Comparative Effectiveness of Anticholinergic Agents for Lower Urinary Tract Symptoms

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ABSTRACT

BACKGROUND: Limited data from short-term clinical trials suggest efficacy advantages of solifenacin and fesoterodine over other anticholinergic agents in the treatment of lower urinary tract symptoms.

OBJECTIVES: To (a) determine the real-world comparative effectiveness of newer anticholinergic agents for lower urinary tract symptoms, as assessed by 1-year persistence, and (b) identify patient factors independently associated with persistence.

METHODS: We conducted a retrospective cohort study of U.S. veterans initiating newer anticholinergic therapy between October 2007 and August 2015. Multiple log-binomial regression was used to contrast 1-year persistence rates across anticholinergic agents while adjusting for measured confounders. Persistence was selected as a measure of effectiveness because nonpersistence is a common pathway encompassing inefficacy and intolerability, particularly in symptom-driven conditions.

RESULTS: A total of 26,775 patients were included, of which 10,386 (38.8%) persisted with anticholinergic therapy at 1 year. Using long-acting tolterodine as the reference agent, superior persistence rates were observed for solifenacin (RR = 1.08, 95% CI = 1.03-1.13) and fesoterodine (RR = 1.25, 95% CI = 1.09-1.43), and a lower rate for short-acting tolterodine (RR = 0.90, 95% CI = 0.85-0.94). Patient factors associated with higher persistence rates included older age, male sex, and comorbidities such as multiple sclerosis, Parkinson's disease, and diabetes.

CONCLUSIONS: Consistent with clinical trial reports, we found evidence for superior effectiveness of solifenacin and fesoterodine relative to other anticholinergics and for long-acting formulations over short-acting formulations.

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What is already known about this subject

- Several newer anticholinergic medications are available for the management of lower urinary tract symptoms and purport lower adverse event risk than oxybutynin.
- Among these agents, short-term (12-week) clinical trials suggest a potential efficacy advantage for solifenacin and fesoterodine relative to other agents, most commonly tolterodine.

What this study adds

- Using real-world administrative data from the Veterans Health Administration, higher rates of 1-year persistence were observed for solifenacin and fesoterodine relative to tolterodine, which is consistent with clinical trial findings.
- Overall, 1-year persistence to newer anticholinergics was poor (< 40%), suggesting a clinical need for more effective alternatives in the management of lower urinary tract symptoms.

The International Continence Society defines lower urinary tract symptoms as symptoms resulting from conditions and diseases effecting the bladder and urethra, including urinary incontinence symptoms, overactive bladder symptoms, voiding symptoms, and post-micturition symptoms.[1] An estimated 29.8 million U.S. men and women aged more than 40 years suffer from overactive detrusor symptoms.[2] In addition, lower urinary tract symptoms can contribute to impairments in health-related quality of life and mental health, leading to increased rates of depression and anxiety.[3]

Current guidelines first recommend behavioral therapy in the management of overactive detrusor symptoms, including bladder training, pelvic floor exercises, fluid restriction, and bladder control strategies.[4] If pharmacologic treatment is initiated, anticholinergic agents are often used as first-line therapy, particularly if overactive bladder is suspected. This drug class provides symptomatic relief by preventing involuntary contractions of the bladder detrusor muscle by inhibiting acetylcholine from binding to the M_2 and M_3 muscarinic receptors. However, these agents also exhibit pharmacologic activity on muscarinic receptors in the central nervous system, gastrointestinal tract, eyes, and salivary glands, which can lead to troublesome adverse events such as dry mouth, constipation, confusion, and blurred vision and contribute to frequent discontinuation in clinical populations.[5]

Oxybutynin has been the mainstay of pharmacologic treatment for over 30 years, but nonselective muscarinic receptor antagonism frequently leads to adverse events.[5] Subsequent congeners differ in selectivity for muscarinic receptors with potential improvements in efficacy and tolerability. However, data concerning comparative effectiveness among these newer agents are generally limited to reports from short-term (12-week) clinical trials.[6-15] It is unclear whether findings from short-term efficacy trials using highly selected, healthy participants generalize to meaningful outcomes in real-world populations using these medications over longer time periods.

