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RESEARCH ARTICLE

Odor identification impairment and cholinesterase inhibitor treatment in Alzheimer's disease

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Abstract

Introduction: This study evaluated acute change in odor identification following atropine nasal spray challenge, and 8-week change in odor identification ability, as a predictor of long-term improvement in patients with mild to moderate Alzheimer's disease (AD) who received open-label cholinesterase inhibitor treatment.

Methods: In patients with clinical AD, the University of Pennsylvania Smell identification Test (UPSIT) was administered before and after an anticholinergic atropine nasal spray challenge. Patients were then treated with donepezil for 52 weeks.

Results: In 21 study participants, acute atropine-induced decrease in UPSIT was not associated with change in the Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-Cog) or Selective Reminding Test (SRT). Decline in odor identification performance from baseline to week 8 was indicative of a future decline in cognitive performance over 52 weeks.

Discussion: Change in odor identification with atropine challenge is not a useful predictor of treatment response to cholinesterase inhibitors. Short-term change in odor identification performance needs further investigation as a potential predictor of cognitive improvement with cholinesterase inhibitor treatment.

KEYWORDS
acetylcholine, Alzheimer's disease, atropine, odor identification, olfaction

1 | INTRODUCTION

Alzheimer's disease (AD) brain pathology is characterized by neurofibrillary tangles and amyloid plaques. In the early stages of the disease, these pathognomonic signs of AD, particularly neurofibrillary tangles, are found in the olfactory bulb and tract,[1] and cholinergic neurons start to degenerate.[2] Cholinergic neurons are prominent in the olfactory bulb and entorhinal cortex[3]; therefore, deficits in odor identification in early AD may indicate the loss of cholinergic inputs to the olfactory brain regions and higher order projection areas for olfactory processing, including the anterior olfactory nucleus, orbitofrontal cortex, piriform cortex, amygdala, entorhinal cortex, and hippocampus.[4,5] These deficits manifest clinically as poor performance on tests of standardized odor identification.[6,7]

The cholinergic system uses the neurotransmitter acetylcholine (ACh), which plays a significant role in learning and memory processes. As AD progresses, the activity of ACh becomes greatly reduced,[2] contributing to memory deficits, which are the hallmark of the disease. The cholinergic hypothesis[8] posits that AD onset and progression relate to the decrease in ACh. Acetylcholinesterase inhibitors (AChEIs) increase

HIGHLIGHTS

- Patients with mild to moderate Alzheimer's disease were treated with donepezil
- Effect of nasal atropine challenge did not predict cognitive change over 52 weeks
- Acute change in odor identification was related to longitudinal change in cognition

RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the published literature (eg PubMed, Scopus) on nasal atropine challenge and Alzheimer's disease (AD). Atropine produces temporary odor identification deficits that are more pronounced in individuals with AD biomarkers; however, the utility of atropine as a prognostic indicator for AD patients undergoing cholinesterase inhibitor treatment is unclear, as previous null trials are limited and have focused on patients with mild cognitive impairment.
2. Interpretation: In the present study, immediate change in odor identification performance following nasal atropine challenge was not a useful predictor of treatment response to cholinesterase inhibitors. Decline in odor identification performance over the first 8 weeks of the trial was related to decline in cognitive performance over the 52-week trial.
3. Future directions: Although atropine challenge was not prognostically informative, expanded investigation of acute change in odor identification during cholinesterase treatment is needed.

the availability of ACh in the synapse and have modest efficacy above placebo for improving cognition in AD. A meta-analysis of 19 AChel trials for patients with AD found a mild-moderate effect (d = -0.38) favoring the AChel donepezil over placebo for improving global cognition.[9] However, all trials except one had a duration of 6 months or less; therefore it is unclear how long gains are sustained. Brain imaging predictors of cognitive improvement on cholinesterase inhibitors have been inconsistent across studies,[10,11] and identifying a simple peripheral marker of likely improvement may have clinical application.

