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## Medication for Alzheimer's Disease and Associated Fall Hazard: a Retrospective Cohort Study from the Alzheimer's Disease Neuro-Imaging Initiative

Noam U. Epstein, MD, MS<sup>1,2,\*</sup>, Rong Guo, MS<sup>3</sup>, Martin R. Farlow, MD<sup>4,5</sup>, Jaswinder P. Singh, MD<sup>2</sup>, and Morris Fisher, MD<sup>1,2</sup> for the Alzheimer's Disease Neuroimaging Initiative (ADNI)<sup>†</sup>

<sup>1</sup>Department of Neurology, Hines VA Medical Center, Hines, IL, USA

<sup>2</sup>Department of Neurology, Loyola University School of Medicine, Maywood, IL USA

<sup>3</sup>Office of Research Services, Health Sciences Division, Loyola University Chicago, Maywood, IL, USA

<sup>4</sup>Indiana Alzheimer Disease Center, Indiana University School of Medicine, Indianapolis, IN, USA

<sup>5</sup>Department of Neurology, Indiana University School of Medicine, Indianapolis, IN, USA

### Abstract

**Background**—Falls are common in the elderly, especially in those with cognitive impairment. The elderly are often treated with several medications which may have both beneficial and deleterious effects. The use and type of medication in Alzheimer's patients and association with falls is limited.

**Objective**—We examined the association between falls and medication use in the Alzheimer's Disease Neuro-Imaging Initiative (ADNI).

**Methods**—Diagnosis, demographics, medication use, apolipoprotein E4 allele status and functional activity level at baseline were gathered for 810 participants enrolled in ADNI including healthy controls and subjects with mild cognitive impairment or Alzheimer's. Adverse event fall reports were tabulated. Baseline characteristics were compared between subjects with and without one or more falls. Cox proportional hazards models were conducted to evaluate the association between subject characteristics and hazard of first fall.

**Results**—Age ( $p < 0.0001$ ), functional activities questionnaire ( $p = 0.035$ ), Beers list ( $p = 0.0477$ ) and medications for treating cognitive symptoms of Alzheimer's ( $p = 0.0019$ ) were associated with hazard of fall in the univariate model. In the final multivariate model, after adjusting for covariates, Alzheimer's medication use ( $p = 0.0005$ ) was associated with hazard of fall. Medication was

\*Address correspondence to this author at the Department of Neurology, Hines VA Medical Center, 5000 South 5<sup>th</sup> Avenue, Hines, IL, 60141, USA, Phone: (708) 202-8387, Fax: (708) 202-7936, nue2you@gmail.com.

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changed after an adverse fall event by the clinician in 9% of the falls. About 7% of the falls were reported as serious adverse events and 6% were reported to be severe.

**Conclusion**—We found a significant association between use of symptomatic medication treating cognitive symptoms in Alzheimer’s disease and hazard of fall after adjusting for age and Beers list medication use. Additional pharmaco-vigilance of the association between falls and Alzheimer’s medication use is warranted.

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## Background

Falls are common in the elderly, especially in those with cognitive impairment such as Alzheimer’s disease (AD)(1). The elderly are often treated with multiple medications which may have both beneficial and adverse effects but polypharmacy has been generally associated with increased incidence of adverse events in the elderly (2). Many medications have been implicated in increasing fall risk in the elderly including antidepressants, antipsychotic and sedatives (3). It has been suggested that cholinesterase inhibitors (ChEIs) can improve gait and balance by enhancing attention and executive function, leading to a reduction in falls (4, 5). Despite the increasing use of ChEIs and N-methyl-D-aspartate receptor antagonists (memantine) in treatment of mild cognitive impairment (MCI) the stage that immediately precedes AD and other dementias and AD, data on the association between Alzheimer’s medication use and falls is limited. We tested the hypothesis that there is a positive association between cholinesterase inhibitor and/or memantine use and falls in the participants of the Alzheimer’s Disease Neuro-imaging initiative (ADNI) cohort.

