Olfactory Deficits and Donepezil Treatment in Cognitively Impaired Elderly

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Olfactory Deficits and Donepezil Treatment in Cognitively Impaired Elderly

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Cover Sheet

Choose ONE option from the following that is applicable to your study
If you are creating a new protocol, select "I am submitting a new protocol." As 5 Year Renewals are no longer required, this option remains for historical purposes.
I am submitting an annual continuation without modifications

Division & Personnel

Division

What Division/Department does the PI belong to?
Geriatric Psychiatry
Within the division/department, what Center or group are you affiliated with, if any?
N/A

Unaffiliated Personnel

List investigators, if any, who will be participating in this protocol but are not affiliated with New York

State Psychiatric Institute or Columbia University. Provide: Full Name, Degrees and Affiliation.
Bruce Levin, PhD -- Co-investigator

Application for Continuation of Research

Status

Current Status of Study:
All research interventions were completed. Only data analysis is ongoing.

Summary of Experiences to Date

Please provide a summary of scientific progress of the study and the experience of research participants, to date. This requirement is designed to allow for the investigator and the IRB to reassess the study's risks and benefits in terms of developments in the field, changing practice patterns, and new IRB policies and procedures.

Subject recruitment has ended. The last subject completed the protocol on March 25, 2019. No other research interventions have been completed since that date, nor will they be completed in the future. Data analysis is ongoing. Project goals are to evaluate odor identification deficits as predictors of improvement in 100 patients with amnestic mild cognitive impairment (MCI, Study 1) and in 70 patients with mild to moderate Alzheimer's disease (AD, Study 2) who are treated openly with the AChеI Donepezil.

Research participants were very amenable to continue the study until completion. The infrequent side effects of the medication, availability of the research team, and comprehensive testing have all contributed to a high pre-screening to enrollment ratio and participant retention rate. When the study was completed, an appropriate referral was always provided to the participant.

As stated in the protocol, if donepezil was not tolerated, galantamine or rivastigmine was used. These alternatives were used for 12 participants. There were no SAEs or other safety concerns among the 12 who received the alternative medications, galantamine or rivastigmine.

As described below, we enrolled 131 participants to date. The distribution of participants is as anticipated. We have consented 108 participants to sample #1: Mild Cognitive Impairment and 23 participants to sample #2: Alzheimer's disease.

Lastly, there are no new developments in the field that impact on the science of the risk/benefit balance of this protocol.

Funding

Have there been any changes in funding status since the prior approval?
No
Have the principal investigator and other investigators made all required disclosures of financial interest in

the study sponsor/product?
Yes

Summary

Have there been any study findings, recent literature, or untoward events occuring here or at other sites in the past year which might affect the analysis of the safety, risks or benefits of study participation?
No
Have there been any serious adverse events (serious and/or unanticipated problems involving risks to subjects or others at this site which occured in the past year)?
No
Have all study staff with a significant role in the design or implementation of the human subject components of this study received required training in human research subject protections?
Yes
Is the study covered by a certificate of confidentiality?
Yes
Certificate expiration date (mm/dd/yyyy)
12/02/2018

Overall Progress

Approved sample size
170
Total number of participants enrolled to date
131
Number of participants who have completed the study to date
94
Have there been any significant deviations from the anticipated study recruitment, retention or completion estimates?
No
Comments / additional information

Sample Demographics

Specify population
Adults with Mild Cognitive Impairment
Total number of participants enrolled from this population to date
108
Specify population #2
Adults with Mild to Moderate AD
Total number of participants enrolled from this population to date
23
Gender, Racial and Ethnic Breakdown

Of the 108 adults with Mild Cognitive Impairment (MCI) recruited for this protocol, 56 have been female and 52 have been male. 59 subjects identify as Caucasian, 3 identify as Asian, 26 identify as African American, 18 identify as Hispanic, and 2 identify as a Mix of two or more races.

Of the 23 adults with Mild to Moderate Alzheimer's Disease (AD) recruited for this protocol, 11 have been female and 12 have been male. 12 subjects identify as Caucasian, 2 identify as Asian, 3 identify as African American, 5 identify as Hispanic, and 1 identifies as a Mix of two or more races.

Of the 131 total subjects recruited for this protocol, 67 have been female and 64 have been male. 71 subjects identify as Caucasian, 29 identify as African American, 23 identify as Hispanic, 5 identify as Asian, and 3 identify as a Mix of two or more races.

Summary of Current Year's Enrollment and Drop-out

Number of participants who signed consent in the past year
0
Did the investigator withdraw participants from the study?
No
Did participants decide to discontinue study involvement?
No

Procedures

To create the protocol summary form, first indicate if this research will include any of the following procedures

✓ Psychiatric Assessment
✓ Neuropsychological Evaluation
✓ Collection of Biological Specimens
✓ Medication Trial
✓ Biological Challenge Procedure
✓ Medication-Free Period or Treatment Washout
✓ Off-label Use of Drug or Device

Population

Indicate which of the following populations will be included in this research

✓ Adults who may have impaired decision-making ability
✓ Adults who lack capacity to consent
✓ Adults over 50
✓ Non-English Speaking Participants

Research Support/Funding

Will an existing internal account be used to support the project?
No
Is the project externally funded or is external funding planned?
Yes
Select the number of external sources of funding that will be applicable to this study

Funding Source #1

Is the PI of the grant/contract the same as the PI of the IRB protocol?
Yes
Select one of the following
The grant/contract is currently funded
Source of Funding
Federal
Institute/Agency
National Institutes of Health
Grant Name
Olfactory deficits and donepezil treatment in cognitively impaired elderly
Grant Number
1 R01 AG041795
Select one of the following
Single Site
Business Office
CU
Does the grant/contract involve a subcontract?
No

Study Location

Indicate if the research is/will be conducted at any of the following
✓ NYSPI
✓ Other Columbia University Medical Center Facilities
This protocol describes research conducted by the PI at other facilities/locations
No

Lay Summary of Proposed Research

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Olfactory identification deficits occur in patients with Alzheimer's disease (AD), are associated with disease severity, predict conversion from mild cognitive impairment (MCI) to AD and are associated with healthy

elderly subjects developing MCI. Odor (olfactory) identification deficits may reflect degeneration of cholinergic inputs to the olfactory bulb and other olfactory brain regions. Acetylcholinesterase inhibitors (ACheI) like donepezil show modest effects in improving cognition but can be associated with adverse effects and increased burden and costs because of the need for prolonged, often lifelong, treatment. Converging findings on odor identification test performance (UPSIT, scratch and sniff 40-item test) from four pilot studies, including two of our own, suggest that acute change in the UPSIT in response to an anticholinergic challenge (atropine nasal spray), incremental change over 8 weeks, and even the baseline UPSIT score by itself, may predict cognitive improvement with ACheI treatment in MCI and AD. If change in odor identification deficits can help to identify which patients should receive ACheI treatment, this simple inexpensive approach will advance the goal of improving personalized treatment, improve selection and monitoring of patients for ACheI treatment, reduce needless ACheI exposure with risk of side effects, and decrease health care costs.

Project goals are to evaluate change in odor identification deficits as predictors of improvement in 100 patients with MCI (Study 1) and in 70 patients with mild to moderate AD (Study 2) during open treatment with the ACheI, donepezil. In both studies, we hypothesize that the decrease in UPSIT scores from pre- to post-atropine nasal spray challenge conducted at baseline will be associated with cognitive and global improvement from baseline to both 26 weeks and 52 weeks of donepezil treatment. The rationale is that those MCI patients who have AD brain pathology will have a cholinergic deficit and worsening of odor identification with the acute atropine challenge, and these patients will be more likely to improve with ACheI treatment. In both studies, we hypothesize that the increase in UPSIT scores from baseline (pre-atropine) to 8 weeks of donepezil treatment will be associated with cognitive and global improvement from 0 weeks to both 26 weeks and 52 weeks of donepezil treatment. This is the first systematic effort to evaluate the clinical utility of short-term changes in odor identification deficits to predict long-term cognitive and global improvement on ACheI treatment, and includes the first use of an anticholinergic challenge that has a sound neurobiological basis.

Background, Significance and Rationale

Background, Significance and Rationale

Background

In autopsies of patients at the earliest pathological stages of AD, neurofibrillary tangles, and to a lesser extent amyloid plaques, are seen in olfactory sensory neurons and the olfactory bulb. The piriform cortex, entorhinal cortex, and periamygdaloid nucleus are olfactory projection areas that show the greatest density of neurofibrillary tangles. Olfactory deficits in early AD likely reflect pathology in the olfactory bulb and higher order projection areas for olfactory processing, including the anterior olfactory nucleus, orbitofrontal cortex, piriform cortex, amygdala, entorhinal cortex and hippocampus.

Olfactory perception, including detection, identification and memory, are impaired in AD. These deficits cannot be explained by naming deficits or lexical difficulty with written words in the test format. All published studies show odor identification deficits in AD and MCI compared to healthy control subjects. The sensory dysfunction is fairly specific to olfaction, as taste and vision remain intact in mild AD. In AD, these deficits may precede or coincide with the onset of memory loss. Patients with MCI show some impairment in olfactory sensitivity (detection threshold) and considerable identification deficits, while

patients with AD are impaired in both these domains and odor discrimination (choice between two contrasting odors). Odor identification deficits remain the most consistently identified olfactory impairment in AD. We showed that odor identification deficits (UPSIT) increased the risk of conversion from MCI to a clinical diagnosis of AD. The effect size may be comparable to that of tests of verbal memory. Odor discrimination also predicts conversion to AD, but to a lesser degree. Overall, the literature strongly supports the use of an odor identification test as the primary measure of olfaction in the proposed project.

Subjective reports of olfactory function may relate more to cognition than objective olfactory impairment. We will obtain self-reports of olfactory functioning with a Likert-type scale (range 1-7, ancillary measure) with one question each about the ability to detect and identify odors; we use this in another MCI study.

Odor identification deficits as a biomarker of response to cholinergic therapy in AD
Olfactory epithelium and bulb cells regenerate throughout life. AD affects neurons and synapses that use acetylcholine, including soluble amyloid oligomers. Neurons with choline acetyltransferase are detected in all olfactory bulb layers, cholinergic synapses are concentrated on dendrites of periglomerular or granule cells, and olfactory bulb function is enhanced by acetylcholine and impaired by anticholinergic agents. In mice, donepezil treatment rescues the cholinergic neurons in the medial septum from the neurodegeneration induced by olfactory bulbectomy. Olfactory bulb cholinergic receptors are mainly muscarinic. Atropine and donepezil act almost entirely on muscarinic, and not nicotinic, cholinergic transmission.

