

Published in final edited form as:

Contemp Clin Trials. 2014 March ; 37(2): 200–208. doi:10.1016/j.cct.2013.11.015.

Donepezil Treatment of Older Adults with Cognitive Impairment and Depression (DOTCODE study): clinical rationale and design

Gregory H. Pelton, M.D.^{1,2}, Howard Andrews, Ph.D.^{1,2}, Steven P. Roose, M.D.^{1,2}, Sue M. Marcus, Ph.D.^{2,3}, Kristina D'Antonio, B.S.¹, Hala Husn⁵, Jeffrey R. Petrella, M.D.⁴, Anthony S. Zannas, M.D., M.Sc.⁵, P. Murali Doraiswamy, M.B.B.S., FRCP^{5,6,7}, and D. P. Devanand, M.D.^{1,2}

¹Division of Geriatric Psychiatry, New York State Psychiatric Institute, New York, USA

²Department of Psychiatry, College of Physicians and Surgeons, Columbia University, New York, USA

³Department of Biostatistics, Mailman School of Public Health, Columbia University, New York, USA

⁴Department of Radiology, Duke University Medical Center, Durham, North Carolina, USA

⁵Department of Psychiatry, Duke University Medical Center, Durham, North Carolina, USA

⁶Department of Medicine, Duke University Medical Center, Durham, North Carolina, USA

⁷Department of Duke Institute for Brain Sciences, Duke University Medical Center, Durham, North Carolina, USA

Abstract

Treatment strategies for patients with depression and cognitive impairment (DEP-CI), who are at high risk to develop a clinical diagnosis of dementia, are not established. This issue is addressed in the donepezil treatment of cognitive impairment and depression (DOTCODE) pilot clinical trial. The DOTCODE study is the first long-term treatment trial that assesses differences in conversion to dementia and cognitive change in DEP-CI patients using a study design of open antidepressant medication plus add-on randomized, double-blind, placebo-controlled treatment with the acetylcholinesterase inhibitor donepezil. In Phase 1, DEP-CI patients receive optimized antidepressant treatment for 16 weeks. In Phase 2, antidepressant treatment is continued with the addition of randomized, double-blind treatment with donepezil or placebo. The total study

© 2013 Elsevier Inc. All rights reserved.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Contributors

DPD, assisted by GHP and SPR, conceived and designed the study. NIA sponsored the trial. DPD was the coordinating investigator and principal investigator at the Department of Psychiatry, New York State Psychiatric Institute and Columbia University College of Physicians and Surgeons. PMD was the principal investigator at the Department of Psychiatry, Duke University School of Medicine and helped with study design. GHP and ASZ were the sub-investigators and JRP was the study neuroradiologist at the Duke site. HA contributed to database development and strategy, and KD and HH contributed to recruitment. SM contributed to statistical consultancy and drafted the statistical part of the manuscript. DPD, GHP, KD drafted the remaining part of the manuscript. All authors have read and approved the final version of the manuscript.

Ethics approval

The study has been approved by the New York State Psychiatric Institute/Columbia University Institutional Review Board and the Duke University Medical Center Institutional Review Board. The study is registered at ClinicalTrials.gov (NCT01658228) and will be carried out under the surveillance of the two Institutional Review Boards and the study Data Safety Monitoring Board.

duration for each patient is 78 weeks (18 months). Eighty DEP-CI outpatients (age 55 to 95 years) are recruited: 40 at New York State Psychiatric Institute/Columbia University and 40 at Duke University Medical Center. The primary outcome is conversion to a clinical diagnosis of dementia. The secondary outcomes are cognitive change scores in Selective Reminding Test (SRT) total recall and the modified Alzheimer's Disease Assessment Scale (ADAS-cog). Other key assessments include the 24-item Hamilton Depression Rating Scale and antidepressant response; Clinical Global Impression (CGI) for depression, cognition, and global status; neuropsychological test battery for diagnosis; informant report of functional abilities (Pfeffer FAQ); Treatment Emergent Symptom Scale (TESS) for somatic side effects. Apolipoprotein E $\epsilon 4$ status, odor identification deficits, and MRI entorhinal/hippocampal cortex atrophy at baseline are evaluated as neurobiological moderators of donepezil treatment effects.

Keywords

Depression; cognitive impairment; memory decline; Alzheimer's disease; randomized clinical trial; donepezil; aging

INTRODUCTION

In the elderly, depression (DEP) and cognitive impairment (CI) commonly co-occur (DEP-CI).¹ Patients with DEP-CI are at high risk of conversion to a clinical diagnosis of dementia, primarily Alzheimer's disease.^{2,3} In these patients there have been few treatment studies. Treatment trials of older adults with depression typically exclude patients with significant memory deficits.^{1,4,5} Conversely, in treatment trials focused on treating cognitive deficits in patients with mild cognitive impairment (MCI), major depression typically is excluded.^{6,7} This is the first systematic study designed to explicitly examine cognitive change, including conversion to dementia, in a randomized, double-blind, placebo-controlled donepezil treatment trial in cognitively impaired, depressed patients who initially receive open antidepressant treatment.

In our group's first pilot treatment study in DEP-CI, 39 DEP-CI patients received open sertraline treatment up to 200 mg daily (mean daily dose 146 mg, SD 47) for 12 weeks. Responders to sertraline improved in only one measure of attention/executive performance from an extensive neuropsychological test battery, indirectly suggesting a potentially increased risk of dementia during follow-up.⁸

In a sample of elderly patients with major depression who received antidepressant treatment plus add-on donepezil (n=67) or placebo (n=63) for two years, at initial evaluation most patients had normal cognition and few patients had MCI.⁹ There was no effect of donepezil in the cognitively normal group. In secondary analyses, donepezil enhanced cognition in the subgroup with cognitive deficits and reduced conversion to dementia over two years. Donepezil was also associated with an increased risk of recurrence of major depression.⁹

In a re-analysis of the long-term study that compared donepezil, Vitamin E and placebo in 769 amnesic MCI patients⁷ without major depression, patients with higher baseline Beck Depression Inventory (BDI) scores were more likely to convert to a clinical diagnosis of AD (p=0.03) than patients with lower BDI scores.¹⁰ In contrast, in MCI subjects without BDI-defined depression, there were no differences between donepezil and placebo at the one-year and two-year time-points.¹⁰ The results suggested that donepezil improves cognitive impairment in depressed subjects with amnesic MCI and may delay conversion to a diagnosis of AD in MCI patients with even mild depressive symptoms.

