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METHODOLOGICAL IMPROVEMENTS IN QUANTIFYING COGNITIVE CHANGE IN CLINICAL TRIALS: AN EXAMPLE WITH SINGLE-DOSE ADMINISTRATION OF DONEPEZIL

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Abstract: *Objectives:* Change in cognitive function in response to a pharmacologic challenge can be observed with greater sensitivity by employing cognitive tests with optimal psychometric properties and a statistical approach that more accurately accounts for individual variability in performance. To demonstrate this approach we examined the cognitive effects of a single acute dose administration of an acetylcholinesterase inhibitor, donepezil, in healthy older adults and in older adults with mild Alzheimer's disease (AD). *Design:* Placebo-controlled crossover study with three separate testing days: baseline, placebo, and donepezil, with assessments at baseline, and 1-, 2-, 3-, 6-, and 8-hrs post-dosing on each day. *Setting:* Early phase I clinical trial. *Participants:* 15 healthy older adults; 14 older adults with mild Alzheimer's disease. *Intervention:* Single acute dose of 5mg donepezil. *Measurements:* Performance on the Groton Maze Learning Test (GMLT), a computerized neuropsychological measure of spatial working memory and error monitoring. *Results:* A single acute dose of donepezil improved GMLT performance in healthy older adults (effect size: 0.83 at 6 hrs post-dosing) and older adults with mild AD (effect size: 0.58 at 3 hrs post-dosing). *Conclusion:* The GMLT detected cognitive improvement following a single, acute dose administration of donepezil in healthy older adults and older adults with mild AD. The choice of cognitive tests designed for repeated administration, as well as an analytic approach that emphasizes individual-level change in cognitive function, provides a sensitive approach to detecting central nervous system drug penetration and activity of cognitive-enhancing agents.

Key words: Cognitive, neuropsychology, donepezil, healthy, Alzheimer's disease.

The cholinergic system is involved in storage and retrieval of new learning and other aspects of cognitive function such as information-processing speed and executive function (1). Stimulation of the cholinergic system with acetylecholinesterase (AChE) inhibitors, which interfere with the breakdown of acetylcholine and promote its accumulation in the synapse, (2, 3) may facilitate improvement in cognitive function in healthy adults, (4-6) as well as in individuals with Alzheimer's disease (AD) (7, 8). However, some studies have failed to find improvement in cognitive function following administration of an AChE inhibitor in healthy younger (5mg donepezil at bedtime for 14 days) and older adults (10mg donepezil 3 times a day for 14 days), (9, 10) and have even noted subtle deterioration in aspects of memory and concentration. These authors concluded that increasing acetylcholine levels in normal healthy individuals may lead to subtle worsening of certain aspects of cognitive function and suggested that the cognitive measures they employed may have been less complex compared to other tests that employed in other studies of healthy individuals (4) that noted significant improvement in cognitive function following donepezil administration.

While task complexity may partly explain the lack of effect in the Beglinger et al. (9, 10) studies, another explanation for this null finding is that the cognitive tests employed in this study were not designed to assess cognitive improvement; rather, they were designed to assess cognitive impairment relative to normal individuals. Decisions regarding whether an individual is impaired on a cognitive test are often one-tailed in nature and the metrics of these tests are often inappropriate for decisions regarding whether an improvement in cognitive performance is evident (11). Another explanation for this lack of effect is that the tests employed were not sensitive to detecting the effects of cholinergic modulation, as they did not assess cognitive functions commonly improved with AChE inhibitors. Thus, it may be possible to detect improvement in cognitive function in healthy individuals following donepezil administration if cognitive tests sensitive to cholinergic modulation and that have metric properties appropriate for detecting cognitive improvement are employed.

