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Jerin Ullah, MS performed the statistical analysis. She has no relevant disclosures.

Scott Fields, PharmD created the medication administration, randomization and blinding scheme, and supervised all aspects of study medication management. He has nothing to disclose.

Joel H. Kramer, PsyD participated in study design including selection of the neuropsychological tests and helped with their interpretation. He has no relevant disclosures.

Jennifer Merrilees, PhD participated in patient recruitment and evaluation, and reviewed the final manuscript.

John Neuhaus, PhD participated in study design including the statistical analysis plan. He supervised Ms. Ullah in her statistical analysis. He has nothing to disclose.

M. Marsel Mesulam, MD participated in patient recruitment and evaluation, reviewed the final manuscript and provided substantive feedback. He has nothing to disclose.

Bruce L. Miller, MD participated in conceptualization of the study, recruiting subjects and revising the manuscript. Dr. Miller serves as board member on the John Douglas French Alzheimer's Foundation and Larry L. Hillblom Foundation, serves as a consultant for TauRx, Ltd., Allon Therapeutics, the Tau Consortium and the Consortium for Frontotemporal research, has received institutional support from Novartis, and is funded by NIH grants P50AG023501, P01AG019724, P50 AG1657303, and the state of CA.

Memantine in frontotemporal lobar degeneration: A multicenter, randomised, double-blind, placebo-controlled trial

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Abstract

Background—Memantine has been used off-label to treat frontotemporal lobar degeneration (FTD). A previous 26 week open label study suggested a transient, modest benefit on neuropsychiatric symptoms as measured by the Neuropsychiatric Inventory (NPI).

Methods—We performed a randomized, parallel group, double blind, placebo controlled trial of 20 mg memantine taken orally daily for 26 weeks in FTD. Participants met Neary criteria for behavioral variant (bvFTD) or semantic dementia (SD) and had characteristic brain atrophy. Use of cholinesterase inhibitors was prohibited. The objective of the study was to determine whether memantine is an effective treatment for FTD. Individuals were randomized to memantine or matched placebo tablets in blocks of two and four. Primary endpoints were the change in total NPI score and Clinical Global Impression of Change (CGIC) scores after 26 weeks. Secondary outcomes included a neuropsychological battery, and other cognitive, global and activity of daily living measures. Clinicaltrials.gov identifier: NCT00545974

Findings—100 subjects were screened, 81 were randomized, 5 (6%) discontinued and 76 completed all visits. Enrollment numbers were lower than planned due to many subjects' preference to take memantine or cholinesterase inhibitors off-label rather than participate in a clinical trial. 39 memantine and 42 placebo subjects entered the primary intent to treat analysis.

There was no effect of memantine treatment on either the NPI (mean difference [MD] 2.2, 95%CI: −3.9, 8.3, p = 0.47) or CGIC (MD 0, 95%CI: −0.4, 0.4, p = 0.90) after 26 weeks of treatment. Memantine was generally well tolerated, however there were more frequent cognitive adverse events in the memantine group.

Interpretation—There was no benefit of memantine treatment in bvFTD or SD. These data do not support memantine use in FTD.

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Introduction

Frontotemporal lobar degeneration or frontotemporal degeneration (FTD) is a common cause of dementia in individuals who develop symptoms before age 65. FTD encompasses three core clinical syndromes, a behavioral variant frontotemporal dementia (bvFTD), and two primary progressive aphasias (PPA), semantic dementia (SD) and progressive nonfluent aphasia (PNFA). [1] BvFTD is the most common form of the disease and features prominent social and behavioral deficits as well as executive dysfunction. SD often begins as an aphasia, with progressive semantic knowledge loss, but also often features prominent behavioral abnormalities similar to bvFTD. [2] PNFA presents as a motor speech disorder with few other cognitive or behavioral impairments. There are no medications approved by the US Food and Drug Administration (FDA) to treat FTD and only a handful of randomized, placebo controlled trials have been conducted in FTD.[3] Despite the lack of efficacy data supporting the use of medications approved for the treatment of Alzheimer's disease (AD), such medications are frequently prescribed to FTD patients off-label in the US, with 55% of patients in a recent study using either an acetylcholinesterase inhibitor (AChI) or memantine. [4]

Memantine is approved by the European Medicines Agency and the FDA for the treatment of moderate-severe AD and has also demonstrated beneficial effects in clinical trials of vascular dementia, Parkinson's-related dementias and dementia of mixed etiologies reviewed in [5]). Although the neuropathology and underlying neurotransmitter deficits are different in FTD than in AD, there is a scientific rationale for using memantine to treat FTD. First, memantine is believed to act as a non-competitive inhibitor of N-methyl D-aspartate (NMDA) receptors that may be over-activated in a variety of neurodegenerative diseases, including FTD. [5] Second, analyses of data from clinical trials of memantine in AD found clear benefits on a variety of abnormal behaviors as assessed by the Neuropsychiatric Inventory (NPI). [6] Since many of these behaviors are prominent features of FTD, memantine might also be predicted to improve these deficits. Third, a number of open label treatment studies in bvFTD and SD have demonstrated symptomatic improvements with memantine treatment. [7,8] In one of these studies, we found that initiation of memantine therapy was associated with a transient improvement in behavior as measured by the NPI [9] in bvFTD and SD subjects. [8] Since the transient improvement in NPI scores might have been attributable to a placebo effect or an effect of memantine treatment, the current study tested the hypothesis that memantine would improve or stabilize behavior as measured by the NPI and Clinical Global Impression Change (CGIC) [10] as compared to placebo after 26 weeks of therapy.

