Double-Blind Crossover Study of the Cognitive Effects of Lorazepam in Healthy Apolipoprotein E (*APOE*)-ε4 Carriers

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Objective: To examine cognitive effects of pharmacologically induced somnolence in cognitively normal carriers and noncarriers of the apolipoprotein E (*APOE*)-ε4 allele, a common Alzheimer's disease susceptibility gene.

Method: Between December 2005 and July 2007, healthy and cognitively normal carriers of the *APOE*-ε4 allele (heterozygotes; n = 18) and noncarriers (n = 18), 50 to 65 years old, participated in a double-blind crossover study of cognitive function before, 2.5 hours after, and 5 hours after administration of 2 mg oral lorazepam or placebo. Main outcome measures included the Groton Maze Learning Test (GMLT) for executive functioning and visuospatial working memory, the Rey Auditory-Verbal Learning Test (AVLT) for verbal memory, and the one-back test for attention and simple working memory.

Results: At 2.5 hours after lorazepam administration, GMLT total errors score ($P = .04$), AVLT long-term memory ($P = .01$), and AVLT percent recall ($P = .005$) reflected worse performance in heterozygotes. By multivariate analysis, the combined set of all 6 measures for heterozygotes versus noncarriers yielded $P = .003$ for 2.5 hours and $P = .58$ for 5 hours. No differences were observed for somnolence, speed, attention, or simple working memory at any time points.

Conclusions: Despite comparable levels of associated somnolence, lorazepam appears to diminish verbal and visuospatial memory more in healthy late–middle-aged heterozygotes than in noncarriers, whereas attention and reaction time are similarly affected in both. Additional studies are needed to determine whether substantial lorazepam-induced memory detriments predict subsequent onset of cognitive decline and conversion to mild cognitive impairment or Alzheimer's disease. Clinicians should be aware of the potential for cognitive decline with lorazepam in healthy late–middle-aged individuals, especially those at a higher risk for Alzheimer's disease.

Trial Registration: clinicaltrials.gov Identifier: NCT00586430

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Benzodiazepines are frequently prescribed in the elderly,[1,2] yet their use can worsen cognition in persons aged 65 and older[3–5] and may affect daily functioning.[5] The general wisdom is to minimize their use in Alzheimer's disease patients. Less is known of the risk in persons 50 to 65 years of age, particularly the 25% of individuals with the apolipoprotein E (*APOE*)-ε4 allele[6]—a major risk factor for Alzheimer's disease.[7]

Cognitively normal *APOE*-ε4 heterozygotes and homozygotes have reduced glucose metabolism in the same brain regions as patients with probable Alzheimer's disease compared with *APOE*-ε4 noncarriers[8]; greater and possibly compensatory activation of brain regions than those in noncarriers during certain cognitive tests in functional magnetic resonance imaging studies[9–13]; and slower recovery from brain injury than noncarriers.[14] Previously, we found that subjective ratings of daytime somnolence were correlated with worse verbal memory scores in homozygotes, significantly more than in noncarriers ($P < .05$).[15] Pomara and colleagues[16] compared verbal memory in cognitively normal heterozygotes aged 60 to 70 years and in noncarriers at 2.5 and 5 hours postchallenge with 1 mg lorazepam. At 5 hours, lorazepam-induced memory deficits recovered more slowly in heterozygotes than in noncarriers, particularly among those with lower baseline scores.

If a single dose of lorazepam exposes neuropsychological deficits in at-risk individuals, then this effect might be clinically relevant in 2 ways. First, it could alert clinicians to the potential for amplified cognitive problems with benzodiazepines in heterozygotes. Second, it could be applied to a pharmacologic challenge to predict subsequent conversion to mild cognitive impairment and Alzheimer's disease.

To extend the findings of Pomara et al,[16] we investigated the effects of a 2-mg lorazepam challenge in cognitively normal adults (50–65 years old) and in domains affected by preclinical and early Alzheimer's disease.[17–20] We selected tests with minimal practice effects that are thought to reflect functional integrity of hippocampal and frontal areas. Because somnolence universally impairs psychomotor

speed and attention, we did not expect measures of speed or attention to differentiate the 2 groups.