Cognitive tests designed to assess change (impairment or improvement) should have a number of characteristics. For example, these tasks should be brief, easy to administer and understand, be sufficiently motivating, have multiple alternate test forms, generate performance data that approximates interval scalar properties, and yield data distributions that are normal or that can be corrected to normal, do not have restriction of range, or floor or ceiling effects (12-17). In addition to a cognitive test battery that features the aforementioned properties, an appropriate statistical framework is needed to guide decisions about cognitive change. One approach is to compute estimates of stability of performance of

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each outcome measure from multiple baseline assessments. Change in performance as a function of treatment may then be compared to this estimate of stability/normal variability in performance over time (16, 17).

We recently examined the utility of the Groton Maze Learning Test (GMLT), a cognitive test that features many of the test characteristics and data properties described above, in assessing cognitive change in a double-blind, placebo-controlled, modified crossover study of a single acute 5mg dose of donepezil in healthy adults (18). This study utilized a well-known pharmacologic model of induced dementia—scopolamine challenge—to examine whether a single acute dose of donepezil could reverse scopolamine-induced cognitive deficits. Results showed that scopolamine administration alone was associated with slowed processing speed and reduced learning efficiency. A single acute dose of donepezil led to improvement in these cognitive functions, and concurrent administration of donepezil with scopolamine significantly reversed these deficits and resulted in faster recovery time.

In the current study, we sought to replicate this finding in a placebo-controlled crossover study that examined the utility of the GMLT in detecting cognitive change in healthy older adults and extend it by evaluating whether a single acute dose of donepezil may also improve GMLT performance in patients with mild AD. Because the GMLT was designed for repeat administration and features many of the test and psychometric properties described above, we hypothesized that it would detect cognitive improvement following donepezil administration in both healthy elders and patients with mild AD. We also hypothesized that the magnitude of cognitive improvement would be greater in healthy older adults compared to individuals with mild AD, as clinical samples are known to evidence greater within-person variability in cognitive performance (19, 20).

Method

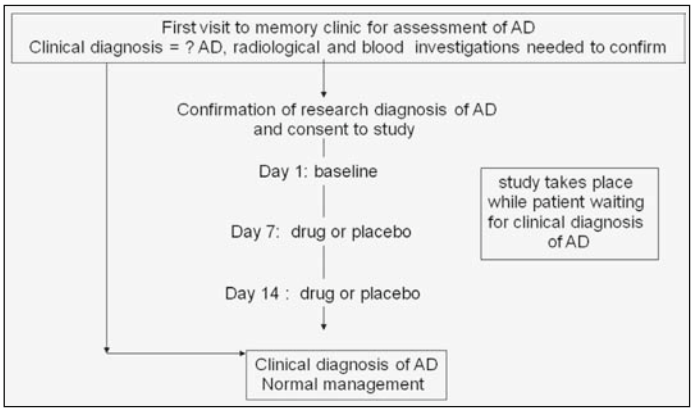
Two separate double-blind, placebo-controlled, crossover studies using the same design examined the effect of single-dose donepezil on cognitive function in healthy older adults and older adults with mild Alzheimer's disease.

Participants

The healthy older adult group consisted of 15 healthy older men (mean age = 69 years, range = 64-75 years). All had normal or corrected to normal visual and auditory acuity, were in good general health or without any clinically significant abnormalities, had a normal ECG, and a Mini-Mental State Exam score > 28/30. The mean number of years education in the healthy older group was 10.9 years (SD=6.2) and the estimated pre-morbid IQ was (103.9, SD = 6.5).

The mild Alzheimer's disease group consisted of 14 healthy adult males aged over 65 (mean age = 68; range = 65 to 72 years). All participants met clinical criteria for AD (21) with the severity of disease mild in all cases. All patients had been diagnosed after referral to a memory clinic for investigation of memory impairment. No patient had received any medications licensed for the treatment of mild AD. The mean number of years education in the AD group was 11.3 years (SD=5.6) and the premorbid estimated IQ was (101.3, SD = 7.6). Patient flow for participants in Study 2 is shown in Figure 1.