In a pilot trial from our group, 23 DEP-CI patients received 8 weeks of open antidepressant treatment followed by 12 weeks of add-on randomized, double-blind, donepezil or placebo treatment. A subsample continued in an 8-month extension phase of open donepezil treatment. Patients treated with an antidepressant plus donepezil had significant improvement in their short-term verbal memory (Selective Reminding Test or SRT total recall) compared to treatment with antidepressant plus placebo, and this was maintained at 52 weeks.¹¹ The improvement with donepezil was greater than reported in MCI treatment studies in non-depressed patients, and the cognitive trajectory was similar to that seen with acetylcholinesterase inhibitors (AChEs), including donepezil, in AD.¹² These initial results provided the basis for the DOTCODE 18-month pilot clinical trial, which is designed to test whether donepezil versus placebo add-on to optimized antidepressant treatment has beneficial cognitive benefits in patients with DEP-CI and whether it reduces the rate of conversion to a diagnosis of dementia.

METHODS

Study Design Features and Rationale

80 patients with DEP-CI are recruited: 40 patients at the New York State Psychiatric Institute/Columbia University (NYSPI/CU, lead coordinating site) and 40 patients at Duke University Medical Center. Patients receive open antidepressant treatment throughout the trial. At 16 weeks after starting antidepressant treatment, patients are randomized to add-on donepezil or add-on placebo. Each subject is followed for a total duration of 18 months.

Recruitment, Eligibility, Consent

NYSPI/Columbia Recruitment—The Late Life Depression Clinic (LLDC) is the main source of recruitment, supplemented by referrals from the Memory Disorders Center (MDC) and the Behavioral Neurologists' practice group and newspaper advertising.

Duke Recruitment—Subjects are recruited from the patient caseload of the investigators, the late-life mood disorders programs, Center for the Study of Aging, community advertisements, and referral by psychiatric, primary care, public health (inner city) and geriatric medicine clinics affiliated with Duke University.

Inclusion/Exclusion Criteria—Salient inclusion criteria are age 55–95 years, subjective cognitive complaints, Folstein Mini Mental State Exam (MMSE) ≥ 21 , and the presence of depression with cognitive impairment (DEP-CI). An informant is required for all subjects. Detailed inclusion/exclusion criteria are in Table 1.

Definition of Depression with Cognitive Impairment (DEP-CI)

1. MCI is defined as a score of ≤ 11 on the Wechsler Memory Scale-Revised (WMS-R) Logical Memory subtest delayed recall (Paragraph A) or a score ≥ 1.5 SD below norms on the Free and Cued Selective Reminding Test (FC-SRT) immediate or delayed recall.
2. Based on a SCID-P interview and consensus diagnosis by study physician investigators, depression is defined as the presence of DSM-IV major depression or dysthymic disorder with symptom criteria for at least 6 months (instead of the 2-year minimum criterion for dysthymic disorder), and a 24-item HAM-D score ≥ 14 .

Treatment Regimen

All patients receive open treatment for depression throughout the study. Assessments for depression are done at each in-person visit, using the Beck Depression Inventory II, 24-item

Hamilton Depression Scale, and the CGI. Cognitive assessments are completed at five time-points: baseline, 16 weeks, 40 weeks, 64 weeks and 78 weeks (Table 2).

Antidepressant Treatment—If the patient is eligible for the study and currently on an antidepressant medication at screening, a washout is initiated as per clinical judgment and may range from 0 to 14 days based on the specific medication and clinical status of the patient. Phase 1 is the open antidepressant phase (week 0 to week 16), in which patients are contacted (clinic visit or phone) at week 0 (baseline, can be merged with screen visit), week 1, week 2, week 4, week 6, week 8, week 10, week 12, week 14 and week 16. Treatment begins with citalopram 10 mg/day for the first week and is increased to citalopram 20 mg/day for the second week. Citalopram is prescribed up to a maximum dose of 20 mg daily in patients > 60 years old because of the FDA warning about prolonged QTc interval with higher doses of citalopram in this age group. Patients 55–60 years old may receive citalopram up to 40mg/day. If the patient's QTc interval > 0.460 ms on the screening ECG, citalopram is not prescribed and venlafaxine ER is preferred as the starting antidepressant medication. If patients on citalopram do not respond after eight weeks, they are switched to the SNRI, venlafaxine ER. Venlafaxine ER treatment begins at 37.5 mg/day and is increased weekly, as tolerated and based on clinical response, to a maximum of 225 mg daily at the fifth visit (Week 12). If a patient does not improve on venlafaxine (at least 25% improvement required in HAM-D scores from baseline) at week 16, then the patient is switched to another antidepressant or an augmenting medication is added to their current medication, as clinically indicated. Antidepressant dosing is flexible based on the study physician's assessment of efficacy and side effects, and if response criteria (24-item HAM-D \leq 8 and CGI depression score of much improved or better) are met there are no further dose adjustments unless clinically indicated.

Patients who previously did not respond to citalopram or venlafaxine, or had intolerable side effects on these medications, can be treated with other antidepressants at any time-point during the trial including from the start of the trial. Antidepressant treatment can be discontinued if the patient is euthymic with 24-item HAM-D score \leq 8 maintained during the trial.

Randomization: Donepezil/Placebo Treatment—Phase 2 is the add-on donepezil/placebo double-blind randomized phase (week 16 to week 78). Generic donepezil or placebo (in identical-looking capsules made up by the NYSPI pharmacy) is dispensed at 5 mg/day for the first 6 weeks and is then increased to 10 mg/day for the remainder of the trial. Each patient randomized to donepezil or placebo is assigned a Drug ID number, which begins with a two-letter character string (either DU or NY) followed by a 3 digit number component. Both the study physician and the patient are blind to the donepezil/placebo assignment, which is generated by the statistician, and executed by the NYSPI Pharmacy. Codes that link Drug ID numbers to treatment are kept under lock and key and are only revealed in cases of emergency. Patients who develop somatic side effects, e.g., nausea or diarrhea, on donepezil 10 mg/day (or placebo) are permitted to remain at 5 mg/day (or placebo) during the trial. The goal is to maintain all patients at the tolerated dose within therapeutic dose ranges. If subjects cannot tolerate 5 mg per day, they are still followed off randomized donepezil/placebo and all protocol visits with intent-to-treat assessments are completed. The permitted window for each visit is 30 days prior to/after the time-point. Interruption of treatment for up to 30 days is permitted.

