Enhancing Memory and Activities of Daily Living in Patients with Early Alzheimer’s Disease Using Memory Stimulation Intervention: A Randomized Controlled Trial

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Abstract

Objective: The objective of this study was to assess the effectiveness of memory stimulation intervention added to donepezil treatment as compared to donepezil alone in patients with early Alzheimer’s disease (eAD). Materials and Methods: Patients in the combined treatment group (CTG = 21) received standard dosages of donepezil and weekly memory stimulation activities sessions for 2 months, whereas the treatment as usual group (TAU = 22) received only standard dosages of donepezil. Each session had extensive tasks on memory and its implied practice on instrumental activities of daily living. After 8 sessions, both groups were evaluated for changes in memory and functional outcomes by administering the mini-mental state examination (MMSE), memory (Postgraduate Institute of Memory Scale), and instrumental activities of daily living scale (IADLS). This trial was registered on the Clinical Trials Registry - India (CTRI/2014/04/004550). Results: Statistical analysis was done using independent t-test, which revealed a significant difference between the groups on MMSE, memory, and IADLS post intervention. The MMSE score in the TAU group, while it increased in the CTG group by 4 points. A similar trend was evident in the memory and IADLS scores as well. Effect size in the CTG group was relatively large as compared to the TAU group where the effects were small and negative on some outcomes. Conclusion: The CTG group showed positive treatment effect on cognitive tests suggesting that combined memory stimulation and donepezil treatment has potential to improve the cognitive and functional performance of patients with eAD.

Keywords: Early Alzheimer’s disease, instrumental activities of daily living, memory stimulation

INTRODUCTION

Most clinicians would probably name Alzheimer’s disease (AD) when it comes to treating “memory loss,” in older adults. It is one of the most common causes of dementia. The involvement of memory in AD is supported by various clinical and radiological studies.[1-3] Memory deficits have direct negative implications on other domains of cognition and instrumental activities of daily living as well,[3] for example, making telephone calls, or managing finances, etc. Thus, making patients with AD insecure of their functionality and eventually hampering their quality of life. Worldwide, a standard pharmacological treatment exists which includes three anti-dementia drugs,[4] i.e., donepezil, rivastigmine, and galantamine. However, till date, this typical treatment has shown limited efficacy,[5] for a short period of 6–18 months.[5] Thereafter, till date, no successful advance has been devised to deal with the further treatment of progressive memory loss and deteriorating quality of life of AD patients.

Due to the limited efficacy of the pharmacological therapy in improving the memory of AD patients, a contemporary approach of cognitive interventions emerged which focused on improving the management of AD by acting complementarily to the drug therapy. Promising preliminary randomized controlled trials (RCTs) have been conducted which emphasized on the potential value of the cognitive intervention in delaying the progression of the memory deficits, but due to various methodological issues,[6] the confidence in such interventions is still questionable.

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Some of the major limitations of such studies include discrete classification of cognitive interventions, discrete “dose” of an intervention (i.e., frequency, intensity, and duration of intervention), use of subjective scales as outcomes, limited effect size (ES), last but not the least, claiming of transfer effects from trained to untrained tasks without using analogs techniques to untrained domains, etc. Therefore due to such issues, various meta-analyses have warranted additional RCTs. Studies with the clear classification of cognitive interventions are needed to provide further support for tentatively promising results.

Considering all these lacunae, the present study was conceptualized where a clear classified cognitive intervention, purely based on memory stimulation in early AD (eAD) patients was developed. Memory stimulation is a training method which focuses on encoding information in areas of the brain that is less affected in the early stages of AD. It targets encoding of the memory and recall function of that area. The intervention used in the present study consisted of memory-based techniques which were analogous to daily life activities and were delivered in uniform dosage throughout the study period to the patients. Besides this, the outcomes used were purely objective and performance-based which were clinically relevant and generalizable to the Indian setting. Finally, the memory intervention was tested as an adjunct to the standard pharmacological therapy for patients with eAD.