In a British study, twenty-five of 28 patients with mild to moderate AD (Mini Mental State Exam/MMSE score 15-25 out of 30) completed a 3-month open trial with donepezil (5 mg/day for 4 weeks followed by 5 mg/day or 10 mg/day). Eighteen of 25 patients remained on donepezil by end-trial. The 40-item UPSIT was given at baseline and at 8 weeks. Using the criterion of a 4-point improvement on the 40-item UPSIT, there were 5 improvers and 13 non-improvers. Patients who received donepezil had improvement in UPSIT and CIBIC-plus (1-7 scale: global assessment of dementia) scores. Increase in UPSIT scores correlated with improvement in the CIBIC-plus ($r=0.7$, $p < 0.01$) and the Bristol Activities of Daily Living Scale ($r=0.7$, $p < 0.01$). In regression analyses that included the MMSE and neuropsychiatric inventory (NPI) scores, only change in UPSIT scores over 8 weeks was associated with improved CIBIC-plus scores at end-point (12 weeks). Short study duration and MMSE as the only cognitive assessment were limitations. We will follow patients for 52 weeks with systematic cognitive assessment, and evaluate change in UPSIT over the first 8 weeks to predict improvement on donepezil at 26 and 52 weeks.

Pilot studies at NYSPI. In a pilot study of patients with comorbid depression and cognitive impairment, we found that, worse performance on the UPSIT predicted cognitive improvement after donepezil treatment. Similar findings may be obtained in amnestic MCI patients without depression as proposed in Study 1. **Pilot study 2.** In our naturalistic follow-up study of 148 MCI patients (R01AG17761) with baseline UPSIT, we examined change in SRT total recall for the first 12 months after an AChEI (most patients were on donepezil) was started (variable time-point, doctor's choice). Low baseline UPSIT was associated with increase in SRT total recall over 12 months in those MCI patients who received AChEI ($n=24$, $r=0.52$, $p=0.009$) and in the subset that converted to AD and received AChEI ($n=16$, $r=0.51$, $p=0.04$). These results were obtained in both the MCI sample treated with AChEI and in the subset that converted from MCI to AD and received AChEI. In regression analyses on the increase in SRT total recall over 12 months, low baseline UPSIT but not baseline SRT total recall predicted improvement in SRT total recall over 12 months of

AChеI treatment; baseline age, sex and education were not significant. To date, no clinical predictor or biomarker has been shown consistently to predict response to AChеI, e.g., MRI hippocampal volume. This may be related to donepezil's small effect size, which makes our olfaction findings quite striking.

Atropine challenge. In the olfactory bulb, increase in cholinergic input enhances odor discrimination, and cholinergic receptor blockade lowers discrimination. The thin cribriform plate separates the olfactory bulb from the nasal cavity. Intranasally-administered drugs can cross the 'nose-brain barrier'. Animal studies using radio-labelled drugs applied intranasally show peak levels in the olfactory bulb, and concentrations in other brain regions decline with distance from the olfactory bulb. The atropine nasal spray challenge strategy was presented by Schofield et al. In patients with mild AD (n=13), MCI (n=14) and healthy control subjects (n=29), change in UPSIT scores from pre- to post-atropine sulfate (1 mg) nasal spray challenge was evaluated. In hierarchical regression analyses on episodic memory domain score, the change in UPSIT scores from pre- to post-atropine explained more variance in episodic memory than left hippocampal volume. We will evaluate the change in UPSIT scores from pre- to post-atropine sulfate nasal spray challenge as a predictor of improvement on donepezil.

Significance and Innovation

1. This is the first systematic effort to evaluate odor identification deficits to predict the likelihood of improvement on AChеI treatment. One small-scale short-term study examined concurrent changes in UPSIT scores and donepezil effects over 8 weeks. We will study the more clinically relevant question of whether short-term change in odor identification deficits predicts long-term response in much larger samples.

2. A simple, inexpensive odor identification test to predict clinical improvement with AChеI has not been tested systematically, in contrast to the extensive efforts with expensive imaging procedures that require complex analytic techniques but have shown inconsistent results in predicting improvement with AChеI in AD.

3. A challenge procedure to predict cognitive improvement has never been conducted for AChеI or other treatments in MCI or AD. This will be the first project to use the atropine nasal spray challenge for this purpose. The first published challenge procedure to examine the pathophysiology of the cholinergic system in AD was conducted with intravenous scopolamine in a small sample, and there has been limited work in MC. The use of an intravenous agent as a predictor is impractical, and scopolamine at higher doses is toxic.

4. We will evaluate an anticholinergic challenge and change in the UPSIT, and baseline UPSIT in exploratory analyses, in order to predict cognitive change with AChеI treatment. Directly testing changes in a specific neurotransmitter system to evaluate changes in response to treatment that works by affecting the same system is unique and innovative in MCI and AD in addition to having a sound neurophysiological basis.

Rationale

Implications of the project. Accurate prediction using short-term change in odor identification deficits (0-8 weeks, pre-post atropine nasal spray in this project) to identify who should receive AChеI improves potential benefit while avoiding the risk of side effects with needless exposure in patients without AD brain

pathology. Treatment for many years increases costs even if costs are low per generic pill. Our MCI study provides a cost-effective, simple approach to personalize selection for treatment that may delay clinical conversion to AD and to select/stratify patients in treatment trials. The olfactory bulb has regenerative capacity throughout the life span. Change in olfactory identification performance may be an early indicator of disease and could prove useful in predicting response to future disease-modifying treatments for MCI and AD. An odor identification test is inexpensive and easy to administer compared to MRI/PET imaging and lumbar puncture for cerebrospinal fluid (CSF). If the hypotheses are supported by the results in one study but not both studies, the results will still provide important information about how change in odor identification deficits should be used as a predictor of improvement for treatment selection or for monitoring treatment in MCI and AD.

Specific Aims and Hypotheses

Specific Aims and Hypotheses
Study 1 Aim. To evaluate short-term changes in odor identification deficits as predictors of long-term cognitive and global improvement in patients with MCI who receive donepezil or other cholinesterase inhibitor treatment.

Hypotheses. 1. Among MCI patients, the acute decrease in UPSIT scores from pre- to post-atropine nasal spray challenge conducted at baseline (0 weeks) will predict cognitive (SRT total recall and modified Alzheimer's Disease Assessment Scale-cog, ADAS-cog) and global improvement (Clinician's Interview Based Impression, CIBIC-plus)93 from 0 weeks to both 26 weeks and 52 weeks of donepezil or other cholinesterase inhibitor treatment. The rationale is that MCI patients who have AD brain pathology will have a cholinergic deficit and worsening of odor identification with the acute atropine challenge, and these patients will be more likely to improve with ACheI.

2. Increase in UPSIT scores from baseline (0 weeks, pre-atropine) to 8 weeks of donepezil or other cholinesterase inhibitor treatment will predict cognitive and global improvement from 0 weeks to both 26 and 52 weeks of donepezil or other cholinesterase inhibitor treatment.

Exploratory hypotheses. 1. Lower baseline UPSIT score will predict cognitive improvement (change in SRT total recall and ADAS-cog) on donepezil or other cholinesterase inhibitor over 12 months (based on our new pilot data). 2. The acute atropine nasal spray-induced decrease in UPSIT scores at baseline, and the increase in UPSIT scores from 0 to 8 weeks, will be associated with a decreased likelihood of conversion to dementia at 52 weeks. This hypothesis is exploratory because the small number of converters to dementia in one year will limit statistical power.

Study 2 Aim. To evaluate short-term changes in odor identification deficits as predictors of long-term cognitive and global improvement in patients with mild to moderate AD who receive donepezil or other cholinesterase inhibitor treatment. The hypotheses are similar to those for the MCI sample.

Hypotheses. 1. Among mild to moderate AD patients, the acute decrease in UPSIT scores from pre- to post-atropine challenge at baseline (0 weeks) will predict cognitive (SRT total recall and modified ADAS-cog) and global (CIBIC-plus) improvement from 0 weeks to both 26 weeks and 52 weeks of donepezil or other

cholinesterase inhibitor treatment.

2. Increase in UPSIT scores from baseline (0 weeks, pre-atropine) to 8 weeks of donepezil or other cholinesterase inhibitor treatment will predict cognitive and global improvement from 0 weeks to both 26 and 52 weeks of donepezil or other cholinesterase inhibitor treatment.

Exploratory hypothesis. Lower baseline UPSIT score will be associated with cognitive improvement (SRT total recall and ADAS-cog) on donepezil over 12 months. This new hypothesis is based on our new pilot data.

Description of Subject Population

Sample #1

Specify subject population
Adults with amnestic mild cognitive impairment
Number of completers required to accomplish study aims
80
Projected number of subjects who will be enrolled to obtain required number of completers
100
Age range of subject population
55-95

Sample #2

Specify subject population
Adults with probable Alzheimer's disease
Number of completers required to accomplish study aims
60
Projected number of subjects who will be enrolled to obtain required number of completers
70
Age range of subject population
55-95

Gender, Racial and Ethnic Breakdown
Based on our previous studies recruiting a similar subject population, we expect a gender distribution of approximately 53% female and the ethnic breakdown of approximately 73% non-Hispanic white, 17% Hispanic, 7% African American, 2% Asian American and 1% other. This distribution of patients represents the gender and ethnic breakdown of the larger group of patients who present to our clinical services, and is comparable to census data from the New York metropolitan area (city and suburbs) that form our referral base. No patients will be excluded from study participation on the basis of gender or ethnicity.
Description of subject population
Study 1 (MCI) will include 100 patients with amnestic MCI (subjective memory complaints, WMS-R

Logical Memory score >1.5 SD below norms, without functional decline consistent with dementia) will be recruited.

Study 2 (AD). In the new NIA diagnostic criteria, probable AD by NINCDS-ADRDA criteria has been updated to "probable AD dementia: core clinical diagnosis with amnestic or nonamnestic initial presentation". In Study 2, all 70 patients whom we will include will need to meet probable AD criteria by both the original and recent NIA core clinical criteria definitions that are virtually identical.