Outcome Measures and Hypotheses—The primary outcome is conversion to the clinical diagnosis of dementia. Hypothesis 1: Antidepressant-treated DEP-CI patients on donepezil will show a lower rate of conversion to dementia (primarily AD) compared to antidepressant-treated DEP-CI patients on placebo by the end of the 18-month trial.

The secondary outcome measures are cognitive change scores. Hypothesis 2: Compared to the placebo group, the donepezil group will show better cognitive outcome at both 40 weeks and 78 weeks (SRT total recall: primary measure; modified ADAS-cog: secondary measure).

Exploratory Analyses Examining Potential Moderators—Potential moderators of donepezil treatment effects on cognition are evaluated, based on the view that patients with incipient AD brain pathology will have superior cognitive outcome on donepezil.

Exploratory hypotheses:

1. Patients with the apolipoprotein E ϵ 4 allele (homozygote or heterozygote), compared to patients without this allele, will have better cognitive outcome on donepezil compared to placebo.
2. Lower scores on the UPSIT (odor identification test) at baseline will be associated with better cognitive outcome on donepezil compared to placebo.
3. Smaller MRI hippocampal and entorhinal cortex volumes (atrophy) will be associated with better cognitive outcome on donepezil compared to placebo.

Depression Diagnosis—We use the DSM-IV criteria to diagnose major depression, dysthymic disorder and other depression subtypes, and other psychiatric disorders, based on the mood disorder module of the SCID-P interview.

Conversion to Dementia—Study physician investigators, who remain blind to assignment to donepezil or placebo during the trial and are highly experienced in making the diagnosis of dementia, make consensus diagnoses (based on clinical evaluation and neuropsychological testing and laboratory test results, taking all available clinical information into account) at the major time-points (Table 2). Criteria for dementia diagnoses: DSM-IV criteria for dementia, NINCDS-ADRDA criteria for possible and probable AD,¹³ DLB Consortium criteria for Lewy body dementia,¹⁴ NINDS-AIREN criteria for vascular and mixed dementia,¹⁵ and Lund-Manchester criteria for frontotemporal dementia, including Pick's disease.¹⁶

Length of Follow-Up—We chose 18 months as our follow up period in order to achieve a balance between power to see conversions (estimated at 10–15% annually in this sample)¹⁷ and decrease dropouts.^{6,7} Conversion rates may be lower than expected; changes in cognitive measures will also be examined.

Clinical Evaluation—History includes the chief complaint, referral source, age, age-at-onset of depression and cognitive decline, handedness, education, occupation, medical history, and medications used. Cerebrovascular risk factors are assessed: hypertension, ischemic and other cardiovascular disease, diabetes mellitus, smoking, family history of heart disease and stroke, TIAs, and hyperlipidemia. Alcohol/substance use, head injury, thyroid disease, other medical conditions, surgery, and hospitalization are also assessed.

Psychiatric Diagnosis and Family History—The Structured Clinical Interview for DSM-IV (SCID) is given at baseline by a trained and certified rater. Family history of dementia, AD, and depression are obtained from patient self-report.

Depression Assessment—The 24-item **Hamilton Rating Scale for Depression** (HAM-D) and the self-report **Beck Depression Inventory II** are completed at each visit.

Physician Evaluation—At baseline, the study physician completes a neurological and psychiatric evaluation. Complete blood count, electrolytes, thyroid, renal and liver function tests, cholesterol and triglycerides, serum folate, B12, urinalysis and ECG are obtained. The Cumulative Illness Rating Scale for Geriatrics (CIRS-G), documenting medical burden in the major organ systems each on a 4-point anchored rating scale, is completed at baseline.

Apolipoprotein E Genotype Testing—Apolipoprotein E (apo E) genetic analysis on a blood sample is done through the laboratory of the Human Genetics Resources Core (HGRC) at Columbia University Medical Center. The sample is labeled with study ID, gender and birth year but without other patient identifying information. Results of apo E genotyping are not released to the patient, as indicated in the informed consent form.

Mini Mental State Exam (MMSE)—The MMSE is administered at the major time points (see Table 2). At consecutive testing visits, three different versions of the recall item are used to reduce practice effects.

Concomitant Medications—Putative cognitive enhancers, narcotics, all classes of psychotropic medications, and over 20 other classes of commonly prescribed and over the counter (and alternative) medications are documented in a rating form at the major time-points. An exclusion criterion is daily use of medication known to worsen cognition: benzodiazepines (lorazepam equivalents > 2 mg daily), high-dose narcotics, anticholinergics, and current alcohol/substance abuse/dependence. For patients with anxiety, lorazepam up to 2 mg/day (or benzodiazepine equivalent if the patient is already taking another benzodiazepine) is permitted. The following hypnotic medications are permitted if patients take them within the FDA-approved dose range: zolpidem, zaleplon, zopiclone, eszopiclone.

Functional Impairment—The Pfeffer Functional Activity Questionnaire¹⁸ is given to the patient and informant, separately, and each total score is examined in exploratory analyses.¹⁹

Baseline Olfaction Assessment—Odor identification is assessed at baseline using the University of Pennsylvania Smell Identification Test (UPSIT), which employs 40 microencapsulated common odorants, each presented with four written response alternatives (scratch and sniff multiple choice format).²⁰ The test score ranges from 0 to 40.

