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Translational Article

Special Issue on the Aging Kidney

Translational

Antihypertensive Drug Class Use and Differential Risk of Urinary Incontinence in Community-Dwelling Older Women

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Background. Medication use is a potentially reversible cause of urinary incontinence (UI). The objective of this longitudinal cohort study was to evaluate whether self-reported UI in community-dwelling older women is associated with the use of different classes of antihypertensive agents.

Methods. The sample consisted of 959 black and white women aged 72–81 years without baseline (Year 1) UI from the Health, Aging, and Body Composition Study. Use of any antihypertensive from 10 drug classes (ie, alpha blockers [central], alpha blockers [peripheral], angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, beta blockers, calcium channel blockers, diuretics [loop], diuretics [potassium-sparing], diuretics [thiazide], and vasodilators) was determined during Year 3 in-person interviews. The number of unique antihypertensive agents used and the standardized daily dosage were also examined. Self-reported UI, operationally defined as leaking urine at least weekly during the previous 12 months, was assessed at Year 4 visits.

Results. A total of 197 women (20.5%) reported UI at Year 4. Although any antihypertensive use, number of agents used, and standardized daily dosage at Year 3 were not associated with UI at Year 4, use of one particular drug class—peripheral alpha blockers (ie, doxazosin, prazosin, and terazosin)—was associated with fourfold greater odds of UI (adjusted odds ratio = 4.47; 95% confidence interval = 1.79–11.21; $p = .0014$). Further, in post hoc analyses, these odds nearly doubled in those also taking loop diuretics (adjusted odds ratio = 8.81; 95% confidence interval = 1.78–43.53; $p = .0076$).

Conclusion. In community-dwelling older women, peripheral alpha blocker use was associated with UI, and the odds nearly doubled when used with loop diuretics.

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BLADDER capacity itself does not change with age; yet 15–35% of American women aged 65 years and older living at home suffer from urinary incontinence (UI) (1,2). With age, bladder outlet and urethral resistance pressures decrease, leaving older women potentially vulnerable to the urologic activity of certain medications, such as

opioid analgesics, anticholinergics, and antihypertensives (3–6). UI presents a significant health, quality of life, and economic burden, and medication use is one of the several potentially reversible causes of UI (7–10).

Despite physiological explanations for the relationship between antihypertensives and development of UI, there is a paucity of rigorously designed studies examining antihypertensive use and UI (3,11,12). Furthermore, methodologies have differed among these studies, and findings have been mixed in terms of which antihypertensive agents increase the risk of UI. Our research group previously reported that use of alpha blockers or estrogens, but not anticholinergics or diuretics, was associated with self-reported UI in community-dwelling older women from the Health, Aging, and Body Composition Study; however, the study by Ruby et al. (13) did not account for use of other antihypertensives. Moreover, it is clinically relevant to consider whether specific combinations could further exacerbate urinary complaints in women. The objective of this study was to evaluate whether any use of specific antihypertensive drug classes or the number of antihypertensives used is associated with self-reported UI in older community-dwelling women and, if so, whether a dose–response relationship exists.

Methods

Study Design, Setting, and Source of Data and Sample

This longitudinal study used data from the Health, Aging, and Body Composition Study cohort. The baseline (Year 1) visit of the Health, Aging, and Body Composition Study occurred between 1997 and 1998 and included 1584 black and white women aged 70–79 from Pittsburgh, Pennsylvania, and Memphis, Tennessee. In order to be included at baseline, subjects had to be free of functional limitation (ie, any difficulty walking one-quarter mile or up 10 steps without resting) (14). For the baseline sample in this study, we excluded women missing either medication or UI information ($n = 12$) and those who reported prevalent UI ($n = 329$), leaving a total of 1243. By Year 4, another 103 women had been lost to follow-up (56 died, 5 withdrew, and 42 could not be contacted), and 181 women did not have either medication or UI information collected, leaving a study sample of 959. Of note, no statistically significant differences were found between the demographics for those who were lost to follow-up and those available at Year 4 (data not shown). This study was approved by the Institutional Review Boards of the University of Pittsburgh and the University of Tennessee, and written informed consent was obtained from each participant prior to data collection.

