

# Are commonly used psychoactive medications associated with lower urinary tract symptoms?

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## Abstract

**Purpose** Lower urinary tract symptoms (LUTS) such as urinary frequency and urgency are bothersome and associated with reduced quality of life. Atypical antipsychotics (AAPs) have been implicated in increasing the risk of urinary incontinence. In a large community-based sample of men and women, we examined the associations of AAP and selective serotonin reuptake inhibitor (SSRIs) use with LUTS.

**Methods** Data were collected (2002–2005) from a generalizable sample of Boston, MA, USA, residents aged 30–79 ( $N=5503$ ). LUTS were assessed using the American Urologic Association Symptom Index (AUA-SI). The prevalence of clinically-significant LUTS was estimated using a cutoff AUA-SI score of 8+ to indicate moderate-to-severe symptoms. Confounder-adjusted odds ratios (ORs) and 95% confidence intervals (CI) were calculated from multivariate logistic regression to estimate the associations for psychoactive drugs used in the previous month (SSRIs, AAPs, both) and LUTS.

**Results** Among women, AAP users had a higher prevalence of LUTS (46.2%) compared with SSRI users (23.5%) and those with depressive symptoms not using SSRIs or AAPs (26.3%). Corresponding prevalence estimates among men were 32.7%, 29.8%, and 33.3%. In multivariate models, AAP use was significantly associated with LUTS among women when used either with (OR=2.72, 95% CI:1.45–

5.10) or without (OR=3.05, 95% CI:1.30–7.16) SSRIs, but SSRI use without AAP use was not associated with LUTS compared with nonusers without depressive symptoms. No associations were observed among men.

**Conclusions** In our study, AAPs but not SSRIs were associated with increased prevalence of LUTS among women only. Further prospective research is needed to determine time sequence and cause and effect.

**Keywords** Antipsychotic agents · Antidepressive agents · Urination disorders · Pharmacoepidemiology · Epidemiology

## Introduction

Recent market research data indicate that in 2008, antipsychotics surpassed lipid regulators as the top-selling therapeutic drug class in the United States [1]. A nationally representative survey of physicians found that the majority (93%) of antipsychotics prescribed in the USA in 2008 were second-generation atypical antipsychotics (AAPs), with a marked shift away from first-generation typical antipsychotics from previous years [2]. This trend appears to be present internationally as well [3]. In the USA, patient populations for AAP use have broadened to include children and older adults [4], and it is estimated that only 40% of all AAP use is on label [2]. The recent dramatic changes in the prescribing landscape have been accompanied by criticisms [5] and have raised concerns about drug safety, especially in children [6], older adults [7], and among new-indication populations, such as persons with depression [8].

Lower urinary tract symptoms (LUTS), such as urinary frequency and urgency, are bothersome and associated with reduced quality of life [9]. Urinary incontinence is a side effect of antipsychotics [10], as is urge incontinence [11]. A

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recent study of clozapine (an AAP) suggested that users suffered from an excess of a broader range of LUTS than incontinence alone [12]. There is also evidence that selective serotonin reuptake inhibitor (SSRI) antidepressants could increase the risk of LUTS [13]. Prior associations between SSRIs and nocturia and risk of urinary incontinence have been documented [14, 15]. Possible pathways include promotion of cholinergic neuromuscular transmission in the detrusor muscle, as well as influence on autonomic function [16, 17]. Furthermore, there is a largely consistent association of depression itself with urologic symptoms in multiple cross-sectional [18–21] or longitudinal [22, 23] studies, making it difficult to sort out any underlying effect of depression from indicated medications. We previously found an association between depression and LUTS [24] in our population-based epidemiologic study. The analyses reported here were conducted to further consider the association of psychoactive medications [specifically, serotonin reuptake inhibitors (SSRIs) and AAPs] with LUTS while accounting for the underlying influence of depression.

