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The Impact of Medication Use on Urinary Incontinence in Community Dwelling Elderly Women

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Abstract

Objectives—To evaluate whether use of certain medications with potential urologic effects is associated with development of incident urinary incontinence in community-resident older women.

Design—Longitudinal cohort study.

Setting—Pittsburgh, PA and Memphis, TN.

Participants—959 healthy black and white women (aged 65 and older) enrolled in the Health, Aging and Body Composition study without baseline (year 1) self-reported urinary incontinence.

Measurements—Use of alpha blockers, anticholinergics, central nervous system medications (opioids, benzodiazepines, antidepressants and antipsychotics), diuretics (thiazide, loop, potassium sparing) and estrogen (all dosage forms) was determined during year 3 interviews. Self-reported

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incident (at least weekly) incontinence in during the previous 12 months was assessed at year 4 interviews.

Results—Overall, 20.5% of these women reported incident incontinence at year 4 (3 years from baseline). The most common medication used with potential urologic activity was a thiazide diuretic (24.3%) followed by estrogen (22.2%); alpha blockers were the least commonly used (2.3%). Multivariable logistic regression analyses revealed that, compared to non users, current users of alpha blockers (Adjusted odds ratio [AOR] 4.98, 95% confidence interval [CI] 1.96 – 12.64) and estrogen (AOR 1.60, 95%CI 1.08 – 2.36) had an increased risk of urinary incontinence. There was no increased risk (p>0.05) of urinary incontinence with the current use of anticholinergics, CNS medications or diuretics. No statistically significant race by medication use interactions were found (all p>0.05).

Conclusion—These results corroborate earlier reports that, in elderly women, use of alpha blockers or estrogens is associated with an increased risk of self-reported incident urinary incontinence.

Keywords

aged; urinary incontinence; medications; pharmacoepidemiology

INTRODUCTION

Urinary incontinence occurs in 17–55% of older women living in the community.[1–3] Medically, it predisposes individuals to perineal rashes, pressure ulcers, falling, insertion of an indwelling catheter, urosepsis, and death.[1–3] Psychosocially, it is associated with stigmatization, anxiety, depression, cessation of sexual intimacy, and institutionalization.[1–3] The annual direct costs for urinary incontinence was estimated to be nearly $20 billion annually in the United States in 2000.[1–3] These cost estimates from a decade ago are conservative because then many individuals with urinary incontinence were unknown to their physician and thus neither evaluated nor treated. Additionally, neither the substantial indirect costs nor the attendant medical or psychosocial morbidity are included in estimates of its impact.

One potentially modifiable risk factor for urinary incontinence in older women is medication use.[4] Unfortunately few rigorously designed studies have examined the impact of medication exposure on incident urinary incontinence. Data from one randomized trial of older women showed that daily oral estrogen and progestin worsened urinary incontinence.[5] Another randomized controlled trial and one cohort study have recently shown that estrogen use increases the risk of incontinence in postmenopausal women.[6,7] Several classes of drugs that affect the central nervous system (i.e., benzodiazepines, antidepressants, antipsychotics and opioids) have also been implicated in observational studies in the development of urinary incontinence.[8–11] Several studies, that did not use a rigorous observational design (i.e., cohort study), have found that alpha blockers and diuretics may increase the risk of incontinence in women.[10–12] Another limitation of current data is the inclusion of few older black women (1–15%).

Given this background, the objective of this longitudinal cohort study was to evaluate whether use of certain medications with potential urologic effects is associated with a higher risk of incident urinary incontinence in older black and white women.

METHODS

Study Design, Setting, Source of Data and Sample

The baseline (year 1) visit of the Health, Aging and Body Composition cohort study occurred between 1997 and 1998 and included 1584 black and white women aged 70–79 residing in specified zip code areas surrounding Pittsburgh, Pennsylvania and Memphis, Tennessee.13 Sample participants were included at baseline only if they initially reported no difficulty walking at least 1/4 mile or up a flight of stairs.13 For the baseline study sample, we excluded those women without medication or urinary incontinence information (n=12), and those that reported any urinary problems (n=329) leaving a total of 1243 women. By year 4, 103 women were lost to followup (56 women died, 5 withdrew and 42 could not be contacted or 8.3%) and 181 did not have either incontinence or medication information collected. This left us with a study sample of. 959. We compared the demographics for those who were lost to followup versus those available at the 4 year followup and found no statistically significant differences (all comparisons P>0.05). This study was approved by the University of Pittsburgh and University of Tennessee Memphis Institutional Review Boards and written informed consent was obtained from each participant prior to data collection.

