

# Risk of Mortality Associated with Non-selective Antimuscarinic medications in Older Adults with Dementia: a Retrospective Study



Nandita Kachru, PhD<sup>1</sup>, Holly M. Holmes, MD, MS<sup>2</sup>, Michael L. Johnson, PhD<sup>1</sup>, Hua Chen, PhD<sup>1</sup>, and Rajender R. Aparasu, PhD, FAPhA<sup>1</sup> 

<sup>1</sup>Department of Pharmaceutical Health Outcomes and Policy, College of Pharmacy, University of Houston, Houston, TX, USA; <sup>2</sup>Division of Geriatric and Palliative Medicine, McGovern Medical School at UTHealth, Houston, TX, USA.

**BACKGROUND:** Selective antimuscarinics may offer a favorable safety profile over non-selective antimuscarinics for the management of overactive bladder (OAB) in patients with dementia.

**OBJECTIVE:** To test the hypothesis that non-selective antimuscarinics are associated with increased risk of mortality compared to selective antimuscarinics in older adults with dementia and OAB.

**DESIGN:** Propensity score-matched retrospective new-user cohort design among Medicare beneficiaries in community settings.

**PATIENTS:** Older adults with dementia and OAB with incident antimuscarinic use.

**MAIN MEASURES:** The primary exposure was antimuscarinic medications classified as non-selective (oxybutynin, tolterodine, trospium, fesoterodine) and selective (solifenacin, darifenacin) agents. All-cause mortality within 180 days of incident antimuscarinic use formed the outcome measure. New users of non-selective and selective antimuscarinics were matched on propensity scores using the Greedy 5 → 1 matching technique. Cox proportional-hazards model stratified on matched pairs was used to evaluate the risk of mortality associated with the use of non-selective versus selective antimuscarinics in the sample.

**KEY RESULTS:** The study identified 16,955 (77.6%) non-selective antimuscarinic users and 4893 (22.4%) selective antimuscarinic users. Propensity score matching yielded 4862 patients in each group. The unadjusted mortality rate at 180 days was 2.6% (126) for non-selective and 1.6% (78) for selective antimuscarinic users in the matched cohort ( $p$  value < 0.01). The Cox model stratified on matched pairs found 50% higher risk of 180-day mortality with non-selective antimuscarinics as compared to selective ones (hazard ratio (HR) 1.50; 95% confidence interval (CI) 1.04–2.16). The study findings remained consistent across multiple sensitivity analyses.

**CONCLUSIONS:** Use of non-selective antimuscarinics was associated with a 50% increase in mortality risk

among older adults with dementia and OAB. Given the safety concerns regarding non-selective antimuscarinic agents, there is a significant need to optimize their use in the management of OAB for older patients with dementia.

**KEY WORDS:** dementia; overactive bladder; antimuscarinic; selective; non-selective; mortality.

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## INTRODUCTION

Overactive bladder (OAB) can be defined as a constellation of urinary symptoms typically characterized by urgency, with or without urge urinary incontinence, and accompanied by frequency and nocturia<sup>1</sup>. Antimuscarinic medications, the first-line pharmacotherapy for OAB, block the muscarinic receptors and inhibit involuntary detrusor contractions, thereby reducing urgency<sup>2, 3</sup>. Although antimuscarinic agents are effective in bladder control, there are differences in the safety and tolerability profiles of individual agents, mainly driven by the differences in receptor selectivity subtypes and capability to cross the blood–brain barrier<sup>4–6</sup>. Antimuscarinics such as oxybutynin, tolterodine, trospium, and fesoterodine are *non-selective* as they have affinity for all muscarinic receptors (M1–M5), while others such as darifenacin and solifenacin are *selective* due to their high affinity for M2/M3 receptors that are responsible for bladder contraction.

Although selective and non-selective agents have comparable efficacy, muscarinic receptor selectivity could offer advantages over non-selective agents with respect to adverse effects<sup>4, 7–12</sup>. On the basis of available evidence, antimuscarinic agents with selectivity for M3 over M1 and M2 receptors, limited CNS penetration, or both may offer a favorable balance of safety and efficacy in treating OAB together with reduced adverse cognitive effects in the older population<sup>13</sup>. Medications with strong anticholinergic properties such as antimuscarinics have been associated with cognitive and other adverse effects including risk of mortality in diverse samples of older adults<sup>14–25</sup>. Two recent studies have

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evaluated the risk of cardiovascular events and overall mortality with antimuscarinics and provided conflicting findings<sup>26, 27</sup>. Arana et al. found increased risk of cardiovascular events and mortality among adults using oxybutynin compared to tolterodine<sup>26</sup>. However, Margulis et al. found no differential risk of cardiovascular events and overall mortality among adults using antimuscarinic agents for OAB<sup>27</sup>.

Dementia and OAB are the most common comorbid conditions affecting older patients. The multifactorial disease pathology of dementia leads to a fourfold increase in urinary incontinence and OAB, and urinary problems affect up to 90% of patients with dementia<sup>28, 29</sup>. Although antimuscarinics are effective for OAB, highly anticholinergic medications including antimuscarinics are considered inappropriate for patients with dementia<sup>30</sup>. Anticholinergic medication use in patients with dementia is of particular concern, because patients with dementia suffer from progressive cognitive decline due to damage to the cholinergic nervous system, and therefore, they are more susceptible to the central anticholinergic adverse effects of antimuscarinics<sup>31–33</sup>. However, no studies evaluated comparative safety of antimuscarinics in older adults with dementia. Therefore, the objective of this study is to examine the comparative risk of all-cause mortality among older adults with dementia and OAB using non-selective versus selective antimuscarinics. We hypothesized that non-selective antimuscarinics would lead to a higher risk of mortality than selective antimuscarinic agents in patients with dementia and OAB.

