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Research Article

A prospective open-label randomized comparative study in Alzheimer's disease between two commonly used drugs in coastal Indian population

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ABSTRACT

Background: Currently, therapy for Alzheimer's disease (AD) is only symptomatic. Only two classes of drugs are approved by the United States Food and Drug Administration. Our study aimed at comparing efficacy and safety of memantine and donepezil in moderate to severe AD patients.
Methods: Totally, 22 patients with moderate to severe AD were randomized into the 2 arms of the study. The study was divided into an initial 4 weeks for determination of onset of efficacy and subsequent 28 weeks of the treatment phase. Onset of efficacy and response was defined as >20% and >50% reduction in the mean total score of functional dementia scale (FDS) and clinical global impression scale (CGIS) from baseline to the study end, respectively.
Results: Onset of efficacy on FDS and CGIS was 16.7% (mean-time 61.25 days) and 80% (mean-time 36 days) with memantine and donepezil, respectively. Response was 89.3% and 40% with memantine and Donepezil, respectively. Total reduction in FDS and CGIS score of from baseline to the study end was 39.50, 40.00, and 25.60, 27.20 with memantine and donepezil, respectively. Tolerability was 86.33% and 20% with memantine and donepezil, respectively. Anorexia, muscle cramps, constipation, headache, and insomnia, were the common side-effects and self-limiting. Safety was 100% in both groups.
Conclusions: Onset of efficacy was faster with donepezil seen at 2 weeks. Response, improvement in CGIS, FDS, and tolerability were better seen with memantine at 40 weeks. Thus, in similar clinical settings, memantine can be preferred.

Keywords: Memantine, Donepezil, Alzheimer's disease, Functional dementia scale, Clinical global impression scale

INTRODUCTION

Approximately 10% of all persons over the age of 70 have significant memory loss and the most common cause is Alzheimer's disease (AD).[1] AD most often presents with subtle onset of memory loss followed by progressive dementia over several years. The disease also causes heavy emotional toll on family members and caregivers. Slowly the

cognitive impairment interferes with daily activities such as keeping track of finances, following instructions on jobs and house-keeping.[1,2] The patient may be lost on walks or while driving an automobile and easily gets confused and requires daily supervision. Patient may become unable to perform simple calculations or tell time or eat or dress properly. In the late stages loss of judgment, reason and cognitive abilities are prominent.[2]

AD cannot be cured and no highly effective drug is available. The focus is on judicious use of anticholinesterases apart from symptomatic management of behavioral problems and building rapport with patients, family members, and other caregivers.[3]

Memantine is a moderate affinity, noncompetitive, voltage-dependent Novel N-Methyl-D-aspartate (NMDA)-receptor antagonist with fast on/off kinetics. It has been evaluated in clinical trials for a range of dementia conditions. In United States of America and Europe, memantine is approved for the treatment of patients with moderate to severe dementia of the Alzheimer's type.[3]

Donepezil hydrochloride is a specific inhibitor of acetylcholinesterase that has consistently been shown to provide benefits in cognition and global function on Functional Dementia Scale (FDS), Care Givers Burden Scale, and Clinical Global Impression Scale (CGIS) in patients with mild-to-moderate AD in double-blind, placebo-controlled clinical studies of up to 1-year.[4]

The present study focuses on a comparison between memantine and donepezil in moderate to severe AD in randomized patients.

Objective of the study

The objective was to compare the efficacy, tolerability, and safety of memantine and donepezil in moderate to severe AD.

METHODS

This was an open-labeled randomized comparative study between memantine and donepezil. The study was divided into an initial 4 weeks for determination of onset of efficacy and subsequent 28 weeks of the treatment phase.

A total number of 40 patients were screened, among which eight patients did not fulfill the inclusion criteria. Thirty-two patients were randomized into memantine 20 mg (n=19) and donepezil 5 mg (n=13) groups. Dose was increased in three patients on donepezil 5 mg to 10 mg after 1-month as they failed to show any improvement on all the scales used. Seven patients from the memantine (20 mg) and three patients from donepezil (10 mg) groups discontinued treatment. Thus, total of 12 patients in the memantine group and 10 patients in donepezil groups could be studied for 28 weeks. Consolidated Standards of Reporting Trials of patient disposition is presented in Figure 1.

Patients were administered 5 mg/day of memantine and 5 mg/day of donepezil. Initially, doses were increased by a sequential increment as depicted in Figure 2. The primary end points were onset of efficacy, response rate, tolerability and safety of memantine, and donepezil. The scales used in the study were FDS, Care Giver Burden Scale, CGIS, and Patient Satisfaction Scale.

The study was conducted in accordance with the principles stated in the revised Declaration of Helsinki. The Local Ethical Committee approval was obtained. The nature and purpose of the investigation was explained to the patient and caregiver, and written informed consent was obtained from both.

