker therapy

Persistence with alpha blocker therapy was analyzed by AM medication adherence (MPR) for patients on AB/AM combination therapy. Among those on AB/AM combination therapy (n = 1265), 44% (n = 557) had an MPR < 50%, 19% (n = 245) had an MPR

between 50%-80%, and 37% (n = 463) had an MPR ≥ 80%. Patients with higher adherence to AM therapy (i.e., MPR ≥ 80%) showed significantly greater persistence on alpha blocker therapy than those with poorer adherence to AM therapy (i.e., MPR < 50%) (multiple pairwise comparisons; $p < 0.05$); at 1 year, persistence rates were 56.4% versus 47.2%, respectively.

Multivariate analysis

Following the univariate analysis, a multivariate model was used to examine the impact of all measurable covariates on persistence with alpha blocker therapy. For the initial multivariate cox proportional hazards model (CPHM), patients' age, choice of alpha blocker, choice of AM, and category of AM adherence (MPR < 50%, 50%-80%, ≥ 80%) were included, to determine each covariate's relative impact on alpha blocker persistence. Only those covariates that were found to have an impact on alpha blocker persistence were included in the final model.

The majority of patients in the cohort were aged 65 years and older (n = 22,982; 91%); one patient was excluded from the analysis because his age was not available. Based on an initial saturated CPHM analysis, the type of alpha blocker index medication was not a statistically significant variable in determining persistence to alpha blocker therapy ($p > 0.05$). Conversely, the type of AM medication, adherence to AM (i.e., MPR category) and age were all statistically significant variables, Table 1. Age was a significant factor in determining persistence to alpha blocker therapy, with patients < 65 being about 27% more likely to discontinue their alpha blocker therapy than patients ≥ 65 ($p < 0.001$). Two variables, type of AM and adherence to AM, were significantly correlated with one another and evaluated separately. Using the reduced CPHM analysis, patients on solifenacin were about 23% more likely to persist on alpha blocker therapy compared to patients on alpha blocker monotherapy ($p = 0.048$; Figure 4). No other type of AM was found to be statistically significant in the multivariate analysis. The analysis also showed that patients with ≥ 80% adherence to their concomitant AM therapy were 19% less likely to discontinue their alpha blocker therapy compared to those on alpha blocker monotherapy ($p = 0.003$).

TABLE 1. **Summary of the results of the saturated Cox Proportional Hazards Model multivariate analysis of persistence with alpha blocker therapy.**

Covariate	Categories	N	HR (95% CI)	p value
Index alpha blocker				0.207
	Tamsulosin*	15,984	1.00	-
	Alfuzosin	1,892	0.954 (0.891-1.021)	0.175
	Doxazosin	2,017	1.008 (0.944-1.075)	0.816
	Terazosin	5,239	1.032 (0.988-1.078)	0.160
Type of AM				< 0.001
	None*	23,867	1.00	-
	Darifenacin	32	0.54 (0.301-0.969)	0.039
	Oxybutynin	223	0.977 (0.782-1.220)	0.835
	Solifenacin	133	0.641 (0.476-0.863)	0.003
	Tolterodine	753	0.860 (0.742-0.998)	0.047
AM adherence (MPR)				0.034
	None*	23,867	1.00	-
	< 50%	557	1.264 (1.051 – 1.520)	0.013
	50%-80%	245	1.237 (0.989-1.545)	0.062
	≥ 80%	463	Colinear**	-
Age (years)				< 0.001
	< 65*	2,150	1.00	-
	≥ 65	22,982	0.735 (0.693-0.779)	< 0.001

*Indicates reference variable in a particular covariate group. **Type of AM and AM adherence (MPR) are linearly correlated, specifically between ≥ 80% MPR category and type of AM covariate group.
HR = hazard ratio; CI = confidence interval; AM = antimuscarinic; MPR = medication possession ratio.