## METHODS

### Data Source

The study used multiyear Medicare claims data from 2013 to 2015 including parts A, B, and D claim data files involving 100% of the national cohort of older patients with dementia and OAB. Medicare data files are available as Research Identifiable Files from the CMS upon request<sup>34, 35</sup>. Medicare Standard Analytical Files (SAF) are available on yearly basis from the CMS. These data files are restricted to claims submitted by fee-for-service (FFS) enrollees. This study used the MedPAR File, Outpatient SAF, Carrier SAF, Master Beneficiary Summary File (MBSF), and Prescription Drug Event (PDE) files. The MBSF segment includes beneficiary enrollment information (A/B/C/D), in addition to demographic information. The PDE files include events from all beneficiaries participating in the part D program.

### Study Design

A retrospective cohort design (Fig. 1) matched on propensity scores was used to examine the comparative risk of all-cause mortality in older patients with dementia and OAB using non-selective versus selective antimuscarinic medications. The entire study duration was from 01/01/2013 to 12/31/2015. Index use of antimuscarinic medications for the older patients

with dementia and OAB was defined as the first prescription of antimuscarinic medication in the patient identification period (01/01/2014–12/31/2015) after 12 months of washout period (01/01/2013–12/31/2013) from the study start date. This ensured that (i) the study included only incident antimuscarinic users to reduce survivor bias among prevalent users and (ii) each patient had a minimum 12 months of baseline period to accurately identify any pre-existing comorbidities/comedications that could influence treatment selection for OAB.

The index antimuscarinic use was classified as non-selective or selective antimuscarinic medication. Consistent with previous research<sup>23</sup>, these antimuscarinic users were followed up to a maximum of 6 months (180 days) from their index date to examine the risk of all-cause mortality with the use of non-selective versus selective antimuscarinic medications. Exclusion criteria also included use of antimuscarinic medications before dementia diagnosis and gaps in continuous enrollment.

### Exposures and Outcome Definitions

Antimuscarinic medication exposure was identified via National Drug Codes (NDC) and generic names (Supplementary Table S1) using PDE files. The selective antimuscarinic cohort included new users of solifenacin or darifenacin. The non-selective antimuscarinic cohort included new users of oxybutynin, fesoterodine, tolterodine, or trospium. The primary outcome of this study was the time to all-cause mortality during the follow-up duration of maximum 6 months (180 days) after initiation of either non-selective or selective drug class (index date). The MBSF part A/B/C/D summary file was used to identify mortality events for all beneficiaries. Patients were followed until they died or were censored if they switched to the other antimuscarinic medication class from the index antimuscarinic medication class, or discontinued their antimuscarinic medication (gap of  $\geq 7$  days between the last date of medication use and the end of follow-up period), or had a gap of  $\geq 7$  days between two consecutive refills, or reached the end of their follow-up period or end of study period (December 31, 2015), whichever happened earlier.

### Cohort Matching

Propensity score matching was used to minimize the differences in baseline characteristics between the two exposure groups such that they differed only based on antimuscarinic treatment assignment<sup>36, 37</sup>. More than 50 covariates were included in the propensity score calculation based on previously published literature, expert opinions of clinicians and geriatricians, and their association with treatment and outcome<sup>20, 22, 23, 26, 27</sup>. These included clinical characteristics such as comorbidities and comedications and socio-demographics such as age and gender. Comorbidities were captured using Elixhauser's index during the 12 months before the index

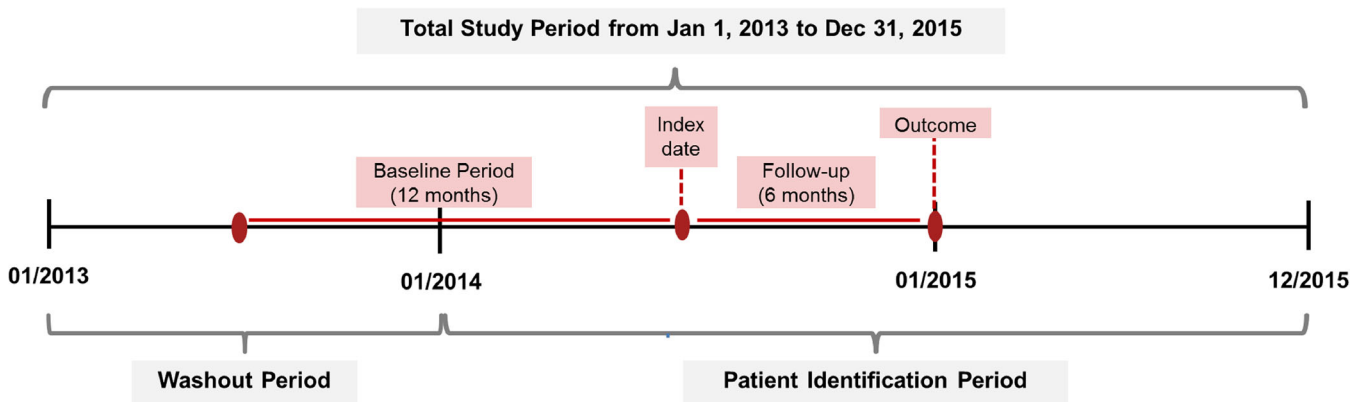


Figure 1 New antimuscarinic use study design.

date<sup>38</sup>. In addition, the Anticholinergic Drug Scale (ADS) was used to account for the baseline anticholinergic load<sup>39</sup>. A logistic regression model was developed using all baseline covariates to predict exposure to selective antimuscarinics versus non-selective agents. Patients taking non-selective antimuscarinics were then matched on this predicted probability of exposure using the GREEDY 5 → 1 matching technique. This matching technique, in general, reduces matched-pair bias caused by incomplete and inexact matching<sup>40</sup>.

