Project Title: Detecting an early response to donepezil with measures of visual attention

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PROBLEM STATMENT

Acetylcholinesterase inhibitors (AChE-I) comprise the major class of drugs used to treat Alzheimer's disease (AD). Despite widespread use, there is controversy about the usefulness of these medications[1,2]. Concerns have been modest response rates of treated versus placebo groups, relatively small effect sizes with respect to efficacy, drug costs, and clinical relevance of the effects. One problem is that measures of efficacy used may not be sufficiently sensitive to detect a true drug effect[3]. Another problem is that changes noted after 4-6 months of therapy represent a confound of the drug effect and the natural progression of the disease. Lastly, patient heterogeneity may contribute to the wide range of degree of response, further decreasing overall effect sizes.

We must address three important issues to improve the clinical usefulness of cholinergic therapy. First, we need outcome measures that are sensitive to the effects of cholinergic treatment. Second, outcome measures should be sensitive to the drug effect *early in the course of treatment* before a measurable decline of the disease progression occurs. Third, improved treatment would be attained if we knew which patient characteristics or performance measures contribute to, or even predict, who will likely benefit. The premise of the current proposal is that measures of higher-order attention, which are currently omitted from standard assessments of treatment outcome, could provide necessary insight into early efficacy of cholinergic treatment. We are conducting a preliminary study that supports our hypotheses testing the value of such attentional measures.

The rationale for using attentional measures is as follows: (1) Attentional deficits are recognized as a critical cognitive change in the earliest phases of AD; (2) Attentional function, particularly tasks that tax available attentional capacity, is mediated by the cholinergic system; and (3) Acetylcholine is depleted in AD. However, the link between attention and cholinergic depletion in AD has not been fully explored, particularly with regard to response to cholinergic treatment. Surprisingly, attentional measures have not been included in the evaluation of AChE-I in the treatment of AD. We propose that attentional performance could serve as a highly sensitive outcome measure and a marker of response.

STUDY AIMS AND HYPOTHESES:

1. To determine that higher-order attentional measures are sensitive to the effect of cholinergic change *early* in the course of treatment. We predict that performance on attentional tasks will improve in AChE-I treated patients compared to placebo controls after 7±1 weeks of treatment.
2. **2a**. To examine the effect of cholinergic treatment on attentional measures as compared with global measures or measures of other cognitive domains. We predict that the performance on tasks of attention is more sensitive than traditional global measures of performance.
   2b. To examine whether cholinergic treatment changes the relationships among measures of attention and measures of other cognitive function. We predict that the relationships among attention and cognitive domain measures will change with treatment.
3. To determine whether performance at 7±1 weeks can predict response at 6 months:
   3a. Patient response to AChE-I may be influenced by demographic variables, or influence performance in one or more cognitive domains. The aim is to determine which cognitive domain or demographic characteristic best predicts treatment response at six months. It is hypothesized that attention and memory (both mediated by cholinergic mechanisms) will best predict treatment response seen at six months.
   3b. To determine whether an attentional change seen in patients early in the treatment course predicts drug response. It is hypothesized that change in attention measured between baseline and 7±1 weeks will predict overall improvement in those patients who show positive treatment response at six months.

Knowledge gained from this project will facilitate and inform our decisions about individual patients undergoing pharmacological treatment. The application of these goals can apply to current AChE-I treatment as well as other treatments, such as those now involving combined cholinergic and glutamanergic agents.

WORKPLAN

Background and significance

Attention and Alzheimer's disease (AD): The vulnerability of higher-order attention tasks in AD occurs in tasks such as selective attention[4,5], and covert orienting[6]. Attentional deficits are documented in patients with prodromal AD who later develop the disease[7], suggesting potential sensitivity of attention to disease onset. Mechanisms of attention are mediated via anterior executive control (required in conjunctive search[8,9] and inhibitory control[9]) and via posterior disengagement[10]. The deficits in AD may be explained by regional frontal or posterior dysfunction, or by a disconnection[11] between the frontal and posterior attentional networks[12] that disrupt the feedback system[13].