Data Collection and Management

The information collected over a three year period included a battery of detailed physiologic and performance measurements and questionnaire material regarding demographic characteristics, multiple aspects of health status, and medication use. For medications at year 3, participants were asked to bring to clinic all prescription and over the counter medications they had taken in the previous two weeks. Well trained examiners transcribed from the medication containers information on medication name, dosage form, and whether the medication was taken as needed.. The medication data was coded using the Iowa Drug Information System (IDIS) codes and then entered into a computerized database.14

Outcome Variable

To determine the presence of urinary incontinence, participants were asked at year 4 whether in the past 12 months, they had leaked even a small amount of urine?15 Participants who answered yes were then asked how often they had leaked urine in the past 12 months. Response choices were less than once per month, one or more times per month, one or more times per week or every day.15 For descriptive purposes, we operationally defined type of incontinence as either “stress” (leakage of urine with an activity like coughing, lifting, standing up or exercise), “urge” (leakage of urine with urge to urinate and can’t get to a toilet fast enough) or “other” (leakage of urine unrelated to coughing, sneezing, lifting, or urge). Based on previously published studies, urinary incontinence was operationally defined as report of leaking urine at least one time per week or daily versus all others.15

Primary Independent Variables

For descriptive purposes only, we created specific medication variables to indicate new use (year three only), continuing use (years two and three) and past use (years one and/or two only). The primary independent variables were current use (combination of new use and continuing use) versus no use of specific medications at year 3 derived from the above mentioned computerized files of participants’ coded prescription medication data. The selection of specific medication classes was based on those previously reported to be potentially associated with urinary incontinence.4 One class we examined was the use of alpha blockers (i.e., prazosin, doxazosin, terazosin). No women reported the use of two other alpha blockers; alfuzosin or tamsulosin. Other classes we examined were diuretics (i.e., thiazide, loop and potassium sparing) and estrogen (oral, vaginal and transdermal dosage forms). We also examined the combined use of central nervous system drugs. Consistent with previous work from our group, opioid receptor agonist analgesics, antidepressants, antipsychotics and benzodiazepine receptor agonists comprised CNS medications.[16] Also consistent with previous work from our group, we examined anticholinergic medication use (defined as those agents with established muscarinic receptor blockage in vitro that were not included in the CNS medications variable as described above or bladder antispasmodics that also appear on a commonly accepted list of medications to be avoided in the elderly).[17]

Covariates

We adjusted for potential confounding variables that may influence the relationship between medication use and urinary incontinence.[6,11,15] Demographic factors were represented by dichotomous variables for site and race. Race was self-reported as being either black or white. A continuous variable was created for age and a categorical variable for education (post secondary education, high school graduate and less than high school graduate). Health-related behaviors were characterized by categorical variables for baseline smoking and alcohol use (current, past, never).[16,17]

Health status factors were represented by dichotomous measures (present/absent) for self-reported health conditions including anxiety, cancer, coronary heart disease, congestive heart failure, diabetes, fecal incontinence, hypertension, osteoarthritis of the knee, pulmonary disease, and stroke. We also created dichotomous measures (present/absent) for cognitive impairment (Teng score <80), depressive symptoms (score >15 on Center for Epidemiologic Studies-Depression scale), persistent lower extremity limitation (operationally defined as self-reports of having any difficulty walking 1/4 mile or climbing 10 steps without resting both at year 3 and six months earlier), and self-rated health (poor/fair versus good/excellent).[13,18,19] Categorical variables were created for body mass index (BMI-under/normal [BMI<25.0]; overweight [BMI: 25.0 to 29.9]; obese [BMI: 30.0 & above]), bodily pain (moderate or worse, mild, none), and vision problems (excellent/good sight, fair sight, poor to completely blind).[13, 20] We also created a dichotomous variable for the use of bladder antispasmodics with anticholinergic properties indicated for treating urinary incontinence (i.e., flavoxate, propantheline, dicyclomine, hyoscyamine, oxybutynin, tolterodine) at year 3. There were no reports of trospium, solifenacin, or darifenacin use. A continuous variable for number of prescription medications (excluding those mentioned above) being taken at year 3 was also created.[16,17] Finally we created a continuous measure for parity and a dichotomous variable for having a hysterectomy.[6,11]

