EXPERT REVIEWS

Possible role of nicotine for the treatment of mild cognitive impairment

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Evaluation of: Newhouse P, Kellar K, Aisen P *et al.* Nicotine treatment of mild cognitive impairment: a 6-month double-blind pilot clinical trial. *Neurology* 78(2), 91–101 (2012).

There have been several drug trials in recent years investigating the efficacy of commonly used Alzheimer's disease therapies for symptoms of mild cognitive impairment (MCI). However, there are no US FDA-approved pharmacological treatments for MCI. As the incidence rates of MCI are considerable, it is clear that better treatments for MCI need to be developed. The reviewed paper presents new data on a pilot clinical trial which shows that transdermal nicotine treatment for 6 months improved cognitive performance in subjects with amnestic MCI. Further studies will possibly bring us wider usage of nicotine for individuals with cognitive dysfunction.

Keywords: continuous performance test • mild cognitive impairment • nicotine • randomized controlled trial

Mild cognitive impairment

Mild cognitive impairment (MCI) is a syndrome defined as cognitive decline greater than expected for an individual's age and education level but that does not interfere notably with activities of daily life [1]. MCI refers to a transitional stage from the cognitive changes of normal aging to early dementia, including Alzheimer's disease (AD). Primarily, MCI can be divided into two subtypes: amnestic (including memory impairment) and nonamnestic (nonmemory cognitive domains impaired) [2,3]. The incidence rates for MCI are substantial. Incidence rates of MCI in the range of 51–76.8 per 1000 person-years have been reported [4,5].

Individuals with MCI are at risk for developing dementia, a highly burdensome disease, and are of high clinical importance. Currently, no pharmacological therapies have demonstrated effectiveness for MCI. However, MCI patients are frequently being treated with 'off-label' cholinesterase inhibitors and memantine, as well as other putative cognitive-enhancing drugs, such as antioxidants [6,7]. There have been several drug trials in recent years investigating the efficacy of commonly used therapies for AD for subjects with MCI [8–11]. While a donepezil study suggested that it might be possible to delay the progression to AD [9], it is clear that better treatments need to be developed.

Nicotine

Nicotine binds to presynaptic nicotinic acetylcholine receptors in the brain and facilitates the release of acetylcholine, dopamine, serotonin, glutamate and other neurotransmitters known to be involved in cognitive processes [12]. Nicotine systems in the brain play an important role in the neural basis of memory and attention. Experimental animal studies have revealed the involvement of $\alpha 7$ and $\alpha 4\beta 2$ nicotinic receptor subtypes in the effects on working memory in the hippocampus [13]. Clinical studies using transdermal nicotine patches have demonstrated the efficacy of nicotine in treating cognitive impairments associated with AD [14], schizophrenia [15] and ADHD [16,17]. Both clinical and animal studies provide mutually supporting information for the development of novel nicotinic treatments for cognitive dysfunction [18]. The recent article by Newhouse *et al.* presents results of a double-blind, parallel-group, placebo-controlled, randomized clinical trial of the effect of chronic transdermal nicotine treatment on cognitive performance and clinical status in adults with MCI [19].

Methods & results

Newhouse *et al.* evaluated the safety, efficacy and tolerability of nicotine dosed at 15 mg/day for 6 months via transdermal nicotine patch

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in subjects with MCI in a double-blind, placebo-controlled, parallel-group, randomized clinical trial, for which 100 subjects were recruited from three sites [19]. MCI diagnosis utilized the following criteria for amnestic MCI: age above 55 years; memory complaints and difficulties verified by an informant; abnormal memory function documented by scoring below the education-adjusted cutoff on the Logical Memory II subscale from the Wechsler Memory Scale-Revised, as used in a prior MCI trial [9]; Mini-Mental State Examination score between 24 and 30 inclusive; and a Clinical Dementia Rating of 0.5 with a memory box score of 0.5 or 1.0 [20]. Exclusion criteria included medical or neurological disease, head injury, structural brain abnormalities, Axis I psychiatric illness or substance abuse within the last 2 years, chronic use of cholinergic or anticholinergic medications and current tobacco or nicotine use.

Seventy-four nonsmoking subjects with amnestic MCI met inclusion criteria and were randomized to transdermal nicotine (15 mg/day) or placebo for 6 months. Transdermal nicotine was initially administered using a 5-mg patch, and titrated to 15 mg by day 21. Thirty-nine subjects were randomized to nicotine treatment (34 completers) and 35 subjects to placebo treatment (33 completers). One subject dropped out owing to progression to AD. Four subjects assigned to nicotine withdrew because of adverse events, whereas two subjects assigned to placebo only withdrew owing to adverse events.

