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The Greater Sensitivity of Elderly *APOE* ε4 Carriers to Anticholinergic Medications Is Independent of Cerebrovascular Disease Risk

Robert D. Nebes, PhD[1], **Bruce G. Pollock, MD, PhD**[1,*], **Subashan Perera, PhD**[2], **Edythe M. Halligan, MA**[1], and **Judith A. Saxton, PhD**[3]

[1]Department of Psychiatry, University of Pittsburgh Medical School, Pittsburgh, Pennsylvania

[2]Department of Medicine, University of Pittsburgh Medical School, Pittsburgh, Pennsylvania

[3]Department of Neurology, University of Pittsburgh Medical School, Pittsburgh, Pennsylvania

Abstract

Background—Recent studies found use of anticholinergic medications to be associated with greater performance decrements in older persons who carry an ε4 allele of the apolipoprotein E (*APOE*) gene than in those carrying only ε2 or ε3 alleles.

Objectives—The present study examined whether the apparently greater behavioral toxicity of anticholinergic drugs in ε4 carriers may result from an increased risk of cerebrovascular disease, which is more common in ε4 carriers.

Methods—Cross-sectional data were available from 240 normal elderly [PE1]community volunteers who had participated in 2 different studies of the cognitive and motor effects of normal aging. As part of these studies, information was gathered on subjects' use of anticholinergic medications (based on an inventory of medications taken within 24 hours of testing), risk of cerebrovascular disease (Framingham Stroke Risk Profile), and *APOE* genotype. Performance data were also available from measures of general cognitive status (Mini-Mental State Examination), executive function (Trail Making Test), mood (Geriatric Depression Scale), sleep (Pittsburgh Sleep Quality Index), and walking speed. Logistic and linear regression models were used to examine how outcomes differed between genotypes and drug use, independent of the risk of cerebrovascular disease.

Results—In persons with a non-ε4 genotype, anticholinergic medication use did not significantly affect any of the behavioral measures. By contrast, among ε4 carriers, those taking anticholinergic drugs performed significantly worse than did those not taking such drugs on tests of general cognitive status, executive function, mood, and sleep. Adjusting for participants' stroke risk had a minimal effect on these results.

Address correspondence to: Robert D. Nebes, PhD, Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, PA 15213. nebesrd@upmc.edu.
*Current affiliation: Center for Addiction and Mental Health, Toronto, Ontario, Canada.

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Conclusions—Anticholinergic medication use was associated with poorer performance on measures of cognition, sleep, and mood only in older persons who carried 1 or more ε4 alleles of the *APOE* gene; this effect did not appear to be the result of an increased risk of cerebrovascular disease.

Keywords

anticholinergic drugs; *APOE*; cerebrovascular disease; cognition; mood; sleep

INTRODUCTION

Anticholinergic medications are widely used by the elderly to treat a variety of common medical conditions. In addition to prescribed medications, older persons also often use over-the-counter drugs with anticholinergic effects (eg, ranitidine, diphenhydramine) and thus may carry a substantial anticholinergic burden.[1] Such drugs interfere with cholinergic metabolism by antagonizing muscarinic receptors[2] and at high doses have been shown to produce a variety of severe behavioral decrements in the elderly including sedation, confusion, and even delirium.[3] More subtle cognitive decrements such as slowed information processing and memory impairment have also been demonstrated in community-dwelling older adults.[4,5] Several studies found that elderly individuals who carry 1 or more ε4 alleles of the apolipoprotein E (*APOE*) gene may be particularly sensitive to anticholinergic drugs. In a placebo-controlled study, Pomara et al[6] showed that acute administration of trihexyphenidyl impaired delayed recall relative to placebo only in those elderly who were ε4 carriers ($P < 0.001$). In a large community-based study, Carriere et al[4] found an interactive effect of anticholinergic drugs and *APOE* genotype such that anticholinergic drug users had a 2-fold higher risk of a longitudinal cognitive decline if they carried the ε4 genotype. A recent study[7] using a measure of subjective mental symptoms showed a significant interaction between drug condition (anticholinergic medication vs. placebo) and *APOE* genotype ($P < 0.03$), with ε4 carriers showing a greater drug effect. Also, the magnitude of this anticholinergic drug effect correlated with memory recall performance only in the ε4 carriers ($P < 0.01$). Finally, among persons with stable atherosclerotic disease, ε4 carriers taking anticholinergic medications had the lowest performance on the Mini-Mental State Examination (MMSE), although an actual interactive effect of *APOE* genotype and anticholinergic drug use on cognitive performance was not found.[8]