## Methods

ADNI is a large cohort study designed to test how neuroimaging, genetic, and clinical markers potentially predict the progression of MCI. More than 800 voluntary participants were recruited from 59 medical and/or academic sites across the United States and Canada, including 400 patients meeting Petersen criteria (6) for MCI, 184 mild stage AD, and 226 healthy controls, aged 55–90 years. Exclusion criteria restricted some types of medication use among subjects during the study period (7).

Data on baseline diagnosis, demographics, medication use, apolipoprotein E4 (ApoE4) allele status, and functional activity level (a measure of disease severity), were collected from the ADNI clinical database (download version February 02, 2011) for 810 participants enrolled in ADNI. Adverse events were based on subject self and/or informant report at every follow up. Adverse events were recorded by ADNI clinical staff in the adverse events database as free text. Adverse event fall reports were defined as any free text field containing the word “fall,” and tabulated by subject and date. Each adverse event was also coded by ADNI clinical staff for severity (incapacitating, with inability to work or perform normal daily activity) and seriousness (fatal, immediately life-threatening, permanent/substantial disability, requires or prolongs inpatient hospitalization (acute), suggests any significant hazard, contraindication, side effect or precaution that may be associated with the use of a study procedure, or regarded by the investigator as a serious adverse event). Diagnosis was defined as early AD, MCI or normal cognition. Age and education were measured in years. Medication use was identified for each ADNI participant. Beers list medication use was

determined for each subject as described previously (2). The Beer's list, which was generated by experts in pharmacology, identifies medications which may be potentially inappropriate for use in adults 65 years and older for various reasons such as sedation, cardiovascular risk and mechanism of elimination (8). Finally, the use of donepezil, rivastigmine, galantamine, or memantine, as well as therapy with combinations of these drugs was tabulated for each participant at baseline. ApoE4 allele status was defined as having one or more ApoE4 alleles.

### Statistical Analyses

Baseline characteristics including age, education, functional activities questionnaire, polypharmacy, ApoE4 genotype, diagnosis of MCI, diagnosis of AD and Alzheimer's, Antidepressants, Antipsychotics, Antihypertensives, Benzodiazepine and Diabetes medication use were compared with t-test (or chi-squared test as appropriate) between subjects with and without a fall. Cox proportional hazards models were conducted to evaluate the association between subject characteristics and hazard of first fall from entry into ADNI. Univariate cox proportional hazard models were fitted. Potential risk factors with  $p \leq 0.15$  were considered in a stepwise selection to search for the final model. All analyses are performed using SAS 9.2 (SAS Institute, Cary, North Carolina).

### Results

The cohort was composed of 226 healthy individuals, 400 with MCI, and 184 with mild AD. A maximum of 12 assessments per participant were made per protocol over a maximum period of 54 months. Average follow up time was 31 months (range 0–54 months). The baseline characteristics of subjects who fell and who did not fall during follow up in the 810 participants from ADNI are presented in Table 1. The age of participants who fell ( $76.80 \pm 6.31$ ) was significantly ( $p=0.0001$ ) higher than those who did not fall ( $74.72 \pm 6.92$ ). There was borderline significant association between Beers list and fall 57/212 (27%) for participants who fell and 122/598 (20%) for participants who did not fall, ( $p=0.05$ ).

Furthermore, Cox proportional hazards models were fitted to assess the association between patient characteristics and hazard of first fall (Table 2). In the univariate Cox models, the effect of each patient characteristic was evaluated individually. Variables significantly or borderline significantly associated with time to first fall included age ( $P = 0.0001$ , hazard ratio [HR]: 1.043 and confidence interval [CI]: 1.04 – 1.07), functional activities questionnaire ( $p = 0.035$ , HR: 1.023 and CI: 1.00–1.04), Beers list ( $P = 0.0668$ , HR: 1.328 and CI: 0.98 – 1.80), treatment with Alzheimer's medications for cognitive symptoms ( $P = 0.0019$ , HR: 1.545 and CI: 1.17 – 2.03), treatment with antidepressants ( $P = 0.0759$ , HR: 1.308 and CI: 0.97 – 1.76), and treatment with benzodiazepines ( $P = 0.0583$ , HR: 1.848 and CI: 0.98 – 3.49). These covariates were used to select for a final multivariate model. In the final multivariate model, after adjusting for the significant covariates of age ( $P < 0.0001$ , HR: 1.05 and CI: 1.02 – 1.07) and Beer's list ( $P = 0.0477$ , HR: 1.36 and CI: 1.00 – 1.84), treatment with Alzheimer's medication ( $P = 0.0005$ , HR: 1.63 and CI: 1.24 – 2.14) was associated with increased risk for fall. When we separated out the esterase inhibitors from memantine and ran the cox model, only the esterase inhibitors persisted in the final