## Statistical Analysis

An a priori total sample size of 1340 was estimated to yield 80% power to demonstrate a hazard ratio of 1.46 based on our previous work involving anticholinergics<sup>23</sup>. The covariate balance before and after matching was checked using bivariate analyses and standardized differences. Kaplan–Meier survival plots were created to depict the crude (unadjusted) relationship between non-selective versus selective antimuscarinic use and time to all-cause mortality. The proportionality hazard assumption, evaluated via the Schoenfeld residuals test, was supported by a non-significant relationship between residuals and time. The stratified Cox proportional-hazards model was conducted to evaluate the risk of all-cause mortality from non-selective antimuscarinic use (selective antimuscarinics as reference), within 180 days after initiating antimuscarinic treatment, with censoring. SAS 9.4 (SAS Institute, Cary, NC) was used for all analyses.

Several sensitivity analyses were conducted to evaluate the robustness of the study findings. The first sensitivity analysis evaluated the mortality risk among users of the most frequently reported individual non-selective versus selective antimuscarinic medication in the matched cohort. In addition, the risk of mortality was evaluated in the matched cohort within a maximum follow-up duration of 3 months (90 days). Since propensity score matching can limit generalizability, Cox proportional-hazards regression with stabilized inverse probability of treatment weighting (IPTW) was implemented on the

entire unmatched sample<sup>41</sup>. Another sensitivity analysis was conducted to evaluate the mortality risk in the unmatched incident antimuscarinic user cohort using propensity score as a covariate. Finally, an unmeasured confounder analysis was conducted, whereby the strength of an unmeasured confounder was calculated based on the mortality risk estimates found in the study<sup>42</sup>. All analyses were conducted using an a priori  $\alpha$  level of 0.05.

The study was approved by the University of Houston Institutional Review Board Committee for the Protection of Human Subjects under the exempt category.

## RESULTS

Figure 2 shows the process of identification of older adults with dementia and OAB who were new users of antimuscarinic medications. Overall, there were 3,383,603 Medicare beneficiaries diagnosed with dementia between 2013 and 2015. Over one million (1,049,897) of these older adults with dementia had OAB for overall prevalence of 31.03%. Among OAB patients, 287,612 (27.01%) were prevalent antimuscarinic users during the study period; 79,397 (7.56%) were incident antimuscarinic users in 2014–2015. After continuous eligibility criteria, the incident users included 21,848 (10.34%) incident antimuscarinic users after dementia diagnosis.

Among the incident antimuscarinic users, 16,955 (77.6%) were non-selective antimuscarinic users and 4893 (22.4%) were selective antimuscarinic users; these antimuscarinic users were used for calculation of propensity scores. The most frequently reported non-selective antimuscarinic medications were oxybutynin (12,295, 72.5%) and tolterodine (2868, 16.9%); among selective antimuscarinic agents, solifenacin (4669, 95.4%) was most frequently prescribed followed by darifenacin (224, 4.6%). Table 1 reports the differences in baseline characteristics between the two groups before and after matching. After matching, both the groups ( $N=4862$  each) were similar in terms of distribution of the baseline

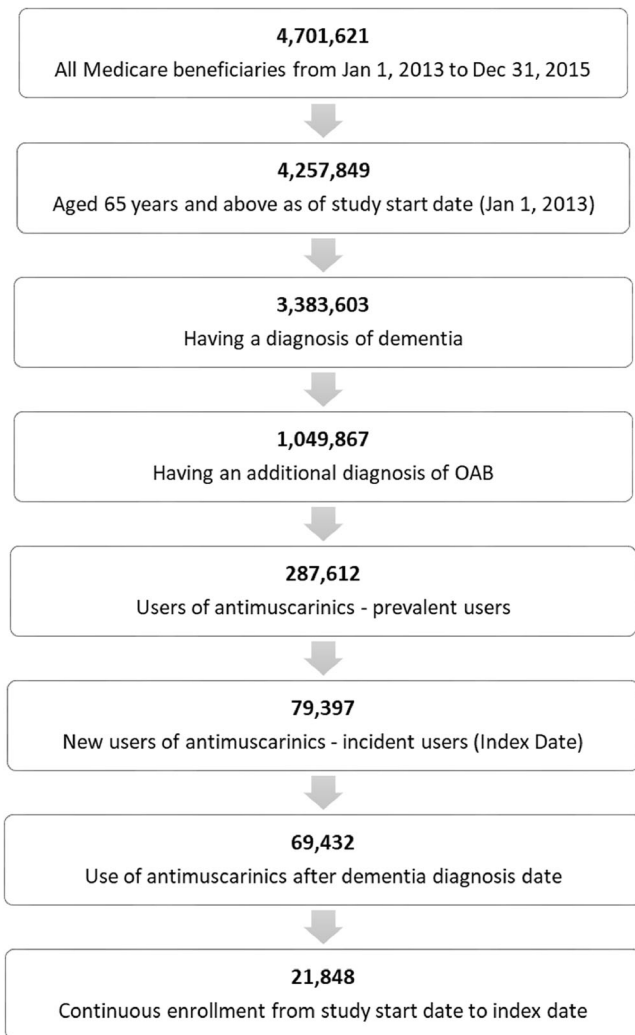


Figure 2 Cohort development flowchart.

characteristics and comparable in terms of distribution of the baseline characteristics. (Fig. 3).

### Risk of All-Cause Mortality

The mortality rate was 2.3% (396) for non-selective and 1.6% (80) for selective antimuscarinic users in the total cohort ( $p$  value  $< 0.01$ ) before matching. The rate of mortality was 2.6% (126) for non-selective and 1.6% (78) for selective antimuscarinic users in the matched cohort ( $p$  value  $< 0.01$ ). This translates to absolute risk reduction of 1% and number needed to harm of 100. Kaplan–Meier survival curves also revealed significant association between antimuscarinic use and risk of all-cause mortality ( $p$  value  $< 0.01$ ) (Fig. 4).

Table 2 presents results from the stratified Cox proportional-hazards model for the risk of all-cause mortality between non-selective and selective antimuscarinic users in the matched cohort. The Cox model found 50% higher risk of 180-day mortality with non-selective antimuscarinics as compared to selective ones (hazard ratio (HR) 1.50; 95% confidence interval (CI) 1.04–2.16).