Although these results suggest that persons carrying the *APOE* ε4 allele may be particularly sensitive to anticholinergic medications, Pomara and Sidtis[9] argued that use of anticholinergic medications could simply be a marker for increased disease burden. Cerebrovascular disease would be one likely possibility[PE2]. Persons with an ε4 genotype have an increased risk of cerebrovascular disease,[10] evident as white matter hyperintensities (WMH) in their brain. WMH are associated with cognitive impairments in the normal old[PE3],[11] especially in ε4 carriers.[12] Cerebrovascular disease is associated with a central cholinergic dysfunction. Bocti et al[13] reported that the severity of WMH present in cholinergic pathways was strongly related to cognitive performance in elderly individuals, whereas total WMH severity was not, suggesting that the behavioral impairments associated with WMH may result from disruption of cholinergic neuronal pathways. Because individuals with central cholinergic dysfunction show an increased sensitivity to anticholinergic medications,[14,15] any cognitive deficits associated with anticholinergic drugs may be magnified in individuals with cerebrovascular disease. This view is supported by a finding[16] that the psychomotor slowing present with elevated WMH volume in normal elderly individuals was exacerbated by the presence of anticholinergic medications in their serum. Finally, there is evidence that persons with substantial WMH show increased

permeability of the blood–brain barrier,[17] allowing greater penetration of the central nervous system by medications. These findings raise the possibility that coexistent cerebrovascular disease may underlie the suggested hypersensitivity of *APOE* ε4 carriers to anticholinergic medications.

The present analysis sought to build on previous findings that the performance decrements associated with taking anticholinergic medications are greater in older ε4 carriers than in noncarriers. Further, it examined whether this apparent sensitivity of ε4 carriers to anticholinergic medications would persist after controlling for the increased risk of cerebrovascular disease known to be associated with the ε4 genotype.

METHODS

Subjects

The data used in these analyses came from 240 subjects aged 65 to 80 years recruited from the community by advertisement for 2 different investigations into the cognitive and motor effects of normal aging carried out from 1999 to 2002 and 2003 to 2007. One of these studies focused on the behavioral effects of WMH and the other on the effects of anticholinergic medications. The samples for the 2 studies were made up of different individuals, but the inclusion and exclusion criteria for the 2 studies were identical. Both studies were approved by the University of Pittsburgh Institutional Review Board (IRB010823 and IRB9602163). In both studies, a nurse practitioner skilled in geriatric assessment obtained a medical history and performed physical and neurological examinations on potential subjects. Information on current medical conditions and medications was also obtained from subjects' primary care physician when available. To participate, individuals could not have a history of central nervous system pathology (eg, stroke, Parkinson's disease) or major psychiatric disease, nor could they be taking psychoactive medications (eg, benzodiazepines, narcotics, antidepressants). Individuals being actively treated for cancer or who had a history of alcohol or drug abuse were also excluded. In both studies, subjects were given a battery of neuropsychological tests (different in the 2 studies), and individuals showing evidence of clinically significant cognitive impairment (eg, mild cognitive impairment), as determined by the chief neuropsychologist (J.A.S.) from the University of Pittsburgh Alzheimer Disease Research Center, were excluded, as was anyone who scored >15 on the 30-point version of the Geriatric Depression Scale (GDS).[18] *APOE* genotyping was performed by the Alzheimer Center Genetics Core.

Anticholinergic Medications

On the day of testing, subjects brought in the containers for all prescription and over-the-counter medications that they had taken in the past 24 hours. These were examined to determine whether they had taken any medications reported as anticholinergic in either of 2 published drug listings: the Anticholinergic Drug Scale[19] and the Anticholinergic Risk Scale.[20] Any medications not found in either of these listings were considered to have no anticholinergic effects.

