

Efficacy of memantine on neuropsychiatric symptoms associated with the severity of behavioral variant frontotemporal dementia: A six-month, open-label, self-controlled clinical trial

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Abstract. Previous studies have focused on the curative effects of memantine in patients with mild-to-moderate frontotemporal lobar degeneration (FTLD); however, its benefits in patients with moderate-to-severe FTLD have not been investigated. The present study explores the behavioral, cognitive and functional effects of memantine on behavioral variant frontotemporal dementia (bvFTD) in patients with mild and moderate-to-severe stage bvFTD. A total of 42 patients with bvFTD completed a 6-month treatment plan of 20 mg memantine daily in an open-label, self-controlled clinical trial. Patients were divided into two groups according to their Mini-Mental State Examination (MMSE) score: Mild (score, 21-26); and moderate-to-severe (score, 4-20). Primary endpoints included Neuropsychiatric Inventory Questionnaire (NPI-Q) and Clinic Dementia Rating (CDR) scores, and secondary endpoints comprised Neuropsychiatric Inventory Caregiver Distress Scale (NPI-D), MMSE, Montreal Cognitive Assessment (MoCA), Activity of Daily Life (ADL) and Hamilton Depression Rating Scale (HAMD) scores. Memantine treatment had no effect on overall NPI-Q scores, with the exception of the agitation subdomain in all patients with bvFTD. However, patients with moderate-to-severe bvFTD exhibited a better performance than patients with mild bvFTD,

demonstrated by improved NPI-Q total scores and subscales of agitation, depression, apathy and disinhibition. In the moderate-to-severe group, CDR and HAMD scores remained stable, but MMSE, MoCA and ADL scores were reduced after 6 months of treatment. Memantine was well-tolerated in patients. In conclusion, patients with moderate-to-severe bvFTD responded significantly better to memantine in comparison to patients with mild bvFTD with regard to their neuropsychiatric scores, while memantine did not present any cognitive or functional benefits in patients with mild bvFTD. A randomized, double-blind, placebo-controlled clinical trial with a larger number of patients is required to verify these promising results for patients with moderate-to-severe bvFTD.

Introduction

Frontotemporal lobar degeneration (FTLD) is increasingly recognized as a prevalent cause of dementia, particularly in individuals <65 years old at the time of diagnosis (1). FTLD encompasses a variety of clinical syndromes with marked behavioral, frontal executive and language symptoms that can be differentiated into the following three clinical syndromes: Behavioral variant frontotemporal dementia (bvFTD), semantic dementia (SD) and progressive non-fluent aphasia (PNFA); these three phenotypes have characteristic clinical manifestations and different patterns of brain atrophy, and are histopathologically heterogeneous (2,3). This creates challenges for the establishment of an optimal pharmacological disease management model. To date, the U.S. Food and Drug Administration (FDA) has not approved any pharmacological treatments that specifically target FTLD and alter the course of the disease (4).

Memantine is a moderate-affinity, non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor and is an FDA-approved treatment for moderate-to-severe Alzheimer's disease (AD) (5). However, a growing body of clinical evidence suggests that the beneficial effect of memantine is not limited to AD. For example, it has beneficial effects in Parkinson's disease-related forms of dementia and other mixed causes of

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dementia (6). In addition, memantine has been demonstrated to ease or improve behavioral and cognitive manifestations of these forms of dementia, in particular various behavioral disturbances (irritability, agitation, aggression and difficulty eating) (7-9).

Previously reviewed studies have observed that NMDA receptors are upregulated in FTLN and suggest that aberrant glutamatergic neurotransmission and glutamate excitotoxicity mediating cellular dysfunction may be implicated in the pathogenesis of FTLN (10). Therefore, it is hypothesized that memantine may be useful for treating the symptoms of FTLN.

Data from a number of clinical trials using memantine to treat mild-to-moderate FTLN [Mini-Mental State Examination (MMSE) score, ≥ 15 ; average Clinical Dementia Rating (CDR), < 2] have been published. In a small case series, memantine was observed to have beneficial effects on the total Neuropsychiatric Inventory (NPI) score, in particular improving the apathy subscale scores, and the level of agitation and anxiety (11). In an open-label study, a transient improvement of the total NPI score was observed in patients with FTLN undergoing memantine treatment (12). In addition, it was reported in one case of FTLN that symptoms of apathy improved in response to treatment with memantine (13). Furthermore, memantine was demonstrated to elevate cortical metabolic activities in the frontal and temporal regions, and in the salience network hubs in FTLN (14,15), thereby improving the quality of life of patients with FTLN and their families (12). These studies highlight the potential clinical applications of memantine in FTLN; however, a randomized controlled trial for memantine demonstrated little efficacy in the treatment of FTLN, and the results suggested that it may even hasten cognitive decline (16,17). This suggests that the drug should not be prescribed to patients with FTLN.