### Sensitivity Analysis

Similar findings were observed with multiple sensitivity analyses (Table 2). A significantly increased hazard ratio was found (HR, 1.68; 95% CI, 1.14–2.48) for the risk of all-cause mortality between non-selective and selective antimuscarinic users in the matched cohort during the reduced follow-up period (90 days). Higher risk of all-cause mortality was also observed among older adults with dementia and OAB who initiated treatment with non-selective oxybutynin (HR 1.58; 95% CI 1.06–2.34) as compared to selective solifenacin.

In the unmatched cohort, an increased mortality risk was observed when propensity score was used as a covariate (HR, 1.33; 95% CI, 1.04–1.69). These findings remained consistent when propensity score weighting approach was used in the unmatched sample (IPTW HR, 1.43; 95% CI, 1.13–1.74). Finally, the strength of unmeasured confounder was 2.36; this shows that the observed HR of 1.50 could be explained away by an unmeasured confounder that was associated with both the antimuscarinic use and mortality by a HR as high as 2.36-fold each, above and beyond the measured confounders.

### DISCUSSION

The study evaluated the risk of mortality in a national cohort of older adults with dementia using antimuscarinics for OAB and found that non-selective antimuscarinics were associated with a 50% increase in risk of all-cause mortality compared to selective antimuscarinics. The study findings remained consistent in multiple sensitivity analyses with 68% increased mortality risk within a 90-day follow-up and a 58% increased risk of mortality with oxybutynin versus solifenacin use. In the unmatched cohort, a 43% increased risk of mortality was observed for the non-selective antimuscarinic group in propensity score weighing approach and a 33% increased mortality risk was observed when propensity score was used as a covariate.

This is the first study to the authors' knowledge that evaluated the comparative risk of mortality for non-selective versus selective antimuscarinics among older patients with dementia and OAB. Previous research by Arana et al. based on UK's Clinical Practice Research Datalink involving patients 18 years or older reported a 26% increased risk of overall mortality among oxybutynin users and 32% reduced risk among solifenacin users when compared to tolterodine users<sup>26</sup>. However, Marguilis et al. did not report any difference in cardiovascular, stroke, acute myocardial infarction, or major acute cardiac event-related mortality risk with use of individual antimuscarinic agents compared to tolterodine<sup>27</sup>. The higher mortality risk reported in the current study cannot be directly compared with the findings of Arana et al. due to differences in study sample, namely older adults with dementia and the comparator used, selective agents<sup>26</sup>.

Our study findings confirm the study hypothesis that non-selective antimuscarinics are associated with a higher risk of



Table 1 Baseline Characteristics of Older Adults with Dementia and OAB Using Non-selective and Selective Antimuscarinic Medications Before and After Matching

Demographics, N [%]	Total cohort (N=21,848)			Matched cohort (N=9724)		
	Selective [N=4893; 22.40%]	Non-selective [N=16,955; 77.60%]	p value	Selective [N=4862; 50%]	Non-selective [N=4862; 50%]	p value
Age (years)						
≥65-75	1434 [29.31]	4853 [28.62]	0.31	1420 [29.21]	1377 [28.32]	0.61
≥75-85	2231 [45.60]	7669 [45.23]		2218 [45.62]	2236 [45.99]	
≥85	1228 [25.10]	4433 [26.15]	<0.0001*	1249 [25.17]	1249 [25.69]	0.89
Gender						
Male	1760 [35.97]	5320 [31.38]	-0.0972	1740 [35.79]	1746 [35.91]	0.0025
Female	3133 [64.03]	11,635 [68.62]		3122 [64.21]	3116 [64.09]	
Race						
White	4150 [84.82]	14,603 [86.13]	<0.0001*	4142 [85.19]	4106 [84.45]	0.59
Black	286 [5.85]	1212 [7.15]	0.0373	285 [5.86]	299 [6.15]	
Other	457 [9.34]	1140 [6.72]		435 [8.95]	457 [9.40]	
Comorbidities, N [%]						
AIM	289 [5.91]	975 [5.75]	-0.0067	288 [5.92]	313 [6.44]	0.0214
Anxiety	1450 [29.63]	5315 [31.35]	0.02*	1442 [29.66]	1440 [29.62]	-0.0009
Bipolar disease	244 [4.99]	973 [5.74]	0.0334	243 [5.00]	246 [5.06]	0.0028
DIAD	2 [0.04]	4 [0.02]	-0.0097	-	-	-0.0117
GERD	1869 [38.20]	6349 [37.45]	-0.0155	1855 [38.15]	1877 [38.61]	0.0093
Insomnia	862 [17.62]	2829 [16.69]	0.13	856 [17.61]	852 [17.52]	-0.0022
IBS	209 [4.27]	632 [3.73]	-0.0278	208 [4.28]	221 [4.55]	0.0130
Muscle spasms/low back pain	1597 [32.64]	5009 [29.54]	-0.0669	1572 [32.33]	1594 [32.78]	0.0097
Neuropathic pain	137 [2.80]	461 [2.72]	-0.0049	135 [2.78]	139 [2.86]	0.0049
Schizophrenia	133 [2.72]	612 [3.61]	0.0509	133 [2.74]	132 [2.71]	-0.0013
Secondary Parkinsonism	73 [1.49]	284 [1.68]	0.0147	73 [1.50]	70 [1.44]	-0.0051
BPH	1206 [24.65]	3364 [19.84]	-0.1158	1190 [24.48]	1208 [24.85]	0.0086
Chronic constipation	1221 [24.95]	4419 [26.06]	0.0255	1212 [24.93]	1229 [25.28]	0.0081
Epilepsy	292 [5.97]	1024 [6.04]	0.0030	290 [5.96]	292 [6.01]	0.0017
Delirium	913 [18.66]	3606 [21.27]	0.0653	911 [18.74]	947 [19.48]	0.0189
Prior falls/fractures	2393 [48.91]	8479 [50.01]	0.0220	2381 [48.97]	2431 [50.00]	0.0206
Myasthenia gravis	15 [0.31]	52 [0.31]	0.0002	-	-	-
Glaucoma	850 [17.37]	2743 [16.18]	-0.0319	842 [17.32]	867 [17.83]	0.0135
Parkinson's disease	556 [11.36]	1850 [10.91]	-0.0144	552 [11.35]	554 [11.39]	0.0013
Myocardial infarction	185 [3.78]	725 [4.28]	0.0252	184 [3.78]	181 [3.72]	-0.0032
Syncope	743 [15.18]	2597 [15.32]	0.00367	740 [15.22]	745 [15.32]	0.0029
Urinary tract infection	2704 [55.26]	9602 [56.63]	0.0276	2687 [55.27]	2725 [56.05]	0.0157
Skin infection	378 [7.73]	1444 [8.52]	0.0289	375 [7.71]	374 [7.69]	-0.0008
Vulvovaginitis	153 [3.13]	627 [3.70]	0.0315	153 [3.15]	163 [3.35]	0.0116
CHD	2061 [42.12]	6971 [41.11]	-0.0204	2044 [42.04]	2056 [42.29]	0.0049
Thromboembolic disorder	449 [9.18]	1729 [10.20]	0.0345	448 [9.21]	460 [9.46]	0.0085
Cerebrovascular disease	1954 [39.93]	6718 [39.62]	-0.0064	1945 [40.00]	2002 [41.18]	0.0238
COPD	1412 [28.86]	4889 [28.84]	-0.0005	1393 [28.65]	1398 [28.75]	0.0023
Other renal disorders	4705 [96.16]	16,201 [95.55]	-0.0303	4675 [96.15]	4669 [96.03]	-0.0064
Gastric disorders	3444 [70.39]	11,834 [69.80]	-0.0129	3421 [70.36]	3413 [70.20]	0.0036
Cataract	1907 [38.97]	6521 [38.46]	-0.0105	1896 [39.00]	1894 [38.96]	-0.0008
Osteoporosis	1136 [23.22]	3747 [22.10]	0.10	1122 [23.08]	1108 [22.79]	-0.0068
Dyslipidemia	3675 [75.11]	12,084 [71.27]	<0.0001*	3645 [74.97]	3634 [74.74]	-0.0052
Pneumonia	723 [14.78]	2678 [15.79]	0.0283	721 [14.83]	746 [15.34]	0.0144
Endocarditis	363 [7.42]	1122 [6.62]	-0.0314	354 [7.28]	347 [7.14]	-0.0056
Suicide attempt	51 [1.04]	213 [1.26]	0.0201	51 [1.05]	48 [0.99]	-0.0061
	537 [10.97]	1685 [9.94]	-0.0339	535 [11.00]	504 [10.37]	-0.0206

