Nicotine treatment of mild cognitive impairment: A 6-month double-blind pilot clinical trial
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ABSTRACT

Objective: To preliminarily assess the safety and efficacy of transdermal nicotine therapy on cognitive performance and clinical status in subjects with mild cognitive impairment (MCI).

Methods: Nonsmoking subjects with amnestic MCI were randomized to transdermal nicotine (15 mg per day or placebo) for 6 months. Primary outcome variables were attentional improvement assessed with Connors Continuous Performance Test (CPT), clinical improvement as measured by clinical global impression, and safety measures. Secondary measures included computerized cognitive testing and patient and observer ratings.

Results: Of 74 subjects enrolled, 39 were randomized to nicotine and 35 to placebo. 67 subjects completed (34 nicotine, 33 placebo). The primary cognitive outcome measure (CPT) showed a significant nicotine-induced improvement. There was no statistically significant effect on clinician-rated global improvement. The secondary outcome measures showed significant nicotine-associated improvements in attention, memory, and psychomotor speed, and improvements were seen in patient/informant ratings of cognitive impairment. Safety and tolerability for transdermal nicotine were excellent.

Conclusion: This study demonstrated that transdermal nicotine can be safely administered to nonsmoking subjects with MCI over 6 months with improvement in primary and secondary cognitive measures of attention, memory, and mental processing, but not in ratings of clinician-rated global impression. We conclude that this initial study provides evidence for nicotine-induced cognitive improvement in subjects with MCI; however, whether these effects are clinically important will require larger studies.

Classification of evidence: This study provides Class I evidence that 6 months of transdermal nicotine (15 mg/day) improves cognitive test performance, but not clinical global impression of change, in nonsmoking subjects with amnestic MCI. Neurology® 2012;78:91–101

GLOSSARY

AD — Alzheimer disease; AE — adverse event; BMI — body mass index; CDR — Clinical Dementia Rating; CGIC — Clinical Global Impression of Change; CPT — Continuous Performance Test; CRT — Choice Reaction Time; MCI — mild cognitive impairment; OASR — Older Adult Self Report; OABCL — Older Adult Behavior Checklist; RT — reaction time.

Mild cognitive impairment (MCI) is defined as a subjective and objective decline in cognition and function that does not meet criteria for a diagnosis of dementia and represents a transitional state between the cognition of normal aging and mild dementia. CNS nicotinic acetylcholine receptor stimulation may be a promising strategy to ameliorate symptoms of MCI and slow progression to dementia. The 2 most prevalent nicotinic receptors in the brain, α4β2 and α7, have both been found to be important for cognitive function. Nicotinic receptor loss has been demonstrated in patients with Alzheimer disease (AD) and is linked to the hallmark plaques and tangles and cognitive impairment.
Cognitive improvement is one of the best-established therapeutic effects of nicotine.\textsuperscript{11} In human studies, nicotine improves performance in smokers on cognitively demanding attentional tasks.\textsuperscript{12–14} In clinical studies, memory improvement was initially seen with IV nicotine in subjects with AD.\textsuperscript{15} Others have also found nicotine administration by subcutaneous injection or transdermal patch to improve cognitive function in AD.\textsuperscript{16–19} MCI may be the optimal diagnosis for which to test the efficacy of nicotinic therapy with relatively large numbers of preserved nicotinic receptors, and only modest declines of cognitive function.

The primary goals of this trial were to evaluate the safety of sustained nicotine treatment in nonsmoking older patients and to determine whether nicotine would improve cognitive performance, as measured by objective tests and clinical ratings.

**METHODS Study population.** One hundred subjects were recruited from 2004 through 2007 at 3 sites. Individuals screened for this study either carried a diagnosis of MCI or had been identified through community memory screening programs or community clinics.

