Memantine in patients with frontotemporal lobar degeneration: a multicentre, randomised, double-blind, placebo-controlled trial

Adam L Boxer, David S Knopman, Daniel I Kaufer, Murray Grossman, Chiadi Onyike, Neill Graf-Radford, Mario Mendez, Diana Kerwin, Alan Lerner, Chuang-Kuo Wu, Mary Koestler, Jill Shapira, Kathryn Sullivan, Kristen Klepac, Kristine Lipowski, Jerin Ullah, Scott Fields, Joel H Kramer, Jennifer Merrilees, John Neuhaus, M Marsel Mesulam, Bruce L Miller

Summary

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). We aimed to determine whether memantine is an effective treatment for FTD.

Methods We did a randomised, parallel group, double-blind, placebo-controlled trial of 20 mg memantine taken orally daily for 26 weeks in patients with FTD. Participants met Neary criteria for behavioural variant FTD (bvFTD) or semantic dementia and had characteristic brain atrophy. Use of acetylcholinesterase inhibitors was prohibited. Individuals were randomly assigned to receive either memantine or matched placebo tablets (1:1) in blocks of two and four patients. All patients and study personnel were masked to treatment assignment. Primary endpoints were the change in total NPI score and clinical global impression of change (CGIC) score after 26 weeks and were analysed by intention to treat. This study is registered with Clinicaltrials.gov, number NCT00545974.

Findings Of 100 patients screened, 81 were randomly assigned to receive memantine (39 patients) or placebo (42 patients). Five (6%) patients discontinued, and 76 completed the 26-week treatment. Enrolment numbers were lower than planned because of many patients' preference to take memantine or cholinesterase inhibitors off-label rather than participate in a clinical trial. Memantine treatment had no effect on either the NPI (mean difference 2·2, 95% CI −3·9 to 8·3, p=0·47) or CGIC (mean difference 0·0, −0·4 to 0·4, p=0·90) after 26 weeks of treatment. Memantine was generally well tolerated; however, patients in the memantine group had more frequent cognitive adverse events (six patients) than those in the placebo group (one).

Interpretation Memantine treatment showed no benefit in patients with FTD. These data do not support memantine use in FTD.

Funding Forest Research Institute.

Published **Online** January 2, 2013 http://dx.doi.org/10.1016/S1474-4422(12)70320-4

Memory and Aging Center, Department of Neurology, University of California, San Francisco, CA, USA (A L Boxer MD, M Koestler PhD, K Sullivan BS, K Klepac BS, J Ullah MS, J H Kramer PsyD, J Merrilees PhD, B L Miller MD); **Department of Neurology, Mayo Clinic, Rochester, MN, USA** (D S Knopman MD); **Department of Neurology, University of North Carolina, Chapel Hill, NC, USA** (D I Kaufer MD); **Department of Neurology, University of Pennsylvania, Philadelphia, PA, USA** (M Grossman MD); **Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, Baltimore, MD, USA** (C Onyike MD); **Department of Neurology, Mayo Clinic, Jacksonville, FL, USA** (N Graf-Radford MD); **Department of Neurology, University of California, Los Angeles, CA, USA** (M Mendez MD, J Shapira RN); **Cognitive Neurology and Alzheimer Disease Center of Northwestern University, Chicago, IL, USA** (D Kerwin MD, K Lipowski, M M Mesulam MD); **Department of Neurology, Case-Western University, Cleveland, OH, USA** (A Lerner MD); **Department of Neurology, Texas Tech University, Lubbock, TX, USA** (C-K Wu MD); **Department of Clinical Pharmacy, University of California, San Francisco, CA, USA** (S Fields PharmD); **and Department of Epidemiology and Biostatistics, University of California, San Francisco, CA, USA** (J Neuhaus PhD)

Correspondence to:
Dr Adam L Boxer, UCSF Memory and Aging Center, Sandler Neurosciences Center, 675 Nelson Rising Lane, Suite 190, Box 1207, San Francisco, CA 94158, USA
aboxer@memory.ucsf.edu

Introduction

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

Memantine is approved by the European Medicines Agency and the FDA for the treatment of moderate-to-severe Alzheimer's disease and has also shown beneficial effects in clinical trials of vascular dementia, Parkinson's-related dementias, and dementia of mixed causes (reviewed in Kalia and colleagues[5]). Although the neuropathological changes and underlying neurotransmitter deficits are different in FTD than in Alzheimer's disease, a scientific rationale exists for the use of memantine to treat FTD. First, memantine is believed to act as a non-competitive inhibitor of NMDA receptors, which might be overactivated in various neurodegenerative diseases, including FTD.[5] Second, analyses of data from clinical trials of memantine in Alzheimer's disease showed clear benefits on various abnormal behaviours, as assessed by the neuropsychiatric inventory (NPI).[6] Since many of these behaviours are

prominent features of FTD, memantine might also be predicted to improve these deficits. Third, several open-label treatment studies in bvFTD and semantic dementia have shown symptomatic improvements with memantine treatment.[7,8] In one of these studies,[8] we showed that initiation of memantine treatment was associated with a transient improvement in behaviour as measured by the NPI[9] in patients with bvFTD and semantic dementia.[8] Since the transient improvement in NPI scores might have been attributable to a placebo effect or an effect of memantine treatment, the present study tested the hypothesis that memantine would improve or stabilise behaviour as measured by the NPI and clinical global impression of change (CGIC)[10] compared with placebo, after 26 weeks of treatment.