MR Imaging—MRI is done at baseline (or within 4 months after baseline evaluation) and is presented in the consent form to all subjects. MRI is optional for patients who do not wish to complete the procedure. Images are acquired on a GE Signa 3 Tesla whole body scanner with the following sequences. 3-Plane Localizer Repetition Time (TR) = 23.4 ms, Echo Time (TE) = 1.7 ms, Flip angle = 30°, Bandwidth = 31.3 MHz, field of view (FOV) = 24 × 24 cm, thickness = 5.0 mm, Spacing = 1.5 mm, 9 slices per volume (3 axials, 3 sagittals, 3 coronals), Matrix 256 × 128. 3D SPGR Anatomical Sequence TI 500 ms, TR 5 ms, TE Minimum (1.3 ms), Flip angle 11°, Band width 31.25 MHz, FOV 26 × 26, Slice thickness 1.1 mm, Spacing 0.0, 128 slices per volume, 1 NEX images × 2 (acquisitions averaged off line), Matrix 256 × 256. This sequence is acquired in the coronal orientation aligned to the long axis of the hippocampus, and these nearly isotropic images are easily reformatted into any plane for definition of ROIs. T2 FLAIR: 2D IR axial images with TR=10,000 msec, TE=122 msec, TI=2000 msec, FOV=24, matrix = 320×256, NEX=1, Slice thickness=5 mm, 31 slices.

Regions of interest (ROIs), chosen a priori, are based on published studies identifying regions predicting increased risk of dementia in MCI. A trained, experienced technician draws the parahippocampus, hippocampus, and entorhinal cortex ROIs using atlas based approaches on MRI scans.²¹

Neuropsychological Evaluation—The MMSE, SRT and ADAS-cog are given at 0 weeks, 16 weeks (randomization), 40 weeks, 64 weeks and 78 weeks (Table 2). **Memory.** Verbal list learning and memory are assessed by the 12-item, 6-trial SRT.²² Total number of words learned over six trials (total immediate recall) and delayed recall (after 15-min delay) is obtained. The logical memory subtest of the Wechsler Memory Scale-Revised (WMS-R)²³ is given at baseline. **Non-verbal learning/memory.** Non-verbal learning is assessed by the WMS-III visual reproduction subtest. **Visuospatial skills.** Visuospatial skills are assessed by the WAIS-III Block Design subtest. **Language tests.** Language skills are assessed by the verbal fluency (Letter and Animal Naming, 60-second trials), and a 15-item version of the Boston Naming Test (total spontaneous responses).²⁴ **Attention.** Attention is assessed by the Trail Making Test - Part A (Trails A), and the WAIS-III Digit Symbol, which also taps into executive function. **Executive function.** (2 measures): (1) Trail Making Test - Part B (Trails B) requires connecting alternating numbers and letters (1-A-2-B-3-C, etc.) as quickly as possible. (2) The Stroop Color-Word Interference Test (45-second trials) is a measure of attention, concentration, and behavioral inhibition under distracting conditions.²⁵ **Summary scores.** For cognitive measures, SRT total recall is the primary outcome and modified ADAS-cog is the secondary outcome. The other cognitive tests help in making the consensus diagnosis (SRT and ADAS-cog results are excluded from the diagnostic process). At Week 0, the UPSIT is administered before all cognitive tests.

Informed Consent and Ethical Aspects—All DEP-CI patients are required to have the capacity to provide informed consent and sign the IRB-approved informed consent form. Local IRB and State regulations for consent are followed. The U.S. FDA has indicated that this study, funded by the National Institute of Aging at the NIH, does not require an Investigational New Drug (IND) application.

The informed consent form states that the information provided by the subject will be kept strictly confidential, with access limited to the research staff with the exception of State or Federal regulatory personnel for audits. Each subject is given a code number and the patient's name does not reside in the computerized master database at NYSPI/Columbia which is password protected and behind an institute and department firewall. The research coordinator at each site enters the data directly into the electronic database with systematic double-checks before and after data entry.

The research data on specific moderators, including UPSIT and apolipoprotein E genotyping, are not released to the patient, and this is specified in the consent form. The clinical reading of the MRI scan is released to the patient (and the patient's primary physician, if requested); the MRI research volumetric ratings are not released.

Study monitoring and inter-site coordination involves pertinent staff and study physicians at both sites with monthly to bimonthly teleconferences throughout the study. The study PI (DPD) leads the executive decision-making for study monitoring, quality control, dispute resolution, and regulatory issues management.

Data Safety and Monitoring Board (DSMB)—Three independent experts form the DSMB: Gary Small, M.D. (DSMP Chair, Professor, Department of Psychiatry and Biobehavioral Sciences/Director of Geriatric Psychiatry, UCLA, Los Angeles, CA, USA), Anton Porsteinsson, M.D. (Professor, Department of Psychiatry, University of Rochester,

NY, USA) and Murray Raskind, M.D. (Professor and Vice-Chairman, Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA, USA). The DSMP reviews all Serious Adverse Events (SAEs) regularly and participates in an annual teleconference to review study status, SAEs and Adverse Events (AEs), and then provides an actionable report to the Principal Investigator who forwards the DSMB report to the IRBs.

Statistical Analysis, Sample Size and Power Calculations

Outcome Measures: To test the primary and secondary outcomes, we plan to use mixed effects regression to model each measure over time, as these models have several characteristics that provide solutions to common problems in the analysis of longitudinal psychiatric data: missing data, serial correlation, time-varying covariates.^{26, 27} We will consider the significance of the treatment effect and the treatment-by-time interaction and will use contrasts to test the primary and secondary hypotheses. We plan to use Supermix software written for the analysis of longitudinal data using mixed-effects logistic and linear regression.²⁸

Primary Hypothesis Testing: Antidepressant-treated DEP-CI patients on donepezil will show a lower rate of conversion to dementia (primarily AD) compared to antidepressant-treated DEP-CI patients on placebo by the end of the 18-month trial (hypothesis 1). We will use mixed effects logistic regression of the logit of conversion (yes/no) as a function of group, time and the interaction of group by time, where group represents a dummy-coded effect (group = 1 for antidepressant+donepezil, group = 0 for antidepressant+placebo), time = 0 weeks, 16 weeks, 40 weeks, 64 weeks, 78 weeks. With this characterization of the time and group effects, we can use a contrast to test this hypothesis.

