Effect of Memantine on Prolonging Safe Driving in Early AD: a Pilot Study

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ABSTRACT

Background

To determine the feasibility of conducting an RCT on the potential effectiveness of memantine hydrochloride in prolonging safe driving in mild AD.

Methods

A placebo-controlled, double blind randomized trial was conducted. Forty-three individuals ≥60 with mild AD met screening criteria and were randomized. Driving ability was measured by a standardized on-road driving test. Outcomes were driving capacity at 6 and 12 months and completion of the 12-month intervention.

Results

Of 43 participants randomized, 59% of the memantine group and 52% of the placebo group completed the on-road test at 12 months ($p = .66$). All 13 memantine group participants maintained their driving status at 12 months, whereas only 8 of the 11 placebo group participants did ($p = .040$, OR = 4.45).

Conclusions

Results provide the framework for designing a rigorous multisite clinical trial of memantine effect on maintaining driving capacity in mild AD.

Key words: dementia, driving, Alzheimer's disease, memantine, feasibility, survival time

INTRODUCTION

Most individuals with early-stage AD are able to drive safely, but eventually become too impaired to drive.[1] Treatment to safely prolong driving could prove beneficial, but few studies have targeted interventions to preserve early AD driving ability.

Daiello and colleagues examined the effect of AD medication on driving in early-stage AD. After three months, acetylcholinesterase inhibitors (AChEIs) were found to enhance multiple driving skills. A modest 4% mean increase was achieved, with no residual after three-month washout.[2] Given the short observation time and non-randomized design, further research on potential treatment is needed.

Memantine is approved for use in the US for the treatment of moderate and severe AD. Pre-clinical studies suggest that it may have neuroprotective effects. Evidence from use of memantine hydrochloride suggests it has an optimal adverse event profile, supporting adherence and slowing decline.[3] In this randomized, placebo-controlled, fixed-dose pilot study of memantine hydrochloride in patients with early AD, we hypothesized that memantine hydrochloride would be well-tolerated and delay progression of driving impairment over one year.

METHODS

Participants

Inclusion criteria were age ≥ 60 years; Mini-Mental State Exam (MMSE) >23; clinical diagnosis of mild AD; valid driver's license; passing score on vision and on-road driving tests; and informed consent. Exclusion criteria were treatment with memantine within 30 days; treatment with a depot neuroleptic within six months; failed vision test; ischemic score >7; clinically significant disease; B12 or folate deficiency, psychiatric/neurologic disorders or medication that interfere with memantine.[4] Cholinesterase inhibitors were allowed if the dose was stable for ≥ three months. The study was approved by a credentialed IRB.

Approach

Following consent, participants were screened and baseline testing done. Eligible participants were randomly assigned to either memantine or placebo using a random number generator.

Intervention

Study medication was prepared by the manufacturer; the placebo was indistinguishable from memantine. Dosage was titrated over three weeks from 5 mg/day to 20 mg/day. Safety

indicators were assessed continuously and recorded at months 0, 3, 6, 9, and 12.

Measures

Age, gender, ethnicity, income, education, and driving habits were obtained at baseline.

Screening Measures

AD was confirmed through clinical history and neuropsychiatric examination. Optec vision test was administered at screening and 12 months.

The Clinical Dementia Rating Scale (CDR) was used to stage severity of dementia on a five-point scale.

Outcome Measures

Survival time was measured by the number who completed the on-road test at 6 and 12 months.

On-Road Driving Test

The DriveABLE on-road driving test was selected for its validity relative to simulator-based assessment.[5,6] Standardized road course and scoring procedures were used. The examiner was blinded to treatment group.

Cognitive Measures

MMSE scores have been found to be associated with driving ability.[7,8] The Fuld Object-Memory Evaluation is an assessment of memory and learning using ten common objects.[9] The Trail Making Test, Part A tests visual tracking; Trail Part B tests executive function, particularly cognitive flexibility and set-shifting, and is considered among the best predictors of driving performance.[10,11,8]

Statistical Analysis

Chi-square and exact tests were used to compare the two groups on survival time, driving test pass rates, and categorical sociodemographic data. T-tests or Wilcoxon rank-sum were used for cognitive assessments. A Cox Regression survival analysis with parametric bootstrapping using left, right, and interval censored survival procedures compared groups in accordance with intention-to-treat analysis using SPSS Version 27.0, and SAS Version 9.4. Results are reported in accordance with the CONSORT 2010 statement: extension to randomized pilot and feasibility trials.[12]

RESULTS

Seventy-one individuals expressed interest in the study; 60 were screened for eligibility. Of these, 43 completed baseline assessments and were randomized to memantine (n=22) and placebo control (n=21). Seventeen were excluded prior to randomization due to MMSE <23 (1); evidence of vascular dementia (2); did not pass the driving test (3); driver's license revoked (1); medically unstable (1) or did not meet AD criteria (2). Of the six eligible participants who declined participation, one moved outside the area, four were concerned about being on placebo and one did not want to take the medication. After initiating treatment, 9 in the memantine group and 10 in the placebo group withdrew due to adverse events or concerns regarding the possibility of being on a placebo. Four participants, two in each group, had serious adverse events not related to the study drug. An additional three in the memantine group and two in the placebo group experienced other adverse events also unrelated to study drug (Figure 1).