Figure 1
Design and study flow in Study 2



All individuals satisfied rigorous inclusion and exclusion criteria (summarized below), and were both willing and able to provide written informed consent. Exclusion criteria included a history of major depression or other Axis I psychiatric disorders (as described in DSM-IV) within the past 2 years, psychotic features, agitation or behavioral problems within the last 3 months, a history of alcohol or substance abuse or dependence within the past 2 years (DSM-IV criteria), a history of schizophrenia (DSM-IV criteria) and significant systemic illness or unstable medical condition which could lead to difficulty complying with the protocol. Such medical conditions included: cancer, cardiovascular disease or angina, obstructive pulmonary disease or asthma, clinically significant and unstable gastrointestinal disorder such as ulcer disease or a history of active or occult gastrointestinal bleeding within two years, clinically significant laboratory test abnormalities (hematology, prothrombin time, chemistry, urinalysis), Insulin-requiring diabetes or uncontrolled diabetes mellitus, uncontrolled hypertension (systolic BP > 170 or diastolic BP > 100), a history of clinically significant liver disease, coagulopathy, or vitamin K deficiency within the past 2 years, narrow-angle glaucoma, or clinically significant obstructive uropathy.

Vitamin supplements (including Vitamin E) were allowed and individuals taking any prescribed medication were required to have been stable on that medication and dose for at least one month prior to screening. Individuals were excluded if they were taking centrally active beta-blockers, narcotics, methyldopa and clonidine within four weeks prior to screening, dopamine agonists or L-DOPA medications within two months prior to screening, neuroleptics or narcotic analgesics within

four weeks prior to screening, long-acting benzodiazepines or barbiturates within four weeks prior to screening, short-acting anxiolytics or sedative-hypnotics more frequently than two times per week within four weeks prior to screening, initiation or change in dose of an antidepressant lacking significant cholinergic side effects within the four weeks prior to screening (use of stable doses of antidepressants for at least four weeks prior to screening was acceptable), systemic corticosteroids within three months prior to screening, any medications with significant cholinergic or anticholinergic side effects (e.g., pyridostigmine, tricyclic antidepressants, meclizine, and oxybutynin) within four weeks prior to screening, anti-convulsants (e.g., Phenytoin, Phenobarbital, Carbamazepine) within two months prior to screening, warfarin (Coumadin) within four weeks prior to screening, or prior use of any FDA approved medications for the treatment of Alzheimer's disease.

Outcome Measure

Groton Maze Learning Test (GMLT)

The Groton Maze Learning Test (GMLT) is a brief, computer-based neuropsychological measure of immediate- and short-term memory for visuospatial information (17). It is loosely based on earlier hidden maze tasks developed by Barker (22) and Milner (23) and also provides measures of executive function (17, 24-26). The GMLT is part of the CogState test battery (www.cogstate.com).

The GMLT consists of a 10×10 grid of grey tiles presented on a computer touch-screen. To complete the maze, the participant has to find a hidden pathway (28 moves, 11 turns) through the grid from the top left corner to a flag in the bottom right corner. Message bars at the top and bottom of the screen inform the participant whether a move is correct. If the move is correct, the participant is prompted to "Go On" by the message bar and a musical tone. If the move is incorrect, it is recorded as a "legal error" and the participant is instructed to go back to the last correct location ('tile') and to try moving in a different direction. If two incorrect responses are made in a row, the second consecutive error is labeled a "perseverative error" and the participant is again instructed to move back to the previous correct tile and to try a new way. If the participant fails to return to the last correct square after making two successive wrong moves (i.e., they make three consecutive incorrect moves), the third error is labeled a "rule-break error," and the tile that corresponds to the last correct move begins to flash. The participant is then asked to touch the flashing tile and then try to continue through the maze. The trial ends once the participant reaches the flag in the bottom right corner of the grid of tiles. The main outcome measure of the GMLT is total errors, which is the sum of legal, perseverative, and rule-break errors (24). Each participant completed five successive learning trials. Each trial was timed (in msec.) and timing began automatically when the participant made his or her first move on each learning trial. In its entirety, the task took each participant 10-15 minutes to complete.