Secondary Hypotheses Testing: Compared to the placebo group, the donepezil group will show better cognitive outcome by the end of the 18-month trial (SRT total recall: primary measure; modified ADAS-cog: secondary measure; hypothesis 2). The analytic approach and time points (baseline/0 weeks, 16 weeks, 40 weeks, 64 weeks, 78 weeks) will be similar to hypothesis testing of the primary outcome analyses, but will utilize mixed-effects linear (rather than logistic) regression. A similar strategy will be used to evaluate the same hypothesis for add-on donepezil or placebo at the end of 24 weeks, with time restricted to 0, 4, 16 and 24 weeks.

As part of our exploratory analyses, we will examine specific potential moderators: (apolipoprotein E ϵ 4 allele, baseline UPSIT score, MRI indices). We will examine, for example, that baseline UPSIT score is a moderator, that the score at baseline is uncorrelated with treatment and has an interactive effect with treatment on outcome.²⁹

Antidepressant management and analyses: We expect that 50% of patients will receive citalopram and another 50% will receive other antidepressants. This potential confound is addressed during the data analysis phase, with type of antidepressant (e.g., citalopram versus the rest) considered a covariate in statistical analysis. To address the potential impact of depression severity on cognitive change, HAM-D scores at the start of the add-on donepezil/placebo phase will be a covariate in statistical analysis.

Power Analysis: All calculations are 2-sided with $\alpha=0.05$ and assume 5% attrition between each consecutive pair of the 6 time-points (total 23% attrition over 18 months). Our power analysis for hypothesis 1 is based upon the power analysis for comparing clustered proportions.^{30, 31} Assuming an intra-cluster correlation of 0.2, $n=40$ subjects per group will provide at least 80% power to detect a 30% versus 10% difference based upon our pilot data

and published data. Our power analysis for hypothesis 2 is based upon the power calculations for longitudinal models.³² We assume 6 time points (0 weeks, 16 weeks, 28 weeks, 40 weeks, 64 weeks, 78 weeks) for our trend line with a two-group design and a random-effects structure with random slope, residual term and auto-correlated residuals, ICC=0.3 and a 5% attrition rate between assessments (total 23% attrition). Tests are 2-tailed with $\alpha = .05$. To test a between groups linear trend effect, 40 subjects per group provide sufficient power to test for a moderate effect (a between groups difference increasing linearly from 0 at baseline to 0.5 SD units at 18 months). The effect size from our pilot data primary measure, SRT total recall, was large and the effect sizes from other donepezil studies in AD have been moderate, so we expect to have sufficient power to test hypothesis 2. Even if the observed effect size is smaller, the information obtained in this pilot trial will allow for estimation of the effect size that can then be projected out to a larger sample in order to determine the feasibility of conducting a future large-scale, definitive trial.

DISCUSSION

Several design features provide unique strengths to this trial. Patients with comorbid depression and cognitive impairment will be identified and recruited from psychiatric, neurological, medical and other settings, thereby avoiding some of the biases seen in patient selection in other trials. The use of broad inclusion/exclusion criteria for DEP and CI increases the potential generalizability to clinical settings in the future, unlike prior studies that excluded MCI from depression trials and major depression from MCI trials. This is the first long-term (18-month) treatment trial in patients specifically identified with DEP-CI that uses antidepressant treatment plus add-on randomized, double-blind, placebo-controlled AChEI treatment. The primary outcome is focused on conversion to dementia, and in addition cognitive changes, over an extended time of treatment. Other than our own group's pilot study with a small sample (Pelton et al, 2008),¹¹ there have been no systematic studies of cognitive enhancers in the DEP-CI patient population.

This study also evaluates, for the first time, the clinical applicability of well-defined genetic (apolipoprotein E $\epsilon 4$) and neurobiological (odor identification deficits, MRI hippocampal and entorhinal cortex volume loss) markers as moderators of cognitive outcome and likelihood of conversion to dementia in patients with DEP-CI. Other early markers of AD were considered: hypometabolism in the parietotemporal, precuneus, and posterior cingulate regions on FDG PET, increased precuneus and posterior cingulate (and global) uptake on amyloid imaging PET, and CSF low ABeta and high tau/phospho tau levels. We decided against these biomarkers because our focus is to initially find a signal and to identify easily available, cost-effective markers in this study funded under the NIA pilot clinical trials program in AD. If such a signal is obtained, a subsequent larger study can help to both establish the utility of this treatment strategy and to investigate other potential neurobiological biomarkers.

Acknowledgments

Funding

The study is supported by grant R01AG040093 from the National Institute of Aging, NIH, Bethesda, MD, USA

Competing Interests

GHP has received research support from Eli Lilly and Forest and speaking fees from Forest, Pfizer, and Wyeth. DPD has received research support from Eli Lilly. PMD has received grants and/or advisory or speaking fees from several pharmaceutical companies. PMD owns shares in Sonexa, Clarimedix, and Adverse Events Inc whose products are not used in this study. HH has received salary support from grants funded by several pharmaceutical companies. JRP has received advisory fees from Elan/Janssen.