## Materials and methods

### Study design and data collection

The Boston Area Community Health (BACH) Survey is a population-based, epidemiologic study conducted among 5,503 men and women aged 30–79 residing in Boston, MA, USA. A multistage, stratified cluster sampling design was used to recruit approximately equal numbers of persons from prespecified age (30–39, 40–49, 50–59, 60–79), race/ethnicity (black, Hispanic, white), and gender groups. This cross-sectional analysis used baseline data collected from 2002 to 2005 during a 2-h, in-person interview conducted by a trained, bilingual interviewer after acquisition of written informed consent. Interviews for 63.3% of eligible persons were completed, with a resulting study population of 2,301 men and 3,202 women (1,767 black, 1,877 Hispanic, 1,859 white). All protocols and procedures were approved by the Institutional Review Board of New England Research Institutes. Further details of the study are available [25].

### Urologic symptoms and depression measures

LUTS were defined using the American Urologic Association (AUA) Symptom Index (AUA-SI) [equivalent to the International Prostate Symptom Score (IPSS) scale] that measures seven urologic symptoms [26]. Higher scores (range 0–35) indicate more symptoms. We defined the presence of LUTS as a score of  $\geq 8$ , corresponding to moderate-to-severe symptoms. For graphical displays, LUTS severity

categories were defined using the AUA-SI, as follows: no symptoms (score=0), mild (1–7), moderate (8–19), severe ( $\geq 20$ ). We also examined mean storage and voiding storage subscales of the AUA-SI. For storage symptoms, relevant questions were related to frequency, urgency, and nocturia, with a possible score range of 0–15. For voiding symptoms, relevant questions were incomplete emptying, intermittency, weak stream, and hesitancy (possible score range 0–20). An individual's scores on the subscales were summed to the full AUA-SI score. Urologic symptom interference with activities of daily living was assessed using the validated Epstein scale [27]. A score of 0 was assigned for “none of the time” and a score of four to “all of the time” for seven questions on usual activities (score range 0–28); higher scores indicate more bother. Depressive symptoms were considered present among participants with at least five of eight symptoms on the abridged Center for Epidemiologic Studies Depression Scale [28].

### Psychoactive medication use

BACH participants were asked to gather medications used in the previous 4 weeks (for the purposes of our survey, considered current use) for label recording by the interviewer and were asked to report medications used for specific indications during the same time period. Medication labels and/or responses were coded by therapeutic class. The main psychoactive drugs of interest for this analysis were: (1) antidepressants, and (2) AAPs (e.g., risperidone, aripiprazole). The antidepressant group includes SSRIs (e.g., fluoxetine), serotonin–norepinephrine reuptake inhibitors (SNRIs) (e.g., venlafaxine), serotonin modulators (trazodone and nefazodone), and bupropion, but excludes tricyclic antidepressants (TCAs). As 76% of the SSRI/SNRI and miscellaneous antidepressant groups were using SSRIs, for simplicity, they are hereinafter called SSRIs. In this analysis sample, TCAs were used much less frequently than SSRIs (2.9% vs. 13.9%). We did not include TCAs with SSRIs as they are directly prescribed for urinary symptoms and thus any observed association may be due to confounding by indication. However, we examined the coprevalence of TCA use with SSRIs and AAPs and the resilience of modeling results to adjustment for TCAs. No BACH participants used duloxetine, an SNRI that may improve stress urinary incontinence among women [29].

### Covariates

Potential covariates were chosen based on prior discovery of associations with LUTS in our survey [24]. A socioeconomic status (SES) variable was constructed as a function of standardized income and education variables for the Northeastern USA and reclassified into low, middle, and high [30]. Other comorbidities were based on the query: “Have

you ever been told by a health care provider that you have or had...?” Cardiovascular disease (CVD) was a composite yes/no variable (see Table 1 notes). Body mass index (BMI) was calculated from interviewer-measured weight and height. Physical activity was defined using the Physical Activity Scale for the Elderly (low 0–99, medium 100–249, high 250+) [31].