**Materials and Methods**

Sixty participants aged 60 years and above with mild memory decline, referred to the memory clinic or cognitive disorder, and memory clinic of the Department of Geriatric Medicine, Neurology and Neuropsychology were screened from July 2014 to November 2015. They were evaluated for their eligibility by the neurologist, geriatricians, and neuropsychologists of All India Institute of Medical Sciences, New Delhi, India. The inclusion criteria were diagnosis of probable AD according to the National Institute of Neurological and Communicative Disorders and Stroke – AD and Related Disorders Association criteria; early stage of the disease was assessed using Clinical Dementia Rating (CDR) score of 1; and standard pharmacological treatment included donepezil 5 mg/day for 3 months from the date of screening. The exclusion criteria were the presence of radiologically diagnosed brain lesions, severe systemic diseases, severe depression assessed using Geriatric Depression Scale (GDS >6), and any major psychiatric symptoms evaluated using MINI questionnaire. Out of 60 participants screened, 43 participants with eAD were recruited and later randomized into the trial. Twenty-one (n = 21) participants were allocated to the combined treatment group (CTG) and 22 participants were allocated to the treatment as usual group (TAU). The CTG group received donepezil 5 mg/day along with weekly memory stimulation sessions for 8 weeks. The TAU group received donepezil 5 mg/day and sham memory stimulation sessions for 8 weeks. Both groups maintained uniform weekly sessions of 45–60 min each for 2 months. The CTG group performed 56 picture-based tasks of memory on a daily basis at home which was thoroughly supervised by their immediate caregiver. It was made sure that only one caregiver continues throughout the entire study period with the patient. The caregivers were extensively trained in the first session by the therapist. After every week, tasks on 7 days were reviewed by the therapist to check the uniformity, and progressiveness of the tasks. On the other hand, the TAU group too was given weekly sessions which involved teaching a few general strategies such as mnemonics to ease out learning and recall; individual and caregiver counseling along with brief medical consultation was also provided. However, no formalized standardized tasks were given for doing at home.

The study was registered under Clinical Trials Registry-India (CTRI/2014/04/004550). Institute ethical clearance was obtained, and informed written consent was obtained from the patients and their caregivers. The study design of the current study was conceptualized following CONSORT guidelines [Figure 1].

As far as the sample size is concerned, since no appropriate study was available to calculate the sample size for the present study due to statistical issues, an interim analysis was done and the sample size was revisited at the time when the results...
for 20 patients in each group were available. After the interim analysis, it was observed that there was 20% attrition rate. Thus, the final estimated sample size of the study is depicted in Table 1.

**Randomization**
Random allocation sequence using block randomization of variable block size was generated using the statistical software, Stata version 14.0 (Stata Corp, Texas, USA). Allocation concealment was done using sequentially numbered, opaque, sealed envelopes which were under the custody of the main supervisor; the researcher had no access to these envelopes until the intervention was assigned to the participant. Finally, at the implementation level, the random allocation sequence was generated by the biostatistician, the participants were enrolled by the researcher and the intervention was assigned by the supervisor as per the sequentially numbered, opaque, and sealed envelopes. This was done to ensure that the implementation of the random allocation sequence occurred without allocation bias.

**Blinding**
The present study was an open-label RCT where the participants and the investigator could not be blinded due to feasibility issues. Only the outcome assessor (other than the data collector) was blinded to the group assignment to ensure unbiased assessing of the outcomes.

**Cognitive measures**
After screening the participants on CDR and GDS, the participants were subjected to standardized neuropsychological testing which included Mini Mental State Examination, Postgraduate Institute of Memory scale which assessed 10 sub-memory domains (recent memory, remote memory, temporal sequencing, digit backward/forward, immediate recall, delayed recall, simple learning, new learning ability, visual retention, and recognition/naming ability); ADLs were assessed using instrumental activities of daily living scale (IADLS). All these cognitive tests were assessed pre- and post-memory stimulation sessions for both the groups. The scoring of the test at both the time-points was done by the examiner who was blinded to the group assignment.

**Memory stimulation intervention**
Memory stimulation intervention (MSI) was a specific home-based program developed and validated on 63 participants (48 healthy controls and 15 early AD cases). It included tasks which were analogous to the daily activities. For example, naming and identifying common day-to-day things, recalling the steps of use of daily things. The weekly therapist-led session opened with temporal and spatial orientation (using calendars and diary) which was based on reality orientation concept. This helped facilitating patients’ greater understanding of their surroundings, possibly resulting in an improved self-control and self-esteem. It also helped in their learning of how to use compensatory strategies.