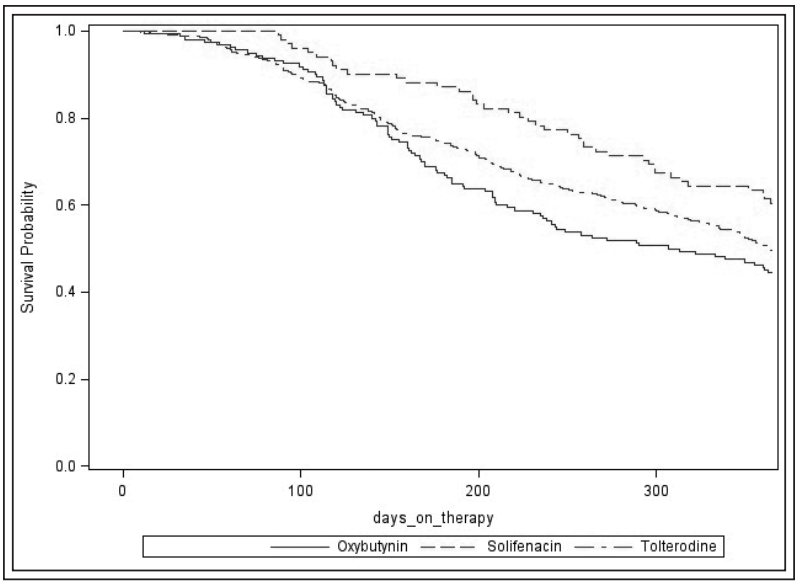

Figure 4. Survival curve (Kaplan-Meier analysis) of time to discontinuation of alpha blocker therapy by type of antimuscarinic.

Discussion

Using retrospective medical claims data, our study analyzed persistence with alpha blocker monotherapy for male patients with symptomatic LUTS/BPH compared to patients on a combination of medications for LUTS/BPH voiding symptoms (alpha blockers) and storage symptoms (AMs). Our data showed that patients on any AB/AM combination therapy were more persistent than those on any alpha blocker monotherapy over a 1 year follow up period. Looking at specific combinations of AB/AM medications, patients on tamsulosin + solifenacin had the highest persistence of any AB/AM combinations. Furthermore, patients with the highest adherence (MPR) to their AM therapy had the longest persistence to their index alpha blocker therapy.

Persistence to treatment tends to fall off substantially over the first year after treatment initiation in a variety of chronic conditions. Yeaw et al measured persistence across six chronic conditions.[17] At 1 year, the highest persistence rate was 54% for patients on oral hypoglycemic agents and the lowest rate was reported for patients on antimuscarinic OAB medications (18%). According to data from the same OPDP claims database that we used, during a 1 year period from April 2012-March 2013, discontinuation rates for AMs ranged from 32% for solifenacin compared to 83% for oxybutynin.[31] Previous studies have also shown that solifenacin is associated with higher rates of persistence compared with other AMs in patients with OAB.[16,29] Persistence to AM monotherapy appears to be low and may be related to unwanted side effects and/or the presence of residual symptoms.[22] Our results, comparing patients taking tamsulosin alone or in combination with an AM, showed the highest persistence for patients on a combination of tamsulosin + solifenacin compared to any other AM in combination with tamsulosin, which may be potentially related to solifenacin's favorable tolerability profile as well as the patient's symptom response. This was supported by a multivariate analysis, which showed that the type of AM concomitant therapy was only a significant factor for combinations involving solifenacin. Indeed, patients taking tamsulosin + solifenacin were 23% less likely to discontinue tamsulosin than those taking tamsulosin monotherapy. These findings suggest that the combination of tamsulosin + solifenacin offers patients benefits in terms of efficacy at relieving symptoms and/or tolerability.

Several studies have demonstrated that AB/AM combination therapy can be effective, safe and well tolerated.[5,8-12] However, there are no studies, to our knowledge, that look at persistence of patients on combinations of alpha blocker plus AM medications in clinical daily practice. Nichol et al reported that patients on a combination of multiple BPH medications, which included patients on either finasteride (a 5-ARI) plus an alpha blocker or a combination of two alpha blockers, were more persistent than patients on alpha blocker monotherapy.[13] The authors suggested the higher persistence was likely due to the fact that patients on finasteride typically have a larger prostate, and that having fewer medical options available to them, these patients are likely to continue therapy in the hope of avoiding surgery.[13] This study also found that patients on a higher number of medications prior to the initiation of BPH medication were less persistent than those on fewer medications. However, because these patients did not stop taking their medication any sooner, the type of medication or dosing may have been a more important factor influencing persistence than polypharmacy.[13] Our results show greater persistence on two medications, despite this representing a greater pill burden to patients. It is possible that a fixed dose combination of AB/AM medications might further improve persistence rates. A combination of 0.4 mg

tamsulosin ER and 6 mg solifenacin has recently become available in some European countries, based on the NEPTUNE I and II trials. The fixed dose combination was superior to tamsulosin alone or placebo across all outcomes including patient quality of life;[32] however, it is too soon to know whether this fixed dose combination offers a benefit in terms of improved persistence.