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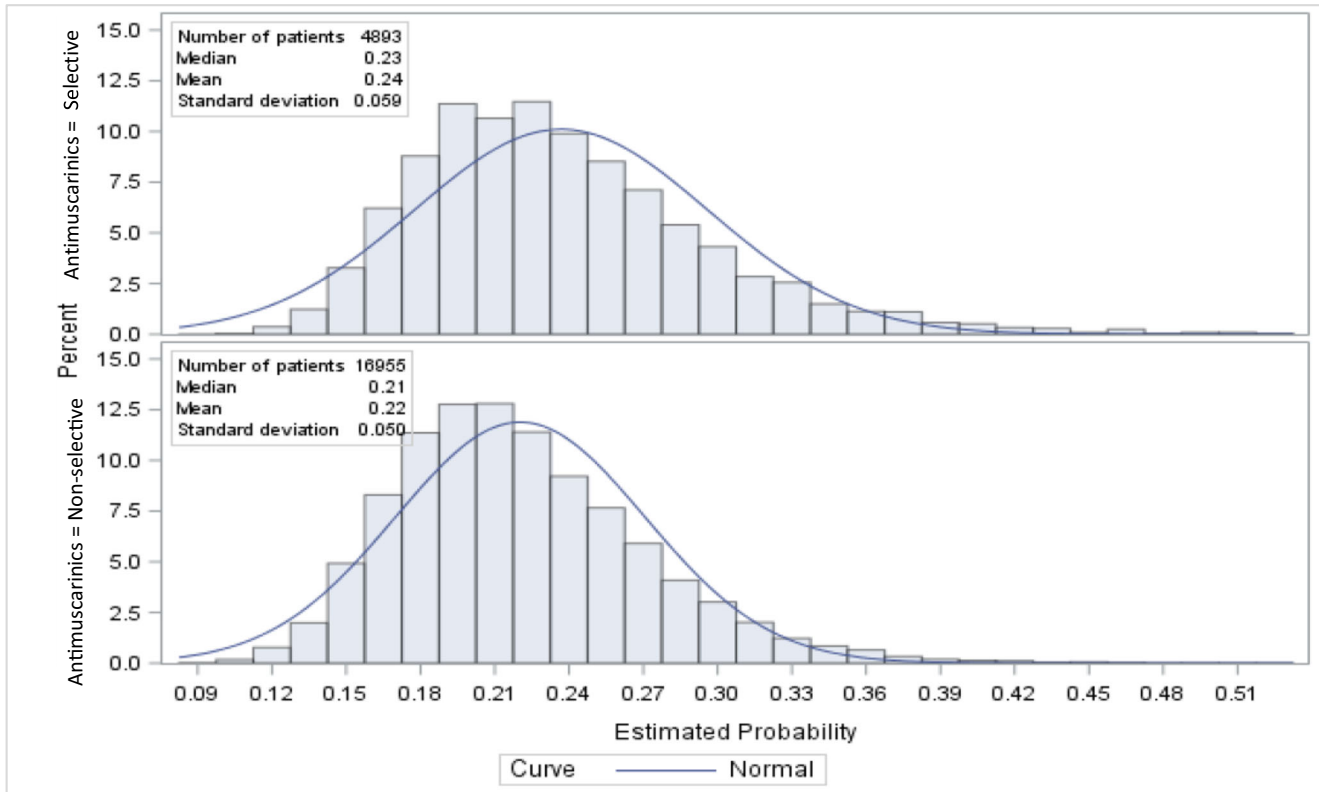
Table 1. (continued)