Data Collection and Management

The information collected annually over the 3-year period from baseline (Year 1) to Year 4 included physiological and performance-based measures as well as interviews and questionnaires addressing demographic characteristics, health-related behaviors, various aspects of health status, and medication use. For medication use at Year 3, participants were asked to bring to clinic all prescription and over-the-counter medications they had taken in the previous 2 weeks. Trained examiners transcribed detailed information from the containers, including medication name and strength, dosage form, frequency of use, and whether the medication was taken on a scheduled basis or only as needed. Medication data were coded using the Iowa Drug Information System codes and entered into a computerized database (13,15).

Outcome Variable

To determine the presence of UI, participants were asked at Year 4 whether in the previous 12 months they had leaked even a small amount of urine. If "yes," then participants were asked how often they had leaked urine in the past 12 months (ie, less than one time per month, one or more times per month, one or more times per week, or every day). Consistent with prior literature, UI was operationally dichotomized as leaking urine at least weekly or daily versus all others (16).

Primary Independent Variables

The primary independent variables were current use of any antihypertensive medication at Year 3 derived from the previously mentioned computerized files of participants' coded prescription medication data. Using categories consistent with the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (17), we examined use of antihypertensives from 10 specific drug classes (ie, alpha blockers [central], alpha blockers [peripheral], angiotensin-converting enzyme [ACE] inhibitors, angiotensin-II receptor blockers [ARBs], beta blockers, calcium channel blockers, diuretics [loop], diuretics [potassium-sparing], diuretics [thiazide], and vasodilators). We considered the number of antihypertensives used (ie, 0, 1, or 2 or more unique agents) to determine if use of multiple agents increased the odds of UI. We also considered a standardized daily dosage (SDD) to measure each participant's antihypertensive drug load and to evaluate a dose–response relationship. To calculate the SDD, we first determined the average daily dose by multiplying the number of dosage forms taken the previous day times the strength of the antihypertensive medication reported. The average daily dose was then converted to the SDD by dividing the average daily dose by the maximum effective dose per day in the geriatric population (17–25). SDDs were summed for all antihypertensives taken by a subject then categorized as 0, 0–0.49, 0.50–0.99, or 1 or more SDDs for that subject. Our SDD computation is consistent with the antihypertensive load index proposed by Wan et al. (26).

Covariates

We adjusted for potential confounding variables that may influence the relationship between medication use and UI (3,16,27). Demographic factors included study site (Pittsburgh or Memphis), race (black or white), age, and education (postsecondary education, high school graduate, and less than high school graduate). Health-related behaviors were characterized by categorical variables (current, past, and never) for baseline smoking and alcohol use (28,29).

Health status was represented by dichotomous measures (present or absent) for 10 self-reported conditions (anxiety, cancer, coronary heart disease, congestive heart failure, diabetes, fecal incontinence, hypertension, osteoarthritis of the knee, pulmonary disease, and stroke), cognitive impairment (Modified Mini-Mental State exam score <80), persistent lower extremity limitation (any difficulty walking one-quarter mile or up 10 steps without resting), depressive symptoms (Center for Epidemiologic Studies-Depression scale score >15), and self-rated health (poor or fair or good, very good, or excellent) (14,30,31). Additional health status covariates were body mass index (BMI; under- or normal weight [BMI < 25.0]; overweight [BMI: 25.0–29.9]; obese [BMI: 30.0+]), bodily pain (moderate or worse, mild, and none), visual acuity (excellent or good sight, fair sight, and poor sight to completely blind), number of prescription medications taken at Year 3 (excluding antihypertensives, estrogens, and bladder antispasmodics), parity, and history of hysterectomy (present or absent) (3,14,27–29,32).

Statistical Analyses

Dichotomous and categorical variables were summarized by frequencies and percentages, and continuous variables by means and standard deviations. Diabetes, cognitive impairment, persistent lower extremity limitation, number of prescription drugs, and estrogen use covariates were from Year 3; all other covariates were from baseline.

Unadjusted logistic regression models were used to examine crude associations between any antihypertensive use, antihypertensive count, SDD, and specific classes of antihypertensive drugs used at Year 3 and UI reported at Year 4. Multivariable logistic regression models using a backward selection approach were used separately for demographic factors and health-related behaviors or health status factors to identify a parsimonious set of covariates in addition to estrogen use (known to be important [13,27,33]), to be included in the final adjusted model. Odds ratio (OR) estimates, 95% confidence intervals (CIs), and statistical significance (p-value) were obtained from unadjusted and final models (34,35). We conducted post hoc analyses by fitting the above models with combinations of drug classes or comorbidities of interest as primary predictor variables. Goodness-of-fit test was assessed using the Hosmer–Lemeshow statistic, and collinearity was examined using the variance inflation factor (34,35). Multiple imputation was used to account for any missing values in covariates. We also conducted collinearity diagnostic testing. All statistical analyses were conducted using SAS Version 9.2 (SAS Institute Inc., Cary, NC).