METHOD

Between December 2005 and July 2007, 18 heterozygotes, all ε3/ε4 genotype, and 18 noncarriers, all ε3/ε3 or ε2/ε3 genotype, were drawn from an ongoing longitudinal aging study of cognitively normal adults.[21] Each heterozygote was matched to a noncarrier by age (mean [SD] difference between matched pairs = 2.6 [2.5] years) and education (mean [SD] difference between matched pairs = 1.2 [2.4] years). We excluded persons with clinically significant medical, psychiatric, or neurologic illness; benzodiazepine use within the previous 4 weeks; or current use of sedating antihistamines. Inclusion criteria were a score of ≥ 28 on the Mini-Mental State Examination (MMSE)[22] and a score of < 10 on the 15-item Hamilton Rating Scale for Depression (HAM-D).[23] We recorded body mass index (kg/m^2) and use of psychotropic medications, caffeine, or cigarettes. Genetic determination of *APOE* genotype was performed using a polymerase chain reaction–based assay,[24] for which participants understood that they would not receive results. All individuals gave their written informed consent, and the study was approved by the Mayo Clinic Institutional Review Board.

Participants were tested at the same time of day: before, 2.5 hours after, and 5 hours after oral administration of either 2 mg lorazepam or placebo in a double-blind crossover design. Subjects in each group were randomly assigned to lorazepam or placebo at the first visit; they returned for the second visit within 4 weeks (mean [SD] interval between visits = 17.6 [7.7] days). Baseline testing included the Groton Maze Learning Test (GMLT),[25] the Rey Auditory-Verbal Learning Test (AVLT),[26] the one-back test,[27] a simple reaction time task (SRT; CogState Ltd, Melbourne, Australia [www.cogstate.com]),[28] and the Profile of Mood States (POMS).[29] Somnolence was assessed 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?" (provided by CogState Ltd, Melbourne, Australia). After receiving either lorazepam or placebo, subjects repeated the somnolence rating and alternate versions of the GMLT, AVLT, one-back test, and SRT at 2.5 hours and 5 hours. A computer malfunction prevented the recording of complete data for 2 heterozygote and noncarrier pairs.

The GMLT assesses visuospatial working memory, error monitoring, information processing speed, and short-term delayed recall for a complex hidden maze. Repeated administration has previously demonstrated minimal practice effect.[25] Subjects are familiarized with the task during 2 untimed practice tests, and once the tester is confident that the subject understands the rules and can move easily around the grid, the timed test is administered. In each of the 5 successive trials of the GMLT exam, the subject is asked to learn to navigate his or her way around a 28-step maze that is hidden beneath a 10 × 10 grid of squares on the computer touch screen. For each trial, the time to completion, number of correct moves, number of wrong moves, and the number of perseverative errors are recorded. Two primary summary scores are obtained: (1) the mean number of correct moves per second, averaged over the 5 learning trials: a measure of information processing speed, and (2) the mean number of errors made over the 5 trials: a measure of accuracy for performance on this spatial working-memory task. Following a 10-minute delay interval, subjects complete a single delayed recall trial to generate measures of delayed recall performance and total errors.

The AVLT, a verbal memory test, is a 15-word list presented over 5 learning trials. After each presentation, the subject immediately repeats as many words as possible, then does so again after 30 minutes, which is the "long-term memory" score. "Percent recall" is long-term memory divided by learning trial 5. The "learning over trials" score reflects the increment in words repeated over the 5 successive learning trials. Six equivalent alternate forms of the AVLT[30] were randomly assigned to each subject.

The one-back test is a task of attention and simple working memory. We used a computer-generated version (CogState Ltd, Melbourne, Australia) that randomly assigns alternate forms; participants viewed a sequence of playing cards presented several seconds apart and decided whether each card matched the previous one. The SRT is a measure of attention that is not dependent on memory. The POMS is a self-report measure of transient affective states.

Baseline characteristics were assessed using the paired *t* test or the McNemar test. Changes from baseline were assessed with the paired *t* test. Impairment due to lorazepam was calculated by subtracting the test scores during the placebo period from the corresponding scores during the lorazepam period. The interaction between genotype and lorazepam was tested using a general linear model with terms for genotype, lorazepam, and matched strata. A multivariate analysis of variance of all 6 outcome measures, stratified by matched pairs, was used to compare lorazepam effects among heterozygotes and noncarriers at each time point.