Recruitment Procedures

Describe settings where recruitment will occur
Patients will be recruited from the Columbia University Medical Center through the ADRC that includes the Memory Disorders Clinic at the New York State Psychiatric Institute (NYSPI), and the Behavioral Neurology Practice Group at the Neurological Institute. Drs. Devanand, Pelton, Huey, Bell, Kerner, **and Deliyannides** are attending psychiatrists in these settings.
How and by whom will subjects be approached and/or recruited?
All patients will be directly recruited by Drs. Devanand, Pelton, Huey, Bell, Kerner, **and Deliyannides**.
How will the study be advertised/publicized?
The study will be supported by advertising to recruit subjects, primarily through newspapers. Typically, we have utilized the Riverdale Press and AM New York for these types of studies.
Do you have ads/recruitment material requiring review at this time?
Yes
Does this study involve a clinical trial?
Yes
Please provide the NCT Registration Number
NCT01951118

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
Yes
Describe concurrent research involvement

Some subjects enrolled in this study may also be concurrently participating in the protocol "Alzheimer's Disease Research Center (ADRC) at Columbia University" (NYSPI IRB #5467R, Principal Investigator Dr. Lawrence Honig), which is a naturalistic follow-up study of all patients with MCI or AD who are seen annually at the Memory Disorders Center until death. This evaluation protocol is conducted entirely through the Memory Disorders Center and is identical to that conducted in the approximately 25 ADRC centers around the U.S., funded by the National Institute of Aging for this purpose. The goal of the ADRC is to characterize patients with MCI and AD, and to facilitate additional research projects that can be piggy-backed on the core annual ADRC assessments (NACC/UDS assessment battery) in these patients. The proposed olfaction-donepezil study fits in with these ADRC goals and therefore does not represent a conflict with the ADRC protocol. To avoid practice effects with the ADRC neuropsychogical test battery, the

NACC/UDS neuropsychological test battery done at 0 and 52 weeks in our proposed study will be scheduled to coincide in time with the ADRC annual assessments. This is feasible because when a patient is diagnosed with MCI and then recruited for the ADRC protocol in the Memory Disorders Center, we will also recruit the patient for our proposed study.
Subjects may also participate in the following protocols outside of the MDC if eligible:

- ANTIDEPRESSANT RESPONSE IN THE TREATMENT OF DEPRESSIVE SYMPTOMS AND FRAILTY CHARACTERISTICS IN OLDER ADULTS (PI Patrick Brown) - IRB #7289R

- PHYSICAL AND MENTAL FATIGABILITY IN LATE LIFE CLINICAL POPULATIONS (PI Patrick Brown) - IRB #7360

Inclusion/Exclusion Criteria

Name the subject group/sub sample
Amnestic MCI patients (Study 1)
Create or insert table to describe the inclusion criteria and methods to ascertain them

Inclusion Criteria	Method of Ascertainment
1. Age 55-95 years	Patient Self-report
2. Diagnosis of amnestic mild cognitive impairment by Petersen (1999) criteria. All the following criteria need to be met: (i) subjective memory complaints, (ii) Wechsler Memory Scale-III Logical Memory combined Story A + B immediate recall score or combined Story A + B delayed recall score OR Free and Cued Selective Reminding Test immediate recall or delayed recall score greater than 1.5 SD below norms OR Selective Reminding Test immediate recall or delayed recall score greater than 1.5 SD below norms, and (iii) no functional impairment consistent with dementia. Patients who have cognitive deficits in domains other than memory without meeting criteria for dementia will be included, i.e., both solely amnestic and amnestic-plus MCI will be included.	Physician and Neuropsychological evaluation (DSM-IV criteria)
3. Folstein MMSE 23 or higher out of 30.	Neuropsychological evaluation
4. Clinical Dementia Rating (CDR) of 0.5 (questionable dementia)	Physician evaluation
5. Availability of informant; patients without an	Patient Self-report

informant will not be recruited.	
6. Retains capacity to consent	Physician evaluation

Create or insert table to describe the exclusion criteria and methods to ascertain them

Exclusion Criteria	**Method of Ascertainment**
1. Medical contraindication to donepezil or other AchEI treatment. Contraindications to donepezil include: Current or recent (past 6 months) epileptic seizure, atrioventricular heart block, sick sinus syndrome, sinus bradycardia, asthma, bronchial muscle spasm resulting from COPD, stomach or intestinal ulcer, bleeding of the stomach or intestines, blockage of urinary bladder, feeling faint, stomach ulcer from aspirin or ibuprofen-like drugs.	Physician Evaluation, EKG
2. Medications with anticholinergic effects that have been shown to adversely impact cognition (e.g. diphenhydramine, all tricyclic antidepressants, antipsychotics with strong anticholinergic effects (thioridazine, chlorpromazine, olanzapine, clozapine) will not be permitted. Benzodiazepines in lorazepam equivalents $\geq$ 2 mg daily and narcotics will also not be permitted. Medications with less prominent anticholinergic effects (e.g. SSRIs including paroxetine) will be permitted for as long as dose is stable for at least 6 months prior to signing consent. If medications with anticholinergic effects are used within the above permitted parameters, the medication dose will be expected to remain stable and will not be changed during the course of the study.	Physician Evaluation
3. Current clinical diagnosis of dementia (includes Alzheimer's disease), schizophrenia, schizoaffective disorder, other psychosis, or bipolar 1 disorder (DSM-IV TR criteria).	Physician Evaluation
4. Current or recent (past 6 months) alcohol or substance dependence (DSM-IV TR criteria).	Physician Evaluation
5. Current untreated major depression or suicidality.	Physician Evaluation
6. Parkinson's disease, Lewy body disease, multiple sclerosis, CNS infection, Huntington's disease, amyotrophic lateral sclerosis, other	Physician Evaluation

major neurological disorder.	
7. Mental Retardation	Physician Evaluation
8. Cystic Fibrosis	Physician Evaluation
9. Clinical stroke with residual neurological deficits. MRI findings of cerebrovascular disease (small infarcts, lacunes, periventricular disease) in the absence of clinical stroke with residual neurological deficits will not lead to exclusion.	Physician Evaluation
10. Patients receiving cholinesterase inhibitors (donepezil, rivastigmine, galantamine) or memantine. Patients already receiving one of these medications at screening who undergo a 2-week washout before starting all study procedures will not be excluded.	Physician Evaluation
11. Acute, severe, unstable medical illness. For cancer, patients with active illness or metastases will be excluded, but past history of successfully treated cancer will not lead to exclusion.	Physician Evaluation
12. Exclusion criterion for olfaction: history of anosmia due to any cause (e.g. traumatic or congenital) verified by UPSIT score of <11 out of 40; head trauma with loss of consciousness; nasal sinus disease; current upper respiratory infection; severe allergies to odors; current smoker > 1 pack daily.	Physician Evaluation, Self report
13. Exclusion criterion for atropine nasal spray: presence of nasal deformity or disease that makes it difficult to administer the atropine nasal spray reliably. A patient who cannot complete the atropine nasal spray procedure can still participate in the rest of the study.	Self-report, Review of medical records as needed.

Inclusion/Exclusion Criteria #2

Name the subject group/sub sample
Probable Alzheimer's disease patients (Study 2)
Create or insert table to describe the inclusion criteria and methods to ascertain them

Inclusion Criteria	**Method of Ascertainment**
1. Age 55-95 years	Patient Self-report

2. Diagnosis of probable AD by the original NINCDS-ADRDA criteria (McKahnn et al, 1984) and the diagnosis of "Probable AD dementia:core clinical diagnosis witn amnsetic or nonamnestic initial presentation" by the new NIA criteria (McKhann et al, 2011). The two sets of diagnostic criteria are virtually identical.	Physician and Neuropsychological evaluation (DSM-IV criteria)
3. Folstein MMSE 18-27 out of 30.	Neuropsychological evaluation
4. Availability of informant; patients without an informant will not be recruited.	Patient Self-report
5. Patient retains capacity to consent for him/herself or retains the capacity to identify a surrogate who will consent on his/her behalf.	Physician evaluation

Create or insert table to describe the exclusion criteria and methods to ascertain them

Exclusion Criteria	**Method of Ascertainment**
1. Medical contraindication to donepezil or other AchEI treatment. Contraindications to donepezil include: current or recent (past 6 months) epileptic seizure, atrioventricular heart block, sick sinus syndrome, sinus bradycardia, asthma, bronchial muscle spasm resulting from COPD, stomach or intestinal ulcer, bleeding of the stomach or intestines, blockage of urinary bladder, feeling faint, stomach ulcer from aspirin or ibuprofen-like drugs.	Physician Evaluation, EKG
2. Medications with anticholinergic effects that have been shown to adversely impact cognition (e.g. diphenhydramine, all tricyclic antidepressants, antipsychotics with strong anticholinergic effects (thioridazine, chlorpromazine, olanzapine, clozapine) will not be permitted. Benzodiazepines in lorazepam equivalents $\geq$ 2 mg daily and narcotics will also not be permitted. Medications with less prominent anticholinergic effects (e.g. SSRIs including paroxetine) will be permitted for as long as dose is stable for at least 6 months prior to signing consent. If medications with anticholinergic effects are used within the above permitted parameters, the medication dose will be expected to remain stable and will not be changed during the course of the study.	Physician Evaluation

3. Current clinical diagnosis of schizophrenia, schizoaffective disorder, other psychosis, or bipolar 1 disorder (DSM-IV TR criteria).	Physician Evaluation
4. Current or recent (past 6 months) alcohol or substance dependence (DSM-IV TR criteria).	Physician Evaluation
5. Current untreated major depression or suicidality as assessed by the study psychiatrists.	Physician Evaluation
6. Parkinson's disease, Lewy body disease, multiple sclerosis, CNS infection, Huntington's disease, amyotrophic lateral sclerosis, other major neurological disorder.	Physician Evaluation
7. Mental Retardation	Physician Evaluation
8. Cystic Fibrosis	Physician Evaluation
9. Clinical stroke with residual neurological deficits. MRI findings of cerebrovascular disease (small infarcts, lacunes, periventricular disease) in the absence of clinical stroke with residual neurological deficits will not lead to exclusion.	Physician Evaluation
10. Patients receiving cholinesterase inhibitors (donepezil, rivastigmine, galantamine) or memantine. Patients already receiving one of these medications at screening who undergo a 2-week washout before starting all study procedures will not be excluded.	Physician Evaluation
11. Acute, severe, unstable medical illness. For cancer, patients with active illness or metastases will be excluded, but past history of successfully treated cancer will not lead to exclusion.	Physician Evaluation
12. Exclusion criterion for olfaction: history of anosmia due to any cause (e.g. traumatic or congenital) verified by UPSIT score of <11 out of 40; head trauma with loss of consciousness; nasal sinus disease; current upper respiratory infection; severe allergies to odors; current smoker > 1 pack daily.	Physician Evaluation, Self report
13. Exclusion criterion for atropine nasal spray: presence of nasal deformity or disease that makes it difficult to administer the atropine nasal spray reliably. A patient who cannot complete the atropine nasal spray procedure can still participate in the rest of the study.	Self-report, Review medical records as needed.