Demographics N [%]	Total cohort (N = 21,848)			Matched cohort (N = 9724)			
	Selective [N = 4893; 22.40%]	Non-selective [N = 16,955; 77.60%]	p value	Selective [N = 4862; 50%]	Non-selective [N = 4862; 50%]	Standardized difference of proportions (D)	p value
Extrapyramidal symptoms (mean; SD)	11.41 [10.47]	11.73 [10.63]	0.03	11.41 [10.45]	11.49 [10.39]	0.0078	0.70
Comedications, N [%]							
Antihypertensives	2753 [56.26]	9313 [54.93]	-0.0270	2732 [56.19]	2707 [55.68]	-0.0104	0.61
Anti-anginals	599 [12.24]	1906 [11.24]	-0.0311	593 [12.20]	598 [12.30]	0.0031	0.87
Antiarrhythmics	212 [4.33]	642 [3.79]	-0.0278	207 [4.26]	223 [4.59]	0.0160	0.43
Other CV drugs	3594 [73.45]	12,530 [73.90]	0.0102	3568 [73.39]	3588 [73.80]	0.0093	0.65
Antidiabetics	1294 [26.45]	4352 [25.67]	-0.0177	1277 [26.26]	1275 [26.22]	-0.0009	0.96
Antihyperlipidemics	2957 [60.43]	9583 [56.52]	-0.0795	2928 [60.22]	2900 [59.65]	-0.0118	0.56
Anti-obesity agents	0 [0.00]	1 [0.01]	-1.7474	-	-	-	-
Analogues	2945 [60.19]	9929 [58.56]	-0.0331	2919 [60.04]	2845 [58.52]	-0.0309	0.13
Estrogen (HRT)	71 [1.45]	227 [1.34]	-0.0096	71 [1.46]	64 [1.32]	-0.0123	0.54
Antihistamines	227 [4.64]	718 [4.23]	-0.0197	225 [4.63]	225 [4.63]	0.0000	1.00
Gastro-intestinal agents	1605 [32.80]	5384 [31.75]	-0.0224	1586 [32.62]	1608 [33.07]	0.0096	0.63
Anticoagulants	826 [16.88]	2840 [16.75]	-0.0035	821 [16.89]	853 [17.54]	0.0174	0.39
Hemopoietic agents	12 [0.25]	61 [0.36]	-0.0209	-	-	-0.0044	-
Hematologic agents	885 [18.09]	2653 [15.65]	-0.0652	864 [17.77]	879 [18.08]	0.0080	0.69
Corticosteroids	1026 [20.97]	3377 [19.92]	-0.0261	1015 [20.88]	1044 [21.47]	0.0146	0.47
Vitamin D	3 [0.06]	15 [0.09]	0.0099	-	-	-0.0091	-
Bronchodilators	1187 [24.26]	3959 [23.35]	-0.0214	1160 [23.86]	1161 [23.88]	0.0004	0.98
Antifungals	372 [7.60]	1372 [8.09]	0.0182	365 [7.51]	379 [7.80]	0.0108	0.59
Anti-infectives	1269 [25.94]	4681 [27.61]	0.03780	1263 [25.98]	1301 [26.76]	0.0177	0.38
Urinary anti-infectives	809 [16.53]	2862 [16.88]	0.0112	806 [16.58]	814 [16.74]	-0.0084	0.83
Antineoplastics	256 [5.23]	930 [5.49]	0.0112	255 [5.24]	246 [5.06]	-0.0084	0.68
Ulcer drugs	252 [5.15]	8381 [49.43]	-0.0419	2493 [51.28]	2492 [51.25]	-0.0004	0.98
Alcohol dependence	0 [0.00]	6 [0.04]	-1.4559	-	-	-	-
Eye, ear, nose agents	1989 [40.65]	6493 [38.30]	-0.0482	1963 [40.37]	1945 [40.00]	-0.0076	0.71
Thyroid agents	1342 [27.43]	4800 [28.31]	0.0197	1335 [27.46]	1363 [28.03]	0.0129	0.53
Hypnotic, sedative, sleep agents	750 [15.33]	2009 [11.85]	-0.1017	722 [14.85]	752 [15.47]	0.0172	0.40
Smoking deterrents	3 [0.06]	21 [0.12]	0.0206	-	-	-	-
Endocrine and metabolic agents	592 [12.10]	1797 [10.60]	-0.0473	581 [11.95]	575 [11.83]	-0.0038	0.85
Antidepressants	2983 [60.96]	10,059 [59.33]	-0.0334	2961 [60.90]	2969 [61.07]	0.0034	0.87
Anxiety agents	1314 [26.85]	4788 [28.24]	0.0310	1309 [26.92]	1334 [27.44]	0.0116	0.57
Anticonvulsants	1751 [35.79]	5852 [34.51]	-0.0266	1731 [35.60]	1717 [35.31]	-0.0060	0.77
Antimantics	1109 [22.67]	3665 [21.62]	-0.0253	1088 [22.38]	1073 [22.07]	-0.0074	0.71
Stimulants	77 [1.57]	239 [1.41]	-0.0135	76 [1.56]	90 [1.85]	0.0222	0.27
AChEI	2384 [48.72]	7313 [43.13]	-0.1124	2356 [48.46]	2362 [48.58]	0.0025	0.90
Memantine	1204 [24.61]	3324 [19.60]	-0.1208	1180 [24.27]	1172 [24.11]	-0.0038	0.85
Baseline ADS exposure	5937 [35.02]	1799 [36.77]	-0.0365	1776 [36.53]	1771 [36.43]	-0.0021	0.92

AChEI acetylcholinesterase inhibitors, ADS anticholinergic drug scale, AIM abnormal involuntary movements, BPH benign prostatic hyperplasia, CHD coronary heart disease, COPD chronic obstructive pulmonary disorder, CV cardiovascular, DIAD drug-induced acute dystonia, GERD gastro-esophageal reflux syndrome, HRT hormone replacement therapy, IBS inflammatory bowel syndrome, SD standard deviation

