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Is Self-Reported Adherence associated with Clinical Outcomes in women treated with anticholinergic medication for Overactive Bladder?

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Abstract

Aim—To determine the association between self-reported adherence to anticholinergic medication and clinical outcomes in women with overactive bladder (OAB).

Methods—Prospective study of women with OAB treated with fesoterodine for 8 weeks. Adherence to medication was measured using the Medication Adherence Self-report Inventory (MASRI). A self reported adherence rate of ≥80% was considered adherent. The association between self-reported adherence and clinical outcomes (Global Index of Improvement, Global impression of Severity, urinary symptom and quality of life scores) was examined. We hypothesized that adherent women would have greater improvement in urinary symptoms and quality of life than non-adherent women.

Results—Based on the MASRI, 115(62.5%) women were adherent and 69 (37.5%) were non-adherent to anticholinergic medication at 8 weeks. Adherent women were more likely to report overall improvement in their symptoms compared to non-adherent women (84% v 24%, p<0.001). Significantly more non-adherent women described their bladder symptoms as “moderate” or “severe” at 8 weeks compared to adherent women (74% v 44%, p=0.03). At 8 weeks, adherent women reported significantly greater improvement (change) in urinary symptoms from baseline to 8 weeks than non-adherent women (−13.3 ± 25.8 versus 2.5 ± 14.4, p = .04). Similarly, adherent

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women reported greater improvement in quality of life scores than non-adherent women (− 7.9 ± 24.0 versus −1.8 ± 11.9, p =.003).

Conclusion—Self-reported non-adherence, as measured by the MASRI, is associated with clinically meaningful outcomes in women with OAB. This further validates the MASRI as a clinically useful tool for measuring adherence to anticholinergic medications in women with OAB.

INTRODUCTION

Overactive bladder (OAB) is a common condition that is characterized by urgency, frequency, or nocturia, with or without incontinence. (1) OAB affects over 17–30% of the adult female population in the United States (2) and is associated with significant impairment in quality of life. (3, 4) Anticholinergic medications are commonly used to treat OAB in women and have been shown to reduce number of incontinence episodes, urgency, frequency and importantly, improve health-related quality of life. (5) Unfortunately, adherence to anticholinergic medication in women with OAB is remarkably low ranging from 12.0% to 39.4% at one year. (6)

Prior studies have identified predictors for poor adherence in women with overactive bladder. Using Health Maintenance Organizations (HMOs) administrative claims data of patient with OAB, Balkrishnan et al reported that poor adherence was associated with severity of co-morbidities, quality of life and total number of medications at baseline (7). In a large population based survey, Brubaker et al reported that lack of awareness of the dosing regimen and the severity of side effects were predictors of poor adherence. (8) Poor adherence also results in increased number of health care visits and greater health care costs (9, 10). Though these studies have identified populations at high risk for poor adherence as well as the economic burden of poor adherence, there remains a key gap in knowledge as to how to measure adherence as well the impact of poor adherence on symptom relief and quality of life in a given patient with overactive bladder in a clinical setting.

Several methods have been used to measure adherence to anticholinergic medication for OAB including pharmacy refill data, pill counts, electronic medication monitors, and patient self-reported or interviewer-administered questionnaires,. Pharmacy refill data are retrospective and do not offer real-time information on adherence. Electronic monitors and pill counts are expensive and difficult to operationalize in the clinical setting. We have previously validated an easy to use self-administered questionnaire, the Medication Adherence Self-Report Inventory (MASRI), to measure adherence to anticholinergic medication in women with OAB. (11) In a prospective study, the MASRI showed high correlation with an interviewer administered questionnaire and moderate correlation with pill counts at 8 and 12 weeks after prescribing anti-cholinergic medication. The MASRI is a 6-item questionnaire that takes only 2–3 minutes to complete and has been used to measure adherence in several chronic conditions in real world clinical practice. (12, 13)

The goal of the present study was to determine the association between self-reported adherence to anticholinergic medication and clinical outcomes in women with overactive bladder. We hypothesized that women who self-reported themselves as adherent would have greater improvement in urinary symptoms and quality of life than non-adherent women.