MCI diagnosis utilized the generally accepted criteria for amnestic MCI:\textsuperscript{4} age 55+; memory complaints and memory difficulties verified by an informant; abnormal memory function documented by scoring below the education-adjusted cutoff on the Logical Memory II subscale (Delayed Paragraph Recall) from the Wechsler Memory Scale–Revised as used in prior MCI trials;\textsuperscript{20} Mini-Mental State Examination score between 24 and 30 (inclusive); Clinical Dementia Rating (CDR)\textsuperscript{21} of 0.5 with a memory box score of 0.5 or 1.0. Exclusion criteria included any significant current or prior medical or neurologic disease, head injury, or significant structural brain abnormalities, Axis I psychiatric illness or substance abuse within the last 2 years, chronic use of medications with centrally active cholinergic or anticholinergic properties, and current tobacco or nicotine use. No subjects were taking any cognitive enhancing medications or acetylcholinesterase inhibitors. Behavioral screening consisted of a partial Diagnostic Interview Schedule,\textsuperscript{22} the Beck Depression Rating Scale,\textsuperscript{3} and the structured Hamilton Depression Rating Scale.\textsuperscript{28}

**Standard protocol approvals, registrations, and patient consents.** This study was approved by the institutional review board at each institution. Subjects received an oral and a written explanation of the purposes, procedures, and potential hazards of this study and provided informed consent (separate consent for APOE genotyping). This study was registered with the NIH clinical trials database (Clinicaltrials.gov), NCT00091468.

**Study design/randomization.** The study was a double-blind, parallel-group, placebo-controlled, randomized clinical trial (figure 1) with a 6-month double-blind period with randomization to either transdermal nicotine or placebo on a one-to-one basis. The randomization and treatment allocation sequence (generated by the study statistician, D.H.) was performed within gender, age (<75 and 75+), and center. Subjects, informants, local site PIs, and local study coordinators were blinded to treatment assignment. The second phase was open-label transdermal nicotine for additional 6 months which was offered to all subjects who completed the double-blind (will be reported separately). Subjects who met criteria for AD during the study were removed by predetermined protocol criteria and were offered treatment with standard approved agents.

**Power.** The study sample size was calculated based on data from a previous 4-week nicotine patch trial in patients with AD.\textsuperscript{16} Using an $\alpha$ level of 0.05, a SD of 3 errors at baseline and at week 26, and a correlation between baseline and week 26 errors of 0.5, we calculated that with 60 subjects, we had 80% power to detect the difference in the average change score in the CPT task between groups of 1 SD. Anticipating dropouts of up to 20%, the planned sample size was 75 subjects (25 per center).

**Study hypotheses/classification of evidence.** We proposed 3 hypotheses: transdermal nicotine treatment 1) would improve cognitive performance in patients with MCI as manifested by improvements in sustained attention, learning, and memory compared to placebo treatment; 2) would improve global ratings of cognitive and functional abilities; and 3) would be tolerable and safe over 6 months of continuous treatment. This study provides Class I evidence that 6 months of transdermal nicotine (15 mg/day) improves cognitive test performance, but not clinical global impression of change, in nonsmoking subjects with amnestic MCI.

**Medication.** Transdermal nicotine was begun utilizing a 5 mg Nicotrol\textsuperscript{10} patch (Pharmacia/Pfizer) transdermal delivery system, in sizes of 10, 20, and 30 cm\textsuperscript{2} each containing 0.83 mg/cm\textsuperscript{2} of nicotine, releasing 5 mg, 10 mg, and 15 mg, respectively, over 16 hours or matching placebo. Treatment (active or placebo) was titrated to 15 mg by day 21. Subjects were contacted by phone during the first week and returned after 7 and 28 days to monitor side effects and medication compliance.

**Assessment.** Performance/behavioral testing was done at 0, 91, and 182 days. The primary cognitive outcome measure was the reaction time standard error performance on the Connors Continuous Performance Test (CPT)\textsuperscript{20,26} as improvement in reaction time standard error performance over varying intervals is a strong indication of overall attentional performance and nicotine effects in AD.\textsuperscript{16} Secondary cognitive measures included the Cognitive Drug Research computerized battery.\textsuperscript{14,27–29} In addition, subjects completed the Immediate and Delayed Paragraph Recall Test (NYU version) and the Digit Symbol Substitution Task. The Clinical Global Impression of Change\textsuperscript{26} (MCI-CGIC) was used as the primary clinical outcome measure.

**Behavioral/functional assessments.** Assessments included the structured Hamilton Depression Rating Scale,\textsuperscript{26} the Alzheimer’s Disease Cooperative Study–Activities of Daily Living,\textsuperscript{30} the Mini Nutritional Assessment\textsuperscript{23} for grading the nutritional state of subjects, the CDR, and the Older Adult Self Report (OARS) and Behavior Checklist (OABCL).\textsuperscript{35}

**Safety assessment.** In addition to collecting adverse event reports, vital signs were measured at all clinical visits and a repeat of the screening laboratory tests was performed at the end of the study. Tolerability and safety were determined by counting specific adverse events and counting dropouts due to adverse events.
Statistical analyses. Primary data analysis focused on the randomized, double-blind, placebo-controlled portion of the study that was conducted for the first 6 months. Cognitive, clinical, and safety variables were assessed both in subjects who received at least 1 dose of treatment (intent to treat) as well as subjects who completed the double-blind. Data are presented as mean ± SE unless indicated.

