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Incidence of New-Onset Seizures in Mild to Moderate Alzheimer Disease

Dr. Michael C. Irizarry, MD, MPH, **Dr. Shelia Jin, MD, MPH**, **Mr. Feng He, MS**, **Ms. Jennifer A. Emond, MS**, **Dr. Rema Raman, PhD**, **Dr. Ronald G. Thomas, PhD**, **Dr. Mary Sano, PhD**, **Dr. Joseph F. Quinn, MD**, **Dr. Pierre N. Tariot, MD**, **Dr. Douglas R. Galasko, MD**, **Dr. Lianna S. Ishihara, PhD**, **Dr. John G. Weil, MD**, and **Dr. Paul S. Aisen, MD**
WorldWide Epidemiology, GlaxoSmithKline, Research Triangle Park, North Carolina, and Stockley Park, United Kingdom (Drs Irizarry, Ishihara, and Weil); Division of Biostatistics and Bioinformatics, Department of Family and Preventive Medicine (Drs Jin, Raman, and Thomas; Mr He; and Ms Emond) and Department of Neurosciences (Drs Raman, Thomas, Galasko, and Aisen), University of California at San Diego; Department of Psychiatry, Mount Sinai School of Medicine, New York, New York (Dr Sano); Department of Neurology, Oregon Health and Sciences University, Portland (Dr Quinn); Banner Alzheimer's Institute, Phoenix, Arizona (Dr Tariot). Dr Weil is now with Novartis Vaccines and Diagnostics, Amsterdam, the Netherlands

Abstract

Objective—To estimate the incidence rate and predictors of seizures in patients with mild to moderate Alzheimer disease (AD).

Design—Cohort study of patients with mild to moderate AD in clinical trials. Risk factors for potential seizures were evaluated by stratified descriptive statistics and univariable and multivariable Cox proportional hazards regressions.

Setting—Pooled patient-level data from 10 Alzheimer Disease Cooperative Study clinical trials in mild to moderate AD from 1995 to 2010.

Patients—Three thousand seventy-eight subjects randomized to the treatment or placebo arms of 10 AD clinical trials. Screening Mini-Mental State Examination scores ranged between 10 and 28.

Results—Eighteen seizures were reported in 3078 randomized subjects, with an incidence rate of 484 per 100 000 person-years (95% CI, 287–764). Statistically significant independent risk factors

Correspondence: Michael C. Irizarry, MD, MPH, WorldWide Epidemiology, GlaxoSmithKline, 17.2123, 5 Moore Dr, Research Triangle Park, NC 27709 (michael.c.irizarry@gsk.com).

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for seizure were younger age (adjusted hazard ratio, 0.80; 95% CI, 0.69–0.93 per every 5 years of age), greater cognitive impairment at baseline (adjusted hazard ratio, 2.79; 95% CI, 1.06–7.33 for Mini-Mental State Examination scores <18 compared with Mini-Mental State Examination scores ≥18), and antipsychotic use at baseline (adjusted hazard ratio, 3.47; 95% CI, 1.33–9.08).

Conclusions—Seizure rates in patients with mild to moderate AD in clinical trials are similar to rates observed in longer observational cohort studies, but they are greater than expected in the general elderly population. Younger age, greater degree of cognitive impairment, and history of antipsychotic use were independent risk factors for new-onset seizures in AD.

Seizures are more common in patients with Alzheimer disease (AD) than in the general elderly population.[1–6] For example, a population-based case-control study in Rochester, Minnesota, from 1955 to 1984 reported that a history of dementia was a risk factor for unprovoked seizures (odds ratio, 6.2; 95% CI, 2.2–17.0).[3] A population-based cohort study from Bronx, New York, suggested that dementia increased the incidence of epilepsy (hazard ratio [HR], 1.96; 95% CI, 0.70–5.48).[4] The incidence of unprovoked seizures in 453 consecutive patients with mild AD followed up at Columbia University, Johns Hopkins University, and Massachusetts General Hospital was 418 per 100 000 person-years, representing an 8-fold increased incidence relative to an age-stratified population from Rochester, Minnesota.[6] Seizures have also been reported as adverse events in AD clinical trials. Establishing the background rate of seizures in AD clinical trial populations can provide a context for emergent safety signals arising in ongoing and future AD clinical trials. We pooled patient-level data from 10 Alzheimer Disease Cooperative Study clinical trials from 1995 to 2010 to obtain an estimate of the background rate and risk factors for new-onset seizures during the course of patient follow-up.

