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Research Article

Anticholinergic Medication Use, Dopaminergic Genotype, and Recurrent Falls

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Abstract

Background: Anticholinergic medications are associated with fall risk. Higher dopaminergic signaling may provide resilience to these effects. We tested interactions between anticholinergic medication use and dopaminergic genotype on risk for recurrent falls over 10 years.

Methods: Participants in the Health, Aging, and Body Composition (Health ABC) study (n = 2 372, mean age = 73.6; 47.8% men; 60.0% White) without disability or anticholinergic use at baseline were followed for up to 10 years for falls. Medication use was documented in 7 of 10 years. Highly anticholinergic medications were defined by Beers criteria, 2019. Recurrent falls were defined as ≥2 in the 12 months following medication assessment. Generalized estimating equations tested the association of anticholinergic use with recurrent falls in the following 12 months, adjusted for demographics, health characteristics, and anticholinergic use indicators. Effect modification by dopaminergic genotype (catechol-O-methyltransferase [COMT]; Met/Met, higher dopamine signaling, n = 454 vs Val carriers, lower dopamine signaling, n = 1 918) was tested and analyses repeated stratified by genotype.

Results: During follow-up, 841 people reported recurrent falls. Anticholinergic use doubled the odds of recurrent falls (adjusted odds ratio [OR] [95% CI] = 2.09 [1.45, 3.03]), with suggested effect modification by COMT (p = .1). The association was present in Val carriers (adjusted OR [95% CI] = 2.16 [1.44, 3.23]), but not in Met/Met genotype (adjusted OR [95% CI] = 1.70 [0.66, 4.41]). Effect sizes were stronger when excluding baseline recurrent fallers.

Conclusion: Higher dopaminergic signaling may provide protection against increased 12-month fall risk from anticholinergic use. Assessing vulnerability to the adverse effects of anticholinergic medications could help in determination of risk/benefit ratio for prescribing and deprescribing anticholinergics in older adults.

Keywords: Anticholinergic medications, Dopamine, Epidemiology, Falls

Falls are a common occurrence in older adults with serious negative impacts on health and well-being (1). Neurobiological drivers of falls are increasingly being recognized and studied (2). Previous research has suggested an association between use of anticholinergic medications and increased risk of falls among community-dwelling older adults (3–9). Anticholinergics have direct effects on the central nervous system and can lead to side effects such as cognitive impairment, dizziness, and lightheadedness, which increase fall risk (10). Animal models of Parkinson's disease have shown that the risk for complex movement control deficits and falls is greatest when in the presence of combined cholinergic and dopaminergic cell losses (11,12). Studies in patients with Parkinson's disease also support an interaction of combined reductions in cholinergic and dopaminergic function in relation to increased fall risk (13). However, this association is untested in community-dwelling older adults without neurological conditions. Genetic variability in dopaminergic function could contribute to differential vulnerability to the adverse effects of anticholinergic medications on fall risk.

Catechol-O-methyltransferase (COMT) is an enzyme that promotes synaptic clearance of dopamine and is the primary regulator

of dopaminergic signaling in the prefrontal cortex (14). The Met allele of the COMT Val^{158}Met gene is associated with lower levels of COMT, resulting in slower synaptic clearance and higher synaptic dopamine levels. Conversely, the Val allele is associated with higher levels of COMT, higher synaptic clearance of dopamine, and lower tonic synaptic levels (14). It has been suggested that the Met/Met genotype provides compensation against cerebral small vessel disease effects on gait speed (15). Similarly, the higher dopaminergic signaling associated with the Met/Met genotype could also provide protection against the effects of anticholinergic medications on fall risk in older adults.

In a cohort of community-dwelling older adults with up to 10 years of follow-up for medication use and self-reported falls, we tested the hypothesis that COMT genotype modifies the association of anticholinergic medication use with recurrent falls. We hypothesize that those with Met/Met genotype, indicative of higher dopaminergic signaling, will have a lower risk of falls in relation to anticholinergic medication use compared with Val carriers.