FTLN can be misdiagnosed as a mental illness, as a number of patients with FTLN may display significant personality changes, behavioral abnormalities and language impairments in the early stages of the disease (18). It was demonstrated that patients with FTLN had significantly shorter survival and faster rates of cognitive and functional decline compared to those with Alzheimer disease (AD). The years from initial evaluation to death in FTLN patients is 4.2 years, but 6.0 years in AD patients (log-rank test=5.17, $P < 0.05$) (19). According to the survey of epidemiology, from the time of symptom onset, the mean survival in all FTLN is estimated to range from 6.6 to 11.0 years. The mean survival from time of clinical diagnosis of FTLN is estimated to range between 3 and 4 years, which means that patients with FTLN admitted to hospital will progress to a moderate or severe stage in no more than 3 and 4 years (20,21). The majority of studies have focused on the effects of memantine on mild-to-moderate (MMSE score, > 15) FTLN and have neglected its possible benefits for the treatment of patients in moderate-to-severe stages of FTLN (16).

One study concluded that memantine demonstrates a lack of efficacy in treating patients with FTLN and therefore suggested that the drug may not improve a patient's overall behavioral and cognitive function (17); however, the study did not closely analyze the effects of memantine on specific subsets of behavioral and neuropsychiatric symptoms or cognitive impairment. Therefore, in the present study, the efficacy, safety and tolerability of a 6-month treatment regimen of memantine was evaluated in patients with FTLN. The difference between

moderate-to-severe (MMSE scores, 4-20) and mild (MMSE scores, 21-26) behavioral variant frontotemporal degeneration outpatients was evaluated, and specific subscales of behavioral and cognitive functions were analyzed.

Materials and methods

Patient selection and exclusion criteria. In this 6-month open-label clinical study, 60 outpatients from October 2008 to October 2014 were diagnosed with bvFTD according to consensus diagnostic criteria (22,23). These patients were enrolled in the Cognitive Impairment Clinic (CIC) at the Neurology Department of Tianjin Huanhu Hospital (Tianjin, China). Memantine drug-naive patients were enrolled in the final trial. Patients that were prescribed oxiracetam (10 patients, 0.8 g thrice daily), a memory-improving agent widely used in senile dementia patients, or a cholinesterase inhibitor (8 patients, 5 mg once daily) were excluded from the present study. Other exclusion criteria were as follows: i) Aphasia, severe illness and difficulty completing procedures of the study; ii) the pattern of deficits was better accounted for by other non-degenerative neurological or psychiatric disorders; iii) serious chronic conditions within the previous year; iv) magnetic resonance imaging (MRI) or computed tomography (CT) findings inconsistent with bvFTD diagnosis criteria; v) biomarker results that strongly indicated a diagnosis of AD or other forms of dementia; vi) acetylcholinesterase inhibitor treatment and other nootropic or antipsychotic medications taken within 4 weeks of baseline measurement recording; vii) metabolic or inflammatory brain disorders.

Patients were 53-84 years old with Montreal Cognitive Assessment (MoCA) scores between 4 and 29 at the initial screening during enrollment. All participants were required to have an MRI or brain CT scan within 1 year to confirm the bvFTD diagnosis, and a number of patients received ^{18}F -fluorodeoxyglucose (^{18}F -FDG) positron emission (PET)/CT in order to further confirm the diagnosis.

Study design and diagnostic procedures. A total of 42 drug-naive patients were treated with 10 mg memantine (Lundbeck, Valby, Denmark), which is the maximal FDA-approved dose for the treatment of AD, twice daily over a 6-month period. Patients were divided into the following groups according to their MMSE score: Mild bvFTD (MMSE score, 21-26); and moderate-to-severe bvFTD (MMSE score, 4-20).

The following five parameters, including subscale scores, were evaluated as primary and secondary endpoints: General condition (CDR); cognitive function [MMSE/Montreal Cognitive Assessment (MoCA)]; neuropsychiatric behavior (NPI); emotional state [Hamilton Depression Rating Scale (HAMD)]; and activities of daily living (ADL). Diagnostic procedures included the evaluation of medical history, psychiatric and neurological examination, and laboratory screening. A confirmed diagnosis from two experienced neurologists was required to conclude the diagnosis. Physical and neurological examinations, in addition to routine laboratory screening, were performed on the first hospital visit and every 4 weeks thereafter. Primary endpoint parameters included the baseline-to-endpoint changes in the NPI Questionnaire (NPI-Q) (24) and CDR; high scores indicate greater

Table I. Baseline demographics and clinical characteristics of mild, moderate-to-severe and combined behavioral variant fronto-temporal degeneration groups.