METHODS

This is a planned analysis of a secondary aim of a study that validated a self-reported instrument to measure adherence to anti-cholinergic medications in women with overactive bladder. Methods have been published previously (11). In brief, a prospective study was performed in women with OAB. Women complaining of OAB symptoms who presented to the Urogynecology and Urology clinics at the Hospital of the University of Pennsylvania were invited to participate in the study. Inclusion criteria were: age >18, urinary urgency for at least 3 months with ≥8 voids and ≥1 urgency episode/24 hours on a bladder diary, and a rating of at least moderate bother on the single item Patient Perception of Bladder Condition (14). Exclusion criteria were: predominant stress incontinence, current or recent (<6 months) use of anticholinergic medication for OAB, contraindication to anticholinergic medication, severe voiding difficulties, severe neurologic disease, recent (<6 months) anti-incontinence or prolapse surgery or pregnancy, history of pelvic neuromodulation, other lower urinary tract disorders such as calculus, urethral diverticulum, and current or recurrent urinary tract infections. The protocol was approved by the Institutional Review Board at the University of Pennsylvania and all patients signed informed consent documents.

All subjects provided demographic data and completed validated urinary symptom forms, the Urinary Distress Inventory (UDI) and the Incontinence Impact Questionnaire (IIQ) (15) at the baseline visit. Eligible women received flexible-dose fesoterodine therapy (Toviaz; Pfizer, Inc, New York, NY) 4–8 mg. Participants were started initially on fesoterodine 4 mg with the option of increasing their dose to fesoterodine 8 mg or receiving a prescription for a different anticholinergic. At the 8 week follow up visit, adherence to medication as well as clinical improvement was measured as described below.

Adherence to medication was measured using the Medication Adherence Self-report Inventory (MASRI). The MASRI is a 12-item questionnaire of self-reported medication adherence that addresses two broad themes. The first section relates to the amount of medication taken (6 items, part A) and the second relates to the timing of the doses (6 items, part B). Since fesoterodine is taken once daily, part B of the MASRI was not administered to study participants. Part A consists of 4 items that asks patients to recall number of missed doses in previous day, two days before the visit, three days before the visit and the two weeks preceding the visit. There are four responses options (0, 1, 2, and “don’t know”). An additional item asks the patient to recall when the last time a dose was missed. The last item is a visual analog scale (VAS) that measures the adherence rate as a percentage ranging from 0 to 100%. Only the VAS item is used to get the numerical estimate of the adherence rate. The other items are designed to help the patients develop this estimate and do not contribute directly to the score. The MASRI is validated for measuring adherence to anticholinergics for the treatment of OAB when compared to an interviewer-administered questionnaire, the Brief Medication Questionnaire (BMQ)($r=0.87$, $p<0.001$) and pill count ($r=0.49$, $p=0.02$) and has a sensitivity of 91%, specificity of 82%, and positive likelihood ratio of 5.1 for detecting non-adherence at 8 weeks. (11). The MASRI has also been validated for measuring adherence in other chronic medical conditions such as HIV and SLE and has been used to measure adherence in a number of prospective studies. (12, 13)

The primary clinical outcome was improvement in urinary symptoms as measured by the Patient Global Impression of Improvement. The Patient Global Impression of Improvement is a validated 7-point scale, ranging from “very much better” to “very much worse” that compares symptoms at 8 weeks to before treatment. It has been validated for use in women undergoing treatment for OAB. (16, 17). Women were defined as having improvement in their symptoms if they reported that their symptoms were “little better”, “much better” or “very much better” compared to baseline. Secondary clinical outcome were Patient Global Impression of Severity and change in the Urinary Distress Inventory (UDI-6) and Incontinence Impact Questionnaire (IIQ-7) score between baseline and 8 weeks. The Patient Global Impression of Severity is a 4-point scale that asks patients to describe their bladder symptom at 8 week as “normal”, “mild”, “moderate”, or severe”. The Urinary Distress Inventory (UDI-6) consists of 6 items and measures the degree of bother from urinary symptoms. The Incontinence Impact Questionnaire (IIQ-7) measures the impact of urinary symptoms on quality of life. Total score for the UDI and the IIQ range from 0 to 100 with higher scores indicating greater bother and worsening impact on quality of life, respectively. (15)

Adherence was defined based on responses to the MASRI. A self reported adherence rate of ≥80% was considered adherent and <80% was considered non-adherent. Descriptive characteristics of the sample at baseline were compared between the adherent and non-adherent groups. Continuous variables were summarized using median and interquartile range and categorical variables were described using relative frequency. The association of non-adherence with demographic, health-related factors, and urinary symptom scores was examined using Mann-Whitney test for continuous variables and chi-squared test for categorical variables. Additionally, we examined if the degree of adherence measured by the MASRI (defined in tertiles, i.e. 0–33%, 34–66%, 67–100% adherence) was associated with the primary clinical outcome using chi-squared test. All analyses were performed in STATA version 12(StataCorp LP, College Station, TX). Statistical tests were two-sides and $p<0.05$ was considered statistically significant. In a prior study (18), at least 50% of women who were adherent to anticholinergic medications reported improvement in their urinary symptoms. At an alpha of 0.05, our sample size gave us >90% power to detect at least a 25% difference in proportion of women reporting improvement in urinary symptoms between adherent and non-adherent women.