multivariate model ( $P = 0.0012$ , HR: 1.577 and CI: 1.197 – 2.078). The hazard ratio estimate for age is 1.05, meaning that an increase of 1 year in age will increase the hazard rate by 5%. Beer's list medication use increased the hazard rate by 36%. The treatment with Alzheimer's medication increases the hazard rate by 63%. Medication was changed after an adverse fall event by the clinician in 9% of the falls. About 7% of the falls were reported as serious and 6% reported as severe.

## Discussion

Falls due to polypharmacy are well known in the elderly. In one recent study the most frequent cause of hospitalization among subjects with Alzheimer's was fracture and fall not causing fracture (9). Dementia compounds the risk of falling by impairing judgment, gait, visual-spatial perception, and the ability to recognize and avoid hazards (1, 10, 11) in either clinical trials or longitudinal reports. Despite the increasing use of ChEIs and memantine in MCI and AD there is limited evidence associating their use with falls as a major adverse effect. In the literature there is some suggestion that ChEIs can improve gait and balance control by their positive effects on attention and executive functions, which may lead to a reduction in falls (5), but several case reports of falls, syncope, and accidental injuries related to ChEIs and memantine have been reported (12, 13). Donepezil has been possibly related to syncope (14) and syncope could have caused a fall. A recent meta-analysis of randomized control trials of dementia medications suggests that ChEIs may increase the risk of syncope by 53% with no effects on falls, fracture, or accidental injury in cognitively impaired older adults while memantine may have a favorable effect on fracture, with no effects on other events (15, 16). Our data would indicate patients on Alzheimer medication have a 63% greater chance of falling with time than those not treated with those medications which is similar in magnitude to the increase in the risk of syncope noted by others. Our study did not show an association between falls and antidepressants but this may have been due to ADNI exclusion of subjects taking antidepressants with anticholinergic properties.

Contrary to some of the reports mentioned above we have found a significant association between falls and Alzheimer's medications in a clinical practice setting. Medication effectiveness is based on the balance between their benefits and adverse effects. Oftentimes clinical trials and registration studies with fairly restrictive inclusion and exclusion criteria may not encounter adverse events which occur during medication utilization in clinical practice. Limitations of this study include unknown confounders such as selection bias due to sampling, clinical susceptibility, medication indication, recall and possibly inconsistent adverse event reporting by study personnel. Falls prior to entry into ADNI were not recorded and could have been a confounder and possible indication for initiation of Alzheimer's treatment. While this analysis was pre-specified, multiple comparisons could also have led to spurious findings. Finally, we may have included unknown intrinsic causes of fall in our definition of fall. We do not mean to imply that the Alzheimer's medications are of questionable clinical value. We believe the medications for symptomatic treatment of Alzheimer's are limited in their ability to provide symptomatic benefit (17) and so when considering drug effectiveness, serious or severe adverse events must be carefully weighed against the small benefit derived from use. Additional pharmaco-vigilance of the association

between falls and Alzheimer's medication use is warranted to confirm these findings in other cohorts.

## Conclusion

This study found an association between treatment with Alzheimer's medication and a 63% increased hazard of fall over time. This finding needs to be confirmed in other cohorts and evaluated further as 7% of the falls were serious.