#### Analytic sample and statistical analysis

Our overall analytic goal was to understand the association between classes of psychoactive medication and LUTS without confounding by established urologic conditions affecting bladder function. We therefore excluded participants

who self-reported a history of genitourinary cancers, prolapsed bladder, previous surgery affecting the bladder or prostate, surgery for urinary incontinence, or use of a catheter recommended. Persons with Parkinson’s disease and multiple sclerosis were also excluded due to the strong influence of these diseases on LUTS; thus, 482 participants were excluded, leaving 5,021 (91.2% of the original sample). Analyses were conducted using v9.2 of SAS and v10.0.1 of SUDAAN. Missing data were replaced using multiple imputation; <1% of data were missing for most variables. Income (used to construct SES) was missing for 3%, 4%, and 11% of white, black, and Hispanic participants, respectively. Medication variables were not imputed. Descriptive analyses were weighted for study design, and the

**Table 1** Demographic and medical characteristics of users of common psychoactive medications [selective serotonin reuptake inhibitors (SSRIs) and atypical antipsychotics (AAPs)] and nonusers by depression status, Boston Area Community Health Survey,  $N=5,021$

	SSRI use only <sup>a</sup> ( $N=576$ )	Any AAP use <sup>b</sup> ( $N=131$ )	No SSRI or AAP use Depressive symptoms ( $N=750$ )	No SSRI or AAP use No depressive symptoms ( $N=3,564$ )
Mean age (SE)	49.9 (1.1)	45.7 (1.5)	46.6 (0.8)	47.4 (0.4)
65+ (%)*	14.5	6.5	9.0	13.4
Women (%)*	60.0	50.7	63.6	48.6
Race/ethnicity*				
Black (%)	13.1	34.8	41.1	28.4
Hispanic (%)	9.7	13.4	23.5	12.5
White (%)	77.2	51.8	35.4	59.1
Socioeconomic status*				
Low	27.7	51.8	48.8	22.6
Middle	46.9	46.7	40.8	49.1
High	25.4	1.4	10.5	28.3
Cardiovascular disease (%)* <sup>c</sup>	26.4	27.3	25.7	16.1
Type I or type II diabetes (%)*	12.5	12.4	14.0	7.2
Arthritis(%)*	30.0	21.9	28.0	19.2
High blood pressure (%)	30.5	21.7	28.4	24.1
Obese (%)* (30+ kg/m <sup>2</sup> body mass index)	37.8	44.3	42.0	32.9
Physical activity scale*				
<100 (low)	39.0	47.7	34.6	21.8
100–250 (middle)	47.7	49.5	50.3	51.8
>250 (high)	13.4	2.7	15.1	26.4
Depressive symptoms (%)*	39.4	49.3	100.0	0.0
Tricyclic antidepressants (%)*	6.7	4.5	5.9	1.7

All analyses were weighted for study design

<sup>a</sup> Use of SSRI/SNRI or miscellaneous antidepressants, including serotonin modulators (trazodone and nefazodone) and bupropion, but users who also used AAPs were not included

<sup>b</sup> Seventy-nine (30 men, 49 women) users of AAPs were also users of the SSRI, SNRI or other miscellaneous antidepressants, as described above

<sup>c</sup> A composite variable containing any of the following: myocardial infarction, angina, congestive heart failure, coronary artery bypass or graft surgery, pulmonary embolism, deep vein thrombosis, carotid artery surgery, Reynaud’s disease, peripheral vascular disease, intermittent claudication, aortic aneurysm, surgery or angioplasty for arterial disease of the leg

\* $P$  value <0.05 for chi-square test of homogeneity for categorical variables, or  $t$  test for continuous variable. For depressive symptoms, the  $p$  value for comparing columns 1 and 2 is 0.23

characteristics of four groups were examined: (1) users of SSRIs only; (2) AAP users; (3) nonusers with depressive symptoms; (4) nonusers without depressive symptoms. Those who used AAPs as well as SSRIs ( $N=79$ ) were placed in the AAP group, as AAP users were much more likely to use SSRIs than SSRI users were to use AAPs. Thus, our grouping better represents typical patterns of community use.

Multivariate logistic regression modeling was used to identify associations between psychoactive medications and LUTS using adjusted odds ratios (ORs) and 95% confidence intervals (CIs). In models, the main exposure variable was constructed to account for overlap and separately estimated ORs for LUTS considering: (1) joint exposure to both SSRIs and AAPs; (2) exposure to AAPs but not SSRIs; (3) exposure to SSRIs but not AAPs; (4) those using neither (as the common referent category). As study design variables, race/ethnicity and age were always retained in models, as were depressive symptoms, to control for confounding by indication and severity (given some drug-exposed persons were still reporting depressive symptoms). Additional potential confounders considered for models included: arthritis, BMI, CVD, diabetes (type I or II), high blood pressure, physical activity, SES, use of statins and antihypertensives. To determine the structure of the final model (model 2), a full model was fit; using backward selection, only those covariates that induced a 15% change in OR at any level of the main exposure or that were significantly associated with the outcome (Wald  $F$  test,  $p<0.10$ ) were included.