METHODS

The study population consisted of all subjects randomized in 10 Alzheimer Disease Cooperative Study clinical trials, beginning in October 1995 with 6 to 24 months duration in mild to moderate AD: Simvastatin (clinicaltrials.gov identifier: NCT00053599), homocysteine lowering (folate, vitamin B_6, and vitamin B_{12}) (clinicaltrials.gov identifier: NCT00056225),[7] rofecoxib/naproxen sodium (clinicaltrials.gov identifier: NCT00004845),[8] valproate sodium neuroprotection (clinicaltrials.gov identifier: NCT00071721),[9] docosahexanoic acid (clinicaltrials.gov identifier: NCT00440050),[10] Receptor for Advanced Glycation End (RAGE) products inhibitor (PF-04494700) (clinicaltrials.gov identifier: NCT00566397), intravenous immune globulin (clinicaltrials.gov identifier: NCT00818662), estrogen (clinicaltrials.gov identifier: NCT00000177), prednisone (clinicaltrials.gov identifier: NCT00000178),[11] and huperzine A (clinicaltrials.gov identifier: NCT00083590). The subjects were recruited from US Alzheimer Disease Research Centers, academic centers, and clinical trial centers. Inclusion criteria for the clinical trials were similar and included: (1) diagnosis of probable AD according to the definition by the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer Disease and Related Disorders Association;[12] (2) people aged older than 50 years; (3) available caregiver; (4) informed consent by patient or representative; (5) mild to moderate AD with Mini-Mental State Examination (MMSE) scores ranging from 10 to 28;[13] and (6) stable use of cholinesterase inhibitors and/or memantine. Exclusion criteria included history of seizures. All clinical trial sites obtained approval from their local institutional review boards. Written informed consent was obtained from study participants, legally authorized representatives, or both, according to local guidelines.

The outcome measure was the rate of incident seizures by person-time of follow up from randomization within the Alzheimer Disease Cooperative Study programs. Seizures were identified by search of the adverse event verbatim terms for the following text strings:

seizure, epil, epilepsy, epileptic, status epilepticus, epileptiform, epilepsia, status, tonic, clonic, convuls, convulsion, convulsive, grand mal, and fit. This was followed by clinical review of the full verbatim text. Safety assessments were performed at each study visit every 1 to 6 months. Because this analysis involved reuse of existing clinical trial data sets, additional clinical information was not available for most subjects to formally adjudicate the seizure adverse events or to evaluate nonspecific adverse events such as fall or confusion.

Person-time was calculated from time of randomization until whichever of the following happened first: (1) end of study; (2) withdrawal from study; (3) death; or (4) onset of adverse events of seizure or convulsion. Exact 95% confidence intervals were calculated for the incidence rates. The valproate neuroprotection, intravenous immune globulin, and RAGE inhibitor clinical trials were blinded at the time of analysis. The intravenous immune globulin and RAGE inhibitor clinical trials were ongoing at the time of analysis.

Univariable Cox proportional hazards modeling was performed to determine whether incidence rates varied by age; sex; age at onset of dementia; duration of dementia; MMSE score; use of acetylcholinesterase inhibitors (AchE-I), memantine, antidepressants, anxiolytics, and antipsychotics; treatment arm (placebo, active treatment, and ongoing blinded); and presence of the *APOE* ε4 allele. Univariable significant terms at the $P<.05$ level were incorporated in a multivariable Cox proportional hazards model. A fully adjusted multivariable model was also performed as a sensitivity analysis (excluding age at onset because it was a linear combination of age and duration of dementia).

RESULTS

The 10 clinical trials randomized 3078 subjects with a total of 3719 person-years of follow-up (Table 1). Consistent with the inclusion criteria, patients were at a mild to moderate stage of AD at randomization (mean [SD] MMSE score, 20.2 [3.9]; mean [SD] duration of dementia, 4.3 [2.6] years). Seventy-two percent were taking AchE-I overall. Of the 2238 individuals tested, 64% carried the *APOE* ε4 allele.