Methods

Subjects

Patients were recruited from nine US academic dementia research centers with expertise in the diagnosis of FTD including the University of California, San Francisco (UCSF) and Los Angeles (UCLA), the Mayo Clinic, Rochester and Jacksonville, Northwestern University

Medical Center, Case Western Reserve Medical Center, University of North Carolina, Johns Hopkins University and the University of Pennsylvania. Study visits occurred between December, 2007 and May, 2012. Because this was a follow-up study to a 26 week open-label study of memantine that showed a similar pattern of changes in bvFTD and SD, but not PNFA, [9] the current study only included subjects with bvFTD or SD. [1] Individuals with FTD-motor neuron disease were included if motor impairments did not interfere with study procedures. Individuals had to be between 40–80 years of age and have a Mini-Mental State Exam (MMSE) score of ≥ 15 at screening. To exclude cases with slowly progressive bvFTD (bvFTD phenocopy) all subjects had a CT or MRI scan of brain within 24 months of randomization consistent with a diagnosis of bvFTD or SD. [11] All subjects had a reliable caregiver who could accompany them to study visits. *Exclusion criteria* included a diagnosis of PNFA, use of memantine, AChI, antipsychotic agents, valproate, lithium or benzodiazepines within four weeks prior to randomization. Use of AChI was prohibited due to potential confounding effects on memantine efficacy and reported adverse reactions in FTD. [12,13] If behavioral symptoms became difficult to control after the baseline visit, individuals were allowed to take an atypical antipsychotic medication (olanzapine, quetiapine or risperidone). Antidepressant use was allowed, if the dose had been stable for one month prior to randomization. Other exclusion criteria included evidence of disorders that preclude diagnosis of FTD. [1] Written informed consent was obtained from the subject and the subject's caregiver in accordance with local IRB regulations. Clinicaltrials.gov identifier: NCT00545974.

Randomization and blinding

Subjects were randomized to memantine 10 mg twice daily or identical placebo tablets lacking memantine, that were packaged into kits (one per subject) of multiple blister packs (one week of treatment per pack). All subjects and study personnel were blinded to treatment assignment. Randomization codes were generated by an unblinded UCSF pharmacist (S.F.) using the Excel (Microsoft) random number generator in blocks of 2 and 4 subjects.

Study procedures

Each subject participated in six study visits over approximately 35 weeks. After the screening visit, a randomization/baseline visit occurred within 35 days, during which initial study medication was dispensed. Individuals were titrated to the full dose of 10 mg memantine or placebo taken orally twice daily, by 5 mg per week, reaching the full dose at week four. Subjects returned at weeks six, 12 and 26 (or early termination) for safety and efficacy assessments. In addition to the in-person visits, on weeks three, nine and 18, individuals received a phone call to assess adverse events and study medication compliance. After the week 26 visit, the study medication was stopped, and individuals returned for a 30 day off drug safety assessment. Compliance was assessed by counting study medication remaining in the blister packs. All outcome measures were assessed at baseline and week 26, with a subset of measures collected at weeks 6 and 12. Adverse events were grouped by Medical Dictionary for Regulatory Activities (MedRA) system organ class (www.meddramsso.com). Serious Adverse Events (SAEs) were defined as those leading to hospitalization or death.

Outcome measures

The primary outcomes were the NPI and CGIC. The NPI is a measure that assesses 12 neuropsychiatric abnormalities that reveals severe abnormalities in FTD. [9] The CGIC is a seven point categorical scale that gives a global impression of change from baseline. Secondary efficacy assessments included the clinical dementia rating sum of boxes (CDR-SB-FTD), with behavioral comportment, personality and language domains added to better

capture FTD-related deficits; [14] the MMSE;[8] the Functional Activities Questionnaire (FAQ) ; [15] Texas Functional Living Scale (TFLS) a performance-based assessment of capacity to perform ADLs;[16] the Executive Interview (EXIT25), a neuropsychological composite to test executive function, [17] a modified Unified Parkinson's Disease Rating Scale (UPDRS); [8] the time to initiation of antipsychotic therapy; and a neuropsychological battery, including a California Verbal Learning Test, category fluency, phonemic fluency, a 15 item Boston Naming Test (BNT), a modified Trails set-shifting task, backward digit span and the Digit Symbol as previously described. [14] Tertiary outcomes were the Zarit Burden Interview (ZBI), a 22 item questionnaire used to measure caregiver burden [18] and subject weight in Kg (since FTD patients often gain weight).

Sample Size Estimate

We based our sample size calculation on a comparison of changes in NPI from baseline to follow-up between the memantine treatment and placebo groups using a two sample t-test. We hoped to detect a medium effect size of half a standard deviation. [19] Standard power calculations for two sample t-tests ($\alpha = 0.05$) with a standard deviation of 2.2 (half of 4.4 from [8]) show that a sample of 65 per group would provide power greater than 80% power to detect this difference.

