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Lorazepam challenge for individuals at varying genetic risk for Alzheimer's disease

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Abstract

INTRODUCTION—This study set out to clarify the differential acute cognitive impact of lorazepam based on varying genetic risk for Alzheimer's disease.

METHODS—Fifty-seven cognitively unimpaired individuals aged 51 to 88, genotyped according to apolipoprotein E (APOE) and translocase of outer mitochondrial membrane (TOMM40) poly-T lengths, completed cognitive testing before, 2.5 and 5 hours after receiving a 1 mg dose of lorazepam.

RESULTS—Post-lorazepam, there were significant ($P < 0.05$) declines from baseline in memory, psychomotor processing speed, and executive function. At 2.5 hours, the magnitude of this lorazepam-induced cognitive change was significantly greater in the APOE3/4 group than in the APOE3/3 group for tests of working memory and visuospatial memory/executive function. At 5 hours post-challenge, verbal memory and working memory deficits persisted in the APOE3/4 group compared to the APOE3/3 group. At 5 hours after lorazepam challenge, as compared to the VL/VL group, the S/S group performed slightly worse on a test of working memory ($P < 0.05$), but no other differences were observed among TOMM40 poly-T variant groups.

DISCUSSION—The lorazepam challenge may be unmasking pre-symptomatic cognitive dysfunction associated with APOE4 carriage.

Keywords

Apolipoprotein E; pre-symptomatic; Alzheimer's disease; lorazepam; executive function; memory

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Conflicts of Interest

P. Maruff is a full-time employee of Cogstate Ltd. B. Harel was a full-time employee of Cogstate Ltd during the data collection and initial data analysis. All other authors report no conflict of interest with this manuscript.

Trial registry: ClinicalTrials.gov Registration number: NCT01780519

URL: <https://clinicaltrials.gov/show/NCT01780519>

BACKGROUND

Carriage of the apolipoprotein E (APOE) 4 allele (e4) is associated with increased β -amyloid accumulation, greater preclinical cognitive decline and increased risk for clinical disease progression and dementia when compared to other APOE allelic variants¹. Carriage of APOE4 among cognitively normal (CN) older adults is associated with greater decline in verbal memory than e4 non-carriers², but there is no strong evidence for cognitive impairment in e4 carriers compared to non-carriers from studies using cross-sectional designs. However, we and others have shown that it is possible to amplify e4 specific cognitive impairment in CN older adults through utilization of pharmacological challenge. For example, Pomara and colleagues reported slower recovery from memory impairment induced by an acute dose of lorazepam (0.5 mg and 1 mg) in e4 carriers aged between 60 and 75 years compared to matched non-carriers³. We showed that an acute 2mg dose of lorazepam given to middle aged (i.e. 50–65 years) CN adults caused greater decline in verbal episodic memory and visuospatial memory/executive function in e4 carriers compared to non-carriers despite equivalent baseline performances⁴. Together these findings suggest that while e4 carriage in CN adults is not associated with cognitive impairment *per se*, deleterious effects of e4 on central nervous system (CNS) function are evident in the greater vulnerability to sedative drugs shown by e4 carriers. These data also show how acute pharmacological challenge may be used practically to study impending Alzheimer's disease (AD) risk in CN adults.

Recently it has been proposed that allelic variation in translocase of the outer mitochondrial membrane 40 homolog (TOMM40) may provide information about AD risk complementary to that provided by APOE^{5,6}. These variations of TOMM40 include short (S), long (L), and very long (VL) poly-T lengths, with APOE3/3 individuals having either an S/S, S/VL, or VL/VL poly-T repeats. Earlier studies indicated that APOE3/3 individuals with VL/VL developed AD earlier than individuals with shorter poly-T repeats⁵. A subgroup of APOE3/3 individuals with VL/VL TOMM40 poly-T lengths also showed decreased gray matter volume in the ventral posterior cingulate and medial ventral precuneus and reduced verbal memory compared to those APOE3/3 individuals with short TOMM40 poly-T lengths (S/S)⁷. Despite these early findings, the extent of risk conferred by TOMM40 for disease progression generally and for CNS dysfunction specifically remains unclear. For example, re-analyses of AD risk cohorts whose APOE4 status was known using TOMM40 classification showed age-related effects of TOMM40 VL/VL independent of APOE with the TOMM40 effect occurring before age 60 and the APOE effect occurring after age 60⁸. However, other studies have either failed to show any benefit of TOMM40 in explaining AD risk⁹ or have indicated opposite results with VL/VL decreasing rather than increasing AD risk¹⁰.