Methods

Study design and participants

In this multicentre, randomised, double-blind, placebo-controlled trial, we recruited patients from nine US academic dementia research centres with expertise in the diagnosis of FTD (University of California, San Francisco [UCSF] and Los Angeles [UCLA]; Mayo Clinic, Rochester and Jacksonville; Northwestern University Medical Center; Case Western Reserve Medical Center; University of North Carolina; Johns Hopkins University; and University of Pennsylvania). Study visits occurred between Dec 12, 2007, and May 7, 2012. Because this study was a follow-up to a 26-week open-label study[8] of memantine that showed a similar pattern of changes in bvFTD and semantic dementia, but not progressive non-fluent aphasia,[8] the present study only included patients with bvFTD or semantic dementia.[1] Individuals with FTD-motor neuron disease were included if motor impairments did not interfere with study procedures. Individuals had to be aged between 40 and 80 years and have a mini-mental state examination (MMSE) score of 15 or higher at screening. To exclude cases with slowly progressive bvFTD (bvFTD phenocopy), all patients had to have a CT or MRI scan of the brain within 24 months before randomisation consistent with a diagnosis of bvFTD or semantic dementia.[11] All patients had a reliable caregiver who could accompany them to study visits. Exclusion criteria included a diagnosis of progressive non-fluent aphasia, and use of memantine, acetylcholinesterase inhibitors, antipsychotic drugs, valproate, lithium, or benzodiazepines within 4 weeks before randomisation. Use of acetylcholinesterase inhibitors was prohibited because of potential confounding effects on memantine efficacy and reported adverse reactions in FTD.[12,13] If behavioural 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 1 month preceding randomisation. Another exclusion criterion was the evidence of disorders that preclude diagnosis of FTD.[1] Written informed consent was obtained from the patient and their caregiver in accordance with local institutional review board (IRB) regulations.

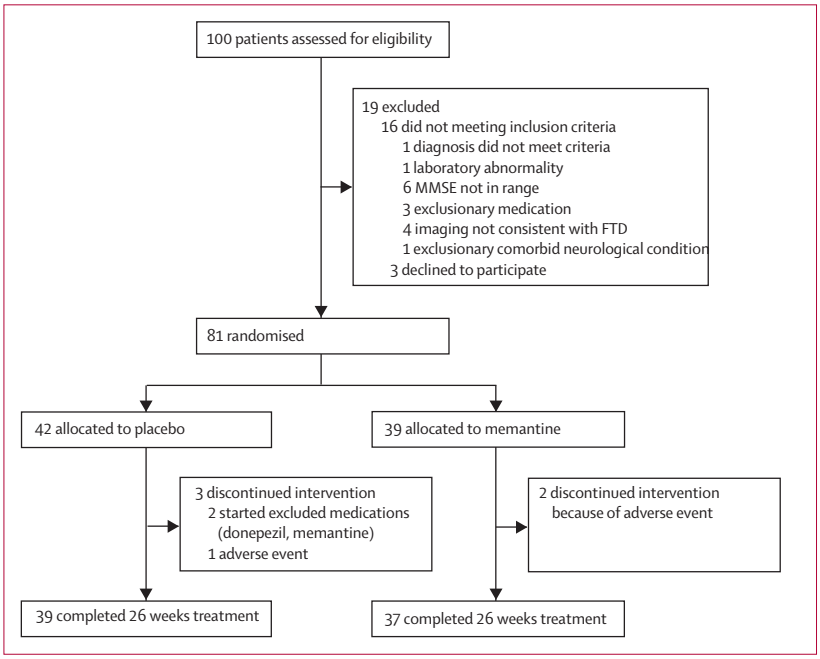

Figure 1: **Trial profile**
FTD=frontotemporal lobar degeneration.

Randomisation and masking

Patients were randomly assigned to receive twice daily either memantine 10 mg or placebo (1:1). Randomisation codes were generated by an unmasked UCSF pharmacist (SF) with the Excel (Microsoft Office) random number generator in blocks of two and four patients. Kits were given sequential numbers that corresponded to the randomisation key that was maintained in a secure location by the UCSF Investigational Pharmacy. When randomised, each successive participant was assigned by the electronic Clinical Trial Management System to the next numbered kit in sequence at each site. Tablets containing memantine 10 mg or placebo with no memantine (identical tablets) were packaged into kits (one per patient) of several blister packs (1 week of treatment per pack). All patients and study personnel were masked to treatment assignment.

Procedures

Every patient participated in six study visits over roughly 35 weeks. After the screening visit, a randomisation or 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 4. Patients returned at weeks 6, 12, and 26 (or early termination) for safety and efficacy assessments.

Additionally to the in-person visits, on weeks 3, 9, and 18, individuals received a phone call to assess adverse events and study medication compliance. After the visit on week 26, 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. We assessed all outcome measures at baseline and at week 26, with a subset of measures obtained at weeks 6 and 12. We grouped adverse events by Medical Dictionary for Regulatory Activities (MedRA) system organ class. Serious adverse events were defined as those leading to hospital admission or death.

Outcomes

The primary outcomes were the NPI and CGIC. The NPI is a measure that assesses 12 neuropsychiatric abnormalities that reveal 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 behavioural 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 activities of daily living;[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 (data for backward digit span and modified trails not shown).[14] Tertiary outcomes were the Zarit burden interview (ZBI 22), a 22 item questionnaire used to measure caregiver burden,[18] and subject weight in kg (since patients with FTD often gain weight).