Eighteen seizures were identified from the verbatim adverse event listings in the study: Cases identified were reported as seizure (n=13), possible seizure (n=2), probable seizure (n=2), or prodrome preseizure symptoms (n=1, included as a possible aura [partial seizure]). Eight of the 18 seizure adverse events were reported as serious adverse events. Four subjects discontinued study medication within 1 week of the seizure adverse event.

The incidence rate during 3719 person-years of follow-up was 484 per 100 000 person-years (95% CI, 287–764). Seizure rates within selected patient subgroups are shown in Table 1, although precision of subgroup estimates is limited by the low numbers of events. Subjects with greater cognitive impairment at baseline had a higher incidence rate: Subjects with an MMSE score less than 18 had an incidence of 1110 per 100 000 person-years, while those with an MMSE score of 18 or greater had an incidence rate of 257 per 100 000 person-years. Seventy-two percent of all subjects were taking AchE-I, and 89% of subjects with seizures were taking AchE-I at baseline; the exact confidence intervals for the seizure rate in subjects taking and not taking AchE-I broadly overlapped. The valproate study had the most reported seizures, likely owing to an overrepresentation of subjects with moderate AD as this study had a lower MMSE inclusion range (MMSE score range, 12–20) than the other studies.

By univariable Cox proportional hazards regression, significant univariable predictors of seizure were younger age (HR, 0.80; 95% CI, 0.70–0.91 per every 5 years of age), younger age at dementia onset (HR, 0.79; 95% CI, 0.70–0.90 per every 5 years of age), lower MMSE score (HR, 3.9; 95% CI, 1.5–10.1 for MMSE scores <18 compared with MMSE scores ≥18), memantine use (HR, 3.87; 95% CI, 1.12–13.49), and antipsychotic use (HR, 4.0; 95% CI,

1.5–10.3) (Table 2). Duration of dementia, *APOE* ε4 allele, treatment arm (omnibus test for placebo, active, or blinded), and cholinesterase inhibitor use were not significant univariable predictors of seizure. In a multivariable model including the factors age, MMSE score (continuous or <18 compared with an MMSE score ≥18), antipsychotic drug use, and memantine use, all factors except memantine use remained significant independent predictors of seizure occurrence, with attenuation of the effect estimates for MMSE score, antipsychotic use, and memantine use relative to the univariable analysis (Table 2). Age and antipsychotic use remained significant in the fully adjusted model; MMSE score, though not significant (P=.07), had an HR of 3.15 (95% CI, 0.93–10.75), with wider confidence intervals relative to the other models, suggesting collinearity with variables in the overparameterized model (Table 2).

COMMENT

The overall incidence rate of 484 per 100 000 person-years in this clinical trial population is slightly higher than the rate of validated epileptic events in a recently published observational cohort of subjects with mild AD at baseline (418 per 100 000).[6] Similar to the latter study, younger age was associated with greater incidence of seizures. Dementia severity at baseline was strongly associated with increased seizure risk, which has also been reported in some studies.[5]

Among the medication treatments, antipsychotic drug use (in univariable and multivariable analyses) and memantine use (in univariable analysis) were associated with an increased incidence of seizures. Memantine is indicated for moderate to severe but not mild dementia. Agitation, hallucinations, and delusions that may require treatment are more common in moderate to severe dementia than mild dementia.[14] Seven of the 18 individuals with seizures took at least 1 antipsychotic drug at baseline, ranging from aripiprazole, chlorpromazine, perphenazine, olanzapine, risperidone, quetiapine fumarate, ziprasidone hydrochloride, and haloperidol. While antipsychotic drugs are reported to reduce the seizure threshold, there is likely residual confounding by indication because use of these drugs or memantine may be markers of more advanced disease.[15]

Incidence rates of seizures in mild to moderate AD are higher than incidence rates reported in other elderly populations. Incidence rates of first unprovoked seizure in a Northern Manhattan study ranged from 45 per 100 000 person-years for individuals aged 65 to 74 years to 144.7 per 100 000 person-years for those aged 75 to 84 years.[16] Higher rates were observed in Rochester, Minnesota, from 1975 to 1984, approximately 120 per 100 000 person-years for those aged 65 to 74 years and 280 per 100 000 person-years for those aged 75 and older.[17] Although rates in AD are higher than the general population, our results and those of Scarmeas et al[6] suggest that seizures are uncommon events in mild to moderate AD.