In this context, acute challenge with lorazepam may provide a means for determining the extent to which re-classification of APOE4 allelic variation according to TOMM40 lengths can improve estimates of CNS vulnerability in CN adults. To date, there has been one small study testing this hypothesis, where an acute 0.5 or 1mg lorazepam dose was administered to 8 older (aged 62–73) APOE3/3 adults with TOMM40 VL/VL and 6 with S/S¹¹. Lorazepam-

related decline in verbal memory from baseline was observed at 2.5 hours post dose for both 0.5 mg and 1 mg doses in both TOMM40 groups although the magnitude of decline for the long poly-T group was almost double that observed for the short poly-T group. The interaction with TOMM40 genotype detected at 2.5 hours after lorazepam challenge was not due to pharmacokinetic factors such as differences in plasma lorazepam concentrations. Thus, these preliminary findings suggest that poly-T variants of TOMM40 may modulate the negative effects of lorazepam on memory in cognitively unimpaired APOE3/3 older adults, independent of any influence from APOE4. However, the very small sample used in this study raises the concern that estimates of lorazepam-related cognitive impairment specific to TOMM40 may be unreliable. Support for this concern is found in conclusions drawn from other studies of APOE3/3 individuals that the VL/VL genotype conveys a low, not high, risk for AD, whereas S/VL and S/S genotypes increase risk for AD in individuals aged 76 and 77 years old respectively¹². Nevertheless, given the importance of this question and the reliability of the lorazepam challenge, further exploration of TOMM40 related CNS vulnerability is warranted. Therefore, the first aim of the current study was to establish the sensitivity of the lorazepam challenge in older adults according to their APOE4 status and identify aspects of cognition most sensitive to this challenge using a lower (1 mg) dose than our previous study. The second aim was to reclassify the sample according to TOMM40 risk variants and determine the extent to which these variants may be differentially sensitive to lorazepam-induced cognitive decline.

METHODS

Participants

Fifty-seven CN adults aged from 51 to 88, who had previously been APOE and TOMM40 genotyped as a part of our longitudinal study of aging^{13,14} participated in this study. All participants were from Maricopa County, most of whom reported having a first-degree relative with AD, denied memory concerns and were recruited through local newspaper advertisements. Participants understood that they would not receive information about their APOE and TOMM40 genotype and were screened using a complete medical history, a structured psychiatric interview for DSM III-R, a neurological examination, the Folstein Mini-Mental State Examination (MMSE)¹⁵, and the Hamilton Depression Rating Scale [HAM-D, 17 item version]¹⁶. Exclusion criteria were significant medical, psychiatric, or neurological illnesses, (e.g., impaired liver or kidney function, prior stroke, traumatic brain injury, memory impairment, cognitive impairment, parkinsonism, a lifetime history of schizophrenia, bipolar disorder, a psychoactive substance use disorder, or current major depression). For this study, participants with known allergy to benzodiazepines, current use (within the previous four weeks) of benzodiazepines or other medications known to interact with lorazepam, concurrent use of sedating antihistamines, or current use of stimulant medications were excluded. Inclusion criteria were a score of 28 or more on the Mini mental status examination (MMSE) and less than 10 on the Hamilton Depression Scale (Ham-D). All participants gave written informed consent and study protocols were approved by the Mayo Clinic institutional review board.