Statistical analysis

Primary and secondary outcomes were analyzed using an intent-to-treat (ITT) approach that included all subjects who received at least one dose of medication and had a post-baseline efficacy assessment. We used a repeated measures approach to assess the difference in changes over time in the repeated primary (NPI) and secondary outcomes between the memantine and placebo groups, that is, the time by treatment group interaction. Specifically, for each subject, we computed changes in outcomes between baseline and the 26 week follow up and assessed the magnitude of the difference in these changes using linear regression methods. Analyses were repeated using gender as a covariate. It was decided *post-hoc* to reduce the CGIC values to "improved, no change or worsened" due to the very few number of responses outside the middle 3 values. Week 26 CGIC values were compared using a Mann-Whitney U test. Exploratory analyses in each FTD subtype and observed cases (OC), subjects who completed all four efficacy visits, were conducted to investigate potential sources of bias in the ITT analyses. Finally, differences in outcome measures at individual time points were compared using least squares means with a two-sample t-test, and differences in adverse event frequencies were analyzed using Chi square tests. Analyses were performed using SAS 9.3 (SAS Inc., Cary, NC) or Stata 12 (StataCorp, College Station, TX).

Results

100 patients were assessed for eligibility and 81 patients (64 bvFTD and 17 SD) were randomly assigned to memantine (n=39) or placebo (n=42; Figure 1). Five patients (2 memantine, 3 placebo) discontinued treatment prior to the end of the study. The planned enrollment for the study was 140 subjects. Despite randomization, there was a greater percentage of men in the placebo group (Table 1; P=0.01). There were no other baseline differences in demographic variables, concomitant medication use, or outcome measures (Supplementary Data). 17 memantine and 13 placebo subjects took 100% of the study medication (p=0.24); for the remaining subjects, mean study medication compliance was 95.6% (95%CI: 92.3, 97.3) in the placebo group and 94.8% (93.0, 98.2) in the memantine group (p = 0.65).

Primary outcomes

In the ITT analysis there were no differences between the memantine and placebo groups on the change in total NPI or CGIC scores after 26 weeks (Table 2). The mean difference in change in NPI score from baseline to week 26 was 2.2 (95%CI: −3.9, 8.3, P=0.47; Figure 2A). Adjusting for baseline gender differences *post-hoc* did not alter the result (Supplementary Table 1). The CGIC showed that at week 26, 27 subjects worsened, 8 remained stable and two improved in the memantine group, whereas 29 subjects worsened, 8 remained stable and four improved in the placebo group (p=0.90; Figure 2B).

Secondary outcomes

No treatment effect was observed on the functional outcome measures, the CDR-SB-FTD, FAQ and TFLS. CDR-SB-FTD scores increased similarly in both groups by 1.5 (0.8, 2.1) points over 26 weeks (Figure 3). Performance on the FAQ and TFLS declined similarly in the placebo and memantine groups (p=0.67).

The memantine group displayed worse neuropsychological performance than the placebo group on tests of naming (BNT) and processing speed (Digit Symbol; Figure 4, Table 2). There were no differences on other neuropsychological composite (MMSE and EXIT25), and individual test scores (Table 2). Consistent with the effects we observed on neuropsychological tests, there were numerically more cognitive AE's (confusion, memory loss, language disorders; six vs. one; p= 0.056, supplementary table 4) in the memantine group than the placebo group, whereas the opposite was true for psychiatric AE's (p=0.03). Two individuals experienced a SAE in the placebo group and one individual experienced two SAEs in the memantine group. SAEs were not judged to be treatment related. There were no differences in UPDRS or other safety assessments (Table 3). Since only three subjects began an antipsychotic medication during the study (Supplementary Data), time to antipsychotic use was not analyzed.

Tertiary outcomes

There was no treatment effect on caregiver burden (ZBI, p=0.13) or change in weight.

Exploratory (post-hoc) analyses

Because we had previously observed a transient improvement in NPI scores in an open-label memantine treatment study, [8] we examined differences in NPI scores at individual time points and found a transient improvement (MD 5.9, 95%CI: 4.2, 7.6) at week six (p=0.01) that converged with changes in the placebo group at weeks 12 and 26 (p>0.30; Figure 2A).

We also investigated whether the effects we found on the BNT and digit symbol test were related to FTD subtype. When analyzed separately, BNT performance was worse in both the bvFTD and SD groups after 26 weeks (Supplementary Figure 1). On the Digit Symbol test, there was a small improvement in performance in the placebo group after 26 weeks of treatment, whereas the memantine group declined (MD: 8.1, 95%CI: 1.1, 15.1, P < 0.001; Figure 4B).