For more on **MedRA** see http://www.meddramsso.com

Statistical analysis

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

	Placebo			Memantine		
	bvFTD (n=33)	Semantic dementia (n=9)	All (n=42)	bvFTD (n=31)	Semantic dementia (n=8)	All (n=39)
Characteristics						
Men (%)*	28 (85%)	4 (44%)	32 (76%)	14 (45%)	5 (62%)	19 (49%)
Age (years)	65·6 (62·8 to 68·4)	68·6 (63·4 to 73·7)	66·2 (63·8 to 68·6)	65·6 (62·7 to 68·3)	67·0 (62·5 to 71·5)	65·8 (63·5 to 68·1)
Education (years)	15·4 (14·4 to 16·4)	15·0 (12·8 to 17·2)	15·3 (14·5 to 16·2)	15·7 (14·8 to 16·7)	15·8 (13·0 to 18·5)	15·7 (14·9 to 16·6)
Disease duration (years)	3·5 (2·6 to 4·4)	2·8 (1·3 to 4·3)	3·3 (2·6 to 4·1)	3·0 (2·1 to 4·0)	2·8 (1·6 to 3·9)	3·0 (2·2 to 3·7)
Weight (kg)	90·6 (83·4 to 97·8)	71·1 (64·9 to 77·2)	86·2 (80·0 to 92·4)	81·8 (75·3 to 88·3)	76·2 (61·4 to 90·9)	80·6 (74·9 to 86·3)
Primary outcomes						
NPI	22·2 (16 to 28·3)	18·6 (13·8 to 23·4)	21·5 (15·7 to 27·3)	21·1 (16 to 26·2)	18·8 (15 to 22·6)	20·6 (15·8 to 25·4)
CGIC	3·3 (3·1 to 3·5)	3·3 (3·2 to 3·4)	3·3 (3·1 to 3·5)	3·5 (3·2 to 3·8)	3·4 (3·2 to 3·6)	3·5 (3·2 to 3·8)
Secondary outcomes						
CDR-SB-FTD	4·8 (4·0 to 5·6)	3·0 (1·7 to 4·3)	4·4 (3·7 to 5·1)	5·8 (4·5 to 7·1)	3·8 (1·5 to 6·0)	5·4 (4·2 to 6·5)
FAQ	15·8 (13·2 to 18·3)	7·4 (0·9 to 13·9)	14·1 (11·6 to 16·6)	14·7 (11·9 to 17·4)	8·5 (1·1 to 15·9)	13·4 (10·8 to 16·0)
TFLS	40·2 (37·5 to 42·9)	42·1 (36·3 to 47·9)	40·6 (38·3 to 43·0)	38·3 (34·2 to 42·4)	43·8 (39·4 to 48·1)	39·4 (36·1 to 42·8)
MMSE	25·0 (23·7 to 26·3)	25·2 (21·3 to 29·1)	25·1 (23·8 to 26·3)	24·0 (22·1 to 25·8)	25·8 (22·7 to 28·8)	24·3 (22·8 to 25·9)
EXIT25	17·2 (14·3 to 20·1)	16·7 (10·7 to 22·6)	17·1 (14·6 to 19·6)	17·0 (13·3 to 20·7)	14·0 (7·5 to 20·5)	16·3 (13·2 to 19·4)
Letter fluency	6·5 (5·0 to 8·0)	7·9 (4·2 to 11·6)	6·8 (5·4 to 8·2)	6·1 (4·3 to 7·8)	5·6 (4·1 to 7·1)	6·0 (4·6 to 7·4)
Category fluency	11·2 (5·8 to 16·6)	7·5 (1·3 to 13·7)	10·2 (6·2 to 14·2)	9·1 (5·8 to 12·5)	9·0 (4·5 to 13·5)	9·1 (6·6 to 11·5)
Digit symbol	37·8 (31·3 to 44·3)	45·0 (36·6 to 53·4)	39·3 (34·0 to 44·7)	34·2 (24·6 to 43·7)	55·8 (42·5 to 69·0)	38·6 (30·3 to 46·9)
Digits backwards	3·5 (3·0 to 4·0)	4·2 (3·0 to 5·4)	3·6 (3·2 to 4·1)	3·4 (2·8 to 4·0)	4·1 (3·2 to 5·1)	3·6 (3·0 to 4·1)
Boston naming test	12·2 (11·2 to 13·2)	6·2 (2·5 to 10·0)	10·8 (9·5 to 12·2)	12·9 (11·1 to 14·7)	7·9 (3·3 to 12·4)	11·9 (10·1 to 13·6)
UPDRS	3·2 (1·2 to 5·1)	3·4 (-1·2 to 8·1)	3·2 (1·5 to 5·0)	2·9 (0·4 to 5·4)	0·9 (-0·6 to 2·3)	2·4 (0·5 to 4·3)
Tertiary outcomes						
ZBI 22	32·5 (27·8 to 37·3)	31·7 (24·7 to 38·6)	32·4 (28·5 to 36·2)	28·3 (23·0 to 33·7)	30·5 (18·6 to 42·4)	28·8 (24·1 to 33·4)

Data are mean (95% CIs) unless otherwise stated. bvFTD=behavioural variant frontotemporal dementia. NPI=neuropsychiatric inventory. CGIC=clinical global impression of change. CDR-SB-FTD=clinical dementia rating sum of boxes modified to better capture FTD-related deficits. FAQ=functional activities questionnaire. TFLS=Texas functional living scale. MMSE=mini-mental state examination. EXIT25=executive interview. UPDRS=modified unified Parkinson's disease rating scale. ZBI 22=Zarit burden interview. *The placebo group had more men at baseline than did the memantine group (p=0·011, χ^2).

