Efficacy of a Cognitive Intervention for the Therapeutic Treatment of Mild to Moderate Alzheimer's Disease

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ABSTRACT

Background: Recent pharmacological advances for the treatment of Alzheimer's disease (AD) have been largely limited to the development of cholinesterase inhibitors[4] *(*Sloan, Zimmerman *et al, 2002)*. Four drugs of this type have been approved by the United States Food and Drug Administration (U.S. FDA) during the past decade: tacrine, donepezil, rivastigmine, and galantamine. Numerous randomized clinical trials with thousands of patients have demonstrated small to moderate effects of these agents on cognitive, global, and physical functioning among patients who respond favourably and who do not have intolerable side effects[4]. As AD predominately affects older populations, projected age demographics point to rapidly growing numbers of persons with AD requiring long term (nursing) care in coming decades. *Hence, there is an urgent need for development of alternative treatment options to reduce the personal, social, and economic impact of the symptoms of AD in the elderly and frail elderly population.*

Objective: The aim of this study was to evaluate the efficacy of a *structured non-pharmaceutical treatment intervention* (consisting of a structured program of person centered facilitated cognitive stimulation exercises and activities) for persons diagnosed with early to moderate dementia of the probable Alzheimer's type.

Method: A single blind, multi-center (United States / Canada), randomized pilot trial (RT) recruited 67 people aged >70 with a diagnosis of AD. The outcome measure was a change in Mini-Mental State Examination (MMSE) scores over a 12 month period. Comparative trial data analysis was completed using estimated annual rate of change scores (ARC) on the Mini-Mental State Examination (MMSE) in Alzheimer's disease (AD). (See Tracking Cognitive Decline in Alzheimer's Disease Using the Mini-Mental State Examination: A Meta-Analysis)[2].

Results: 17 sites were polled for possible inclusion in the study. 67 people were enrolled for inclusion in the trial and were randomized over five sites. Over the course of the study, MMSE scores increased by 1.98 points, with most of the gain occurring between the baseline and the end of the first quarter of treatment. In order to test the statistical significance of this trend a One-Way Repeated Measures Analysis of Variance was conducted. The main effect of Time was statistically significant (F

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(1,156) = 56.479; $p < .001$). Thus, patients in the treatment group exhibited significant gain in cognitive functioning compared with their baseline level. This pattern stands in marked contrast to the decline in cognitive functioning that is characteristic of patients with AD. MMSE scores in the present sample can also be compared with typical trends that have been established in the literature on changes in mental status among patients with AD. Using published meta-analysis of Annual Rate of Change (ARC) in MMSE scores by Han and colleagues[2], patients with AD will show an average decline of 3.3 points on the MMSE over the course of the year. Patients in the trial sample had an average baseline score of 22.36. Based on the Han *et al* (2000) review, the expected decline of 3.3 points over the course of a year would result in an expected MMSE score of 19.06 at the one-year follow up. In the trial sample, the average MMSE score at the one year follow up (Quarter 4) was 24.34, 5.28 points higher than the predicted MMSE value. In order to test the statistical significance of this difference, a one-sample t-test was conducted. Specifically, this procedure tested the Null Hypothesis that the sample was drawn from a population in which the mean MMSE score at the one-year follow up was 19.06. The differences between the predicted and observed MMSE mean score was statistically significant ($t(49) = 13.180$; $p < .001$). This finding suggests that patients in the treatment group had better cognitive functioning compared with normative patterns of decline in patients with Alzheimer's disease.

Conclusion: Results compare favourably to presently available AD medications. The structured cognitive stimulation therapy program studied may offer significant benefits as an alternative therapeutic option / adjunctive therapy for persons with mild to moderate AD. A larger scale multicenter placebo controlled trial employing additional outcome measures is needed to further clarify the efficacy of the program studied.

INTRODUCTION

Alzheimer's disease (AD) is a chronic neurodegenerative disease characterized by progressive deterioration of cognitive functioning[4]. It (AD) begins insidiously, with early signs including patchy memory loss and subtle behavioural changes. The illness gradually progresses until, after a decade or more, the individual is no longer able to speak or comprehend language, and requires assistance with all aspects of personal care. Persons in the early stages of the disease are most often cared for at home by family, while persons in the later stages of the disease transition to long term care or "memory care" facilities. Long term care facilities are increasingly populated by older persons with cognitive impairment.

