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Featured Article

Bladder antimuscarinics and cognitive decline in elderly patients

Daniela Claudia Moga[a,b,c,*], Erin L. Abner[b,c], Qishan Wu[b], Gregory A. Jicha[c,d]

[a]Department of Pharmacy Practice and Science, College of Pharmacy, University of Kentucky, Lexington, KY, USA
[b]Department of Epidemiology, College of Public Health, University of Kentucky, Lexington, KY, USA
[c]Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY, USA
[d]Department of Neurology, College of Medicine, University of Kentucky, Lexington, KY, USA

Abstract

Introduction: The evidence on the impact of bladder antimuscarinics initiation on cognitive function in older adults is inconsistent.

Methods: A retrospective analysis of data from the National Alzheimer's Coordinating Center (NACC) on enrollees 65 years and older evaluated the association between antimuscarinic initiation and cognitive decline. We defined decline from baseline (yes/no) for cognitive assessments included in the NACC Uniform Data Set 2.0 battery. New users were matched on year of enrollment and time in the cohort to randomly selected nonusers. Analyses were conducted using inverse probability of treatment weights based on baseline propensity scores.

Results: Our analyses included 698 new users and 7037 nonusers. The odds ratio (OR) and 95% confidence interval for cognitive decline in users as compared to nonusers was 1.4 (1.19–1.65) for Mini–Mental State Examination (MMSE), and 1.21 (1.03–1.42) for Clinical Dementia Rating; in addition, the odds of decline were 20% higher in users compared to nonusers for semantic memory/language and executive function. The effect estimate for MMSE was 1.94 (1.3–2.91) for those with mild cognitive impairment, 1.26 (0.99–1.62) in those with normal cognition, and 1.44 (1.04–1.99) in those with dementia at baseline.

Discussion: Our results show that antimuscarinic initiation is associated with cognitive decline and raise questions about their use, especially in those with impaired cognition.

Keywords: Bladder antimuscarinics; Cognitive function; National Alzheimer's Coordinating Center; Cholinergic; Alzheimer

1. Introduction

The cholinergic system in the brain plays an important role in working memory, attention, awareness, psychomotor speed, and selection of relevant stimuli from the environment [1]. By blocking cholinergic receptors in the central nervous system (CNS), drugs with anticholinergic activity could potentially cause undesirable effects on these important cognitive functions, depending on the drug bioavailability and metabolism, as well as its ability to cross the blood–brain barrier [2,3]. Changes in the acetylcholine-mediated neurotransmission and the increased permeability of the blood–brain barrier caused by aging inflate the risk of CNS adverse effects of anticholinergic drugs. Similar effects are the result of different comorbidities (e.g., diabetes mellitus, Alzheimer's disease [AD], vascular dementia), which are also more prevalent in the elderly population [4–6]. Previous studies showed that drugs with anticholinergic properties could result in cognitive decline and even precipitate dementia in older adults [7,8]. Moreover, a recent prospective cohort study investigating the effect of cumulative anticholinergic exposure demonstrated an increased risk of dementia with higher use of anticholinergics in adults aged 65 years and older [9].

Bladder antimuscarinics (referred to as antimuscarinics hereafter), the main pharmacological option for treating

*Corresponding author. Tel.: (859) 323-9682; Fax: (859) 323-0069.
E-mail address: daniela.moga@uky.edu

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urge and mixed urinary incontinence, are among the most commonly used drugs with anticholinergic properties in the elderly [9]. Of the available antimuscarinics, the most frequently used by patients is oxybutynin, a nonselective agent that can bind to receptors throughout the body, including CNS [9]. Previous studies investigating the potential role of antimuscarinics in causing cognitive decline in older adults included a small number of patients, measured cognitive performance with scales less sensitive to longitudinal change, or followed participants for a short period and led to inconclusive results. Some of the studies suggested that in patients with AD, antimuscarinics produce cognitive, behavioral, and physiological changes [10,11], but other studies failed to support these findings [12]. The primary objective of our study was to further evaluate the association of antimuscarinic initiation with cognitive decline in older adults by using the rich data collected as part of the ongoing National Alzheimer's Coordinating Center (NACC) cohort and to address some of the limitations of previous studies.

2. Methods

2.1. Setting

We conducted a retrospective evaluation using data collected as part of the prospective NACC cohort. Data available from the Uniform Data Set (UDS) between September 1, 2005 and December 31, 2013 were used to identify new antimuscarinic users [13] and nonusers as controls and conduct all of the analyses described in the following.