Discussion

We found no benefit of 20 mg daily memantine treatment in FTD on either of the primary outcome measures, the NPI or the CGIC, after 26 weeks of treatment. There was evidence of worse cognitive performance on tests of naming (BNT) and processing speed (Digit Symbol) associated with memantine treatment, and a trend towards more cognitive adverse events. However, the worse neuropsychological performance in the memantine group was not associated with a difference in the rate of decline in activities of daily living as measured

by CDR-SB-FTD, FAQ and TFLS. Although memantine was safe and well tolerated in FTD, our results do not support a claim of benefit for memantine treatment in FTD patients. Since approximately 30% of bvFTD patients in the US take memantine,[4] our findings have immediate public health implications.

Our results are similar to those from a recent 52 week randomized placebo controlled trial of memantine in 49 subjects with bvFTD that also demonstrated no benefit on the primary outcome, the Clinician's Interview-Based Impression of Change (similar to the CGIC) or the NPI.[20] Like the previous study, a major limitation of the current study was that we failed to enroll the planned number of subjects, which may have limited our ability to detect a treatment effect. This under-enrollment was due to many potential subjects' preference to take memantine (and in many cases an AChI as well) rather than participate in a clinical trial during which they risked being randomized to placebo. Unfortunately, altering the enrollment criteria to allow use of these medications would have prevented us from testing our hypothesis that memantine might have benefit in the treatment of FTD. Instead, to improve recruitment, sites stressed equipoise regarding the efficacy of memantine when recruiting subjects. A second limitation of the study was the small size of the SD group, which limits the generalizability of our results to this FTD syndrome. Finally, since this trial was designed, a number of rating scales that better capture FTD-specific behaviors have been developed that might have been more sensitive to potential benefits of memantine than those we employed (reviewed in [21]).

Despite these limitations, we believe that our study provides strong evidence that memantine is not an effective treatment for FTD. First, in an exploratory analysis, there was a transient improvement in NPI scores after six weeks of treatment that was similar in magnitude and time course to what we observed in a previous open-label treatment study (n= 34 bvFTD and SD patients) [8] suggesting that the pattern of changes observed on the NPI (Figure 2) did not arise by chance. Second, we conducted a study-level meta-analysis, combining six month CGIC data from the current study and 12 month CIBICplus data presented in the manuscript from the previous bvFTD clinical trial, [20] for a combined total of n=64 placebo and n=55 memantine cases. This meta-analysis found no difference between placebo and memantine on the combined global impression (MD = 0.082, 95%CI: −0.18, 0.34; P = 0.553). Third, we observed worse visuomotor and naming function in the memantine group in the pre-specified analyses (Table 2). Consistent with these findings, there was a greater number of cognitive adverse events in the memantine group (Table 3). Finally, the rate of decline in CDR-SB-FTD scores was identical in both groups, and numerically, FAQ scores appeared to decline more rapidly in the memantine group at week 12 (Figure 3), although this was an exploratory finding that should be interpreted with caution.

We found fewer psychiatric (behavioral) side effects in the memantine group than the placebo group (Table 3). The simplest explanation for the divergent effects of memantine we observed in this study would be that memantine had a general suppressive effect on attention and cognition that led to less distressing behavior as well a reduced ability to perform visuomotor processing and lexical retrieval tasks.

Our study suggests that FTD patients may respond differently to memantine than other forms of dementia, underscoring the importance of accurate diagnosis. In moderate-severe AD, memantine has demonstrated benefits on global and cognitive function alone or in combination with donepezil. [12] Although a pilot study of memantine in PPA (not differentiated by subtype) suggested a modest benefit of treatment on the Western Aphasia Battery, [22] some forms of PPA are due to underlying AD pathology which could explain this finding. Clinical trials of memantine for VaD also suggest a modest benefit on cognition in patients with mild to moderate impairment. [23] Two clinical trials of memantine in

Parkinson's-related dementia demonstrated efficacy for treatment of cognitive and behavioral symptoms.[24,25] We speculate that the lack of benefit of memantine treatment in FTD could reflect a different pattern of neurotransmitter abnormalities in this disorder.[3]

This is the largest randomized placebo controlled trial conducted in FTD to date. In addition to the implications for the current treatment of FTD, we demonstrate that clinical trials are feasible in this disorder. Since approximately half of all FTD cases have underlying tau pathology, as in AD, it has been suggested that tau-directed therapeutics might eventually be used in both disorders.[26] We found that the rate of decline as measured by the CDR-SB-FTD was approximately twice as fast as has been reported for the CDR-SB in AD. [27] The more rapid progression of FTD as compared to AD may allow for faster clinical trials in FTD than in AD to test the efficacy of therapies targeting proteins such as tau that are common to both disorders. [21] This study provides clear evidence of a lack of efficacy of memantine treatment for mild to moderate FTD, highlighting the urgent need to develop more effective FTD therapeutics.

Research in Context

Systematic review

We searched Pubmed using the following terms: "memantine," and "frontotemporal dementia," "semantic dementia," "frontotemporal lobar degeneration," "Pick's," "FTD," "FTLD," "primary progressive aphasia," "PPA," "corticobasal," or "aphasia." We included randomized, placebo-controlled trials in FTD or a related disorder that involved memantine. We identified one prior RCT in bvFTD[21] and one in PPA (not differentiated by subtype). [22] We conducted a study-level meta-analysis, combining six month CGIC data from the current study and 12 month data from Table 4 from the previous bvFTD clinical trial [21], but not the PPA trial because it was not limited to SD, for a combined total of n=64 placebo and n=55 memantine cases. There was no difference between placebo and memantine on the combined global impression scores (MD = 0.082, 95%CI: −0.18, 0.34; p = 0.553, Mann-Whitney U).