In order to address some of these limitations, the primary objective of this study was to determine the comparative effectiveness of newer anticholinergic agents, using real-world clinical data from the Veterans Health Administration (VA). Based on existing clinical trials suggesting superior efficacy,[6-15] our principal hypotheses were that solifenacin and fesoterodine would correspondingly demonstrate superior effectiveness

over extended-release tolterodine, where effectiveness was determined by 1-year persistence rates. The secondary objective of this study was to explore patient factors associated with persistence, including demographic characteristics and medical conditions.

Methods

Data Source and Design

This retrospective cohort study was approved by the University of Iowa Institutional Review Board and the Iowa City VA Research and Development Committee. National administrative data from the VA Corporate Data Warehouse were accessed via the VA Informatics and Computing Infrastructure. Dispensing events from pharmacy files were used to identify new anticholinergic medication prescriptions and characterize persistence over time. Outpatient encounter files were used to determine the presence of medical comorbidity.

Patient Selection

Patients initiating a newer anticholinergic medication (tolterodine, trospium, solifenacin, darifenacin, or fesoterodine) were identified by a first prescription fill released for any of these agents between October 1, 2007, and February 28, 2014, which was also preceded by a 1-year period of regular VA medication use but no fills of these anticholinergic medications.[16] If a patient received more than 1 of these agents during the study period, only the first episode of care was included. Previous use of oxybutynin was allowed and adjusted for in the statistical analysis. Patients with an outpatient encounter coded for narrow-angle glaucoma (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] code 365.02) in the year before the index date were excluded because patients with this contraindication to anticholinergic therapy would likely have systematically different clinical outcomes. For the primary analysis, at least 1 VA medication fill for any drug was required in the 6 months following the 1-year observation period to ensure adequate follow-up and that apparent anticholinergic discontinuation was not attributable to the patient exiting VA care. We conducted a sensitivity analysis omitting this exclusion in which these patients were classified as nonpersistent, rather than being excluded from the analysis.

Anticholinergic Persistence

The primary outcome was 1-year persistence of the anticholinergic agent and was determined based on the sequence of prescription refills in the administrative pharmacy files during the year following initiation according to a cabinet supply approach.[17] The index anticholinergic drug was considered discontinued at the first point a fill was dispensed that was followed by a period of more than 2 times the days supply value of that fill before a subsequent fill was observed. For example, if the index fill was a 30-day supply on Day 1, then the drug would be considered discontinued if another fill was not observed before Day 61. The days supply ratio of 2 allowed patients to be up to 50% nonadherent without considering therapy as discontinued.

Since we could not determine the exact date of discontinuation, we first made the assumption that patients took their entire last supply before discontinuation, such that the discontinuation date in the primary analysis was assigned as the date of last fill plus the days supply value from that fill. In the previous example, this would be Day 31. We explored the alternative assumption in a sensitivity analysis, that the patient took no medication beyond the fill date, so that the discontinuation date would be Day 1 in the previous example. If no discontinuation date was observed before Day 365, the patient was considered persistent at 1 year.

Using the same approach, we also examined 90-day persistence as an alternative outcome variable in a sensitivity analysis. We further examined the proportion of days covered compliance metric as an alternative outcome definition, where a value ≥ 0.8 was considered compliant.[18] For patients starting tolterodine or trospium, transition between short-acting and long-acting formulations over time was not considered discontinuation.

Statistical Analysis

Associations between model variables and dichotomous outcomes were represented by relative risks (RRs) and estimated using log-binomial regression. First, unadjusted RRs were determined for each variable in separate bivariate models. Next, a fully specified multivariable log-binomial model was constructed to contrast 1-year persistence between newer anticholinergics, adjusted for confounding variables, using a generalized linear mixed model with a log link.

The multivariable model also included random intercepts for VA medical center and year to account for patient clustering within facility and potential temporal effects. Long-acting tolterodine was identified as the index medication for over half of the study population and therefore served as the comparator agent. All statistical tests were conducted using SAS version 9.4 (SAS Institute, Cary, NC) and were 2-tailed with $\alpha = 0.05$ as the threshold for significance.