Cerebrovascular Disease

Results from a medical questionnaire, the physical examination, and the subject's primary care physician were used in an algorithm (Framingham Stroke Risk Profile) that estimates an individual's percentage of risk for having a stroke within the next 10 years based on the presence of vascular risk factors such as hypertension, diabetes, and heart disease.[21] This score served as an operational measure of the subject's risk of cerebrovascular disease and as an indirect marker of WMH severity. The Stroke Risk Profile is strongly correlated (r =

0.68) with the volume of WMH present in community-dwelling elders[22] as well as with cognitive impairment.[23]

Behavioral Measures

The behavioral data available for analysis were limited because only a few of the tasks administered in the 2 studies were identical. The Mini-Mental State Examination[24] is a brief 30-point measure commonly used to screen for cognitive impairment. The Trail Making Test (TMT)[25] is composed of 2 parts. TMT-A consists of 25 circles numbered 1 through 25 distributed over a page. The subject is instructed to connect the circles with a pencil line as quickly as possible in ascending numerical order. TMT-B also consists of 25 circles, but these circles contain the numbers 1 through 13 and letters A through L. The subject must connect the circles alternating between numbers and letters in ascending order (ie, 1, A, 2, B, 3…). The time required to complete each part is recorded. Although both TMT-A and -B involve visuomotor and perceptual scanning skills, TMT-B also requires subjects to repeatedly shift mental set between the 2 series while keeping track of their position in each series. Subtracting the time taken to complete TMT-A from that taken to complete TMT-B served as our measure of the efficiency of set shifting, commonly thought to be a component of executive functioning.

In addition to using the GDS to exclude potential cases of clinical depression (ie, scores >15), we determined the relationship of anticholinergic drug use with the total GDS score as well as with 2 subsets of GDS questions based on a factor analysis of data from elderly adults.[26] One subset consisted of 9 questions dealing with mood symptoms (eg, sadness, helplessness, worry), whereas the other subset consisted of 6 questions dealing with functional symptoms (eg, difficulty concentrating or making decisions, loss of motivation/energy). Previous work has shown self-reported functional symptoms to be more closely linked to WMH severity[27] than are mood symptoms.

Because over-the-counter anticholinergic medications are commonly used by elderly as a sleep aid,[28] we examined the results of the Pittsburgh Sleep Quality Index (PSQI), a widely used questionnaire that assesses subjective sleep quality and quantitative sleep-wake parameters over the preceding month.[29] Responses to questions in the PSQI were entered into an equation to provide a global PSQI score ranging from 0 to 21, with higher scores representing poorer sleep quality.

We also measured the gait speed of participants because anticholinergic medications have been linked to problems with mobility in the elderly.[30] The time that participants took to walk a 15-foot course was measured to the nearest one tenth of a second from the signal to begin until the subject's foot crossed the 15-foot mark. A subject walked the course twice, and the 2 times were averaged and transformed into walking speed in meters per second.

Statistical Analysis

Subjects were divided into 2 groups based on their *APOE* genotype: the ε4 group included persons carrying 1 or more ε4 alleles, and the non-ε4 group included persons carrying ε2 and ε3 alleles. The 2 *APOE* groups were then dichotomized between those who took no anticholinergic medications (nonusers) and those who took at least 1 anticholinergic medication (ACh users). Given the restricted range, the ordinal nature, and the skew of the distribution, the GDS motivation and mood subscores were dichotomized based on whether individuals scored ≥2 and ≥1, respectively.

We used independent-sample *t* tests to compare relevant participant characteristics (age, years of education, stroke risk) between ACh users and nonusers within each *APOE* genotype. For the main analysis, we fit (2-way ANOVA type) linear models or logistic

regression models depending on whether a measure was continuous or dichotomous. First, we included APOE genotype (ε4/non-ε4), ACh user/nonuser and APOE genotype × ACh user/nonuser interaction as factors of interest. Appropriately constructed contrast estimates were used to estimate the magnitude and obtain the statistical significance of the interaction effect (ie, between-genotype difference of the ACh user vs. nonuser difference) and ACh user/nonuser differences within each *APOE* genotype. Next, we repeated the analyses after adding stroke risk as an additional predictor to determine whether our findings would persist independent of cerebrovascular disease risk. SAS software version 9.2 (SAS Institute, Inc., Cary, North Carolina) was used for all statistical analyses.