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Statistical Analyses

Dichotomous and categorical variables were summarized by percentages and continuous variables were summarized by means (standard deviations) for all variables. At baseline, 9.5% of participants had one or more missing values for covariates. For the multivariable analyses, missing covariate values were replaced with those generated using the multiple imputation (MI) procedure in SAS® software (Cary, NC). In MI, missing values of variables are simultaneously predicted using existing values of variables by modeling the joint distribution of all the covariates plus selected other predictors. Conditional on the nonmissing values for each individual, the missing values have a distribution from which several joint random samples are drawn. Each imputation dataset is analyzed separately as if there were no missing values, then the results are combined in a manner that reflects the uncertainty due to missing values. The results from five imputation datasets were combined to obtain regression coefficient estimates and confidence intervals (CIs). Bivariable logistic regression was conducted to examine any associations between current (new and continuing combined) and past medication use and incontinence. Multivariable logistic regression

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analyses using a backward selection approach (alpha=0.15) identified those demographic, health behaviors and health status factors to be added as covariates along with the seven drug use independent variables in the final model. This final model calculated adjusted odds ratios and 95% confidence intervals relating urinary incontinence (yes/no) in the previous 12 months before year 4 (three years from baseline) with specific classes of medication use at year 3 (two years from baseline).21 All other variables were fixed at baseline values except bladder antispasmodics, number of prescription drugs and persistent lower extremity limitation which reflect data from year 3. We also tested all two way interactions between race and the various forms of current medication use with potential urological activity. Underlying statistical assumptions were evaluated and verified. 21 All statistical analyses were conducted using SAS® Version 9.1.

RESULTS

The baseline characteristics of this sample of 959 older women are presented in Table 1. The average age was 73 and few (13%) self reported their health as fair or poor. Half of participants had a hysterectomy. At year 4, urinary incontinence (daily/weekly) was reported by 113/518 (21.8%) of white women and 84/441 (19.1%) of black women (p=0.29). Overall, the majority of those with incident incontinence had “urge” symptoms (62.4%), nearly a quarter had “stress” symptoms (25.4%) and some had neither stress or urge symptoms (12.2%).

Table 2 shows the current (new at year 3 and continuing at years 2 and 3) and past medication use with potential urologic activity. Thiazide diuretic and estrogen use were the most common medications used. Only 10 individuals used estrogen vaginal cream and 13 used an estrogen patch. The remainder used oral conjugated estrogens and estradiol dosage forms. Slightly more than one quarter of estrogen users took a progestin concurrently (56/213 or 26.3%). The use of alpha blockers was the least common. CNS medications were taken by 17.1% of the sample of which two-thirds were continuing use. The majority of other drug classes were also taken continuously.

Table 3 shows the results of the bivariable analyses examining current (new use at year three and continuing use at years two and three) and past use of specific medications. There were no statistically significant associations between the past use of any type of medication with urinary incontinence. There was, however, a statistically significant increase in the incidence of urinary incontinence demonstrated with current alpha blocker and estrogen use. These findings were consistent even after adjustment in the multivariable analyses for the following covariates: hypertension, hysterectomy, race, age, education, smoking status, drinking status, vision, anxiety, knee osteoarthritis and persistent lower extremity limitation. Specifically, current users of alpha blockers (Adjusted odds ratio [AOR] 4.98, 95% confidence interval [CI] 1.96 – 12.64) and estrogen (AOR 1.60, 95%CI 1.08 – 2.36) had an increased risk of incident urinary incontinence. There was no increased risk (p>0.05) of incident urinary incontinence with the current use of anticholinergics (AOR 1.33, 95%CI 0.82 – 2.16), CNS medications AOR 0.79, 95%CI 0.49 – 1.24), loop (AOR 0.70, 95%CI 0.36 –1.34), potassium sparing (AOR 1.34, 95%CI 0.73 – 2.47) or thiazide diuretics (AOR 0.91, 95%CI 0.58 – 1.43). There was no significant increased risk of urinary incontinence in those taking both estrogen and alpha blocker use although confidence intervals were wide (n=6; AOR 1.97; 95% CI 0.33–11.89; p=0.46). No statistically significant race by medication use interactions were found (all p>0.05).

