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Adherence and Persistence Patterns in Medication Use Among Men With Lower Urinary Tract Symptoms/Benign Prostatic Hyperplasia

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Abstract

Medication adherence and persistence patterns among patients with lower urinary tract symptoms/benign prostatic hyperplasia (LUTS/BPH) were analyzed. Electronic medical records of patients from the Reliant Medical Group were examined to evaluate adherence and persistence patterns. A total of 1,807 patients with LUTS/BPH were included in the study, and the number of patients at least 50 years of age was 1,748/1,807 (97%). Overall, 15.77% of patients were prescribed index prescription once, and no patients on combination alpha-blocker and 5-alpha reductase inhibitor therapies were prescribed their index prescriptions once. For all patients with LUTS/BPH, the mean number of prescriptions filled was 6.26, and the percentage of men persisting on index therapy for ≥4 years was 48%. Patients with LUTS/BPH showed a high proportion of both adherent and persistent treatment patterns, especially among patients taking combination therapy. The long follow-up time in our study provides evidence that patients are experiencing sufficient symptom relief to tolerate the challenges of remaining adherent and persistent.

Keywords

benign prostatic hypertrophy, erectile dysfunction, outcomes research

Background

One of the most prevalent prostatic disorders affecting aging men is the onset and progression of lower urinary tract symptoms suggestive of benign prostate hyperplasia (LUTS/BPH; Prajapati, Gupta, Mistry, & Gupta, 2013). LUTS/BPH refers to a combination of obstructive and/or irritative voiding symptoms (Roehrborn, 2001). Such symptoms may arise from glandular-stromal hyperplasia of the prostate, lead to prostatic enlargement and bladder outlet obstruction, and increase bladder pressure and reduce urine flow. While not life-threatening, LUTS/BPH may negatively affect men's quality of life in many ways, including the development of sleep disturbances, sexual dysfunction, and reduced sexual satisfaction (Eryildirim et al., 2010).

Several classes of pharmaceutical agents have demonstrated efficacy in reducing LUTS/BPH, including α-adrenergic receptor antagonists (alpha-blockers), 5-alpha reductase inhibitors (5-ARIs), and phosphodiesterase type 5 inhibitors (Filson, Wei, & Hollingsworth, 2013; Liu, Zheng, Han, & Wei, 2011). Combination therapies, including alpha-blocker and 5-ARI and tadalafil and 5-ARI, have been reported to provide additional clinical benefit in some men compared with either therapy alone (Casabé et al., 2014; McConnell et al., 2003). Patients with significant symptom or disease progression while on medical therapy may be escalated to minimally invasive therapy or standard surgical therapy (Oelke et al., 2013). Lack of adherence to medication therapies is a common, multifactorial problem that poses a challenge for treating a wide range of chronic medical conditions, can result in serious adverse health outcomes for patients (Ho, Bryson, & Rumsfeld, 2009; Kaplan et al., 2006), and is associated with higher health care costs (Ho et al., 2009). There is discussion about whether patients with symptomatic conditions are more adherent to their medication regimens than patients with asymptomaticconditions. On the one hand, symptomatic patients have a direct

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indicator of lack of adherence to medication in the form of the bother associated with symptoms (Ho et al., 2009); on the other hand, some studies reported that symptomatic patients feel less control over their illness and are less adherent (Chen, Tsai, & Lee, 2009).

While the introduction of safe and effective medical therapy for LUTS/BPH has transformed a predominantly surgical condition into a chronic medical illness, few studies have examined adherence in patients with LUTS/BPH (Nichol, Knight, Wu, Barron, & Penson, 2009; Schoenfeld, Shortridge, Gelwicks, Cui, & Wong, 2014; Verhamme et al., 2003). One study in a U.S. Medicaid population observed relatively low adherence rates overall with one third of patients adherent over all categories of therapy and higher adherence for combination therapy use (62.3%; Verhamme et al., 2003). Only 69 men were on combination therapy in the study. The authors noted that the decision to initiate and continue therapy was based solely on the patient's perception of the level of bother of the condition; hence, factors like side effects or perceived lack of efficacy might be more important for this disease state. Another study using a general practice database from the Netherlands reported that a quarter of patients discontinued shortly after initiating a therapy, and patients persisted on therapy for an average length of approximately 3 months (Nichol et al., 2009). The authors suggested that patients, primarily older patients, had more severe LUTS/BPH and might be less likely to discontinue treatment due to adverse events. A U.S. claims database study observed low rates of adherence to alpha-blockers only and little difference for men on selective versus nonselective alpha-blockers (Schoenfeld et al., 2014). The authors suggest that perceived efficacy, cost and other unmeasured factors might explain the poor adherence. Some prospective studies have reported alpha-blocker treatment failure rates of 11.2% and 13.9%, which included patients who reported lack of efficacy or adverse events as reasons for discontinuation (Lukacs, Leplège, Thibault, & Jardin, 1996; Roehrborn, et al., 1996). Within this context, this study examined adherence and persistence across medication therapies for LUTS/BPH in a general U.S. health plan that included men on private and public insurance.