## Results

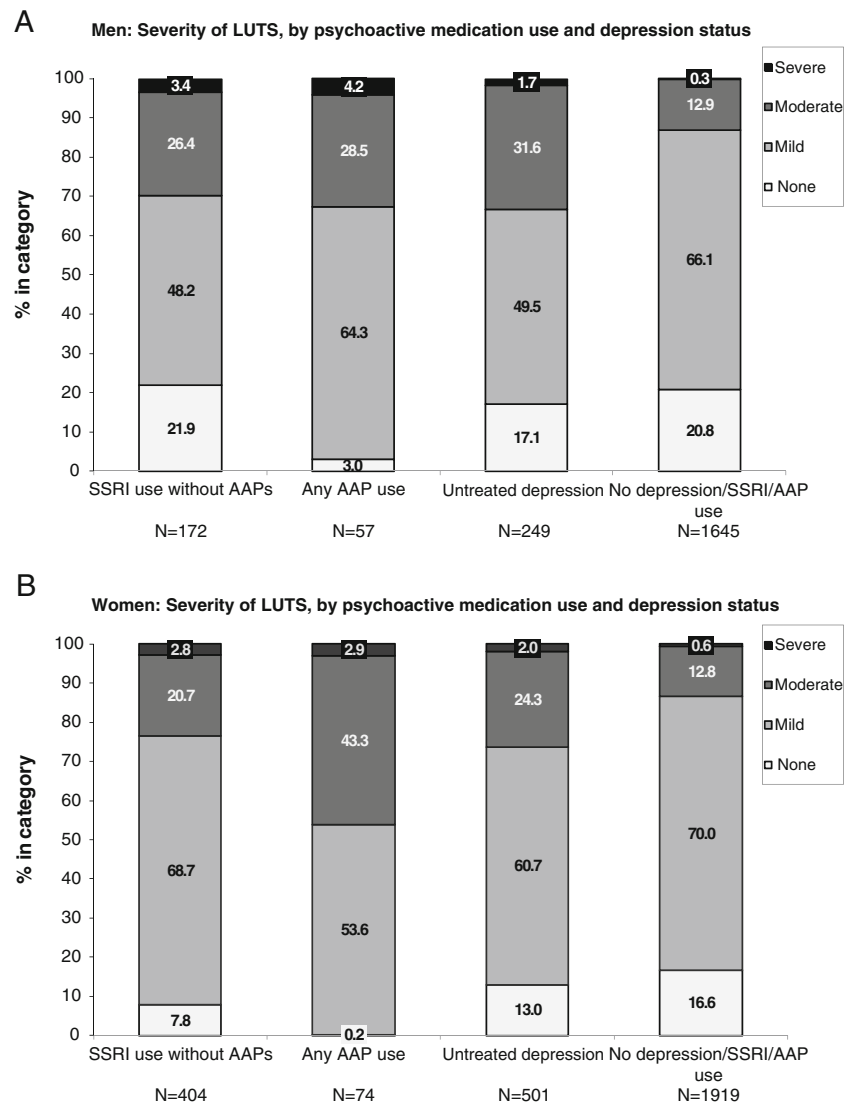
Approximately 40% and 50% of current users of SSRIs only and AAPs, respectively, met our definition of having depressive symptoms (Table 1). SSRI users had the oldest mean age of the four groups (49.9 years), with AAP users the youngest (45.7 years). Considering all four groups, the highest proportion of white participants was observed among SSRI users (77.2%); the highest proportions of black and Hispanic participants (41.5% and 23.5%, respectively) were always observed in the group who reported depressive symptoms and were not SSRIs or AAPs users. The proportion of high SES persons was greatest in the no drug use/no depressive symptoms group, followed by the SSRI group (28.3% and 25.4%, respectively). Among AAP users, only 1.4% was high SES. Except for high blood pressure, there was a general pattern of higher comorbidities and obese BMI among the three groups with either medication use or untreated depressive symptoms compared with those without; differences were especially marked for CVD and diabetes; 49.1% of AAP users also used SSRIs, whereas a small proportion of all groups (highest, 6.7% among SSRI users) used TCAs.