Results

The characteristics of this sample of 959 older women are presented in Table 1. At baseline, 46% of participants were black, the average age was 73 years, and few (13%) reported their health as fair or poor. One half had hysterectomies and nearly two thirds (65.9%) were overweight or obese.

At Year 4, 197 women (20.5%) reported UI (Table 2). Among those with UI, 4 in 10 took two or more antihypertensive medications, but only 18.37% took one or more SDD. Table 2 also shows the relationship between UI and use of any, multiple, and SDDs of antihypertensive medications. UI was not significantly associated with the presence of any antihypertensive or with increasing numbers or SDDs of antihypertensive agents.

Table 3 shows the results of analyses examining use of specific classes of antihypertensive medications after combining ARBs and vasodilators, which share similar vasodilatory properties, due to small numbers of participants. Overall, use of specific antihypertensive drug classes ranged from a high of 42.2% for diuretics (8.1% for loop, 9.8% for potassium-sparing, and 24.3% for thiazide) to a low of 2.3% for peripheral alpha blockers (ie, doxazosin, prazosin, and terazosin). Among those with UI, the most commonly used antihypertensive drug class was thiazide diuretics (25.4%), and the least commonly used was central alpha blockers (3.6%). Only peripheral alpha blocker use was associated with increased odds of UI, which remained significant even after adjusting for site, race, age, education, anxiety, osteoarthritis of the knee, persistent lower extremity limitation, visual acuity, drinking status, smoking status, and estrogen use (adjusted OR [AOR] = 4.47; 95% CI = 1.79–11.21; $p = .0014$).

Finally, post hoc analyses were conducted to investigate potential relationships between peripheral alpha blockers and drugs and diseases which could further worsen UI by increasing urine production (ie, diuretic use and diabetes) (5,12). Post hoc analyses identified an even greater likelihood of UI with peripheral alpha blockers when taken in combination with loop diuretics (AOR = 8.81; 95% CI = 1.78–43.53; $p = .0076$); however, use of peripheral alpha blockers with either thiazide diuretics or potassium-sparing diuretics was not associated with an increased likelihood of UI (AOR = 3.56; 95% CI = 0.63–20.16; $p = .1510$ and AOR = 4.13; 95% CI = 0.51–33.69; $p = .1853$, respectively). Furthermore, use of peripheral alpha blockers in subjects with diabetes was associated with increased odds of developing UI by Year 4, although the point estimate was similar to that of peripheral alpha blocker use alone in the overall study sample (AOR = 5.15; 95% CI = 1.37–19.40; $p = .0155$). The Hosmer–Lemeshow goodness-of-fit test indicated no lack of fit, and no collinearity problems were detected in logistic regression models.

Table 1. Characteristics of Older Women at Baseline (n = 959)

Variables	N (%) or $M \pm SD$
Demographics	
Black	441 (46.0)
Age (y)	73.3 ± 2.8
Site (Pittsburgh)	496 (51.7)
Education	
Postsecondary	384 (40.0)
High school graduate	374 (39.0)
Less than high school	201 (21.0)
Health-related behaviors or health status	
Smoking status	
Current	79 (8.2)
Past	311 (32.4)
Never	569 (59.3)
Alcohol use	
Current	425 (44.3)
Past	161 (16.8)
Never	373 (38.9)
Anxiety	323 (33.7)
Cancer	144 (15.0)
Congestive heart failure	6 (0.6)
Coronary heart disease	98 (10.2)
Diabetes mellitus*	161 (16.8)
Fecal incontinence	67 (7.0)
Hypertension	452 (47.1)
Osteoarthritis of the knee	147 (15.3)
Pulmonary disease	41 (4.3)
Stroke	19 (2.0)
Cognitive impairment (Modified Mini-Mental State exam score <80)*	99 (10.3)
Persistent lower extremity limitation*	325 (33.9)
Depression (Center for Epidemiologic Studies-Depression scale score >15)	36 (3.8)
Self-rated health fair to poor	125 (13.0)
Bodily pain	
None	318 (33.2)
Mild pain	233 (24.3)
Moderate pain or worse	408 (42.5)
Body mass index	
Under- or normal weight	327 (34.1)
Overweight	368 (38.4)
Obese	264 (27.5)
Visual acuity	
Excellent-to-good sight	799 (83.3)
Fair sight	145 (15.1)
Poor to completely blind	15 (1.6)
Number of prescription drugs*,†	3.6 ± 2.7
Estrogen use*	213 (22.2)
Bladder antispasmodic use*	7 (0.7)
Parity	2.8 ± 2.3
Hysterectomy	452 (47.1)

*Assessed at Year 3.
†Excludes antihypertensives, estrogens, and bladder antispasmodics.