2.2. Participants

A description of the NACC cohort, its eligibility criteria, and data collection are available elsewhere [14–17]. In summary, NACC was established in 1999 with the purpose of facilitating research related to AD. This cohort includes not only patients with AD and related disorders but also cognitively normal subjects and those with mild cognitive impairment (MCI). Beginning in 2005, UDS data were collected through standardized evaluations of enrollees from National Institute on Aging–funded Alzheimer's Disease Centers (ADC). Each ADC has its own recruitment protocol, and participants are recruited through clinician or self-referral (patients or family members), or through active community recruitment strategies. Of the 32,532 participants enrolled in NACC between 2005 and beginning of 2016, about 89% were 60 years or older, 80% were white, 70% had 12 or more years of education, 37% had normal cognition at enrollment, about 21% had MCI, and about 37% had dementia. In addition to the ADC-specific inclusion/exclusion criteria, the eligibility criteria for our investigation included (1) participants enrolled on or after September 1, 2005 with a minimum of one follow-up visit; (2) age 65 years and older at the visit when antimuscarinic use was first reported (or the equivalent visit for nonusers—see the following for additional information regarding nonusers selection); (3) with medication data available at all visits, and (4) with no antimuscarinics reported at enrollment. We excluded participants with non-MCI or non–AD-related cognitive impairment, specifically (1) cognitive status categorized as "impaired not mild cognitive impairment"; (2) frontotemporal dementia; (3) primary progressive aphasia; (4) progressive supranuclear palsy; (5) corticobasal degeneration; (6) Huntington's disease; (7) prion disease; (8) Down's syndrome; (9) CNS neoplasm; (10) traumatic brain injury; (11) hydrocephalus; (12) alcohol-related dementia; (13) dementia of undetermined etiology. A flow diagram to describe the participants' selection process and the groups included in the analyses is depicted in Fig. 1.

Exposure to antimuscarinics was identified from the self-reported data collected at enrollment and yearly thereafter using the "brown bag" medication review approach (i.e., the participant or a family member were asked to bring all current medications to the research assessment) on prescription and over-the-counter medications for the two-week window preceding the index date [15]. Antimuscarinic exposure was measured as antimuscarinics yes/no by identifying at least one mention of the following medications: oxybutynin, tolterodine, flavoxate, hyoscyamine, darifenacin, trospium, solifenacin, fesoterodine, propantheline. Antimuscarinic exposure was further categorized based on muscarinic receptor selectivity: nonselective antimuscarinics (oxybutynin, tolterodine, flavoxate, hyoscyamine, trospium, fesoterodine, propantheline) and M_3 selective antimuscarinics (darifenacin or solifenacin). When exposure to more than one antimuscarinic was reported, exposure category was assigned as nonselective in the presence of at least one nonselective drug. Antimuscarinic users were considered prevalent users if antimuscarinic exposure was reported at enrollment and incident (new) users if exposure was first

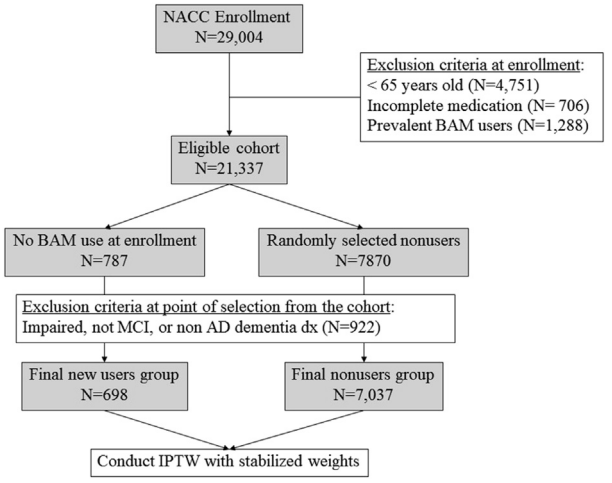

Fig. 1. Inclusion/exclusion cascade and study groups. Abbreviations: BAM, bladder antimuscarinics; IPTW, inverse probability of treatment weights; MCI, mild cognitive impairment; NACC, National Alzheimer's Coordinating Center.