RESULTS

Baseline characteristics of the 2 groups are outlined in Table 1. The mean HAM-D score was less than 2 in both groups. The POMS scores and use of medications and supplements did not differ substantially between heterozygotes and noncarriers. Mean POMS scores of heterozygotes were within 3 points of noncarriers (data not shown). Compared with noncarriers, heterozygotes had 1 more subject using psychotropic medication, 3 fewer using nonsteroidal anti-inflammatory drugs, 1 fewer using hormone replacement therapy, an equal number using statins, and 3 fewer using vitamin E (data not shown).

Table 1. Baseline Characteristics of Apolipoprotein E (*APOE*)-ε4 Carriers and Noncarriers[a]

Variable	*APOE*-ε4 Carriers (n = 18)	*APOE*-ε4 Noncarriers (n = 18)	*P* Value
Age, y	59.5 ± 4.7	62.1 ± 3.6	…[b]
Years of education	16.0 ± 2.1	14.8 ± 1.8	…[b]
Female sex, n (%)	12 (67)	14 (78)	.50
Body mass index, kg/m^2	28.4 ± 6.9	26.5 ± 6.2	.44
Family history (≥ 1 parent with AD), n (%)	15 (83)	11 (61)	.22
Mini-Mental State Examination score	30.00 ± 0.00	29.94 ± 0.24	.33

[a]Values are mean ± SD unless indicated otherwise.
[b]*P* value is not applicable because age and years of education were matched.
Abbreviation: AD = Alzheimer's disease.

Table 2. Comparison of Mean Lorazepam Effect on Somnolence, Speed, and Attention in Apolipoprotein E (*APOE*)-ε4 Carriers and Noncarriers

				APOE-ε4 Carriers			*APOE*-ε4 Noncarriers			ΔHeterozygotes –
Test	No. of Pairs	95% CI	*P* Value	Lorazepam	Placebo	ΔHeterozygotes	Lorazepam	Placebo	ΔNoncarriers	ΔNoncarriers (SD)
Groton Maze Learning Test timed-chase correct moves, no.										
2.5 h	17	−6.0 to 5.0	.83	34	44	−10	31	41	−10	0 (11)
5 h	17	−9.0 to 10.0	.90	37	42	−5	36	41	−5	0 (18)
Somnolence rating score										
2.5 h	17	−3.1 to 0.8	.24	3.5	1.2	2.3	3.9	0.5	3.4	−1.1 (3.8)
5 h	15	−4.0 to 0.3	.09	2.7	1.9	0.8	3	0.3	2.7	−1.9 (3.9)
Simple reaction time task score										
2.5 h	16	−0.1 to 0.1	.77	2.6	2.5	0.1	2.6	2.5	0.1	0.0 (0.15)
5 h	15	−0.1 to 0.04	.44	2.5	2.5	0.0	2.5	2.5	0.0	0.0 (0.10)

Symbol: Δ = change from placebo condition.

Baseline scores of the 6 outcome measures for heterozygotes were approximately equal (within 5%) to those for noncarriers. We found significant somnolence and impaired performance compared with placebo 2.5 hours after lorazepam administration for all measures except the one-back test ($P = .12$) in heterozygotes and the GMLT total errors ($P = .06$) and AVLT learning over trials ($P = .19$) tests in noncarriers.

Comparison of combined group measures during the placebo condition at baseline and after 5 hours suggests no clear evidence of practice effect. Rather, subjects had significant declines in AVLT long-term memory ($P < .001$) and percent recall ($P < .001$) at 5 hours compared with baseline, whereas the GMLT total errors score did not change significantly (95% CI = −9 to 1; data not shown). No significant differences between heterozygotes and noncarriers were observed for any measure during the placebo condition (data not shown).

As predicted, heterozygotes and noncarriers did not differ significantly in postlorazepam ratings of visuomotor speed, somnolence, and reaction times (Table 2). Ratings were similar for GMLT timed chase correct moves scores (measuring visuomotor speed before presentation of the hidden maze), somnolence scores, and SRT scores.