REFERENCES

1. Steffens DC, Otey E, Alexopoulos GS, Butters MA, Cuthbert B, Ganguli M, et al. Perspectives on depression, mild cognitive impairment, and cognitive decline. *Arch Gen Psychiatry*. 2006 Feb; 63(2):130–138. <http://archpsyc.jamanetwork.com/article.aspx?articleid=209350>. [PubMed: 16461855]
2. Devanand DP, Sano M, Tang MX, Taylor S, Gurland BJ, Wilder D, et al. Depressed mood and the incidence of Alzheimer's disease in the elderly living in the community. *Arch Gen Psychiatry*. 1996 Feb; 53(2):175–182. <http://archpsyc.jamanetwork.com/article.aspx?articleid=497539>. [PubMed: 8629893]
3. Byers AL, Covinsky KE, Barnes DE, Yaffe K. Dysthymia and depression increase risk of dementia and mortality among older veterans. *Am J Geriatr Psychiatry*. 2012 Aug; 20(8):664–672. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3229643/>. [PubMed: 21597358]
4. Taylor WD, Wagner HR, Steffens DC. Greater depression severity associated with less improvement in depression-associated cognitive deficits in older subjects. *Am J Geriatr Psychiatry*. 2002 Sep-Oct; 10(5):632–635. <http://www.ncbi.nlm.nih.gov/pubmed/12213698>. [PubMed: 12213698]
5. Nebes RD, Pollock BG, Houck PR, Butters MA, Mulsant BH, Zmuda MD, et al. Persistence of cognitive impairment in geriatric patients following antidepressant treatment: a randomized, double-blind clinical trial with nortriptyline and paroxetine. *J Psychiatr Res*. 2003 Mar-Apr; 37(2):99–108. <http://www.sciencedirect.com/science/article/pii/S0022395602000857> DOI: [http://dx.doi.org/10.1016/S0022-3956\(02\)00085-7](http://dx.doi.org/10.1016/S0022-3956(02)00085-7). [PubMed: 12842163]
6. Salloway S, Ferris S, Kluger A, Goldman R, Griesing T, Kumar D, et al. Efficacy of donepezil in mild cognitive impairment: a randomized placebo-controlled trial. *Neurology*. 2004 Aug; 63(4):651–657. <http://www.neurology.org/content/63/4/651.long>. [PubMed: 15326237]
7. Petersen RC, Thomas RG, Grundman M, Bennett D, Doody R, Ferris S, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med*. 2005 Jun; 352(23):2379–2388. <http://www.nejm.org/doi/full/10.1056/NEJMoa050151>. [PubMed: 15829527]
8. Devanand DP, Pelton GH, Marston K, Camacho Y, Roose SP, Stern Y, et al. Sertraline treatment of elderly patients with depression and cognitive impairment. *International Journal of Geriatric Psychiatry*. 2003; 18:123–130. <http://onlinelibrary.wiley.com/doi/10.1002/gps.802/abstract;jsessionid=E2087E96DB3D7DFC7EB6A4D8E9AD2250.d02t04>. [PubMed: 12571820]
9. Reynolds CF 3rd, Butters MA, Lopez O, Pollock BG, Dew MA, Mulsant BH, et al. Maintenance treatment of depression in old age: a randomized, double-blind, placebo-controlled evaluation of the efficacy and safety of donepezil combined with antidepressant pharmacotherapy. *Arch Gen Psychiatry*. 2011 Jan; 68(1):51–60. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3076045/>. [PubMed: 21199965]
10. Lu PH, Edland SD, Teng E, Tingus K, Petersen RC, Cummings JL. Alzheimer's Disease Cooperative Study Group. Donepezil delays progression to AD in MCI subjects with depressive symptoms. *Neurology*. 2009 Jun; 72(24):2115–2121. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2697965/>. [PubMed: 19528519]
11. Pelton GH, Harper OL, Tabert MH, Sackeim HA, Scarmeas N, Roose SP, et al. Randomized double-blind placebo-controlled donepezil augmentation in antidepressant-treated elderly patients with depression and cognitive impairment: a pilot study. *Int J Geriatr Psychiatry*. 2008 Jul; 23(7):670–676. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3104294/>. [PubMed: 18088076]
12. Winblad B, Engedal K, Soininen H, Verhey F, Waldemar G, Wimo A, et al. Donepezil Nordic Study Group. A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD. *Neurology*. 2001 Aug; 57(3):489–495. <http://www.neurology.org/content/57/3/489.long>. [PubMed: 11502918]
13. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984 Jul; 34(7):939–944. <http://www.neurology.org/content/34/7/939.full.pdf+html>. [PubMed: 6610841]

14. McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology*. 2005 Dec; 65(12):1863–1872. <http://www.neurology.org/content/65/12/1863.long>. [PubMed: 16237129]
15. Roman GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology*. 1993 Feb; 43(2):250–260. <http://www.ncbi.nlm.nih.gov/pubmed/8094895>. [PubMed: 8094895]
16. Lund-Manchester-Group. Clinical and neuropathological criteria for frontotemporal dementia. *J Neurol Neurosurg Psychiatry*. 1994 Apr; 57:416–418. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1072868/>. [PubMed: 8163988]
17. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol*. 1999 Mar; 56(3):303–308. <http://archneur.jamanetwork.com/article.aspx?articleid=774828>. [PubMed: 10190820]
18. Pfeffer RI, Kurosaki TT, Harrah CH Jr, Chance JM, Filos S. Measurement of functional activities in older adults in the community. *J Gerontol*. 1982 May; 37(3):323–329. <http://www.ncbi.nlm.nih.gov/pubmed/7069156>. [PubMed: 7069156]
19. Koontz J, Baskys A. Effects of galantamine on working memory and global functioning in patients with mild cognitive impairment: a double-blind placebo-controlled study. *Am J Alzheimers Dis Other Dement*. 2005 Sep-Oct; 20(5):295–302. <http://aja.sagepub.com/content/20/5/295.long>. [PubMed: 16273995]
20. Doty RL, Perl DP, Steele JC, Chen KM, Pierce JD Jr, Reyes P, et al. Olfactory dysfunction in three neurodegenerative diseases. *Geriatrics*. 1991 Aug; 46(Suppl 1):47–51. <http://www.ncbi.nlm.nih.gov/pubmed/1894145>. [PubMed: 1894145]
21. Devanand DP, Pradhaban G, Liu X, Khandji A, De Santi S, Rusinek H, et al. Hippocampal and entorhinal atrophy in mild cognitive impairment: prediction of Alzheimer disease. *Neurology*. 2007 Mar; 68(11):828–836. <http://www.neurology.org/content/68/11/828.long>. [PubMed: 17353470]
22. Buschke H, Fuld PA. Evaluating storage, retention, and retrieval in disordered memory and learning. *Neurology*. 1974 Nov; 24(11):1019–1025. <http://www.neurology.org/content/24/11/1019.short>. [PubMed: 4473151]
23. Wechsler, D. Wechsler Memory Scale-Revised. San Antonio, TX: The Psychological Corporation; 1987.
24. Goodglass, H.; Kaplan, E. The assessment of Aphasia and Related Disorders. 2nd ed.. Philadelphia: Lea & Febiger; 1983.
25. Lezak, M. Neuropsychological Assessment. 3rd ed.. New York: Oxford University Press; 1995.
26. Laird NM. Missing data in longitudinal studies. *Stat Med*. 1988 Jan-Feb; 7(1–2):305–315. <http://onlinelibrary.wiley.com/doi/10.1002/sim.4780070131/abstract>. [PubMed: 3353609]
27. Gibbons RD, Hedeker D, Elkin I, Waternaux C, Kraemer HC, Greenhouse JB, et al. Some conceptual and statistical issues in analysis of longitudinal psychiatric data. Application to the NIMH treatment of Depression Collaborative Research Program dataset. *Arch Gen Psychiatry*. 1993 Sep; 50(9):739–750. <http://archpsyc.jamanetwork.com/article.aspx?articleid=496334>. [PubMed: 8357299]
28. Hedeker D, Gibbons. MIXREG: a computer program for mixed-effects regression analysis with autocorrelated errors. *Comput Methods Programs Biomed*. 1996 May; 49(3):229–252. <http://www.sciencedirect.com/science/article/pii/0169260796017233> DOI: [http://dx.doi.org/10.1016/0169-2607\(96\)01723-3](http://dx.doi.org/10.1016/0169-2607(96)01723-3). [PubMed: 8800609]
29. Kraemer HC, Wilson GT, Fairburn CG, Agras SW. Mediators and moderators of treatment effects in randomized clinical trials. *Arch Gen Psychiatry*. 2002 Oct; 59(10):877–883. <http://www.ncbi.nlm.nih.gov/pubmed/12365874>. [PubMed: 12365874]
30. Hsieh FY. Sample size formulae for intervention studies with the cluster as unit of randomization. *Stat Med*. 1988 Nov; 7(11):1195–1201. <http://www.ncbi.nlm.nih.gov/pubmed/3201045>. [PubMed: 3201045]