Waiver of Consent/Authorization

Indicate if you are requesting any of the following consent waivers
Waiver of consent for use of records that include protected health information (a HIPAA waiver of Authorization)
No
Waiver or alteration of consent
No
Waiver of documentation of consent
Yes
Waiver of parental consent
No

Consent Procedures

Is eligibility screening for this study conducted under a different IRB protocol?
No
Describe procedures used to obtain consent during the screening process
Subjects referred to the study will first undergo a screening process (MMSE, WMS-III Logical Memory Test, FC-SRT and Clinical Dementia Rating (CDR), initial check for inclusion/exclusion criteria). When the Selective reminding test (SRT) immediate and delayed has been administered within three months prior to the start of the study, and the patient scored greater than 1.5 SD below norms on the test, that score can also be used for the patient to meet inclusion criteria in place of the WMS-III Logical Memory Test or FC-SRT. If the patient appears eligible based on screening, Drs. Devanand, Pelton, Huey, Bell, Kerner, **or Deliyannides** will confirm by patient interview that all inclusion/exclusion criteria are met and they will go over the details of the study with the patient and the informant as described in the informed consent form. Subjetcs will also be informed that they need to have an informant available to be interviewed in order to be in the study. Patients will be given ample time to review the consent form and will be given the opportunity to ask questions. Only Drs. Devanand, Pelton, Huey, Bell, Kerner, **or Deliyannides** will obtain consent from the patients. Throughout the study, the study physicians will cross-cover each other for patient assessments and management in the study. All study physicians are board certified psychiatrists and their clinical role is to serve as the study physicians.

The week 0 baseline visit will occur approximately 1 week after the screening visit. MMSE, WMS-III Logical Memory, and FC-SRT test done at screening will not be repeated at week 0.
Describe Study Consent Procedures

Clinical Settings.

Memory Disorders Clinic. All patients who come to the clinic first sign a consent form (IRB protocol # 6562R) that indicates that their data will be used in research as part of the ADRC consortium (national

Alzheimer's consortium; we are a site) and are informed that they may be approached for participation in other studies if they are eligible. Memory Disorders Clinic physicians include Drs. Devanand, Pelton, Huey, Bell, Kerner, **and Deliyannides** who work in a supervisory capacity or follow patients whom they have seen for a long period of time. New evaluations are conducted by Neurology fellows. If a patient is potentially eligible, these fellows will briefly describe the study and if the patient is interested then refer the patient to Dr. Devanand or Dr. Pelton or Dr. Huey, Dr. Bell, Dr. Kerner, **or Deliyannides** (whoever is available at that time). Therefore, in this setting patients will first be approached about the study by a non-study physician.

Behavioral Neurology Practice Group. Dr. Huey and Dr. Bell, but not Dr. Devanand or Dr. Pelton **o**r Dr. Kerner **or Dr. Deliyannides** is a member of this group. If Dr. Huey or Dr. Bell evaluates a patient who may be eligible, he/she will explicitly inform them that they have the option of getting a second opinion regarding study participation from a physician in the clinical setting who is not an investigator in the study, and immediately arrange for that second opinion if requested.

Documenting Consent.

Voluntary written informed consent will be obtained from all MCI and AD subjects by Drs. Devanand, Pelton, Huey, Bell, Kerner, **or Deliyannides**. All patients at enrollment will be assessed for capacity to consent and this will be documented in the chart.

The consent form describes the nature of the procedures and time requirements, potential risks, the confidentiality of information, and the rights of research subjects, including their right to withdraw from the research at any time without loss of benefits to which they are otherwise entitled. It is made explicit that this protocol involves open treatment with donepezil or other Acetylcholinesterase Inhibitors with return visits at specified time points, and a description of the research assessments. The consent process also includes documentation of permission to obtain previous medical records.

The informant must give verbal consent indicating his or her willingness to provide information about the patient and complete questionnaires and interviews with the research staff. The waiver of consent/authorization only applies to informants only is allowed according to the Federal Regulation 45 CFR 46.117(c)(2) which states, "the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context."

The IRB-approved forms for informed consent and for assessment of capacity are made part of the patient's permanent medical record, with a copy being filed in the research chart. Specific consent issues and risks pertaining to apolipoprotein E genotyping are described below.

Indicate which of the following are employed as a part of screening or main study consent procedures
✓ Consent Form

Waiver of Documentation of Consent

Would the consent form signature be the only link between the subject's identity and the research data?
Yes

Is breach of confidentiality the main study risk?
No
Describe the study component(s) for which waiver of documentation is requested.
The informant must give verbal consent indicating his or her willingness to provide information about the patient and complete questionnaires and interviews with the research staff. The waiver of consent/authorization only applies to informants and is allowed according to the Federal Regulation 45 CFR 46.117(c)(2) which states, "the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context."

Assent Procedures

Describe procedures by which subject assent will be assessed and/or recorded
The IRB-approved forms for informed consent and for assessment of capacity are made part of the patient's permanent medical record, with a copy being filed in the research chart.

Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent
Deliyannides, Deborah, MD
Devanand, Davangere, MD
Huey, Edward, MD
Pelton, Gregory, MD
Type in the name(s) not found in the above list
Dr. Karen Bell

Independent Assessment of Capacity

You have indicated that your study involves subjects who MAY LACK capacity to consent.
Does this study require an independent assessment of capacity?
Yes
Methods/procedures for capacity assessment

For NYSPI/Columbia, New York State regulations regarding capacity to consent, as used by the New York State Psychiatric Institute IRB, will be followed as we do in all IRB protocols for the following two groups within the study. Under no circumstance will a patient objecting to participation be included in the study.

Baseline

I. MCI Patients: All MCI patients will have an MMSE score greater than 20 at the beginning of the study and therefore are expected to have the capacity to provide informed consent. Before beginning the study, all MCI patients will be approached to appoint a surrogate. If the patient does not appoint a surrogate, the

patient will still be included in the study. If the patient decides to appoint a surrogate (in case they lose the capacity to consent while participating in the study), we will use the following forms to document the choice of surrogate: PCS Form III(b) Record of Choice of Surrogate, PCS Form III(c) Statement by Witnesses, and PCS Form IV Consent by Surrogate. In order to complete these three forms, the patient, surrogate, study physician, and two witnesses must be present and sign in various places on the form. The complete PCS Model Consent Form does not need to be completed in these cases since all MCI patients are expected to have the capacity to appoint a surrogate and therefore do not need to undergo assessment by an independent evaluator.

II. AD Patients: At the beginning of the study, AD patients may have an MMSE score less than or greater than 20.

(1) All AD patients with an MMSE score equal to or greater than 20 are expected to have the capacity to provide informed consent. In order to be included in the study, AD patients with an MMSE score greater than 20 will be required to appoint a surrogate. We will use the following forms to document the choice of surrogate: PCS Form III(b) Record of Choice of Surrogate, PCS Form III(c) Statement by Witnesses, and PCS Form IV Consent by Surrogate. In order to complete these three forms, the patient, surrogate, study physician, and two witnesses must be present and sign in various places on the form. The complete PCS Model Consent Form does not need to be completed in these cases since AD patients with MMSE scores equal to or greater than 20 are expected to have the capacity to appoint a surrogate and therefore do not need to undergo assessment by an independent evaluator.

(2) All AD patients with an MMSE score less than 20 will undergo a formal assessment of capacity to consent. The patient will be evaluated by Drs. Devanand, Pelton, Huey, Bell, Kerner**, or Deliyannides** who will document the findings of the assessment in the progress note and on the Assessment of Capacity to Consent forms, and based on this assessment the patient will either participate or not participate in the study. In order to be included in the study, AD patients with an MMSE score less than 20 will be required to appoint a surrogate. However, unlike the MCI patients and the AD patients with MMSE scores equal to or greater than 20, AD patients with MMSE scores less than 20 are less likely to retain the capacity to appoint a surrogate and therefore must first undergo an assessment by an independent evaluator before appointing a surrogate. In these cases, the complete PCS Model Consent Form must be completed (PCS Form I Capacity to Consent and Capacity to Choose a Surrogate, PCS Form II Consent Form Signature Page, PCS Form III(b) Record of Choice of Surrogate, PCS Form III(c) Statement by Witnesses, PCS Form IV Consent by Surrogate, and a Consent Procedure Note written by the Independent Evaluator).

<u>During the study</u>

Although all MCI patients and some AD patients will have MMSE scores equal to or greater than 20 at baseline, it is a possibility that these patients may have cognitive decline during the study, raising the question about continued capacity to consent. MCI patients. If the MMSE score drops to <20 or the study physician believes that there is a loss of capacity, a formal reassessment of capacity to consent for continued participation will be completed. The patient will be evaluated by Drs. Devanand, Pelton, Huey, Bell, Kerner, **Deliyannides** who will document the findings of the assessment in the progress note and on the Assessment of Capacity to Consent for Continued Participation form, and based on this assessment the patient will continue in the study if capacity is maintained. If capacity is not maintained, the surrogate will be asked to

provide informed consent for the patient's continued participation. If capacity is not maintained and there is no surrogate, the patient will be terminated from the study with subsequent clinical follow-up in the Memory Disorders Center.

AD patients. If during the study the MMSE score is <20 or the study physician believes that there is a loss of capacity, a formal reassessment of capacity to consent for continued participation will be completed. The patient will be evaluated by Drs. Devanand, Dr. Pelton, Huey, Bell, Kerner, **or Deliyannides** who will document the findings of the assessment in the progress note and on the Assessment of Capacity to Consent form, and based on this assessment the patient will continue in the study if capacity is maintained. If capacity is not maintained, the surrogate will be required to provide informed consent for the patient's continued participation. If the surrogate does not provide informed consent for the patient's continued participation, the patient will be terminated from the study with subsequent clinical follow-up in the Memory Disorders Center.

Choice of Surrogate: Both MCI and AD patients will decide who they want their surrogates to be. The study physician will ask the patient whom he or she would like to appoint as the surrogate. If any AD patient does not know someone who can act as his or her surrogate, or does not have the capacity to appoint a surrogate, then the patient will not be included in the study.