Table 1: **Baseline characteristics**

calculations for two sample *t* tests (α=0·05) with an SD of 2·2 (half of 4·4 from Boxer and colleagues[8]) show that a sample of 65 patients per group would provide power greater than 80% to detect this difference. The planned enrolment for the study was 140 participants.

We analysed primary and secondary outcomes using an intention-to-treat approach that included all patients 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 every patient, 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. We repeated analyses using sex as a covariate. It was decided post hoc to reduce the CGIC values to "improved, no change, or worsened" because of the very few responses outside the middle three values. We compared CGIC values at week 26 using a Mann-Whitney *U* test. We did exploratory analyses in each FTD subtype and observed cases (patients who completed all four efficacy visits) to investigate potential sources of bias in the intention-to-treat analyses. Finally, we compared differences in outcome measures at individual timepoints using least squares means with a two-sample *t* test, and analysed differences in frequencies of adverse events using χ^2 tests. Analyses were done with SAS 9.3 (SAS Inc, Cary, NC) or Stata 12 (StataCorp, College Station, TX). This study is registered with Clinicaltrials.gov, number NCT00545974.

See Online for appendix

	Difference (95% CI)	p value
Primary outcomes		
NPI	2·2 (–3·9 to 8·3)	0·47
CGIC	0·0 (–0·4 to 0·4)	0·90
Secondary outcomes		
Functional		
CDR-SB-FTD	0·0 (–0·9 to 0·9)	0·99
FAQ	–1·5 (–4·0 to 1·0)	0·23
TFLS	0·9 (–1·7 to 3·5)	0·49
Cognitive		
MMSE	0·1 (–1·3 to 1·5)	0·69
EXIT25	–1·2 (–3·8 to 1·4)	0·34
Letter fluency	–0·2 (–1·5 to 1·1)	0·75
Category fluency	0·4 (–1·7 to 2·4)	0·72
Digit symbol	8·1 (1·1 to 15·1)	0·024
Digits backwards	–0·3 (–0·8 to 0·2)	0·28
Boston naming test	2·2 (0·7 to 3·6)	0·004
Motor		
UPDRS	–0·3 (–3·0 to 2·4)	0·83
Tertiary outcome		
ZBI 22	1·6 (–2·0 to 5·3)	0·38

Mean difference is placebo group minus memantine group. NPI=neuropsychiatric inventory. CGIC=clinical global impression of change. CDR-SB-FTD=clinical dementia rating sum of boxes. FAQ=functional Activities Questionnaire. TFLS=Texas functional living scale. MMSE=mini-mental state examination. EXIT25=executive interview. UPDRS=modified unified Parkinson's disease rating scale. ZBI 22=Zarit burden interview.

Table 2: **Mean differences in longitudinal change from baseline**

Role of the funding source

This was an investigator-initiated study that was designed by the authors and managed by the UCSF Memory and Aging Center Clinical Trials Program. The study was funded by Forest Research Institute (FRI), the research arm of Forest Laboratories, the company that manufactures and markets memantine for treatment of Alzheimer's Disease in the US. Additionally to funding, FRI provided memantine and matched placebo tablets to the UCSF Investigational Pharmacy, which created blister packs to improve compliance, monitored lot expiration, and resupplied sites. FRI had no role in study design, data collection, analysis or interpretation. All data were available to and the manuscript was written by the corresponding author with assistance from other authors. FRI had no role in manuscript preparation.

Results

Of the 100 patients assessed for eligibility, 81 patients (64 with bvFTD and 17 with semantic dementia) were randomly assigned to memantine (39 patients) or placebo (42 patients; figure 1). Five patients (two given memantine, three given placebo) discontinued treatment before the end of the study (figure 1). Despite randomisation, the placebo group contained more men than the memantine group (table 1; p=0·01). There were no other baseline differences in demographic variables, concomitant medication use, or outcome measures (table 1, appendix). 17 (44%) of 39 patients given memantine and 13 (31%) of 42 patients given placebo took 100% of the study medication (p=0·24); for the remaining patients, 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.

In the intention-to-treat analysis, the change in total NPI or CGIC scores after 26 weeks did not differ between the memantine and placebo groups (table 2, figure 2). A post-hoc adjustment for baseline sex differences did not alter the result (appendix). The CGIC showed that at week 26, 27 patients worsened, eight remained stable, and two improved in the memantine group, whereas 29 patients worsened, eight remained stable, and four improved in the placebo group (p=0·90; figure 2).

We noted no treatment effect on the functional outcome measures, the CDR-SB-FTD, FAQ, and TFLS (table 2). CDR-SB-FTD scores increased similarly in both groups by 1·5 (95% CI 0·8–2·1) points over 26 weeks (figure 3). Performance on the FAQ and TFLS declined similarly in the placebo and memantine groups (table 2).