DISCUSSION

In this longitudinal cohort study we found that estrogen use increased the risk of incident urinary incontinence by 60% after controlling for other important risk factors such as hysterectomy and parity in older black and white community dwelling women. Moreover, there was no increased risk with past use of estrogen, and the association was observed even after adjusting for concurrent use of other medications that can independently increase the risk of incontinence. The findings with estrogen confirm data reported by Grodstein et al. from the Nurses Health Study (NHS) cohort study.[7] That study followed 39,436 females aged 50–75 for the development of urinary incontinence defined as leaking urine or losing control of urine at least weekly. The study found that oral and transdermal estrogen, with or without progestin, increased the risk of urinary incontinence by 45–60%.[7] Our data also replicates information from a recent summary of 17 randomized controlled trials found that oral estrogen use resulted in a 50–80% relative increase in urinary incontinence compared to placebo in postmenopausal women.[22] Estrogen has a number of effects on the lower urinary tract but it is unclear which of these may mediate its association with urinary incontinence.[23] One of estrogen's effects is restoration of bladder contractility, which is most clearly seen in studies of ovariectomized animals.[23] However if this was the mechanism in humans, one might have expected to see a further increased risk among our subjects taking both estrogen and alpha blockers. This was not observed, although our power to detect it was low.

This study also found that the use of alpha blockers increased the risk of urinary incontinence in older black and white women by nearly five fold. This finding corroborates work by Marshall et al. who reported that 20 of 49 (40.8%) women taking an alpha blocker (prazosin, terazosin, and doxazosin) had urinary incontinence.[24] This adverse effect was confirmed by dechallenge where withdrawal of the drug from 17 patients reduced the number of patients with incontinence to 6 (14%). In a follow-up analysis that controlled for potential confounders, this same group of investigators found a nearly two fold increased risk of urinary incontinence with the use of α-blockers.[12] It is biologically plausible that alpha blockers can increase the risk of urinary incontinence in women because its use can cause urethral relaxation. This may be particularly problematic in older women since urethral length and sphincter strength both decline with age in older women [3] and alpha adrenergic tone may be the last barrier to stress urinary incontinence. Given this data, the high risk of orthostatic hypotension associated with the use of these agents in older adults and the results from ALLHAT study which disclosed an increased hospitalization rate for heart failure among users of doxazosin, other approaches should be preferred for the treatment of hypertension in elderly women.[25]

It is also interesting to note that CNS medication, anticholinergic and diuretic use were not statistically associated with incident urinary incontinence. This contrasts with other work from our group in which CNS drug use increased the risk of two other important geriatric syndromes, recurrent falls and cognitive impairment.[16,17] Although drug-induced urinary incontinence is biologically plausible with diuretic use due to polyuria, we were not able to demonstrate an increased risk in the present study.[4] While it is possible that participants receiving diuretics could have had urinary frequency side effects leading to discontinuation prior to year 3, it was reassuring that past use was not shown to be protective. The lack of finding with current or past anticholinergic use is also notable. The use of anticholinergics is a two edge sword for urinary incontinence. By decreasing detrusor overactivity (also known as overactive bladder), such agents may improve urge urinary incontinence whereas for patients with detrusor weakness, with or without detrusor overactivity, chronic retention of urine with associated urinary incontinence may be provoked. Our definition of anticholinergic did not include psychotropics with anticholinergic properties (included in the CNS drug use variable). Post hoc sensitivity analyses found that the use of anticholinergic

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psychotropics, as defined by Rudolph et al., was not statistically significantly associated with urinary incontinence in the 40 individuals using this class of drugs (OR=1.68, 95% CI= 0.81–3.51, p=0.17). 26 It is important to note though that the point estimate is greater than one and may be suggestive of the true magnitude of the association.

This study has several strengths. It was conducted prospectively over three years, had a low drop out rate, had a large number of functionally-intact older adults, included a large proportion of older African Americans, and provided detailed data on medication use including route of administration. It also has a number of potential limitations. The incontinence measure we used was subjective self report rather than an objective determination by a physician. However, self-report of incontinence correlates well with objective determination and is consistent with the approach used by other epidemiological studies. 7,11 Moreover, self report of urge incontinence, the most common type of incontinence reported by older women in other studies, has been found to have positive predictive values between 70 to 85% with urodynamically assessed urge urinary incontinence.27 A second limitation is that we may have lacked power to examine the multivariable impact of the use of various medications/classes (i.e., anticholinergics, alpha blocker and estrogen use, CNS drugs, and various diuretics). Also due to small numbers we were not able to conduct analyses stratified by race and type of urinary incontinence. A third limitation is as always, unmeasured factors (e.g., other behavioral or surgical treatment of urinary incontinence) may have confounded the findings. We did however control for numerous potential confounders, including common indications for medications. Finally, this is a study of well functioning community dwelling older women at baseline living in two US states and may not be representative of older women elsewhere.