Cognitive performance. Mixed models repeated-measures analysis of variance was used to assess the effect of nicotine treatment vs placebo as a between-subjects factor and efficacy testing time point (0, 91, 182 days) as the categorical within-subjects factor. Baseline scores and APOE genotype were used as covariates if appropriate. A secondary analysis also added site and gender to the model.

Global ratings. Analysis of the MCI-CGIC compared global ratings for nicotine and placebo utilizing ordered polychotomous logistic regression and the CGIC rating at the end of double-blind treatment (182 days). Site and gender were included in the model as covariates.

Safety outcome. Differences for rates of adverse events or other safety abnormalities between groups were assessed using $\chi^2$ analysis.

RESULTS Of the 100 subjects screened for the study, 74 subjects passed screening criteria and were
Wechsler Memory Scale; WTAR

Ham-D
menta Rating Scale; GDS

tween treatment groups. Data are mean (SD) or n (%).

Mini-Mental State Examination; MNA

cebo group (51%) and 14 in the nicotine-treated
30 of 70 subjects with 18 being present in the pla-
never smokers. At least 1

smokers (36) and 15 (43)

Age
76.2 (8.5) 75.7 (6.5)

Weight, kg
76.9 (15.7) 73.9 (14.7)

Education, y
15.6 (2.9) 16.2 (2.4)

Cognitive assessment

CDR
0.5 0.5

Sum of boxes
1.4 (0.7) 1.5 (0.8)

DRS
132.2 (7.6) 132.0 (7.9)

GDS
2 (0.2) 2 (0.2)

HAM-D Total
2.7 (2.5) 3.7 (3.6)

MMSE
27.4 (1.9) 27.5 (2.1)

Hachinski
0.92 (1.13) 0.88 (1.01)

MNA
13.2 (1.2) 13.3 (1.0)

WMS

Immediate
7.4 (3.6) 7.5 (3.8)

Delayed
4.4 (3.2) 4.7 (3.8)

WTAR standard
112 (11) 113 (13)

Predicted
108 (8) 111 (7)

WAIS

Verbal
112 (10) 114 (11)

Performance
109 (7) 111 (9)

Full-scale
112 (9) 114 (11)

Genetics, n (%)

APOE4 genotype
(n = 70)

APOE4 present
(n = 30)

1.4 (38) 18 (51)

APOE4 absent
(n = 40)

23 (62) 17 (49)

Abbreviations: CDR – Clinical Dementia Rating; DRS – Dementia Rating Scale; GDS – Global Deterioration Scale; Ham-D – Hamilton Depression Rating Scale; MMSE – Mini-Mental State Examination; MNA – Mini-Nutritional Inventory; WAIS – Wechsler Adult Intelligence Scale; WMS – Wechsler Memory Scale; WTAR – Wechsler Test of Adult Reading.

There were no significant differences on measures between treatment groups. Data are mean (SD) or n (%).

Data missing for 1 patient.

Data missing for 2 subjects.

randomized to treatment, 45 male and 29 female (table 1). Forty subjects reported being former cigarette smokers (>100 cigarettes lifetime) and 34 were never smokers. At least 1 APOE4 allele was present in 30 of 70 subjects with 18 being present in the placebo group (51%) and 14 in the nicotine-treated group (38%) (p = 0.25). Thirty-nine subjects were randomized to nicotine treatment (34 completers) and 35 subjects were randomized to placebo treatment (33 completers) (figure 1). The mean ages for the nicotine-treated and placebo-treated subjects were 76.2 ± 1.4 and 75.7 ± 1.1, respectively. No clinical or baseline variables were significantly different between treatment groups or sites. The target dose was 15 mg daily and 73/74 subjects received this dose for the double-blind phase following titration.