Atropine is an anticholinergic drug that acts primarily on muscarinic receptors and may have potential for identifying individuals with preclinical AD. Administration of atropine as a nasal spray is an anticholinergic "challenge" that can be made to cross the "nose-brain barrier" by positioning the individual in the "Mecca" position. Using this approach, atropine has been shown to cause a temporary decrease in odor identification performance in patients with underlying AD pathology.[14] In a sample of 56 elderly individuals (14 probable AD, 13 cognitive impairment no dementia, 29 cognitively intact),[14] decline in odor identification scores from pre- to post-atropine nasal spray challenge was strongly correlated with lower memory performance and reduced magnetic resonance imaging (MRI) hippocampal volume. The atropine effect of reducing odor identification may be more pronounced in patients with already compromised cholinergic pathways, as in AD. Therefore, the degree of reduction in odor identification test scores following atropine nasal spray would serve as an indicator of reduced cholinergic neurotransmission, whereby individuals with the greatest reduction in odor identification stand to benefit the most from a medication that blocks the breakdown of ACh and increases ACh synaptic availability. Taken together, the atropine effect could serve as a prognostic indicator for who will respond to AChel treatment.

The current study aimed to evaluate acute change in odor identification following atropine nasal spray challenge as a predictor of long-term improvement in patients with mild to moderate AD who receive AChel (donepezil) treatment. Results for patients with mild cognitive impairment (MCI) from an independent sample enrolled in a separate study conducted in parallel have been reported previously.[7] In the current study of patients with mild to moderate AD treated with donepezil, we hypothesized that: (1) the atropine effect (an acute decrease in odor identification test scores from pre- to post-atropine challenge at baseline) would predict improved cognitive and global functioning from baseline to weeks 26 and 52; and (2) increase in odor identification test scores after 8 weeks would predict improved cognitive and global functioning from baseline to weeks 26 and 52.

2 | METHODS

2.1 | Participants

This study was approved by the New York State Psychiatric Institute (NYSPI)/Columbia University Institutional Review Board (IRB). The trial is registered on clinicaltrials.gov (identifier: NCT01951118). Participants were recruited from the Memory Disorders Clinic at NYSPI and the Behavioral Neurology practice at Columbia University Medical Center (CUMC), and by advertising in local media. Recruitment began in October 2013, with the final patient completing the trial in March 2019. Inclusion criteria were age 55-95 years, diagnosis of probable AD by National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association criteria[15] and core clinical diagnosis of "Probable AD dementia" by the new National Institute on Aging (NIA) criteria,[16] Folstein Mini-Mental State Exam (MMSE) 18-27 of 30,[17] availability of an informant, and ability to provide informed consent.

Exclusion criteria included current use of cholinesterase inhibitors, history of intolerance or contraindication to donepezil, and use of medications with anticholinergic properties including diphenhydramine, tricyclic antidepressants, and antipsychotics. Benzodiazepine use in lorazepam dose equivalents less than 2 mg daily was permitted. Other

exclusion criteria were severe unstable medical illness; specific neurological disorders including Parkinson disease, multiple sclerosis, and stroke with residual neurological deficits; psychotic disorders including schizophrenia, bipolar disorder, and schizoaffective disorder; alcohol/substance dependence in the past 6 months; current major depression; and suicidality. Exclusion criteria for olfaction testing were current smoker > 1 pack daily, current upper respiratory infection, nasal trauma or sinus surgery, and head trauma with loss of consciousness.

2.2 | Measures

The screening visit comprised a medical, psychiatric, and neurological evaluation; cognitive assessment to determine inclusion criteria; and blood was drawn for hematocrit, electrolytes, liver, kidney, and thyroid function tests, folate, vitamin B12 levels, and urinalysis to exclude primary medical causes of cognitive impairment.