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). The groups did not differ on other neuropsychological composite (MMSE and EXIT25) and individual test (letter fluency, category fluency, digit symbol, digits backwards, Boston naming test) scores (table 2). Consistent with the effects we observed on neuropsychological tests, we noted numerically more cognitive adverse events (confusion, memory loss, language disorders) in the memantine group than the placebo group (six *vs* one; p=0·056, table 3, appendix) whereas the opposite was true for psychiatric adverse events (eight *vs* 16; p=0·03). Two individuals experienced a serious adverse event in the placebo group (diverticulitis leading to hospital admission and vasovagal episode) and one individual experienced two serious adverse events in the memantine group (right-sided facial weakness and loss of consciousness, both leading to hospital admission). Serious adverse events were not judged to be related to treatment. UPDRS (table 2) and safety assessments did not differ between groups (data not shown); appendix). Since only three patients began an antipsychotic medication during the study (appendix), time to antipsychotic use was not analysed. With respect to tertiary outcomes, treatment did not have an effect on caregiver burden (ZBI, p=0·13) or change in weight (data not shown).

Because we had previously observed a transient improvement in NPI scores in an open-label memantine treatment study,[8] we examined in a post-hoc analysis the differences in NPI scores at individual timepoints and noted a transient improvement (mean difference 5·9, 95% CI 4·2–7·6) at week 6 (p=0·01) that converged with changes in the placebo group at weeks 12 and 26 (p>0·30; figure 2).

We also investigated whether the effects we noted on the BNT and digit symbol tests were related to FTD subtype. When analysed separately, BNT performance was worse in both the bvFTD and semantic dementia groups after 26 weeks (appendix). On the digit symbol test, the placebo group showed a small improvement in performance after 26 weeks of treatment, whereas the memantine group worsened (MD 8·1, 95% CI 1·1–15·1, p=0·001; figure 4).

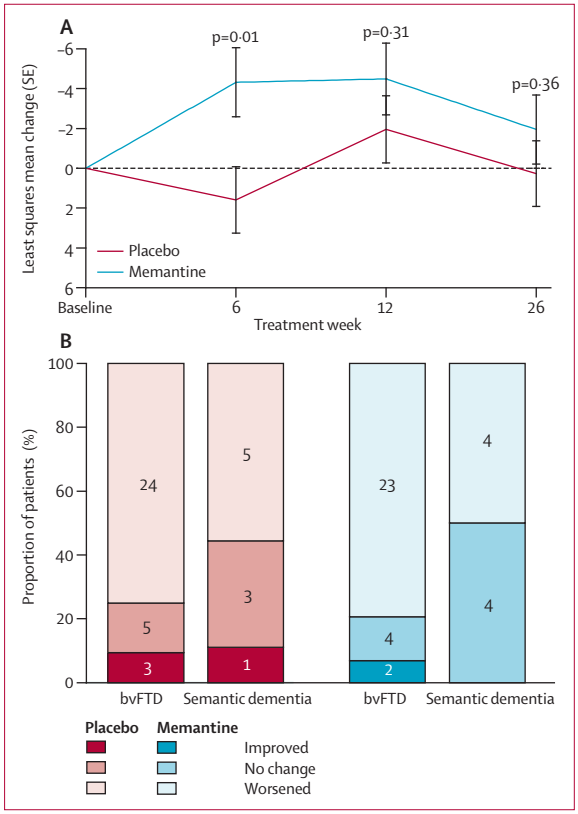

Figure 2: **Primary outcome variables**
NPI=neuropsychiatric inventory. CGIC=clinician's global impression of change. (A) Change from baseline of total NPI scores from the intention-to-treat population are shown with p values for a paired *t* test at every study visit. Groups did not differ in the repeated measures analysis (p=0·47). (B) CGIC values are shown at week 26 for 76 patients who completed this visit. Only improved (includes slightly improved category), no change, and worsened (includes slightly worsened category) are shown since no other values were recorded. No difference was noted in CGIC distributions with a Mann Whitney *U* test (p=0·90).

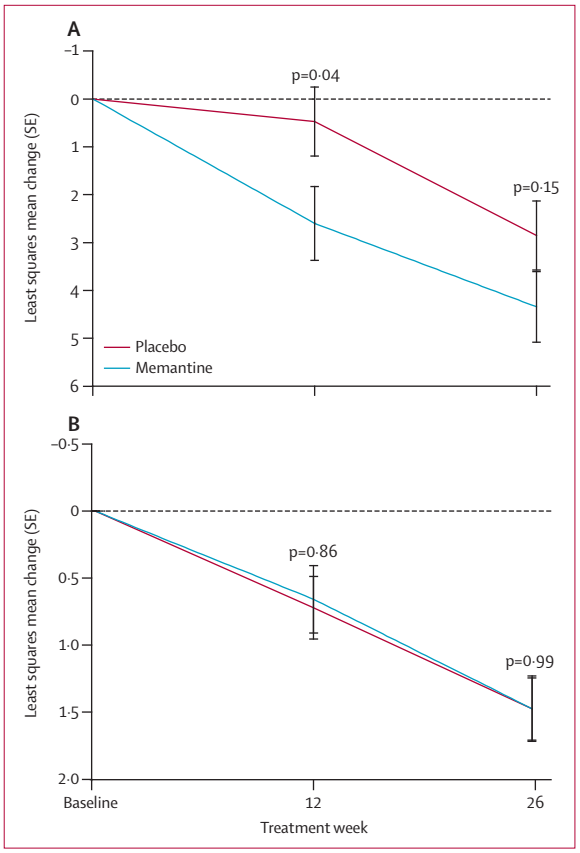

Figure 3: **Functional rating scales**
(A) Change from baseline functional activities questionnaire (FAQ) scores in the intention-to-treat population. (B) Change from baseline in clinical dementia rating sum of boxes (CDR-SB-FTD) scores in the intention-to-treat population.