Primary efficacy measures. Cognitive performance. CPT. Cognitive performance is detailed in table 2. Hit reaction time (RT) standard error over interstimulus interval (the primary outcome measure) showed a significant (F1, 57 = 4.89, p = 0.031) main effect of nicotine treatment with the variability in RT over the varying interstimulus intervals being significantly improved (reduced) on nicotine treatment compared to placebo (figure 2A) by days 91 and 182 (p = 0.005). The 67 completers showed significant nicotine-induced improved performance on this measure (F1, 54 = 14.96, p = 0.0003) compared to placebo treatment. There were no significant treatment-related changes in errors (Omission, Commission), overall hit RT, or overall RT variance. The nicotine treatment effect size was 0.78 at week 26 (Cohen d).

Global measure. CGIC. There was no statistical difference between treatment groups in the distribution of subjects rated improved or not improved (p = 0.13) (figure 2B). Reducing the outcomes into just 3 categories (any improvement, no change, any worsening) revealed that 3 subjects in the placebo group were rated as improved (9.1%) vs 8 subjects (23.5%, p = 0.12) after nicotine treatment.

Secondary efficacy measures. Cognitive measures. Paragraph recall. Cognitive measures are detailed in table 2. Examining change from baseline (days 91, 182) for the 67 completers showed a significant (F1, 60 = 6.19, p = 0.02) main effect with the placebo-treated group showing greater immediate recall (but not delayed recall) of story units over time compared to the nicotine-treated group. Analysis of forgetting between immediate and delayed trials showed a significant (F1, 60 = 4.42, p = 0.04) effect of nicotine treatment showing reduced loss of information compared to the placebo-treated group (figure 3A).

Digit Symbol Substitution Task. There was a trend (p = 0.13) for nicotine-treated subjects to show improved accuracy by day 182.

Computerized cognitive battery. Memory. Delayed word recall accuracy (table 1) showed a significant effect of treatment (F1, 70 = 5.92, p = 0.018) with
Table 2  Continuous Performance Task, paragraph recall, and Cognitive Drug Research Battery individual scores (adjusted means and standard errors) for all subjects (74)