Four sensitivity analyses were conducted to assess the stability of the findings under alternative methodology parameters, as previously outlined. The log-binomial regression model failed to converge in one of the sensitivity analyses, so a logistic regression model was substituted using identical adjustment variables and random intercepts, with results presented in terms of odds ratios (ORs) instead of RRs.

Because drug selection in this observational study was made according to routine clinical practice, regression models were adjusted for demographic and clinical

TABLE 1 Clinical Characteristics of Veterans Initiating Second-Generation Anticholinergic Agents for Lower Urinary Tract Symptoms (N = 26,775)

Clinical Characteristic	%	(n)
Bladder antispasmodic		
Tolterodine, long acting	58.1	(15,563)
Tolterodine, short acting	14.0	(3,736)
Trospium, long acting	1.3	(355)
Trospium, short acting	9.1	(2,425)
Solifenacin	13.6	(3,652)
Darifenacin	2.9	(768)
Fesoterodine	1.0	(276)
Demographics		
Age, years		
<65	35.6	(9,542)
65-75	27.0	(7,242)
>75	37.3	(9,991)
Sex		
Male	86.8	(23,252)
Female	13.2	(3,523)
Race		
White	71.2	(19,061)
Black	14.4	(3,854)
Other	5.1	(1,364)
Unknown	9.3	(2,496)
Residence		
Urban	84.3	(22,574)
Rural	15.7	(4,201)
Clinical conditions		
Overactive bladder	22.5	(6,024)
Benign prostatic hypertrophy	16.2	(4,343)
Neurogenic bladder	11.2	(3,002)
Multiple sclerosis	2.1	(567)
Parkinson's disease	3.9	(1,042)
Stroke/TIA	3.1	(842)
Diabetes	32.4	(8,681)
Pelvic organ prolapse	1.0	(267)
Prostate cancer	24.5	(6,547)
Urinary tract infection	16.6	(4,451)
Urological management		
Urology prescriber	31.5	(8,437)
Oxybutynin use in previous year	67.9	(18,172)

TIA = transient ischemic attack.

characteristics that may have confounded the relationship between anticholinergic treatment choice and persistence. Demographic factors included age, sex, race, and rural residence. Medical conditions that were potential clinical indications for anticholinergic therapy, whether appropriate or inappropriate, were identified by the presence of an ICD-9-CM-coded outpatient encounter occurring within 365 days before or within 365 days following the index date and included overactive bladder (596.51, 596.52, and 596.59); benign prostatic hyperplasia (600.10, 600.11, 600.21, 600.91, 601.8, 602.3, 788.21, and 790.93); neurogenic bladder (344.61 and 596.54); urinary incontinence (788.3, 788.91, 788.91, 788.39, 788.41, 788.61, 788.62, 788.64, 788.69, and 788.99); and urinary tract infection (599.0 and V13.02).

Since anticholinergic therapy may be prescribed symptomatically before establishing a definitive diagnosis, this time window allowed for revision to medical diagnoses over the course of treatment. Medical comorbidities that we hypothesized may be associated with diminished clinical response to anticholinergic therapy were also identified based on the presence of an ICD-9-CM coded outpatient encounter within the year before the index date and included multiple sclerosis (340.0); Parkinson's disease (332.0); history of cerebral infarction or transient ischemic attack (435.8, 435.9, 434.91, 434.11, 434.01, 433.91, 433.81, 433.31, 433.21, 433.11, and 433.01); diabetes mellitus (249.00-249.99 and 250.00-250.99); pelvic organ prolapse (618); and history of malignant disease in the pelvic region (185.0, 188.0, 188.1, 188.2, 188.3, 188.4, 188.5, 188.8, 188.9, 198.1, 222.2, 233.4, 233.7, 233.9, 236.7, 236.90, 236.99, 239.4, V10.51, V10.50, and V10.59).

Finally, our statistical models were adjusted for oxybutynin use in the year before the index date and whether the prescriber initiating anticholinergic medication was a urological specialist.