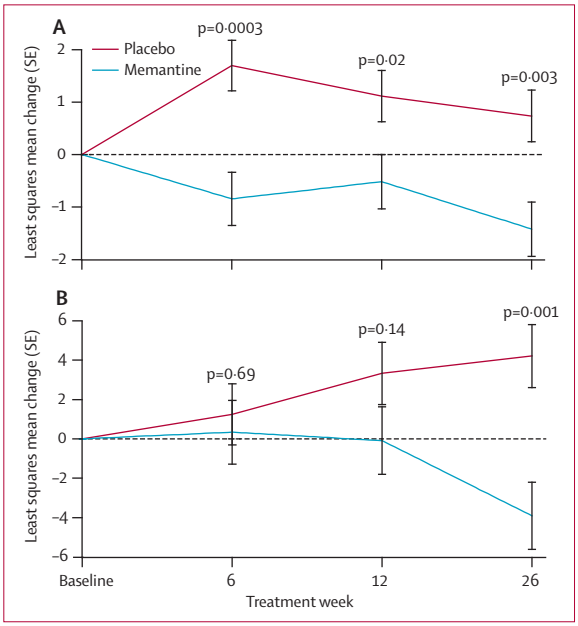

Figure 4: **Neuropsychological tests**
(A) Change from baseline modified Boston naming test (BNT) in the intention-to-treat population. (B) Change from baseline digit symbol substitution test scores in the intention-to-treat population.

	Placebo (n=42)	Memantine (n=39)
Body as whole		
Fatigue	1 (2%)	1 (3%)
Cognitive disorders		
Language problems	0	3 (8%)
Memory loss	0	2 (5%)
Gastrointestinal disorders		
Diverticulitis	2 (5%)	0
Nausea	3 (7%)	0
Injury		
Abrasion	0	2 (5%)
Fall	2 (5%)	5 (13%)
Nervous system disorders		
Back pain	0	2 (5%)
Dizziness	2 (5%)	2 (5%)
Headache	3 (7%)	1 (3%)
Psychiatric disorders		
Agitation	2 (5%)	0
Behavioural rigidity	1 (2%)	1 (3%)
Inappropriate sexual behaviour	4 (10%)	0
Insomnia	4 (10%)	0
Obsessive compulsive symptoms	1 (2%)	2 (5%)
Somnolence	1 (2%)	1 (3%)
Renal and urinary disorders		
Urinary tract infection	0	2 (5%)
Urinary frequency	1 (2%)	1 (3%)
Respiratory disorders		
Upper respiratory infection	0	2 (5%)
Skin and subcutaneous tissue disorders		
Rash	1 (2%)	1 (3%)

Data are number of patients (%). Adverse events (all severities combined) occurring in two or more individuals in either group combined, and percent of intention-to-treat population in each group. Adverse events occurring in only one individual are not shown. A complete list of adverse events is given in the appendix.

Table 3: **Adverse event summary by system organ class and preferred term**

Discussion

We noted 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 suggestive increase in cognitive adverse events compared with the placebo group. 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 patients with FTD, our results do not support a claim of benefit for memantine treatment in FTD. Since about 30% of patients with bvFTD in the USA take memantine,[4] our findings have immediate implications in public health.

Our results are similar to those from a recent 52-week randomised placebo-controlled trial[20] of memantine in 49 patients with bvFTD that also showed no benefit on the primary outcome, the clinician's interview-based impression of change (ie, CIBICplus; similar to the CGIC) or the NPI.[20] Similar to the previous study, a major limitation of the present study was that we failed to enrol the planned number of patients, which might have limited our ability to detect a treatment effect. This under-enrolment was due to many patients' preference to take memantine (and in many cases an acetylcholinesterase inhibitor as well) rather than participate in a clinical trial during which they risked being randomly assigned to placebo. Unfortunately, altering the enrolment 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 about the efficacy of memantine when recruiting patients. A second limitation of the study was the small size of the semantic dementia group, which limits the generalisability of our results to this FTD syndrome. Finally, since this trial was designed, several rating scales that better capture FTD-specific behaviours have been developed that might have been more sensitive to potential benefits of memantine than those we used.[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 6 weeks of treatment that was similar in magnitude and timecourse to what we observed in a

previous open-label treatment study (34 patients with bvFTD and semantic dementia)[8] suggesting that the pattern of changes observed on the NPI (figure 2) did not arise by chance. Second, we did a study-level meta-analysis, combining 6-month CGIC data from the current study and 12-month CIBICplus data presented in the report from the previous bvFTD clinical trial,[20] for a combined total of 64 patients receiving placebo and 55 receiving memantine.This meta-analysis found no difference between placebo and memantine on the combined global impression (mean difference 0·082, 95% CI –0·18 to 0·34; p=0·553). Third, we observed worse visuomotor (digit symbol test) and naming function in the memantine group in the pre-specified analyses (table 2). Consistent with these findings, the memantine group had a greater number of cognitive adverse events than did the placebo group (table 3). Finally, the rate of decline in CDR-SB-FTD scores was identical in both groups, and numerically, FAQ scores seemed to decrease more rapidly in the memantine group at week 12 (figure 3), although, similar to the analysis of NPI scores at 6 weeks, this was an exploratory finding that should be interpreted with caution.