<table>
<thead>
<tr>
<th></th>
<th>Day 0</th>
<th>Day 7</th>
<th>Day 21</th>
<th>Day 91</th>
<th>Day 182</th>
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<tr>
<td>Continuous performance</td>
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<tr>
<td>No. of omissions</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Nicotine</td>
<td>20.2 (8.3)</td>
<td>13.7 (5.1)</td>
<td>22.2 (9.9)</td>
<td>12.2 (3.7)</td>
<td>19.7 (9.3)</td>
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<tr>
<td>Placebo</td>
<td>8.97 (1.75)</td>
<td>15.97 (9.92)</td>
<td>14.44 (6.23)</td>
<td>17.03 (9.88)</td>
<td>22.27 (10.65)</td>
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<tr>
<td>Percent of omissions</td>
<td></td>
<td></td>
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<tr>
<td>Nicotine</td>
<td>6.3 (2.6)</td>
<td>4.3 (1.6)</td>
<td>6.9 (3.1)</td>
<td>3.8 (1.2)</td>
<td>6.1 (2.9)</td>
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<td>Placebo</td>
<td>2.8 (0.5)</td>
<td>4.9 (3.1)</td>
<td>4.5 (1.9)</td>
<td>5.3 (3.1)</td>
<td>6.9 (3.3)</td>
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<tr>
<td>No. of commissions</td>
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<td></td>
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<tr>
<td>Nicotine</td>
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<td>11.1 (0.8)</td>
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<td>9.5 (0.8)</td>
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<td>Placebo</td>
<td>12.4 (1.1)</td>
<td>11.3 (1.2)</td>
<td>11 (1.3)</td>
<td>10.9 (1.2)</td>
<td>10.9 (1.4)</td>
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<tr>
<td>Percent of commissions</td>
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<tr>
<td>Nicotine</td>
<td>30.4 (2.4)</td>
<td>31.0 (2.2)</td>
<td>26.4 (2.8)</td>
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<td>26.4 (2.2)</td>
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<td>Placebo</td>
<td>34.6 (3.0)</td>
<td>31.3 (3.4)</td>
<td>30.6 (3.6)</td>
<td>10.9 (1.2)</td>
<td>10.9 (1.4)</td>
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<td>Hit reaction time</td>
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<tr>
<td>Nicotine</td>
<td>487 (26)</td>
<td>454 (10)</td>
<td>452 (10)</td>
<td>453 (10)</td>
<td>454 (11)</td>
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<td>Placebo</td>
<td>468 (13)</td>
<td>470 (16)</td>
<td>463 (13)</td>
<td>482 (19)</td>
<td>475 (13)</td>
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<td>Paragraph recall</td>
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<td>Immediate</td>
<td></td>
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<tr>
<td>Nicotine</td>
<td>5.3 (0.4)</td>
<td>3.4 (0.4)</td>
<td>4.4 (0.4)</td>
<td>4.0 (0.4)</td>
<td>3.8 (0.4)</td>
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<td>5.4 (0.4)</td>
<td>4.4 (0.4)</td>
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<td>Delayed</td>
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<td>Nicotine</td>
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<td>3.2 (0.5)</td>
<td>3.3 (0.5)</td>
<td>4.3 (0.5)</td>
<td>3.8 (0.5)</td>
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<td>3.2 (0.5)</td>
<td>3.2 (0.5)</td>
<td>4.8 (0.5)</td>
<td>3.8 (0.5)</td>
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<td>Cognitive Drug Research Battery individual item scores</td>
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<td>Simple reaction time</td>
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<td>Nicotine</td>
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<td>355 (9)</td>
<td>353 (11)</td>
<td>370 (15)</td>
<td>370 (12)</td>
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<td>Placebo</td>
<td>378 (19)</td>
<td>366 (13)</td>
<td>376 (18)</td>
<td>377 (18)</td>
<td>373 (16)</td>
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<tr>
<td>Choice reaction time</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Nicotine</td>
<td>552 (13)</td>
<td>532 (10)</td>
<td>541 (13)</td>
<td>529 (11)</td>
<td>543 (14)</td>
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<tr>
<td>Placebo</td>
<td>556 (19)</td>
<td>560 (22)</td>
<td>552 (21)</td>
<td>567 (21)</td>
<td>566 (22)</td>
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<td>Delayed picture recognition sensitivity</td>
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<tr>
<td>Nicotine</td>
<td>0.55 (0.03)</td>
<td>0.56 (0.03)</td>
<td>0.57 (0.03)</td>
<td>0.59 (0.04)</td>
<td>0.60 (0.04)</td>
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<td>0.56 (0.03)</td>
<td>0.63 (0.04)</td>
<td>0.58 (0.04)</td>
<td>0.54 (0.05)</td>
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<td>Delayed word recognition sensitivity</td>
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<tr>
<td>Nicotine</td>
<td>0.50 (0.05)</td>
<td>0.51 (0.04)</td>
<td>0.55 (0.03)</td>
<td>0.52 (0.03)</td>
<td>0.54 (0.03)</td>
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<tr>
<td>Placebo</td>
<td>0.56 (0.04)</td>
<td>0.49 (0.04)</td>
<td>0.53 (0.04)</td>
<td>0.55 (0.05)</td>
<td>0.53 (0.04)</td>
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<td>Spatial memory reaction time</td>
<td></td>
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<tr>
<td>Nicotine</td>
<td>1436 (70)</td>
<td>1159 (143)</td>
<td>1225 (49)</td>
<td>1153 (49)</td>
<td>1396 (80)</td>
</tr>
<tr>
<td>Placebo</td>
<td>1617 (194)</td>
<td>983.5 (57)</td>
<td>1252 (91)</td>
<td>1342 (133)</td>
<td>1535 (168)</td>
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<td>Spatial memory sensitivity</td>
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<tr>
<td>Nicotine</td>
<td>0.75 (0.04)</td>
<td>0.78 (0.05)</td>
<td>0.75 (0.04)</td>
<td>0.86 (0.03)</td>
<td>0.75 (0.04)</td>
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<tr>
<td>Placebo</td>
<td>0.68 (0.06)</td>
<td>0.89 (0.04)</td>
<td>0.77 (0.04)</td>
<td>0.75 (0.07)</td>
<td>0.66 (0.06)</td>
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<td>Digital vigilance accuracy</td>
<td></td>
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<tr>
<td>Nicotine</td>
<td>96.2 (0.6)</td>
<td>97.1 (0.6)</td>
<td>96.0 (1.2)</td>
<td>96.5 (0.8)</td>
<td>94.51 (1.3)</td>
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<tr>
<td>Placebo</td>
<td>97.5 (0.7)</td>
<td>97.4 (0.5)</td>
<td>97.1 (0.6)</td>
<td>95.8 (0.9)</td>
<td>95.6 (1.0)</td>
</tr>
</tbody>
</table>
the nicotine-treated group showing a significant improvement over time compared to the placebo group (figure 3B). Analysis of the 67 completers demonstrated that the nicotine-treated group had a significant ($F_{1,61} = 5.37, p < 0.02$) improvement compared to the placebo-treated subjects. The spatial memory and delayed picture recognition sensitivity revealed trends ($p = 0.10$ and $p = 0.12$, respectively) favoring the nicotine-treated group with improvement over baseline at both time points.