You have indicated that your study involves subjects who DO LACK capacity to consent. Please justify
We expect that all MCI patients and most AD patients will have capacity to consent at baseline. The nature of Alzheimer's disease is that some patients may not have the capacity to consent but it is important to include these patients if possible in the protocol to ensure representativeness of the sample and to avoid inclusion bias. The tests administered, primarily olfaction and neuropsychological tests, are minimal risk and the treatment being administered, donepezil, is the standard FDA-approved treatment for Alzheimer's disease. Therefore, inclusion of these subjects is justified.
Procedures for surrogate consent
At NYSPI, OMH regulations require that in patients who lack the capacity to consent, surrogate consent is acceptable when all the following procedures are conducted:

1. A psychiatrist or licensed clinical psychologist who is independent of the research must confirm that that the patient still retains the capacity to designate a surrogate, i.e., identify the surrogate and indicate that the surrogate can consent on the patient's behalf for the research study. Drs. Steven Roose, Bret Rutherford, Joel Sneed, Karen Marder, Scott Small, Patrick Brown, and Jamie Noble will be the independent evaluators for this study. They will follow the procedures described here using the forms attached as an addendum to the Informed Consent Form.

2. The document designating the research surrogate must be witnessed by two persons who are independent of the research. The psychiatrist or licensed clinical psychologist who assesses the patient's capacity to choose a surrogate may also witness to the choice of the surrogate.

3. If the patient chooses a surrogate but is unable to sign the document, another person may sign for the

patient and the two witnesses shall, in writing, confirm the patient's choice of a surrogate and witness the signature of the person signing for the patient.

4. The surrogate cannot function as a witness to the choice of the surrogate. A family member or friend of the patient who is not the surrogate may function as a witness.

5. The surrogate cannot be an administrator or employee of the facility at which the research is conducted or the facility conducting the research. This restriction does not apply if the person is related to the patient by blood, marriage, or adoption. The selection of a patient's spouse as a surrogate is revoked upon the legal separation or divorce of the patient and spouse unless the patient specifies otherwise.

6. Notice of the appointment of a surrogate must be provided to the Mental Health Legal Service (MHLS). These procedures for surrogate consent will be followed for patients who lack the capacity to consent to this research protocol as specified in the earlier paragraphs in this section.

These procedures for surrogate consent will be followed for patients who lack the capacity to consent to this research protocol as specified in the earlier paragraphs in this section.

Study Procedures

Describe the procedures required for this study

Roles and Responsibilities:

Dr. Devanand will be the Principal Investigator as well as the primary study physician. He will make executive decisions including study monitoring, regulatory issues, quality control (QC), and dispute resolution. He will have overall responsibility for the clinical care of the patients during the course of the study.

Dr. Pelton will be the Co-Investigator and the second study physician. He will evaluate the patients during the visits and be responsible for the clinical care of the patients during the course of the study.

Dr. Huey will be a Co-Investigator and will play a clinical and research role in the conduct of this study on the utility of olfactory identification deficits in predicting cognitive improvement with donepezil treatment of patients with mild cognitive impairment and Alzheimer's disease. He will recruit, treat and follow patients in this project. He has been involved in the preparation of this grant with Dr. Devanand and will be involved in the analysis of data and publications ensuing from this project.t

Dr. Bell will be a Co-Investigator and will play a clinical and research role in the conduct of this study on the utility of olfactory identification deficits in predicting cognitive improvement with donepezil treatment of patients with mild cognitive impairment and Alzheimer's disease. She will recruit, treat and follow patients in this project. She has been involved in the preparation of this grant with Dr. Devanand and will be involved in the analysis of data and publications ensuing from this project.

Dr. Kerner will be the Study Physician. She will evaluate the patients during the visits and be responsible for the clinical care of the patients during the course of the study.

Dr. Deliyannides will be the Study Physician. She will evaluate the patients during the visits and be responsible for the clinical care of the patients during the course of the study.

Study Assistants (2) (To Be Hired) will screen charts and assist in the recruitment of patients through the ADRC, including a designated research clinic, the Memory Disorders Center, and a Behavioral Neurology private practice group comprising faculty neurologists and psychiatrists (includes Drs. Devanand, Pelton, Huey, Bell, Kerner, **and Deliyannides**). They will be responsible for the conduct of research procedures, including administration of the UPSIT at all time-points, the Selective Reminding Test, the ADAS-cog, the NACC/UDS battery, and other interviews and procedures in in the project. They will be responsible for data checking and integrity for all the data ensuing from this project and will enter the data into the web-based data entry system. The research assistants will liaison with the Data Management group (Dr. Howard Andrews and Mr. David Merle) that will develop the web-based data entry system and which will be responsible for monitoring all data entry. They will also ensure that the blood samples for apolipoprotein E genotyping are collected, processed and sent correctly for assay.

The flow diagram (attached below) and procedures (main procedures are in the flow diagram; further details are in the table attached below) apply to both Study 1(MCI) and Study 2(AD). At the initial screening visit (not shown in the flow diagram), the MMSE, WMS-III Logical Memory Test, FC-SRT and Clinical Dementia Rating (CDR) are done. If all inclusion/exclusion criteria are met, signed informed consent is obtained. The week 0 baseline visit occurs approximately 1 week after the screening visit (MMSE, WMS-III Logical Memory, FC-SRT and CDR done at screening will not be repeated at week 0). Clinical Eval refers to the physician's clinical evaluation that covers vital signs monitoring, depression (Geriatric Depression Scale), stroke (Hachinski and vascular risk factors), medical illnesses and medications taken.

SCREENING VISIT

As part of the screening evaluation, a comprehensive history will be taken to include age, age-at-onset of memory problems, handedness, education, occupation, medical and psychiatric history. Concurrent medications including putative cognitive enhancers (vitamin E, gingko biloba, estrogen), and over 20 other classes of common prescription and over the counter and alternative medications will be documented at all visits. Use of medications known to worsen cognition such as, but not limited to, benzodiazepines (lorazepam equivalents of equal or greater than 2 mg daily), narcotics, anticholinergics, and current alcohol/ substance abuse/dependence will not be allowed. Medications with uncertain adverse impact on cognition, e.g, theophylline, nifedipine, beta blockers, will not lead to exclusion and will not be washed out.

Olfaction history will be obtained to screen out patients who meet any of the specified exclusion criteria for olfaction.

The Folstein Mini Mental State Exam (MMSE), the Wechsler Memory Scale-III (WMS-III) Logical Memory Test, and FC-SRT will be administered to determine inclusion. The physician will complete the CDR.

All eligible patients will also be asked to provide an informant who will be available (in-person or by phone) and willing to provide information or responses to questionnaires and interviews.

For patients who meet the study entry criteria, informed consent will then be obtained by the study physician.

BASELINE VISIT

Patients who are enrolled will be asked to come for the baseline visit, typically 1 week after the screening visit.

Medical, history, physical examination, UPSIT with atropine challenge, SRT, ADAS-cog, E-cog, extensive clinical (NACC) and neuropsychological (UDS) evaluation, and blood draw for apolipoprotein E genotyping will be completed. Vital signs (sitting blood pressure and pulse rate, respiratory rate, weight and height) will be measured and recorded.

UPSIT and atropine challenge.

The full 40-item University of Pennsylvania Smell Identification Test (UPSIT) will be given with birhinal administration (odors presented to both nostrils) followed by a 1 mg atropine nasal spray.

The UPSIT is a 40-item scratch-and-sniff multiple choice odor identification test. It comprises 4 booklets with 10 odorants apiece, and one odorant per page. Stimuli are embedded in microencapsulated crystals (10-50 micrometer diameter) located on a brown strip at the bottom of each page (UPSIT odor stimuli were originally developed by the 3M company). The subject uses a pencil (provided with the test) to scratch each odorant strip left to right several times and then sniff the label before completing the circle against one of four multiple choice items, e.g, "this odor smells most like: a) chocolate; b) banana; c) onion; d) fruit punch." The subject is given up to a minute to circle 1 of the 4 alternatives even if no smell is perceived, i.e., the test is forced-choice. Patients who score less than 11 will be excluded if there is a history of anosmia due to any cause (e.g. traumatic or congenital). In other words, we will exclude patients with congenital anosmia or anosmia after a remote event (e.g. head injury).

Atropine nasal spray is not commercially available but atropine eye drops are available and our pharmacy will provide them for use as a nasal spray. The study physician will administer the spray, consistent with Schofield et al.[94] The 1 mg dose was used very safely in Schofield's study in MCI and AD. Doses of 0.3 to 0.5 mg are typically used in ENT clinics where nasal anticholinergic effects reach a ceiling at 0.5 mg.[38] Therefore, the 1 mg dose ensures maximum anticholinergic effects on olfaction and overcomes any loss of dose that is intrinsic to a nasal spray. Immediately after the spray, the patient will be in the "Mecca" position for 1 minute to ensure that the atropine reaches the cribriform plate at the upper end of the nasal cavity[94].

This posture involves kneeling on a mat with the body and arms stretched forward with the forehead touching the mat. The half-life of atropine nasal spray is approximately 2 hours, and therefore the administration of the repeat UPSIT 45 minutes after the spray as done by Schofield et al takes into account the expected peak and duration of atropine effects.

We will also administer the two-item Awareness of Odor Detection and Identification Scale (developed by Drs. Tabert and Devanand) that assesses the ability to detect odors, and to identify odors, on a 7-point Likert scale for each of the two items (takes 1 to 2 minutes).

Apolipoprotein E genotype. Apolipoprotein-E genotype will be examined as a potential moderator of UPSIT prediction of donepezil response. Blood obtained and the Columbia University Human Genetics Resource Core will be used as the laboratory resource that will prepare and process the de-identified blood sample for APOE genotyping. De-identified samples are sent to the Columbia University Human Genetics Resource Core (HGRC) lab. The HGRC then assigns a new sample number and bar-codes the sample. DNA is extracted and stored. The HGRC functions as a sample processing and storage facility in this study. It is not a CLIA lab and does not do genetic testing.

The HGRC then sends an aliquot of DNA to a different laboratory for genotyping. This laboratory belongs to the company, Prevention Genetics, which serves as the vendor for APOE genotyping. The alleles are "translated" by the HGRC to the APOE 2, 3 and 4 that are familiar to clinical investigators, and the modified spreadsheet is then sent by the HGRC to the PI.