Method

Study Population

Participants were from the Health, Aging, and Body Composition (Health ABC) study, a population-based, longitudinal cohort that enrolled Black and White community-dwelling older adults. In 1997, this study enrolled 3075 community-dwelling adults between the ages of 70–79 years old at baseline from Pittsburgh, PA and Memphis, TN. Eligibility criteria included no self-reported difficulties with activities of daily living, climbing 10 steps and/or walking ¼ of a mile, no life-threatening illnesses, and no plans to move. Men and Black individuals were oversampled. All Health ABC participants provided informed consent and protocols were approved by the IRBs of all involved institutions.

Participants were excluded from the analytic sample if they were missing COMT genotype (n = 220) or had no data on falls (n = 1) or medication use (n = 117). It is unclear whether including those with anticholinergic medication use at baseline may result in a biased sample; therefore, we excluded individuals who were users at the baseline visit (n = 365), creating a new-user cohort. This resulted in an analytic sample of 2 372. Participants included in our analytic sample were more likely to be White, were better educated, were less likely to be fallers at baseline, had faster gait speed, better cognitive function, were more likely to have hypertension or urinary incontinence, and were less likely to have anxiety or depressive symptoms (all $p < .05$) compared with those excluded (N = 703). They were similar in age, gender, COMT genotype, body mass index (BMI), smoking status, and had similar rates of pulmonary disease, cardiovascular disease, diabetes, back pain, and sleep problems (all $p > .2$).

Anticholinergic Medication Use

Medication data were collected at years 1, 2, 3, 5, 6, 8, and 10 of the study. Medication information were assessed directly from packaging for all products taken in the prior month (16). Medication data were coded using the Iowa Drug Information System (IDIS) Drug Vocabulary and Thesaurus, which allowed for the identification of specific drug ingredients.

As there is currently no gold standard for measuring anticholinergic medications, we opted to identify those with the highest risk of side effects from a list widely known to clinicians. Highly anticholinergic medications (see Supplementary Table S1) were identified using the 2019 American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults list of drugs with strong anticholinergic properties (17). We classified anticholinergic medication users as anyone using at least one of these medications. As needed (PRN) usage was coded and was excluded from our classification. We did not include information on dose as we hypothesized it is likely less important in the context of drug–gene interactions.

COMT Genotyping

The COMT Val^{158}Met (rs4680) gene was extracted from participant DNA samples from EDTA anticoagulated whole blood using validated methods (Gentra Systems, Minneapolis, MN). COMT was genotyped via PCR-based methods describe in detail elsewhere (15,18). Participant sequenced genotypes were cross-referenced to sequence-verified control samples, and Hardy–Weinberg equilibrium for genotype distribution was confirmed.

Recurrent Falls

We assessed recurrent falls (≥2) rather than single falls as recurrent falls are more strongly associated with functional and clinical outcomes (19,20). Participants were asked annually if they had fallen to the floor or ground in the past 12 months. Fall recall over 12 months has previously been shown to have good accuracy (21). Participants reporting 2 or more falls in a 12-month period were considered recurrent fallers. Fall data were used from study years 2, 3, 4, 6, 7, 9, and 11 such that fall reporting corresponded to the 12 months following each medication assessment.

Covariates

Variables related to fall risk were considered as covariates. Demographic information concerning age (years), race (Black or White), sex (male or female), and highest education level (less than high school, high school, or postsecondary) were self-reported at the year 1 visit. Usual pace gait speed over 20 m was measured at years 1–6, 8, and 10. BMI (kg/m^2) was measured annually. Self-reported smoking status was coded as ever or never and was collected in years 1, 3, and 5. Pulmonary diseases were assessed by self-report in years 1, 5, 6, and 8–10. Cardiovascular disease, hypertension, and diabetes were assessed annually through self-report, physician diagnoses, recorded medications, and laboratory data. Total number of medications was ascertained as described above and included all prescription and over the counter medications.

Many underlying health conditions for which anticholinergics are prescribed are also risk factors for recurrent falls. Therefore, these health conditions were measured for possible confounding by indication. Anxiety symptoms were based on the Hopkins Symptom Checklist (22) and were assessed in years 1, 3, and 6. Depressive symptoms were scored based on the Center for Epidemiologic Studies Depression Scale (CES-D) (23) and assessed in years 1, 3–7, 8, and 10. The presence of back pain was self-reported at years 1, 2, and 6. Sleep problems were defined by self-reported difficulty sleeping of at least 2–4 times per month and reported at years 1, 3, and 5. Urinary incontinence was defined as any reported leakage in the past 12 months and was measured at years 1 and 4.