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

Our study suggests that patients with FTD might respond differently to memantine than do patients with other forms of dementia, underscoring the importance of accurate diagnosis. In moderate-to-severe Alzheimer's disease, memantine has shown 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 Alzheimer's disease pathological changes, which could explain this finding. Clinical trials of memantine for vascular dementia also suggest a modest benefit on cognition in patients with mild-to-moderate impairment.[23] Results from two clinical trials[24,25] of memantine in Parkinson's-related dementia showed efficacy for treatment of cognitive and behavioural symptoms.[24,25] We speculate that the absence of benefit of memantine treatment in FTD could indicate a different pattern of neurotransmitter abnormalities in this disorder.[3]

This is, to the best of our knowledge, the largest randomised placebo-controlled trial done in FTD so far (panel). In addition to the implications for the current treatment of FTD, we show that clinical trials are feasible in this disorder. Since about half of all FTD cases have underlying tau pathological changes, as in Alzheimer's disease, it has been suggested that tau-directed therapeutics might eventually be used in both disorders.[26] We showed that the rate of decline as measured by the CDR-SB-FTD was about twice as fast as has been reported for the CDR-SB in Alzheimer's disease.[27] The more rapid progression of FTD as compared with Alzheimer's disease might allow for faster clinical trials in FTD than in Alzheimer's disease 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, stressing the urgent need to develop more effective FTD therapeutics.

***Panel:* Research in context**

Systematic review

We searched PubMed for reports published between 1946 to November, 2012, 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 randomised, placebo-controlled trials in frontotemporal dementia (FTD) or a related disorder that involved memantine. We identified one previous randomised trial in behavioural variant FTD (bvFTD)[21] and one in primary progressive aphasia (PPA; not differentiated by subtype).[22] We did a study-level meta-analysis, combining 6-month clinical global impression of change data from the current study and 12-month data from table 4 from the previous behavioural variant FTD clinical trial,[21] but not the primary progressive aphasia trial because it was not limited to semantic dementia, for a combined total of 64 patients in the placebo group and 55 patients in the memantine group.

Interpretation

No difference was noted between placebo and memantine on the combined global impression scores (mean difference=0·082, 95% CI –0·18 to 0·34; p=0·553, Mann-Whitney *U*). This study confirms the absence of benefit of memantine for treatment of FTD.

Contributors

ALB obtained funding, designed and supervised the study, and wrote the report. DSK, DIK, MG, CO, NG-R, and MM participated in study design, enrolled patients at their sites, reviewed and made substantive comments on the report. DK enrolled patients at her site, and reviewed and made substantive comments on the report. AL and C-KW participated in study design, enrolled patients at their sites, reviewed and made substantive comments on the report. MK participated in study design, helped supervise study conduct and reviewed the report. JS participated in study design, helped supervise enrolment at her site and reviewed the report. KS and KK assisted with study conduct, data collection, cleaning, and analysis. KL assisted with patient recruitment and data collection. JU performed the statistical analysis. SF created the medication administration, randomisation, and blinding scheme, and supervised all aspects of study medication management. JHK participated in study design, including selection of the neuropsychological tests, and helped with their interpretation. JM participated in patient recruitment and evaluation, and reviewed the final report. JN participated in study design, including the statistical analysis plan; he supervised JU in her statistical analysis. MMM participated in patient recruitment and evaluation, reviewed the final report, and provided substantive feedback. BLM participated in conceptualisation of the study, recruiting patients, and revising the report.

Conflicts of interest

ALB has been a consultant for Plexikkon, Phloronol, Registrat-Mapi, Envivo, Neurophage, TauRx, Archer, and Iperian; receives research support from Allon Therapeutics, Bristol-Myers Squibb, EnVivo, Janssen, Forest, Pfizer, and Genentech; and is funded by NIH grants R01AG038791, R01AG031278, the John Douglas French Foundation, the Alzheimer's Drug Discovery Foundation, the Association for Frontotemporal Degeneration, the Silicon Valley Foundation, the Agouron Institute, the Tau Research Consortium and the Bluefield Project to Cure Frontotemporal Dementia. DSK served on a Data Safety Monitoring Board for Lilly Pharmaceuticals; served as a consultant to TauRx; was an investigator in clinical trials sponsored by Baxter, Elan Pharmaceuticals, and Forest Pharmaceuticals; and receives research support from the NIH. AL has received research grant support from Allon Therapeutics, Ceregene, and Baxter, and has been a consultant for Eli Lilly and Siemens PETNET. BLM serves as board member on the John Douglas French Alzheimer's Foundation and Larry L Hillblom Foundation; serves as a consultant for TauRx, 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 California. All other authors declare that they have no conflicts of interest.

Acknowledgments

This was managed by the UCSF Memory and Aging Center Clinical Trials Program. The study was funded by Forest Research Institute (FRI), the research arm of Forest Laboratories in response to a grant application from ALB. Additionally to funding, FRI provided memantine and matched placebo tablets to the UCSF Investigational Pharmacy which created blister packs to improve compliance, monitored lot expiration and resupplied sites. We thank Heidi Kirsch, Michael Greicius, Catherine Lomen-Hoerth, and Ron Finley for their service on the Data Safety Monitoring Board.

References

1 Neary D, Snowden JS, Gustafson L, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology* 1998; **51:** 1546–54.

2 Rosen HJ, Allison SC, Ogar JM, et al. Behavioral features in semantic dementia vs other forms of progressive aphasias. *Neurology* 2006; **67:** 1752–56.

