Chronic Nicotine Treatment Improves Cognitive Performance in Mild Cognitive Impairment (MCI): A Six-Month Multi-Center Double-Blind Study

Paul Newhouse, MD1,2; Ken Kellar, PhD2; Paul Aisen, MD3; Heidi White, MD2; Keith Wesnes, PhD2; Ashley Pfaff, BA2; Emily Coderre, BA2; Heather Wilkins, BA2; Diantha Howard, MS3; Edward D. Levin, PhD4

1Center for Cognitive Medicine, Department of Psychology, Vanderbilt University School of Medicine, 2Clinical Neuroscience Research Unit, Department of Psychiatry, University of Vermont College of Medicine, 3Department of Pharmacology, Georgetown University School of Medicine, 4Department of Neuropsychology, University of California San Diego School of Medicine, 5Clinical and Translational Science, University of Vermont College of Medicine, 6Department of Psychiatry and Behavioral Science, University of California, San Diego

Introduction

Interest in nicotinic treatment of Alzheimer’s disease (AD) developed following recognition of the loss of nicotinic receptors and that short-term administration of nicotine and novel nicotinic agonists improves cognitive performance in AD. Mild Cognitive Impairment (MCI) may also be an appropriate target for nicotinic treatment as nicotinic receptor systems may be better preserved and thus more responsive to stimulation.

Research Question

Will nicotine treatment produce improvements in cognitive performance and clinical ratings in amnestic MCI while being well tolerated?

Methods

Sites:
University of Vermont (coordinating site): 27 subjects; Duke University: 28 subjects; Georgetown University: 19 subjects

Diagnostic Criteria for Amnestic MCI:
- Memory complaints/difficulties verified by an informant.
- Abnormal memory function documented by scoring below the education adjusted cutoff on the Delayed Paragraph Recall from the Wechsler Memory Scale.
- Mini-Mental State Exam score between 24 and 30 (inclusive).
- Clinical Dementia Rating of 0.5; memory box score of 0.5 or 1.0. Memory complaints/difficulties verified by an informant.
- Abnormal memory function documented by scoring below the education adjusted cutoff on the Delayed Paragraph Recall from the Wechsler Memory Scale.
- Mini-Mental State Exam score between 24 and 30 (inclusive).
- Clinical Dementia Rating of 0.5; memory box score of 0.5 or 1.0.
- All recruited subjects were non-smokers.

Clinical and Cognitive Ratings:
Subjects were assessed at baseline, 91, and 182 days Cognitive Drug Research battery, Conners CPT, non-computer verbal and visual tasks, and clinical global impression of change (CGIC).

Results

Four-month analysis showed that nicotine treatment produced significant (p<0.05) improvements in delayed word recall accuracy, speed of memory, choice reaction time accuracy from the CDR battery, and CPT accuracy and reaction time standard error compared to placebo treated patients.

Continuous Performance Task:
Hit Reaction Time standard error change over ISI: Nicotine treatment effect (p<.001)

Conclusion

- Transdermal nicotine treatment of MCI showed significant improvements in measures of memory and speed with several other measures also showing strong trends towards improvement. The CGIC scores favored nicotine but was underpowered for this effect.
- Treatment was well tolerated and did not produce clinically meaningful worsening of vital signs.
- We conclude that transdermal nicotine treatment has significant promise as a symptomatic treatment for MCI and deserves further exploration in a larger trial.


References

This study was conducted with support from the followingNIH R01 AG023262 and WYETH-MC-003038, and Pfizer Incorporated provided for the transdermal nicotine and placebo patches. Please direct correspondence to: Paul A Newhouse: newhouse@vanderbilt.edu