Performance/behavioral assessments were carried out 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), as improvement in this variable over varying intervals is a strong indication of overall attentional performance in AD [14]. In addition, the Clinical Global Impression of Change was used as the primary clinical outcome measure. Secondary cognitive measures included performance on the Cognitive Drug Research computerized battery, the Immediate and Delayed Paragraph Recall Test and the Digit Symbol Substitution Task. Behavioral and functional ratings by subjects and observers included the Older Adult Self Report and Behavior Checklist. Safety and tolerability were evaluated by counting specific adverse events and dropouts owing to adverse events.

Mixed models repeated-measures analysis of variance were used to assess the effect of nicotine treatment on cognitive performance over time. Baseline scores and *APOE* genotype were included in the analysis as covariates. Analysis of the MCI-Clinical Global Impression of Change compared global ratings utilizing ordered polychotomous logistic regression at the end of double-blind treatment (182 days). Differences for rates of adverse events were assessed using χ^2 analysis.

The primary cognitive outcome measure, CPT hit reaction time standard error change over interstimulus intervals, showed a significant improvement (reduced variability in reaction time), in those assigned to the nicotine group compared with those receiving placebo. Improvement over time was observed in the group assigned to nicotine compared with placebo in patient and caregiver ratings but not clinician ratings of global clinical improvement. The secondary outcome of attention, memory and psychomotor speed showed significant improvements in the group receiving nicotine compared with the placebo-treated group. Cognitive activities in attention and response speed showed a significant advantage for nicotine treatment in the *APOE4* double-allele group compared with the E4/E3 and E3/E3 groups. Safety and tolerability for transdermal nicotine were excellent, although more nicotine-treated subjects discontinued treatment for adverse events than placebo-treated subjects.

Discussion

While several studies to date have evaluated the cognitive effects of nicotine in AD, this study is significant in that it targeted MCI with nicotine therapy. Nicotine may have superior efficacy in MCI than AD because those with MCI have had only a modest decline in cognitive function and tend to have relatively larger numbers of nicotinic acetylcholine receptors intact. This study found that transdermal nicotine, dosed at 15 mg/day over 6 months, is well tolerated by nonsmoking adults with MCI, and associated with improvement in measures of attention, memory and psychomotor performance. This finding provides strong justification for further treatment studies of nicotine for older adults with early evidence of cognitive dysfunction.

The results of this trial must nonetheless be viewed in the context of the study's limitations. The sample size was relatively modest, yet there were significant effects in several cognitive domains. Power was calculated on the basis of the CPT task, but the power to detect effects from clinical global ratings was limited. As this pilot clinical trial measured a broad number of cognitive and behavioral domains, some of which showed no effect of treatment, further study will be needed to clarify which cognitive domains are directly influenced by nicotinic stimulation in this population. This study tested only nonsmokers to simplify dose ranging. Future studies will require potentially different dose ranges in order to apply these findings to current smokers. In the present study, nicotine dose titration was only performed to limit side effects. Further clinical benefit of nicotine might be achieved by titration based on not only side effects but also efficacy.

Five-year view

This study included only subjects with amnestic MCI. As noted above, MCI also includes the other clinical subtype, nonamnestic. There are several cognitive domains such as language, learning, executive functions or visuospatial skills other than memory and attention that were investigated in this study. Of course, few studies have examined these domains owing to methodological difficulties [21]. Thus, research that attempts to simulate complex behavior in the laboratory might complement our knowledge of nicotine's cognitive effect [22].

There were no withdrawal symptoms reported by patients or informants and no subjects continued to use nicotine products after this study. Thus, there seems to be no evidence for abuse liability of transdermal nicotine in the nonsmoking population of this study. However, treatment periods longer than 1 year may be necessary in future studies to investigate the durability of its

cognitive effects. Abuse liability will need to be evaluated in these longer term studies.

Nicotine is best known as the principal psychoactive chemical in tobacco and a critical component of tobacco addiction. However, nicotine, like other drugs such as morphine, has a spectrum of effects that may be therapeutically useful. Our understanding of how nicotine affects cognitive function is enhanced by this kind of trial in diverse clinical populations.

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Key issues

- Although the incidence rate of mild cognitive impairment (MCI) is substantial, no pharmacological therapies have been identified to improve cognitive performance or prevent the subsequent development of dementia.
- It is important to evaluate the effect of nicotine for cognitive impairment in MCI since nicotine has been shown to improve cognitive impairment in Alzheimer's disease.
- To our knowledge, Newhouse *et al.* have conducted the first trial of nicotine as a therapeutic agent for enhancing cognitive function of people with MCI.
- This trial found that transdermal nicotine improved attention, memory and psychomotor speed, as well as patient and informant ratings of cognitive impairment in MCI, but did not find a significant effect on clinician-rated global improvement.
- Larger studies with longer follow-up are needed to evaluate the effect of nicotine on cognitive performance and progression to dementia in adults with MCI.