Drs. Devanand, Pelton, Huey, Bell, Kerner, **or Deliyannides** will then give the patient generic donepezil (purchased for this project and prepared by the NYSPI pharmacy) in dispensing vials. The patient will be instructed to take donepezil 5 mg/day for the first 4 weeks and then increase the dose to 10 mg/day for the rest of the trial. Patients who develop side effects, e.g., nausea or diarrhea, on 10 mg/day will remain at 5 mg/day during the trial. If side effects persist, donepezil will be stopped and alternative treatment will be prescribed (e.g., Exelon patch for gastrointestinal side effects). This is an intent to treat study, therefore, patients will be followed for the full 52 weeks. If the patient has taken donepezil in the past and experienced side effects that were not serious but caused the patient to be unwilling to try the medication again, the study physician can prescribe galantamine or rivastigmine, instead of donepezil, at the start of this study. **This has been done for 12 participants. There have been no SAEs or other safety concerns among the 12 participants who have received the alternative medications, galantamine or rivastigmine.**

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pasting

Drs. Devanand and Stern will make a consensus diagnosis based on the NACC/UDS and other available information at 0, 26, and 52 weeks. The baseline consensus diagnosis at 0 weeks will be made prior to starting donepezil**.** These two raters will remain blind to UPSIT, CIBIC-plus, SRT and ADAS-cog scores, ensuring that the diagnostic process is independent of the predictor and outcome variables.

FOLLOW-UP VISITS (Weeks 2, 4, 8, 26 and 52)
A telephone contact will be made by the study physician at Week 2 during which an open clinical interview

to monitor any side effects and complete the CIBIC-plus will be conducted. If needed the patient will be brought in for evaluation at this time.

All patients in Study 1 and 2 will be asked to come to the clinic for follow-up at Weeks 4, 8, 26 and 52. At each of these visits, vital signs (sitting blood pressure and pulse rate, respiratory rate, and weight) will be measured and recorded.

At Week 26, the Folstein MMSE, which is one of the components of the NACC UDS Neuropsychological test battery, will be administered.

At Weeks 8, 26, and 52, the SRT and ADAS-cog will be administered.

At Weeks 4, 8, 26, and 52, the study physician will complete the CIBIC-plus for global measurement of improvement. Adverse events will be recorded using the TESS. The FAQ as well as the Ecog will also be completed with the informant at these time points.

At Weeks 8, 26 and 52, the odor identification test will be administered, using the full 40-item University of Pennsylvania Smell Identification Test (UPSIT) birhinally (odors presented to both nostrils).

At study visits, donepezil will be prescribed by the study physician.

At Week 52, the clinical evaluation by Dr. Devanand, Dr. Pelton, Dr. Huey, Dr. Bell, Dr. Kerner, **and Deliyannides** using the ADRC NACC UDS clinical evaluation will be repeated. In addition, the ADRC NACC UDS neuropsychological test battery will also be administered.

At Weeks 26 and 52, consensus diagnosis will be made by Drs. Devanand and Stern based on the NACC UDS and other available information, which will be considered the final diagnosis for study purposes. Diagnostic raters will remain blind to the UPSIT, CIBIC-plus, SRT and ADAS-cog scores, thereby ensuring independence of the diagnostic process from the predictor and cognitive/global outcomes.

Cognitive test scores and UPSIT test scores are shared with the patient throughout the protocol. Results of apolipoprotein E genotyping are not shared with the patient.

DROPOUT. Criteria under which loss of capacity to consent leads to study termination have been specified. Patients who cannot tolerate donepezil will be offered treatment with alternative cholinesterase inhibitors, e.g., galantamine, rivastigmine patch in doses that are FDA-approved to treat patients with AD. If they are able to tolerate one of these medications, they will complete the study at 52 weeks as planned. If they are unable to tolerate the medication or medication is interrupted for more than 30 days, they will be terminated from the protocol but the study visits and evaluations will occur at the scheduled time-points using the intent-to-treat principle, i.e., even if the patient is no longer on study medication. For patients who do not make an appointment, every effort will be made to maintain the patient in the study including making a home visit if feasible. Patients who develop intolerable side effects even at the lowest permitted dose will be terminated from the protocol by the study investigator. The study investigator can also terminate the protocol if severe medical illness warrants study termination. After an interruption of treatment for any reason, e.g., medical illness, the patient can resume the protocol if the interruption is less than 30 days. This

is an intent-to treat protocol. Therefore, a patient who is discontinued early in the study due to the above reasons will be followed and evaluated (whenever feasible) until the Week 52 visit or until the patient withdraws his/her consent to participate.

Safety Monitoring during the course of the entire study will include vital signs assessment, physical exams, baseline routine laboratory tests, monitoring of adverse events (TESS plus open-ended interview), and monitoring and maintenance of concurrent medication records.

All adverse events occurring after signing the consent forms, regardless to adherence to study treatment, will be recorded at all contacts with the patient. At scheduled visits, patients will be interviewed about whether he/she experienced any symptoms or side effects since the last visit. Adverse events will be recorded and an adverse event form will be completed. If adverse events are noted, they will be rated as mild, moderate, or severe based on their clinical severity and frequency. The PI will inform the IRB immediately after knowledge of death, or of an event that is life-threatening that results in hospitalization, or that involves persistent or significant disability or incapacity. Data collected regarding these serious adverse events will include the treatment provided, outcome, and presumed relationship to study drug and will be updated as new information becomes available. Dr. Howard Andrews, who leads the data management team, will generate a data output that covers AEs, SAEs and study progress which will be reviewed by the Independent Safety Monitor. The project comprises of two open-label proof-of-concept trials, and therefore blindness to treatment is not an issue.

Dr. Jose Luchsinger, Associate Professor of Medicine at New York Presbyterian Hospital (board-certified internist), will serve as the Independent Safety Monitor. The Independent Safety Monitor will receive all reports of adverse events and serious adverse events, including deaths, and review all unanticipated problems involving risk to subjects or others. He will then provide a written report of the event with conclusions and advice for the PI, Dr. Devanand, who will then forward it to the IRB and the Program Officer at the National Institute of Aging.

STATISTICS

General considerations and approach to multiple comparisons. In this proof-of-concept study, we do not consider it essential or even important to control for making one or more Type I errors between the two different study samples (MCI, AD) or between any of the cognitive or global clinical endpoints (SRT, ADAS-cog, CIBIC-plus). Testing this study's hypothesis (do changes in UPSIT predict outcome?) in these different samples with these different measures represents very different research questions, such that a positive finding from one sample or with one outcome cannot be claimed to support a positive result in a different sample or with a different outcome. However, for a given patient sample and a given outcome, our analysis will consider four parameters of interest, any one of which could be used as evidence supporting the scientific hypothesis that changes in UPSIT predict the given outcome in the given sample. This creates a four-dimensional parameter space and a corresponding family of hypotheses within which we will control the probability of making one or more Type I errors at 5%. Therefore, we will repeat the analyses described for each study sample and for each endpoint, controlling the family-wise type I error rate in each repetition at the 0.05 level. Any positive findings will be viewed as hypothesis-generating for a subsequent, larger confirmatory study in the given sample and with the given cognitive or overall clinical endpoint.

(i) All measures other than the hypothesized predictor and outcome variables will be evaluated in secondary analyses, e.g., E-cog and FAQ as functional outcomes. Pearson correlation coefficients will be used to examine the associations between these measures and UPSIT, other cognitive measures, and continuous baseline demographic variables. Student's t test will compare differences for dichotomous variables (e.g., sex). The statistical analytic approach will be similar for testing the primary hypotheses.

(ii) In another secondary analysis we will attempt to confirm the findings of the British study108 using their choice of dichotomization at 4 or more points change in week eight UPSIT for predicting outcome. We will not use that (or any other) dichotomization for our primary analysis in order to retain full power. We will, however, be able to evaluate whether the four-point change in 8-week UPSIT cut-point is better or worse than other cut-points in predicting outcomes. For this we will use ROC methods for predicting a good clinical outcome, such as a 4-point improvement in SRT or ADAS-cog, or a 2-point improvement in CIBIC-plus.

(iii) In other secondary analyses we will determine the robustness of our findings by preparing completers-only analyses (see Handling of Missing Data below) and comparing the results to the primary analyses.

Exploratory analyses. We will not assume any time-evolution curve for the responses at 26 and 52 weeks. The response-curve is unlikely to be linear over the year of follow-up, as evidence shows a plateau or a small decline in cognitive and global measures after an initial positive response to donepezil. In exploratory analyses we will check if a simple parametric model in time with subject-specific parameters can parsimoniously fit the response data and if the findings relating to UPSIT persist. We will check for interactions between the slope parameters $\beta 11$, $\beta 12$, $\beta 21$, $\beta 22$ and the other covariates of age, sex, education, and baseline MMSE, each at the alpha = 0.10 level given reduced power to detect interactions compared with main effects. For exploratory hypothesis with baseline UPSIT as a significant predictor in both the MCI and AD samples, we will conduct separate simple regression analyses with covariates as appropriate. We will also explore the relative utility of the baseline UPSIT compared to the change scores by entering them in the same regression model and examining which has a larger standardized coefficient (i.e., the regression coefficient times the ratio of standard deviations of the predictor and dependent variables).

IMPLICATIONS

The UPSIT (or a comparable test like Sniff'n Sticks) is inexpensive and easy to administer compared to conducting MRI/PET imaging and obtaining CSF measures for which the evidence for predicting improvement on AChEI remains to be clearly established. If our hypotheses are supported by the results obtained, odor identification tests may have clinical utility to predict cognitive improvement and monitor treatment with AChEI. If the atropine challenge test is shown to be useful, this research can be expanded to the conduct of sequential challenge tests to monitor change with AChEI treatment at more than one time-point. These approaches to predicting treatment response can be tested in the future for new disease-modifying drugs for MCI and AD as and when they are developed.

You can upload charts or diagrams if any

Criteria for Early Discontinuation

Criteria for Early Discontinuation

The reasons for early discontinuation of a patient from the study are as follows:

(1) intervening severe medical illness that either the PI or the Medical Monitor determines that it requires study discontinuation;

(2) discontinuation of treatment with donepezil for more than 30 days. After an interruption of treatment for any reason, e.g., medical illness, the patient can resume the protocol if the interruption is less than 30 days.

This is an intent-to treat protocol. Therefore, a patient who is discontinued early in the study due to the above reasons will be followed and evaluated (whenever feasible) until the Week 52 visit or until the patient withdraws his/her consent to participate.

Blood and other Biological Samples

Please create or insert a table describing the proposed collection of blood or other biological specimens

Routine Laboratory Tests: At baseline, blood will be collected for the following screening laboratory tests that will be performed by the OMH Clinical Laboratories-Nathan Kline Institute: CBC, BUN, creatinine, electrolytes, liver and thyroid function studies, B-12, lipid panel and folate (total of 20 ml).