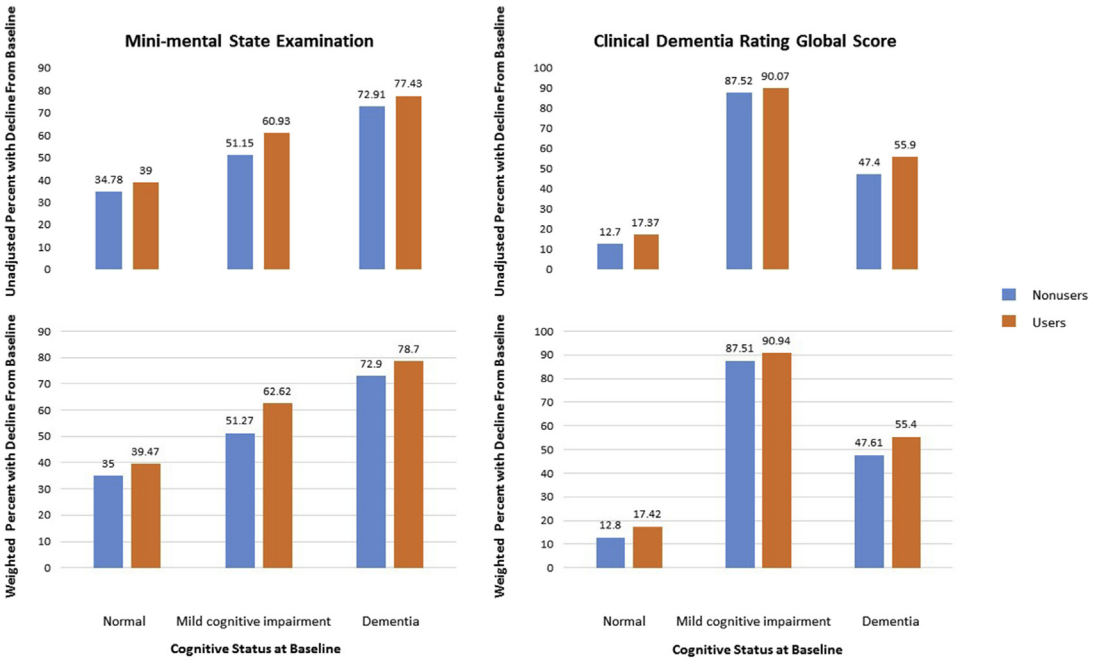

Fig. 2. Figure shows percent with cognitive decline in antimuscarinic users and nonusers stratified by baseline cognitive status. Top panels include unadjusted analyses; Bottom panels include adjusted (weighted) analyses.

reported at one of the follow-up visits. Prevalent users were excluded from further analyses.

2.3. Outcome description

Cognitive function was measured based on the information collected at follow-up UDS visits. From the comprehensive cognitive evaluation conducted as part of the cohort, we selected our measures of interest based on the evidence from prior research to suggest areas potentially impacted by medications with anticholinergic properties in general, and therefore antimuscarinics. Our outcomes included two measures of global cognitive status—Mini–Mental State Examination (MMSE) [18] and Clinical Dementia Rating (CDR) [19] global score. In addition, we also evaluated the association between antimuscarinic initiation and decline in clinical diagnosis status by assessing the likelihood of decline from normal to MCI or dementia, and from MCI to dementia within 1 year from baseline. Furthermore, specific cognitive domains were evaluated using the following measures: (1) memory, orientation, and judgment domain scores from CDR; (2) semantic memory and language using category fluency tests (Animals and Vegetables) and Boston Naming Test; (3) psychomotor speed using WAIS-R Digit-Symbol Substitution and the Trail Making Test Part A; and (4) executive function using the Trail Making Test Part B. Detailed descriptions of these tests, including information about score range and interpretation for the NACC ADC cohort, are available elsewhere [17]. Decline was identified as a dichotomous variable and was defined considering the scoring algorithm for each cognitive outcome. Specifically, a participant was categorized as experiencing cognitive decline from baseline in case of a higher score at the follow-up visit (CDR global score, memory, orientation, and judgment domain scores from CDR), or a lower score at follow-up visit (MMSE, Animals and Vegetables, Boston Naming Test), or a longer time for completion at follow-up as compared to baseline (WAIS-R Digit-Symbol Substitution, Trail Making Test Part A, Trail Making Test Part B), as compared to their score (or time) at baseline. We also coded decline if the score was in the valid range at baseline but was missing due to "cognitive/behavior problem" at follow-up. In addition, we conducted sensitivity analyses to test the robustness of our outcome definition (i.e., cognitive decline) by excluding those with missing data and using a more conservative approach that considered decline in the presence of a clinically meaningful change based on the standard deviations for cognitively intact older adults reported in a previous study using NACC data [17]. Specifically, we considered two additional definitions, one where decline was defined based on a minimum change equal to half the reported standard deviation, and one where decline was defined based on a minimum change equal to one reported standard deviation. Because the reported standard deviations contained decimals, we rounded up to the next whole point to define decline.

2.4. Statistical analysis

Analyses were conducted after the comparison group of nonusers was selected, and we applied all eligibility criteria for both groups. For each new user, we randomly selected 10 nonusers that were matched by year of enrollment and time since enrollment (visit year). Baseline was defined as the prior UDS assessment (i.e., last assessment before the first one reporting antimuscarinic use, or the equivalent for the nonusers group). We evaluated group differences between antimuscarinic users and nonusers at baseline using chi-square analysis (or Fisher's exact test where appropriate) for categorical variables, and t-tests for continuous variables.