Further, the MSI was based on the following memory techniques:

1. **Expanding rehearsal technique**
   It basically involved presenting the stimuli (consisted of daily routine items) in spaced order. It involves testing for the repeated recall of newly acquired information at increasingly longer intervals. In this method, the participant was asked to recall the target stimuli with progressive intervening items (e.g., five, six, eight,... and so on). This method was used to retrain the verbal and learning memory. A set of common picture was presented to the participant and was asked to recall the same in any order after 2 min. Five successive trials were taken for one set of pictures. The number of pictures and the time interval was progressive in nature to utilize the neuroplasticity mechanism to its maximum capacity.

2. **Vanishing cues**
   This technique consists of several attempts to recall information, using prompts that are gradually decreased until the recall is successfully achieved. This method was mainly based on backward chaining and behavioral modification principles. In the current study, this technique was used to teach names of routinely used items such as BRUSH and COMB. In this technique, initially, the complete word was presented (BRUSH) to the participant and was asked to repeat the word. After 5 seconds, the initial two letters were presented, BR, and was asked to recall, then other remaining letters BRUS was presented and so on. This helped in strengthening the associative learning.

3. **Errorless learning**
   It emphasizes on avoiding guesswork. With errors kept to a minimum during the training, it was 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. This technique had been found to be beneficial in subjects with amnesia. Hence, in the current study, participants were encouraged not to guess. Whenever a mistake was committed by a participant, it was corrected every time to stop processing of wrong
information. This technique was basically used in conjunction with the spaced retrieval and the vanishing cues technique.

4. Visual imagery
It refers to making the best use of the residual skills to aid recollection. Many of the studies suggested that image information is much more easily remembered than information that is purely verbal or abstract.\(^{[18]}\) The key task was to try to form an association between the cue and the action using visual modality based tasks.

5. Use of external memory aids
Since in India, very few older adults are technology literate, hence, we used nonelectronic external memory aid such as a diary, calendars, and notes which were basically used as external cues to compensate memory loss. The use of these external aids were strategically trained where the utility and functionality of each external aid in the real-life situations was taught which provided the participants with a high degree of retrieval support, lowered their necessity of self-initiated cognitive operations for prospective memory requirements, and helped them keep time oriented, thereby supporting the continuation of routinized performance.

Taking all these specific techniques of memory stimulation, an extensive picture based tasks were developed for eAD patients. Each patient was given three tasks to complete per day (each focusing individually on episodic memory, semantic memory, and implicit memory) after extensive instructions and practice. Hence, throughout 8 weeks, the participants’ visual memory, verbal memory, learning capacity, spatial memory were thoroughly retrained, eventually facilitating the optimal level of ADLs.

The model of the MSI is briefly described in Figure 2.

While the sham intervention sessions included routine treatment with their treating consultants along with individualized counseling sessions on drug side effects, memory management techniques, and discussion disease evolution.

Statistical analysis
Data were recorded on a pre-designed pro-forma and was arranged on an excel spreadsheet. Categorical variables were summarized as frequencies, and Fisher’s exact test was used to compare frequencies between the two groups. Quantitative variables were summarized as mean and standard deviation, and pre-post values were compared using Wilcoxon signed-rank test. Effect size (ES) was calculated using the formula\(^{[19]}\)
\[
ES = \frac{\text{Follow-up mean} - \text{Baseline mean}}{\text{Baseline standard deviation}}
\]
The analysis was done using Stata 14.0 statistical software. In this study, \(P < 0.05\) was considered statistically significant.

Results
Table 2 depicts the baseline comparison of the CTG and the TAU groups on socio-demographic characteristics comprising of age, gender, marital status, and education where no significant difference among the groups was observed.

![Figure 2: Memory stimulation intervention model](image-url)
As evident in Table 3, CTG showed significant improvement *(P ≤ 0.001)* in MMSE (ES = 0.84 vs. 0.03), overall memory (ES = 1.25 vs. 0.15) and IADLS (ES = −0.38 vs. −0.12) outcomes as compared to the TAU. In contrast, TAU performance was stabilized in two outcomes, i.e., MMSE (16.4 ± 3.1 vs. 16.5 ± 4.1) and memory (−3.5 ± 1.3 vs. −3.3 ± 1.6), while the performance on IADLS (49.9 ± 15.4 vs. 55.9 ± 15.8) declined. This implied that the MSI in CTG complimented the drug therapy to induce improvement in memory as well as ADLs outcomes as compared to the TAU. This increases the added value of the memory stimulation to be used in the management of eAD [Figures 3-5].