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Dr. Epstein conceived of the idea, developed the protocol, collected the data and wrote the manuscript. Dr. Guo who is an academic biostatistician performed the statistical analysis. Dr. Singh helped with planning of the analysis. Drs. Singh, Farlow and Fisher helped with manuscript composition. All authors edited and approved the final manuscript.

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**Table 1**

Baseline characteristics of subjects who fell or did not in 810 participants from ADNI.

Characteristics	No fall (n=598)	Fall (n= 212)	P Value
Age [years (+/- SD)]	74.72 (6.92)	76.80 (6.31)	0.00
Male [n (% of cohort)]	354 (59)	117 (55)	0.31
Education [years (+/- SD)]	15.55 (3.06)	15.59 (2.96)	0.86
FAQ [score (+/- SD)]	4.92 (6.56)	4.86 (6.42)	0.90
Co-medications [n (+/- SD)]	7.33 (4.10)	7.74 (3.53)	0.17
APOE carrier [n (% of cohort)]	299 (50)	99 (47)	0.41
Diagnosis MCI [n (% of cohort)]	286 (48)	114 (54)	0.18
Diagnosis AD [n (% of cohort)]	145 (24)	39 (18)	0.18
Medication use			
Alzheimer's [n (% of cohort)]	256 (43)	103 (49)	0.15
Antidepressants [n (% of cohort)]	145 (24)	62 (29)	0.15
Antipsychotics [n (% of cohort)]	3 (1)	2 (1)	0.48
Antihypertensives [n (% of cohort)]	309 (52)	309 (52)	0.32
Benzodiazepine [n (% of cohort)]	15 (3)	10 (5)	0.11
Diabetes's [n (% of cohort)]	36 (6)	9 (4)	0.33
Beers list [n (% of cohort)]	122 (20)	57 (27)	0.05

Abbreviations include standard deviation (SD), Alzheimer's Disease Neuro-imaging initiative (ADNI), functional activities questionnaire (FAQ), apolipoprotein E (APOE), mild cognitive impairment (MCI), Alzheimer's disease (AD),

Table 2

Cox Proportional Hazard Model of Time to first fall in 810 subject from ADNI.<sup>1</sup>

Variable	Univariate			Multivariate		
	Hazard ratio	95% CI	p Value	Hazard ratio	95% CI	p Value
Age	1.043	1.04 – 1.07	0.0001	1.05	1.02 – 1.07	<.0001
Male	1.181	0.90 – 1.55	0.2299	-	-	-
Education	0.985	0.94 – 1.03	0.5172	-	-	-
FAQ	1.023	1.00–1.04	0.035	-	-	-
Comedications	1.018	0.99 – 1.05	0.248	-	-	-
APOE	0.965	0.74 – 1.26	0.7947	-	-	-
Diagnosis MCI	1.277	0.93–1.75	0.265	-	-	-
Diagnosis AD	1.314	0.87–1.99	0.265	-	-	-
Medication use						
<b>Alzheimer's</b>	<b>1.545</b>	<b>1.17 – 2.03</b>	<b>0.0019</b>	<b>1.63</b>	<b>1.24 – 2.14</b>	<b>0.0005</b>
Antidepressants	1.308	0.97 – 1.76	0.0759	-	-	-
Antipsychotics	2.137	0.53 – 8.60	0.2849	-	-	-
Antihypertensives	1.185	0.90 – 1.55	0.2207	-	-	-
Benzodiazepines	1.848	0.98 – 3.49	0.0583	-	-	-
Diabetes's	0.735	0.38 – 1.43	0.3657	-	-	-
Beers list	1.328	0.98 – 1.80	0.0668	1.36	1.00 – 1.84	0.0477

<sup>1</sup> Univariate and multivariate Cox proportional hazards model results are presented for the entire ADNI cohort. The univariate and multivariate survival analysis, point estimate of hazard ratio, lower and upper bounds of the 95% CI and P values are presented.

Abbreviations include Alzheimer's Disease Neuro-imaging initiative (ADNI), functional activities questionnaire (FAQ), apolipoprotein E (APOE), mild cognitive impairment (MCI), Alzheimer's disease (AD).