Outcome Measures

The main outcome measure was the Groton Maze Learning Test (GMLT)¹⁷ total errors, which measures visuospatial memory and executive function using a maze learning paradigm. In this task, the participant is shown a 10 × 10 grid of boxes on a computer screen. A 28-step pathway is hidden among these 100 possible locations. Each box represents move locations, and the grid refers to the box array (i.e., 10 × 10). Participants are required to find the hidden pathway guided by four search rules. These rules are: do not move diagonally, do not move more than one box (i.e., do not jump), do not move back on the pathway, and return to the last correct location after an error. At each step only the most recently selected box is shown. Feedback is given with visual and auditory cues (green check marks and red crosses) to indicate whether the selected box is correct or incorrect. The head of path, or the last correct location, flashes with a green check when two errors are made in succession (failing to return errors). There are 20 well-matched alternate pathways available. The primary outcome is total number of errors made in attempting to learn the same hidden pathway over five consecutive trials. A decomposition of the total errors results in a learning efficiency factor (exploratory errors), which reflects how efficiently individuals are able to learn the maze, and an error monitoring factor (rule break errors), which reflects how well an individual monitors performance while learning the maze¹⁷.

Secondary measures included tests of verbal memory (the Rey Auditory Verbal Learning Test (AVLT) long-term memory score, with alternate forms to reduce practice effect¹⁸), visual recognition memory (the One Card Learning Test (OCL)), working memory (the Two-Back Test (TBK)), and psychomotor processing speed (the Detection test (DET)). The OCL, TBK, and DET are computerized tests using playing card stimuli^{17,19} and, along with the GMLT, were selected because of their extensive use in psychopharmacological studies and demonstrated sensitivity to effects of benzodiazepines^{19–21}. In the DET, the playing cards are all red and black jokers. The participant is asked to press the **Yes** key as soon as the card in the center of the screen flips over. The primary outcome is speed of performance. In the OCL, the playing cards are identical to those found in a deck of playing cards with the exception of the joker. The participant is asked whether the card currently being presented in the center of the screen was seen previously in this task. The participant responds by pressing the **Yes** or **No** key. Because no card has been presented yet, the first response is always **No**. The primary outcome is accuracy of performance. In the TBK, the playing cards are identical to those found in a deck of playing cards with the exception of the joker. The participant is asked whether the card currently being presented is the same as the one presented two cards previously. The participant responds by pressing the **Yes** or **No** key. Because no card has been presented yet, the first response is always **No**. The primary outcome is accuracy of performance.

Study Procedure

Participants completed cognitive testing before receiving a 1 mg dose of lorazepam and 2.5 and 5 hours after administration. The level of somnolence was also assessed at each time point with a computerized 10-point Likert scale (from 1 for “I feel fast asleep” to 10 for “I feel fully awake”) for the question, “How sleepy are you feeling right now?”

Data Analysis

Demographics, baseline medical and psychiatric characteristics, and baseline cognitive outcome measures were compared between APOE 3/4 and 3/3 groups using two sample t-tests or Chi-square tests or Fisher's exact tests when appropriate. The same characteristics were compared among the five TOMM40 groups using ANOVA tests or Chi-square tests or Fisher's exact tests when appropriate. The cognitive scores between 2.5 hour and baseline for all the participants were compared using paired t-tests. The 2.5 hour and 5 hour cognitive scores were compared in groups (2 groups for APOE or 5 groups for TOMM40) using an ANCOVA model with age and baseline scores as covariates. All analyses were executed using SAS 9.4.

RESULTS

Sample characteristics

Baseline characteristics and demographics are summarized on Tables 1 and 2. Groups (APOE3/4 versus APOE 3/3; and S/S vs. S/L vs. S/VL vs. L/VL vs. VL/VL) were equivalent for age, sex, education, MMSE, HAM-D, somnolence, and baseline cognitive scores, although the APOE3/3 had a higher average BMI than the APOE3/4 group. When using non-parametric tests (Mann-Whitney), the difference in BMIs between groups was not statistically significant ($p=0.07$).