Attention/response speed. The speed of memory summary measure (table e-1 on the Neurology® Web site at www.neurology.org) showed a strong trend ($F_{3,70} = 2.56, p = 0.06$) in the intent-to-treatment sample for a treatment-by-time interaction with the nicotine-treated group showing improved overall memory speed by day 91. RT variability (a measure of attentional fluctuation) showed a strong trend for improvement with nicotine ($F_{1,66} = 3.34, p = 0.07$). In the Choice Reaction Time task (CRT), there was a main effect of treatment ($F_{1,66} = 4.44, p = 0.04$) on accuracy performance with nicotine treatment associated with greater accuracy over time (also seen in completers, $p < 0.06$) (table 1). Continuity of attention (table e-1) showed a trend ($F_{1,61} = 2.96, p < 0.09$) for a positive effect of nicotine treatment as did the picture recognition task ($F_{1,70} = 3.62, p = 0.061$) and delayed word recognition ($F_{1,70} = 2.88, p = 0.09$).

For the power of attention summary measure (table e-1), there was an interaction between treatment and APOE genotype ($p = 0.047$) such that the APOE4 double allele subgroup had a significant ($p = 0.019$) improvement with nicotine treatment but the E4/E3 and E3/E3 groups did not. Completers showed a significant treatment-by-genotype interaction ($F_{3,50} = 3.26, p = 0.047$) with nicotine improving the double allele group only ($t = 2.39, p = 0.021$). For the Digit Vigilance Task, speed showed a similar significant ($p = 0.01$) advantage for nicotine treatment in the APOE4 double allele group compared to the other groups.

Safety. Body weight. Change in body weight (figure e-1) showed that there was a significant treatment-by-day interaction ($F_{3,71} = 5.55, p = 0.002$) with the nicotine-treated group showing a decline in body weight by day 91 compared to placebo: $-1.3$ kg for the nicotine-treated group (range $-6.9$ to $+1.6$ kg) vs $-0.12$ kg for the placebo-treated subjects (range $-4.4$ to $+4.1$ kg). A significant treatment effect was also seen for body mass index (BMI) by day 91. However, by day 182, mean BMI values remained in the normal range and were similar between treatment groups: $25.9 \pm 3.6$ for placebo and $25.8 \pm 4.2$ for nicotine (NS).

Vital signs. There was a significant nicotine treatment effect ($F_{1,71} = 9.01, p = 0.004$) with a significant reduction in systolic blood pressure compared to placebo (figure e-2). By day 182, the placebo group showed an average increase of $9.6$ mm Hg in systolic blood pressure (range $+30$ to $-38$ mm Hg) compared to a reduction of $4$ mm Hg (range $+30$ to $-47$ mm Hg) in the nicotine-treated group. There was no effect of treatment on diastolic blood pressure, pulse, or oral temperature. There was a significant ($F_{1,70} = 5.16, p = 0.03$) nicotine-associated reduction in respirations.

Adverse events. Total adverse events (AEs) for the double-blind treatment period were 82 for nicotine vs 52 for placebo ($\chi^2[1] = 3.92, p < 0.05$). However, the majority of AEs were mild and there was no statistically significant difference in the proportion of adverse events within the different severity classifications between treatments (Mann-Whitney test $p = 0.97$). No severe AEs were classified as related to drug treatment in either treatment group. Adverse event rates by body systems (figure e-3) were generally comparable, with the exception of gastrointestinal and neurologic, for which there were more AEs reported in the nicotine-treated group. More nicotine-treated subjects (4) discontinued treatment

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<td>Digital vigilance reaction time</td>
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for adverse events than placebo-treated subjects (0) ($\chi^2[1] = 3.79; p = 0.05$). No withdrawal symptoms were reported by subjects or informants nor were any subjects reported to be continuing to use nicotine after the study was completed.