Patients with LUTS/BPH are more commonly prescribed AB/AM combination therapy in cases where storage symptoms are present.[7,33] Alpha blockers and AMs have different mechanisms of action whereby alpha blockers decrease smooth muscle tone at the neck of the bladder and inside the prostate, whereas AMs decrease detrusor overactivity by altering sensation or contractility.[2] For patients with significant storage symptoms that continue after alpha blocker monotherapy, the addition of an AM could offer a synergistic effect that maximizes the impact of the medications while further relieving symptoms. Our results could also indicate that symptoms for these patients were more bothersome or severe, and that patients perceived greater benefits to staying on the medications for longer. In the case of LUTS suggestive of benign prostatic obstruction, Speakman infers that factors such as symptom severity, patient bother, and quality of life must all be balanced against potential medication side effects and treatment morbidity.[34] Patients with more severe symptoms and bother, for example, may complain less about adverse side effects, a factor that can influence discontinuation of medication.[15,33]

It is also possible that patients were misdiagnosed with LUTS/BPH and may have actually had primary OAB. This could explain the higher persistence observed in the combination AB/AM therapy group. If a patient did not have LUTS secondary to BPH, then they might not have stayed on alpha blocker monotherapy because their storage symptoms would not have been treated with the alpha blocker alone.

Verhamme et al found that early discontinuation of BPH therapy was higher in younger patients with predominantly voiding symptoms and with fewer comorbidities.[21] The median duration on therapy was only 3 months (93 days). In our study, patients on combination therapy may have been more likely to have had residual storage symptoms, rather than voiding symptoms alone.

Our investigation examined the association between adherence to AM and patient persistence to alpha blocker therapy. In the univariate analysis, patients with the highest adherence to their AM medication were more persistent to their alpha blocker medication. In the multivariate analysis, the increase in persistence was observed when patients were highly adherent to AM therapy according to a relatively stringent definition (i.e., ≥ 80 MPR). Based on this definition, the combination of tamsulosin + solifenacin was associated with higher persistence than alpha blocker monotherapy. This is important from a clinical perspective because patients often discontinue combination therapy within the first 3 months due to side effects or lack of efficacy, which is often before a maximum clinical response is achieved.

Other studies have used retrospective prescription claims data and its use is supported in the literature.[35] However, there are also well established limitations to this approach. In this analysis, no information is provided on the diagnostic profile of patients, the severity of their condition, their reason for discontinuing medication, or the type of prescribing physician (i.e., urologist or family physician). Men taking 5-ARIs were excluded from our study, as they were not considered the right candidates since alpha blocker monotherapy or AB/AM combination therapy would not be expected to be effective.[26-28] Further, the medication dispensed, as per the prescription, may not represent the actual adherence to the treatment regimen. There were differences in statistical power among study groups due to varying n-values in the prescription claims database. The aggregation of all formulations of oxybutynin and of tolterodine may have obscured any potential differences between the available immediate release and long-acting formulations; however, it is difficult within the scope of this analysis to separate the effect of differences in adherence between the IR and ER formulations, from any other intrinsic differences between the two formulations.

Despite the limitations of this study, there are also strengths in the data we collected and analyzed. For seniors (over the age of 65) living in Ontario, Canada, the Ontario Public Drug Plan covers the majority of the cost for the 3800 prescription drugs.[36] Prescription records are entered into the OPDP, which is the second largest prescription database in Canada. The accuracy and reliability of this database has been shown to have an error rate of less than 1% and is cited as being an important information source regarding prescription drug use among the larger population.[37] The data in this study were derived from this robust database.

Conclusion

This is the first study to report on persistence patterns of patients with LUTS/BPH taking alpha blocker therapy with or without a concomitant AM. Compared with patients on alpha blocker monotherapy, those

taking a concomitant AM with their alpha blocker had greater persistence to alpha blocker therapy over a 1 year period. There was wide variability in persistence rates for individual AM medications in combination with tamsulosin, with the highest rates reported for tamsulosin plus solifenacin. This suggests that the addition of a specific AM, solifenacin, to alpha blocker therapy may offer LUTS/BPH patients with persistent voiding and storage symptoms, benefits that translate into better persistence with alpha blocker therapy. Further studies are needed to confirm patient perspectives and reasons for prescribing and for discontinuing alpha blocker therapy when taken either as monotherapy or in combination with an AM.

Disclosures

Dr. Barkin has received consulting fees and honoraria in the last 2 years from Astellas Pharma Canada, Inc., GlaxoSmithKline Inc., Actavis, Paladin Labs Inc., Eli Lilly and Company, Abbott Canada, Amgen Canada, Ferring Pharmaceuticals, AstraZeneca Canada, Pfizer Canada and Janssen Inc. Demitri Diles is a full employee of Astellas Pharma Canada, Inc. Billy Franks is an employee of Astellas Scientific & Medical Affairs, Inc. Todd Berner is formerly an employee of Astellas Scientific & Medical Affairs, Inc. □

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