Drug and Alcohol Dependence 126 (2012) 263–267

Contents lists available at SciVerse ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Short communication

Cognitive effects of the acetylcholinesterase inhibitor, donepezil, in healthy, non-treatment seeking smokers: A pilot feasibility study

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ARTICLE INFO

Article history:
Received 19 January 2012
Received in revised form 18 April 2012
Accepted 21 April 2012
Available online 15 May 2012

Keywords:
Smoking
Nicotine
Acetylcholine
Cognition
Cognitive enhancers
Working memory

ABSTRACT

Background: There is a need to identify medications to aid in smoking cessation. Reducing withdrawal-related cognitive deficits represents a pharmacological target for new pharmacotherapies. Endogenous acetylcholine levels, which are modulated by acetylcholinesterase inhibitors (AChEIs), play an important role in smoking behavior and cognition. This pilot feasibility study tested whether an AChEI, donepezil, enhanced cognitive performance among healthy smokers.
Methods: Eighteen non-treatment seeking daily smokers (6 female) received either donepezil (5 mg q.d) or placebo (double-blind; 2:1 allocation ratio) for 4 weeks. Smoking rate, side effects, and neurocognitive measures of working memory (Letter-N-back) and sustained attention (Penn Continuous Performance Task) were assessed weekly.
Results: For the working memory task, there was a significant group × load × time interaction ($p = 0.03$) indicating that the donepezil group demonstrated an increase in true positives from baseline to week 4 at the highest working memory load (3-back). The placebo group showed no change in accuracy. For the sustained attention task, there was a marginal effect in the same direction for discriminability, or d', $p = 0.08$. There were no significant effects on reaction time during either task. There was also a reduction in cigarettes per day in the placebo group, but not the donepezil group.
Conclusions: AChEIs, such as donepezil, may have pro-cognitive effects among healthy smokers while they continue to smoke as usual. Given the association between cognitive deficits and relapse, AChEIs should be explored as potential therapeutics for smoking cessation.
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1. Introduction

Cigarette smoking remains the most significant public health problem globally (World Health Organization, 2008). Despite availability of FDA-approved medications for smoking cessation, only 1 in 4 smokers in the United States can maintain abstinence (Schnoll and Lerman, 2006). Indeed, most relapse within the first days following a quit attempt (Hughes et al., 2004). During this period, deficits in attention and working memory and alterations in task-induced neural activation are commonly observed (Addicott et al., 2012; Ashare and Hawk, 2012; Loughead et al., 2010; Myers et al., 2008); these deficits, in turn, predict relapse (Patterson et al., 2010; Powell et al., 2010). Thus, withdrawal-related cognitive deficits represent a novel target for nicotine dependence treatment development.

Several lines of research provide a rationale for examining acetylcholinesterase inhibitors (AChEIs) as potential therapeutics. First, nicotine administration enhances levels of acetylcholine (ACh) and the choline acetyltransferase (ChAT) enzyme, which is involved in the biosynthesis of ACh; whereas nicotine withdrawal in animals decreases ChAT enzyme activity (Arnold et al., 2003; Hernandez and Terry, 2005; Slotkin et al., 2008). AChEIs, which increase ACh in the synapse through inhibition of the catabolic enzyme, acetylcholinesterase (AChE), may substitute for the effects of nicotine. Further, genetic variation in the choline acetyltransferase (*ChAT*) gene, which regulates endogenous ACh levels, is associated with smoking cessation and nicotine dependence in independent cohorts (Ray et al., 2010; Wei et al., 2010). Lastly, AChEIs enhance cognition in patients with Alzheimer's disease (Birks, 2006) and some healthy populations (Repantis et al., 2010). These studies support the biological plausibility of targeting endogenous acetylcholine levels to alleviate withdrawal-related cognitive deficits.

AChEIs are FDA-approved for treating the cognitive symptoms of Alzheimer's disease (Terry and Buccafusco, 2003). Donepezil is the most commonly prescribed AChEI, and may have neuroprotective

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http://dx.doi.org/10.1016/j.drugalcdep.2012.04.019

effects which are important for its pro-cognitive properties (Delrieu et al., 2011). Chronic treatment with donepezil increases functional up-regulation of the α7 and α4β2 nicotinic receptors (nAChRs), which are important for cognition (Takada-Takatori et al., 2009). Donepezil's pro-cognitive effects in healthy populations are mixed (Repantis et al., 2010) and studies have begun to explore AChEI effects on smoking behavior (De la Garza and Yoon, 2011; Diehl et al., 2006; Kelly et al., 2008). However, no study to the best of our knowledge has focused on the general population of smokers.

This pilot feasibility study examined: (1) tolerability and medication adherence, and (2) the effects of donepezil versus placebo on smoking behavior and cognitive performance in non-treatment seeking smokers. We predicted that 4 weeks of donepezil would improve working memory at the highest task difficulty level and sustained attention. Because participants in this study were not trying to quit, change in smoking behavior was a secondary outcome.