The subsequent baseline (week 0) visit involved assessment with the two main cognitive outcome measures: Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-Cog, 11-item version)[18] and 12- item 6-trial Selective Reminding Test (SRT).[19] For diagnostic purposes, neuropsychological tests in the National Alzheimer's Coordinating Center-Uniform Data Set (NACC–UDS) battery were administered: Wechsler Memory Scale-III digit span forward and backward[20]; Wechsler Adult Intelligence Scale-Revised digit symbol[21]; Trail Making A and B[22]; verbal fluency using the letters C, F, and L and animal, vegetable, and fruit list generation[22]; and Boston Naming Test (60 items).[23] If a participant's preferred language was Spanish, neuropsychological tests were administered in Spanish using standardized versions that have been validated in other studies.[6] Otherwise, tests were administered in English to patients, including bilingual patients who were fluent in English and preferred to be tested in English. The study physician completed the NACC clinical assessment, Clinician's Interview Based Impression of Change-plus (CIBIC-plus) and Clinician Interview Based Impression of Severity (CIBIS) global assessment ratings,[24] Clinical Dementia Rating (CDR),[25] and the Treatment Emergent Symptoms Scale (TESS),[26] which evaluates 26 common somatic side effects that include gastrointestinal and central nervous system (CNS) side effects known to occur with ACheI. The study physician completing these measures remained blind to the cognitive outcome measures. An informant completed the Pfeffer Functional Activities Questionnaire (FAQ).[27] Apolipoprotein E genotyping was conducted at Lgc Genomics, a reference laboratory. To determine AD diagnostic eligibility, two experienced raters (Drs. Devanand and Stern) made a consensus diagnosis while remaining blind to scores on predictor (UPSIT) and cognitive outcome (ADAS-Cog total score and SRT total immediate recall) measures.

2.3 | Olfactory assessment

The University of Pennsylvania Smell Identification test (UPSIT) was administered. This standardized scratch and sniff test consists of 40 booklet pages with a single odor embedded in a microcapsule on each page. Scratching with a pencil releases the odor and the participant checks one of 4 choices, for example, chocolate, banana, onion, or fruit punch. The total UPSIT score ranges from 0 (all answers incorrect) to 40 (all answers correct). At the baseline visit, immediately after UPSIT administration, atropine solution 1 mg, with the dose divided approximately equally between the two nostrils, was administered using the "squirt system."[28] This was delivered via plastic tube attached to a syringe while the patient reclined their head. The tube was placed in the nasal cavity parallel to the nasal septum and directed toward the olfactory cleft. Next, the patient assumed a crouching head-down posture (the "Mecca" position) for 2 min to facilitate atropine crossing the cribriform plate into the olfactory bulb.[14] The UPSIT was repeated 45 min later to ensure sufficient time for the atropine to take effect.

2.4 | Treatment

Research assessments were repeated at 8, 26, and 52 weeks, with the exception of the diagnostic neuropsychological battery that was repeated only at 26 and 52 weeks in order to reduce practice effects. At baseline, donepezil was started at 5 mg daily followed by assessment at 4 weeks for tolerability before increasing the dose to 10 mg daily. This dose was kept constant for the rest of the 52-week study. Patients who could not tolerate donepezil 10 mg were maintained at 5 mg.

2.5 | Statistical analyses

The baseline characteristics of the study sample were described by mean and SD for continuous variables and percent and frequency for categorical variables. Wilcoxon signed rank test was used to test whether there is any change in UPSIT scores from pre- to post-atropine challenge at week 0 (denoted as $\Delta UPSIT_a$) and from pre-atropine challenge at week 0 to 8 weeks of donepezil treatment (denoted as $\Delta UPSIT_{8wk}$). Spearman correlation coefficients examined bivariate associations between baseline quantitative variables. The bivariate association of $\Delta UPSIT_a$ and $\Delta UPSIT_{8wk}$ with baseline covariates were evaluated using Spearman correlation and Kruskal-Wallis test for continuous and categorical baseline variables, respectively. The trajectories of UPSIT scores and cognitive measures were summarized using mean $\pm$ SD. Fisher exact test and Wilcoxon rank sum test detected differences between those who completed 52 weeks of follow-up and those who dropped out for continuous and categorical baseline variables, respectively.