Until recently, treatment of AD has been entirely supportive. Management has consisted of provision of a safe, prosthetic environment, education and support of family caregivers, assistance with daily activities and personal care, and management of behavioural problems using non-pharmacological strategies and psychoactive drugs. Although these treatments remain the mainstay of AD management today, drugs are increasingly being used not just for problem behaviours but also to retard the disease progression.

Recent pharmacological advances have been largely limited to the development of cholinesterase inhibitors. Four drugs of this type have been approved by the U.S. FDA during the past decade: tacrine, donepezil, rivastigmine, and galantamine. Numerous randomized clinical trials with thousands of patients have demonstrated small to moderate effects of these agents on cognitive, global, and physical functioning among patients who respond favourably and who do not have intolerable side effects; however, as many as two thirds of patients fail to respond[4]. These relatively poor treatment effects of presently available AD medications when viewed in the context of projected estimates of increasing AD prevalence provide the impetus to research, develop, and test a non-invasive treatment alternative for early to moderate AD.

The aim of the study reported here was to evaluate the efficacy of a *structured non-pharmaceutical treatment intervention* (consisting of a structured program of person centered facilitated cognitive stimulation exercises and activities) on cognition of persons diagnosed with early to moderate dementia of the probable Alzheimer's type in a single blind, multicenter, randomized trial (RT).

METHODOLOGY

We extensively reviewed previous work[1, 3] regarding the efficacy of stimulation programs in Alzheimer's disease symptom remediation. We then selected interventions which had demonstrated greater efficacy for inclusion in a new platform paradigm. These results were used to develop a selected program of evidence-based therapy for the symptomatic treatment of early to moderate AD. The resulting cognitive stimulation therapy program was evaluated during a beta-test single blind, multi-center (United States / Canada), randomized (randomizer.com) pilot trial (RT). Comparative trial data analysis was completed using estimated Annual Rate of Change (ARC) scores on the Mini-Mental State Examination (MMSE) in Alzheimer's disease (AD). (See Tracking Cognitive Decline in Alzheimer's Disease Using the Mini-Mental State Examination: A Meta-Analysis).[2]

Participants

A total of 17 program provider sites were

polled for inclusion in the RT. An inclusion criteria flow chart was made available to help site facilitators determine participant trial eligibility. Of the 17 sites polled, 5 sites responded. These sites were in Nevada, Florida, and New Hampshire in the United States as well as Vancouver, and Calgary, Canada. All participants in the trial were private duty home care recipients living in their own homes, assisted living facilities (ALFs), or retirement residences.

Inclusion/Exclusion Criteria

Participants were screened for inclusion in the trial (RT) according to the following criteria:

a. Met the DSM-IV-TR criteria for dementia (American Psychiatric Association 2000);
b. Scored between 10-27 baseline Mini-Mental State Exam (MMSE; Folstein *et al*, 1975);
c. Ability to speak, read aloud, and communicate:
d. Able to see, hear, and participate in program exercises and activities;
e. No significant co-morbidities;
f. Diagnosis of dementia of the probable Alzheimer's type (DSM-IV-TR, American Psychiatric Association 2000);
g. Stabilized on Alzheimer's medications (minimum 3 months) prior to trial entry;
h. Age >70 prior to trial entry;
i. Not receiving any other defined cognitive stimulation therapies.

Data Randomization Process

Site facilitators were assigned randomized number blocks (randomizer.org) prior to data collection based on estimated site participant numbers. Site facilitators randomly assigned each potential participant a number from the site's block of available numbers. Site facilitators subsequently provided serial MMSE scores (at baseline, 3 months, 6 months, 9 months, and 1 year) for program participants selected by the research randomizer program who met the inclusion criteria. Participants not completing the study were excluded from the data pool.