**DISCUSSION**

Memory loss is the first symptom of eAD which gradually starts interfering in IADL functioning. It may be possible to reduce these deficits using strategies that target implicit memory which will further facilitate learning/relearning of information and thereby improving their everyday functioning.

The current findings demonstrated that the CTG showed statistically significant improvement *(P ≤ 0.001)* on overall memory score [Table 3] as compared to the TAU. Moreover, the value of the ES was large in the CTG as compared to the TAU which implied that the MSI along with the Donepezil brought 1.5 standard deviations of improvement more than TAU [Figure 3]. This observation is in accordance with the latest studies[20,21] as well which has shown that the memory intervention along with the Donepezil significantly brings greater benefit on memory and other cognitive measures than Donepezil alone as it brings synergistic effect on the neuro-plasticity mechanism. This has been further supported by various functional magnetic resonance imaging and electroencephalography studies[22] where improved hippocampal neurochemistry has also been identified using magnetic resonance spectrometry with memory rehabilitation intervention, along with positive changes in brain metabolism in the early AD.

Similar results were evident on MMSE as well where CTG performance increased by 4.3 points (ES = 0.84) than TAU (ES = 0.03) where only 0.1 points of improvement was observed [Table 3]. It can also be seen graphically in box-and-whisker plot [Figure 4] where the absolute difference between the groups was wide. This suggests that the combination of MSI with the Donepezil treatment seemed to slow the rate of decline, relative to the Donepezil alone in patients with eAD. This

### Table 3: Comparison of the postintervention means adjusted for respective baseline variables at 2 months for both groups on Postgraduate Institute-Memory Scale

| Domain                  | Time-points mean±SD (n) | Effect size* |
|-------------------------|-------------------------|--------------|
|                         | Baseline                | At 2 months  |
| MMSE                    |                         |              |
| TAU                     | 16.4±3.1 (26)           | 16.5±4.1 (22) | 0.03 |
| CTG                     | 18.5±5.1 (27)           | 22.8±2.3 (21) | 0.84 |
| P                       | 0.102                   | <0.001       |
| Total memory            |                         |              |
| TAU                     | −3.5±1.3 (26)           | −3.3±1.6 (22) | 0.15 |
| CTG                     | −2.8±1.2 (27)           | −1.3±1.6 (21) | 1.25 |
| P                       | 0.054                   | <0.001       |
| Remote memory           |                         |              |
| TAU                     | −2.3±2.3 (26)           | 0.5±4.6 (22)  | 1.21 |
| CTG                     | −3.2±3.2 (27)           | −1.8±2.3 (21) | 0.43 |
| P                       | 0.245                   | 0.007        |
| Recent memory           |                         |              |
| TAU                     | −3.5±3.2 (26)           | −4.7±2.7 (22) | −0.37 |
| CTG                     | −4.7±4.4 (27)           | −2.9±3.1 (21) | 0.40 |
| P                       | 0.279                   | 0.005        |
| Mental balance          |                         |              |
| TAU                     | −1.0±1.0 (26)           | −1.1±0.6 (22) | −0.10 |
| CTG                     | −1.2±1.2 (27)           | −0.6±1.5 (21) | 0.60 |
| P                       | 0.463                   | 0.175        |
| Attention and concentration |                     |              |
| TAU                     | −1.0±1.2 (26)           | −0.7±1.3 (22) | 0.25 |
| CTG                     | −0.6±1.0 (27)           | 0.6±1.2 (21)  | 0.00 |
| P                       | 0.184                   | 0.004        |
| Delayed recall          |                         |              |
| TAU                     | −1.5±1.2 (26)           | −1.5±1.5 (22) | 0   |
| CTG                     | −1.2±1.5 (27)           | −0.3±0.9 (21) | 0.60 |
| P                       | 0.468                   | 0.005        |
| Immediate recall        |                         |              |
| TAU                     | −1.4±0.9 (26)           | −1.2±1.1 (22) | 0.22 |
| CTG                     | −1.0±1.0 (27)           | −0.01±1.3 (21) | 0.99 |
| P                       | 0.220                   | 0.002        |
| Simple learning         |                         |              |
| TAU                     | −2.2±1.4 (26)           | −1.8±1.3 (22) | 0.42 |
| CTG                     | −1.4±1.5 (27)           | −0.7±1.4 (21) | 0.52 |
| P                       | 0.050                   | 0.074        |
| New learning ability    |                         |              |
| TAU                     | −1.6±0.7 (26)           | −1.5±1.0 (22) | 0.14 |
| CTG                     | −1.3±0.7 (27)           | −0.8±1.2 (21) | 0.71 |
| P                       | 0.124                   | 0.143        |
| Visual retention        |                         |              |
| TAU                     | −2.2±1.1 (26)           | −2.1±1.1 (22) | 0.09 |
| CTG                     | −1.6±1.6 (27)           | −1.3±1.5 (21) | 0.18 |
| P                       | 0.176                   | 0.254        |
| Recognition             |                         |              |
| TAU                     | −2.8±1.8 (26)           | −2.5±1.4 (22) | 0.16 |
| CTG                     | −2.6±1.7 (27)           | −1.8±1.7 (21) | 0.47 |
| P                       | 0.655                   | 0.196        |
| IADLS                   | 49.9±15.4 (26)          | 55.9±15.8 (21) | 0.38 |