Linear models with repeated measures were applied to assess the effect of acute change in odor identification following atropine nasal spray challenge on the cognitive outcomes measured at baseline, 26, and 52 weeks. Those outcomes include ADAS-cog, SRT, CIBIC-plus SRT-delayed, and CIBIS. The ADAS-Cog was skewed and therefore transformed to reduce the impact of extreme values. The generalized estimating equation (GEE) approach was employed to estimate

model parameters. For each outcome variable, patients with data missing at baseline were excluded from analysis. We choose GEE over mixed-effects models, as it is more robust to misspecification of correlation structure in repeated measures.

For each outcome, two models were considered. The first model started with the time indicator (week 0, 26, or 52), $\Delta UPSIT_a$, their interaction, baseline pre-nasal challenge UPSIT score (UPSIT0), and any baseline variables that were significantly correlated with $\Delta UPSIT_a$ in the bivariate analysis. The non-zero coefficients of the time-by-$\Delta UPSIT_a$ interaction indicated whether a time trend in the outcome was modified by $\Delta UPSIT_a$, or whether there was time-varying association between $\Delta UPSIT_a$ and outcome. The final model excluded non-significant interaction terms and non-significant baseline covariates other than UPSIT0. The second model was constructed similarly as the first model with $\Delta UPSIT_a$ replaced by $\Delta UPSIT_{8wk}$. All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

3 | RESULTS

Descriptive statistics for baseline demographic and clinical characteristics, neuropsychological assessments, and olfactory test scores are presented in Table 1 for patients with AD enrolled in the trial. The patients between 56 and 70 years of age had a mean age of 70.3 (SD 9.6) years, with 42.9% being female. Twenty patients remained in the trial at week 8 and 17 remained at week 52. Patients withdrew from the study for the following reasons: death due to natural causes, withdrew consent/no longer interested in participation, moved, and medical illness/moved. There were no significant differences in baseline characteristics between dropouts (n = 4) and those who completed 52 weeks of follow-up.

Bivariate analysis showed that smoking status was not associated with education ($P = .80$) or UPSIT0 ($P = .81$), whereas it tended to differ by baseline age ($P = .085$) and by sex ($P = .076$) in that 64% (7/11) non-smokers were female, and 60% (3/5) smokers and all 5 with unknown smoking status were male. UPSIT0 was not significantly associated with age, sex, education, MMSE, smoking status, donepezil dose, or apolipoprotein E (*APOE*) genotype ($P > .10$). Similarly, we did not observe significant associations between these variables and pre-post nasal challenge UPSIT score difference $\Delta UPSIT_a$, as well as pre- to 8-week treatment UPSIT score difference $\Delta UPSIT_{8wk.}$ There was no significant change between pre- ($M = 20.86$, $SD = 5.04$) and post- ($M = 19.76$, $SD = 5.73$) nasal challenge UPSIT ($t(20) = 1.51$, $P = 0.146$). The atropine effect was variable, with n = 11 patients exhibiting a decrease in UPSIT, n = 5 remaining the same, and n = 5 exhibiting an increase in UPSIT.

Summary statistics of cognitive measures and UPSIT scores are given in Table 2. Cognitive measures varied over 52 weeks, with an increase in ADAS-Cog scores (denoting worse performance) and an increase in SRT total recall scores (denoting improved performance). ADAS-Cog score changed from mean 21.7 (SD 6.1) at baseline to 19.3 (SD 5.8) at 8 weeks, 19.6 (SD 7.2) at 26 weeks, and 22.7 (SD 9.0) at