Significant differences in impairment due to lorazepam were apparent between heterozygotes and noncarriers for GMLT total errors, AVLT long-term memory, and AVLT percent recall scores at 2.5 hours (Table 3). The multivariate analysis of variance for all 6 measures for heterozygotes versus noncarriers yielded $P = .003$ for 2.5 hours and $P = .58$ for 5 hours. Among individual measures, the effect of lorazepam on the GMLT maze efficiency index or the one-back test did not differ significantly between heterozygotes and noncarriers. Figure 1 outlines the change from baseline to 2.5 hours and 5 hours for the GMLT total errors score; Figure 2 illustrates those changes for the AVLT percent recall score. Figures 3 and 4 compare individual matched pairs at 2.5 hours on both tests.

DISCUSSION

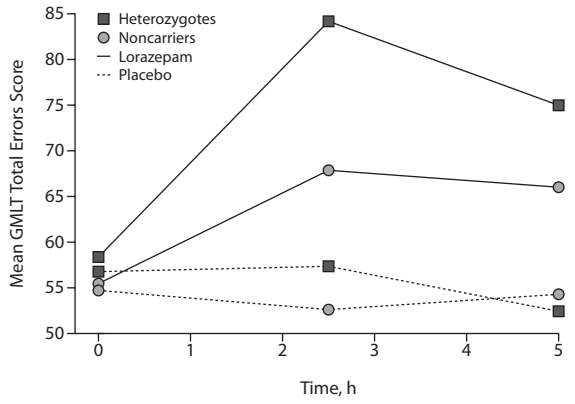
We found that a 2-mg oral dose of lorazepam produced significant declines in both groups in attention, reaction time, and memory. However, a differential effect of genotype was apparent only in visuospatial working memory (GMLT total errors score) and long-term verbal memory (AVLT long-term memory and percent recall). We did not observe a similar differential effect on measures of attention and speed. The GMLT total errors score largely measures error monitoring and working memory.[25] The AVLT long-term memory score is sensitive to the mild memory deficits occurring in the transition from presymptomatic memory decline[31] to mild cognitive impairment and from mild cognitive impairment to early Alzheimer's disease.[32] Larger studies are needed to confirm these results, but our findings indicate that medications known to impair alertness and cognition will have a greater impact on memory in heterozygotes than in noncarriers. Although a demonstrated effect of lorazepam was somnolence, we did not study whether it was the somnolence or some other effect of lorazepam interacting

Table 3. Comparison of Mean Lorazepam Effect on Main Outcome Measures in Apolipoprotein E (*APOE*)-ε4 Carriers and Noncarriers

				APOE-ε4 Carriers			*APOE*-ε4 Noncarriers			ΔHeterozygotes –
Test	No. of Pairs	95% CI	*P* Value	Lorazepam	Placebo	ΔHeterozygotes	Lorazepam	Placebo	ΔNoncarriers	ΔNoncarriers (SD)
Groton Maze Learning Test total errors score										
2.5 h	16	1 to 25	.04	84	59	25	65	53	12	13 (23)
5 h	17	−5 to 27	.17	75	52	23	66	54	12	11 (31)
Groton Maze Learning Test maze efficiency index										
2.5 h	16	−2.6 to 2.4	.93	58	61	−3	58	61	−3	0 (4.8)
5 h	17	−3.9 to 2.1	.54	59	63	−4	58	61	−3	−1 (5.9)
Rey Auditory-Verbal Learning Test long-term memory score										
2.5 h	18	−5.4 to −0.7	.01	1.3	8.8	−7.5	2.9	7.3	−4.4	−3.1 (4.7)
5 h	18	−2.6 to 3.4	.79	3.5	7.0	−3.5	3.2	7.1	−3.9	0.4 (6.1)
Rey Auditory-Verbal Learning Test percent recall										
2.5 h	18	−44 to −9	.005	13	70	−57	27	56	−29	−28 (35)
5 h	18	−18 to 31	.59	36	59	−23	27	56	−29	6 (50)
Rey Auditory-Verbal Learning Test learning over trials score										
2.5 h	18	−10 to 2	.21	10	17	−7	12	15	−3	−4 (12)
5 h	18	−3.3 to 4.9	.67	11	16	−5	11	17	−6	1 (8.3)
One-back test score										
2.5 h	17	−2 to 19	.09	89	92	−3	84	96	−12	9 (20)
5 h	15	−8 to 9	.91	89	95	−6	90	96	−6	0 (15)