Effect of e4 carriage

At 2.5 hours after the 1 mg dose of lorazepam, the sample as a whole showed a statistically significant decline from baseline for measures of verbal memory, visual recognition memory, working memory, psychomotor processing speed, and visuospatial memory/executive function (Table 3). The magnitude of lorazepam-induced cognitive change was significantly greater in the APOE3/4 group than in the APOE3/3 group for tests of visuospatial memory/executive function ($p=0.03$, effect size=0.65) and working memory ($p=0.04$, effect size=0.59), but the decline was similar between groups for tests of verbal memory, visual recognition memory, and psychomotor processing speed (Figure 1, Table 4). A sub-analysis of GMLT total errors showed the effect was driven primarily by exploratory errors ($p=0.01$), i.e., learning efficiency, rather than the rule-break errors, i.e., error monitoring ($p=0.28$). At 5 hours after lorazepam challenge, we observed a trend for a persistent deficit in verbal memory and working memory scores for the APOE3/4 group compared to APOE 3/3 (verbal memory: $p=0.06$, effect size=0.53; working memory: $p=0.12$, effect size=0.44), whereas the visuospatial memory/executive function score was similar and largely returned to baseline (Figure 1).

Effect of TOMM40

Results of the VL/VL and S/S comparison are shown in Table 5. At 5 hours after lorazepam challenge, as compared to the VL/VL group, the S/S group performed slightly worse on the TBK ($p=0.03$, effect size=1.11). Otherwise, there were no differences observed among individual TOMM40 poly-T variant groups, nor combination grouping by S/S+S/L vs. L/VL

+VL/VL; S/L+S/VL vs. VL/VL; S/S+S/L vs. L/VL+VL/VL; S/L vs. L/VL; S/S+S/VL vs. S/L+L/VL+VL/VL, or S/VL+S/S vs. VL/VL (data not shown).

DISCUSSION

In this study, which differed from our previous study by using a lower dose (1 mg) lorazepam challenge and a slightly older population, we replicated our previous findings of significant declines in memory, working memory, psychomotor processing speed, and executive function in response to the lorazepam challenge among individuals who were cognitively unimpaired at baseline. We again found a greater decline on a test of visuospatial memory and executive function as measured by the GMLT at 2.5 hours post-lorazepam in APOE3/4 carriers than APOE3/3 carriers. We also found a greater decline in working memory as measured by the TBK in the APOE3/4 group than the APOE3/3 group at 2.5 hours post-lorazepam. In contrast to our previous study, we did not find an effect of lorazepam on verbal memory as measured by AVLTL at 2.5 hours post-lorazepam challenge, but we did see a moderate effect of the drug 5 hours post dose, with the e4 group appearing to show a persistent memory deficit compared to the APOE3/3 group. The differential effect in episodic memory performance at 5 hours is consistent with that reported by Pomara and colleagues, who tested a group of similarly aged APOE e4 carriers and e4 non-carriers with a 1 mg lorazepam challenge³. We were, however, unable to replicate the results of a more recent study by Pomara and colleagues¹¹ that showed increased memory impairment in TOMM40 VL/VL carriers compared to S/S individuals at 2.5 hours after a 1mg dose lorazepam challenge. If anything, in our study the S/S subgroup performed slightly worse than VL/VL subgroup at 5 hours post-lorazepam challenge.

The GMLT may be particularly sensitive to disruptions in learning occurring early in AD. In a study comparing the performance on GMLT between cognitively normal individuals and those with amnesic Mild Cognitive Impairment (aMCI), the aMCI group showed a substantially less steep learning curve from the first to second learning trial of the maze²². Others have shown that worse GMLT scores correlate ($p=0.001$) with smaller hippocampal volumes in cognitively normal individuals and a trend for correlation of hippocampal volume with AVLTL ($p=.06$)²³. In replicating our previous results with GMLT in response to lorazepam among cognitively normal individuals⁴, this study provides further evidence that the GMLT may be a sensitive test when used with a lorazepam challenge to differentiate those cognitively unimpaired individuals who are at greater risk for AD. Additionally, the fact that the effect on the GMLT was driven primarily by exploratory errors (i.e., learning efficiency) suggests that the lorazepam-induced cognitive dysfunction in cognitively unimpaired individuals at greater risk for AD might, in part, be mediated by disruptions in learning similar to those seen early in AD.