The results of the onset of efficacy and response in the number of patients on the FDS and CBS were computed using Chi-square test. The results of change in mean score of FDS and on the Subscales of FDS (Activities of Daily Living Subscale [ADLSS], Orientation Subscale [OSS], affect subscale [ASS]) in between the groups at 4 weeks and at the end of study (28 weeks) were computed using Mann–Whitney U-test. Side effect profile for assessing the tolerability was computed using Chi-square test. The safety parameters such as vital signs and body weight were computed using Student's unpaired t-test between the groups.

RESULTS

Efficacy: Onset of efficacy, mean scores, and response rate of the patient to the investigational drugs was assessed using ADLSS, ASS, and OSS.

Onset of efficacy defined as ≥20% reduction in total score in the FDS at 4 weeks was seen in n=2 (16.7%) and n=8 (80%)

Table 1: Onset of response and response rate on FDS.

	Onset of response on FDS		Response rate on FDS	
	Memantine	Donepezil	Memantine	Donepezil
No				
Percentage (n)	83.3 (10)	20 (2)	16.7 (2)	80 (8)
Yes				
Percentage (n)	16.7 (2)	80 (8)*	83.3 (10)**	20 (2)

FDS: Functional dementia scale. *χ^2=8.8244; p<0.01 (significant), **χ^2=8.8244; p<0.01 (significant)

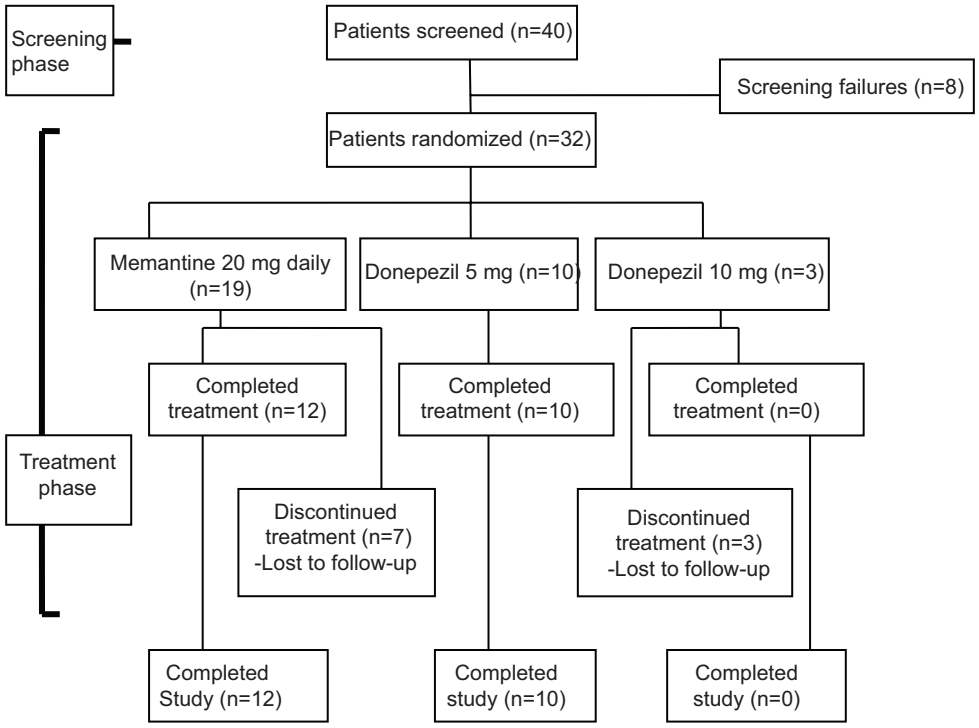

Figure 1: Consolidated Standards of Reporting Trials Diagram of patient disposition.