Anticholinergic medications may be avoided in patients with lower cognitive function, which is also related to fall risk. The Modified Mini-Mental State exam (3MS) (24) was assessed in years 1, 3, 5, 8, and 10 as measure of general cognitive function. The digit symbol substitution test (DSST) was assessed in years 1, 5, 8, and 10 as a measure of processing speed.

Statistical Analyses

As year 1 medication use data were used to select the analytic sample, our analytic baseline is year 2 of the study. For the purposes of summarizing participant characteristics for Table 1 only, anticholinergic medication use at any time during follow-up and occurrence of recurrent falls at any time during follow-up was ascertained. Participant characteristics were compared by medication use and recurrent falls by *t*-tests for continuous variables and chi-square tests for categorical ones.

Generalized estimating equations (GEEs) assessed the association of anticholinergic medication use at 1 year with retrospectively reported recurrent falls reported at the next year's visit (eg, medication use at year 2 was associated with recurrent falls for the previous 12 months reported at year 3). GEE models account for the correlation of repeated measures within individuals. Models were first run to assess the association of anticholinergic medication use with recurrent falls without and then with adjustment for covariates. All adjusted models included age, gender, and education. Selection of additional health-related covariates was based on a priori known associations with anticholinergic medication use and fall risk and associations with anticholinergic medication use at $p < .1$. Given the small number of events, covariates were added one at a time to the model to determine which might have a possible confounding effect. These included smoking status, diabetes, anxiety, back pain, sleep problems, urinary incontinence, depressive symptoms, and history of recurrent falls at years 1 and 2 (ie, baseline). All health-related covariates were updated through follow-up time when available. When covariate data were not remeasured in a given year, the values from the last available time point were used. We did not include gait speed as a covariate as it is more likely to be in the mechanistic pathway between anticholinergic use and falls (25,26) than it is to be a confounder. Additionally, total medication count was not

Table 1. Baseline Demographic and Health Characteristics of the Sample by Ever Using Anticholinergic Medications or Having Recurrent Falls During Follow-up

		Anticholinergic Use During Follow-up*			Recurrent Falls During Follow-up†		
	Total (n = 2 372)	No Use (n = 1 898)	Any Use (n = 474)	*p* Value‡	No Falls (n = 1531)	Ever Falls (n = 841)	*p* Value‡
	Mean (*SD*) or *n* (%)	Mean (*SD*) or *n* (%)	Mean (*SD*) or *n* (%)		Mean (*SD*) or *n* (%)	Mean (*SD*) or *n* (%)	
Age, y	73.6 (2.9)	73.6 (2.9)	73.8 (2.9)	.06	73.5 (2.9)	73.8 (2.9)	.06
Male gender	1 134 (47.8%)	942 (49.6%)	192 (40.5%)	.0004	741 (48.4%)	393 (46.7%)	.4
White race	1 424 (60.0%)	1 134 (59.8%)	290 (61.2%)	.6	875 (57.2%)	549 (65.3%)	.0001
Education				.1			.3
Less than HS	557 (23.5%)	462 (24.4%)	95 (20.1%)		373 (24.4%)	184 (22.0%)	
HS grad	783 (33.1%)	621 (32.8%)	162 (34.3%)		507 (33.2%)	276 (32.9%)	
Postsecondary	1 027 (43.4%)	812 (42.9%)	215 (45.6%)		649 (42.5%)	378 (45.1%)	
Baseline recurrent falls	268 (12.1%)	195 (11.0%)	73 (16.6%)	.002	37 (2.6%)	231 (29.0%)	<.0001
COMT %				.2			.07
Met/Met	454 (19.1%)	367 (19.3%)	87 (18.4%)		272 (17.8%)	182 (21.6%)	
Met/Val	1 138 (48.0%)	893 (47.0%)	245 (51.7%)		743 (48.5%)	395 (47.0%)	
Val/Val	780 (32.9%)	638 (33.6%)	142 (30.0%)		516 (33.7%)	264 (31.4%)	
Gait speed (m/s)§	1.34 (0.26)	1.35 (0.25)	1.32 (0.26)	.1	1.34 (0.25)	1.34 (0.26)	.8
BMI	27.5 (4.8)	27.4 (4.8)	27.5 (4.8)	.7	27.3 (4.8)	27.7 (4.8)	.07
3MS	90.5 (8.0)	90.5 (7.8)	90.4 (8.6)	.9	90.1 (8.2)	91.2 (7.4)	.001
DSST	36.2 (14.4)	36.2 (14.5)	36.2 (13.9)	1.0	35.5 (14.4)	37.4 (14.3)	.003
Ever smoker	1 330 (56.1%)	1 087 (57.3%)	243 (51.4%)	.02	868 (56.8%)	462 (55.0%)	.4
Pulmonary diseases	276 (11.7%)	214 (11.3%)	62 (13.1%)	.3	160 (10.5%)	116 (13.8%)	.02
Cardiovascular disease	648 (27.9%)	512 (27.6%)	136 (29.1%)	.5	389 (26.0%)	259 (31.3%)	.006
Diabetes	347 (14.7%)	266 (14.0%)	81 (17.1%)	.09	203 (13.3%)	144 (17.1%)	.01
Hypertension	1247 (53.0%)	992 (52.7%)	255 (54.3%)	.5	803 (52.9%)	444 (53.2%)	.9
Total medications	5.7 (3.5)	5.6 (3.4)	7.4 (4.2)	<.0001	5.7 (3.4)	6.7 (4.0)	<.0001
Anxiety	394 (16.7%)	289 (15.3%)	105 (22.3%)	.0003	216 (14.2%)	178 (21.3%)	<.0001
CES-D	4.6 (5.2)	4.4 (5.0)	5.3 (5.9)	.0009	4.1 (4.6)	5.4 (5.9)	<.0001
Back pain	1 005 (42.4%)	753 (39.7%)	252 (53.1%)	<.0001	583 (38.1%)	422 (50.2%)	<.0001
Sleep problems	757 (32.0%)	585 (30.9%)	172 (36.4%)	.02	454 (29.7%)	303 (36.1%)	.001
Urinary incontinence	941 (39.8%)	709 (37.4%)	232 (49.2%)	<.0001	559 (36.6%)	382 (45.5%)	<.0001