RESULTS

Twenty-two percent of the subjects (n = 53) carried at least 1 ε4 allele. Based on the anticholinergic medications found in the 2 published drug listings,[19,20] the percentage of individuals using at least 1 anticholinergic medication was 32% in the ε4 and 28% in non-ε4 groups, whereas the mean number of anticholinergic drugs taken was 1.41 and 1.43, respectively, in the 2 groups[PE4]. Thus, there was no evidence that anticholinergic burden differed as a function of *APOE* genotype. Anticholinergic medications were most commonly being taken for allergies, acid reflux or excess stomach acid, or incontinence. The specific medications taken by subjects in this analysis were bromph[PE5]eniramine, captopril, cetirizine, chlordiazepoxide, chlorpheniramine, dexamethasone, digoxin, diphenhydramine, dipyridamole, famotidine, furosemide, hydroxyzine, isosorbide, loratadine, meclizine, metoclopramide, nifedipine, oxybutynin, prednisolone, prednisone, ranitidine, theophylline, tolterodine, tramadol, and warfarin. Stroke risk was significantly higher in persons taking anticholinergic medications in both *APOE* groups (Table I).

Significant or marginally significant interactions between *APOE* genotype and anticholinergic medication use were found for most behavioral measures (Table II). Genotype and anticholinergic drug use interacted significantly for TMT-B time ($t = -3.86$; $P = 0.0001$), TMT-B time minus TMT-A time ($t = -3.78$; $P = 0.0002$), GDS ($t = -3.11$; $P = 0.0021$), and GDS motivation symptoms ($\chi^2 = 11.7$; $P = 0.0006$) and marginally significantly for GDS mood symptoms ($\chi^2 = 3.78$; $P = 0.052$), MMSE ($t = 1.77$; $P = 0.0786$), and PSQI ($t = -1.88$; $P = 0.0618$). Thus, we proceeded to interpret associations between anticholinergic medication use and behavioral measures within each *APOE* group.

In the non-ε4 group, use of anticholinergic medications did not significantly affect any of the behavioral measures, even before adjusting for stroke risk. By contrast, ε4 carriers who were taking anticholinergic medications performed significantly worse than did individuals not taking such drugs (Table II) on all the measures except for gait speed. Adjusting for participants' stroke risk had a minimal effect on these results, with only the MMSE and TMT-A results falling to a marginally significant level. Thus, ε4 carriers who used anticholinergic medications performed worse than ε4 carriers who did not use such medications on most of the measures examined, even after differences in cerebrovascular disease risk were taken into account.

DISCUSSION

Anticholinergic medication use was associated with impaired performance on the TMT only in the ε4 carriers. The effect on TMT-A, which assesses primarily psychomotor speed, was relatively small and became only marginally significant after controlling for stroke risk. By contrast, measures of mental-set shifting (TMT-B and TMT-B minus TMT-A) were impaired in ACh users only if they carried an *APOE* ε4 genotype. Controlling for stroke risk did not eliminate this differential sensitivity of the ε4 carriers to anticholinergic medications,

despite stroke risk being significantly higher in individuals who were taking anticholinergic medications (Table I). The effect of anticholinergic drug use on the MMSE was relatively small and became only marginally significant after controlling for stroke risk. This is not too surprising given that the MMSE is less sensitive at the upper end of its range where most of our subjects tended to perform. Anticholinergic drug use did not affect walking speed in this study, even in ε4 carriers. Although a previous study showed anticholinergic medication use to be associated with slower walking speed,[30] unlike the present analysis, it did not exclude persons taking psychoactive medications, which include some of the stronger anticholinergic drugs.

Subjective measures also showed an interactive effect of anticholinergic medications and *APOE* genotype in that ε4 carriers who used anticholinergic medications reported significantly poorer sleep and more depressive symptoms than did nonusers. The association of anticholinergic drug use with impaired sleep quality is consistent with findings of a previous epidemiological study,[28] showing that older persons with sleep difficulties often use anticholinergic medication as a sleep aid. Thus, the poorer sleep quality seen in persons using anticholinergic medications may not be an effect of anticholinergic use, but rather a reason for it. However, why this relationship between sleep quality and anticholinergic drug use should be stronger in ε4 carriers is not clear. The relationship of the anticholinergic drug use with depressive symptomatology is somewhat surprising. Depressive symptomatology has not typically been associated with anticholinergic medication use except for antidepressant medications such as amitriptyline or imipramine, which do have anticholinergic properties. However, use of such medications was a specific exclusion criterion for this study. Pomara et al[7] examined the effect that acute administration of an anticholinergic medication had on the Mood Rating Scale, but analyzed only questions related to sedation and confusion. Of these, only self-rated mental slowing showed a greater anticholinergic effect in ε4 carriers. Although the present study also demonstrated an effect on functional symptoms (eg, problems making decisions and ability to concentrate), ε4 carriers taking anticholinergic medications also reported increased mood symptoms (eg, feeling hopeless or downhearted). The present association-type data cannot definitively show the direction of the relationship between anticholinergic medication use and mood, but it does show that it is stronger in persons who carry an ε4 genotype.