While it is difficult to find cross-sectional associations with amyloid and cognitive test scores²³, the combination of A β and APOE4 has been associated with longitudinal cognitive decline in preclinical AD²⁴. β -amyloid deposition has also been associated with decreased prefrontal fMRI activation with greater working memory loads in cognitively unimpaired elderly²⁵. We had amyloid imaging in 12 of the 57 study participants, and, not surprisingly, in this subset we found significantly greater amyloid uptake in the APOE3/4 than APOE3/3

individuals. Others have examined CSF levels of A-beta associations with APOE4 and TOMM40 variants, demonstrating significant reductions in A-beta 1–42 levels in APOE4 carriers compared to non-e4 carriers and no such differences across TOMM40 variants²⁶. Our findings suggest that the low dose lorazepam challenge may be unmasking occult disease associated β -amyloid deposition in frontal lobes, which is more closely associated with APOE4 carriage than TOMM40 poly-T variants; this may be disrupting frontal-hippocampal circuits that underlie working memory and episodic memory^{27,28}.

One other important issue arising from this study is that lorazepam is often prescribed to elderly individuals²⁹, and benzodiazepines may increase risk for dementia³⁰, though the data on benzodiazepine and risk of dementia is conflicting^{31,32}. While this study did not address long-term impact, our results are consistent with the view that even short-term use of lorazepam could unmask cognitive difficulties in at-risk individuals. For example, when the AVLT scores are translated into age-normed scores, the average baseline scores for the group as a whole are high end of average, while the scores at 2.5 hours post-lorazepam challenge reflect a 1.3 SD decline to low end of average, which is a clinically significant difference. Clinicians should therefore weigh the benefit of reducing anxiety symptoms against the risk of worsening cognitive function in elderly who are at highest risk of AD, particularly if the anxiety being treated is in response to subtle cognitive decline.

Pharmacogenomics testing is increasingly used to guide medication selection³³. Further study specifically designed to compare prescribing practices and patient outcomes of providers who did or did not know the patients' APOE genotype is needed to determine whether APOE4 genotyping would be useful in guiding physicians away from prescribing benzodiazepines in at risk patients. Conversely, if a CN patient does experience substantial cognitive problems in response to benzodiazepines, it may warrant further diagnostic evaluation. APOE testing is not currently recommended in CN individuals³⁴, in part because there are no currently approved medical interventions to reverse the disease. More importantly, APOE4 carriers are not certain to develop dementia, nor are e4 noncarriers necessarily protected from it. Unfortunately, the public often misunderstand how to interpret the risk associated with APOE genotyping³⁵, which may increase the chance for unintended consequences of gaining such information³⁶. Therefore, we are not specifically recommending genotyping in the evaluation of a CN individual who experiences cognitive impairment brought on by benzodiazepines, but, depending on the clinical circumstances and confirmation of our results with a larger study, a standard evaluation, closer monitoring of cognition over time, avoidance of ongoing use of benzodiazepines and encouragement of healthy lifestyle changes may be appropriate.