Notes: 3MS = Modified Mini-Mental State exam; BMI = body mass index; COMT = catechol-O-methyltransferase; CES-D = Center for Epidemiologic Studies Depression Scale; DSST = digit symbol substitution test; HS = high school.

*Ever used anticholinergic medications from year 2 to year 10.

†Ever reported recurrent falls from year 2 to year 11.

‡*p* Value is calculated from chi-square test for categorical variables and *F*-test for continuous variables.

§12 missing for gait speed at year 1.

considered as a covariate as anticholinergic medications are included in this measure.

Models were rerun including a multiplicative interaction term between anticholinergic use and COMT genotype with a p value of < .2 being considered suggestive of an interaction. In the presence of a suggested interaction, models were then stratified on COMT to assess potential differences by COMT genotype in associations of anticholinergic medication use with falls. As unadjusted results were similar between Val/Met and Val/Val groups, they were combined as a Val carrier group in further analyses to preserve power given the relatively small number of events distributed over 3 strata. Sensitivity analyses were run that exclude individuals with baseline recurrent falls as this is the strongest risk factor for future falls. All analyses were conducted in SAS 9.4 (SAS Institute, Inc., Cary, NC).

Results

The analytic sample was 73 years old on average at baseline. Approximately half the sample was male and 60% were White (Table 1). Twenty percent of participants used an anticholinergic medication and 35.5% of participants experienced recurrent falls at some point during the 10-year follow-up. There were general trends toward increasing prevalence over follow-up time for both anticholinergic use and recurrent falls (Table 2). In any given year, only 0.1%–3% of participants were taking 2 or more anticholinergic medications, and this prevalence of anticholinergic medication use was consistent over time. Prevalence of recurrent falls was consistently higher among anticholinergic users compared with nonusers at all time points. The difference in fall rate among anticholinergic users compared with nonusers increased over time (Table 2).

Participants who used anticholinergic medications at any point during follow-up were less likely to be male or an ever smoker. They were more likely to have baseline recurrent falls, anxiety, back pain, sleep problems, or urinary incontinence and had higher depressive symptoms and took more total medications (Table 1). Individuals who experienced recurrent falls at any point during follow-up were more likely to be White, to have recurrent falls at years 1 or 2, and to have any of the baseline health conditions, except hypertension (Table 1). They were also taking more total medications. Counter to expectations, those who experienced recurrent falls during the 10-year follow-up had higher baseline 3MS and DSST scores. Notably, those with the COMT Met/Met genotype were slightly more likely to experience recurrent falls; however, this appears to be due to known differences in distribution of COMT alleles by race (27) as the association disappeared after adjustment for race (data not shown).