Results

A total of 29,667 veterans initiated newer anticholinergic therapy during the study period. After applying exclusion criteria for narrow angle glaucoma (n = 121) and loss to follow-up (n = 2,771), 26,775 patients were included in the primary analysis. Clinical characteristics for the study group are summarized in Table 1. The most commonly initiated anticholinergic medication was long-acting tolterodine (58.1%), followed by short-acting tolterodine (14.0%) and solifenacin (13.6%). The majority of patients were male (86.8%), white race (71.2%), and urban residents (84.3%). Common clinical conditions included diabetes (32.4%) and prostate cancer (24.5%). Over two thirds of patients had a history of VA prescription fills for oxybutynin in the previous year (67.9%).

The overall rate of medication persistence at 1 year was 38.8% (n = 10,386) and varied among individual agents (Table 2). Unadjusted persistence frequencies ranged from 33.5% for short-acting trospium to 44.9% for fesoterodine. Before statistical adjustment, persistence was significantly lower among short-acting tolterodine (RR = 0.92; 95% confidence interval [CI] = 0.88-0.96) and short-acting trospium (RR = 0.85, 95% CI = 0.80-0.90) users, relative to long-acting tolterodine (Table 2).

After controlling for confounding factors including demographics, clinical conditions, and urological management variables, short-acting tolterodine remained inferior to long-acting tolterodine (RR = 0.90, 95% CI = 0.85-0.94), but short-acting

TABLE 2 Correlates of 1-Year Persistence with Second-Generation Anticholinergic Agents Following Initiation (N = 26,775)

Clinical Characteristic	Frequency of 1-Year Persistence % (n)		Unadjusted Models[a] RR (95% CI)		Multivariable Model[b] RR (95% CI)	
Bladder antispasmodic						
Tolterodine, long acting	39.5	(6,150)	1.0	[Reference]	1.0	[Reference]
Tolterodine, short acting	36.4	(1,358)	0.92	(0.88-0.96)	0.90	(0.85-0.94)
Trospium, long acting	37.2	(132)	0.94	(0.82-1.08)	0.97	(0.85-1.12)
Trospium, short acting	33.5	(813)	0.85	(0.80-0.90)	0.95	(0.89-1.02)
Solifenacin	40.6	(1,483)	1.03	(0.98-1.07)	1.08	(1.03-1.13)
Darifenacin	42.4	(326)	1.07	(0.99-1.17)	1.04	(0.95-1.13)
Fesoterodine	44.9	(124)	1.14	(0.99-1.30)	1.25	(1.09-1.43)
Demographics						
Age, years						
< 65	36.4	(3,475)	0.93	(0.90-0.97)	0.95	(0.91-0.99)
65-75	39.0	(2,825)	1.0	[Reference]	1.0	[Reference]
> 75	40.9	(4,086)	1.05	(1.01-1.09)	1.02	(0.98-1.06)
Sex						
Male	39.3	(9,147)	1.0	[Reference]	1.0	[Reference]
Female	35.2	(1,239)	0.89	(0.85-0.94)	0.90	(0.86-0.95)
Race						
White	39.3	(7,484)	1.0	[Reference]	1.0	[Reference]
Black	34.7	(1,337)	0.88	(0.84-0.93)	0.96	(0.91-1.01)
Other	38.9	(530)	0.99	(0.92-1.06)	0.97	(0.91-1.05)
Unknown	41.5	(1,035)	1.06	(1.01-1.11)	0.99	(0.95-1.05)
Residence						
Urban	38.5	(8,694)	0.96	(0.92-0.99)	0.97	(0.93-1.01)
Rural	40.3	(1,692)	1.0	[Reference]	1.0	[Reference]
Clinical conditions						
Overactive bladder	38.7	(2,328)	1.00	(0.96-1.03)	1.01	(0.97-1.05)
BPH	34.3	(1,488)	0.86	(0.83-0.90)	0.89	(0.85-0.93)
Neurogenic bladder	38.0	(1,141)	0.98	(0.93-1.03)	0.96	(0.91-1.01)
Multiple sclerosis	45.9	(260)	1.19	(1.08-1.30)	1.26	(1.15-1.38)
Parkinson's disease	45.8	(477)	1.19	(1.11-1.27)	1.15	(1.07-1.23)
Stroke/TIA	41.3	(348)	1.07	(0.98-1.16)	1.10	(1.01-1.19)
Diabetes	41.6	(3,615)	1.11	(1.08-1.15)	1.12	(1.08-1.15)
Pelvic organ prolapse	30.0	(80)	0.77	(0.64-0.93)	0.87	(0.72-1.05)
Prostate cancer	35.4	(2,317)	0.89	(0.86-0.93)	0.89	(0.86-0.93)
Urinary tract infection	34.5	(1,535)	0.87	(0.83-0.91)	0.91	(0.88-0.94)
Urological management						
Urology prescriber	35.6	(3,003)	0.88	(0.85-0.91)	0.91	(0.88-0.94)
Oxybutynin use, previous year	39.0	(7,085)	1.02	(0.98-1.05)	1.04	(1.01-1.08)