Discussion

This longitudinal cohort study found that peripheral alpha blocker use was associated with more than a four-fold increased odds of UI. This finding was consistent with Marshall et al. (11) and Ruby et al. (13). What sets this study apart though is that we accounted for confounding by other antihypertensives, and the two previous studies did not. The strong association between peripheral alpha blocker use and UI was confirmed by point estimates well above 2 in our study. This is a biologically plausible relationship because physiologically alpha receptor blockade can relax the bladder neck and urethral smooth muscle, thus compromising bladder outlet resistance. Although alpha blocker use is relatively uncommon, it represents a powerful contributor to UI with a number need to harm of 24.

Given the proposed mechanism by which alpha blocker use might lead to UI, we hypothesized that this risk would be worse if alpha blockers were concomitantly taken with medications (eg, lithium and diuretics) or conditions (eg, diabetes) that can increase bladder volume via polyuria. Unfortunately, the number of lithium users was small (n = 2), and we were only able to assess diuretic use. We chose to conduct post hoc analyses looking at the three diuretic subclasses separately, as there is a clinical perception that certain types of diuretics (ie, loop) may have a more brisk response than others (ie, thiazide and potassium-sparing). As suspected, we found that the addition of loop diuretics nearly doubled the odds of UI seen with peripheral alpha blockers alone. It is interesting that no increased risk was seen with other types of diuretics in those taking alpha blockers. We also substantiated the possible mechanism of polyuria by demonstrating a trend toward an increased risk with diabetes.

What should clinicians take away from these post hoc analyses? First, it is important to recognize that the sample size was small and CIs were wide; so, further studies are needed to replicate our finding that alpha blockers in combination with loop diuretics are particularly risky for UI in community-dwelling women. Having said that, clinicians who prescribe loop diuretics for older women with certain comorbid diseases (eg, congestive heart failure) requiring additional antihypertensive therapy should consider adding on agents other than peripheral alpha blockers. This recommendation is clinically sensible because, in addition to UI, peripheral alpha blockers are associated with dizziness, fatigue, somnolence, and orthostatic hypertension. Moreover, in 2000, the doxazosin arm of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial was halted after the drug was found to double the risk of heart failure compared with chlorthalidone in subjects aged 55 and older with hypertension and one or more cardiovascular disease risk factor (36).

Another interesting finding from our study was the lack of association between any antihypertensive use, antihypertensive count, SDD, or individual drug classes except peripheral alpha blockers and UI. A priori, we expected to identify a relationship with diuretic use, regardless of type, and UI, but such a relationship was not seen in bivariable or multivariable analysis. Other antihypertensives with potential urologic activity include calcium channel blockers, which may decrease bladder contractility, and beta blockers, which may increase bladder contractility (3,5,8), but these drug classes were not found to be associated with UI either. Furthermore, the side effect of cough associated with ACE

Table 2. Logistic Regression of Urinary Incontinence and Antihypertensive Use and Intensity in Older Women (n = 959)

Medication Use at Year 3	UI (n = 197), n (%)	No UI (n = 762), n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)*,†
Any antihypertensive	117 (59.39)	464 (60.89)	0.94 (0.68–1.29)	0.89 (0.63–1.26)
Antihypertensive count				
0	80 (40.61)	298 (39.11)	Reference	Reference
1	38 (19.29)	202 (26.51)	0.70 (0.46–1.07)	0.69 (0.44–1.08)
2+	79 (40.10)	262 (34.38)	1.12 (0.79–1.60)	1.05 (0.71–1.55)
Standardized daily dosage‡				
0	80 (40.82)	298 (39.16)	Reference	Reference
0–0.49	29 (14.80)	173 (22.73)	0.62 (0.39–0.99)	0.63 (0.39–1.03)
0.50–0.99	51 (26.02)	155 (20.37)	1.23 (0.82–1.83)	1.13 (0.73–1.75)
1+	36 (18.37)	135 (17.74)	0.99 (0.64–1.55)	0.94 (0.58–1.52)

Note. UI = urinary incontinence; OR = odds ratio; CI = confidence interval.