*All the effect sizes were adjusted for baseline scores. TAU=Treatment as usual group, CTG=Combined treatment group, IADLS=Instrumental Activities of Daily Living Scale, MMSE=Mini-Mental State Examination, SD=Standard deviation

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Contd...
point is found to be consistent with the results of recent studies\(^{[23,24]}\) where the additive positive effect of memory intervention was seen in delaying the memory progression in AD. However, a greater sample size was required to claim such changes.

In specific to the memory domains, the intervention showed positive results with medium to large ES with statistical significance. However, there were few domains where the ES was medium without statistical significance. This was attributed to the small sample size for those particular subdomains. Many social sciences research studies\(^{[25]}\) have shown that in such conditions, the confidence of improvement in that particular domain is not lost as the ES gives more added real value as compared to the statistical significance.

Besides memory outcome, there was evidence of positive results on IADLS \[^{[3]}\] as well with a medium ES of \(-0.38\) (lesser the score, higher the improvement). The CTG improved in their IADLS tasks such as communication skills, house management skills, and recreational skills by 8 points as compared to the TAU. This is supported by a recent methodological review\(^{[26]}\) which suggested that memory stimulation not only improves memory performance in patients with cognitive decline, but it also improves the competence of managing activity of daily living, though with modest ES. Thus, considering the literature and the current findings, memory training in eAD not only improves memory skills but also help in engaging in worthwhile activities, which may potentially increase their autonomy and independence, and ultimately their subjective quality of life.

Efficacy of MSI in eAD patients associated with the pharmacological approach has been researched since decades.\(^{[27,28]}\) A recent meta-analytic study\(^{[29]}\) too demonstrated consistent results where moderate training effect on episodic memory function in older adults (Cohen’s \(d = 0.31\)) compared to treatment as the usual group was observed. Current findings too were consistent with the literature but with a medium to large ES which adds value to the current study findings. Moreover, this was the first clinical trial which was conducted in India to report the efficacy of the memory stimulation in the early AD.

However, this study has certain limitations such as small sample size which resulted into the non-significance of some memory domains. Given the kind of interventions implemented, a complete blinding of the subjects involved in the study was not possible. Moreover, there was only one performance-based measure of functional abilities, which was included along with cognitive measures to assess change in daily functioning abilities. Functional outcomes are probably best measured with performance-based tests, rather than informant reports, which have multiple inherent biases and limitations.

Despite these limitations, the current study suggests that memory intervention is probably one of the best adjuncts to drug therapy to improve the memory deficits and delay the further progression.
in patients with the early AD. Hence, to further validate the current findings, a large multicenter trial is underway.

**Conclusion**

The current findings strongly support the view that a memory stimulation combined with donepezil treatment applied to early AD patients seems to improve memory and learning or slow down the rate of decline thereby improving the patients’ functional independence.

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**Conflicts of interest**

There are no conflicts of interest.

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