Interpretation

This study confirms the lack of benefit of memantine for treatment of FTD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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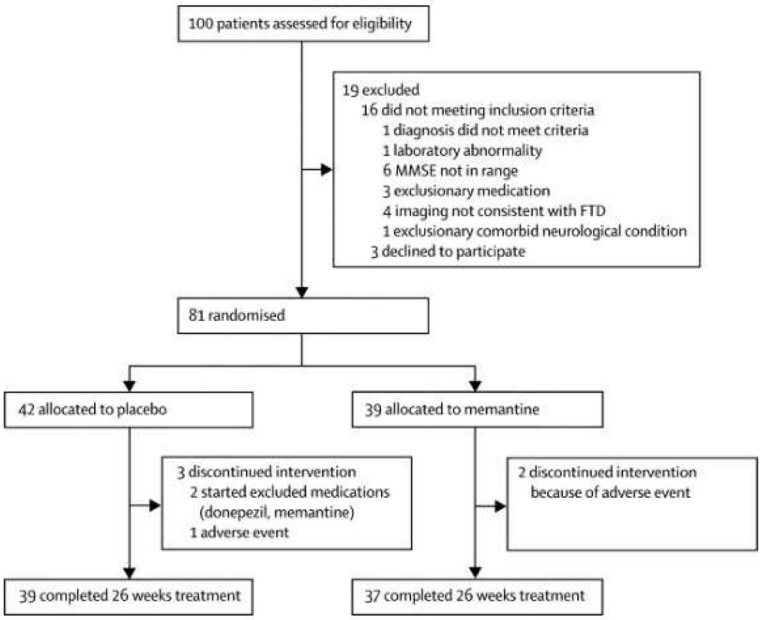

Figure 1.
Patient flow diagram.

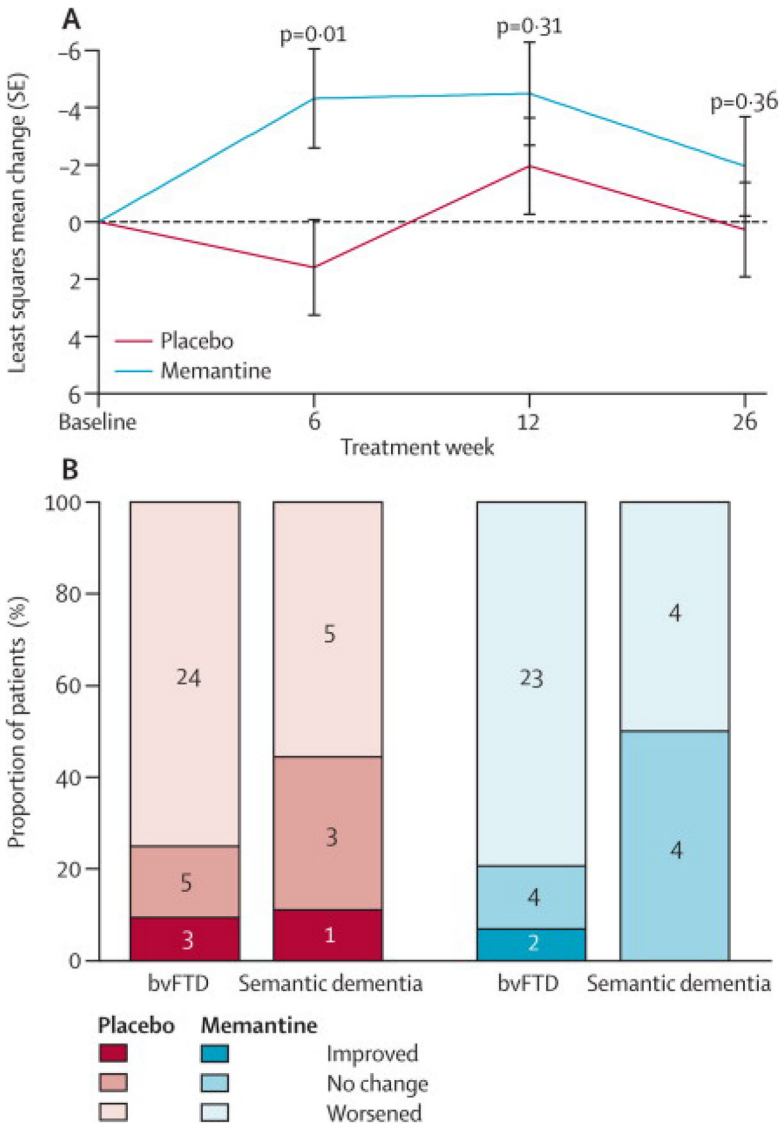

Figure 2. Primary outcome variables

(A) Change from baseline of total Neuropsychiatric Inventory (NPI) scores from the intent to treat population are shown with p values for a paired t test at each study visit. In the repeated measures analysis there was no group difference (p = 0.39). **(B)** Clinician's Global Impression of Change (CGIC) values are shown at week 26 for n = 76 subjects who completed this visit. Only improved = "slightly improved (3)", no change = "no change (4)" and Worsened = "slightly worsened (5)" are shown since no other values were recorded. Using a Mann Whitney test there was no difference in CGIC distributions (p = 0.90).