**Subject- and informant-completed behavioral measures. OASR and OABCL.** The self-rated Worries and Anxiety subscales showed significant ($F_{2,86} = 3.48, p = 0.04$ and $F_{2,86} = 3.14, p = 0.05$) interactions with the nicotine-treated group showing improved scores by day 182. There was a strong trend ($F_{2,86} = 2.74, p = 0.07$) for nicotine to improve scores in the DSM-oriented dementia subscale (consisting of items from the OASR commonly associated with a DSM dementia diagnosis). The informant-completed OABCL showed lower ratings on the Anxiety/Depression subscale ($F_{2,90} = 5.00, p = 0.009$) for placebo treatment. The Beck Depression Inventory showed no significant treatment effect ($p = 0.72$) or interactions ($p = 0.50$).

**DISCUSSION** This study demonstrated that transdermal nicotine treatment for 6 months improved cognitive performance in subjects with amnestic MCI. The primary cognitive outcome (Connors CPT) showed a significant nicotine-induced improvement with an effect size of 0.78 which compares favorably to a previous study of nicotine in AAMI$^{34}$ in which the effect size was 0.53 at 4 weeks on the same measure. Several secondary cognitive measures showed significant nicotine-induced improvement including psychomotor speed and atten-
tion on several tasks as well as significant effects on long-term memory seen in both the paragraph recall task and computerized word recall task (e.g., figure 3B). This is consistent with prior studies of nicotinic stimulation in AD, where we saw more robust effects on long-term recall than short-term recall, and suggests that this is a specific effect on patients with memory impairment, as studies have indicated that nicotine does not generally improve performance unless subjects are impaired. There were trends for improvements in a number of other cognitive measures. Whether these trends would become statistically significant with larger sample sizes is unclear and will require further study to assess the overall impact of nicotinic stimulation. There was no evidence for loss of cognitive effects over time. The primary clinical outcome, the Clinical Global Impression by the clinician, did not show significant improvement; however, patients and their informants did report nicotine-induced improvements.

Nicotine was well-tolerated with few subjects withdrawing because of medication side effects. All but one subject tolerated the highest administered dose. Transdermal administration method probably contributed to improved tolerability, particularly reducing the incidence of potential gastrointestinal side effects. Nicotine treatment was associated with a modest reduction in systolic blood pressure. The reduction in weight (approximately 2.5 kg by day 182) is not unexpected considering the mild anorectic effects of nicotine. No significant medical consequences related to the loss of weight occurred in the nicotine-treated subjects and no subject developed a clinically low BMI (<18.5) over the course of the trial. However, further study will be necessary to confirm that there are no long-term negative conse-

![Figure 3](image-url)  
**Figure 3** Secondary verbal memory cognitive performance variables

(A) Paragraph recall; immediate recall minus delay recall; change from baseline (n = 67). Note that negative score indicates improvement (less forgetting from immediate to delay trials). Nicotine treatment produced a significant (F_{1,60} = 4.42, p = 0.04) effect showing reduced loss of information between the immediate and delayed trials compared to the placebo-treated group. (B) Delayed word recall accuracy, Cognitive Drug Research Battery. Change from baseline (n = 67). There was a significant effect of nicotine treatment (F_{1,70} = 5.92, p = 0.018) with the nicotine-treated group showing a significant improvement over time in delayed word recall accuracy compared to the placebo group.
quences of nicotine-induced weight loss in patients with MCI and the treatment of patients with low BMI with nicotine should be approached with caution. There was no withdrawal syndrome and no subjects continued to use nicotine products. Thus, in this nonsmoking population, there was no evidence for abuse liability of transdermal nicotine. Only non-smokers were utilized for this study to simplify dosing. As former smoking status was not a focus of this study and the number of former smokers was small, an analysis of prior smoking status and efficacy was not performed. Whether these findings of cognitive enhancement would apply to individuals with substantial histories of tobacco use or active smoking will require further study and potentially different dose ranges.

While strategies that attempt to mitigate directly or indirectly the molecular pathology that leads to synaptic loss will be important in treating/preventing MCI and AD, it is likely that neurotransmitter-based treatments will continue to be necessary to directly enhance cognitive functioning, particularly in domains that are relevant to the aging process and to the loss of synaptic connectivity in MCI and AD. Furthermore, there is strong evidence that nicotine itself may be neuroprotective and may have a role in amyloid processing\(^37\) (although nicotine has been shown to exacerbate tau pathology in a rodent model\(^38\)). Thus there may be an additional motivation for nicotinic treatment in patients with biomarker or clinical evidence for early cognitive impairment. Treatment periods longer than 1 year may be necessary in future studies to look for disease-modifying effects.