\*Statistical significance at p value < 0.05

**a**



**b**

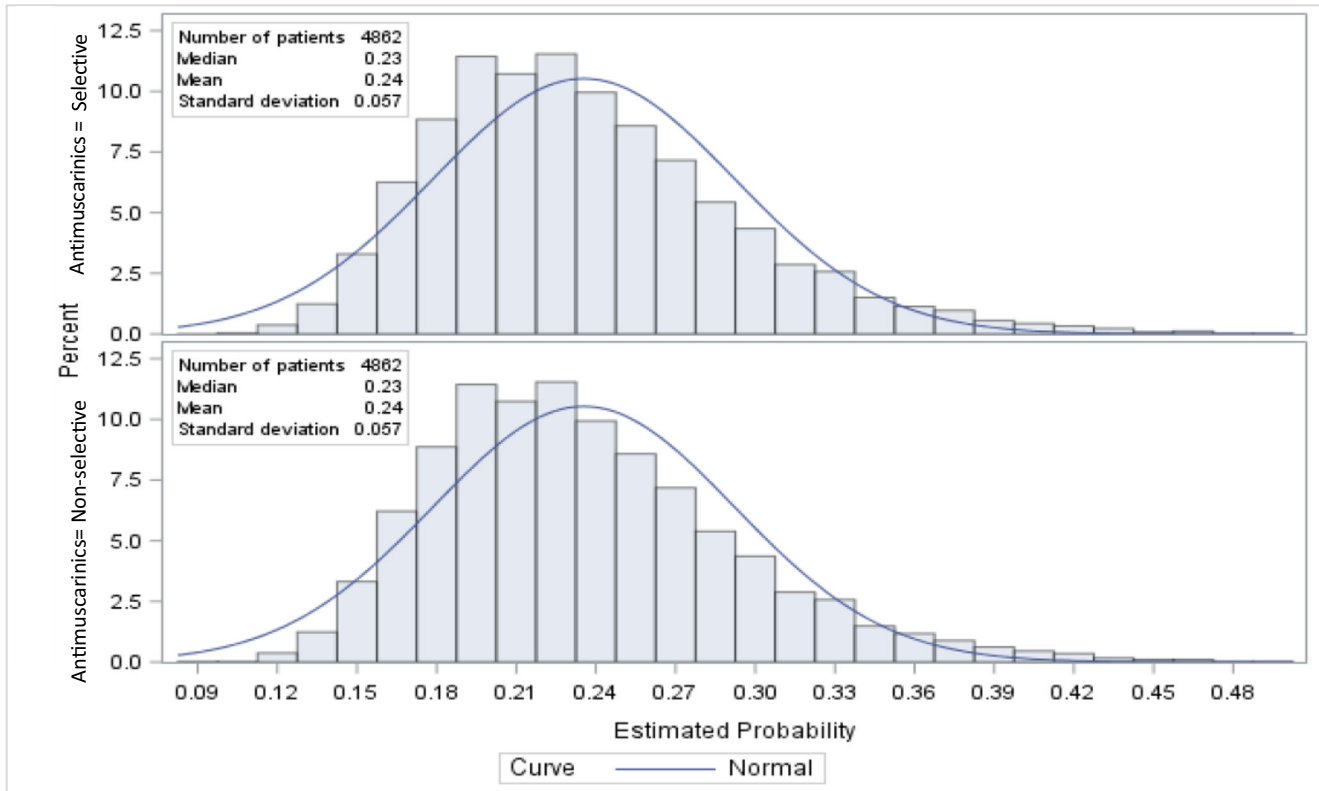


Figure 3 Distribution of propensity scores among non-selective and selective antimuscarinic medication users before (a) and after (b) matching.

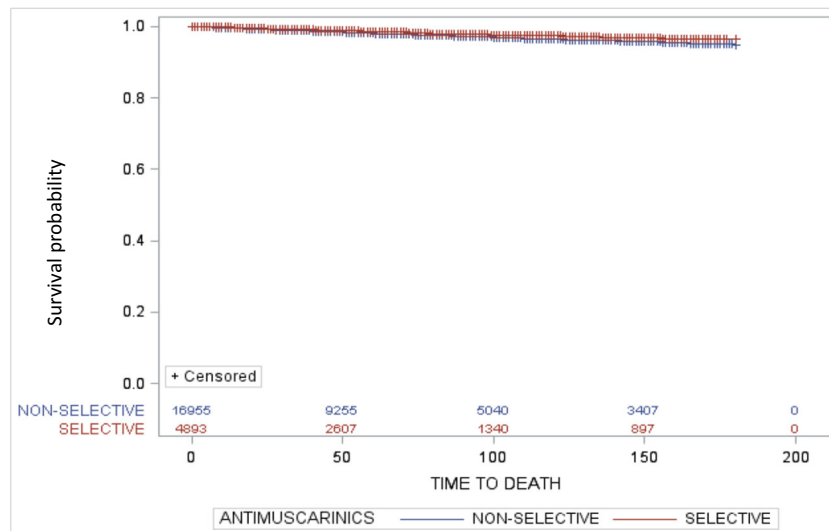


Figure 4 Kaplan–Meier plot of crude association between non-selective and selective antimuscarinic medication users and risk of all-cause mortality. Log-rank test: *p* value = 0.008.

mortality than selective antimuscarinic agents in patients with dementia and OAB. The adverse effects of non-selective antimuscarinics are a consequence of their binding to different receptor subtypes that have minimal or no involvement in bladder detrusor contractions, such as M1 and M4 muscarinic receptors<sup>7</sup>. This leads to central and peripheral adverse events including heart rate, secretions, pneumonia, sedation, visual disturbances, and others. The effect of M1/M4 is particularly problematic in dementia as inhibition of the M1 receptors leads to adverse cognitive effects<sup>7</sup>. Oxybutynin, the first non-selective drug approved for OAB in 1975, has a slightly higher affinity for M1 and M3 receptors than for M2 receptors<sup>43</sup>. Additionally, the pro-arrhythmic and pro-ischemic effects of non-selective agents can attribute to their increased cardiovascular risk<sup>44, 45</sup>.