Acetylcholine and attention: A primary modulator of attention is acetylcholine (ACh)[14]. Decreased ACh impairs attentional function in animals and humans including vigilance in rat[15], covert orienting in primate[16] and AD[17], and complex attention in human pilots[18]. ACh functions in a dose related manner, with increased task load of higher background noise[19] correlating with increased ACh release[20]. Cholinergic antagonists (e.g., scopolamine) slow reaction time (RT) and increase omission errors on visual search[21,22], and increase omission and commission errors on signal detection[23]. Higher scopolamine doses slow RT in covert orienting in primates involving inferoparietal regions[16].

AD, attention and cholinesterase inhibitors: The relationship between attention and acetylcholine has not been well demonstrated in the assessment of AChE-I. Efficacy studies of donepezil[24], galantamine[25] or rivastigmine[26] show modest effect sizes[3] ranging from 1.8–4.1 points on the 70 point ADAS-Cog scale. These small effect sizes may partially be a function of using this outcome measure, which obscures the sensitivity to attention and memory with a global score. Targeted cognitive domains may be better response indicators. In a post-mortem analysis of AD patients, regions of low cholinergic activity correlated to memory and attention[27]. Moreover, after 12 weeks of galantamine treatment[28], AD patients who reached therapeutic dose showed faster RT, better choice reaction time and in memory, recognition of faces. Also, on functional imaging, early response to AChE-I appears to affect regions[29] that mediate directed attention. In summary, *if attentional function is intrinsically linked to the level of cholinergic activity, it should used be an outcome measure of AChE-I treatment in AD to improve treatment sensitivity.*