For the main analyses, the propensity score (PS) method was used to address treatment selection bias and to balance observed baseline covariates between the study groups. The PS for each participant was estimated through logistic regression as the probability of starting treatment with an antimuscarinic during study period (i.e., report antimuscarinic use during a UDS evaluation) based on their characteristics measured at baseline from the standardized NACC data collection based on self-reported information or proxy respondents. The logistic regression model to predict antimuscarinic initiation and calculate PS included variables related to antimuscarinic use and also variables for which empirical evidence exists to support their impact on cognitive function [20,21]. Specifically, the model included demographic characteristics (age, race, sex, education), living situation, indicators for each recruiting center (ADC), year at enrollment, year at assessment, body mass index (BMI), lifestyle-related risk factors (hypercholesterolemia, alcohol use, smoking), urinary and fecal incontinence status, cognitive status (i.e., normal, MCI, or dementia), level of independence, comorbidities (cardiovascular disease, congestive heart failure, stroke, transient ischemic attack, Parkinson's disease, hypertension, diabetes, recent depression episodes, psychiatric disorders), other medications used (antiadrenergic agents, beta blockers, diuretics, calcium channel blocking agents, angiotensin-converting enzyme inhibitors, antidepressants, antipsychotic agents, anxiolytic, sedative, or hypnotic agents, antiparkinsonian agents, medications approved by the Food and Drug Administration for the treatment of AD's cognitive symptoms [i.e., memantine or cholinesterase inhibitors], and total number of medications reported at visit), and anticholinergic load measured using the anticholinergic drug scale [22]. When calculating propensity scores, to address the issues of missing data for some of the categorical variables included in the model, missing values were treated as a separate category.

The association between antimuscarinic exposure and cognitive outcomes was measured based on each patient's change in score from baseline. The odds ratios with 95% confidence limits for cognitive decline associated with antimuscarinic initiation were calculated using inverse probability of treatment weights (IPTWs) with stabilized weights based on the PS for initiating antimuscarinics and trimming nonoverlapping regions of the PS distribution [23,24]. Analyses were conducted for all antimuscarinic users and also after restricting the new users group to those treated with nonselective agents. For a clinical interpretation of the results, we also calculated the number needed to treat to cause decline for the overall cognitive performance measures [25]. As an exploratory analysis, we evaluated whether the association of antimuscarinics and cognitive decline measured through MMSE was different by cognitive status at baseline (normal, MCI, or dementia), for all antimuscarinics users and also restricted to nonselective antimuscarinics.

3. Results

Of the 29,004 participants enrolled in the NACC cohort between September 1, 2005 and December 31, 2013, 2075 reported antimuscarinic use during follow-up. Of these, 787 participants did not report antimuscarinics at enrollment, and 698 met all the eligibility criteria for the study and were considered new antimuscarinic users for our analyses (Fig. 1). About 70% of users reported a nonselective antimuscarinic, most commonly oxybutynin and tolterodine (about 40% of the nonselective antimuscarinics for each). Of those using M_3 selective antimuscarinics, about 66% used solifenacin. Of the 7870 nonusers randomly selected after matching by year of enrollment and year of first antimuscarinic report, 7037 met the inclusion/exclusion criteria and were included in our analyses (Fig. 1).

The magnitude of cognitive decline from baseline as evaluated through MMSE and CDR was larger in antimuscarinic users as compared to nonusers (Table 1 and Fig. 2). When antimuscarinic users and nonusers were compared at baseline, several significant differences were noted in the unadjusted analyses (Table 1). New users were mostly women, older, less likely to live in a single family residence, and more likely to need assistance. Nonusers were healthier, with lower BMI and fewer comorbid conditions (less likely to have diabetes, Parkinson's disease, depression, other psychiatric diagnosis, or active fecal incontinence), were taking fewer drugs, and had a lower anticholinergic load. New users were more likely to have hallucinations or agitation indicated at baseline and were more frequently cognitively impaired (Table 1 and Supplementary Table 1). After calculating the PS for each participant and applying weights through the IPTW method, the groups included in the analyses were balanced on the measured confounders (Supplementary Table 2).