TABLE 1 Baseline clinical and demographic characteristics of 21 AD participants

Variable	% (n) or Mean ± SD
Sex	
Male	57.14 (12)
Female	42.86 (9)
Race	
White	52.38 (11)
African American	9.52 (2)
Hispanic	23.81 (5)
Asian	9.52 (2)
Other	4.76 (1)
APOE ε4 allele	
Negative	33.33 (7)
Positive	61.90 (13)
Unknown	4.76 (1)
Smoking status	
Never	52.38 (11)
Past	19.05 (4)
Current	4.76 (1)
Unknown	23.81 (5)
Age in years	70.33 ± 9.63
Years of schooling	16.71 ± 3.20
MMSE	23.048 ± 2.40
UPSIT score at baseline	20.86 ± 5.04
Pre-post nasal challenge test	
UPSIT score change	-1.10 ± 3.16
UPSIT reduction >25%	14.29% (3)
Over first 8 weeks (n = 20)	
UPSIT score change	-2.40 ± 4.64[a]
UPSIT reduction >25%	20.0% (4)
ADAS-Cog	21.67 ± 6.12
SRT-Total	21.19 ± 8.23
SRT-delayed	0.81 ± 1.44
WAIS-R digit symbol (n = 19)	25.47 ± 9.27
FAQ (n = 16)	11.25 ± 6.19
ECOG (n = 20)	90.80 ± 28.11
CIBIS	3.62 ± 0.50
TESS (n = 18)	1.89 ± 2.05

Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Schedule-cognitive subscale; ApoE, apolipoprotein E; CIBIC, Clinician's Interview Based Impression of Change; CIBIS, Clinician Interview Based Impression of Severity; ECOG, Everyday Cognition Scale; FAQ, Functional Activities Questionnaire; MMSE, Mini-Mental Status Exam; SD, standard deviation; SRT, Selective Reminding Test; TESS, Treatment Emergent Symptoms Scale; UPSIT, University of Pennsylvania Smell Identification Test; WAIS-R, Wechsler Adult Intelligence Scale-Revised.

[a]Paired *t*-test to detect UPSIT score change: from baseline to week 8, $P = .0320$; pre-post nasal challenge test $P = .1457$.

TABLE 2 Summary statistics of cognitive measures, UPSIT score, and clinical variables by time

	Baseline	Week 8	Week 26	Week 52
	Mean ± SD (n)	Mean ± SD (n)	Mean ± SD (n)	Mean ± SD (n)
UPSIT	20.86 ± 5.04 (21)	18.26 ± 5.18 (20)	17.50 ± 5.19 (20)	17.40 ± 5.07 (15)
Primary outcomes				
ADAS-Cog	21.67 ± 6.12 (21)	19.30 ± 5.80 (20)	19.63 ± 7.15 (20)	22.69 ± 8.99 (15)
SRT-Total	21.19 ± 8.23 (21)	24.10 ± 9.82 (20)	23.00 ± 8.07 (20)	24.38 ± 9.69 (16)
CIBIC-plus	—	3.55 ± 0.69 (20)	3.75 ± 0.64 (20)	4.38 ± 0.96 (16)
Secondary outcomes				
SRT-delayed	0.81 ± 1.44 (21)	1.25 ± 2.31 (20)	0.70 ± 1.34 (20)	0.75 ± 1.81 (16)
CIBIS	3.62 ± 0.50 (21)	3.70 ± 0.47 (20)	3.60 ± 0.50 (20)	3.88 ± 0.96 (16)

Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Schedule-cognitive subscale; CIBIC, Clinician's Interview Based Impression of Change; CIBIS, Clinician Interview Based Impression of Severity; SD, standard deviation; SRT, Selective Reminding Test; UPSIT, University of Pennsylvania Smell Identification Test.

52 weeks (Table 2). SRT total immediate recall score changed from 21.2 (SD 8.2) at baseline to 24.1 (SD 9.8) at 8 weeks, 23.0 (SD 8.1) at 26 weeks, and 24.4 (SD 9.7) at 52 weeks.