In addition to stroke risk, there was 1 other potential confound. Among the non-ε4 individuals, those who used anticholinergic medications were significantly more educated than were nonusers (Table I). However, because the detrimental effect of anticholinergic medications on behavior was in the ε4 individuals, this education difference is unlikely to be an important factor in the pattern of results.

If an increased risk of cerebrovascular disease does not explain the greater behavioral vulnerability of ε4 carriers to anticholinergic medications, what does? One possibility is subclinical Alzheimer's disease (AD), because persons carrying an ε4 genotype have a greater risk of the development of AD,[31] and AD patients are highly sensitive to anticholinergic medications. Although our subjects were thoroughly screened for significant cognitive impairment, it is difficult to detect AD early in its course, especially in well-educated individuals who made up a substantial segment of our sample. Another possibility raised by several articles[6,32] is that ε4 carriers have a decreased acetylcholine synthetic capacity due to reductions in phospholipid transport. Studies of brain tissue showed lower choline acetyltransferase activity in normal elderly individuals who are ε4 carriers[33] as well as a lower concentration of acetylcholine in the synapses of older ε4 individuals.[34]

There are several limitations to this study. The effect of anticholinergic medications was measured by whether subjects had taken any such medications within the previous 24 hours,

without considering the number of anticholinergic medications, dosage, or the likelihood that a medication crossed the blood–brain barrier. Similarly, cerebrovascular disease was determined from the presence of stroke risk factors and not by magnetic resonance imaging evidence of actual cerebrovascular disease such as WMH or lacunes. Finally, this was not a double-blind study in which we administered a specific anticholinergic medication to randomly selected individuals from the 2 genotypes. Instead, these data were obtained from older volunteers who took part in 2 different cross-sectional studies, and the present analysis examined the preexisting relationship between anticholinergic medication use and performance. Thus, we cannot be certain that the anticholinergic drugs being taken by some ε4 carriers was the actual factor responsible for their poorer cognitive performance and their sleep and mood problems.

Study strengths lie in the evidence that cerebrovascular disease may not underlie the interactive effect that *APOE* genotype and anticholinergic medication use have on performance. The results also extend the observed number and type of measures for which there is evidence of a greater sensitivity of ε4 carriers to anticholinergic medications. Previous results focused on memory,[6,7] general mental function,[4,8] and self-rated mental speed.[7] The present study added to these a component of executive function (attention switching) as well as measures of mood and sleep, behavioral areas not previously shown to be differentially affected by anticholinergic medications in ε4 individuals. With respect to these latter results, it should be remembered that persons taking psychoactive medications including strong anticholinergic drugs such as imipramine and chlorpromazine were specifically excluded from the study, as was anyone with evidence of a clinically significant depression, factors that may have decreased the strength of the results found in the present analyses.

CONCLUSIONS

Overall, the present results are consistent with the hypothesis that anticholinergic drugs have a greater effect on performance in elderly individuals who carry 1 or more ε4 alleles of the *APOE* gene, even after controlling for the increased risk of cerebrovascular disease [PE6]present in ε4 carriers. This effect was not restricted to cognitive tasks, but also was present for measures of sleep and of depression, including both symptoms of mood and function. These results support the position that an interactive effect of anticholinergic medication use and *APOE* genotype may be an important source of between-person performance variability in the elderly population independent of the increased risk of cerebrovascular disease present in individuals carrying an *APOE* ε4 genotype.

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Table I

Characteristics of users and nonusers of antichohnergic medications.