References

1 Gauthier S, Reisberg B, Zaudig M *et al.* Mild cognitive impairment. *Lancet* 367(9518), 1262–1270 (2006).

2 Petersen RC. Mild cognitive impairment as a diagnostic entity. *J. Intern. Med.* 256(3), 183–194 (2004).

3 Winblad B, Palmer K, Kivipelto M *et al.* Mild cognitive impairment – beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J. Intern. Med.* 256(3), 240–246 (2004).

4 Luck T, Luppa M, Briel S, Riedel-Heller SG. Incidence of mild cognitive impairment: a systematic review. *Dement. Geriatr. Cogn. Disord.* 29(2), 164–175 (2010).

5 Roberts RO, Geda YE, Knopman DS *et al.* The incidence of MCI differs by subtype and is higher in men: the Mayo Clinic study of aging. *Neurology* 78(5), 342–351 (2012).

6 Roberts JS, Karlawish JH, Uhlmann WR, Petersen RC, Green RC. Mild cognitive impairment in clinical care: a survey of American Academy of Neurology members. *Neurology* 75(5), 425–431 (2010).

7 Weinstein AM, Barton C, Ross L, Kramer JH, Yaffe K. Treatment practices of mild cognitive impairment in California Alzheimer's Disease Centers. *J. Am. Geriatr. Soc.* 57(4), 686–690 (2009).

8 Jack CR Jr, Petersen RC, Grundman M *et al.* Longitudinal MRI findings from the vitamin E and donepezil treatment study for MCI. *Neurobiol. Aging* 29(9), 1285–1295 (2008).

9 Petersen RC, Thomas RG, Grundman M *et al.* Vitamin E and donepezil for the treatment of mild cognitive impairment. *N. Engl. J. Med.* 352(23), 2379–2388 (2005).

10 Feldman H, Scheltens P, Scarpini E *et al.* Behavioral symptoms in mild cognitive impairment. *Neurology* 62(7), 1199–1201 (2004).

11 Thal LJ, Ferris SH, Kirby L *et al.* A randomized, double-blind, study of rofecoxib in patients with mild cognitive impairment. *Neuropsychopharmacology* 30(6), 1204–1215 (2005).

12 Di Matteo V, Pierucci M, Di Giovanni G, Benigno A, Esposito E. The neurobiological bases for the pharmacotherapy of nicotine addiction. *Curr. Pharm. Des.* 13(12), 1269–1284 (2007).

13 Levin ED, Rezvani AH. Development of nicotinic drug therapy for cognitive disorders. *Eur. J. Pharmacol.* 393(1–3), 141–146 (2000).

14 White HK, Levin ED. Four-week nicotine skin patch treatment effects on cognitive performance in Alzheimer's disease. *Psychopharmacology (Berl.)* 143(2), 158–165 (1999).

15 Barr RS, Culhane MA, Jubelt LE *et al.* The effects of transdermal nicotine on cognition in nonsmokers with schizophrenia and nonpsychiatric controls. *Neuropsychopharmacology* 33(3), 480–490 (2008).

16 Levin ED, Conners CK, Sparrow E *et al.* Nicotine effects on adults with attention-deficit/hyperactivity disorder. *Psychopharmacology (Berl.)* 123(1), 55–63 (1996).

17 Potter AS, Newhouse PA. Acute nicotine improves cognitive deficits in young adults with attention-deficit/hyperactivity disorder. *Pharmacol. Biochem. Behav.* 88(4), 407–417 (2008).

18 Rezvani AH, Levin ED. Cognitive effects of nicotine. *Biol. Psychiatry* 49(3), 258–267 (2001).

19 Newhouse P, Kellar K, Aisen P *et al.* Nicotine treatment of mild cognitive impairment: a 6-month double-blind pilot clinical trial. *Neurology* 78(2), 91–101 (2012).

20 Petersen RC, Doody R, Kurz A *et al.* Current concepts in mild cognitive impairment. *Arch. Neurol.* 58(12), 1985–1992 (2001).

21 Heishman SJ, Kleykamp BA, Singleton EG. Meta-analysis of the acute effects of nicotine and smoking on human performance. *Psychopharmacology (Berl.)* 210(4), 453–469 (2010).

22 Sauer J, Wastell DG, Hockey GR, Earle F. Performance in a complex multiple-task environment during a laboratory-based simulation of occasional night work. *Hum. Factors* 45(4), 657–669 (2003).