Methods

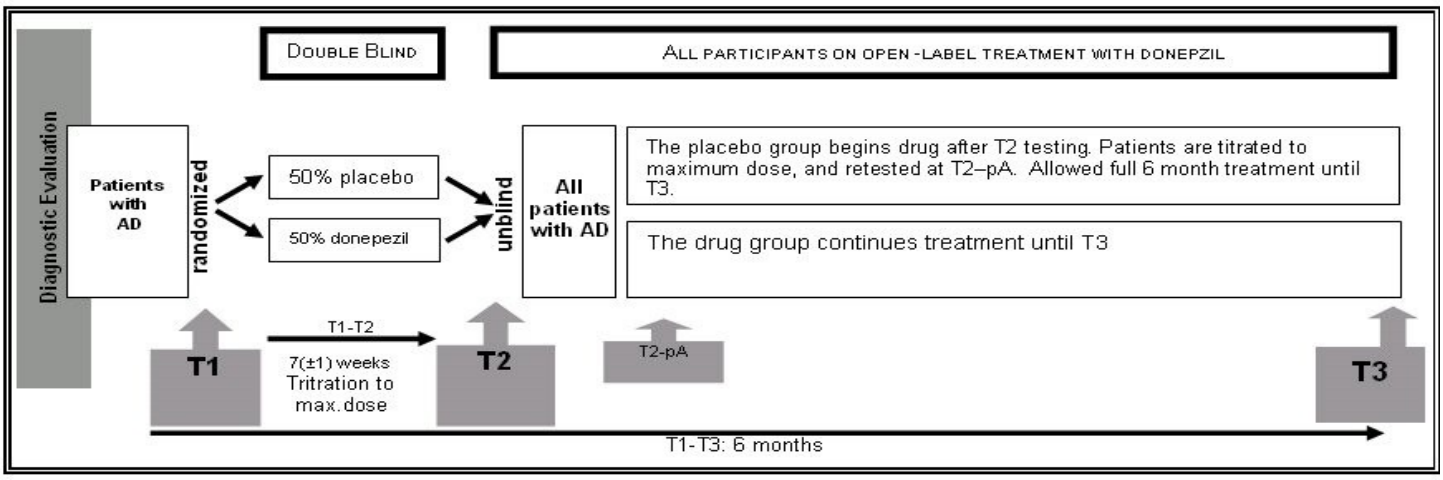
I. EXPERIMENTAL DESIGN

The proposed study is a 6-month longitudinal design assessing 40 newly diagnosed patients with AD as they start donepezil treatment (see Figure 1). The brief *first arm* (between T1-T2) is randomized, double-blind, placebo controlled, after which all patients are treated open label. Visual attentional measures will be contrasted with global and cognitive domain measures. The baseline assessment is before treatment, **T1,** after which patients will be randomized into treatment and placebo groups. The **T2** assessment occurs at 7±1 weeks, after approximately 2 weeks of optimum treatment dose in the treated group. After the T2 assessment, the treatment assignment will be unblinded, and placebo patients will begin treatment. In order to include all participants in the final 6 month analyses, participants initially treated with placebo will undergo an additional testing (**T2-pA**). At **T3** all participants will have been treated for a full 6 month period.

Drug choice and placebo: Donepezil has been chosen for this protocol: We have preliminary data with this agent; effective dose can be achieved *early* in the course of treatment; it requires only once-daily administration; it requires single dose titration step from 5mg to max. dose of 10 mg. Randomization, preparation, and treatment with drug vs. placebo will be managed by the pharmacy director of the hospital site

Rationale for double-blind placebo design: Our preliminary data (see below) is based on a repeated measures, longitudinal design without a placebo group. Inclusion of the placebo arm, T1-T2, would allow us improve our ability to test our hypotheses and determine the validity of an early treatment effect. We are cognizant of the

Figure 1.



short delay of treatment for 50% of the participants; however, given the current controversy of the efficacy of the drug[1], we feel that being able to answer whether effects are detectable early, and whether those effects occur in responders, outweighs this minimal risk.

INSTRUMENTS – MEASURES

Experimental tasks (‡) were developed and/or programmed in our laboratory. Task selection was based on: avoidance of floor or ceiling effects assuring that patients with a range from mild to moderate AD can perform tasks; availability of alternate forms. Patients with no computer experience are allowed and sufficient practice.

Global measures: *1.ADAS-Cog* (70-point scale); standard pharmacological rating tool; 2. *DRS* (Dementia Rating Scale) total score and subtest profiles; 3. *MMSE* (MiniMental Status examination); standard cognitive measure; 4. *CDR* (Clinical Dementia Rating scale) including standard and sum of box-scores to measure function.

Cognitive Domains

Attention Focused and sustained attention: A. *Digits Forward* - WAIS III;

B. ‡ *Simple Reaction Time:* RT to a single stimulus presented on a computer screen at randomized intervals.

C. ‡*Visual Selective Attention*: This is a computer version of a paper and pencil cancellation task, developed by the PI for patients with AD. Participants indicate presence or absence of a target among an array of distractors, which vary in density (number of items on screen). Outcome measures include RT, hits, and false alarms.

D. ‡*Visual covert orienting:* Posner's paradigm assesses covert orienting by comparing response to a target preceded by a valid or an invalid cue. Outcome measure is RT to target detection. In valid conditions, the target (i.e., 'X') follows a cue in the ipsilateral visual field and in invalid conditions the contralateral field. Valid and invalid tasks are equally frequent (50%) and presented randomly. On 80% of the trials, the cue to target interval (Stimulus Onset Asynchrony, SOA) is 150 msec; the remaining 20% of the trials are catch trials (SOA=700 msec), which are included in the task, but excluded from analyses.

E. ‡*Choice Reaction Time:* a computer task examines RT on a same/different choice response of two stimuli. The task demonstrates participants' ability to discriminate shapes in a non-search condition.

Memory: 1) Hopkins Verbal Learning Test (measures of total learning, delay, intrusions, serial position).