Figure 1a and b depict the prevalence of LUTS severity categories among the four groups by gender. Among men (Fig. 1a), 97% of AAP users reported LUTS of any severity compared with 78.1% of SSRI users. The prevalence of moderate-to-severe symptoms (AUA-SI score  $\geq 8$ ), however, was approximately equal across the SSRI, AAP, and depressive symptom groups (29.8%, 32.7%, and 33.3%, respectively). Among women (Fig. 1b), most SSRI and AAP users (92.2% and 99.8%, respectively) reported at least mild LUTS, but the prevalence of moderate-to-severe LUTS was much higher in the AAP group (46.2%) compared with any other group (next highest: untreated depression, 26.3%). Considering overall AUA-SI mean scores, AAP users consistently had the highest scores, although differences were stronger for women (7.8) than men (6.2) (Fig. 2a). Among men and women, AUA-SI scores were similar considering SSRI users and those with untreated depression. Mean storage scores were always higher than voiding scores in all groups and generally higher among women than men, but among women, the highest voiding and storage scores were observed in the group using AAPs. Finally, mean urologic symptom interference scores among women were markedly higher among AAP users (7.8) compared with SSRI users (3.2) and those with depressive symptoms without use of these medications (3.1) (Fig. 2b), suggesting that women AAP users are more bothered by symptoms. Among men, scores were not markedly different between the AAP and untreated depression groups (2.4 and 2.2, respectively) and were lowest among SSRI users (1.2).

We further considered whether AUA scores were different by depression status among psychoactive medication users (data not shown in figure). Mean scores among SSRI users were always higher among those with concurrent depressive symptoms (men: 7.0 with depressive symptoms, 4.6 without; women: 6.2 with depressive symptoms, 5.0 without). Differences in mean scores were of similar magnitude for male AAP users (men: 7.0 with depressive symptoms, 5.7 without), but female AAP users had greater differences in mean scores by depression status (9.4 with depressive symptoms, 5.6 without). We subsequently tested for statistical interaction between psychoactive drug use and depression status in models for LUTS but found no significant interactions (all  $p>0.22$ ), suggesting that the association of psychoactive medications and LUTS did not differ by depression status.

Multivariate logistic regression models for prevalent LUTS are presented in Table 2. Among men, there were no significant associations observed for use of AAPs with SSRIs, use of AAPs without SSRIs, or use of SSRIs without AAPs following adjustment for age, race/ethnicity, and depressive symptoms (model 1) or further covariate adjustment (model 2). Whereas use of SSRIs and AAPs were not associated with LUTS among men, depression was strongly

**Fig. 1 a** Severity of lower urinary tract symptoms (LUTS) among men by selective serotonin reuptake inhibitor (SSRI) or atypical antipsychotic (AAP) medication use and depression status. Untreated depression was defined as depressive symptoms without use of SSRIs or AAPs. The SSRI group also contains those taking serotonin–norepinephrine reuptake inhibitors (SNRIs), serotonin modulators, and bupropion. **b** Severity of LUTS among women by SSRI or AAP use and depression status. Untreated depression was defined as depressive symptoms without the use of SSRIs or AAPs. The SSRI group also contains users of SNRIs, serotonin modulators, and bupropion