Program

The Cognitive Stimulation Training (CST) consisted of a structure series of directed thinking and activity focused exercises. The program steps included an in-depth life story interview involving the participant and significant other family members. Information was gathered in order to select relevant person-centered program materials. Program participants received program facilitation 45 – 60 minutes 1:1 with a facilitator twice weekly for a minimum of 52 weeks. Program exercises and activities consisted of person centered interactive exercises and related activities incorporating selected techniques drawn from the reviewed stimulation programs listed. Program structure consisted of selected pen and paper based, challenge based, and activity based exercises facilitated following a rotating sequence.

Process and Search Design

Seventeen sites were selected for polling for possible inclusion in the study. All 17 sites had previously received training in the use of the program and all had current program participants. Five of the seventeen potential sites had participants on the program for which MMSE data was available (meeting the inclusion criteria). Participant trial data (sequential participant MMSE scores

collected at baseline and quarterly over a 12 month period) was randomized (designation numbers assigned by site facilitators) and the collected pooled data then entered into a spreadsheet for statistical review. Comparative trial data analysis was completed using estimated annual rate of change scores (ARC) on the Mini-Mental State Examination (MMSE) in Alzheimer's disease (AD). (See Tracking Cognitive Decline in Alzheimer's Disease Using the Mini-Mental State Examination: A Meta-Analysis)[2].

Following an earlier review[1] we conducted an internet search using the following terms: memory remediation; memory remediation and dementia; cognitive remediation; cognitive remediation and dementia; vanishing cues; spaced retrieval; errorless learning; cue utilization and Alzheimer's disease; and visual imagery and Alzheimer's disease. For the first four items, a search was also performed using the terms "stimulation" and "rehabilitation" instead of "remediation". In addition we conducted a manual search of the references listed in the articles to identify additional relevant articles. Articles were included for review only if they met specific criteria: the population studied suffered only from AD; a structured cognitive rehabilitation program was described; external aids were used; the data was specific to our needs; cognitive rehabilitation was used as an intervention; and the referenced article was written in English. Articles were excluded if they used a reality orientation approach; if subjects presented with other neuropathological processes or more than one type of dementia and other neuropathological processes; or if the data represented pooled results from various populations having different neuropathological processes; or small sample size (n=<11).

(Selected) Stimulation Programs Reviewed

1) *Visual Imagery*[1]

The use of visual imagery techniques is based on the concept that visual associations improve the encoding, consolidation, and recall capacities of verbal material because the memory system does not rely on the verbal semantic mode alone. According to Breuil *et al*.[5], even when several cognitive functions are compromised in AD, patients are still able to elaborate some cognitive strategies. Recall failures would occur because the retrieval strategies are not well applied. Thus, mental imagery is used to simultaneously stimulate visual and verbal semantic modes to facilitate the encoding, consolidation, and retrieval capacities in the everyday environment. Since many systems (mainly the visual and verbal semantic systems) are stimulated with visual imagery, generalization of learning from one environment to another or from one type of information to another has been hypothesized to occur[5]. Examples of visual imagery include asking a subject to pay attention to specific visual details of the information being learned (focus on facial features, for example) or to form a mental image of an object presented in the verbal modality. [1]

2) *Encoding Specificity with Support at Retrieval*[1]

These strategies were developed to provide supportive conditions at both encoding and retrieval phases of episodic learning. The encoding specificity paradigm necessitates the use of similar cues for acquisition (or encoding) and retrieval[6-9] since this paradigm holds that the amount of informational overlap between a cue

presented at retrieval and the memory representation established at encoding is critical to episodic memory proficiency[10]. In other words, the more congruent a cue is with the context prevailing during encoding or with the cognitive operations carried at encoding, the more effective it will be at retrieval. Early studies have shown a modest, almost no significant improvement of recall in subjects with mild and moderate AD when the same semantic cues were provided by the experimenter at encoding and retrieval[7, 11, 12]. The lack of efficacy of the experimenter-provided semantic cues in subjects with dementia has been attributed to a semantic encoding specificity deficit early in the AD process[8-12]. On the other hand, the self-generated cues with encoding-retrieval compatibility have been hypothesized to optimize episodic recall in AD because an elaborative activity is taking place at encoding[13]. Self-generated cueing strategies were then developed to be used similarly at encoding and retrieval: self-generated and semantic cues, that is, choice of category or description of the item to be remembered by the subject[14, 15]; self-generated and motor cues, that is, pantomime of the movements associated with the use of the object to be remembered[14, 16]; or combinations of these cues[14]. [1]