3.1 | Effect of acute decrease in UPSIT scores with atropine challenge

Effect of $\Delta UPSIT_a$ on cognitive outcomes was presented in model A in Table 3. The ADAS-Cog model for the effect of $\Delta UPSIT_a$ (change in UPSIT score due to nasal challenge) controlling for baseline UPSIT score was fit to 56 observations from 21 patients. The estimated coefficient of time variable indicated that ADAS-Cog significantly decreased (corresponding to improved performance) over 26 weeks from baseline (B = −0.13, 95% CI = −0.25 to −0.02), whereas not over 52 weeks, that is, the mean within-patient change in level of ADAS-Cog over 52 weeks was not significantly different from zero. ADAS-Cog score was unrelated to $\Delta UPSIT_a$ (Table 3).

The SRT-Total model for the effect of $\Delta UPSIT_a$ was fit to 57 observations from 21 patients. SRT-Total score increased significantly over time (improved) from baseline to 52 weeks (B = 2.36, 95% CI = 0.19 to 4.53). Baseline UPSIT score was unrelated to SRT-Total score. The change in UPSIT score due to atropine nasal challenge, $\Delta UPSIT_a$, was unrelated to SRT-Total score.

SRT Delayed Recall was a secondary outcome measure. The SRT-Delay model for the effect of $\Delta UPSIT_a$ was fit to 57 observations from 21 patients. SRT-Delay scores were unchanged over time. Baseline UPSIT score was positively associated with SRT-Delay score, suggesting that lower UPSIT score at baseline was related to lower SRT-delayed score over time. SRT-Delay score over time was unrelated to $\Delta UPSIT_a$.

The CIBIC-plus model for the effect of $\Delta UPSIT_a$ was fitted to 36 observations from 20 patients. There was positive change (increase) over time with larger change over 52 weeks than over 26 weeks. The change was unrelated to $\Delta UPSIT_a$. Baseline UPSIT scores were unrelated to change in CIBIC-plus scores over time.

The CIBIS model for the effect of $\Delta UPSIT_a$ fit to 57 observations from 21 patients. CIBIS scores were unchanged over time, unrelated to baseline UPSIT score, and unrelated to $\Delta UPSIT_a$.

3.2 | Effect of change in UPSIT scores from 0 to 8 weeks

Effect of $\Delta UPSIT_{8wk}$ on cognitive outcomes were presented in model B in Table 3. The ADAS-Cog outcome model for the effect of $\Delta UPSIT_{8wk}$ was fit to 55 observations from 20 patients because one patient had missing UPSIT at week 8. ADAS-Cog significantly decreased (corresponding to improved performance) over 26 weeks from baseline, whereas not over 52 weeks, as seen in the model for effect of $\Delta UPSIT_a$. Higher ADAS-Cog score was significantly associated with lower baseline UPSIT score (B = −0.03, 95% CI = −.05 to −.002). Negative $\Delta UPSIT_{8wk}$ (decline in UPSIT over the first 8 weeks) was significantly associated with increased ADAS-Cog score over time (B = −.02, 95% CI = −.05 to −.003).

The SRT-Total outcome model for the effect of $\Delta UPSIT_{8wk}$ was fit to 56 observations from 20 patients because one patient had missing UPSIT at week 8. SRT-total score significantly increased over time (improved) from baseline to 52 weeks for patients with no change in UPSIT score over the first 8 weeks (B = 4.12, 95% CI = 2.36 to 5.89). The significant interaction of $\Delta UPSIT_{8wk}$ by 52 weeks indicated that a unit decline in UPSIT over 8 weeks was associated with a decline in SRT-Total score (B = 0.63, 95% CI = 0.30 to 0.98) over 52 weeks.

The SRT-Delay outcome model for the effect of $\Delta UPSIT_{8wk}$ was fit to 56 observations from 20 patients because one patient had missing UPSIT at week 8. SRT-Delay scores were unchanged over time. Baseline UPSIT score was positively association with SRT-delayed score. SRT-Delay score over time was unrelated to $\Delta UPSIT_{8wk}$.