Procedure

For each group, the cross-over study required three testing days. Day 1 was a "baseline day" in which no drug or placebo was administered and all participants completed the GMLT at baseline and at 1, 2, 3, 6, and 8 hours postbaseline. Day 2 occurred 7-14 days later, when participants returned and were randomized to either placebo or active drug. They then completed the GMLT at baseline, and 1, 2, 3, 6, and 8 hours after receiving placebo or drug. Day 3 occurred 14-21 days later, when participants returned again to complete the drug or placebo condition (depending on which they had already received) and again completed the GMLT at baseline, and 1, 2, 3, 6, and 8 hours after receiving placebo or drug. The order in which subjects received placebo or drug was counterbalanced across the 2 and Day 3.

Data analysis

Scores on the GMLT outcome measure of total errors at each assessment were submitted to a repeated-measures analysis of variance with day (baseline, placebo, drug) and time (baseline, 1hr, 2hr, 3hr, 6hr, 8hr) entered as independent variables, and GMLT total errors entered as the dependent variable. The magnitude of difference between means for each subject was computed using a standardized change score (17). This score was calculated by dividing the mean difference in total errors at each timepoint within each condition by the within-subject standard deviation (WSD), as expressed in this formula:

[Baseline (total errors) – Postbaseline (total errors)/(WSD for group)]

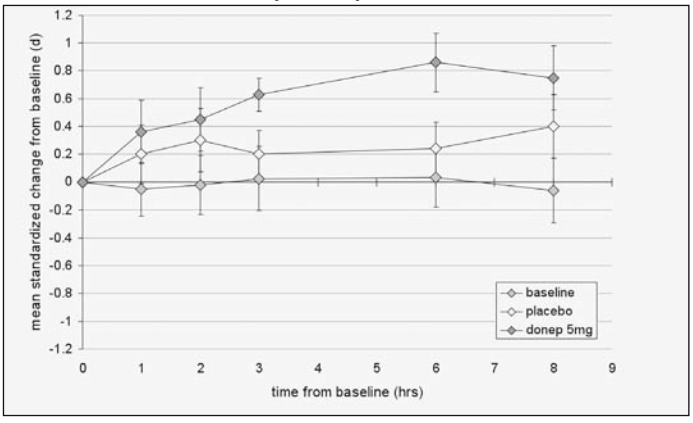
The WSD was determined by computing the square root of the mean square residual (27). To compute effect sizes, change from baseline (for each evaluation on each day of assessment) was estimated and standardized using the relevant WSD. Group mean effect sizes (i.e., group mean change from baseline) were then compared between active and placebo conditions using paired-samples t tests.

Results

Study 1 – Healthy elderly

Figure 2 shows mean standardized change in GMLT performance by condition (baseline, placebo, 5mg donepezil) from 0 to 9 hours post-dosing in healthy elderly participants. In the donepezil condition, effect sizes of change from baseline increased from 0.19 at 1 hr to 0.83 at 6 hr, before dropping to 0.41 at 8 hr post-dosing.

Figure 2
Mean standardized change from baseline by condition in healthy elderly volunteers

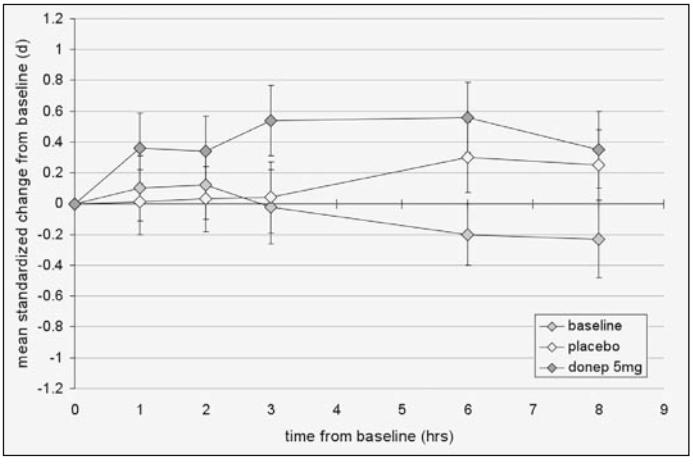


Difference in change from baseline between placebo and donepezil (d)	
1hr	0.19
2hr	0.17
3hr	0.79
6hr	0.83
8hr	0.41