Materials and Method

Patient Selection and Inclusion Criteria

The study was performed using patient information extracted from electronic medical records (EMRs) in the Reliant Medical Group in Central Massachusetts. The study population consisted of adult men at least 18 years of age diagnosed with LUTS/BPH and who were identified from the 2000 to 2010 Reliant Medical Group EMR database. Men were eligible for inclusion if they had at least two diagnoses of LUTS/BPH (International Classification of Diseases, Ninth Revision [ICD-9] 222.2 and 600.xx) within the selection window of January 1, 2000 through December 30, 2010. Patients were required to have a second diagnosis within 6 months of their first diagnosis to prevent misclassification.

Measures

Medication adherence refers to how well a patient's medication-taking behavior aligns with a health care provider's treatment plan (Verhamme et al., 2003). A prescription fill, the unit from which adherence and persistence are derived, is a prescription order entered by a physician in the EMR that includes a quantity, days' supply of therapy, and an authorized number of refills. While most fills were for 365 days or fewer, for ease of analysis and interpretation, fills of greater than 1 year were truncated at 365 days. Medication persistence assesses the length of time on therapy and was calculated based on the time in consecutive days from initiation of index medication class until end of treatment, as captured in the EMR. The length of time on therapy includes reasonable gaps between fills or new prescription orders by the physician. Days' supply for each drug class was assessed based on number of days covered by the prescriptions and refills. Adherence and persistence were assessed for patients with at least two prescription orders.

Analyses

The demographic and clinical characteristics of patients with LUTS/BPH were described using frequency and percentage distributions for categorical variables. The normally distributed continuous and count variables were described using a mean, standard deviation, and median. All analyses were conducted using SAS® Version 9.2 (SAS Institute, Inc., Cary, NC).

Results

Patient Characteristics

A total of 1,807 patients with LUTS/BPH were identified from the EMR database. The majority (96.7% [1,748/1,807]) of the patient population were 50 years of age or older. Eighty-one percent (1,458/1,807) of all patients with LUTS/BPH had diabetes or diabetes-related comorbidities, and 68% (1,234/1,807) of all patients with LUTS/BPH had cardiovascular comorbidities (Table 1).

Adherent Treatment Patterns

Overall, all patients with LUTS/BPH refilled their index prescription an average of 6.3 times (SD = 5.5), with

Table 1. Baseline Characteristics: All Patients and Patients With Benign Prostatic Hyperplasia and Erectile Dysfunction.

Characteristic	All LUTS/ BPH patients (*N* = 1,807)
Age at index (years), *n* (%)	
18-29	0 (0)
30-39	3 (0.2)
40-49	56 (3.1)
50-64	462 (25.6)
65+	1,286 (71.2)
Age (years), mean	70.8
Specialty at index, *n* (%)	
Primary care	1,110 (61.4)
Urology	383 (21.2)
Other and unknown	314 (17.3)
Comorbidities, *n* (%)	
Cardiovascular	1,234 (68.3)
Diabetes and diabetes-related	1,458 (80.7)
Bladder dysfunction	511 (28.3)
Other	151 (8.4)
None	330 (18.3)
Outpatient physician visits	
Patients with physician visits, *n* (%)	1,621 (89.7)
Mean (*SD*)	3.4 (3.3)
Prostate-specific antigen blood test, *n* (%)	723 (40.0)
N	602
Mean (*SD*)	4.3 (6.0)
Median	2.5
Testosterone level, *n* (%)	33 (1.8)
N	28
Mean (*SD*)	410.5 (156.1)
Median	399.5

Note. LUTS/BPH = lower urinary tract symptoms/benign prostatic hyperplasia.

combination therapy users refilling an average of 9.4 times (*SD* = 6.2). Only 15.8% (285/1,807) of patients filled their index prescription once, though no patients on combination therapy were prescribed their index prescription one time (Table 2).

Persistent Treatment Patterns

Overall, patients persisted on their index prescription therapy for an average of 1757.0 days (*SD* = 1244.6 days), with patients who initiated on combination therapy persisting for an average of 2174.3 days (*SD* = 1248.6 days; Table 3). Slightly over 7% (110/1,522) of all patients persisted on their index therapy for less than a year, with 11.6% (62/534) of patients initiating on alpha-blocker therapy persisting for less than a year. Nearly 50% (723/1,522) of all patients persisted on their index therapy for over 4 years, with 63.5% (455/717) of patients initiating on combination therapy persisting for more than 4 years (Table 3).