Unstratified adjusted models confirm a greater risk of recurrent falls among anticholinergic medication users (odds ratio [OR] = 2.09; 95% CI: 1.45, 3.03; Table 3) compared with nonusers. A suggested interaction between anticholinergic use and COMT genotype was observed in adjusted models (p for interaction = .1). In analyses stratified on COMT genotype, a significantly increased odds of recurrent falls related to anticholinergic medication use were found only among COMT Val carriers (adjusted OR = 2.16; 95% CI: 1.44, 3.23; Table 3). There was no significant association of anticholinergic medication use and recurrent falls among those with Met/Met genotype (adjusted OR = 1.70; 95% CI: 0.66, 4.41; Table 3). There was minimal effect from adjustment for covariates on the effect estimates. No one covariate seemed to have a particularly large effect on the estimates (individual variable adjustments shown in Supplementary Table S2). Effect sizes in models that excluded those with baseline recurrent falls were stronger than when simply adjusting for baseline falls (Table 3). However, the effect size was still smaller among those with Met/Met genotype compared with Val carriers and was nonsignificant among those with the Met/Met genotype.

Discussion

In a sample of community-dwelling older adults, we found that highly anticholinergic medication use was associated with greater odds of recurrent falls in the subsequent 12 months. Notably, nearly all anticholinergic medication users were taking only a single medication, suggesting that even low exposure to highly anticholinergic medications can increase risk for falls. This association was also stronger for those who were Val carriers for the COMT gene, indicating an effect of lower tonic prefrontal dopamine signaling. In contrast, those with the Met/Met COMT genotype had a weaker and nonsignificant increased odds of recurrent falls related to anticholinergic medication use.

Although not all prior studies have found a significant association between anticholinergic medication use and fall risk, the findings have been fairly consistent in establishing this relationship (3–9). We extend this work by showing that vulnerability to the effects of anticholinergic medications on fall risk differs by dopaminergic genotype. This increased vulnerability could simply be due to insults to multiple neurotransmitter pathways leading to a general loss of resilience. However, existing research suggests that there is a specific impact on fall risk related to the combined loss of cholinergic and dopaminergic function (11,13). Low dopaminergic signaling is related to slow gait speed (28) and poor gait quality (29), even in older adults without Parkinson's disease. Poor gait quality can lead

Table 2. Annual Anticholinergic Drug Use and Recurrent Falls at Each Year of Follow-up in a Sample of Adults Aged >70 (n = 2 372)

	Year 2	Year 3	Year 5	Year 6	Year 8	Year 10
Total n	1 991	1 883	1 673	1 872	1 293	1 112
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Anticholinergic users	97 (4.9)	117 (6.2)	142 (8.5)	165 (8.8)	150 (11.6)	109 (9.8)
Recurrent falls*, total	175 (7.1)	146 (7.8)	158 (9.4)	155 (8.3)	129 (10.0)	175 (15.7)
Recurrent falls*, nonanticholinergic users	129 (6.8)	122 (6.9)	137 (9.0)	135 (7.9)	109 (9.5)	145 (14.5)
Recurrent falls*, anticholinergic users	13 (13.4)	24 (20.6)	21 (14.8)	20 (12.1)	20 (13.3)	30 (27.5)

*Recurrent falls were asked at the following year clinical visit and occurred in the 12 mo after the medication assessment.

Table 3. Generalized Estimating Equation Results for the Association of Recurrent Falls by Anticholinergic Medication Use in a Sample of Adults >70 Years Old, Without and With Stratification on COMT Genotype

	Unadjusted	Demographic Adjusted*	Fully Adjusted†	Fully Adjusted†, Excluding Baseline Fallers
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Unstratified (n = 2 372)	2.13 (1.74, 2.60)	2.18 (1.75, 2.72)	2.09 (1.45, 3.03)	3.04 (2.05, 4.52)
Stratified by COMT‡				
Met/Met (n = 454)	1.46 (0.87, 2.44)	1.75 (1.02, 3.01)	1.70 (0.66, 4.41)	2.23 (0.80, 6.22)
Val carrier (n = 1 918)	2.30 (1.85, 2.86)	2.27 (1.78, 2.89)	2.16 (1.44, 3.23)	3.31 (2.15, 5.09)

Notes: CI = confidence interval; COMT = catechol-O-methyltransferase; OR = odds ratio.