Study 2 – Mild AD

Figure 3 shows mean standardized change in GMLT performance by condition (baseline, placebo, 5mg donepezil) from 0 to 9 hours post-dosing in patients with Mild AD. In the donepezil condition, effect sizes of change from baseline increased from 0.43 at 1 hr to 0.58 at 3 hr, before dropping to 0.30 at 6 hr and 0.11 at 8 hr post-dosing.

Figure 3
Mean standardized change from baseline by condition in older adults with mild Alzheimer's disease



Difference in change from baseline between placebo and donepezil (d)	
1hr	0.43
2hr	0.38
3hr	0.58
6hr	0.30
8hr	0.11

In order to examine the overall magnitude of donepezil-related improvement in GMLT performance relative to placebo, standardized effect sizes were computed. Donepezil yielded greater improvement in GMLT performance in the healthy elderly (d=0.82) versus individuals with mild AD (d=0.30).

Discussion

This study examined the utility of a neuropsychological test designed for repeat administration and a statistical approach that characterizes individual-level change in detecting cognitive improvement following a single acute dose administration of donepezil in healthy older adults and individuals with mild Alzheimer's disease. Results indicated that donepezil improved cognitive function on a hidden maze learning test in both samples, suggesting that cognitive tests designed for repeat administration such as the Groton Maze Learning Test and an analytic framework that emphasizes individual-level change facilitates detection of cognitive improvement using a single dose administration of an AChE inhibitor.

Study 1 examined whether the GMLT was useful in detecting cognitive impairment following administration of a single acute 5mg dose in healthy elderly individuals. Results showed the cognitive improvement was most evident at 6 hours post-dosing. These findings corroborate results of a previous study that administered a single dose of donepezil concurrently with scopolamine (18) and provide further support for the utility of the GMLT in assessing donepezil-related improvement in spatial executive function in healthy older adults. GMLT performance did not improve or decline significantly in the baseline or placebo conditions, suggesting that this instrument is resistant to practice effects, even when administered multiple times over the course of a day. Further, the linear increase and overall magnitude of change in cognitive function in the donepezil condition suggests that the GMLT is useful in detecting improvement in cognitive function. In this condition, GMLT performance improved steadily, with the greatest magnitude of improvement evident at 6 hours post-dosing. This is consistent with the pharmacokinetic profile of a single dose administration of donepezil in healthy adults, in which the mean peak plasma concentration (Cmax) is observed at 4.1+/-1.5 hrs (28). Taken together, these findings suggest that even though the GMLT relies on complex cognitive operations such as spatial working memory and error monitoring, the design of the test, which features multiple alternative forms and data characteristics suitable for detecting improvement or impairment in cognition, renders it substantially less susceptible to practice effects commonly observed after repeated administrations. Cognitive improvement in the donepezil condition was also consistent with the pharmacokinetic profile of this medication. More research is needed to examine the durability and magnitude of cognitive improvement observed in this study, especially after down-regulation of acetylcholine receptors in response to chronic donepezil administration.

Results of this study also suggest that a study design that employs a baseline day, placebo day, drug day, and baseline and postbaseline assessments at 1, 2, 3, 6, and 8 hours is useful in modeling a reasonable range of differential magnitudes of cognitive improvement in healthy individuals. Employing a baseline condition in addition to a placebo condition promotes more accurate assessment of normal variability in cognitive performance for each individual, which leads to a better estimate of "true change" and decreased likelihood of making Type I and Type II errors. Further, by using effect sizes to characterize the magnitude of cognitive change, comparisons of deterioration or improvement in cognitive function across tasks, doses, and time may be made, thereby permitting generalizability across studies and samples (29).