Similar to the unadjusted results, in the IPTW analyses that accounted for baseline differences between groups, new users were more likely to show statistically significant cognitive decline in the overall cognitive status

Table 1
Baseline and follow-up characteristics in bladder antimuscarinics users and nonusers

Characteristic	Nonusers (N = 7037)	New users (N = 698)
Baseline		
Time from enrollment (days): mean (SD)	463.1 (550.1)	425.9 (535.5)
Year of enrollment: *n* (%)		
2005	845 (12.01)	87 (12.46)
2006	2855 (40.57)	279 (39.97)
2007	1448 (20.58)	149 (21.35)
2008	696 (9.89)	62 (8.88)
2009	521 (7.40)	51 (7.31)
2010	390 (5.54)	39 (5.59)
2011	186 (2.64)	20 (2.87)
2012	96 (1.36)	11 (1.58)
Age: mean (SD)	76.98 (7.63)	77.88 (7.15)
Male: *n* (%)	2993 (42.53)	289 (41.40)
Race: *n* (%)		
White	5784 (82.19)	584 (83.67)
Black	831 (11.81)	82 (11.75)
Other	422 (6.00)	32 (4.58)
Education: *n* (%)		
High school or less	2054 (29.19)	199 (28.51)
College degree	2883 (40.97)	282 (40.40)
Graduate degree	2100 (29.84)	217 (31.09)
Living situation: *n* (%)		
Lives alone	1903 (27.04)	202 (28.94)
Lives with spouse or partner	4171 (59.27)	412 (59.03)
Lives with relative or friend	655 (9.31)	55 (7.88)
Lives with group	129 (1.83)	16 (2.29)
Other or unknown	179 (2.54)	13 (1.86)
Residence type: *n* (%)		
Single family residence	6051 (85.99)	565 (80.95)
Retirement community	585 (8.31)	80 (11.46)
Assisted living/boarding home/adult family home	177 (2.52)	31 (4.44)
Skilled nursing facility/nursing home	113 (1.61)	6 (0.86)
Unknown	111 (1.58)	16 (2.29)
Level of independence: *n* (%)		
Able to live independently	4546 (64.60)	394 (56.45)
Requires some assistance with complex activities	1486 (21.12)	198 (28.37)
Requires some assistance with basic activities	733 (10.42)	87 (12.46)
Completely dependent	272 (3.87)	19 (2.72)
BMI category: *n* (%)		
Normal	2356 (33.48)	210 (30.09)
Overweight	2512 (35.70)	231 (33.09)
Obese	1332 (18.93)	162 (23.21)
Underweight	86 (1.22)	8 (1.15)
Unknown	751 (10.67)	87 (12.46)
Smoking history—100 lifetime cigarettes: *n* (%)	3289 (46.74)	318 (45.56)
Alcohol abuse: *n* (%)	355 (5.04)	35 (5.01)
Comorbidities: *n* (%)		
Hypercholesterolemia	4016 (57.07)	399 (57.16)
Cardiovascular disease	555 (7.89)	56 (8.02)
Diabetes	916 (13.02)	110 (15.76)
Parkinson's disease	134 (1.90)	45 (6.45)
Depression	1923 (27.33)	233 (33.38)
Psychiatric diagnosis	360 (5.12)	51 (7.31)
Stroke	428 (6.08)	51 (7.31)
Urinary incontinence (active)	408 (5.80)	59 (8.45)
Fecal incontinence (active)	460 (6.54)	60 (8.60)
Number of medications reported at visit: mean (SD)	5.68 (3.72)	6.44 (4.19)
Anticholinergic burden: mean (SD)	0.66 (1.12)	0.91 (1.34)
Other medications: *n* (%)		
Antiadrenergic agent	598 (8.50)	93 (13.32)
Beta-adrenergic blocking agent	1587 (22.55)	174 (24.93)
Angiotensin-converting enzyme inhibitor	1357 (19.28)	138 (19.77)

(*Continued*)

Table 1
Baseline and follow-up characteristics in bladder antimuscarinics users and nonusers (*Continued*)