Baseline Participant Characteristics

Those randomized included 16 (37%) females and 27 (63%) males, age 63 to 92 years, 98% European American and 2% Hispanic American. There were no differences between groups (treatment vs. placebo) in age, education, gender, ethnicity/race, or driving history with the exception of Trails A & B and crashes in last five years (Table 1).

Primary Outcomes at 6 and 12 Months

Study Completion

Twenty-four (56%) of the 43 participants enrolled completed the final on-road driving test. At 12 months, 13/22 (59%) in the memantine group and 11/21 (52%) in the placebo group completed the on-road test. The difference in percent completion was not significant (*p* = .66). One placebo group participant failed the on-road test at six months and another's visual acuity fell below legal limits; neither took the 12-month on-road test. At 6 months, 14 in the memantine group and 12 in the placebo group completed the cognitive assessments; at 12 months, 13 in the memantine group and 11 in the placebo group completed them.

Driving Test Outcomes

A Cox Regression survival analysis was conducted to assess the effectiveness in the memantine group compared to the placebo group on retaining one's driving ability over 12 months as measured by an on-road test, yielding survival proportions of 13 of 13 (100%) for the memantine group and 8 of 11 in the placebo (72%) among those who completed the 12-mounth driving test and had not been dropped from the study due to reasons other than failing the driving test. Parametric bootstrapping analysis using BCa correction on 2,000 resamples was employed to improve the stability of the estimates. This nonparametric test considering interval censored data was statistically significant (β = 1.49, *p* = .040, OR = 4.45) with a meaningful difference in survival percentages of 100% vs. 72% between memantine and placebo groups.

Cognitive Measures

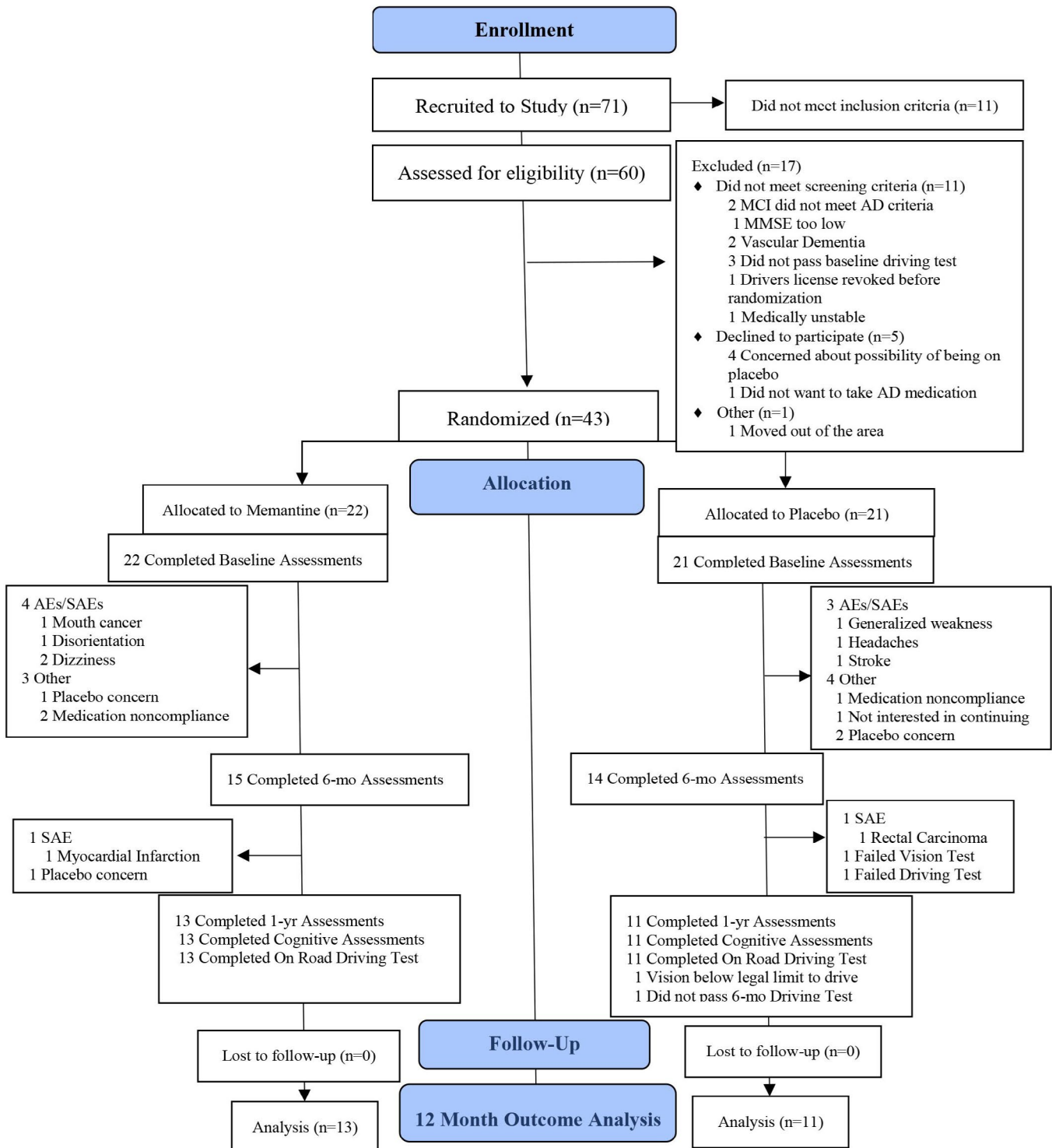At six months, there was a statistically significant decrease in the CDR in the memantine group from 2.5 to 1.6, compared to a smaller decrease for the placebo group from 2.6 to 2.2 (t[27] = 1.75, *p* = .045) (Table 2).