3) *The Errorless Learning Approach*[1]

The errorless learning approach favours the elimination or reduction of incorrect or inappropriate responses during memory training[17, 18]. In other words, using this paradigm; subjects are not allowed to commit errors when they are receiving memory training. This technique was first designed to facilitate the acquisition of new information in individuals with learning disabilities, and it was successfully adapted to memory training in subjects who had suffered brain injuries[17, 19-22]. Clare et al. have adapted this method for patients with AD[17]. With errors kept to a minimum during the training, it is hypothesized that interferences in the memory stores will be avoided, which will facilitate the encoding process of new information. Learning, retention, and retrieval should thus be easier[19]. Baddeley and Wilson[19] have shown that errorless learning improves the learning process in subjects with amnesia. The errorless learning training program is often conducted in conjunction with the spaced retrieval technique or the vanishing cues technique. In the errorless learning programs, subjects are instructed to say that they do not know an answer instead of giving a wrong answer; they are encouraged not to guess. [1]

4) *The Vanishing Cues Technique*[1]

The vanishing cues technique consists of several attempts to recall information, using prompts that are gradually decreased until recall is successfully achieved. This method is mainly based on two well-established and related principles: the backward chaining procedure of behavioural modification[22, 23] and some preservation of implicit memory in subjects with amnesia[24]. Some authors view the vanishing cues technique as a complementary method to achieve an errorless learning training[25]. An example of the vanishing cues technique is to first present complete words to the subject and then ask him to say the word when the last letter or last few letters are missing. Wilson[22] provides the following example: PEGGY is first presented, then PEGG_, then PEG_ _, and so on. [1]

5) *The Spaced Retrieval Technique*[1]

The spaced retrieval technique or the expanded retrieval practice involves testing

for the repeated recall of newly acquired information at increasingly longer intervals[26-28] or with an increasing number of intervening items[29, 30]. This technique is based on experimental evidence suggesting that the longer the distracting interval between the first and the second successful recall, the greater the likelihood of recall at a third recall attempt[31]. The expanded retrieval practice also potentially contains a practice effect and therefore implies some preservation of implicit/procedural memory, since the subjects repeat the same items over different trials. In this method, the subject is asked to recall the information with increasing numbers of intervening items (for example, zero, three,…nine, and so on interpolated items between recalls of the learned item) or at increasing intervals of time (for example, 5 seconds, 10 seconds, … 60 seconds, and so on after presentation of the item to learn, or 2, 4, …20 days after the last test). In terms of the time interval between recalls, the subject has either to reach a predetermined goal (for example, 60 seconds or 20 days) or to increase the time interval until he or she can no longer recall the information. [1]

6) The Dyadic Approach[1]

In the dyadic approach, the patient's caregiver becomes instrumental in carrying out different memory and cognitive improvement strategies. These strategies are used for several purposes: to facilitate the recall of significant life events; to improve memory functioning through visual and verbal mnemonic strategies designed to facilitate recall and recognition; to improve executive functioning through problem-solving exercises using planning, conceptualization, and classification within the context of interpersonal skills; and to increase social interaction by improving communication skills with targeted conversation exercises of word fluency and verbal exchange[32]. In the reviewed literature, some specific memory training procedures can be used within the dyadic approach, but the training and theoretical focuses are more on the patient-caregiver dyad than on the memory systems. [1]

Assessment Measures

The primary outcome measure for this study was the MMSE (MMSE; Folstein *et al*, 1975). The MMSE is a brief 30-point questionnaire test that is used to screen for cognitive impairment, and is also used to estimate the severity of cognitive impairment at a given point in time and to follow the course of cognitive changes in an individual over time, thus making it an effective way to document an individual's response to treatment. The MMSE has good reliability and validity.

Quality of Life

A (modified) Quality of Life – Alzheimer's disease scale (Logsdon *et al*, 1999) was used as a secondary outcome measure. A modified survey was used covering 10 domains – physical health, mood, energy, living situation, family, fun, friends, marriage, self, life as a whole, Study participant information for modified Q of L-AD provided by reporting sites was not completed satisfactorily and it was therefore decided to exclude the information from use in the study in favour of a separate review of this outcome measure at a later date.