We did not employ a placebo control in this study, because the previous studies^{3,4,11} all showed a clear separation from placebo, our participants were not aware of their genotype, and the primary comparison was between genotypes. Nonetheless, the lack of placebo is a limitation of this study as it is possible that a differential effect between genotypes could also occur in the placebo condition. We also did not measure blood levels of lorazepam, so we do not know whether some of the effects were due to differences in metabolism or possibly associated with differences in BMI. However, there was no difference in BMI between e4 carriers and non-carriers with our previous study that showed similar results⁴,

and others have previously demonstrated that the interaction of genotype and lorazepam challenge had no associations with plasma lorazepam concentrations^{3,11}. Finally, this study is limited by its small sample size. The power to detect differences between the TOMM40 poly-T variant groups may have been insufficient given our small numbers in each of those groups, particularly since we did not have the power to separate those older than 76 years. We also may not have had sufficient power to detect differences in verbal memory between the APOE3/4 and APOE3/3 groups. After adjusting for multiple comparisons by controlling false discovery rate (FDR) at 0.05 level, the significant results in decline from baseline for measures of verbal memory, visual recognition memory, working memory, psychomotor processing speed, and visuospatial memory/executive function for the group as a whole as depicted in Table 3 still hold. However, likely due to the small sample size of this study, the significant results in the APOE (Table 4) and TOMM40 (Table 5) group differences will not hold up to multiple comparisons. Given that the effect sizes for the significant results in Table 4 and Table 5 are moderate to large (from 0.59 to 1.11), the difference between groups may still be clinically meaningful, but clearly further study with sufficient sample size to confirm the findings is needed.

In conclusion, lorazepam challenge is associated with acutely worsened cognition in all participants regardless of genotype, and working memory and visuospatial memory and executive function decline is more pronounced in APOE4 carriers than e4 non-carriers. The relative lack of differences in the TOMM40 poly-T variant groups may be due to lack of power and/or less of an association of TOMM40 allelic variations with amyloid pathology than APOE4. Next steps would ideally include a placebo controlled randomized trial stratified by the pertinent genotypes with sufficient sample size to account for multiple outcomes and comparisons.

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Figure 1. APOE3/3 and APOE3/4 Comparison of Outcome Measures at Baseline, 2.5 Hours, and 5 Hours after Lorazepam Challenge

Baseline scores were adjusted for age; 2.5 hour and 5 hour scores were adjusted for baseline score and age.

AVLT LTM=Rey Auditory Verbal Learning Test, Long-Term Memory Score;

GMLT=Groton Maze Learning Test; DET= Detection Test; OCL=One Card Learning Test;

TBK=Two-Back Test

Table 1

APOE3/4 and APOE3/3 Comparison of Baseline Demographics and Outcome Measures

Variable	APOE3/4 N=20	APOE3/3 N=37	P Value
	Mean (SD)		
Age, years	68.8 (8.7)	70.8 (7.0)	0.34
Education, years	16.1 (2.4)	16.2 (2.4)	0.96
Height, cm	164.6 (9.1)	165.4 (8.1)	0.75
Weight, kg	66 (11)	76 (18)	0.04
BMI, kg/m ²	24.5 (3.3)	27.6 (5.8)	0.03
MMSE (0–30)	29.80 (0.41)	29.76 (0.55)	0.76
HAM-D (0–50)	2.05 (0.22)	2.11 (0.66)	0.7
Female, n (%)	17 (85)	28 (76)	0.51
Baseline AVLT LTM	9.6 (3.1)	9.1 (3.3)	0.58
Baseline somnolence score	9.3 (1.1)	9.2 (1.4)	0.87
Baseline GMLT total errors	55 (21)	63 (22)	0.17
Baseline DET	2.55 (0.10)	2.60 (0.09)	0.08
Baseline OCL	0.97 (0.10)	0.97 (0.10)	0.86
Baseline TBK	1.26 (0.20)	1.23 (0.16)	0.54

BMI=Body Mass Index; MMSE=Folstein Mini-Mental State Exam; HAM-D=Hamilton Depression Scale; AVLT LTM=Rey Auditory Verbal Learning Test, Long-Term Memory Score; GMLT=Groton Maze Learning Test; DET=Detection Test; OCL=One Card Learning Test; TBK=Two-Back Test