DISCUSSION

A recent systematic review found no randomized clinical trials evaluating interventions directed toward prolonging ability to drive safely in individuals with mild AD.[13] Intervention has

been directed primarily toward cessation rather than extending safe driving.[14] Yet this is not the preference of most older adults. Shimada *et al.* found 61% of older men with moderate cognitive impairment (MMSE <20) drove, indicative of reluctance to stop driving.[15]

This is the first randomized clinical trial to provide evidence of the potential for prolongation of safe driving in older adults with early AD. Several methodologic issues emerged from this trial that inform the design and implementation of future trials.

Enrollment

Recruited to Study (n=71) → Did not meet inclusion criteria (n=11)

Assessed for eligibility (n=60)

Excluded (n=17)
- ◆ Did not meet screening criteria (n=11)
  - 2 MCI did not meet AD criteria
  - 1 MMSE too low
  - 2 Vascular Dementia
  - 3 Did not pass baseline driving test
  - 1 Drivers license revoked before randomization
  - 1 Medically unstable
- ◆ Declined to participate (n=5)
  - 4 Concerned about possibility of being on placebo
  - 1 Did not want to take AD medication
- ◆ Other (n=1)
  - 1 Moved out of the area

Randomized (n=43)

Allocation

Allocated to Memantine (n=22)

22 Completed Baseline Assessments

Allocated to Placebo (n=21)

21 Completed Baseline Assessments

4 AEs/SAEs
- 1 Mouth cancer
- 1 Disorientation
- 2 Dizziness
3 Other
- 1 Placebo concern
- 2 Medication noncompliance

3 AEs/SAEs
- 1 Generalized weakness
- 1 Headaches
- 1 Stroke
4 Other
- 1 Medication noncompliance
- 1 Not interested in continuing
- 2 Placebo concern

15 Completed 6-mo Assessments

14 Completed 6-mo Assessments

1 SAE
- 1 Myocardial Infarction
1 Placebo concern

1 SAE
- 1 Rectal Carcinoma
1 Failed Vision Test
1 Failed Driving Test

13 Completed 1-yr Assessments
13 Completed Cognitive Assessments
13 Completed On Road Driving Test

11 Completed 1-yr Assessments
11 Completed Cognitive Assessments
11 Completed On Road Driving Test
1 Vision below legal limit to drive
1 Did not pass 6-mo Driving Test

Follow-Up

Lost to follow-up (n=0)

Lost to follow-up (n=0)

12 Month Outcome Analysis

Analysis (n=13)

Analysis (n=11)

Reference: Altman, D.G., Schulz, K.F., Moher, D., Egger, M.. Davidoff, F., Elbourne, D., Gøtzsche, P.C., & Lang, T. (2001). The revised CONSORT statement for reporting randomized trials: Explanation and elaboration. *Annals of Internal Medicine; 134*(8), 663-694.