Language: 1) Fluency: Letter cue (FAS); 2) Semantic cue; 3) Boston Naming Test-15 item (multiple forms).

Visuospatial function 1) Clock drawing; 2) Benton - Visual Form Discrimination[30].

Frontal-executive function: 1) D-KEFS Trails[31] (measures of set-switch; speed; contrast)

Psychiatric Status: 1) Geriatric Depression Scale[32] (GDS); 2) Neuropsychiatric inventory[33].

II. PARTICIPANTS: Recruitment: Patients will be recruited through the Memory and Cognitive Disorders Center at Winthrop-University Hospital. The PI has a 12 year established network of geriatricians, psychiatrists and neurologists throughout the Long Island, NY area who refer patients for diagnostic determination. Additional resources will allow the current average of 5-8 weekly referrals to be screened.

Patient characteristics: This is a particularly difficult patient population to access, as many patients entering primary research centers have already initiated medication prescribed by community physicians. *A major strength of this proposal is access to patients who are being newly diagnosed, and are undergoing de novo treatment with AChE-I.* Neuropsychological tests used for diagnosis will not overlap with tests used as study dependent measures. Inclusion criteria: Study inclusion criteria include satisfying NINDS-ADRDA criteria for AD, with ruled out vascular, mixed or other etiology of dementia. Diagnosis will be reached by consensus of neuropsychology (NSF), geriatrics (JB and LO), neurology (LSH), and neuroradiology (LSH, OO). Stable concurrent therapy with non-cholinesterase inhibitors will be allowed including NSAIDS, Vitamin E, or SSRI antidepressants. Patients must be able to perform attention tasks (MMSE >15) and have corrected vision. If a patient meets criteria both patient and kin provide written consent Exclusion criteria: any prior AChE-I use, or concurrent anticholinergic treatment (e.g., incontinence medication) or use of memantine.

Sample size: 50 patients will be recruited. Power analysis tests the null hypothesis that an average yearly decline in unmedicated AD patients is 3 MMSE points. With criterion for significance (alpha) of 0.05, and a 2-tailed test, a proposed *sample size of 40* (drug = 20; placebo = 20)**,** will have power exceeding 80% to yield a statistically significant result on Covert orienting task (most stringent attention task). Current attrition rate of 22% requires recruitment of additional 10 participants.

IRB: A preliminary longitudinal study using only treated AD patients has been approved by both University and Hospital IRBs (#01-06-05-03) through 5/1/05. All patients and a responsible kin (or legal guardian) will give written consent in compliance with risk to vulnerable populations. IRB application for the proposed design (using treated and placebo groups) is pending. All data will be managed in compliance with HIPAA and IRB regulations, including secure electronic transfer via encrypted SSL protocols.

III. PROCEDURES Neuropsychological and computer testing will be administered by the PI or GRA at Winthrop-University Hospital, lasting 2½ hours with appropriate breaks. Patients will be paid $30 for each session at that visit. Compliance for multiple visits will be insured via phone and mail contacts with families.

IV. DATA MANAGEMENT Raw data and analyses will be managed with SPSS and S-PLUS. The heterogeneity of AD can result in wide variation, particularly on RT data. Data will be reviewed and undergo necessary transformation to insure normal distribution of error variance, reduced skew, and minimized effects of extreme values. When indicated, RT data will be treated in a two step procedure omitting individual trials of extreme outliers ($-3 < z > +3$) and a logarithmic (log10) transformation. All analyses will be evaluated with and without transformations and be reported if discrepancies arise.