2. Methods

2.1. Participants

Eligible smokers were 18–50 years old, smoked at least 10 cigarettes per day for the previous 6 months, and had no plans to quit smoking in the next 2 months. Exclusion criteria included: pregnancy, lactation, or planning pregnancy; heart attack/stroke in previous 6 months; peptic ulcer disease; current diagnosis or history of DSM-IV Axis I disorders (except nicotine dependence); and current use of smoking cessation treatment, psychotropic medications, or contraindicated medications (e.g., anti-seizure medications).

2.2. Study design and procedures

This is a double-blind, between-subjects human laboratory study comparing 4 weeks of treatment with donepezil (5 mg q.d.) to placebo. To gain more information about responses to donepezil, while minimizing loss of power, we employed a 2:1 allocation ratio (Friedman et al., 2010). Placebo and active study medication were packaged in identical capsules by Investigational Drug Services at the University of Pennsylvania. Following an intake to confirm eligibility, participants completed a baseline session, four testing days (at the end of each week during the 4-week treatment period), and four observation days (one in-between each testing day). During all visits, participants completed measures of smoking rate, pill count, and side effects and provided carbon monoxide breath samples. This manuscript focuses on the neurocognitive tasks (described below) assessed during baseline and testing days. The University of Pennsylvania Institutional Review Board approved all procedures and all participants provided written informed consent.

2.3. Measures

2.3.1. Demographics and smoking behavior. Sex, age, race, education, nicotine dependence (FTND; Heatherton et al., 1991), and cigarettes per day were assessed at baseline. At each visit, smoking rate was assessed using standard Timeline Followback methods (Brown et al., 1998). Weekly averages were computed to assess group differences in changes in smoking behavior from baseline to week 4.

2.3.2. Medication adherence and side effects. Medication adherence was calculated as the percentage of pills consumed (out of 28). Side effect severity was rated on a 4-point scale (0 = not present, 1 = mild, 2 = moderate, 3 = severe) using a 38-item self-report measure based on common side effects of donepezil (e.g., nausea). The side effect summary score at week 4 (when medication reached steady state) was the dependent measure.

Table 1
Demographic and smoking characteristics by group (total $N = 18$).

	Group		
	Placebo ($n = 6$)	Donepezil ($n = 12$)	p-Value
Sex (n female)	2	4	–
Age (years)	36 (12)	38 (7)	0.53
Race (n, %Caucasian)	5, 83%	7, 58%	0.29
Education (n, %college degree)	5, 83%	7, 58%	0.68
Nicotine dependence	3.7 (0.42)	5.2 (0.52)	0.08
Baseline cigarettes per day	15 (1.7)	16 (1.5)	0.74
Years smoking	22 (6)	20 (2)	0.75

Notes: values are mean (standard error) unless otherwise noted.

2.3.3. Neurocognitive task performance. Neurocognitive task performance was assessed during baseline and each testing day (Day 7, 14, 21, and 28) using computerized tasks. Working memory was assessed with the Letter-N-back task (Ragland et al., 2002) and the primary outcomes were true positives and median correct reaction time. Sustained attention was assessed with the Penn Continuous Performance Task (P-CPT; Kurtz et al., 2001) and the primary outcomes were discriminability (d'), a signal detection measure calculated from hit rate (i.e., true positives) and false alarm rate (i.e., errors of commission) and the median correct reaction time. These tasks have been validated in healthy volunteers and patient populations (Gur et al., 2010; Kurtz et al., 2001; Ragland et al., 2002) and are sensitive to medication effects on cognition during abstinence and predict relapse (Patterson et al., 2009, 2010) (For detailed task descriptions see Patterson et al., 2009).

2.4. Data analysis

ANOVA models were used to examine medication adherence, side effects (controlling for baseline side effects), and smoking rate. Repeated-measures ANCOVAs tested the effects of donepezil on working memory (e.g., true positives, reaction time) and sustained attention (e.g., d', reaction time). For all models, group (donepezil vs placebo) was a between-subjects factor and time (baseline, week 1–4) was a within-subjects factor. For working memory, n-back load (0-, 1-, 2-, 3-back) was an additional within-subjects factor. Based on evidence that the 3-back condition is most sensitive to abstinence (Loughead et al., 2009) and medication effects (Loughead et al., 2010) and that performance during the 3-back condition predicts relapse (Patterson et al., 2010), post hoc tests focused on the 3-back condition. The time by group interaction was tested, and sex, age, and baseline cigarettes per day were covariates in all models (results were comparable when FTND was a covariate).

3. Results

3.1. Participants

Of the 89 participants eligible at phone screen, 55 scheduled an intake, and 22 were randomized (7 ineligible, 26 missed/refused). Eighteen (6 female) participants completed all study measures (4 withdrew). Using a 2:1 allocation ratio, 12 participants were randomized to donepezil and 6 to placebo. Demographic and smoking characteristics are presented in Table 1. Except for a marginal difference in nicotine dependence, $F(1,17) = 3.5$, $p = 0.08$, the groups did not differ on any demographic characteristics, all $ps > 0.18$ (Table 1).

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