FIGURE 1. CONSORT flow diagram

Placebo as a Deterrent to Participation

The prospect of receiving placebo was the most common deterrent: 4 of 60 (7%) potential enrollees were dissuaded from enrolling; an additional 4 of 43 (10%) enrolled participants withdrew due to this possibility. In future trials, participants can be instructed in 'equipoise', that investigators do not know if the active medication is beneficial. A plan for the placebo group to receive the medication after the study year may also increase participation.

Withdrawals Due to Nonadherence to Medication

Three participants (7%) were withdrawn after enrollment due to medication nonadherence. Future trials could incorporate modest monetary incentives and more frequent contact with participants to increase adherence.

TABLE 1.
Characteristics of treatment and placebo groups at baseline

	Memantine (n=22)		Placebo (n=21)		
Demographics					
Categorical Variables	n	%	n	%	P value
Gender – Male	12	54	15	71	.25
Ethnicity European American	21	95	19	90	.58
Continuous Variables	mean	SD	mean	SD	
Age (years)	78.13	6.38	80.47	5.92	.22
Education (years)	15.13	2.62	15.23	5.26	.91
Cognitive Measures	mean	SD	mean	SD	P value
CDR	2.40	1.11	2.30	1.30	.80
Fuld Object-Memory Evaluation	17.93	5.84	18.86	4.99	.63
MMSE	28.12	1.99	27.66	1.63	.49
Trails A – seconds	39.62	12.37	50.05	17.27	.05[a]
Trails B – seconds	117.75	43.03	195.33	128.57	.02[a]
Driving Related History					
Categorical Variables	n	%	n	%	P value
Crashes in last 5 years	8	36	1	5	.02[a]
Crashes in last 1 year	5	23	2	10	.41
Tickets in last 5 years	3	14	3	15	.99
Tickets in last 1 year	0	0	2	10	.13
Limit driving	5	22	9	42	.15
In last 3 months driven alone	22	100	21	100	1.00

[a]$p \leq .05$

TABLE 2.
Descriptive statistics for cognitive measures at 6 and 12 months by treatment group (memantine vs. placebo)

	Memantine Group						Placebo Group						6-Mth	12-Mth
	Baseline		6 months		12 months		Baseline		6 months		12 months		p value	P value
	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD		
Cognitive Measures														
CDR	2.5	1.3	1.6	0.9	1.8	1.6	2.6	1.2	2.2	1.8	2.3	2.7	.04[a]	.51
Fuld	19.2	5.3	18.7	8.5	18.4	8.8	17.5	6.3	18.3	8.2	19.1	8.5	.91	.95
MMSE	27.7	1.8	27.3	2.7	27.2	2.3	27.9	2.1	26.9	2.8	26.0	3.6	.15	.12
Trails A (sec)	50.0	18.6	38.1	13.6	38.5	16.3	39.1	13.4	51.4	18.7	53.5	22.0	.91	.64
Trails B (sec)	202.9	135.3	157.3	126.6	195.3	128.6	108.6	36.6	239.6	164.1	233.2	159.5	.17	.81

[a]$p \leq .05$
CDR = Clinical Dementia rating; Fuld = Fuld Object Memory Evaluation; MMSE = Mini Mental State Examination.

Multiple Data Points

Survival analysis increases in accuracy and power as the number of data collection points increase. Testing every two or three months and the addition of new technologies to continuously monitor the quality of driving can provide multidimensional analyses of change.

Baseline Group Characteristics

Although generally comparable at baseline, the groups differed on Trails A & B (sec.) and crash history. Dichotomized driving-related scores may be used as stratification variables, and a larger sample may yield more balanced groups.

Effect Size

This was the first RCT to assess the efficacy of a pharmaceutical intervention to extend safe driving in early AD. Thirteen of the original 22 (59%) in the memantine group and 8 of original 21 (38%) participants in the placebo group passed the on-road test at 12 months, an approximate 20% difference between the groups. This magnitude of difference was supported by the nonparametric interval censored survival model. For a statistical estimate with $\alpha = .05$, two-tailed test with 80% power, 1:1 randomization ratio, an estimated 107 participants per group is needed for multivariate analyses.

CONCLUSION

Compensatory strategies are needed before driving cessation becomes necessary. Until disease-altering treatments are available, there is a great need to evaluate treatments that can prolong safe driving for those with mild AD.

This feasibility trial identified important methodologic considerations for design of a rigorous randomized trial to evaluate the effect of memantine on safe driving in mild AD. Given the importance of driving to most older adults and high tolerance levels of memantine in this population, this study provides direction for designing and implementing a rigorous multisite clinical trial to test the effects of memantine on driving capacity of older adults with mild AD.

ACKNOWLEDGEMENTS

CONFLICT OF INTEREST DISCLOSURES

The authors declare that no conflicts of interest exist.

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