Apolipoprotein E genotype testing. At baseline, a blood sample will also be collected for ApoE genotyping (total of 8.5 ml). All procedures related to Apo E genotyping were described earlier.

DNA will not be extracted and stored for any other genetic testing.

Assessment Instruments

Create a table or give a brief description of the instruments that will be used for assessment

1. University of Pennsylvania Smell Identification Test (UPSIT) is a 40-item scratch-and-sniff multiple choice odor identification test. It consists of four booklets containing 10 odorants apiece, with one odorant per page. The stimuli are embedded in 10-50 micrometer diameter urea-formaldehyde polymer

microencapsulated crystals located on a brown strip at the bottom of each page. The subject is asked to use a pencil (provided with the test) to scratch each odorant strip left to right several times and then sniff the label before completing the circle against one of four multiple choice items, e.g, "this odor smells most like: a) chocolate; b) banana; c) onion; or d) fruit punch. The subject is required to answer one of the four alternatives, even if no smell is perceived, i.e., the test is forced-choice. It comes in multiple language versions including English, French, German, and Spanish. We will use the English and Spanish versions that we evaluated in an epidemiological study of 1293 subjects where English and Spanish speakers had similar UPSIT scores after controlling for age and education. Test norms have been developed, based on UPSIT administration to 1819 men and 2109 women of various ages, with norms categorized within 5-year intervals. Rather than obtaining percentile scores, we will evaluate the raw UPSIT scores with relevant demographic (age, sex, education) and clinical variables included as covariates in the analyses. In healthy subjects, the test-retest reliability coefficients for the UPSIT are uniformly high, ranging from r=0.918 for tests administered 6 or more months apart to r=0.949 for tests administered two weeks apart. The UPSIT and similar tests show high test-retest reliability with no significant improvement over test sessions 10 minutes apart, 4 hours apart, and 4 days apart.
The 8-week time-point UPSIT administration is needed to address hypothesis 2 for this protocol. The 26 and 52 week time-points will be useful to explore the changes in the UPSIT over time relative to changes in cognitive, functional, and global measures and to obtain information on its potential in monitoring treatment with AChеI.

The research coordinator will administer the UPSIT to patients with MCI. Subjects will be allowed to sniff each item for up to a minute before making a response (each item takes only a few seconds if the subject is confident about the odor and selects the multiple choice item). The UPSIT requires rule-based administration and scoring and the lack of blindness of the research coordinator or assistant who administers the test will not influence the results obtained.

2. **Selective Reminding Test (SRT).** Verbal list learning and memory will be assessed by the 12-item, 6-trial SRT. Total number of words learned over six trials (total immediate recall) will be examined. Delayed word recall (15 min delay) will be an ancillary measure. Our use of the total immediate recall measure is supported by its wide range in scores with greater sensitivity to small changes (0-72 for total recall versus 0-12 for delayed recall for the SRT), use in prior clinical trials and our pilot data in DEP-CI.

The choice of the SRT compared to similar tests of episodic verbal memory, e.g., Auditory Verbal Learning Test (AVLT) that is used in ADNI, was partly based on our pilot data in the donepezil-placebo add-on trial in DEP-CI, our own extensive use for over two decades in our ADRC, and the fact that it is a well-established neuropsychological test of episodic verbal memory that has been used successfully in clinical trials of AChеI. Different equivalent versions will be administered at the specified time-points to reduce practice effects.

3. **Alzheimer's Disease Assessment Scale-cognition (ADAS-cog, modified version)** is used in essentially all FDA registration clinical trials in MCI and AD. It covers several areas of neuropsychological functioning that include attention, category fluency, episodic verbal memory, non-verbal memory, and naming. There is overlap in the cognitive areas assessed between the ADAS-cog and the NACC UDS neuropsychological test battery, but we chose to retain the modified ADAS-cog because it is the current standard instrument in the

field for clinical trials in MCI and AD, thereby allowing for direct comparison of our results with the extant literature in AChеI trials.

4. **National Alzheimer's Coordinating Centers (NACC) Uniform Data Set (UDS) Clinical Evaluation.** All patients will receive the full NACC physician evaluation at 0 and 52 weeks. The evaluation takes 30-40 minutes to complete and includes history with in-depth evaluation of family history, neurological examination including the Unified Parkinson's Disease Rating Scale for extrapyramidal signs, psychiatric assessment that includes the Neuropsychiatric Inventory and the short version of the Geriatric Depression Scale, assessment of all major vascular risk factors in addition to the Hachinski scale, and a Clinical Dementia Rating (CDR).

5. **National Alzheimer's Coordinating Centers (NACC) Uniform Data Set (UDS) Neuropsychological Test Battery.** Tests in the UDS battery: Folstein MMSE, WMS-R digit span forward and backward, WAIS-R digit symbol, Trail Making Test Part A and Part B, WMS-R Logical Memory Story A immediate and delayed recall, Verbal Fluency animal and vegetable list generation, Boston Naming Test (30 odd items). Validated English and Spanish versions exist for these tests. This test battery will be employed to assist in diagnosis and is separate from the cognitive outcome measures.

The SRT and ADAS-cog are the main cognitive outcome measures and have validated English and Spanish versions.

6. **Clinician's Interview Based Impression of Change plus Caregiver Input (CIBIC-plus).** The CIBIC-plus is a well-validated, reliable and widely used measure (range 1-7) of global improvement used in AD trials. It also has a version specific for MCI that has been used successfully in AChеI treatment studies in MCI. The CIBIC-plus versions specific for MCI will be administered at all study time-points and will be the global measure of improvement.

7. **Pfeffer Functional Activities Questionnaire (FAQ)**. FAQ is a widely used 10-item instrument that takes 3 minutes to administer and focuses on instrumental, social and cognitive functioning. We published the first report showing that informant-reported, but not self-reported, FAQ deficits strongly predicted conversion from MCI to AD. We recently showed that specific FAQ items, particularly the financial items and the item on remembering appointments/remembering to take medications, strongly distinguished patients with AD, MCI and healthy controls in baseline ADNI data. The FAQ is also part of the NACC assessment and will be the secondary function measure.

8. **Measurement of Everyday Cognition (Ecog)**. We will administer the ECog as the primary function measure. This instrument has 40 items, takes 20 minutes to administer, and focuses on functional correlates of cognitive deficits. It is used in the Alzheimer's Disease Neuroimaging Initiative-GO (ADNI-GO) and ADNI-II studies.

9. **Treatment Emergent Symptom Scale (TESS).** TESS is widely used to evaluate somatic side effects. For each item, a rating is made on a 3-point scale, with an additional rating on the likelihood tht the medication caused the side effect. The total score of this safety assessment of possible AChеI side effects will be an ancillary measure.

Other Scales/Assessments

Demographic and Family History Form	5 min
Pfeiffer Functional Activities Questionnaire (FAQ)	3 min
Everyday Cognition (Ecog)	20 min
University of Pennsylvania Smell Identification Test (UPSIT)	20 min

Neuropsychological Testing

Folstein Mini Mental State Exam (MMSE)	5 min
Wechsler Memory Scale-R (WMS-R) Logical Memory Story A immediate and delayed recall	15 min
WMS-R digit span forward and backward	5 min
WAIS-R digit symbol	5 min
Trail Making Test – Part A and Part B	5 min
Verbal Fluency – Animal and Vegetable List Generation	5 min
Boston Naming Test – 30 odd items	10 min
Selective Reminding Test	20 min
Alzheimer's Disease Assessment Scale – cognition (ADAS-cog)	20 min

Please attach copies, unless standard instruments are used

Off label and investigational use of drugs/devices

Choose from the following that will be applicable to your study
✓ Drug
Select the number of drugs used in this study
2

Drug #1

Name of the drug
Donepezil
Manufacturer and other information
Donepezil, which became generic in 2011, is also marketed under the trade name Aricept. It is manufactured by its developer Eisai and marketed by Pfizer. We will use the generic version supplied to the NYSPI pharmacy.
Approval Status
No IND is required
Choose one of the following options

FDA has determined that IND is not required

Drug #2

Name of the drug
Atropine Nasal Spray
Manufacturer and other information
Atropine sulfate ophthalmic solution 1%, which is also generic, will be constituted by the NYSPI Pharmacy as a nasal spray for use as the acute atropine challenge at baseline. A single acute dose of 1 mg of atropine nasal spray will be administered to one nostril. The dose chosen reflects clinical doses typically used by ENT physicians and this dose was used very safely in the pilot report presented by Schofield et al at ICAD 2010. It exceeds the threshold required for cholinergic blockade and therefore any loss of dose because of the use of a nasal spray will not pose a problem in this study.
Approval Status
No IND is required
Choose one of the following options
FDA has determined that IND is not required

Research Related Delay to Treatment

Will research procedures result in a delay to treatment?
Yes
Maximum duration of delay to any treatment

Donepezil treatment will begin immediately, as long as there is no wash-out period for a cholinesterase inhibitor or memantine. If a wash-out period is required, the patient will need to stop taking the cholinesterase inhibitor or memantine for two weeks. Afterwards, donepezil treatment can be started immediately. Maximum duration of delay to standard care or treatment of known efficacy.

Maximum duration of delay to standard care or treatment of known efficacy
During the two-week wash-out period, the patient will be monitored closely by the study physician.
Treatment to be provided at the end of the study
Patients will be on open label treatment with donepezil (range 5 to 10 mg per day) or other acetylcholinesterase inhibitor during the entire course of the study. After the study ends, the patient will continue to be followed in our ADRC by the physician who was following the patient prior to the start of the study.

Clinical Treatment Alternatives

Clinical treatment alternatives
Donepezil has been approved for the treatment of Alzheimer's disease, however it is not approved for the treatment of mild cognitive impairment. The efficacy of donepezil to slow or halt cognitive decline or conversion to AD in patients with mild cognitive impairment is not established. There is no FDA-approved treatment for mild cognitive impairment.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period

Donepezil. Nausea, diarrhea, insomnia (sleep disturbance), vomiting, dizziness, drowsiness, weakness, shakiness (tremor), muscle cramp, fatigue and anorexia (loss of appetite with weight loss) are possible side effects of donepezil. These side effects are often of mild intensity and transient, resolving during continued donepezil treatment without the need for dose modification. The patient may also experience an increase in anxiety or nervousness, restlessness, or allergic reactions with donepezil. The patient is instructed to inform the study physician about medical history, especially of: breathing problems (such as asthma, chronic obstructive pulmonary disease), fainting, heart disease (such as sick sinus syndrome, other heart conduction disorder), seizures, stomach/intestinal disease (such as ulcers, bleeding), trouble urinating (such as enlarged prostate). Patients will come for detailed evaluation at baseline and will be monitored during open treatment with donepezil. Donepezil is sometimes used off-label to treat patients with mild cognitive impairment but it is not approved by the FDA for the use indicated in this study. However, the dose of donepezil treatment will not differ from what would be administered clinically in regular practice, and hence the treatment does not entail any research risks beyond the risks of lack of efficacy or the advent of side effects that may occur clinically with donepezil treatment.