31. Hsieh A. Sample Size Program for Clinical and Epidemiologic Studies. *The American Statistician*. 1991; 45(4):338. <http://www.jstor.org/stable/2684466>.
32. Hedeker D, Gibbons RD, Waternaux C. Sample size estimation for longitudinal designs with attrition: comparing time-related contrasts between two groups. *Journal of Educational and Behavioral Statistics*. 1999; 24(1):70–93. <http://www.uic.edu/classes/bstt/bstt513/rrmpow.pdf>.

Table A.1**Inclusion/Exclusion Criteria****Inclusion Criteria:**

- 1 Male or female; age 55–95 years.
- 2 Meets diagnosis of major depression, or dysthymic disorder of 6 months' duration by SCID-P evaluation.
- 3 Minimum 24-item Hamilton Rating Scale for Depression (HAM-D) score ≥ 14 .
- 4 Subjective memory or other cognitive complaints.
- 5 Meets criteria for cognitive impairment (CI) defined as a score ≤ 11 on the Logical Memory II subscale (Delayed Paragraph Recall, Paragraph A Test) from the Wechsler Memory Scale – Revised (the maximum score is 25); OR meets criteria for cognitive impairment (CI) defined as a score ≥ 1.5 SD below norms on the FC-SRT (immediate or delayed recall). These criteria define a broad group of cognitively impaired subjects and encompass both early MCI (eMCI) and late MCI (LMCI) as described in the ADNI-GO and ADNI-2 studies (www.adni-info.org).
- 6 Folstein Mini Mental State (MMSE) score ≥ 21 out of 30.
- 7 Clinical Dementia Rating (CDR) by study physician of 0.5 on the memory item, and global rating of 0.5 indicating questionable dementia.
- 8 Willing and capable of giving informed consent.

Exclusion Criteria:

- 1 Meets criteria for dementia (DSM-IV) or probable Alzheimer's Disease (NINCDS-ADRDA criteria).
- 2 Current clinical evidence of schizophrenia, schizoaffective disorder, psychotic depression, other psychosis, bipolar I disorder, or alcohol or substance dependence or abuse (current or within the past 6 months).
- 3 Active suicidal ideation or suicidal attempt in the last 6 months.
- 4 Clinical stroke with residual neurological deficits.
- 5 Use of medications known to have a negative impact on cognition: benzodiazepines in lorazepam equivalents > 2 mg daily, narcotics, anticholinergics, current alcohol abuse/dependence, other substance dependence.
- 6 Presence of any of the following disorders: a) active CNS infections such as meningitis, encephalitis, septicemia, or any other infectious process; b) Post-traumatic dementia, defined as dementia with a clear temporal relationship to a severe head injury where consciousness was lost; c) Huntington's disease; d) Multiple sclerosis; e) Parkinson's disease; f) Other neurologic disorders with focal signs, e.g., amyotrophic lateral sclerosis; g) Mental retardation.
- 7 Any acute, severe unstable medical condition. For cancer, acutely ill patients (including those with metastases) are excluded, but past history of successfully treated cancer does not result in exclusion.
- 8 Contra-indication to MRI scan: pacemaker, metal implants following surgery, any other contraindication to MRI (e.g., ferromagnetic aneurysm clips, heart valves). Patients with possible claustrophobia may do the MRI scan, if they are willing to take lorazepam 0.5 mg to reduce anxiety. Patients who cannot tolerate the MRI scan, but are still eligible for the clinical trial, will not complete the MRI scan. The MRI scan is optional.
- 9 Hypertension (BP $\geq 140/90$ mm Hg) at the evaluation visit. However, if the patient's primary care physician is comfortable with the patient's blood pressure being above 140/90, but below 150/100 mm Hg, the patient can be included in the protocol.
- 10 Patients currently on an effective antidepressant medication will be excluded.
- 11 Patients with QTc > 460 ms on baseline EKG will be excluded. Patients with a baseline QTc > 460 ms have the option of receiving venlafaxine ER as the initial treatment. All absolute contraindications listed in the package inserts for citalopram, venlafaxine and donepezil will be followed.