Characteristic	Nonusers (N = 7037)	New users (N = 698)
Antidepressant	1732 (24.61)	227 (32.52)
Antipsychotic agent	286 (4.06)	33 (4.73)
Anxiolytic, sedative, or hypnotic agent	676 (9.61)	102 (14.61)
Antiparkinson agent	244 (3.47)	69 (9.89)
Medication for Alzheimer's disease symptoms	2134 (30.33)	249 (35.67)
Diuretic	1280 (18.19)	128 (18.34)
Calcium channel blocking agent	1096 (15.57)	121 (17.34)
Hallucinations: *n* (%)	242 (3.44)	32 (4.58)
Delusions: *n* (%)	555 (7.89)	56 (8.02)
Agitation	1260 (17.91)	150 (21.49)
Cognitive status: *n* (%)		
Normal	3269 (46.45)	259 (37.11)
MCI	1306 (18.56)	151 (21.63)
Dementia	2462 (34.99)	288 (41.26)
Mini–Mental State Examination: mean (SD)		
All	25.24 (6.12)	25.46 (5.09)
Baseline cognitive status: normal	28.82 (1.54)	28.82 (1.40)
Baseline cognitive status: MCI	26.88 (2.65)	26.97 (2.74)
Baseline cognitive status: dementia	19.42 (7.01)	21.52 (5.56)
Mini–Mental State Examination: *n* (%)		
Normal	3985 (56.63)	363 (52.01)
Mild impairment	1646 (23.39)	216 (30.95)
Moderate impairment	833 (11.84)	77 (11.03)
Severe impairment	266 (3.78)	13 (1.86)
Missing	307 (4.36)	29 (4.15)
Clinical Dementia Rating Global score: *n* (%)		
No impairment	3119 (44.32)	249 (35.67)
Questionable impairment	2055 (29.20)	251 (35.96)
Mild impairment	1168 (16.60)	143 (20.49)
Moderate impairment	460 (6.54)	48 (6.88)
Severe impairment	235 (3.34)	7 (1.00)
Follow-up		
Mini–Mental State Examination: mean (SD)		
All	24.70 (6.64)	24.26 (6.21)
Baseline cognitive status: normal	28.72 (1.72)	28.68 (1.53)
Baseline cognitive status: MCI	26.22 (3.33)	25.98 (3.29)
Baseline cognitive status: dementia	17.72 (7.17)	19.04 (6.42)
Mini–Mental State Examination: *n* (%)		
Normal	3730 (53.01)	321 (45.99)
Mild impairment	1388 (19.72)	173 (24.79)
Moderate impairment	973 (13.83)	124 (17.77)
Severe impairment	350 (4.97)	23 (3.30)
Cognitive or behavioral problems	83 (1.18)	6 (0.86)
Missing	513 (7.29)	51 (7.31)
Clinical Dementia Rating Global score: *n* (%)		
No impairment	3003 (42.67)	227 (32.52)
Questionable impairment	1777 (25.25)	208 (29.80)
Mild impairment	1110 (15.77)	147 (21.06)
Moderate impairment	718 (10.20)	86 (12.32)
Severe impairment	429 (6.10)	30 (4.30)
Cognitive decline (Mini–Mental State Examination): *n* (%)		
Including decline based on information regarding missing	3600 (51.15)	416 (59.60)
Including only those with available data	2972 (46.71)	356 (56.15)
Baseline cognitive status: normal	1137 (34.78)	101 (39.00)
Baseline cognitive status: MCI	668 (51.15)	92 (60.93)
Baseline cognitive status: dementia	1795 (72.91)	223 (77.43)

Abbreviations: SD, standard deviation; MCI, mild cognitive impairment.

(Table 2) as measured by MMSE (odds ratio [OR] = 1.4, 95% confidence interval [CI]: 1.19–1.65) and CDR (OR = 1.21, 95% CI: 1.03–1.42). In addition, the association with decline on different specific cognitive domains was statistically significant in the areas of memory (OR = 1.27, 95% CI: 1.05–1.52) and orientation (OR = 1.25, 95% CI: 1.04–1.51) domains of CDR, semantic memory/languages as measured by category fluency tests (Vegetable Naming: OR = 1.23, 95% CI: 1.05–1.44), and executive function as measured by the Trail Making Test Part B (OR = 1.23, 95% CI: 1.08–1.51). Our sensitivity analyses including the more conservative outcome definitions supported the results of our main analyses (Supplementary Table 3). In our exploratory analyses, when evaluating the association with decline on MMSE stratified by cognitive status at baseline, although not statistically significantly different, the effect estimate was larger for those with MCI at baseline (OR = 1.94, 95% CI: 1.3–2.91), then in those with normal cognition (OR = 1.26, 95% CI: 0.99–1.62), or dementia (OR = 1.44, 95% CI: 1.04–1.99). In addition, the effect estimate for MMSE decline was larger when analyses were restricted to new users of nonselective antimuscarinics (Table 2). The estimated numbers needed to treat to produce a harmful effect (NNH) (i.e., cognitive decline) in one participant were NNH = 22 (95% CI: 12–142) for decline in the CDR global score, and NNH = 13 (95% CI: 9–24) for decline in MMSE, with the smallest number in those with MCI at baseline: NNH = 7 (95% CI: 3–16) (Table 3). These results indicate that for every 22 patients treated with antimuscarinics, one would experience decline in the CDR global score; similarly, for every 13 patients treated with antimuscarinics, or for every 7 patients with MCI at baseline treated with antimuscarinics, one would experience decline as measured by MMSE.