The strengths of the study include the consistent diagnostic criteria (National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer Disease and Related Disorders Association) used to classify AD in centers experienced with the disease and the standardized clinical assessment of adverse events at least every 6 months. Pooling studies enabled incidence calculations of seizure events that were rare in individual trials. However, the small number of events limited detailed evaluation of risk factors and effect modifiers of the seizure incidence rate. The study assumes that the clinical trial populations were similar. While patients were recruited from similar study sites, the individual clinical trial participants may differ by severity or concomitant medications based on differences in inclusion criteria. The population of subjects with AD recruited into clinical trials may not be a random sample of all subjects with mild to moderate AD in the community. Subjects generally must be free of other neurologic, psychiatric, or systemic diseases that could

significantly impair clinical trial participation and may thus be healthier than the general AD population. Nonetheless, the incidence rates of seizures observed in the pooled Alzheimer Disease Cooperative Study clinical trials provide context for seizure safety signals that may arise in future clinical trials in mild to moderate AD.

Seizure diagnoses were based on adverse event reporting by clinical study sites. While this took advantage of the careful collection of adverse event data by study physicians during safety assessments at each visit (every 1–6 months), confirmation and clinical adjudication of seizure diagnoses were not performed. Clinically evident tonic-clonic seizures are more likely to be recognized than non-convulsive partial seizures. Other alterations of consciousness such as syncope or delirium and motor manifestations such as tremor and myoclonus may be misdiagnosed as seizures. The incidence rates in this meta-analysis reflect diagnosed seizures; other alterations of consciousness that were not diagnosed as seizures by the clinical trial physicians are not included in the estimates.

The seizure rates were pooled across treatment and placebo arms. The seizure rate may be modified by the specific treatment in the clinical trial. For instance, divalproex sodium treatment arms may have had a reduced seizure rate since divalproex is an anticonvulsant. Subjects in the valproate neuroprotection study overall had a higher seizure rate, likely attributable to the greater dementia severity at baseline.

COMMENT

Pooling data across AD clinical trials can provide valuable information regarding rates and risk factors for uncommon medical events. The results suggest that younger age and greater cognitive impairment at baseline are risk factors for seizures in mild to moderate AD. Antipsychotic drug use (in univariable and multivariable analyses) and memantine use (in univariable analysis) were associated with increased risk of seizures, although use of these may be a marker for more advanced disease. Current AD data aggregation initiatives such as the Coalition Against Major Diseases are focusing initially on predictors of diagnosis and disease progression.[18] Supplementing these proposals with adverse events data can further clarify the background rates of adverse events and incident comorbidities in AD, facilitate safety monitoring of clinical trials, and provide insight into the overall medical course of AD.

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References

1. Amatniek JC, Hauser WA, DelCastillo-Castaneda C, et al. Incidence and predictors of seizures in patients with Alzheimer's disease. Epilepsia. 2006; 47(5):867–872. [PubMed: 16686651]
2. Hauser WA, Morris ML, Heston LL, Anderson VE. Seizures and myoclonus in patients with Alzheimer's disease. Neurology. 1986; 36(9):1226–1230. [PubMed: 3092131]
3. Hesdorffer DC, Hauser WA, Annegers JF, Kokmen E, Rocca WA. Dementia and adult-onset unprovoked seizures. Neurology. 1996; 46(3):727–730. [PubMed: 8618673]
4. Hussain SA, Haut SR, Lipton RB, Derby C, Markowitz SY, Shinnar S. Incidence of epilepsy in a racially diverse, community-dwelling, elderly cohort: results from the Einstein aging study. Epilepsy Res. 2006; 71(2–3):195–205. [PubMed: 16870396]
5. Romanelli MF, Morris JC, Ashkin K, Coben LA. Advanced Alzheimer's disease is a risk factor for late-onset seizures. Arch Neurol. 1990; 47(8):847–850. [PubMed: 2375689]