Table B

B.1. Flow Sheet and Procedures for Selected Major Time Points – Antidepressant Trials

| Pre-Randomization Phase (Phase 1). | | | | | | | | | | | | | |
|-------------------------------------|-------------------------------------|-----------|-----------|-----------|-----------|-----------|------------------------------------|---------------------|---------------------|---------------------|---------------------|--------------------|---|
| | Antidepressant Trial 1 (Citalopram) | | | | | | Antidepressant Trial (Venlafaxine) | | | | | | |
| | Screen & 0 10mg | 1 20mg | 2 20mg | 4 20mg | 6 20mg | 8 20mg | 9 20mg 75mg | 10 20mg 150mg | 12 20mg 225mg | 14 20mg 225mg | 16 20mg 225mg | Add Don 5mg/pla | |
| | | | | | | | OR Switch to Ven37.5mg | | | | | | |
| Citalopram dose: | | | | | | | | | | | | | |
| Venlafaxine dose: | | | | | | | | | | | | | |
| Donepezil/placebo dose: | | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | |
| Psychiatric Evaluation | X | | | | | | | | | | | | |
| Hamilton Depression Scale (24-item) | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Beck Depression Inventory II | X | X | X | X | X | X | X | X | X | X | X | X | X |
| CGI-Depression, Cognition & Global | X | X | X | X | X | X | X | X | X | X | X | X | X |
| CDR | X | | | | | | X | | | | | | X |
| Diagnosis Conversion Form | X | | | | | | | | | | | | |
| TESS (somatic side effects) | X | X | X | X | X | X | X | X | X | X | X | X | X |
| CIRS-G | X | | | | | | | | | | | | |
| Physical Exam | X | | | | | | | | | | | | |
| Bloods | X | | | | | | | | | | | | |
| Urine (Urinalysis) | X | | | | | | | | | | | | |
| Blood pressure, heart rate | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Weight | X | | | | | | | | | | | | |
| EKG | X | | | | | | | | | | | | |
| Demographic & Family History Form | X | | | | | | | | | | | | |
| Logical Memory (WMS-R) | X | | | | | | | | | | | | |
| MMSE, SRT, ADAS-Cog | X | | | | | | | | | | | | X |
| MRI Metal Screening | X | | | | | | | | | | | | |
| UPSIT | X | | | | | | | | | | | | |
| MRI Scan | X | | | | | | | | | | | | |
| Apo E genotyping | X | | | | | | | | | | | | |

B.1. Flow Sheet and Procedures for Selected Major Time Points – Antidepressant Trials

Pre-Randomization Phase (Phase 1).

| | Antidepressant Trial 1 (Citalopram) | | | | | | Antidepressant Trial (Venlafaxine) | | | | | |
|----------------------------|-------------------------------------|-----------|-----------|-----------|-----------|------------------------------|------------------------------------|------------|------------|------------|--------------------|--|
| | Screen & 0 10mg | 1 20mg | 2 20mg | 4 20mg | 6 20mg | 8 20mg | 9 75mg | 10 20mg | 12 20mg | 14 20mg | 16 20mg | |
| Citalopram dose: | | | | | | | | | | | | |
| Venlafaxine dose: | | | | | | | | | | | | |
| Donepezil/placebo dose: | | | | | | | | | | | | |
| | | | | | | OR Switch to Ven37.5mg | | | | | Add Don 5mg/pla | |
| Pfeiffer FAQ – Patient | X | | | | | | | | | | X | |
| Pfeiffer FAQ Informant | X | | | | | | | | | | X | |
| Neuropsych Battery | X | | | | | | | | | | X | |
| Randomization | | | | | | | | | | | X | |

B.2.

Post-Randomization Phase (Phase 2).

| | 19 ATD + 5mg don/pla | 22 ATD + 10mg don/pla | 28 ATD + 10mg don/pla | 40 ATD + 10mg don/pla | 64 ATD + 10mg don/pla | 78 ATD + 10mg don/pla |
|--|----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Time (weeks) on add-on donepezil/placebo: | | | | | | |
| Informed Consent | | | | | | |
| Psychiatric Evaluation | | | | | | |
| Hamilton Depression Scale (24-item) | X | X | X | X | X | X |
| Beck Depression Inventory II | X | X | X | X | X | X |
| CGI-Depression, Cognition & Global | X | X | X | X | X | X |
| CDR | | | | | | X |
| Diagnosis Conversion Form | | | X | X | X | X |
| TESS | X | X | X | X | X | X |
| CIRS-G | | | | | | |
| Physical Exam | | | | | | |
| Bloods (electrolytes) | | | | X | | |
| Urine (Urinalysis) | | | | | | |
| Blood pressure, heart rate | X | X | X | X | X | X |
| Weight | | | | | | X |
| EKG | | | | | | |

B.2.

Post-Randomization Phase (Phase 2).

| Time (weeks) on add-on donepezil/placebo: | 19 ATD + 5mg don/pla | 22 ATD + 10mg don/pla | 28 ATD + 10mg don/pla | 40 ATD + 10mg don/pla | 64 ATD + 10mg don/pla | 78 ATD + 10mg don/pla |
|--|----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Demographic & Family History | | | | | | |
| Logical Memory (WMS-R) | | | | | | |
| MMSE, SRT, ADAS-Cog | | | | X | X | X |
| MRI Metal Screening | | | | | | |
| UPSIT | | | | | | |
| MRI Scan | | | | | | |
| Apo E genotyping | | | | | | |
| Pfeffer FAQ - Patient | | | | X | | X |
| Pfeffer FAQ - Informant | | | | X | | X |
| Neuropsych Battery | | | | X | X | X |
| Randomization | | | | | | |
| X. These measures are to be completed at this time point. Visits 1, 2, 4, 6, 9, 10, 12, 14, 19 and 22 may be completed over the phone. | | | | | | |
| Ven, Venlafaxine | | | | | | |
| Don, Donepezil | | | | | | |
| Pla, Placebo | | | | | | |
| CGI, Clinical Global Impression | | | | | | |
| CDR, Clinical Dementia Rating | | | | | | |
| TESS, Treat Emergent Symptom Scale | | | | | | |
| CIRS-G, Cumulative Illness Rating Scale for Geriatrics | | | | | | |
| EKG, Electrocardiogram | | | | | | |
| Logical Memory (WMS-R), Logical Memory (Wechsler Memory Scale-R) | | | | | | |
| MMSE, Mini Mental State Examination | | | | | | |