Drugs Aging (2014) 31:125–129
DOI 10.1007/s40266-013-0143-3

SHORT COMMUNICATION

Medication for Alzheimer's Disease and Associated Fall Hazard: A Retrospective Cohort Study from the Alzheimer's Disease Neuroimaging Initiative

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Published online: 20 December 2013

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 disease (AD) patients and association with falls is limited.
Objective We examined the association between falls and medication use in the Alzheimer's Disease Neuroimaging Initiative (ADNI).
Methods Diagnosis, demographics, medication use, apolipoprotein E4 allele status and functional activity level at baseline were gathered for 810 participants enrolled in the ADNI, including healthy controls and subjects with mild cognitive impairment or Alzheimer's. Reports detailing adverse event falls 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 the 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 changed by the clinician after an adverse fall event 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 the use of symptomatic medication treating cognitive symptoms in AD and hazard of fall after adjusting for age and Beers List medication use. Additional pharmacovigilance of the association between falls and Alzheimer's medication use is warranted.

For the Alzheimer's Disease Neuroimaging Initiative (ADNI).

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1 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, antipsychotics 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 the 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 ChEIs and/or memantine use and falls in the participants of the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort.

2 Methods

The 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 US and Canada, including 400 patients meeting the Petersen criteria [6] for MCI, 184 patients with 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 2 February 2011) for 810 participants enrolled in the ADNI. Adverse events were based on subject's self report 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 Beers List, which was generated by experts in pharmacology, identifies medications that may potentially be inappropriate for use in adults aged 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, 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 the 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 were performed using SAS 9.2 (SAS Institute, Cary, NC, USA).

3 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 the ADNI are presented in Table 1. The age of participants who fell (76.80 ± 6.31) was significantly higher ($p = 0.0001$) than those who did not fall (74.72 ± 6.92). There was a borderline significant association between Beers List and a 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 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 Beers List

Table 1 Baseline characteristics of subjects who fell or did not fall in 810 participants from the 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 [n (% of cohort)]			
Alzheimer's	256 (43)	103 (49)	0.15
Antidepressants	145 (24)	62 (29)	0.15
Antipsychotics	3 (1)	2 (1)	0.48
Antihypertensives	309 (52)	309 (52)	0.32
Benzodiazepine	15 (3)	10 (5)	0.11
Diabetes	36 (6)	9 (4)	0.33
Beers list	122 (20)	57 (27)	0.05

Co-medications refer to the total number of medications

ADNI Alzheimer's Disease Neuroimaging Initiative, *SD* standard deviation, *FAQ* Functional Activities Questionnaire, *APOE* apolipoprotein E, *MCI* mild cognitive impairment, *AD* Alzheimer's disease

Table 2 Cox proportional hazard model of time to first fall in 810 subjects from the ADNI

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	<0.0001
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						
Alzheimer's	1.545	1.17–2.03	0.0019	1.63	1.24–2.14	0.0005
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	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

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

ADNI Alzheimer's Disease Neuroimaging Initiative, *FAQ* Functional Activities Questionnaire, *APOE* apolipoprotein E, *MCI* mild cognitive impairment, *AD* Alzheimer's disease

($p = 0.0477$, 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 HR estimate for age is 1.05, meaning that an increase of 1 year in age will increase the hazard rate by 5 %. Beers List medication use increased the hazard rate by 36 %, and treatment with Alzheimer's medication increased the hazard rate by 63 %. Medication was changed by the clinician after an adverse fall event in 9 % of the falls. About 7 % of the falls were reported as serious and 6 % were reported as severe.

4 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's 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 the 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 pharmacovigilance of the association between falls and Alzheimer's medication use is warranted to confirm these findings in other cohorts.

5 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.

Acknowledgments Data used in the preparation of this article were obtained from the ADNI database (adni.loni.ucla.edu). As such, the investigators within the ADNI contributed to the design and implementation of the ADNI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at http://adni.loni.ucla.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

Dr. Epstein conceived the idea, developed the protocol, collected the data and wrote the manuscript. Dr. Guo, 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.

Dr. Farlow receives research funding from Bristol Myers Squibb Company, Danone Research, Elan Pharmaceuticals, Inc., Eli Lilly and Company, Genentech, Novartis Pharmaceuticals Corporation, Octa-Pharma AG, Pfizer Inc., Sanofi-aventis, and Sonexa Therapeutics, Inc.; receives honoraria as a scientific consultant for Accera, Inc., Astellas Pharma US Inc., Baxter Healthcare Corp., Bayer Pharmaceuticals Corporation, Bristol Myers Squibb, DDB Remedy, Eisai Medical Research, Inc., GE Healthcare, Helicon, Medavante, Medivation, Inc., Merck & Co., Inc., Novartis Pharmaceuticals Corp., Pfizer, Inc., Prana Biotechnology Ltd, QR Pharma., Inc., the Sanofi-aventis Group, and Toyama Chemical Co., Ltd; is speaker for Eisai Medical Research, Inc., Forest Laboratories, Pfizer Inc. and Novartis Pharmaceuticals Corporation; and is a partial owner of Chemigen, Inc., core leader for P30.

Data collection and sharing for this project was funded by the ADNI (National Institutes of Health Grant U01 AG024904). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: Abbott; Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Amorfix Life Sciences Ltd; AstraZeneca; Bayer HealthCare; BioClinica, Inc.; Biogen Idec Inc.; Bristol-Myers Squibb Company; Eisai Inc.; Elan Pharmaceuticals Inc.; Eli Lilly and Company; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; GE Healthcare; Innogenetics, N.V.; Janssen Alzheimer Immunotherapy Research & Development, LLC; Johnson & Johnson Pharmaceutical Research & Development, LLC; Medpace, Inc.; Merck & Co., Inc.; Meso Scale Diagnostics, LLC; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Servier; Synarc Inc.; and Takeda Pharmaceutical Company. The Canadian Institutes of Health Research provides funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (http://www.fnih.org). The grantee organization was the Northern California Institute

for Research and Education, and the study was coordinated by the Alzheimer's Disease Cooperative Study at the University of California, San Diego. ADNI data are disseminated by the Laboratory of Neuro Imaging at the Rev. August 16, 2011 University of California, Los Angeles. This research was also supported by NIH grants P30, AG010129, K01 AG030514, and the Dana Foundation.

Drs. Epstein, Singh and Fisher, and Rong Guo have nothing to disclose.

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