6. Scarmeas N, Honig LS, Choi H, et al. Seizures in Alzheimer disease: who, when, and how common? Arch Neurol. 2009; 66(8):992–997. [PubMed: 19667221]
7. Aisen PS, Schneider LS, Sano M, et al. Alzheimer Disease Cooperative Study. High-dose B vitamin supplementation and cognitive decline in Alzheimer disease: a randomized controlled trial. JAMA. 2008; 300(15):1774–1783. [PubMed: 18854539]
8. Aisen PS, Schafer KA, Grundman M, et al. Alzheimer's Disease Cooperative Study. Effects of rofecoxib or naproxen vs placebo on Alzheimer disease progression: a randomized controlled trial. JAMA. 2003; 289(21):2819–2826. [PubMed: 12783912]
9. Profenno LA, Jakimovich L, Holt CJ, Porsteinsson A, Tariot PN. A randomized, double-blind, placebo-controlled pilot trial of safety and tolerability of two doses of divalproex sodium in outpatients with probable Alzheimer's disease. Curr Alzheimer Res. 2005; 2(5):553–558. [PubMed: 16375658]
10. Quinn JF, Raman R, Thomas RG, et al. Docosahexaenoic acid supplementation and cognitive decline in Alzheimer disease: a randomized trial. JAMA. 2010; 304(17):1903–1911. [PubMed: 21045096]
11. Mulnard RA, Cotman CW, Kawas C, et al. Estrogen replacement therapy for treatment of mild to moderate Alzheimer disease: a randomized controlled trial: Alzheimer's Disease Cooperative Study. JAMA. 2000; 283(8):1007–1015. [PubMed: 10697060]
12. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 1984; 34(7):939–944. [PubMed: 6610841]
13. Folstein MF, Folstein SE, McHugh PR. Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975; 12(3):189–198. [PubMed: 1202204]
14. Ropacki SA, Jeste DV. Epidemiology of and risk factors for psychosis of Alzheimer's disease: a review of 55 studies published from 1990 to 2003. Am J Psychiatry. 2005; 162(11):2022–2030. [PubMed: 16263838]
15. Hedges D, Jeppson K, Whitehead P. Antipsychotic medication and seizures: a review. Drugs Today (Barc). 2003; 39(7):551–557. [PubMed: 12973403]
16. Benn EK, Hauser WA, Shih T, et al. Estimating the incidence of first unprovoked seizure and newly diagnosed epilepsy in the low-income urban community of Northern Manhattan, New York City. Epilepsia. 2008; 49(8):1431–1439. [PubMed: 18336560]
17. Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935–1984. Epilepsia. 1993; 34(3):453–468. [PubMed: 8504780]
18. Critical Path Initiative. [Accessed September 30, 2009] Coalition Against Major Diseases (CAMD): Work scope 1.1. Jul. 2009 http://www.c-path.org/pdf/CAMDWorkScope.pdf

Table 1

Demographic and Clinical Characteristics of Patients

Baseline Characteristic	No. (%)			Incidence Rate per 100 000 Person-y (95% CI)
	Entire Cohort	Seizure	No Seizure	
No.	3078	18	3060	484 (287–764)
Age, y [SD]	74.5 [9.5]	67.8 [11.0]	74.5 [9.5]	
<75	1343 (44)	13 (72)	1330 (44)	818 (436–1394)
≥75	1735 (56)	5 (28)	1730 (56)	235 (76–546)
Sex				
Male[a]	1293 (42)	8 (44)	1285 (42)	503 (218–990)
Female	1785 (58)	10 (56)	1775 (58)	469 (225–860)
Age at onset of dementia, [SD] y	70.2 [9.7]	62.9 [10.7]	70.3 [9.7]	NA
Duration of dementia, [SD] y	4.3 [2.6]	5.0 [3.7]	4.3 [2.6]	NA
MMSE score, mean [SD]	20.2 [3.9]	16.6 [4.1]	20.2 [3.9]	
≥18	2266 (74)	7 (39)	2259 (74)	257 (103–528)
<18	802 (26)	11 (61)	791 (26)	1110 (555–1977)
Cholinesterase inhibitor use				
Yes	2214 (72)	16 (89)	2198 (72)	569 (325–922)
No	855 (28)	2 (11)	853 (28)	221 (27–796)
Memantine use				
Yes	1576 (51)	15 (83)	1561 (51)	767 (430–1262)
No	1502 (49)	3 (17)	1499 (49)	170 (35–496)
Antidepressant use				
Yes	1226 (40)	8 (44)	1218 (40)	523 (226–1027)
No	1852 (60)	10 (56)	1842 (60)	456 (219–838)
Anxiolytic use				
Yes	250 (8)	4 (22)	246 (8)	1307 (357–3313)
No	2828 (92)	14 (78)	2814 (92)	410 (224–687)
Antipsychotic use				
Yes	363 (12)	7 (39)	356 (12)	1446 (583–2957)
No	2715 (88)	11 (61)	2704 (88)	340 (170–607)
Treatment arm				
Placebo	824 (27)	4 (22)	824 (27)	372 (101–950)
Active	1208 (39)	3 (17)	1205 (39)	199 (41–580)
Blinded	1033 (33)	11 (61)	1022 (33)	970 (485–1729)
APOE genotype				
ε4 present	1441 (64)	8 (62)	1433 (64)	456 (197–896)
No ε4	797 (36)	5 (39)	792 (36)	525 (171–1221)
Study				
Docosahexanoic acid	402 (13)	0 (0)	402 (13)	0 (0–655)
Homocysteine lowering	409 (13)	4 (22)	405 (13)	692 (189–1762)
Simvastatin	406 (13)	2 (11)	404 (13)	318 (39–1146)