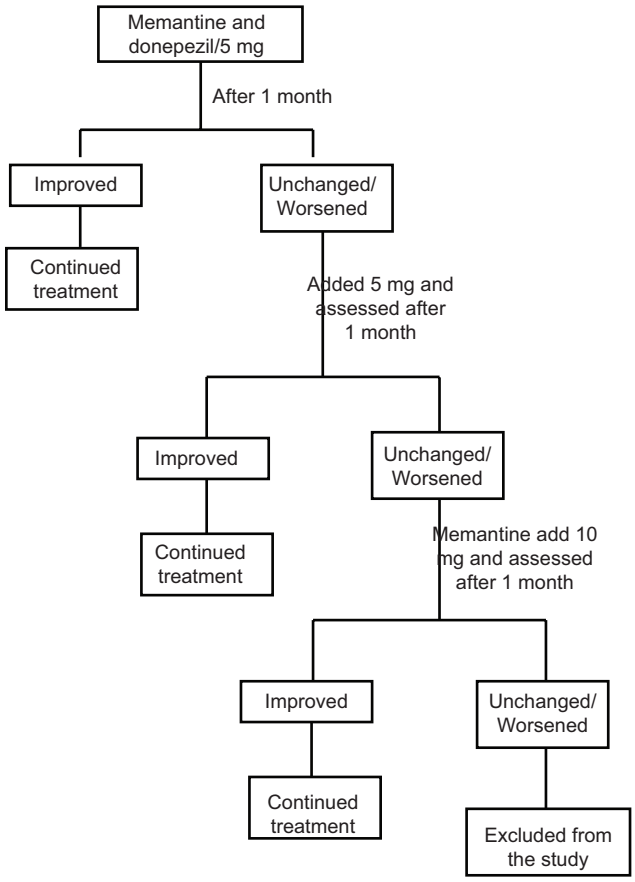

Figure 2: Memantine and donepezil treatment schedule.

with memantine and donepezil respectively as tabulated in Table 1 and depicted in Figure 3. The onset of efficacy in all patients with memantine n=12 and donepezil n=10 was achieved at 90 and 60 days respectively. Donepezil showed faster onset of efficacy and was statistically significant in number of patients achieving onset as compared to memantine. Response rate, defined as ≥50% reduction in FDS scale at the end of study, was n=10 (83.3%) and n=2 (20%) with memantine and donepezil respectively as tabulated in Table 1 and depicted in Figure 3. Though the onset of efficacy was late with memantine, it showed a greater response rate and was statistically significant in number of patients achieving response rate in comparison with donepezil at the end of study.

Mean change in scores at the end of the study from baseline: the scores at baseline, 1st month, 4th month, and the end of the study is as shown in Table 2 and depicted in Figure 4. FDS scores at the end of the study from baseline is statistically very highly significant (p=0.001) as memantine showed a greater reduction in comparison with donepezil at the end of the study. The ADLSS, ASS, and OSS total scores of memantine similarly showed a greater reduction in comparison with donepezil at the end of the study.

Tolerability

Constipation, headache, and insomnia were the common side effects reported for memantine only during the initial 6 weeks following the use of memantine. These were mild and self-limiting with the development of tolerance to these side effects. Anorexia, muscle cramps, headache, and insomnia were the common side effects reported for

Table 2: Mean change in FDS, ADL, ASS, and OSS Scores at the end of study from baseline.

Group	N	FDS mean score (SD)	ADL mean score (SD)	ASS mean score (SD)	OSS mean score (SD)
Baseline visit					
Memantine	12	66.49 (1.26)	23.83 (1.26)	22.5 (1.16)	20.16 (1.26)
Donepezil	10	65.2 (1.22)	23.00 (1.22)	21.40 (1.07)	21.2 (1.22)
1st month					
Memantine	12	63.76 (1.35)***	22.6 (1.35)*	21.32 (1.50)**	19.78 (1.35)*
Donepezil	10	58.53 (1.37	21.2 (1.37)	18.21 (2.27)	18.01 (1.37)
4th month					
Memantine	12	48.35 (2.29)	20.22 (1.4)	15.68 (0.84)	14.78 (2.29)
Donepezil	10	48.15 (0.84)	18.65 (2.67)	15.43 (0.84)	14.43 (0.84)
8th month					
Memantine	12	31.58 (0.93)***	12.42 (0.93)***	10 (0.52)***	9.16 (0.93)***
Donepezil	10	42 (1.22)	15.2 (1.22)	13.6 (0.96)	13.2 (1.22)

*p=0.05 - Significant, **p=0.01 - Highly significant, ***p=0.001 - Very highly significant. FDS: Functional dementia scale, ADL: Activities of Daily Living, ASS: Affect Subscale, OSS: Orientation Subscale Scores

donepezil only during the initial 6 weeks following the use of donepezil. They were mild and self-limiting with development of tolerance to the side effects. No other side effects were reported after 6 weeks in both the groups and hence it can be concluded that both memantine and donepezil are well tolerated in given doses as shown in Table 3.

Safety

There have been no symptoms and signs and results of laboratory investigations suggestive of organ damage to the liver, kidney in both the groups of patients indicating that both drugs show good margin of safety.

Table 3: Side effects observed at 4 and 6 weeks.