The finding that APOE genotype impacted the response to nicotine is intriguing. A recent study in young individuals demonstrated that nicotine had a greater cognitive activity in APOE4-positive individuals\(^39\) suggesting that the cholinergic system may be upregulated in APOE4-positive individuals or in MCI.\(^40\) Thus it is possible that nicotinic augmentation may be a particularly appropriate choice for these individuals.

Limitations in the study included a relatively small sample size (74). Power was calculated on the basis of a cognitive measure (CPT task), so the power to detect effects from clinical global ratings was quite limited. Because of the length of the study, no data on progression could be obtained. To simplify dosing—only nonsmokers were tested. Nicotine dose titration was only performed to limit side effects. Further clinical benefit might be achieved by titration also based on efficacy.

This study found that transdermal nicotine over 6 months is a safe treatment for nonsmoking subjects with MCI. As this was a pilot clinical trial, we wanted to measure a broad number of cognitive and behavioral domains which might be influenced by nicotinic stimulation. Thus, it is not surprising that some measures showed no effect of treatment. However, measures of attentional, memory, and psychomotor performance did show an effect of nicotine and this finding provides strong justification for further treatment studies of nicotine for patients with early evidence of cognitive dysfunction.

**AUTHOR CONTRIBUTIONS**

Dr. Newhouse: designed and conceptualized the study, conducted the study as principal investigator including supervising the coordinating center research team, supervised analysis and interpretation of the data, and drafted and revised the manuscript. Dr. Kellar: assisted with design and conceptualization of the study, assisted with drafting and revising the manuscript. Dr. Aisen: assisted with design and conceptualization of the study, conducted the study as site principal investigator, assisted with drafting and revising the manuscript. Dr. White: assisted with design and conceptualization of the study, conducted the study as site principal investigator, assisted with drafting and revising the manuscript. Dr. Wernes: developed and tested key cognitive outcome measures, performed data analysis and interpretation for secondary outcome measures, assisted with drafting and revising the manuscript. E. Codere: supervised the acquisition of subject data, responsible for design and implementation of clinical databases and data analysis, assisted with drafting and revising the manuscript. A. Pfaff: responsible for implementation of clinical databases and data analysis, assisted with drafting and revising the manuscript, conducted reanalysis of adverse event data. H. Wilkins: supervised the acquisition of subject data, responsible for ongoing implementation of clinical databases and data analysis, assisted with drafting and revising the manuscript, conducted analysis of clinical trial visits and vital signs data. D. Howard: lead statistician with responsibility for randomization, subject assignment, and data analyses as well as assistance with data interpretation. Dr. Levin: co-designed and conceptualized the study, conducted certain data analyses, assisted with drafting and revising the manuscript.

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**DISCLOSURE**

Dr. Newhouse has served as a consultant for AstraZeneca, Gerson Lehrman Group, Guidepoint Global, Summer Street Research Partners, and Biotechnology Value Fund, L.P.; and receives research support from AstraZeneca, Eli Lilly and Company, Targacept, Inc., and the NIH (NIA, NIDA, NIAMDS). Dr. Kellar holds patent(s) re: Nicotinic receptor desensitizing ligands and methods for their testing and use; and receives research support from the NIH (NIDA, NIMH). Dr. Aisen serves on a scientific advisory board for NeuroPhage and Novartis; serves on the editorial boards of *BMC Medicine* and *Alzheimer's Research & Therapy*, is listed as inventor on a patent re: DHA therapy for allopripoprotein E4 negative Alzheimer’s disease (potential royalties assigned in full to UCSF); serves as a consultant to Elan Corporation, Wyeth, Eisai Inc., Schering-Plough Corp., Bristol-Myers Squibb, Eli Lilly and Company, NeuroPhage, Merck & Co, Roche, Amgen, Genentech, Inc., Abbott, Pfizer Inc, Novartis, Bayer Schering Pharma, Astellas Pharma Inc., Daiichi-Sankyo, AstraZeneca, Janssen, and Medivation, Inc.; receives research support from Pfizer Inc, Bayer Schering Pharma, Baxter International Inc., and the NIH/NIA; and has received stock options from Medivation, Inc. and NeuroPhage. Dr. White has received research support from Merck Serono; has served as a consultant for GlaxoSmithKline; participates in a
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