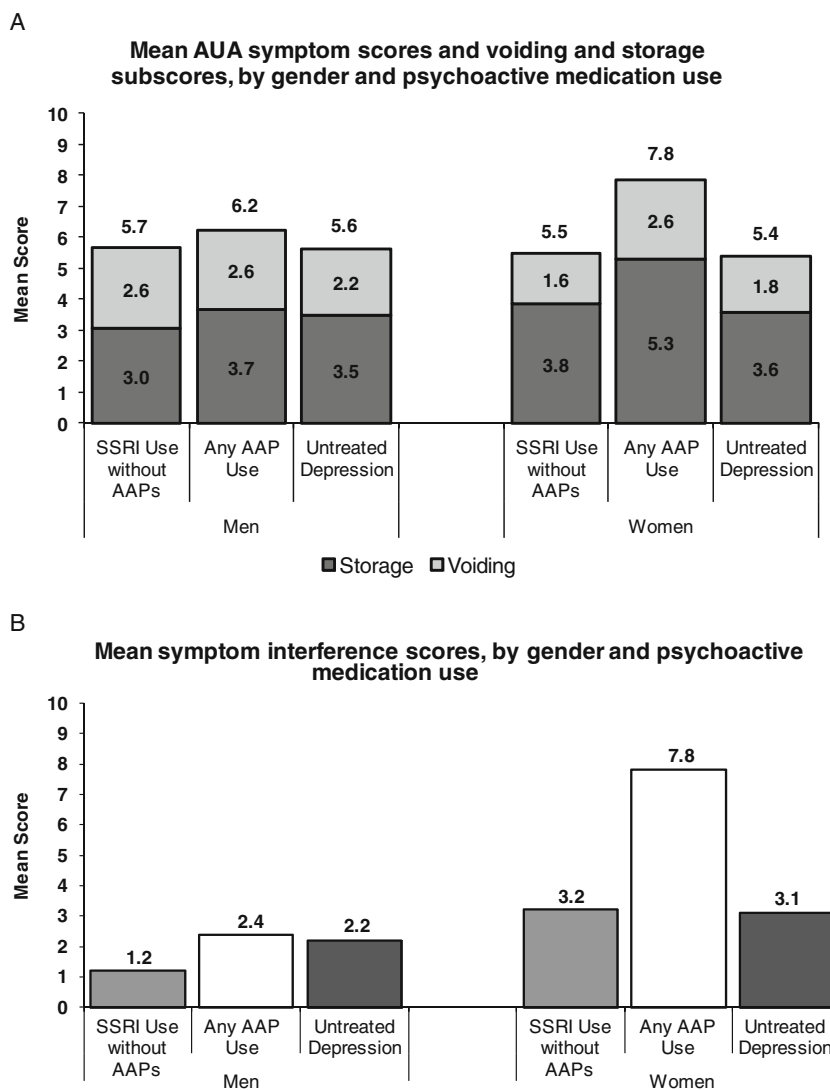


and significantly associated (model 2: OR=3.17, 95% CI: 2.35–4.27). Among women, however, there were significant associations for all three drug groupings in the minimally adjusted model (model 1). After further adjustment (model 2), joint use of AAPs and SSRIs, as well as AAP but not SSRI use, had persistent, significant associations with LUTS. The observed associations for joint AAP and SSRI use or AAP use without SSRIs had imprecise confidence intervals but were of strong magnitude (joint use: OR=2.72, 95% CI 1.45–5.10; AAP use only: OR=3.05, 95% CI: 1.30–7.16), suggesting that AAP users have a higher prevalence of LUTS after multivariate adjustment and that the joint-use association is driven by AAP use. The magnitude of these associations exceeded that of depression in the model (OR for depression=1.72, 95% CI: 1.38–2.15).

We further examined whether confounding by TCA use explained the associations between AAP use and LUTS among women. Adjustment for use of these drugs changed

the ORs minimally (<10%) and did not attenuate the previously observed associations. Among women, to examine whether confounding by depression could still play a role, we ran additional models among a subsample of only those who had depression symptoms. Although the smaller sample size reduced the precision of CIs, the finding of significant positive associations with LUTS for AAP use with and without SSRI use was persistent. We also ran our final models among women considering an exposure group taking only SSRIs rather than SSRI/SNRIs/miscellaneous antidepressants and found our results largely consistent, with changes in magnitude of ORs <15% and no changes in statistical significance (data not shown). Similarly among men, although we had insufficient numbers to model a joint exposure category for “pure” SSRI and AAP use, our estimate for use of “pure” SSRIs without AAPs was similar to the estimate for use of SSRI/SNRI/miscellaneous antidepressants without AAPs.