[a]*Unadjusted models conducted using log-binomial regression.*

[b]*The multivariable log-binomial regression model was adjusted for all demographic, clinical conditions, and urological management variables and included random intercepts for VA medical center and year.*

BPH = benign prostatic hypertrophy, CI = confidence interval, RR = relative risk, TIA = transient ischemic attack; VA = Veterans Affairs.

trospium was no longer statistically different. Mulitvariable analyses further revealed significantly greater 1-year persistence for solifenacin (RR = 1.08, 95% CI = 1.03-1.13) and fesoterodine (RR = 1.15, 95% CI = 1.09-1.43).

We further conducted 4 sensitivity analyses to test the stability of primary analysis results given alternative approaches to several key study design parameters (Table 3). The main findings of lower persistence with short-acting tolterodine and higher persistence with solifenacin and fesoterodine, relative to the comparator agent (long-acting tolterodine), were corroborated in all sensitivity analyses with minimal variability in risk estimates.

The secondary objective of this study was to use the fully specified multivariable log-binomial model to explore relationships between clinical characteristics and 1-year persistence (Table 2). Patients aged less than 65 years were less persistent

TABLE 3 Sensitivity Analyses

Bladder Antispasmodic	Primary Analysis Main Findings RR (95% CI)	Sensitivity Analyses[a] 1. Lost to Follow-up Treated as Discontinued RR (95% CI)	2. Alternative Persistence Definition RR (95% CI)	3. Alternative Outcome, PDC ≥ 80% RR (95%CI)	4. Persistence > 90 Days OR (95% CI)[b]
Tolterodine, long acting	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]
Tolterodine, short acting	0.90 (0.85-0.94)	0.90 (0.86-0.95)	0.89 (0.84-0.94)	0.83 (0.78-0.87)	0.89 (0.82-0.97)
Trospium, long acting	0.97 (0.85-1.12)	0.98 (0.85-1.13)	1.01 (0.87-1.18)	0.91 (0.78-1.06)	0.98 (0.77-1.25)
Trospium, short acting	0.95 (0.89-1.02)	0.94 (0.88-1.01)	0.96 (0.89-1.04)	0.87 (0.81-0.94)	0.91 (0.81-1.02)
Solifenacin	1.08 (1.03-1.13)	1.08 (1.03-1.14)	1.09 (1.03-1.15)	1.06 (1.01-1.12)	1.17 (1.07-1.29)
Darifenacin	1.04 (0.95-1.13)	1.02 (0.93-1.12)	1.07 (0.97-1.17)	1.07 (0.98-1.17)	1.10 (0.93-1.31)
Fesoterodine	1.25 (1.09-1.43)	1.27 (1.10-1.47)	1.31 (1.12-1.52)	1.23 (1.06-1.43)	1.54 (1.14-2.09)

[a]*All log-binomial regression models included random intercepts for VA medical center and year and were adjusted for all demographic, clinical conditions, and urological management variables included in the primary analysis (see Table 2).*

[b]*The log-binomial model did not converge. We therefore presented findings for sensitivity analysis #4 in terms of ORs based on logistic regression using the same random intercepts and adjustment variables. While the magnitude of the OR and RR estimates are not directly comparable, the treatment effects reaching statistical significance are consistent with the primary analysis and other sensitivity analyses.*

CI = confidence interval, OR = odds ratio; PDC = proportion of days covered, RR = relative risk.

(RR = 0.95, 95% CI = 0.91-0.99) as were women (RR = 0.90, 95% CI = 0.86-0.95). No differences were observed across racial groups or between urban and rural residents.