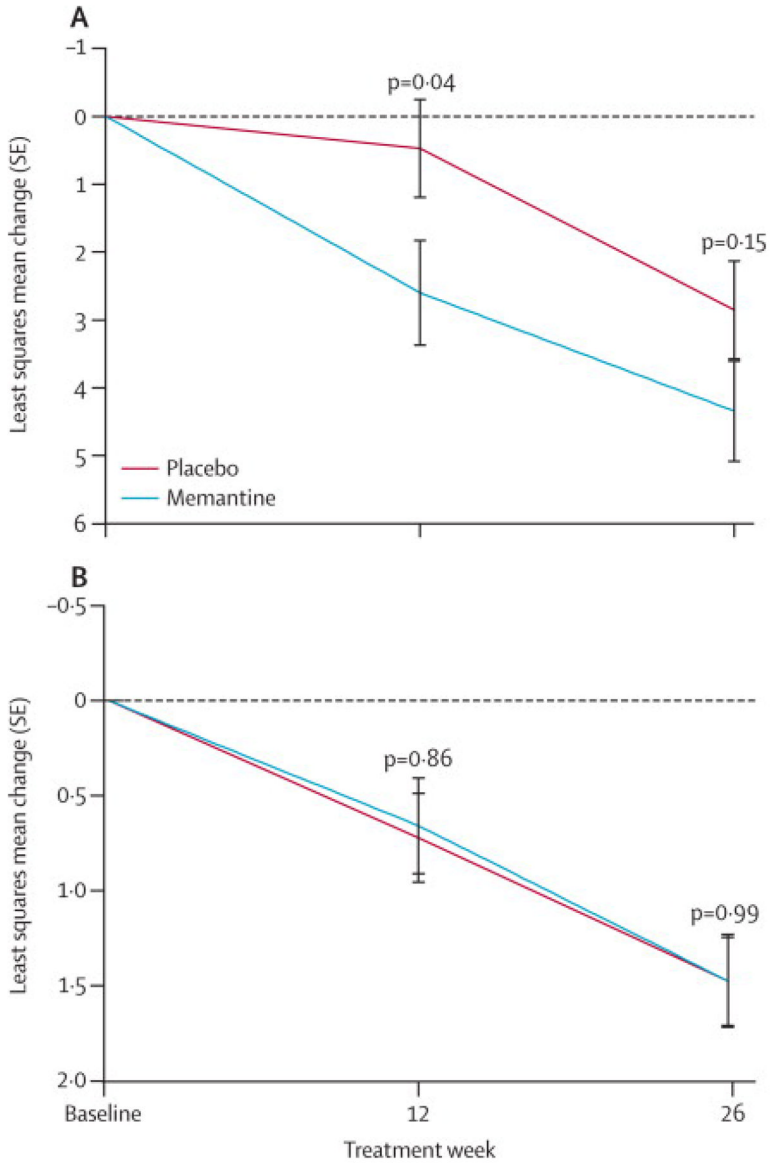

Figure 3. Functional rating scales

(A) Change from baseline Functional Activities Questionnaire (FAQ) scores in the intent to treat population. **(B)** Change from baseline in Clinical Dementia Rating sum of boxes (CDR-SB-FTD) scores.