A/E	Memantine	Donepezil
Side effects at 4 weeks		
Nil	91.7 (11)	50 (5)
Anorexia	0	30 (3)
Constipation	8.3 (1)	0
Muscle cramps	0	20 (2)
Side effects at 6 weeks		
Nil	91.7 (11)	70 (7)
Headache	8.3 (1)	0
Insomnia	0	30 (3)

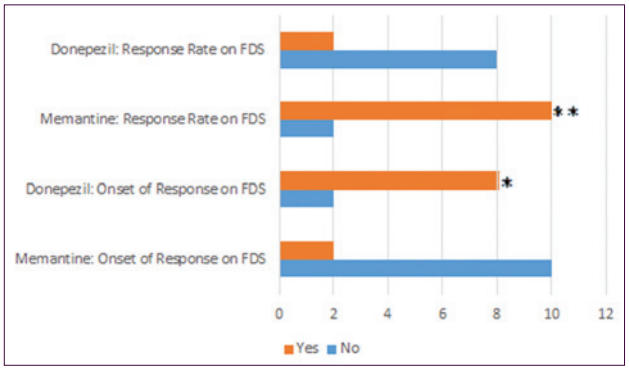

Figure 3: Onset of response and response rate on functional dementia scale, *χ^2=8.8244; p<0.01 (Significant). **χ^2=8.8244; p<0.01 (Significant).

DISCUSSION

Approximately 10% of all persons over the age of 70 have significant memory loss and the most common cause is AD. AD most often presents with subtle onset of memory loss followed by progressive dementia over several years.1 AD cannot be cured and no highly effective drug is available. The focus is on judicious use of anticholinesterases apart from symptomatic management of behavioral problems and building rapport with patients, family members, and other caregivers.

Donepezil, tacrine, rivastigmine, and galantamine are the approved inhibitors of cholinesterase which result in an increase in cerebral levels of acetylcholine. Controlled studies have indicated that they cause improvement in the rate of decline in cognitive test scores and caregivers rating of patients functioning. Donepezil is given in an initial dose of 5 mg orally once daily, increased if necessary after 4 weeks to a maximum of 10 mg once daily.[5,6]

Recent evidence of the involvement of glutaminergic neuronal excitotoxicity in AD led to the development and introduction of memantine. Memantine is a novel NMDA-receptor antagonist and has been shown to be clinically efficacious.

In October 2003, Food and Drug Administration (FDA) approved memantine (Namenda) for treatment of AD and haled as first drug approved for sever form of the disease. All the previous treatments have been studied in less sever

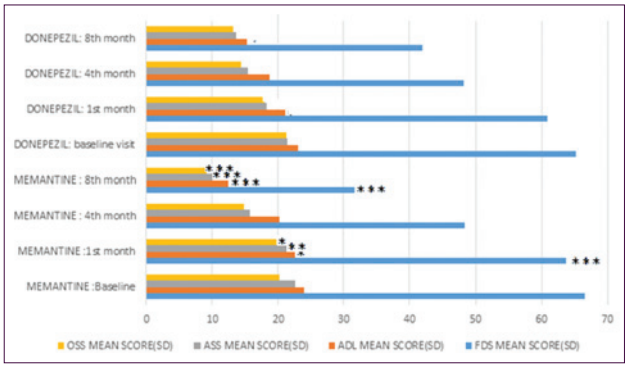

Figure 4: Mean change in functional dementia scale, Activities of Daily Living, Affect Subscale and Orientation Subscale Scores at the end of study from baseline *p=0.05 - Significant, **p=0.01 - Highly significant, ***p=0.001 - Very highly significant

forms of the disease stages.[7]

The first 2 double-blind studies each of about 6 months duration were conducted in USA and involved about 250 and 400 patients, respectively. The target study was carried out in patients already taking donepezil. Both studies showed that patients on memantine experienced less deterioration in their symptoms compared to patients treated with placebo during the study. The third study conducted in nursing homes in Latvia was a 12 weeks double-blind study in 166 patients with severe AD and also showed a statistical significant advantage of memantine over placebo.[8]

In a study published in January 2008 in the Journal of AD, researchers from the University of Aberdeen report that the drug memantine has a much more complex pharmacological profile than originally described. It does in fact work rather similar to the originally introduced drugs that affects acetylcholine related signaling, in addition to weak action on glutamate and has negative effects on neuronal communications at high concentrations.[9] At lower concentrations memantine was able to enhance signaling between the neurons of the hippocampus and was indeed able to reverse learning and memory deficits. However, a pharmacological analysis showed that this was not due to its ability to block glutamate signaling but rather to an additional and more potent action on the acetylcholine system. Therefore, the investigators data indicates that memantine shows promising features for the treatment of AD only in narrow concentration range.[9] More importantly, its complex pharmacological action requires careful consideration concerning suitable doses and suitable patient groups, so that the best use can be achieved for patients suffering from AD.[10]

Our comparative study, demonstrates that improvement is faster in donepezil than memantine, however, when the assessment is made at the end of 28 weeks, the improvement as indicated in the scores was seen in more number of patients taking memantine than patients taking donepezil. This leads to draw the inference that though there is a definite and prompt improvement in the symptoms of AD with donepezil at the end of study period of 28 weeks, improvement in symptoms was seen to be better in memantine. This leads to the conclusion that probably glutamatergic mechanisms are more crucial for sustained therapeutic benefits and hence memantine can be preferred to donepezil for prolonged and sustained benefits in moderate to severe AD.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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