Supply of Index Therapy

Overall, a mean of 1640.5 days were prescribed for the index therapy (*SD* = 1302.2 days), with patients on combination therapy at index receiving a mean of 2152.7 days (*SD* = 1457.2 days) of therapy. Only 8.0% (122/1,522) of patients had index therapy prescriptions written for less than 1 year, and 41.6% (633/1,522) had prescriptions written for the index therapy for more than 4 years. As with the other measures of adherence and persistence, combination therapy patients received a longer supply (Table 4).

Patients With LUTS/BPH and Erectile Dysfunction

The subgroup of patients with LUTS/BPH and ED showed similar adherent and persistent treatment patterns and similar patterns for written prescriptions for the index therapy when compared with patients with LUTS/BPH (results not shown).

Discussion

The safety and efficacy of a prescribed drug are two critical factors that help physicians determine a patient's treatment plan; however, also important is the commitment from the patient to take their medication as prescribed and for the duration of time necessary for the particular treatment. In this study, medication adherence and persistence patterns were examined in a population of men with LUTS/BPH. The results from the study demonstrated that a high percentage of men with LUTS/BPH were reasonably adherent and persistent with their index therapies, especially men taking combination therapy. Similar to this study, Verhamme et al. (2003) and Nichol et al. (2009) reported higher rates of persistence among patients who used combination therapy. Overall persistence in this study was considerably longer than that seen in the Verhamme et al. (2003) study and adherence was better than that reported in Schoenfeld et al. (2014); however, this study had a longer follow-up period than the Verhamme and Schoenfeld studies, hence a longer average length of time on therapy would be expected. Longer persistence may be, in part, due to the type of health plan studied. Theoretically, patient follow-up may be better in an integrated delivery system that includes an EMR system (Yeaw, Benner, Walt, Sian, & Smith, 2009); however, system-related variables were not measured in this study. One possible explanation for the considerably higher rates of persistence and refills among patients on combination therapy

Table 2. Number of Index Prescription Fills by Drug Category.

	All LUTS/BPH patients			
Measure	All patients, *N* = 1,807	Alpha-blockers, *N* = 709	5-ARIs, *N* = 381	Combination of alpha-blockers and 5-ARIs, *N* = 717
1 Fill, *n* (%)	285 (15.77)	175 (24.68)	110 (28.87)	0 (0.00)
2 Fills, *n* (%)	216 (11.95)	124 (17.49)	53 (13.91)	39 (5.44)
3 Fills, *n* (%)	224 (12.40)	103 (14.53)	56 (14.70)	65 (9.07)
≥4 Fills, *n* (%)	1,082 (59.88)	307 (43.30)	162 (42.52)	613 (85.50)
Mean (*SD*)	6.26 (5.48)	4.31 (3.70)	4.04 (3.44)	9.35 (6.19)
Median	5.00	2.75	3.16	8.00

Note. LUTS/BPH = lower urinary tract symptoms/benign prostatic hyperplasia; 5-ARIs = 5-alpha reductase inhibitors. Combination of alpha-blockers and 5-ARIs is based on patients who had at least two prescriptions filled (one for alpha-blocker and one for 5-ARIs).

Table 3. Persistence on Index Therapy.

	LUTS/BPH patients with ≥2 prescriptions			
Measure	All patients, *N* = 1,522	Alpha-blockers, *N* = 534	5-ARIs, *N* = 271	Combination of alpha-blockers and 5-ARIs, *N* = 717
Patients with at least two prescriptions filled (%)	84.23	75.32	71.13	100.00
<1 Year, *n* (%)	110 (7.23)	62 (11.61)	24 (8.86)	24 (3.35)
1-2 Years, *n* (%)	254 (16.69)	131 (24.53)	63 (23.25)	60 (8.37)
2-3 Years, *n* (%)	266 (17.48)	111 (20.79)	57 (21.03)	98 (13.67)
3-4 Years, *n* (%)	169 (11.10)	41 (7.68)	48 (17.71)	80 (11.16)
>4 Years, *n* (%)	723 (47.50)	189 (35.39)	79 (29.15)	455 (63.46)
Mean (*SD*), days	1756.95 (1244.60)	1454.13 (981.38)	1249.35 (882.85)	2174.33 (1248.63)
Median, days	1379.50	1260.36	1028.98	1929.00

Note. LUTS/BPH = lower urinary tract symptoms/benign prostatic hyperplasia; 5-ARIs = 5-reductase inhibitors. Combination of alpha-blockers and 5-ARIs is based on patients who had at least two prescriptions filled (one for alpha-blocker and one for 5-ARIs).