*Adjusted for age, gender, education.

†Adjusted for age, gender, education, smoking status, diabetes, anxiety, back pain, sleep problems, urinary incontinence, baseline recurrent falls, and Center for Epidemiologic Studies Depression Scale.

‡p for interaction of anticholinergic medications and COMT = 0.1.

to instability and predispose older adults to falls (30,31). When this is coupled with low cholinergic signaling, which can limit attentional resources and postural monitoring, fall risk increases greatly (11).

The effect of dual loss in cholinergic and dopaminergic signaling on fall risk has been documented in Parkinson's disease (13,32) but has not been studied in community-dwelling older adults without neurological disorders. Here, we define low cholinergic activity through identification of individuals using highly anticholinergic medications and low dopaminergic signaling by COMT genotype. Neither of these is a direct measure of neurotransmitter function and we may, therefore, be misclassifying some individuals. However, we used the Beers Criteria list to identify highly anticholinergic medications to avoid including medications with low anticholinergic activity. We were limited in our ability to determine whether or not individuals actually took the medications and whether use was continued throughout the following year. Our determination of dopaminergic function was limited in that it was from a single gene, which has the strongest effects on dopaminergic signaling in the prefrontal cortex, whereas striatal dopamine may be more relevant to fall risk (11). However, prior studies have shown robust associations of COMT genotype with outcomes such as gait speed (33) and have also demonstrated that COMT genotype can act as an effect modifier for physical function outcomes (15). Furthermore, any misclassification was likely to lead to underestimations of effects in this study.

Our analyses were limited by the number of fall events in any given year, particularly once analyses were stratified on genotype. This limited the precision of effect size estimates, which may have accounted for the nonsignificant findings among the individuals with the Met/Met genotype. However, despite the wide confidence intervals for the Met/Met strata, the effect estimate was still much smaller (approximately 70% higher odds) for this genotype compared with the Val carriers (more than doubling of odds). Effect sizes were stronger in sensitivity analyses excluding baseline fallers but were still stronger among Val carriers compared with Met/Met genotype. We did not consider dosage of anticholinergics in our analyses, which could be an important consideration. However, in those with high genetic risk, it is possible that any exposure to anticholinergic medications could lead to poorer health outcomes. In addition, we did not account for competing risks of death or drop out due to functional decline that may be differential by medication use and fall risk. However, our analyses only assessed 1 year of follow-up after each medication assessment, which may have limited the effects of competing risks.

Our study had several strengths, including repeated assessment of medication usage and determination of falls in the year subsequent to the medication assessment. Medication use was assessed directly from packages, limiting mistakes due to participant recall. We also had data on many potential confounders, including the prominent indications of use for anticholinergic medications.

These results provide the first evidence that higher dopaminergic signaling may offer some resilience to the effect of anticholinergic medications on fall risk. Future studies should examine whether dual impairments in dopaminergic and cholinergic signaling may have synergistic impacts on fall risk in older adults without Parkinson's disease. The risk of falls related to anticholinergic medications is increasingly recognized and understanding factors that place some individuals at increased risk is critical for considering the risk/benefit ratio of their use. Further assessment of genetic and epigenetic determinants of both dopaminergic and cholinergic function in relation to falls should be explored as they could be valuable risk indicators. Future studies should consider whether assessment of dopaminergic function is beneficial in considering prescribing and/or deprescribing anticholinergics, though precise, inexpensive, and safe ways to measure dopamine function routinely in the clinic are not yet available.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

Supplemental Table S1. List of highly anticholinergic drugs.

Supplemental Table S2. Generalized estimating equation (GEE) results with individual covariates.

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Author Contributions

All authors contributed to manuscript preparation, and study concept and design. C.R. contributed to acquisition of subjects and/or data. A.L.R., X.Z., and C.R. contributed to analysis and interpretation of data.

Conflict of Interest

None reported.

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