4. Discussion

Using the rich data collected as part of the ongoing NACC cohort, our study evaluated the association between antimuscarinic initiation and odds of decline on various cognitive measures in older adults. Our analyses showed that, after controlling for baseline differences between groups, participants who initiated an antimuscarinic were statistically significantly more likely to exhibit cognitive decline as compared to nonusers. Specifically, antimuscarinic initiators experienced decline when cognitive function was measured with overall measures, and also they showed decline in cognitive domains for which there is biological plausibility for such an effect. To further investigate this association, we investigated and identified a potentially stronger negative effect on cognitive function when restricting our analyses to those using nonselective antimuscarinics. In terms of the clinical impact, a previous study estimated that 32 patients (95% CI: 17–125) needed to be treated to obtain improvement in urinary incontinence in one patient after 90 days of treatment [12]. In this context, our estimates for the NNH for different cognitive outcomes are striking and raise important concerns with these drugs by suggesting that we need to treat only a small number of patients to detect cognitive decline in one, and more patients

Table 2
Cognitive decline (any decline) associated with bladder antimuscarinics use

Cognitive domain	Cognitive test	IPTW*—all users, OR (95% CI)	IPTW*—NS users, OR (95% CI)
Overall cognitive status	Mini–Mental State Examination		
	Overall	1.4 (1.19–1.65)	1.54 (1.26–1.89)
	By baseline cognitive function		
	Normal	1.26 (0.99–1.62)	1.42 (1.05–1.92)
	Mild cognitive impairment	1.94 (1.3–2.91)	1.73 (1.03–2.92)
	Dementia	1.44 (1.04–1.99)	1.76 (1.17–2.67)
	Clinical Dementia Rating		
	Global score	1.21 (1.03–1.42)	1.22 (1.01–1.48)
	Memory	1.27 (1.05–1.52)	1.32 (1.05–1.65)
	Orientation	1.25 (1.04–1.51)	1.36 (1.09–1.7)
	Judgment	1.08 (0.9–1.31)	1.12 (0.88–1.41)
Semantic memory/language	Category fluency		
	Animals	1.1 (0.94–1.29)	1.14 (0.94–1.39)
	Vegetables	1.23 (1.05–1.44)	1.19 (0.97–1.44)
	Boston	1.13 (0.96–1.32)	1.17 (0.96–1.42)
Psychomotor speed	WAIS-R Digit Symbol	1.04 (0.88–1.23)	1.09 (0.89–1.33)
	Trail A	1.11 (0.95–1.31)	1.16 (0.95–1.42)
Executive function	Trail B	1.23 (1.08–1.51)	1.16 (0.95–1.43)

Abbreviations: IPTW, inverse probability of treatment weights; OR, odds ratio; CI, confidence interval; NS, nonselective; ADC, Alzheimer's Disease Centers.
*Propensity score used to calculate stabilized weights for IPTW included indicators for each ADC, year of enrollment and time from enrollment, sociodemographic information (age, sex, race, education, residence type, and living situation), level of dependency, behavioral risk factors (body mass index, alcohol, smoking), comorbidities (urinary and fecal incontinence, cardiovascular conditions, diabetes, Parkinson's disease, depression, stroke, psychiatric diagnosis), number of and other medications used, anticholinergic burden.

Table 3
Number needed to harm in relationship to bladder antimuscarinic use

Cognitive test	NNH* (95% CI); all users	NNH (95% CI); NS users
CDR Global score†	22 (12–142)	21 (14–422)
MMSE‡		
All	13 (9–24)	10 (7–18)
Baseline cognitive status: normal	19 (9–442)	13 (7–90)
Baseline cognitive status: MCI	7 (3–16)	8 (5–136)
Baseline cognitive status: dementia	16 (9–131)	11 (7–34)

Abbreviations: NNH, number needed to harm; CI, confidence interval; NS, nonselective; CDR, Clinical Dementia Rating; MMSE, Mini–Mental State Examination; MCI, mild cognitive impairment; OR, odds ratio.

*NNH derived from OR estimates [25].

†From normal to either MCI or dementia, or from MCI to dementia.

‡At least one-point decrease in MMSE score.

to see improvement in one. Importantly, the potential for an even larger effect if antimuscarinics are prescribed to patients with MCI are to be considered in the clinical decision-making process.