3 Huey ED, Putnam KT, Grafman J. A systematic review of neurotransmitter deficits and treatments in frontotemporal dementia. *Neurology* 2006; **66:** 17–22.

4 Hu B, Ross L, Neuhaus J, et al. Off-label medication use in frontotemporal dementia. *Am J Alzheimers Dis Other Demen* 2010; **25:** 128–33.

5 Kalia LV, Kalia SK, Salter MW. NMDA receptors in clinical neurology: excitatory times ahead. *Lancet Neurol* 2008; **7:** 742–55.

6 Cummings JL, Schneider E, Tariot PN, Graham SM. Behavioral effects of memantine in Alzheimer disease patients receiving donepezil treatment. *Neurology* 2006; **67:** 57–63.

7 Swanberg MM. Memantine for behavioral disturbances in frontotemporal dementia: a case series. *Alzheimer Dis Assoc Disord* 2007; **21:** 164–66.

8 Boxer AL, Lipton AM, Womack K, et al. An open label study of memantine treatment in 3 subtypes of frontotemporal lobar degeneration. *Alzheimer Dis Assoc Disord* 2009; **23:** 211–17.

9 Cummings JL. The Neuropsychiatric Inventory: assessing psychopathology in dementia patients. *Neurology* 1997; **48:** S10–16.

10 Schneider LS, Olin JT, Doody RS, et al. Validity and reliability of the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change. The Alzheimer's Disease Cooperative Study. *Alzheimer Dis Assoc Disord* 1997; **11** (suppl 2)**:** S22–32.

11 Kipps CM, Nestor PJ, Dawson CE, Mitchell J, Hodges JR. Measuring progression in frontotemporal dementia: implications for therapeutic interventions. *Neurology* 2008; **70:** 2046–52.

12 Tariot PN, Farlow MR, Grossberg GT, Graham SM, McDonald S, Gergel I. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. *JAMA* 2004; **291:** 317–24.

13 Mendez MF, Shapira JS, McMurtray A, Licht E. Preliminary findings: behavioral worsening on donepezil in patients with frontotemporal dementia. *Am J Geriatr Psychiatry* 2007; **15:** 84–87.

14 Knopman DS, Kramer JH, Boeve BF, et al. Development of methodology for conducting clinical trials in frontotemporal lobar degeneration. *Brain* 2008; **131:** 2957–68.

15 Pfeffer RI, Kurosaki TT, Harrah CH Jr, Chance JM, Filos S. Measurement of functional activities in older adults in the community. *J Gerontol* 1982; **37:** 323–29.

16 Cullum CM, Saine K, Chan LD, Martin-Cook K, Gray KF, Weiner MF. Performance-based instrument to assess functional capacity in dementia: the Texas Functional Living Scale. *Neuropsychiatry Neuropsychol Behav Neurol* 2001; **14:** 103–08.

17 Royall DR, Mahurin RK, Gray KF. Bedside assessment of executive cognitive impairment: the executive interview. *J Am Geriatr Soc* 1992; **40:** 1221–26.

18 Bedard M, Molloy DW, Squire L, Dubois S, Lever JA, O'Donnell M. The Zarit Burden Interview: a new short version and screening version. *Gerontologist* 2001; **41:** 652–57.

19 Cohen J. Statistical power analysis for the behavioral sciences. 2nd edn. Hillsdale, NJ: L Erlbaum Associates, 1988.

20 Vercelletto M, Boutoleau-Bretonniere C, Volteau C, et al. Memantine in behavioral variant frontotemporal dementia: negative results. *J Alzheimer Dis* 2011; **23:** 749–59.

21 Boxer AL, Gold M, Huey E, et al. The advantages of frontotemporal degeneration drug development (part 2 of frontotemporal degeneration: The next therapeutic frontier). *Alzheimers Dement* 2012; published online Oct 9. http://dx.doi.org/10.1016/j.jalz.2012.03.003.

22 Johnson NA, Rademaker A, Weintraub S, Gitelman D, Wienecke C, Mesulam M. Pilot trial of memantine in primary progressive aphasia. *Alzheimer Dis Assoc Disord* 2010; **24:** 308.

23 Kavirajan H, Schneider LS. Efficacy and adverse effects of cholinesterase inhibitors and memantine in vascular dementia: a meta-analysis of randomised controlled trials. *Lancet Neurol* 2007; **6:** 782–92.

24 Aarsland D, Ballard C, Walker Z, et al. Memantine in patients with Parkinson's disease dementia or dementia with Lewy bodies: a double-blind, placebo-controlled, multicentre trial. *Lancet Neurol* 2009; **8:** 613–18.

25 Emre M, Tsolaki M, Bonuccelli U, et al. Memantine for patients with Parkinson's disease dementia or dementia with Lewy bodies: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2010; **9:** 969–77.

26 Boxer AL, Gold M, Huey E, et al. Frontotemporal degeneration, the next therapeutic frontier: molecules and animal models for frontotemporal degeneration drug development. *Alzheimers Dement* 2012; published online Oct 5. http://dx.doi.org/10.1016/j.jalz.2012.03.002.

27 Williams MM, Storandt M, Roe CM, Morris JC. Progression of Alzheimer's disease as measured by Clinical Dementia Rating Sum of Boxes scores. *Alzheimers Dement* 2012; published online Aug 1. http://dx.doi.org/10.1016/j.jalz.2012.01.005.