Baseline Characteristic	No. (%)			Incidence Rate per 100 000 Person-y (95% CI)
	Entire Cohort	Seizure	No Seizure	
Rofecoxib/naproxen	351 (11)	0 (0)	351 (12)	0 (0–1048)
RAGE inhibitor[b,c]	419 (14)	3 (17)	416 (14)	625 (129–1816)
Valproate neuroprotection[b]	313 (10)	7 (39)	306 (10)	1370 (552–2802)
Intravenous immune globulin[b,c]	301 (10)	1 (6)	300 (10)	704 (18–3861)
Estrogen	120 (4)	1 (6)	119 (4)	746 (19–4088)
Prednisone	138 (5)	0 (0)	138 (5)	0 (0–2265)
Huperzine A	210 (7)	0 (0)	210 (7)	0 (0–2110)

Abbreviations: *APOE*, apolipoprotein E; MMSE, Mini-Mental State Examination; NA, Not applicable; RAGE, Receptor for Advanced Glycation End.

[a] Percentages are based on column percentages (ie, percentage of entire cohort that is male).

[b] Studies blinded at time of data analysis.

[c] Studies ongoing at time of data analysis.

Table 2

Univariable and Multivariable Models of Seizures in Alzheimer Disease

Risk Factor	Univariable, HR (95% CI)	Multivariable Model/Only Univariable Significant Covariates, HR (95% CI)[a]	Multivariable Model/All Covariates, HR (95% CI)[b]
Age, per 5 y	0.80 (0.70–0.91)[c]	0.80 (0.69–0.93)[c]	0.71 (0.51–0.98)[c]
MMSE (<18 vs ≥18)	3.88 (1.50–10.06)[c]	2.79 (1.06–7.33)[c]	3.15 (0.93–10.75)[d]
Antipsychotic drug use	4.00 (1.55–10.34)[c]	3.47 (1.33–9.08)[c]	5.32 (1.61–17.58)[c]
Memantine use	3.87 (1.11–13.49)[c]	2.77 (0.78–9.75)	1.86 (0.37–9.29)
Sex, male vs female	1.07 (0.42–2.72)		1.37 (0.45–4.18)
Duration of dementia, per 5 y	1.56 (0.73–3.32)		1.79 (0.61–5.28)
Cholinesterase inhibitor use	2.26 (0.52–9.89)		2.31 (0.29–18.31)
Antidepressant use	1.06 (0.42–2.70)		0.60 (0.18–2.04)
Anxiolytic use	2.89 (0.95–8.79)		2.05 (0.54–7.86)
Placebo treatment arm vs active	1.82 (0.41–8.15)[e]		2.89 (0.52–16.07)
Blinded treatment arm vs active	3.84 (1.05–14.04)[e]		4.63 (0.91–23.63)
APOE genotype, ε4 present	0.87 (0.29–2.67)		0.87 (0.27–2.80)

Abbreviations: *APOE*, apolipoprotein E; HR, hazard ratio; MMSE, Mini-Mental State Examination.

[a] Adjusted for univariable significant terms at the $P < .05$ level.

[b] Adjusted for the other variables in the table.

[c] $P < .05$.

[d] $P = .07$.

[e] Likelihood ratio test for treatment arm (df = 2); $P = .08$.