RESULTS

We enrolled 242 women in the study. At eight weeks, 49(20.2%) women were lost to followup and 9 (3.7%) had incomplete data; thus adherence and outcome data was available for 184 (76.0%) women and are included in the analysis. Patients included in this analysis did not differ significantly from those that were lost to follow up with respect to median age (61.0 ± 13.8 vs. 58.9 ± 13.9), baseline UDI score (52.6 ± 22.3 vs. 51.9 ± 24.3), or baseline IIQ score (32.6 ± 28.1 vs. 43.7 ± 29.2, all $p>0.05$).

Based on the MASRI, 115(62.5%) women were adherent and 69 (37.5%) were non-adherent to anticholinergic medication at 8 weeks. (Table 1) Mean age, BMI, and educational level

were not significantly different between the two groups. Prior use of anticholinergic medication was also similar between the two groups.

Baseline urinary symptom scores (UDI) as well as the impact of urinary symptoms on quality on life (IIQ) were similar in both groups. (Table 2). At 8 weeks, both urinary symptom and quality of life scores decreased (improved) for both adherent and non-adherent women. Following treatment at 8 weeks, urinary symptom scores did not differ significantly between adherent and non-adherent women. Quality of life scores were lower (better) in adherent compared to the non-adherent women although the difference did not reach statistical significance (p=0.06). However, adherent women reported significantly greater improvement (change) in urinary symptom and quality of life scores from baseline to 8 weeks than non-adherent women.

Overall, 113/184 (61.4%) of women reported improvement in the their symptoms, reflecting a response of “little better”, “much better” or “very much better” on the PGI-I at 8 weeks compared to baseline. Women who were adherent to the medication were more likely to report improvement in their symptoms compared to women who were non-adherent (84% v 24%, p<0.001) (Table 3). Conversely, women who were non-adherent were more likely to report “no change” in their symptoms compared to adherent women (77% v 11%, p<0.001). Significantly greater proportion of non-adherent women described their bladder symptoms as “moderate” or “severe” on the Patient Global Impression of Severity Index at 8 weeks than adherent women (74% v 44%, p=0.03).(Table 3)

When we examined the degree of adherence in tertiles, majority of the women fell in the first (0 – 33% adherence) and third tertile (67 to 100% adherence) with relatively few women in the middle tertile (34 to 66% adherence). Improvement in symptoms was reported by 4/55(7%) v. 7/9(77%) v. 101/120(84%) of women in the first second and third tertiles based on MASRI adherence, respectively (p <.001).

DISCUSSION

Our study shows that adherence as measured by the MASRI is associated with clinically meaningful outcomes such as improvement in urinary symptoms and quality of life and underscores the ability of the MASRI to reliably identify adherence. The MASRI even allows measurement of the degree of adherence. Though majority of women report either high or low adherence, the degree of adherence is also associated with clinical outcomes.

While objective methods such as pill counts and electronic monitors have been used extensively especially in research settings, they are not practical for use in clinical settings or in pragmatic research trials. Self-reported questionnaires remain the easiest and most “pragmatic” method to assess adherence. In other clinical conditions as well, self-reported measures of non-adherence have been found to be associated with clinical outcomes. Wu et al found that a single-item self-report tool assessing adherence to heart failure medication was associated with important outcomes such as hospitalizations and death. (19) Similarly, in HIV, self-reported adherence to antiretroviral medications is associated with outcomes such as viral load and symptom burden. (20) Our study shows that a simple self

administered instrument, the MASRI, measures adherence that is associated with clinically meaningful outcomes in women with OAB.