The CIBIC-plus model for the effect of $\Delta UPSIT_{8wk}$ was fit to 36 observations from 20 patients. There was positive change (increase) in CIBIC-plus over time with larger change over 52 weeks than over 26 weeks. The change was unrelated to $\Delta UPSIT_{8wk}$. The negative coef-

TABLE 3 Estimated coefficients with 95% confidence interval (CI) in the models for cognitive outcomes

	Model A	Model B
log(ADAS-Cog)	B (95% CI)	B (95% CI)
Week 26 vs 0	-0.132 (-0.248, -0.016)*	-0.133 (-0.249, -0.016)*
Week 52 vs 0	0.045 (-0.087, 0.177)	0.046 (-0.087, 0.178)
Baseline UPSIT	-0.017 (-0.039, 0.0046)	-0.026 (-0.050, -0.002)*
$\Delta UPSIT_a$	-0.004 (-0.054, 0.047)	––
$\Delta UPSIT_{8wk}$	––	-0.024 (-0.0448, -0.003)*
SRT-total		
Week 26 vs 0	1.510 (-0.6549, 3.6745)	1.6649 (-0.553, 3.883)
Week 52 vs 0	2.360 (0.192, 4.527)*	4.122 (2.357, 5.886)****
Baseline UPSIT	0.336 (-0.152, 0.823)	0.585 (0.145, 1.026)*
$\Delta UPSIT_a$	-0.187 (-1.381, 1.008)	––
$\Delta UPSIT_{8wk}$	––	0.242 (-.404, .887)
$\Delta UPSIT_{8wk}$ by wk 26	––	0.090 (-0.186, 0.364)
$\Delta UPSIT_{8wk}$ by wk 52	––	0.633 (0.300, 0.975)***
SRT-delay		
Week 26 vs 0	-0.139 (-0.618, 0.341)	-0.150 (-0.636, 0.336)
Week 52 vs 0	-0.273 (-0.803, 0.258)	-0.278 (-0.821, 0.266)
Baseline UPSIT	0.075 (0.023, 0.128)**	0.084 (0.001, 0.167)*
$\Delta UPSIT_a$	0.184 (-0.020, 0.387)	––
$\Delta UPSIT_{8wk}$	––	0.033 (-0.085, 0.151)
CIBIC-plus		
Week 52 vs 26	0.710 (0.315, 1.105)**	0.718 (0.333, 0.102) **
Baseline UPSIT	-0.044 (-0.099, 0.011)	-0.036 (-0.071, -0.002)*
$\Delta UPSIT_a$	0.007 (-0.044, 0.059)	––
$\Delta UPSIT_{8wk}$	––	0.018 (-0.093, 0.129)
CIBIS		
Week 26 vs 0	-0.022 (-0.195, 0.152)	-0.050(-0.218, 0.118)
Week 52 vs 0	0.245 (-0.159,0.648)	0.210 (-0.194, 0.614)
Baseline UPSIT	0.018 (-0.028,0.065)	0.024 (-0.035, 0.082)
$\Delta UPSIT_a$	-0.046 (-0.099,0.007)	––
$\Delta UPSIT_{8wk}$	––	-0.002 (-0.051,0.047)

Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Schedule-cognitive subscale; CI, confidence interval; CIBIC, Clinician's Interview Based Impression of Change; CIBIS, Clinician Interview Based Impression of Severity; SRT, Selective Reminding Test; UPSIT, University of Pennsylvania Smell Identification Test. Outcome of ADAS-Cog was transformed by logarithmic function. Model A examines the effect of a predictor for the UPSIT score change in response to nasal challenge ($\Delta UPSIT_a$) defined as pre-post nasal challenge UPSIT score difference at baseline. Model B examines the effect of a predictor for the UPSIT score change over the first 8 weeks from baseline pre-nasal challenge ($\Delta UPSIT_{8wk}$).