Galantamine. Nausea, vomiting, diarrhea, and anorexia (loss of appetite with weight loss) are possible side effects of galantamine. These side effects are often of mild intensity and transient, resolving during continued galantamine treatment without the need for dose modification. The patient may also experience headache, abdominal pain, fatigue, slow heart rate, depression, sleepiness and fainting. The patient is instructed to inform the study physician about medical history. Patients will come for detailed evaluation at baseline and will be monitored during open treatment with galantamine.

Rivastigmine. Nausea, vomiting, anorexia (loss of appetite with weight loss), diarrhea, weakness, dizziness, drowsiness, and shakiness (tremor). These side effects are often of mild intensity and short-lived, resolving during continued rivastigmine research treatment without the need for dose modification. The patient is instructed to inform the study physician about medical history. Patients will come for detailed evaluation at baseline and will be monitored during open treatment with galantamine.

In this elderly patient group, it is not uncommon for inter-current medical illness to lead to interruption of treatment, usually for short intervals (e.g., surgery). During the study, interruption of treatment for up to 30 days will be permitted. Treatment and data collection will resume after the interruption and the patient will continue in the protocol.

Medication Washout: Patients who are already on cholinesterase inhibitors or memantine at screening will undergo a two-week wash-out period. No withdrawal syndrome has been reported for any of these medications. Since donepezil or other cholinesterase inhibitors or memantine have a marginal effect in improving memory at best in AD (0-5% improvement in memory test scores over a few months) and have not yet been shown to significantly improve memory in MCI, the clinical risk associated with discontinuation of any of these medications for two weeks is minimal. There is consistent evidence that reinstatement of these medications after a brief interval of a few weeks leads to the therapeutic effect being regained (if there has been a therapeutic effect in that patient to begin with). Although the wash-out period is unlikely to put subjects at risk, precautions will still be taken to minimize any possible risks. Patients that agree to undergo the wash-out will be instructed that if they feel marked worsening in memory or other cognitive abilities or develop other new symptoms during the wash-out they should call the clinic and they will be seen immediately by the study doctor to determine if they can complete the two-week wash-out safely. If it is determined at the visit that the patient cannot complete the wash-out safely, the cognitive enhancer (cholinesterase inhibitor or memantine) will immediately be reinstituted and the patient will not be enrolled in the study.

Atropine Nasal Spray: Atropine is routinely used in ENT offices and does not pose undue risk. In this study, a single acute dose of 1.0 mg spray to one nostril will be administered at baseline. The atropine dose is within the range used in ENT practice and systemic absorption is minimal so side effects are not expected (and have not been reported in the ENT literature). The only exclusion criterion for atropine administration will be the presence of nasal deformity or disease that makes it difficult to administer the atropine nasal spray reliably. Dryness of nose and throat are possible side effects; visual effects do not occur with nasal administration. It is usually mild and short-lived and will be expected to disappear before the study procedures are completed and before the patient leaves the clinic. If the patient experiences any adverse events after the atropine nasal spray is administered, the study doctor will examine the patient and appropriate clinical action will be taken.

University of Pennsylvania Smell Identification Test (UPSIT). The UPSIT (odor identification test) uses mainly synthetic odors and there is little risk of an allergic reaction with this procedure. Patients with a history of severe allergies to odors will be excluded. The test has been administered to several hundred thousand subjects around the world and does not lead to any known side effects.

Neuropsychological Assessment. During neuropsychological testing, some subjects may find some questions upsetting. If so, they are not obliged to answer them.

Blood Draw. The risks associated with blood draw include local tenderness, redness, bruising, infection and mild bruising at the puncture site. Also, a feeling of lightheadedness may occur.

Apolipoprotein E genotyping. In the informed consent form, we will state (1) the presence of specific subtypes of apolipoprotein may be associated with an increased risk of memory disorders, (2) the results will be kept strictly confidential and not released to the subject or to other parties. This approach, required by our IRB for all apolipoprotein genotyping studies, follows from the current ambiguities for clinical application of apolipoprotein E genotyping. Further, given that this involves genotyping, as per our NYSPI IRB requirements, a Certificate of Confidentiality has been obtained from NIA, as we have done in other

studies. Procedures to ensure that samples are stored without identifying information have already been described.

Describe procedures for minimizing risks
There are three areas in which safeguards to protect subjects from undue risk require discussion. These include the procedures used to obtain informed consent, the procedures used to ensure confidentiality of subjects' responses and findings on tests, and the procedures used to minimize possible risks associated with the research procedures.

Informed Consent. Informed consent is obtained and documented with a signed consent statement giving full information about the study. In the consent form and in discussion with an investigator, subjects are advised fully of the procedures to be used, the amount of time required of them, the fact that this is a longitudinal treatment study with repeated assessment at specified time points, the possible risks and benefits of the procedures and the treatment conditions, their right to refuse participation in the study without prejudice, their right to terminate participation at any moment without prejudice, and the name and telephone number of the Principal Investigator.

Capacity to Consent. Based on IRB requirements, patients will be recruited by a study physician who signs the consent form in addition to the patient and informant. As described earlier, the inclusion/exclusion criteria are such that essentially all patients at the time of study entry should have the capacity to consent to the protocol. All patients with MCI will have the capacity to consent to the study. In the rare instance that a patient with mild AD lacks the capacity to consent based on the patient's inability to understand the protocol as elicited by interview, the patient will not be recruited into the protocol. We will follow the procedures required by the NYSPI IRB (based on New York State regulations) regarding assessment of capacity to consent.

Confidentiality of Subjects' Responses. In the informed consent form, subjects are told that the information they provide and all findings will be kept strictly confidential, with access limited to the research staff with the possible exception of State or Federal regulatory personnel for audits. All records are kept in locked files. Each subject is given a code number for database purposes, and the patient's name does not reside in the database. Computer files will be stored in a database which is password protected and behind an institute and department firewall. No one but the project staff has access to the master list linking subjects' names to code numbers, and all information obtained is coded. The master list is kept under strict lock and key. The research data on specific predictors are not released to the patients, and this is specified in the consent form. This applies particularly to the apolipoprotein E genotyping, because of uncertainty as to what these results really mean and the risk of misinterpretation.

Research Procedures. We have described above the potential risks of the research procedures and the safeguards that will be used to minimize risks. These include termination of subjects from research participation if it is believed that such participation endangers their welfare. Monitoring procedures are used

to evaluate potential side effects of research procedures. The protocol stipulates an extensive medical, neurological, and psychiatric evaluation of all subjects as a condition for research participation.

Procedures for minimizing risk for donepezil, medication washout, atropine nasal spray, UPSIT, neuropsychological assessment, and APOE genotyping are included in the above discussion of 'Risks that could be encountered during the study period'.

Methods to Protect Confidentiality

Describe methods to protect confidentiality

Confidentiality of Subjects' Responses. In the informed consent form, subjects are told that the information they provide and all findings will be kept strictly confidential, with access limited to the research staff with the possible exception of State or Federal regulatory personnel for audits. All records are kept in locked files. Each subject is given a code number for database purposes, and the patient's name does not reside in the database. Computer files will be stored in a database which is password protected and behind an institute and department firewall. No one but the project staff has access to the master list linking subjects' names to code numbers, and all information obtained is coded. The master list is kept under strict lock and key. The research data on specific predictors are not released to the patients, and this is specified in the consent form. This applies particularly to the apolipoprotein E genotyping, because of uncertainty as to what these results really mean and the risk of misinterpretation.

In addition to the confidentiality protections described, a Federal law called the Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against the patient based on his/her genetic information. GINA does not protect a patient against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance or by adoption agencies. GINA also does not protect a patient against discrimination based on an already diagnosed genetic condition or disease. If a patient would like to know more about it, he /she can discuss this with the principal investigator of this study or can go to the following website: http://ww.genome.gov/24519851.

Research records will be stored in a confidential manner so as to protect the confidentiality of subject information.

Will the study be conducted under a certificate of confidentiality?
Yes, we have already received a Certificate of Confidentiality

Direct Benefits to Subjects

Direct Benefits to Subjects

Patients will obtain free clinical evaluation, neuropsychological testing, and will receive open clinical treatment with donepezil. The treatment is clinically consistent with treatment typically received by patients with AD (Study 2), and is used in a significant proportion of patients with MCI clinically. For Study 1, even though ACheI, including donepezil, are not FDA-approved for treatment of patients with MCI, there is considerable evidence that a sizeable proportion of patients with MCI do improve on donepezil as reviewed in the Approach section.

Potential benefits to society may be considerable. If the hypotheses in both studies are supported by the results, the use of an odor identification test like the UPSIT, which is very inexpensive compared to MRI/PET imaging and CSF measures and is easy to administer, may have clinical utility to predict and monitor treatment with AChel like donepezil, and potentially other treatments in the future. Further, if a patient is being treated with an AChel but is having side effects, the change in odor identification deficits may prove to be a useful adjunct in determining whether the patient is indeed benefiting from treatment and whether to continue or discontinue the medication. The aging of the population means that more patients will develop MCI and AD and require treatment. Even though donepezil and other AChels are now generic, the costs of prolonged treatment are considerable and the development of a method to identify patients likely to benefit from treatment is of great public health importance.

If the atropine challenge test is shown to be useful, this can be used clinically to select patients likely to improve with AChel. Further, research using this challenge strategy can be expanded to sequential challenge tests to monitor change with AChel treatment at more than one time-point. Overall, our approach can be used to stratify patients who are likely to respond in intervention studies of patients with MCI or AD, and potentially support the clinical use of odor identification tests for predicting likely improvement and monitoring treatment for symptomatic treatments like AChel.

Compensation and/or Reimbursement

Will compensation or reimbursement for expenses be offered to subjects?
Yes
Please describe and indicate total amount and schedule of payment(s).
Include justification for compensation amounts and indicate if there are bonus payments.
Patients will be given $50 for participating in the study at study entry and for each of the visits at weeks 8, 26 and 52) for a total of $200 for each participant. This will be paid upon completion of each study visit. This amount is commensurate with the amount of compensation paid by other protocols in our center. There are no bonus payments.

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