Table 4. Adherence to Index Therapy.

	LUTS/BPH patients with ≥2 prescriptions			
Measure	All patients, *N* = 1,522	Alpha-blockers, *N* = 534	5-ARIs, *N* = 271	Combination of alpha-blockers and 5-ARIs, *N* = 717
Patients with at least two prescriptions filled (%)	84.23	75.32	71.13	100.00
<1 Year, *n* (%)	122 (8.02)	73 (13.67)	27 (9.96)	22 (3.07)
1-2 Years, *n* (%)	300 (19.71)	168 (31.46)	59 (21.77)	73 (10.18)
2-3 Years, *n* (%)	264 (17.35)	103 (19.29)	63 (23.25)	98 (13.67)
3-4 Years, *n* (%)	203 (13.34)	56 (10.49)	52 (19.19)	95 (13.25)
>4 Years, *n* (%)	633 (41.59)	134 (25.09)	70 (25.83)	429 (59.83)
Mean (*SD*), days	1640.47 (1302.18)	1180.43 (992.06)	1191.73 (752.41)	2152.71 (1457.18)
Median, days	1230.00	850.04	1048.89	1783.00

Note. LUTS/BPH = lower urinary tract symptoms/benign prostatic hyperplasia; 5-ARIs = 5-alpha reductase inhibitors. Combination of alpha-blockers and 5-ARIs is based on patients who had at least two prescriptions filled (one for alpha-blocker and one for 5-ARIs).

is that, consistent with the literature on combination therapy (Filson et al., 2013; Nichol et al., 2009), patients observe positive changes in their urinary symptoms and have an incentive to be persistent (Nichol et al., 2009). It is also possible that physicians who prescribe combination therapy provide better expectations for the patients

about when to anticipate results, perhaps based on guideline recommendations and recent clinical trial work (Casabé et al., 2014; Kaplan et al., 2006; McConnell et al., 2003; Oelke et al., 2012). The type of physician (e.g., specialty) prescribing a treatment pattern was not examined.

Limitations

Given that the sample size for this study is small, one should use caution when interpreting these findings. The relatively high prevalence of diabetes and cardiovascular disease from the sample size is due to the baseline incidence of these conditions in the population of Central Massachusetts where the data were collected. These higher comorbidity rates might also explain why this patient population had a higher than expected rate of medication adherence. Perhaps patients that have already become accustomed to taking prescribed medications on a daily basis have a higher likelihood of adhering to their prescribed medications for treating LUTS/BPH. Dropout rates and noncompliance may be a greater challenge in a younger and healthier population that is not accustomed to taking medications. These results may, therefore, limit the generalizability of this study's findings. The measures of adherence and persistence are derived from prescriptions appearing in the EMR, not dispensed prescriptions from the pharmacy, which makes this study fundamentally different from comparable studies. The number of prescription fills might look small in the context of the relatively long average amount of time patients spent on therapy; however, this quantity is suitable given that fills included refill days, which often exceeded 180 total days of therapy; the days on therapy for fills and gaps between fills were truncated. The incidence of diabetes and cardiovascular disease was higher in the Reliant Medical Group EMR database than in the general population; it is possible that chronic sexual dysfunction was present in these men which might have affected compliance rates. Findings from the study are generalizable to similar integrated delivery networks (IDNs), and the results may not be representative of all group practices in the United States. The Reliant Medical Group EMR database contains practitioner physician records within the IDN, so patients treated outside the IDN were not captured in this analysis; all data were subject to recording errors. In the absence of symptom assessments, no assumptions or adjustments for disease severity were possible. Causality cannot be attributed to findings in observational studies.

Conclusions

Although BPH/LUTS is not a life-threatening disease, rates of persistence and adherence were reasonably high in this group. These findings are consistent with the literature on adherence and persistence in this disease state and extend the current understanding by providing a much longer follow-up period. The key finding is that men, especially on combination therapy, persist for years. The findings about combination therapy drive the difference in observed persistence levels. Physicians familiar with the results of the combination therapy trials, such as the Combination of Avodart and Tamsulosin trial and the Medical Therapy of Prostatic Symptoms trial (McConnell et al., 2003; Roehrborn et al., 2010), may have more confidence in setting therapeutic goals that emphasize the need for chronic therapy, thereby translating into long-term persistence. Although combination therapy was not the most common index therapy, the observed adherence and persistence rates suggest that, consistent with the Medical Therapy of Prostatic Symptoms trial findings (Kaplan et al., 2006), patients likely experience urinary symptom improvement to the extent that they are willing to tolerate the challenges of remaining persistent, including cost and inconvenience, for an average of 5.9 years.

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