Of clinical conditions that might serve as the focus of treatment with anticholinergic medications, persistence was significantly lower for patients with benign prostatic hypertrophy, compared with patients without this diagnosis (RR = 0.89, 95% CI = 0.85-0.93). In contrast, no differences were observed for patients with overactive bladder or neurogenic bladder. We also examined several clinical conditions that we hypothesized may adversely affect the effectiveness of anticholinergic therapy. Consistent with this hypothesis, patients with prostate cancer or history of urinary tract infection had lower persistence (Table 2). However, several conditions ran contrary to our hypothesis and were associated with higher persistence rates, including multiple sclerosis, Parkinson's disease, and diabetes. Anticholinergic therapy initiated by a urological specialist was associated with lower persistence rates (RR = 0.91, 95% CI = 0.88-0.94), whereas previous oxybutynin use was associated with greater persistence (RR = 1.04, 95% CI = 1.01-1.08).

Discussion

Clinicians have an array of therapeutic alternatives in the management of lower urinary tract symptoms. Anticholinergic agents vary in receptor affinity profiles, but there is limited evidence that these differences translate into clinically meaningful differences in real-world patients. Data concerning comparative effectiveness among newer anticholinergic agents are limited to 12-week clinical efficacy trials. The majority of these reports used tolterodine immediate release or extended release as the active comparator and found evidence of potential superiority for fesoterodine[9,10,12-14] and solifenacin.[6-8,11] The only head-to-head trial of these 2 drugs reported equivalency between fesoterodine and solifenacin.[15]

While suggesting a potential benefit for fesoterodine and solifenacin over tolterodine, there are several important limitations. First, these studies generally used multiple outcome measures, and superiority was typically demonstrated on some, but not all measures. Outcome measures in clinical trials included measures such as frequency of voiding, volume of voiding, and frequency of incontinence episodes, which may be difficult to directly translate into meaningful patient-oriented outcomes. In addition, all studies demonstrating superiority were funded by that drug's manufacturer, raising a potential concern regarding publication bias or other biases in trial design. Finally, it is unclear whether findings of short-term efficacy trials using highly selected and relatively healthy participants will generalize to clinical populations using these medications over longer time periods. Thus, our study provides an important complement to the existing literature in that it was independently conducted, examined a clinical population in a real-world practice environment, and used a clinically meaningful outcome measure applied over a longer time frame. Using this approach, our results were consistent with existing clinical trial literature supporting superior effectiveness of solifenacin and fesoterodine over tolterodine.[6-14]

One previous study contrasted persistence among the newer anticholinergic agents and similarly favored solifenacin.[19] Medication persistence has several strengths as a measure of effectiveness. Medication discontinuation is a common endpoint for lack of perceived clinical benefit and the occurrence of intolerable adverse effects, particularly for symptom-driven conditions such as overactive bladder. It further reflects patient and provider decision making, since either partner in this dyad has the authority to discontinue therapy. Therefore, persistent

medication use generally reflects the joint agreement between patients and prescribers that the benefit of ongoing therapy outweighs existing or potential harms in a way that is meaningful to individual patients. Importantly, we are not arguing that evidence based on observational data using medication persistence is inherently more valuable than objectively measured outcomes from short-term clinical trials. Rather, we see that these divergent approaches are complementary and support the same result, thus lending greater credibility to the findings of both.

The stability of our findings across multiple sensitivity analyses varying key methods parameters also strengthens confidence in our results. Of note, the sensitivity analysis examining 90-day persistence revealed that comparative differences were already evident within this time frame, which is consistent with the typical clinical trial duration of 12 weeks.