The association between non-adherence and patient-reported outcomes is complicated and does not necessarily represent a dose-response relationship. In our study, women who were adherent reported greater improvement in their urinary symptoms and quality of life scores as compared to non-adherent women. While this may have been due to the beneficial effect of medication, it is also possible that women who experience greater improvement in their urinary symptoms and quality of life are more likely to be adherent. Several prior studies have reported on reasons for discontinuation of anti-cholinergic medications prescribed for overactive bladder. In a survey that included 1322 US adults that discontinued anticholinergic medication prescribed for OAB, Benner et al reported the most common reason for discontinuing medication for OAB was “didn’t work as expected”, reported by 46.2%.(21) Similarly, in a cohort of 262 treatment naïve patients, Kruht et al reported that the most common reason for discontinuation was “treatment not effective”, reported by 31% patients. (22) These studies suggest that adherence is closely allied with perceived benefit of treatment and patient expectation is an important factor in adherence to anti-cholinergic medications.

Strengths of our study are that we measured adherence and patient reported outcomes using validated instruments that included global evaluation questionnaires as well as a disease-specific symptom and HRQOL instruments. A potential limitation of our study is that we did not use more objective outcomes such as bladder diaries or pad weight. However, our study was purposefully designed to be pragmatic and mimic clinical practice as this is the setting in which use of a self-reported adherence tool would be most valuable.

In conclusion, we have prospectively evaluated the clinical utility of a simple self-administered medication adherence questionnaire in women with OAB taking anticholinergic medication. Self-reported non-adherence is significantly associated with clinically meaningful outcomes of OAB treatment. This further validates the MASRI as a simple self-administered tool to measure adherence to anticholinergic medications in the clinical setting.

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Table 1

Demographic data of 184 women with overactive bladder prescribed anti-cholinergic medication

	Adherent N = 115	Non-adherent N = 69	p-value
Age (years) (mean ± SD)	62.2 ± 12.7	59.5 ± 13.7	0.25[1]
BMI (kg/m2) (mean ± SD)	31.9 ± 8.0	32.0 ± 7.8	0.96[1]
Race (N, %)			
White	72(63%)	36(52%)	
African-American	40(35%)	32(47%)	0.21[2]
Other	3(2%)	1(1%)	
Parity (median, range)	2 (0–7)	2 (0–9)	0.26[3]
Post-menopausal (N, %)	95(83%)	53(77%)	0.31[2]
Education: Highschool or more (N, %)	112(97%)	61(89%)	0.15[2]
Any prior anticholinergic use (N, %)	58(50%)	31(45%)	0.55[2]
≥2 prior anticholinergic meds	15(13%)	11(16%)	0.77[2]
Prior pelvic floor exercises (N, %)	51(44%)	24(35%)	0.27[2]
Baseline Urinary Distress Inventory score (mean ± SD)	52.2±21.1	51.0±29.5	0.75[1]
Baseline Incontinence Impact Questionnaire score (mean ± SD)	32.5±27.4	39.9±29.8	0.19[1]

[1] Mann-Whitney, non-paramentric t-test;

[2] Chi-squared test;

[3] Equality of medians test

Table 2

Urinary symptom scores in women adherent or non-adherent to anti-cholinergic medication for overactive bladder

Urinary Symptom Score		**Adherent N=115**	**Non-Adherent N=69**	**P-value[1]**
Urinary Distress Inventory	Baseline	52.2 ± 21.1	51.0 ± 29.5	0.75
	8-weeks	40.8 ± 25.6	43.6 ± 27.5	0.73
	Change	−13.3 ± 25.8	−2.5 ± 14.4	**0.04**
Incontinence Impact Questionnaire	Baseline	32.5 ± 27.4	39.9 ± 29.8	0.19
	8-weeks	23.6 ± 25.7	33.9 ± 27.9	**0.06**
	Change	−7.9 ± 24.0	−1.8 ± 11.9	**0.003**

[1]Mann-Whitney, non-parametric t-test

Table 3

Symptom Improvement and Patient Impression of Severity at 8 week in women adherent or non-adherent to anti-cholinergic medication for overactive bladder.

	Adherent N=115	Non-Adherent N=69	P-value[1]
Patient Global Impression of Improvement			
Very much better	18%	2%	
Much better	31%	4%	
Little better	35%	18%	
No change	11%	77%	**<0.001**[3]
Little worse	3%	0	
Much worse	1%	0	
Very much worse	1%	0	
Patient Global Impression of Severity			
Normal	12%	13%	
Mild	44%	13%	
Moderate	33%	61%	**0.03**[3]
Severe	11%	13%	

[1] Chi-squared test