Table 2

TOMM40 Subgroup Comparison of Baseline Demographics and Outcome Measures

Variable	S/S N=8	S/L N=12	S/VL N=16	L/VL N=8	VL/VL N=12	P Value
	Mean (SD)					
Age, years	70.7 (6.7)	69.7 (9.7)	68.2 (7.2)	67.4 (7.3)	74.5 (5.8)	0.19
Education, years	16.1 (3.2)	16.9 (1.9)	16.4 (1.9)	15.0 (2.6)	16.1 (2.5)	0.53
Height, cm	165.4 (10.0)	163.5 (7.7)	166.4 (8.3)	166.4 (11.1)	163.8 (7.3)	0.88
Weight, kg	77.6 (22.2)	64.4 (9.4)	75.0 (16.0)	69.5 (13.9)	75.8 (20.1)	0.33
BMI, kg/m ²	28.2 (6.9)	24.1 (2.8)	27.1 (5.2)	25.0 (4.2)	28.1 (6.4)	0.27
MMSE (0–30)	29.88 (0.35)	29.92 (0.29)	29.69 (0.70)	29.63 (0.52)	29.75 (0.45)	0.67
HAM-D (0–50)	2.25 (0.71)	2.08 (0.29)	1.88 (0.50)	2.00 (0.00)	2.42 (0.67)	0.08
Female, n (%)	6 (75)	11 (92)	11 (69)	6 (75)	10 (83)	0.66
Baseline AVLT LTM	8.4 (2.4)	9.6 (3.4)	9.8 (4.0)	9.5 (2.8)	8.5 (3.0)	0.77
Baseline somnolence score	9.25 (1.04)	9.42 (0.90)	8.94 (1.73)	9.00 (1.41)	9.42 (1.08)	0.83
Baseline GMLT total errors	71 (22)	56 (26)	58 (24)	53 (12)	66 (20)	0.37
Baseline DET	2.61 (0.12)	2.52 (0.10)	2.61 (0.07)	2.59 (0.10)	2.58 (0.09)	0.12
Baseline OCL	1.00 (0.08)	1.00 (0.10)	0.98 (0.11)	0.93 (0.08)	0.94 (0.11)	0.39
Baseline TBK	1.30 (0.14)	1.31 (0.21)	1.23 (0.11)	1.17 (0.17)	1.16 (0.20)	0.12

BMI=Body Mass Index; MMSE=Folstein Mini-Mental State Exam; HAM-D=Hamilton Depression Scale; AVLT LTM=Rey Auditory Verbal Learning Test, Long-Term Memory Score; GMLT=Groton Maze Learning Test; DET=Detection Test; OCL=One Card Learning Test; TBK=Two-Back Test

Table 3

Overall Change From Baseline at 2.5 Hours After Lorazepam Challenge

Variable	Baseline	2.5 Hour	Difference	95% CI	P Value
	n=57				
	Mean (SD)				
AVLT LTM	9.2 (3.2)	5.0 (4.1)	-4.2 (3.6)	-5.2 to -3.2	<.001
GMLT total errors	60.1 (22.2)	70.7 (36.8)	10.6 (26.5)	3.5 to 17.6	0.004
DET	2.58 (0.10)	2.60 (0.10)	0.02 (0.06)	0.01 to 0.04	0.006
OCL	0.97 (0.10)	0.88 (0.09)	-0.09 (0.09)	-0.11 to -0.07	<.001
TBK	1.24 (0.17)	1.11 (0.22)	-0.13 (0.16)	-0.17 to -0.09	<.001

AVLT LTM=Rey Auditory Verbal Learning Test, Long-Term Memory Score; GMLT=Groton Maze Learning Test; DET=Detection Test; OCL=One Card Learning Test; TBK=Two-Back Test