Analysis

Analysis was completed using the Statistical Package for the Social Sciences, for Windows (SSPS, 2001). An intent- to-treat analysis was conducted and analysis of covariance (ANOVA) was chosen as the

method of analysis. Analysis of non-completing participant numbers was made. No information regarding covariates such as age or gender was available for analysis (see Inclusion criteria). Pooled study data for the remaining 50 participants was entered into the spreadsheet in addition to control data: Estimated annual rate of change scores (ARC). (See Tracking Cognitive Decline in Alzheimer's Disease Using the Mini-Mental State Examination: A Meta-Analysis)[2].

RESULTS

67 participants were enrolled in the study. At the end of the study, 50 participants remained in the data pool with 17 participants not completing. Reasons for non-completion were: a.) voluntary withdrawal from program (9.09%); b.) death (0.03%); c.) inability to continue due to health deterioration (1.4%); and d.) non-compliance (14.78%). Mean attendance was 93.5 sessions (SD = 3.2; Range = 83 – 101), with 47 participants attending a minimum of 92 or more sessions.

In order to assess the effects of the structured cognitive stimulation program on patients' cognitive functioning, two analytic strategies were employed. First, in order to test the hypothesis that patients' cognitive functioning improved relative to baseline, a one-way repeated measures analysis of variance (ANOVA) was conducted. Second, in order to compare changes in cognitive functioning between the treatment group and a no-treatment group, we utilized a one-sample t-test to compare MMSE scores at the end of one year with the level of MMSE performance that would be predicted from Annual Rate of Change (ARC) in Alzheimer's patients.

Improvement in MMSE Relative to Baseline

Table 1 shows mean scores on the MMSE at baseline and for each quarter. Over the course of one year, MMSE scores increased by 1.98 points, with most of the gain occurring between the baseline and the end of the first quarter of treatment. In order to test the statistical significance of this trend, a One-Way Repeated Measures Analysis of Variance was conducted. The main effect of Time was statistically significant ($F(1,156) = 56.479$; $p < .001$). Thus, patients in the treatment group exhibited significant gains in cognitive functioning compared with their baseline level.

MMSE Relative to Age Related Change in Alzheimer's Disease

Though the present study lacks a placebo control group, changes in MMSE scores over the course of one year of treatment can be compared with typical ARC in MMSE scores among patients with Alzheimer's disease. According to the meta-analysis of ARC conducted by Han and colleagues (Han *et al*, 2000), patients with Alzheimer's disease will show an average decline of 3.3 points on the MMSE over the course of one year. Patients in the present study had an average baseline score of 22.36. Based on the Han *et al* (2000) review, the expected decline of 3.3 points over the course of a year would result in an expected MMSE score of 19.06 at the one-year follow up. In the present sample, the average MMSE score at the one year follow up (Quarter 4) was 24.34, 5.28 points higher than the predicted MMSE value. In order to test the statistical significance of this difference, a one-sample t-test was conducted. Specifically, this procedure tested the Null Hypothesis that the sample was drawn from a population in which the mean MMSE

score at the one-year follow up was 19.06. The differences between the predicted and observed MMSE mean score was statistically significant ($t(49) = 13.180$; $p < .001$). This finding suggests that patients in the treatment group had better cognitive functioning compared with normative patterns of decline in patients with Alzheimer's disease.

CONCLUSIONS

The results of these analyses suggest that the cognitive stimulation therapy program studied results in a significant improvement in the cognitive functioning of patients with Alzheimer's disease. Scores on the MMSE were significantly higher following treatment compared with baseline. This pattern of improved functioning stands in marked contrast to the decline in cognitive functioning that is characteristic of patients with Alzheimer's disease. Indeed, levels of cognitive functioning following one year of cognitive stimulation therapy were significantly higher than the level that would be predicted based on ARC in Alzheimer's patients.

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Table 1

MMSE Scores at Baseline and Follow up (n = 50)

	Baseline	Quarter 1	Quarter 2	Quarter 3	Quarter 4
Mean	22.36	24.24	24.46	24.32	24.34
SD	3.06	3.12	2.92	2.86	2.83

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