Study 2 found that a single acute dose of donepezil improved GMLT performance in patients with mild AD. This finding extends results of a previous study which demonstrated a single acute dose effect of donepezil in healthy adults, (18) as well as other studies demonstrating cognitive improvement following more chronic administration, (7, 8) to suggest that a cognitive test designed to assess cognitive change and an analytic approach that emphasizes individual-level change in cognitive function, may enhance one's ability to detect cognitive change following a single acute dose administration of donepezil in patients with mild AD. The acute effect of a single-dose of donepezil was most pronounced at 3 hrs post-dosing. One possible explanation for why this effect was evident earlier in the patients with mild AD compared to healthy older adults is that patients with mild AD evidenced greater improvement on placebo at 6hrs, which decreased the effect size estimate of standardized change in the donepezil condition. As we predicted, compared to the healthy controls in Study 1, individuals with mild AD showed greater variability in cognitive performance, even after a high degree of familiarization with the test in multiple baseline assessments. Previous studies have similarly suggested that patients with AD yield highly variable performance on cognitive tests (19, 20). Because greater variability leads to higher WSD values, a smaller overall effect size of donepezil on GMLT performance was observed in individuals with mild AD compared to the healthy older adults in this study. More research is needed to examine whether longer trials of donepezil maintain the improvements in cognitive function noted following a single acute dose, and whether these improvements are evident in other cognitive domains relevant to mild cognitive impairment and AD, such as verbal learning and memory, and decision-making.

Methodological limitations of this study must be noted. First, the samples were relatively small and geographically and ethnically homogeneous. While the nature of this sample is representative of those enrolled in clinical trials, more research in larger and more diverse is needed to determine the generalizability of these results. Second, only one measure of cognitive function was analyzed in this report. Further studies are needed to examine the effect of donepezil on other cognitive domains, particularly those that are commonly impaired in AD, such as learning and memory. Given the magnitude of intra-individual variability in patients with mild AD and lower treatment effect size, it is important to employ tests designed for repeat administration and with psychometric properties that render them able to detect both impairment and improvement in cognitive function. Finally, this study administered a single acute dose of donepezil. Whether the magnitude of donepezil-related cognitive improvement is evident in healthy older adults and individuals with mild AD after chronic administration of donepezil or related agents awaits further research.

The current study was designed specifically to examine the utility of the GMLT, a neuropsychological test designed to assess cognitive change, and statistical methods that emphasize individual-level change in response to drug intervention, in detecting cognitive improvement following a single acute dose administration of donepezil in healthy older adults and individuals with mild AD. Results of these studies suggest that the GMLT provides a sensitive measure of central nervous system (CNS) drug penetration and activity of a cognitive-enhancing agent in healthy older adults and individuals with mild AD. In addition to the GMLT, several other cognitive measures with psychometric properties that make them suitable for repeated administration have also been developed to assess cognitive functions such as psychomotor speed, attention/vigilance, verbal and visual memory, working memory, and social cognition (12, 30-32). These tests and methods can easily be extended to phase II and III trials, in which the absence of a practice effect in the placebo condition is critical to detecting the presence or absence of treatment-related cognitive change. Importantly, with real-world testing conditions and clinical samples evidencing greater variability in cognitive performance (19, 20), the magnitude of effects will likely be attenuated relative to healthy controls. Nevertheless, utilization of these types of tests and analytic methods may help reduce the likelihood of making Type II errors in CNS drug development. Because these methods standardize change from baseline as a function of specific interventions, comparisons of the magnitudes of cognitive change may be made across studies. This may facilitate the development of a meta-analytic framework that allows direct comparisons of effect sizes in examining deterioration and/or improvement of cognitive function across studies.

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