Table 4

APOE3/4 and APOE 3/3 Comparison of Outcomes at 2.5 and 5 Hours*

Variable		APOE3/4 (n=20)	APOE3/3 (n=37)	Difference (95% CI)	P Value	Effect Size
		Adjusted Mean (SE)				
Somnolence score	2.5 hour	6.5 (0.38)	7.2 (0.28)	-0.7 (-1.6 to 0.3)	0.16	0.39
	5 hour	7.4 (0.44)	8.0 (0.32)	-0.5 (-1.6 to 0.6)	0.35	0.26
AVLT LTM	2.5 hour	4.8 (0.79)	5.2 (0.58)	-0.4 (-2.3 to 1.6)	0.71	0.11
	5 hour	5.2 (0.60)	6.6 (0.44)	-1.4 (-2.9 to 0.1)	0.06	0.53
GMILT total errors	2.5 hour	81.3 (5.66)	64.9 (4.14)	16.4 (2.2 to 30.5)	0.03	0.65
	5 hour	64.7 (3.51)	62.6 (2.57)	2.1 (-6.7 to 10.9)	0.63	0.14
DET	2.5 hour	2.6 (0.01)	2.6 (0.01)	0.00 (-0.04 to 0.03)	0.77	0.08
	5 hour	2.6 (0.01)	2.6 (0.01)	-0.01 (-0.04 to 0.01)	0.3	0.3
OCL	2.5 hour	0.88 (0.02)	0.88 (0.01)	0.00 (-0.03 to 0.04)	0.83	0.06
	5 hour	0.90 (0.02)	0.92 (0.01)	-0.02 (-0.06 to 0.02)	0.38	0.25
TBK	2.5 hour	1.0 (0.03)	1.1 (0.02)	-0.09 (-0.17 to -0.01)	0.04	0.59
	5 hour	1.1 (0.03)	1.2 (0.03)	-0.07 (-0.16 to 0.02)	0.12	0.44

* Adjusted for baseline score and age

AVLT LTM=Rey Auditory Verbal Learning Test, Long-Term Memory Score; GMLT=Groton Maze Learning Test; DET = Detection test; OCL=One Card Learning Test; TBK=Two-Back Test

Table 5

TOMM40 VL/VL and S/S Comparison of Outcomes at 2.5 and 5 Hours*

Variable		TOMM40 S/S (n=8)	TOMM40 VL/VL (n=12)	Difference (95% CI)	P Value	Effect Size
		Adjusted Mean (SE)				
Somnolence score	2.5 hour	7.0 (0.70)	6.8 (0.57)	0.2 (-1.7 to 2.2)	0.81	0.11
	5 hour	7.9 (0.79)	8.0 (0.64)	-0.04 (-2.3 to 2.2)	0.97	0.02
AVLT LTM	2.5 hour	4.6 (1.21)	3.9 (0.98)	0.7 (-2.7 to 4.0)	0.69	0.19
	5 hour	5.3 (0.91)	6.1 (0.74)	-0.9 (-3.4 to 1.7)	0.49	0.33
GMLT total errors	2.5 hour	74.6 (11.57)	77.4 (9.32)	-2.8 (-35.3 to 29.7)	0.86	0.09
	5 hour	72.9 (5.52)	66.1 (4.44)	6.8 (-8.7 to 22.4)	0.36	0.44
DET	2.5 hour	2.6 (0.02)	2.6 (0.02)	-0.0 (-0.1 to 0.1)	0.78	0.14
	5 hour	2.6 (0.02)	2.6 (0.01)	-0.0 (-0.1 to 0.0)	0.65	0.22
OCL	2.5 hour	0.83 (0.01)	0.86 (0.01)	-0.03 (-0.07 to 0.00)	0.08	0.87
	5 hour	0.86 (0.03)	0.90 (0.03)	-0.04 (-0.13 to 0.06)	0.41	0.4
TBK	2.5 hour	1.0 (0.06)	1.1 (0.05)	-0.02 (-0.19 to 0.15)	0.83	0.11
	5 hour	1.1 (0.05)	1.2 (0.04)	-0.14 (-0.27 to -0.01)	0.03	1.11

* Adjusted for baseline score and age

AVLT LTM=Rey Auditory Verbal Learning Test, Long-Term Memory Score; GMLT=Groton Maze Learning Test; DET= Detection Test; OCL=One Card Learning Test; TBK=Two-Back Test