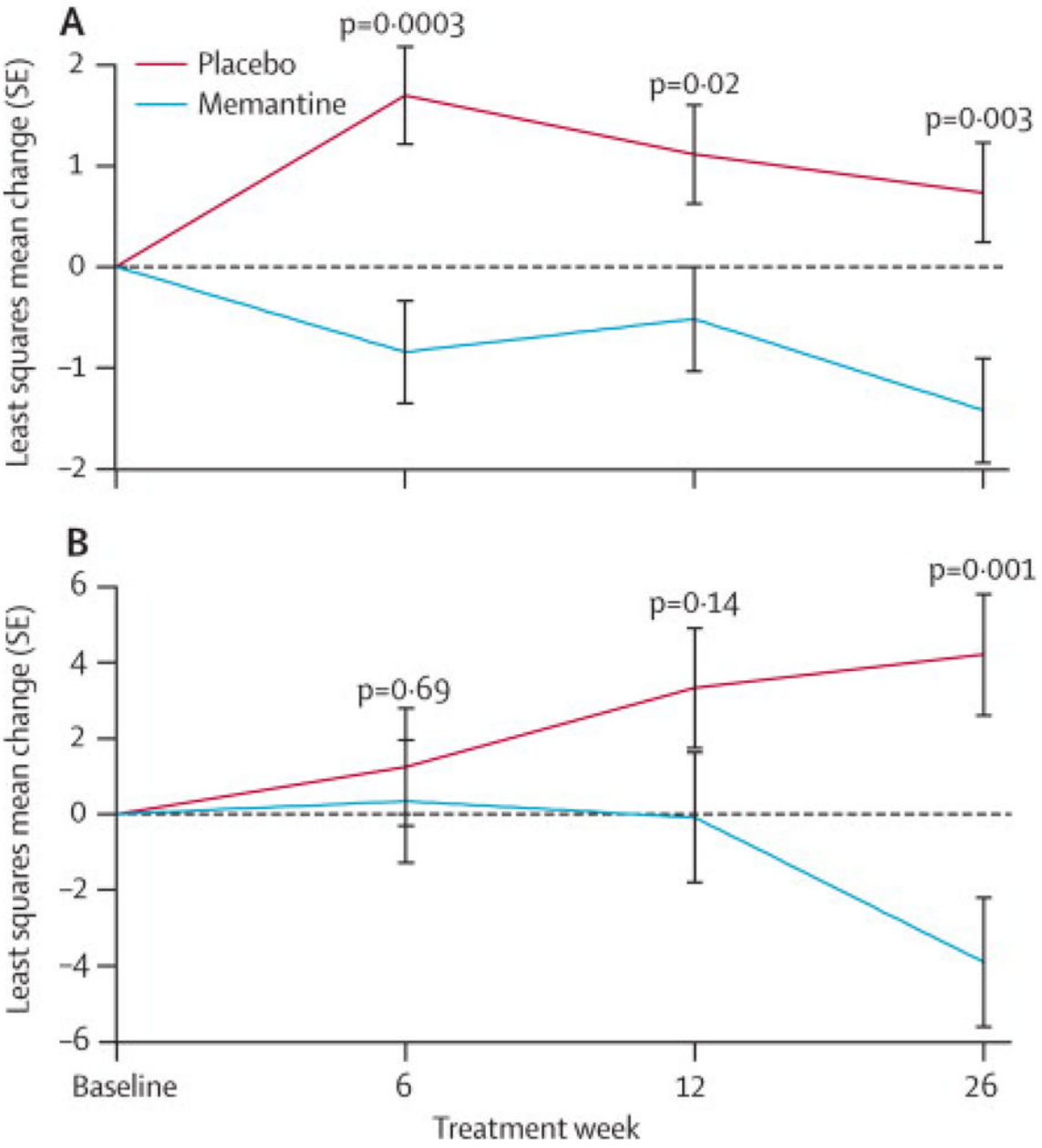

Figure 4. Neuropsychological tests

(A) Change from baseline modified Boston Naming Test (BNT). **(B)** Change from baseline Digit Symbol Substitution Test scores.

Table 1

Baseline Characteristics

	Placebo N = 42			Memantine N = 39		
Characteristics Mean (95% CI)	**bvFTD N = 33**	**SD N = 9**	**All N = 42**	**bvFTD N = 31**	**SD N = 8**	**All N = 39**
Men, (%) *	28 (84.9)	4 (44.4)	32 (76.2)	14 (45.2)	5 (62.5)	19 (48.7)
Age, y	65.6 (62.8, 68.4)	68.6 (63.4, 73.7)	66.2 (63.8, 68.6)	65.6 (62.7, 68.3)	67.0 (62.5, 71.5)	65.8 (63.5, 68.1)
Education, y	15.4 (14.4, 16.4)	15.0 (12.8, 17.2)	15.3 (14.5, 16.2)	15.7 (14.8, 16.7)	15.8 (13.0, 18.5)	15.7 (14.9, 16.6)
Disease duration, y	3.5 (2.6, 4.4)	2.8 (1.3, 4.3)	3.3 (2.6, 4.1)	3.0 (2.1, 4.0)	2.8 (1.6, 3.9)	3.0 (2.2, 3.7)
Weight, lbs.	199.7 (183.8, 215.6)	156.7 (143.0, 170.3)	190.0 (176.3, 203.7)	180.3 (166.0, 194.6)	167.9 (135.4, 200.3)	177.7 (165.1, 190.2)
Primary Outcomes						
NPI	22.2 (16, 28.3)	18.6 (13.8, 23.4)	21.5 (15.7, 27.3)	21.1 (16,26.2)	18.8 (15, 22.6)	20.6 (15.8, 25.4)
CGI	3.3 (3.1, 3.5)	3.3 (3.2, 3.4)	3.3 (3.1,3.5)	3.5 (3.2, 3.8)	3.4 (3.2,3.6)	3.5 (3.2, 3.8)
Secondary Outcomes						
CDR-SB-FTD	4.8 (4.0, 5.6)	3.0 (1.7, 4.3)	4.4 (3.7, 5.1)	5.8 (4.5, 7.1)	3.8 (1.5, 6.0)	5.4 (4.2, 6.5)
FAQ	15.8 (13.2, 18.3)	7.4 (0.9, 13.9)	14.1 (11.6, 16.6)	14.7 (11.9, 17.4)	8.5 (1.1, 15.9)	13.4 (10.8, 16.0)
TFLS	40.2 (37.5, 42.9)	42.1 (36.3, 47.9)	40.6 (38.3, 43.0)	38.3 (34.2, 42.4)	43.8 (39.4, 48.1)	39.4 (36.1, 42.8)
MMSE	25.0 (23.7, 26.3)	25.2 (21.3, 29.1)	25.1 (23.8, 26.3)	24.0 (22.1, 25.8)	25.8 (22.7, 28.8)	24.3 (22.8, 25.9)
EXIT25	17.2 (14.3, 20.1)	16.7 (10.7, 22.6)	17.1 (14.6, 19.6)	17.0 (13.3, 20.7)	14.0 (7.5, 20.5)	16.3 (13.2, 19.4)
Letter fluency	6.5 (5.0, 8.0)	7.9 (4.2, 11.6)	6.8 (5.4, 8.2)	6.1 (4.3, 7.8)	5.6 (4.1, 7.1)	6.0 (4.6, 7.4)
Category fluency	11.2 (5.8, 16.6)	7.5 (1.3, 13.7)	10.2 (6.2, 14.2)	9.1 (5.8, 12.5)	9.0 (4.5, 13.5)	9.1 (6.6, 11.5)
Digit symbol	37.8 (31.3, 44.3)	45.0 (36.6, 53.4)	39.3 (34.0, 44.7)	34.2 (24.6, 43.7)	55.8 (42.5, 69.0)	38.6 (30.3, 46.9)
Digits backwards	3.5 (3.0, 4.0)	4.2 (3.0, 5.4)	3.6 (3.2, 4.1)	3.4 (2.8, 4.0)	4.1 (3.2, 5.1)	3.6 (3.0, 4.1)
Boston Naming Test	12.2 (11.2, 13.2)	6.2 (2.5, 10.0)	10.8 (9.5, 12.2)	12.9 (11.1, 14.7)	7.9 (3.3, 12.4)	11.9 (10.1, 13.6)
UPDRS	3.2 (1.2, 5.1)	3.4 (−1.2, 8.1)	3.2 (1.5, 5.0)	2.9 (0.4, 5.4)	0.9 (−0.6, 2.3)	2.4 (0.5, 4.3)
Tertiary Outcomes						
ZBI 22	32.5 (27.8, 37.3)	31.7 (24.7, 38.6)	32.4 (28.5, 36.2)	28.3 (23.0, 33.7)	30.5 (18.6, 42.4)	28.8 (24.1, 33.4)