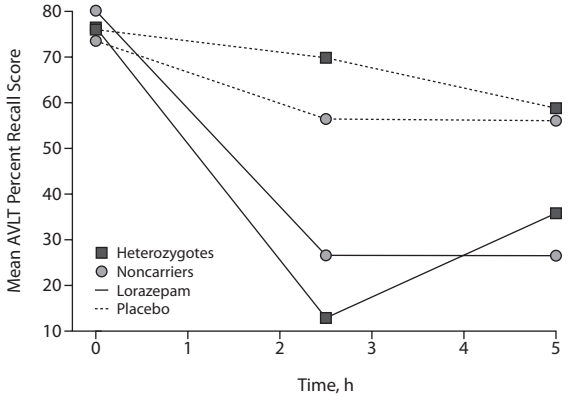
Symbol: Δ = change from placebo condition.

Figure 1. Mean Groton Maze Learning Test (GMLT) Total Errors Score Over Time[a]



[a]Higher scores indicate worse performance. Apolipoprotein E (*APOE*)-ε4 carriers (heterozygotes) performed significantly worse ($P = .04$) than noncarriers at 2.5 hours after administration of lorazepam.

Figure 2. Mean Rey Auditory-Verbal Learning Test (AVLT) Percent Recall Score Over Time[a]

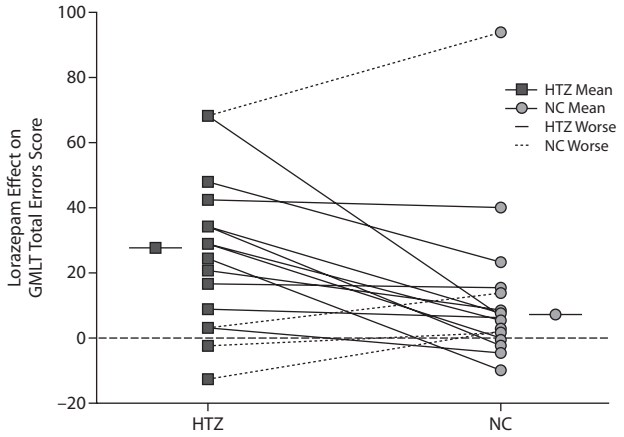


[a]Lower scores indicate worse performance. Placebo was associated with mild declines over time. Apolipoprotein E (*APOE*)-ε4 carriers (heterozygotes) performed significantly worse ($P = .005$) than noncarriers at 2.5 hours after administration of lorazepam.

with genotype that caused the memory decline. However, our results are consistent with a previous study that correlated AVLT scores with a measure of daytime sleepiness in homozygotes and noncarriers in which the long-term memory score and the percent recall scores (but not learning over trials) were statistically different.[15] It remains to be seen whether daytime use of sedating medications such as lorazepam or exposure to extreme fatigue (eg, as in physicians and pilots or persons with known sleep disorders such as inadequately treated obstructive sleep apnea) would be a greater concern for at-risk persons; some activities of daily living may be more affected than others.

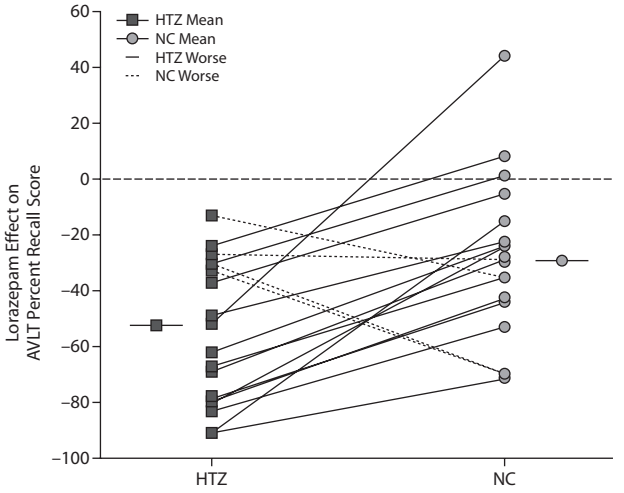
Even though the changes induced by lorazepam and the differences between groups were statistically significant, that does not necessarily mean they are clinically or functionally significant. In the case of the AVLT, there are age-adjusted norms (Mayo Older Americans Normative Studies[33]) with which we can compare our results. By the current interpretive standards, any scaled score of 5 or less would be at or below the 5th percentile, which is most likely clinically significant. Our scores at 2.5 hours postlorazepam averaged below 5 for both groups. If one interprets that lorazepam has a clinically significant effect, a difference that large again might also be considered clinically significant. Indeed, the