CONCLUSIONS

We conclude that alpha blocker or estrogens use increase the risk of incident urinary incontinence in elderly women. Health professionals working with older women with urinary incontinence should consider discontinuing these medications.

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Table 1

Characteristics of Older Women at Baseline (N=959)

Variables	N	% or Mean (sd)
Sociodemographics		
Black Race	440	45.9
Age (in years)	-	73.3 (± 2.8)
Site (Pittsburgh)	496	51.7
Education		
Post secondary	383	40.0
High school graduate	374	39.0
< High school	202	21.0
Health-related behaviors		
Smoking Status		
Current	79	8.2
Past	311	32.4
Never	569	59.4
Alcohol Use		
Current	425	44.3
Past	159	16.6
Never	375	39.1
Health-Status		
Anxiety	322	33.6
Cancer	145	15.1
Congestive Heart Failure	17	1.8
Coronary Heart Disease	117	12.2
Diabetes	116	12.1
Fecal Incontinence	69	7.2
Hypertension	451	47.0
Osteoarthritis (knee)	147	15.3
Pulmonary Disease	41	4.3
Stroke	20	2.1
Cognitive Impairment (Teng<80)	100	10.4
Depression (CES-D>15)	37	3.9
Persistent Lower extremity Limitation*	325	33.9
Self-rated health (fair/poor)	126	13.1
Bodily Pain		
None	318	33.2
Mild pain	233	24.3
Moderate pain or worse	408	42.5
Body Mass Index		
Under/normal weight	325	33.8
Over weight	371	38.7

Variables	**N**	**% or Mean (sd)**
Obese	263	27.5
Vision Problems		
Excellent/good sight	799	83.3
Fair sight	145	15.1
Poor to completely blind	7	1.6
Bladder Antispasmodics*	7	0.7
Number of Prescription Drugs*	-	6.8 (± 3.8)
Parity	-	2.8 (± 2.3)
Hysterectomy	452	47.1

*assessed at year 3

Table 2

New, Continuing and Past Drug Use with Potential Urologic Activity by Older Women (n=959)*

Type/Class of Drug Use	N	%
New alpha blocker use	6	0.6
Continuing alpha blocker use	16	1.7
Past alpha blockers use	6	0.6
New anticholinergic use	49	5.1
Continuing anticholinergic use	71	7.4
Past anticholinergic use	123	12.8
New central nervous system drug use	55	5.7
Continuing central nervous system drug use	109	11.4
Past central nervous system	76	7.9
New loop diuretic use	22	2.3
Continuing loop diuretic use	56	5.8
Past loop diuretic use	27	2.8
New potassium sparing diuretic use	16	1.7
Continuing potassium sparing diuretic use	78	8.1
Past potassium sparing diuretic use	51	5.3
New potassium sparing diuretic use	16	1.7
New thiazide diuretic use	45	4.7
Continuing thiazide diuretic use	188	19.6
Past thiazide diuretic use	85	8.9
New estrogen use†	23	2.4
Continuing estrogen use†	190	19.8
Past estrogen use	202	21.1

*New (year 3 use only), Continuing (year 2 and 3 use) and Past Drug Use (not year three and either year 1 and/or 2 use)

†Only 10/213 (4.7%) individuals used estrogen vaginal cream and 13/213(6.1%) used an estrogen patch; 56/213 (26.3%) used progestin concurrently.

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Table 3

Bivariable Logistic Regression Analysis of Urinary Incontinence and Current and Past Medication Use in Older Women (n=959)*

Type/Class of Current Drug Use	N	Crude OR	95% CI
Current alpha blocker	22	4.04	1.72–9.46
Past alpha blockers	6	†	
Current anticholinergic	120	1.15	0.73–1.82
Past anticholinergic	123	0.69	0.41–1.16
Current CNS drug use	164	0.96	0.63–1.46
Past CNS drug use	76	0.86	0.47–1.57
Diuretics			
Current loop	78	1.09	0.62–1.91
Past loop	27	1.12	0.44–2.81
Current potassium sparing	94	1.38	0.84–2.26
Past potassium sparing	51	1.11	0.56–2.21
Current thiazide	233	1.09	0.76–1.58
Past thiazide	85	1.15	0.67–1.99
Current estrogen current use	213	1.49	1.03–2.16
Past estrogen past use	202	0.80	0.52–1.23

*Current (year 3 New and Continuing use combined) and Past Drug Use (not year three and either year 1 and/or 2 use)

†Too few to calculate