**Fig. 2 a** American Urologic Association Symptom Index (Mean AUA-SI) symptom scores and voiding and storage subscores by gender, selective serotonin reuptake inhibitor (SSRI) or atypical antipsychotic (AAP) medication use and untreated depression (symptoms of depression without use of SSRIs or AAPs). Higher scores indicate more symptoms. Mean scores for those who were not users of these medications and who did not have depressive symptoms were 3.3 and 3.6 for men and women, respectively. The SSRI group also contains users of serotonin-norepinephrine reuptake inhibitors (SNRIs), serotonin modulators, and bupropion. **b** Mean symptom interference scores, by gender, SSRI or AAP medication use, and untreated depression (symptoms of depression without use of SSRIs or AAPs). Higher scores indicate more symptom interference with activities of daily living. Mean scores for those who were not users of these medications and who did not have depressive symptoms were 1.0 and 1.4 for men and women, respectively. The SSRI group also contains users of SNRIs, serotonin modulators, and bupropion



## Discussion

In a population-based study, we examined the characteristics of users, prevalence of LUTS, symptom severity, and urinary symptom interference scores considering current users of popular psychoactive medications (SSRIs including SNRIs, and AAPs) and nonusers with and without depressive symptoms and used multivariate methods to estimate adjusted associations for drug use and LUTS. Our results were consistent with respect to women users of AAPs having the highest overall prevalence of LUTS of any severity, the highest prevalence of moderate-to-severe symptoms, and the greatest symptom interference scores. Elevation in voiding scores suggested that the excess of symptoms in this group was not merely explained by storage alone. We found the excess LUTS persisted after risk factor adjustment, resulting in substantial and statistically significant positive associations of AAP use (with and without SSRIs) with LUTS

among women. Our cross-sectional analysis measures correlation/association and cannot determine cause and effect. A prospective analysis of this research question is planned among persons participating in a second phase of BACH data collection.

The reasons for our observed gender differences for AAPs are not known. Antipsychotics are lipophilic drugs likely to be metabolized differently among women and men due to differences in body composition, with a resulting higher volume distribution and higher serum levels in women at similar doses to men [32, 33]; female users of antipsychotics have also been found to have greater incidence of adverse events compared with male users [34]. However, SSRIs are also lipophilic, and a similar gender difference in prevalent LUTS was not observed. It is also possible that women in our study using antipsychotics may differentially report symptoms compared with women taking only SSRIs, but the fact that we did not observe the same for men using

**Table 2** Odds ratios (ORs) and 95% confidence interval (CI) for use of psychoactive medications [selective serotonin reuptake inhibitors (SSRIs), atypical antipsychotics (AAPs)] and prevalent lower urinary tract symptoms (LUTS) from multivariate logistic regression models,  $N=5,021$ 

	No.	Model 1		Model 2	
		Age, race/ethnicity, depressive symptom adjusted <sup>a</sup>		Adjusted for additional covariates <sup>b</sup>	
		OR for LUTS	95% CI	OR for LUTS	95% CI
Women, $N=2,898$					
Use of both AAPs and SSRIs <sup>c</sup>	49	<b>3.07</b>	<b>(1.67, 5.66)</b>	<b>2.72</b>	<b>(1.45, 5.10)</b>
AAP use without SSRIs	25	<b>3.05</b>	<b>(1.37, 6.78)</b>	<b>3.05</b>	<b>(1.30, 7.16)</b>
SSRI use without AAPs	404	<b>1.47</b>	<b>(1.14, 1.91)</b>	1.23	(0.94, 1.61)
No use of these drugs	2420	1.00 (referent)	–	1.00 (referent)	–
Men, $N=2,123$					
Use of both AAPs and SSRIs <sup>c</sup>	30	2.01	(0.87, 4.65)	2.07	(0.85, 5.04)
AAP use without SSRIs	27	1.09	(0.39, 3.06)	1.33	(0.46, 3.83)
SSRI use without AAPs	172	1.43	(0.96, 2.12)	1.34	(0.89, 2.02)
No use of these drugs	1894	1.00 (referent)	–	1.00 (referent)	–

<sup>a</sup> Adjusted for depressive symptoms as some drug users continued to report these symptoms

<sup>b</sup> ORs and 95% CI shown in bold are statistically significant. Model 2 for women adjusted for continuous age, race/ethnicity, depressive symptoms, high blood pressure, cardiovascular disease, arthritis, body mass index, and physical activity. Association for depressive symptoms in this model was OR=1.72 (95% CI 1.38–2.15)

Model 2 for men adjusted for continuous age, race/ethnicity, depressive symptoms, cardiovascular disease, arthritis, diabetes, and physical activity. Association for depressive symptoms in this model was OR=3.17 (95% CI 2.35–4.27)