Our results are in line with other studies that previously investigated the relationship between antimuscarinic initiation and cognitive decline. A single-blind crossover design study on nine patients with AD measured MMSE, the Neuropsychiatric Inventory, and the Memory and Behavior Problems Checklist on and off antimuscarinics and showed that antimuscarinics produce cognitive, behavioral, and physiological changes; moreover, the study showed that antimuscarinics with stronger anticholinergic activity were associated with greater decline in MMSE [10]. Similarly, a randomized clinical trial on 150 healthy volunteers found that antimuscarinics decreased delayed recall and suggested differences in effects for different antimuscarinics depending on their selectivity for different muscarinic receptors; specifically, the study identified significantly more important impairment associated with the nonselective antimuscarinics (oxybutynin) as compared to the bladder-selective one (darifenacin) [11]. A retrospective cohort study conducted in a nursing home population evaluated the long-term functional and cognitive outcomes in elderly that received antimuscarinics concomitant with cholinesterase inhibitors and showed that those taking both medications had greater rates of functional decline as compared to those who received cholinesterase inhibitors alone [26].

Our study has important strengths as compared to these previous studies investigating the association between antimuscarinics and cognitive decline. Our investigation included more new users of antimuscarinics from a large cohort of participants with different levels of cognitive function. All of the participants underwent extensive cognitive testing using well-established and validated instruments. Moreover, the testing was independent of antimuscarinic use in our study; therefore, differential misclassification or bias in our analyses is of lesser concern. In addition, our analyses were conducted after careful consideration of confounding by using the IPTW approach to balance study groups [27,28].

Given the nature of the data available and the issues arising with repeated testing in longitudinal studies (i.e., practice effects), our study has some limitations. Repeated testing and potential for learning effects, or ceiling/flooring effects would potentially bias our results and underestimate the true effect size [29,30]. With data collection scheduled at enrollment and yearly after, and given that the question on medication use asks about current medications taken by the participant (i.e., all medications taken within 14 days of the visit), we could not ascertain the exact date for antimuscarinic initiation, and, therefore, the duration of exposure to antimuscarinics for our users group. In addition, some of the BAM users may have been misclassified as nonusers in the situation in which they started and stopped treatment between two consecutive study visits. Finally, we were able to discern between selective and nonselective antimuscarinics; however, we could not differentiate between immediate-release and extended-release nonselective antimuscarinic formulations. Nevertheless, the bias resulting from these study design issues would not change the interpretation for our results, but would rather provide an underestimate for the true antimuscarinic effect on cognition. For instance, patients misclassified as nonusers, would be more likely those experiencing adverse effects soon after antimuscarinic initiation or those not tolerating these medications [31]; as a result, we can make the assumption that those participants would also be more likely to experience cognitive outcomes (i.e., decline) and be analyzed in the nonusers group, thus biasing the results toward the null. Similarly, our inability to restrict our analyses to those using immediate-release formulations prevented us from seeing a larger effect to that seen after restriction to nonselective antimuscarinics. The potential for residual confounding in our study remains given our inability to discern whether antimuscarinic initiation was due to treatment of incontinence as a prodromal symptom of cognitive decline. We addressed this issue by incorporating a measure of incontinence severity in our propensity score calculation that allowed for balance between the groups. Another limitation of our study is driven by the population recruited in

the NACC cohort. Given the recruitment strategies that differ among ADCs, participants enrolled in this cohort are not necessarily a representative random sample for the entire population of patients with MCI or dementia, or for elderly with no cognitive impairment. Participants in the NACC cohort, and therefore in our study, are in general more educated, have higher income, and more likely to receive care in academic hospitals and clinics. Therefore, the generalizability of these findings to all community-dwelling elderly may be limited. Replication of our results in independent samples is needed.

In conclusion, our results support the growing evidence for the association between antimuscarinic initiation and cognitive decline in patients aged 65 years and older. Importantly, our data show that patients with MCI might be more sensitive to these antimuscarinic effects. Considering our findings suggesting that one would have to treat fewer individuals to cause an adverse outcome than to achieve the hoped-for benefit, prescribers should consider this potential effect when contemplating antimuscarinic initiation for their elderly patients with urinary incontinence and should always weigh the risks and the benefits of such treatment for each patient individually.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.trci.2017.01.003.

RESEARCH IN CONTEXT

1. Systematic review: We conducted a standard literature review using PubMed to identify studies investigating the association between bladder antimuscarinics and cognitive decline in elderly patients. These previous studies led to inconclusive results and they have important limitations, including small sample size, short follow-up, or measuring cognitive function with scales less sensitive to longitudinal change.
2. Interpretation: We demonstrated a statistically significant association between bladder antimuscarinic initiation and different measures of cognitive function in adults aged 65 years and older; specifically, our study showed that antimuscarinic initiation was associated with worsening cognition. In addition, we investigated association with specific cognitive outcomes for which biologic plausibility supports such effects. Importantly, our data showed that patients with mild cognitive impairment might be more sensitive to these effects.
3. Future directions: Further investigations are needed to explore the potential for a differential effect of different types of BAM to allow for proper disease management when medication is needed in this population.

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