PRELIMINARY DATA

Preliminary data from our laboratory support our hypothesis that attentional measures can detect effects of AChE-I treatment**. 1) Effect of load:** We first confirmed[8] that higher load levels in selective cancellation affected 18 AD patients more than 18 age-matched controls, with higher commission errors and longer RTs as load increased. At high-load, the task was very sensitive in capturing attentional deficits even in high functioning patients. **2) Effect of drug:** In subsequent analyses[34], subgroups of these patients (on donepezil, n=8; off donepezil, n=9) were matched on demographic variables of age, duration, or severity of illness. The ability to discriminate targets from distractors, d-prime p=.058, and the likelihood of endorsing a target correctly was better in treated compared to non-treated patients, beta p=.029. Treated patients were better at discriminating targets and rejecting non-salient stimuli correctly, implicating an attentional benefit of treatment. **3) Preliminary results of longitudinal study**: 13 patients with AD (CDR 0.5-1.0) treated with open-label donepezil have been evaluated on all tests pretreatment (T1) and after a mean of 7.75 weeks (T2). Global measures fail to capture significant T1–T2 change (ADAS-Cog, DRS, CDR, CDR-Box score: p>.10). However, our experimental attentional tasks *are* detecting change. On selective attention, accuracy of target detection is faster (p<.001) at low density, while maintaining accuracy (p=.19). On the more dense arrays, there is a small but significant drop in accuracy, but slower detection (p<.01) suggesting a speed-accuracy tradeoff. On covert orienting, validity effect changed over time (p=.031; effect size=0.33). The degree of load interacts with

response. *These data suggest that attentional functions (e.g., search, speed/accuracy tradeoff, disengagement) detect early cholinergic effects, while global measures do not.* The study with increased power and inclusion of a placebo group will permit more general conclusions.

ANALYSES

Aim 1. To document that higher-order attentional measures are sensitive to the effect of cholinergic change *early* in the course of treatment, Ancovas on Group (treated, placebo) will be performed with measures of attention (e.g., simple RT, Covert orienting, Choice RT and Selective Attention) at T2 as the dependent variables and measures of attention at T1 as covariates.

Aim 2a. To determine the relative sensitivity of attention compared with other measures. The effect size of each attentional measure will be compared with the effect sizes of global and cognitive domain measures[35].

Aim 2b. To determine whether change of certain measures covary, change data from placebo and drug groups will be pooled, and Pearson correlations of the reliable change[36] among measures T2-T3 will be compared. To determine whether the relationships among measures differ between drug and placebo groups, measures at T2 will be correlated with one another within each group, and individual differences multidimensional scaling will be applied to each of the two matrices.

Aim 3a. To document which cognitive domains or demographic variables best account for treatment response at six months, a hierarchical, multiple regression will be performed. Reliable change scores of each cognitive domain (T2–drug group; T2-pA–placebo group) will be predictor variables, and ADAS-cog T3-T1 difference scores serve as the dependent variable. DRS will be entered first into the regression to control for disease severity, followed by attention and memory, with frontal-executive, visuo-spatial and language variables following. The incremental-F tests will evaluate the unique variances contributed by attention or memory to ADAS-cog without the contribution of the remaining domains. We will conduct additional analyses using a dichotomous responder/non-responder dependent variable (defined by >4 point improvement on ADAS-Cog).

Aim3b. To determine whether the change on the experimental attentional measures seen in patients early in the treatment course predicts treatment change at 6 months, a hierarchical regression analyses will be conducted with attention score change T2-T1 (T2 for drug group; T2-pA for placebo group) used as the predictor variables, and ADAS-cog score (difference T3-T1) used as the dependent variable. Group membership (drug/placebo), DRS, and demographic variables will be entered into the regression to control for age, education, initial dementia severity.

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ABSTRACTS

3000 character abstract for general public.

Although the majority of patients with Alzheimer's disease (AD) are receiving acetylcholinesterase inhibitor treatment, there are no objective measures to determine whether the drug is working. This has frustrated families and physicians, and resulted in more scrutiny about the medications' efficacy, cost, and clinical utility. These medications still remain part of standard treatment regimens, but we are remiss by not developing ways to assess if the drug is effective, and by not determining efficacy early in the course of treatment.