*$P < .05$.

**$P < .01$.

***$P < .001$.

****$P < .0001$.

ficient of baseline UPSIT score suggested that lower UPSIT score at baseline was related to positive change (increase) in CIBIC-plus over time.

The CIBIS model for the effect of $\Delta UPSIT_{8wk}$ was fit to 56 observations from 20 patients because one patient had missing UPSIT at week 8. CIBIS scores were unchanged over time, unrelated to baseline UPSIT score and unrelated to $\Delta UPSIT_{8wk}$.

4 | DISCUSSION

Acute decrease in odor identification performance following atropine challenge was not predictive of change in cognitive performance or functional measures of AD patients during the 52-week open treatment trial with donepezil. Our group previously reported atropine-induced decrease in UPSIT was associated with increased

verbal memory (SRT total recall) and global improvement (CIBIC-plus), but not global cognition (ADAS-Cog) over 52 weeks in a sample of 37 patients with MCI treated with donepezil.[29] These earlier findings were not replicated in a more recent trial with a larger sample of 100 MCI patients, where atropine-induced decrease in UPSIT was not associated with longitudinal change in any cognitive or functional outcome measures.[7] Collectively, results of these studies do not support the use of atropine challenge to reliably improve selection of patients to receive clinical treatment with cholinesterase inhibitors, regardless of phase of clinically defined AD. One potential reason for this null finding is that atropine may not have reached the olfactory bulb. We could not localize or quantify the extent to which atropine crossed the cribriform plate, and given the nonsignificant change in UPSIT immediately following atropine challenge, it is possible that for some patients atropine did not reach the area required for its anticholinergic effects to fully manifest.

Although atropine-induced change in odor identification was not related to clinical outcomes, baseline pre-atropine odor identification was associated with baseline global cognition (ADAS-Cog) and verbal memory (SRT Total Score), consistent with the existing literature.[30–32] Furthermore, decline in odor identification from baseline to week 8 was indicative of future decline in ADAS-Cog and SRT performance over 52 weeks. This finding raises the possibility that progressive decline in olfactory identification performance could be an indicator of disease progression and AChEI nonresponse in the long term. Olfactory deficits consistently precede cognitive decline in early phases of AD. Indeed, in longitudinal studies, impaired odor identification manifests before impairments in other cognitive domains and confers increased risk of conversion to dementia in community dwelling[33] and MCI populations.[34]

A key limitation of this preliminary study is small sample size (n = 21) and absence of a placebo control condition. Another limitation is that the study was conducted with clinical diagnoses, and without biomarkers. This design consideration is balanced by the potential benefits of developing a cost-effective approach. The lack of an atropine placebo condition precludes us from estimating expected change in UPSIT performance immediately following a nasal challenge procedure. In the absence of a waitlist or placebo control for the treatment portion of the study, changes in cognitive test performance may be due in part to practice effects. Although practice effects likely influenced cognitive test performance as seen by the increase in SRT indices in the first 8 weeks, practice effects are generally absent for odor identification tests over short-term[35] and long-term[36] follow-up. There was no objective measure of olfactory functioning as an anosmic-based exclusionary criteria. It is possible that some patients already had significantly reduced olfactory capabilities to the point where atropine would not reduce them further. Another limitation is that there was no statistical correction performed for multiple samples analyzed in parallel across multiple studies from the same working group.

In conclusion, these results do not support the use of atropine challenge as a prognostic indicator for patients with AD treated with cholinesterase inhibitors. These results align with previous findings that odor identification performance is related to global cognition and verbal memory, and that short-term decline in odor identification indicates risk of long-term cognitive decline. Further work, including larger longitudinal studies, is needed to explore the value of repeated olfactory assessments in predicting cognitive and functional changes with AChEI treatment in AD.

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CONFLICT OF INTEREST

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