Figure 3. Effect of Lorazepam on Groton Maze Learning Test (GMLT) Total Errors Score at 2.5 Hours Among Apolipoprotein E (*APOE*)-ε4 Carriers (heterozygotes [HTZ]) Versus Noncarriers (NC)[a]



[a]Higher scores indicate more errors and worse performance. Only 4 noncarriers performed worse than their matched heterozygotes. The lorazepam effect reflects the scores in the lorazepam condition minus the scores in the placebo condition. The dashed line at 0 indicates no difference between the lorazepam and placebo conditions. The mean group scores are shown by the black bars on either side of the figure.

Figure 4. Effect of Lorazepam on Rey Auditory-Verbal Learning Test (AVLT) Percent Recall Score at 2.5 Hours Among Apolipoprotein E (*APOE*)-ε4 Carriers (heterozygotes [HTZ]) Versus Noncarriers (NC)[a]



[a]Lower scores indicate worse performance. Only 4 noncarriers performed worse than their matched heterozygotes. The lorazepam effect reflects the scores in the lorazepam condition minus the scores in the placebo condition. The dashed line at 0 indicates no difference between the lorazepam and placebo conditions. The mean group scores are shown by the black bars on either side of the figure.

difference between heterozygotes and noncarriers for GMLT total errors was as large as the difference between lorazepam and placebo in noncarriers. These comparisons suggest that the effects described may also be clinically significant.

This study extends the findings of a similar, previous study[16] by using a higher dose of lorazepam, a younger cohort, and the testing of additional cognitive domains. Pomara and colleagues[16] reported a differential impairment of heterozygotes and noncarriers at 5 hours but not at 2.5 hours for persons with lower baseline performance, whereas we found a greater differential impairment at 2.5 hours but not at 5 hours. The difference in lorazepam dose may largely account for this disparity. Studies of functional magnetic resonance imaging[9–13] in healthy middle-aged and elderly persons with similar performance on memory tasks found increased neural activity in heterozygotes compared with noncarriers, suggestive of compensatory neural processing. We suspect that the 2-mg lorazepam dose overwhelmed any compensatory activity for heterozygotes, leading to greater impairment at 2.5 hours.

Heterozygotes and noncarriers did not differ substantially on baseline or placebo measures, nor on demographic characteristics; these factors are unlikely to be important confounders. Other factors believed to influence cognition (eg, age, education, psychotropic medications, mood, and anxiety) were either weighted in favor of heterozygotes or relatively balanced. The worse memory performance of heterozygotes after pharmacologic challenge could be due to a reduction in ability to compensate for certain effects of somnolence. The differential effect might have been more dramatic with more subjects and the inclusion of homozygotes.

The combined group data for the placebo condition at baseline and at 5 hours suggest that fatigue may influence AVLT scores more negatively than GMLT scores. This decline in AVLT scores is unlikely to be related to methodological issues such as different evaluators or placebo effect of perceived somnolence since the AVLT was given by the same evaluator and at the same time as the GMLT, which did not show a similar decline. It is possible that a verbal test is less engaging or motivating than an interactive computerized test such as the GMLT and therefore more subject to fluctuations of effort, boredom, or fatigue. Further investigation of how fatigue and repeated testing affect the integrity of scores will help establish the optimal tests for serial neuropsychological evaluations in healthy and diseased persons.

Limitations of this study are the relatively small number of participants and the lack of longitudinal follow-up. Thus, we cannot show significant differences when correcting for multiple comparisons, nor can we draw conclusions about lorazepam for a de facto cognitive stress test. However, we plan to follow these persons longitudinally and to compare those with the least and greatest impairments due to lorazepam to assess how well this pharmacologic challenge predicts later cognitive decline. Using a pharmacologic challenge clinically to predict subsequent cognitive decline is worthy of further study. We do not yet advocate

APOE genotyping in healthy people for clinical decision-making. Nonetheless, prescribers might consider the fairly dramatic effect, amplified for persons at higher risk for Alzheimer's disease, of a single dose of lorazepam in 50- to 65-year-olds in their risk-to-benefit analysis.

Drug name: lorazepam (Ativan and others).
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