	Non-ε4			ε4		
	Nonuser (n = 134)	**ACh User (n = 53)**	***P* Value**	**Nonuser (n = 36)**	**ACh User (n = 17)**	***P* Value**
Age	72.5 (4.0)	73.1 (4.3)	0.3006	73.4 (3.5)	72.7 (4.3)	0.5055
Years of education	14.7 (2.5)	15.5 (2.5)	0.0408	14.9 (2.5)	14.3 (2.2)	0.4290
Stroke risk, %	12.1 (9.6)	15.6 (11.2)	0.0315	11.5 (6.1)	20.9 (15.9)	0.0296
No. of anticholinergic medications	0	1.43 (0.82)	–	0	1.41 (0.62)	–

ACh = anticholinergic medication.

Values shown are mean (SD).[PE8]

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Table II

Performance effects [PE9] of anticholinergic drug use by *APOE* ε4 and non-ε4 carriers before and after adjusting for stroke risk.

	Anticholinergic Drug Use		Unadjusted		Adjusted for Stroke Risk	
	Nonuser, Mean (SD) or n (%)	**ACh User, Mean (SD) or n (%)**	**Nonuser vs. User, MD (SE) or OR (95% CI)**	***P* Value**	**Nonuser vs. User, MD (SE) or OR (95% CI)**	***P* Value**
APOE Non-ε4						
MMSE *	28.1 (1.5)	28.1 (1.6)	−0.03 (0.26)	0.9208	0.03 (0.26)	0.8926
TMT-A time, sec	34.7 (11.6)	36.7 11.8)	2.02 (1.86)	0.2790	1.46 (1.87)	0.4340
TMT-B time, sec †	85.2 (30.5)	79.1 (28.5)	−6.12 (5.18)	0.2383	−7.70 (5.19)	0.1390
TMT-B and -A time, sec †	51.0 (27.8)	42.4 (22.0)	−8.65 (4.62)	0.0626	−9.68 (4.65)	**0.0385** [PE10]
Gait speed, m/sec	1.08 (0.22)	1.11 (0.23)	0.04 (0.04)	0.3304	0.04 (0.04)	0.2430
PSQI *	4.6 (2.7)	4.9 (3.3)	0.33 (0.48)	0.4881	0.34 (0.49)	0.4856
GDS †	3.0 (3.2)	3.4 (3.4)	0.33 (0.54)	0.5408	0.16 (0.54)	0.7647
Motivation ≥2 †	54 (40.3)	16 (30.2)	0.64 (0.32–1.27)	0.1997	0.63 (0.32–1.26)	0.1909
Mood ≥1 *	29 (21.6)	18 (34.0)	1.86 (0.92–3.76)	0.0824	1.82(0.89–3.69)	0.0991
APOE ε4						
MMSE *	28.1 (1.7)	27.2 (1.6)	−0.96 (0.46)	0.0393	−0.80 (0.47)	0.0905
TMT-A time, sec	35.3 (10.5)	43.0 (11.5)	7.71 (3.38)	0.0232	6.24 (3.42)	0.0695
TMT-B time, sec †	81.0 (23.8)	116.2 (57.8)	35.22 (9.38)	**0.0002**	31.05 (9.50)	**0.0012**
TMT-B and -A time, sec †	45.7 (21.7)	73.2 (54.1)	27.50 (8.37)	**0.0012**	24.78 (8.52)	**0.0040**
Gait speed, m/sec	1.12 (0.21)	1.02 (0.22)	−0.09 (0.07)	0.1655	−00.07 (0.07)	0.2841
PSQI *	4.3 (2.7)	6.6 (3.9)	2.26 (0.90)	**0.0133**	2.27 (0.93)	**0.0148**
GDS †	1.9 (2.6)	5.7 (4.7)	3.79 (0.97)	**0.0001**	3.34 (0.99)	**0.0008**
Motivation ≥2 †	8 (22.2)	12 (70.6)	8.40 (2.28–31.01)	**0.0014**	8.12 (2.15–30.62)	**0.0020**
Mood ≥1 *	3 (8.3)	8 (47.1)	9.78 (2.14–44.61)	**0.0032**	9.13 (1.96–42.62)	**0.0049**

ACh = anticholinergic medication; GDS = Geriatric Depression Scale; MD = means difference; MMSE = Mini-Mental State Examination; OR = odds ratio; PSQI = Pittsburgh Sleep Quality Index; TMT = Trail Making Test.

* $0.05 \leq P < 0.10$.

† $P < 0.05$ for *APOE* × anticholinergic-drug use interaction (ie, comparing drug user – nonuser difference across *APOE* genotypes).