<sup>c</sup> SSRI group also contained users of serotonin–norepinephrine reuptake inhibitors (SNRIs), serotonin modulators, and bupropion

antipsychotics suggests otherwise. In a previous clinical study of LUTS measured using an adapted version of the IPSS scale among 101 clozapine users, women had only nonsignificantly higher mean scores than men (7.78 and 7.18, respectively) [12]. Because AAPs are not currently indicated as first-line therapy for depression, it is reasonable to speculate that women using AAPs alone had more severe, potentially uncontrolled, depression, even after adjustment for residual depressive symptoms. However, we observed similar associations comparing joint users of SSRIs and AAPs to AAP-only users, suggesting that confounding by severity did not explain the association.

Among both genders, depression had a significant association with LUTS in multivariate models adjusted for the use of antidepressants. This finding is consistent with many previous studies [18–23]. In our study, the association for depressive symptoms was stronger among men than among women. Whereas the reasons for this are unknown, the gender difference has also been observed in the BACH Survey for urinary incontinence [35] and in the large EPIC study for symptoms of overactive bladder with incontinence [36]. A qualitative study of BACH participants found that men as well as women felt that urologic symptoms, including frequency and urgency, were stigmatizing and that the nature of the stigma was different than for women [37]. This, in turn, suggests that the psychological impact of symptoms may also differ by gender.

We did not confirm an association between SSRI use and LUTS in either gender. A recent large study by Wuerstle et al. found a significant association of antidepressant use with LUTS among men aged 45–69 years (OR=1.36, 95% CI 1.29–1.44) [13]. This result [adjusted for benign prostatic hyperplasia (BPH) status] was similar in magnitude to our adjusted findings for men for SSRIs (Table 2) but was not further adjusted for comorbidities such as depressive symptoms and diabetes, which may explain the differences compared with our results. When minimally adjusted for age and race/ethnicity, our association for use of SSRIs without AAPs among men was also statistically significant (OR=1.98, 95% CI 1.36–2.87, data not shown). In their analysis, Wuerstle et al. combined all antidepressants, which may further explain differences between our results. Other studies of SSRIs and related LUTS included nocturia (a symptom on the AUA/IPSS scale). A study of Swedish men and women found that both depression and SSRI use were significantly associated with nocturia (OR for SSRI use=2.2, 95% CI 1.1–4.5) [14]. However, as with Wuerstle et al., the analysis was unadjusted for the influence of comorbid risk factors. Another study of nocturia conducted in Finland found antidepressants positively associated with nocturia (OR=3.16, 95% CI 1.29–7.73) after multivariate adjustment, but only among men [38]. The subtypes of antidepressants studied were not defined. Finally, a recent longitudinal analysis found that men with depression at baseline were more likely

to develop moderate to severe nocturia 5 years later, with an effect apparent only in those whose depression was not treated with drugs; antipsychotics were also not associated with incident nocturia. These results lend some support to the findings of our study by suggesting that the use of psychoactive medications does not cause incident nocturia among men [23].

Despite this population-based evidence, however, there are case reports of urinary disturbances associated with SSRI use [39], suggesting that unique effects may occur on an individual level. Each SSRI has a unique pharmacologic profile, and this could explain the opposing actions on voiding behavior reported in the literature, which range from urinary incontinence to retention [15]. Our analysis combined all SSRIs and potentially missed opposing drug effects. In addition to the cross-sectional analysis, our study is limited by a small number of exclusive users of AAPs. However, our grouping of AAP use with SSRI users may best represent patterns of real-world drug use. Our modeling results suggest that the chosen groupings in Table 1 were supported, considering that AAP use appeared to confer the association among women, whether with or without SSRIs. We did not consider dose or duration of use, and risk of adverse urologic effects may vary by these factors. There is also the potential for misclassification of depression, as severity may vary over time. Strengths of our study include inclusion of both genders, the ability to consider overlap with other medications, and the ability to adjust for a wide variety of known risk factors for LUTS. Our results provide some evidence that SSRIs are not associated with an increased prevalence of LUTS in the community. As our gender-specific results for the association of AAP use with increased prevalence of LUTS among women are novel, these findings should be further investigated.

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