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Short Report

# Microdosing of scopolamine as a "cognitive stress test": Rationale and test of a very low dose in an at-risk cohort of older adults

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**Abstract**

**Background:** Abnormal β-amyloid (Aβ) is associated with deleterious changes in central acetylcholinergic tone in the very early stages of Alzheimer's disease (AD), which may be unmasked by a cholinergic antagonist. We aimed to establish an optimal "microdose" of scopolamine for the development of a "cognitive stress test."

**Methods:** Healthy older adults ($n = 26$, aged 55–75 years) with two risk factors for AD, but with low cortical Aβ burden, completed the Groton Maze Learning Test (GMLT) at baseline and then received scopolamine (0.20 mg subcutaneously). Participants were reassessed at 1, 3, 5, 7, and 8 hours postinjection.

**Results:** There were significant differences, of a moderate magnitude, in performance between baseline and 3 hours postinjection for total errors, rule break errors, and the GMLT composite ($d \approx 0.50$) that were all unrelated to body mass.

**Conclusions:** A very low dose of scopolamine leads to reliable cognitive impairment at 3 hours postdose ($T_{max}$) and full cognitive recovery within 5 hours, supporting its use as a prognostic test paradigm to identify individuals with potential preclinical AD. This paradigm is being implemented in a larger cohort of healthy adults, with high or low Aβ, to identify pharmacodynamic differences between groups.



*Keywords:* Alzheimer disease; Preclinical Alzheimer's disease; Early detection; Cholinergic; Cognition; Biomarkers; Diagnosis; Anticholinergic drugs; Scopolamine; β-Amyloid protein

## 1. Introduction

To protect cognitive function for as long as possible, putative neuroprotective treatments must be administered during the preclinical stages of Alzheimer's disease (AD) [1]. Hence, there is a need to identify reliably healthy individuals at high risk of developing AD. Current biomarkers, obtained through positron emission tomography (PET) neuroimaging or lumbar puncture, are invasive, costly, and labor-intensive. As such, we are currently exploring whether the use of a microdose pharmacologic challenge using a muscarinic cholinergic antagonist, paired with a well-validated cognitive assay, may lead to a "cognitive stress test" to identify older adults with substantial cortical β-amyloid (Aβ) burden. In this brief report, we aim to present the rationale for a

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cognitive stress test for preclinical AD as well as initial study results from a sample of older adults with known risk factors for the disease, but with low Aβ burden, to determine that a low dose of the cholinergic antagonist, scopolamine, can cause detectable cognitive change.

Multiple aspects of cognitive function rely on the integrity of the cholinergic system, and disruptions to this system are seen in AD, with substantial neuronal loss in the basal forebrain cholinergic system [2]. In the early stages of the disease, there is a change in cholinergic tone [3–5] that affects cognitive status [6]. Moreover, cortical cholinergic denervation may also precede and play a causal role in the cortical deposition of fibrillar Aβ peptides in this early disease stage [7].

The combination of pharmacologic challenges with targeted cognitive measures ("cognitive stress test") has been supported by animal and human models of aging and dementia [8–10]. The specific use of anticholinergics in pharmacologic models of aging and dementia is further supported by evidence of the amelioration of resulting cognitive impairments with acetylcholinesterase inhibitors in rodents [11,12] as well as humans (e.g., donepezil [13,14]). In healthy adults, scopolamine has been used to create a dose-dependent impairment in memory and information processing speed and efficiency that resembles impairments in patients with AD [13,15–17]. Previously, we used 0.30 mg of subcutaneously (s.c.) administered scopolamine to elicit cognitive deficits; however, although no subjects experienced any serious adverse events, most subjects still required over 9 hours to return to baseline cognitive performance [13]. Such a lengthy recovery period would limit the use of this challenge as an outpatient prognostic test. However, an early report that relied on an older generation of pencil-and-paper cognitive tests showed that 0.25 mg scopolamine led to no observable pharmacodynamic response in healthy older adults [15]. This lack of discernible effect could have been due to small sample size and/or the use of instruments with suboptimal metric properties. By comparison, when the Groton Maze Learning Test (GMLT) was used, 0.2 mg s.c. scopolamine administered to healthy young adults resulted in significantly worse performance 2 hours postinjection [18].

Our prior work [13,18,19] demonstrates that it is important to select a suitable cognitive assay that is sensitive to acetylcholine modulation and possesses metric properties that are appropriate for detecting improvement in healthy adults. The GMLT has been shown to be sensitive to impairments in memory and executive function in mild cognitive impairment and to the effects of induced pharmacologic challenges [13,18,20]. In addition, we have shown repeatedly that performance on the GMLT does not change when subjects were administered a placebo, as opposed to scopolamine [13,18], thus supporting the design of the current study to enable us to observe cognitive performance pre- and postdose (i.e., a within-subjects A-B-A design). The overarching aim was to determine whether a microdose of scopolamine (0.20 mg s.c.) would result in reliably measured cognitive changes and a rapid recovery period in a sample of healthy older adults with two known risk factors for AD but who have low Aβ retention on Aβ PET imaging. We hypothesized that a 0.2-mg s.c. dose of scopolamine would lead to reliable and expected significant differences between performance at baseline and 3 hours in a vulnerable cohort of "at-risk" older adults with low cortical Aβ. Because scopolamine is lipophilic, we also explored whether individual differences in body mass might confound interpretation of pharmacodynamic effects [21,22].

## 2. Methods

### 2.1. Participants

Participants were recruited from two academic memory disorder clinics in Rhode Island and via the Alzheimer's Association *TrialMatch* website between June and November 2013. Fifty-six older adults volunteered for the study, and 24 did not meet inclusion/exclusion criteria. Study volunteers were required to be between 55 and 75 years of age and have two known risk factors for AD (i.e., subjective memory complaints and a positive first-degree relative with AD). Volunteers were excluded if they had a diagnosis of AD or mild cognitive impairment, history of neurological disease or insult, psychiatric disorder, any significant systemic illness or unstable medical condition, Mini-Mental State Examination (MMSE) total scores less than 27, a Geriatric Depression Scale (GDS) score of 6 or greater, and current use of any medications known to affect cognition. The study team was blinded to PET results at participants' baseline assessment. Thirty-two participants were enrolled, but in this report, only data from participants with low Aβ (i.e., standardized uptake value ratio [SUVR] $< 1.1$; $n = 26$) were analyzed. Table 1 summarizes the demographic and clinical characteristics of this group. The study was approved by and complied with the regulations of Rhode Island Hospital's Institutional Review Board. All participants provided written informed consent.

Table 1
Sample demographic and clinical characteristics

| | Aβ- ($n = 26$) |
|---|---|
| | $n$ (%) or mean (SD) |
| $n$ (%) female | 15 (57.70%) |
| Age (years) | 62.31 (5.48) |
| Years of education | 17.17 (2.29) |
| SUVR | 0.88 (0.18) |
| Body mass index | 25.89 (5.13) |
| 15-item GDS | 1.77 (2.29) |
| MAC-Q | 22.77 (2.94) |
| MMSE | 29.04 (1.00) |

Abbreviations: SD, standard deviation; SUVR, standardized uptake value ratio; GDS, Geriatric Depression Scale; MAC-Q, Memory Complaints Questionnaire; MMSE, Mini-Mental State Examination.

NOTE. Age range = 55–75 years old. SUVR range = 0.73–1.05.