Surprisingly, important measures that should be used to assess cholinergic change are lacking: the measures omitted involve attention. Attention is very sensitive to levels of acetylcholine. Research shows that acetylcholine directly mediates attention, and that attention is one of the earliest cognitive changes that occurs in the course of the disease, even during the pre-clinical, MCI phase. Animal models show that attention improves with increased acetylcholine, and deteriorates when acetylcholine levels are lowered. Yet, the link between attention and acetylcholine depletion in AD has never been fully explored, especially with regard to response to cholinergic treatment. To date, no study has investigated how acetylcholinesterase inhibitors affect attentional function in AD. We have preliminary data that now shows that measures of attention do change even after a few weeks of treatment, where traditional global measures do not show significant change. We predict that attentional measures will be excellent, more sensitive measures of response.

We propose a 6-month longitudinal study, testing patients with standard measures and new experimental visual attention tasks. A first testing occurs before treatment, after which patients are randomized with half the patients treated with donepezil and half with placebo. A brief double-blind control period follows, during which treated patients will be titrated to optimal medication dose. After a second testing compares the subgroups, all patients receive open-label medication. The third testing occurs after 6 months, to determine the degree of response as measured by the traditional global scale (ADAS-Cog), and to determine whether the change at the second testing can predict the performance at 6 months.

We predict 1) that measures of attention are more sensitive than standard global measures; 2) that acetylcholinesterase inhibitor treatment affects attentional function early in the course of treatment; 3) that attentional measures can serve as important outcome measures to differentiate and predict good versus poor responders.

This project provides tools to help us decide whether cholinergic treatment is effective. Our findings are generalizable and apply to other cholinergic treatments, and treatments now involving combined cholinergic and glutamanergic agents.

3000 character abstract for technical audience

Acetylcholinesterase inhibitors (AChE-I) comprise the major class of drugs used to treat Alzheimer's disease (AD), but controversy about the usefulness of these medications[1,2] remains. Modest response rates of treated versus placebo groups, small effect sizes with respect to efficacy, drug costs, and clinical relevance of the effects are problematic Standard efficacy measures of efficacy are not sufficiently sensitive, and cognitive change after 4-6 months of therapy represent a confound of the drug effect and the natural progression of the disease. Patient heterogeneity that may contribute to the wide range of response may also be further decreasing overall effect sizes.

Surprisingly, attention has never been included in the assessment of AChE-I drugs. The rationale for using attentional measures is obvious: (1) Attentional deficits are recognized as a critical cognitive change in the earliest phases of AD; (2) Attentional function is directly mediated by the cholinergic system, and responds rapidly to cholinergic augmentation, particularly on tasks that tax available attentional capacity are dose dependent; and (3) Acetylcholine is depleted in AD. However, the link between attention and cholinergic depletion in AD has not been fully explored, especially with regard to response to cholinergic treatment. We propose that attentional performance could serve as a highly sensitive outcome measure and a marker of response

The proposed 6-month longitudinal study examines attentional, cognitive and behavioral performance in 40 de novo AD patients undergoing donepezil treatment. New visual attentional measures will be contrasted with global cognitive measures and cognitive domain scores on three occasions (T1: pre-treatment; T2: 7 weeks (plus or minus 1 week); T3: post 6 months treatment). The T1-to-T2 arm of the design includes a double-blind placebo control period, after which all patients undergo open-label treatment. The assessment at 6 months will allow us to determine whether the changes seen earlier at T2 can predict patients who respond, or determine which measures best predict response.

We present our preliminary data that support our rationale. Attentional measures are showing significant change after 7 weeks, while global measures are not.

The proposed study predicts: 1) that measures of attention are more sensitive than standard global measures; 2) that AChE-I treatment affects attentional function early in the course of treatment. It is critical to determine efficacy before disease progresses.

Knowledge gained from this project will facilitate and inform our decisions about individual patients undergoing pharmacological treatment. The application of these goals can apply to current AChE-I treatment as well as other treatments, such as those now involving combined cholinergic and glutamanergic agents.