P values are for comparison between all placebo and all memantine subjects.

* There were more men in the placebo group at baseline (p = 0.011, Chi square.)

Table 2

Mean differences in longitudinal change from baseline

Measure	Difference	95% CI	P value
Primary outcomes			
NPI	2.2	−3.9, 8.3	0.47
CGIC	0	−0.4, 0.4	0.90
Secondary outcomes Global			
CDR-SB-FTD	0	−0.9, 0.9	0.99
FAQ	−1.5	−4.0, 1.0	0.23
TFLS	0.9	−1.7, 3.5	0.49
Cognitive			
MMSE	0.1	−1.3, 1.5	0.69
EXIT25	−1.2	−3.8, 1.4	0.34
Boston Naming Test	2.2	0.7, 3.6	0.004
Category fluency	0.4	−1.7, 2.4	0.72
Digits backwards	−0.3	−0.8, 0.2	0.28
Digit symbol	8.1	1.1, 15.1	0.024
Letter fluency	−0.2	−1.5, 1.1	0.75
Motor			
UPDRS	−0.3	−3.0, 2.4	0.83
Tertiary outcome			
ZBI 22	1.6	−2.0, 5.3	0.38

Mean difference is placebo - memantine group.

Table 3

Adverse Event Summary

	Placebo		Memantine	
Body Class/Preferred Term	**N**	**%**	**N**	**%**
Body as Whole				
Fatigue	1	2.4	1	2.6
Cognitive Disorders				
Language Problems	0	0.0	3	7.7
Memory Loss	0	0.0	2	5.1
Gastrointestinal Disorders				
Diverticulitis	2	4.8	0	0.0
Nausea	3	7.1	0	0.0
Injury				
Abrasion	0	0.0	2	5.1
Fall	2	4.8	5	12.8
Nervous System Disorders				
Back Pain	0	0.0	2	5.1
Dizziness	2	4.8	2	5.1
Headache	3	7.1	1	2.6
Psychiatric Disorders				
Agitation	2	4.8	0	0.0
Behavioral Rigidity	1	2.4	1	2.6
Inappropriate Sexual Behavior	4	9.5	0	0.0
Insomnia	4	9.5	0	0.0
Obsessive Compulsive Symptoms	1	2.4	2	5.1
Somnolence	1	2.4	1	2.6
Renal and Urinary Disorders				
Urinary Tract Infection	0	0.0	2	5.1
Urinary Frequency	1	2.4	1	2.6
Respiratory Disorders				
Upper Respiratory Infection	0	0.0	2	5.1
Skin and Subcutaneous Tissue Disorders				
Rash	1	2.4	1	2.6

Adverse events (AEs, all severities combined), occurring in two or more individuals (N), in either group combined, and percent of ITT population (%) in each group. AEs occurring in only one individual are not shown. A complete list of adverse events is given in the Supplementary Materials (Supplementary Table 4).