*Adjusted for site, race, age, education, anxiety, knee osteoarthritis, persistent lower extremity limitation, visual acuity, drinking status, smoking status, and estrogen use.

†Assumptions of the logistic regression model were met according to the Hosmer–Lemeshow goodness-of-fit test (34,35).

‡Two standardized daily dosages were unable to be calculated with available data; therefore, n = 957, and percentage calculations are based on 196 subjects with urinary incontinence and 761 without.

Table 3. Logistic Regression of Urinary Incontinence and Antihypertensive Drug Class Use in Older Women (n = 959)

Medication Use at Year 3	UI (n = 197), n (%)	No UI (n = 762), n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)*,†
Antihypertensive drug classes				
Beta blockers	27 (13.71)	131 (17.19)	0.77 (0.49–1.20)	0.72 (0.45–1.16)
Peripheral alpha blockers	11 (5.58)	11 (1.44)	4.04 (1.72–9.46)	4.47 (1.79–11.21)
Central alpha blockers‡	7 (3.55)	23 (3.02)	1.18 (0.50–2.80)	1.25 (0.50–3.11)
Loop diuretics	17 (8.63)	61 (8.01)	1.09 (0.62–1.90)	0.96 (0.51–1.81)
Thiazide diuretics	50 (25.38)	183 (24.02)	1.08 (0.75–1.55)	0.91 (0.57–1.45)
Potassium-sparing diuretics	24 (12.18)	70 (9.19)	1.37 (0.84–2.25)	1.48 (0.79–2.76)
Calcium channel blockers	44 (22.34)	196 (25.72)	0.83 (0.57–1.21)	0.76 (0.51–1.14)
ACE inhibitors	35 (17.77)	128 (16.80)	1.07 (0.71–1.62)	1.10 (0.70–1.71)
ARBs and vasodilators	12 (6.09)	51 (6.69)	0.90 (0.47–1.73)	0.88 (0.44–1.76)

Note. ACE = angiotensin-converting enzyme; ARBs = angiotensin-II receptor blockers; CI = confidence interval; OR = odds ratio; UI = urinary incontinence.

*Adjusted for site, race, age, education, anxiety, knee osteoarthritis, persistent lower extremity limitation, visual acuity, drinking status, smoking status, and estrogen use.

†Assumptions of the logistic regression model were met according to the Hosmer–Lemeshow goodness-of-fit test (x^2 = 3.21, df = 8, p = .92) (34,35).

‡Includes methyldopa, reserpine, clonidine, guanfacine, guanabenz, and guanethidine.

inhibitors has the potential to affect stress UI in women who take a medication from this drug class (7).

Strengths of this study include its longitudinal cohort design and the rigorous analytical approach used. The sample of older, generally well-functioning women included in this study was large, included a high proportion of black participants, and had a low dropout rate. Furthermore, medication use data collected from each woman were thorough and included medication name and strength, dosage form, frequency of use, and whether the medication was taken on a scheduled basis or only as needed. A potential limitation of this study is reliance on self-report to assess UI; however, self-report is commonly used to measure UI in epidemiological studies (3,33). Moreover, self-reported UI has been shown to be consistent with urodynamic testing and physician diagnosis of UI, with the sensitivity (0.56–0.85) and specificity (0.66–0.96) of self-report varying by type of UI (ie, stress, urge, or mixed) (38). Of note, type of UI, details of UI severity beyond its occurring at least weekly, and impact on quality of life were not included in our analyses. Additionally, due to sample size constraints, we were unable to restrict the analyses to only those who had hypertension. Therefore, antihypertensive drug classes could have been used for other indications; however, we did create control variables for some of the most common indications for which antihypertensive agents can be prescribed (ie, hypertension, congestive heart failure, and coronary heart disease). As with any study, unmeasured factors that could have confounded the relationship between medication use and UI are possible. The women in this study were well functioning at baseline and lived in or near two cities in the United States, which may limit generalizability.

Conclusion

In older community-dwelling women, peripheral alpha blocker use was associated with UI, and the odds nearly doubled when used in combination with loop diuretics. These findings suggest that older, well-functioning community-dwelling women suffering from UI may benefit from a review of medications, especially combinations of antihypertensive agents. In light of our findings, future research should investigate other combinations of drugs with alpha blockers and/or loop diuretics, including non-antihypertensive drug classes with potential urologic activity, like acetylcholinesterase inhibitors.

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