Solifenacin and darifenacin, on the other hand, are selective muscarinic M3 receptor antagonists; the relatively high

selectivity of darifenacin for the M3 receptors as compared to the M1 receptors minimizes cognitive adverse effects<sup>46, 47</sup>. Therefore, the study findings strongly suggest that selective antimuscarinics can offer a favorable safety profile over non-selective antimuscarinics for the management of OAB in patients with dementia. It should be noted that the current study did not evaluate the specific reasons for mortality. Therefore, more research is needed to understand the role of specific mechanisms contributing to increased mortality risk due to non-selective antimuscarinics in older patients with dementia.

The high use of non-selective antimuscarinic medications, especially oxybutynin, further raises concerns. There was a 58% increased risk of all-cause mortality among oxybutynin users compared to those using solifenacin. Given the relatively higher utilization of oxybutynin (*n* = 12,295; 56%) observed in the overall population, there is a significant need to reduce

Table 2 Stratified Cox Proportional-Hazards Model for Risk of All-Cause Mortality Due to Non-selective vs Selective Antimuscarinic Medication Use in Older Adults with Dementia and OAB

Exposure	Hazard ratio (HR)	95% confidence interval [95% CI]	<i>p</i> value
<b>Main analysis</b>			
Non-selective antimuscarinic [N= 4862]	1.50	1.04–2.16	0.03*
Selective antimuscarinic [N= 4862]	1.00	Reference	
<b>Sensitivity analysis</b>			
Mortality risk with the most frequently reported antimuscarinics in each category (oxybutynin vs solifenacin)			
Non-selective antimuscarinic—oxybutynin [N= 4624]	1.58	1.06–2.34	0.02*
Selective antimuscarinic—solifenacin [N= 4624]	1.00	Reference	
Mortality risk within maximum follow-up of 90 days			
Non-selective antimuscarinic [N= 1201]	1.68	1.14–2.48	0.008*
Selective antimuscarinic [N= 1201]	1.00	Reference	
Mortality risk in unmatched sample using PS as covariate			
Non-selective antimuscarinic [N= 16,955]	1.33	1.04–1.69	0.02*
Selective antimuscarinic [N= 4893]	1.00	Reference	
Inverse probability of treatment weight analysis			
Non-selective antimuscarinic [N= 16,955]	1.43	1.13–1.74	0.003*
Selective antimuscarinic [N= 4893]	1.00	Reference	

\*Statistical significance at *p* value < 0.05



oxybutynin use in older adults with dementia. The higher use of oxybutynin compared to other antimuscarinics could be due to its preferred tier status that may lead physicians to prefer this drug compared to other antimuscarinics<sup>48</sup>. Also, antimuscarinic treatments other than oxybutynin may not be affordable to some patients based on insurance coverage. This poses a considerable challenge in the management of OAB in older adults with dementia. Given the high mortality risk and adverse cognitive safety profile of oxybutynin, the better safety profiles with selective antimuscarinic agents observed in the current study provide support for expanding patient access to include the selective antimuscarinics as preferred agents, especially for older adults with dementia. Careful screening of patients for cognitive deficits prior to any non-selective antimuscarinic treatment can also be one of the ways to improve antimuscarinic prescribing.

This study had several strengths including the study design and analytical approach used. A new-user retrospective cohort design based on propensity-matched approach provided an efficient method of assessing the causal relationship between the antimuscarinic exposure and risks of mortality. Although randomization of exposure did not take place, this pseudo-randomization technique of propensity score matching strengthened our study findings. The study used relevant covariates in the propensity score model including baseline anticholinergic exposure and Elixhauser's index, a widely used risk adjustment tool proven to be statistically superior for predicting various outcomes including mortality. Additionally, the main findings did not change when propensity score weighting approach was used to increase the generalizability.

## Limitations

The study findings should be interpreted in the light of potential limitations. Due to the use of claims data, actual use of medication could not be ascertained. However, by allowing only a 7-day gap in medication use, a conservative definition of continued medication persistence was applied which may have excluded patients who stopped the medication. The diseases, exposures, and outcome measurements were based on medical claims and could be subject to coding issues. Variables included for the propensity-matched cohort were limited to those available in the data source; hence, residual confounding due to unmeasured covariates such as physician preferences and other clinical measures might have affected the study findings. Although the study controlled for patients with high baseline anticholinergic load, the dosage of these medications was not controlled. Our sensitivity analysis revealed that an unmeasured confounder must be strongly associated with a HR of 2.36 with the treatment and the outcome to explain away the association. The use of prescription data did not include use of over-the-counter drugs and prescription drugs in inpatient settings. The study is limited to Medicare beneficiaries in community settings; therefore, future studies are needed to assess the safety of antimuscarinics in diverse settings.

## CONCLUSIONS

The current study found that non-selective antimuscarinic use was associated with 50% increased risk of mortality compared to selective agents in older adults with dementia and OAB. The findings remained consistent across several sensitivity analyses. The study findings suggest that physicians should prefer selective antimuscarinics over non-selective agents to manage OAB in older adults with dementia. Expanding patient access for selective agents can also help to improve quality of care in dementia. Given the increased risk of all-cause mortality observed in this study, future research should focus on cause-specific mortality and other drug-related morbidity.

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**Corresponding Author:** Rajender R. Aparasu, PhD, FAPhA; Department of Pharmaceutical Health Outcomes and Policy, College of Pharmacy University of Houston, Houston, TX, USA (e-mail: rraparasu@uh.edu).

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## Compliance with Ethical Standards:

The study was approved by the University of Houston Institutional Review Board Committee for the Protection of Human Subjects under the exempt category.

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