Physiological factors may explain the superior persistence of solifenacin and fesoterodine observed in this study. Solifenacin is a selective antagonist of the M_3 muscarinic receptor subtype on the bladder and is hypothesized to yield a more tolerable adverse effect profile, which could yield greater persistence. In addition, solifenacin has a long half-life of 45-68 hours, which allows for extended pharmacologic activity. Fesoterodine, an isomer of tolterodine, is also dosed once daily but does not selectively inhibit muscarinic receptors. Previous studies have suggested that patients taking fesoterodine report less urinary urge incontinence and bothersome symptoms compared with tolterodine.[10,14]

Our observation that long-acting formulations of tolterodine and trospium were superior to their short-acting counterparts also coincides with existing literature.[20-22] American Urological Association guidelines recommend that long-acting formulations be preferentially prescribed over short-acting formulations because of lower rates of dry mouth.[4] It remains unclear whether this effect is explained by improved adherence through simplification of the regimen or physiologic advantages resulting from reduced peak-trough variation relative to immediate release dosage forms.

Since comparative effectiveness was our primary focus, adjusting for potential sources of confounding was important. Moreover, our multivariable statistical model afforded important information concerning patient characteristics associated with persistence. Several studies have examined demographic characteristics, but information concerning other correlates is scant. Observing greater persistence among older patients is consistent with existing literature that either shows the same association or no effect of age.[19,23-29] Women are generally reported to have higher persistence to anticholinergic medication than men, although our findings run contrary.[23,25-27] It is possible that women receiving care in the VA health care system are not representative of typical female patients receiving anticholinergic medication for lower urinary tract symptoms in the community setting, which could explain this discrepancy.

We also hypothesized that comorbid conditions contributing to neurogenic bladder (e.g., Parkinson's disease, multiple sclerosis, stroke, or transient ischemic attack) would be associated with lower persistence, since these conditions may be more difficult to treat.[30] However, we found these conditions to be generally associated with higher persistence rates, which is consistent with 1 previous report.[23] Our findings were also consistent with previous evidence supporting anticholinergic pharmacotherapy as an effective treatment option for neurogenic bladder.[31] Previous oxybutynin use was associated with higher persistence, which may be a marker for previous symptomatic improvement from anticholinergic therapy. Finally, persistence was lower among patients managed by a urology specialist, which may reflect higher severity or overall complexity among patients referred to specialists.

Limitations

Our study has several important limitations. Anticholinergic medications were not randomly assigned but selected according to clinical judgment, which likely involved factors that we were unable to measure and adjust for but that may also relate to outcome. While we cannot completely rule out selection bias, our findings are consistent with clinical trials where treatment was randomly assigned. In addition, our selection criteria only included treatment episodes for the first newer anticholinergic medication prescribed to an individual patient. Since prescribers often follow a particular sequence in selecting therapy, drugs that typically come later in that sequence may appear to have poorer outcomes, since they are more commonly reserved for patients with a history of previous treatment failure.

A second concern is that we were unable to account for formulary restrictions in place during the study period, which can vary across individual VA medical centers. Such restrictions could be another source of confounding due to nonrandom treatment selection.

One further concern is that mandated conversions would require patients to switch to an alternative therapy, which would appear as discontinuation in our analysis. We examined this by looking at persistence rates across individual VHA facilities, and while sample sizes were small, we saw no evidence of a major shift in prescribing that would explain our findings. Further, we are not aware of any formulary changes that would specifically favor solifenacin and fesoterodine. We did not control for the effect of existing anticholinergic burden from concurrent medications, which could have contributed to higher rates of adverse events and discontinuation.

Finally, we were unable to adjust for previous or concurrent use of behavioral strategies, which would likely have a positive effect on outcomes, but we have no reason to suspect that rates of behavioral interventions would vary across anticholinergic agents.

Conclusions

Approximately 40% of patients were persistent with anticholingergic therapy at 1 year. Patients and providers are often forced to choose between a treatment that has the potential to elicit adverse events or live with a condition that negatively affects health-related quality of life. Our findings support previous studies favoring long-acting formulations over their short-acting counterparts, as well as a potential advantage for solifenacin and festorerodine. Ultimately, these observations require confirmation in independently conducted, prospective head-to-head trials. If confirmed, additional economic analyses would be helpful to discern whether modest differences in clinical effectiveness are also cost-effective given differences in drug acquisition cost.

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Study concept and design were contributed by all the authors. Shaw took the lead in data collection, along with Lund, and data interpretation was performed by Lund, Goodson, and Cantrell. The manuscript was written by Goodson, Cantrell, Lund, and Shaw and revised by Lund, Goodson, Cantrell, and Shaw.

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