Variable	Mild	Moderate-to-severe	Total	P-value
Age, years ^a	67.40±1.88	68.05±1.83	67.74±1.30	0.807
Gender, male/female	8/12	10/12	18/24	0.721
Marriage, n (%)	16 (36.50)	20 (90.91)	36 (85.71)	0.570
Body mass index, kg/m ² ^a	23.45±1.04	21.82±0.78	22.60±0.65	0.212
Education, years ^a	10.60±0.93	8.05±0.96	9.26±0.70	0.064
Hypertension, n (%)	3 (15.00)	9 (40.91)	12 (28.57)	0.130
Diabetes mellitus, n (%)	2 (10.00)	3 (13.64)	5 (11.90)	1.000
Coronary heart disease, n (%)	2 (10.00)	3 (13.64)	5 (11.90)	1.000
Cerebral trauma, n (%)	0 (0.00)	0 (0.00)	0 (0.00)	
Smoking, n (%)	5 (25.00)	6 (27.27)	11 (26.19)	0.867
Drinking, n (%)	3 (15.00)	4 (18.18)	7 (16.67)	1.000
Dementia family history, n (%)	0 (0)	5 (22.73)	5 (11.90)	0.073
Disease duration, years ^a	2.13±0.31	1.77±0.29	1.94±0.21	0.408
Patient number (completed 26 weeks)	20 (20)	22 (21 ^b)	42 (41 ^b)	

^aData are presented as the mean ± standard error. ^bOne subject completed 6 months of treatment, but Neuropsychiatric Inventory evaluation data was not available; another subject succumbed to mortality during the follow-up period.

impairment. Secondary endpoint assessments included the following: Chinese version of the MoCA (25,26) and MMSE (27,28) scores (range, 0-30 for both; high scores indicate better cognitive function); ADL scale including two major categories, Basic Activity of Daily Life (BADL) and Instrumental Activity of Daily Life (IADL; high scores indicate greater impairment) (29,30); and the HAMD (high scores indicate greater impairment) (31).

Adverse effects. Patient safety was monitored at each hospital visit by physical and neurological examination, the recording of adverse events and performing routine laboratory analysis on the blood of the patients. Adverse events were recorded by spontaneous reporting from patients or their caregivers.

Ethical considerations. Each patient that participated in the present study provided informed consent. At each study visit, a reliable caregiver was present and supervised the administration of the patients' medication. The present study was approved by the local institutional ethical standards committee of Tianjin Huanhu Hospital (Tianjin, China) on human experimentation.

Statistical analysis. Baseline demographic qualitative variables were analyzed using the χ^2 test, while normally distributed quantitative variables were analyzed using independent two-sample t-tests. The changes in outcome parameters between the baseline and the six-month endpoints were analyzed using the Wilcoxon-Mann-Whitney test. Statistical analyses were performed using SPSS version 21.0 (IBM SPSS, Armonk, NY, USA). Values are recorded as the mean ± standard error or mean ± standard deviation. All tests were two-tailed, and $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Patient enrollment and baseline demographic data. A total of 42 patients were included in the study and 41 completed the trial. The mild and moderate-to-severe bvFTD groups comprised 20 and 22 patients, respectively. The two groups were comparable with regard to age, gender, marital status, body mass index, level of education, disease duration, accompanying diseases and family history of dementia (Table I).

Adverse events. No medically significant changes were observed during the study with regard to routine laboratory parameters or vital signs. In patients treated with memantine, the adverse events with the highest frequency were constipation (6/42), somnolence (6/42), mild headache (4/42) and dizziness (3/42). None of the patients withdrew from the study due to the experiencing of side effects.

Memantine treatment. Efficacy was determined by primary and secondary outcome measurements of the patients with bvFTD. Primary endpoints included the evaluation of CDR and NPI-Q between the baseline and final hospital visit of the memantine-treated patients with bvFTD. The mean CDR results at the final visit, in comparison with baseline values at the initial visit, were 1.77 ± 0.12 and 1.68 ± 0.125 , respectively; there was no significant difference between the scores of the full cohort (Table II).

Longitudinal NPI-Q data displayed an overall change from baseline to 6 months of 3.81 ± 2.18 points ($Z = -0.856$, $P = 0.392$, Table III). A detailed analysis of the NPI-Q subscale scores revealed no significant changes in the majority of subcategories such as delusions, hallucinations, depression, anxiety, elation, apathy, disinhibition, irritability, aberrant motor behavior (AMB), nighttime behavior and appetite/eating. The subscale

Table II. Analysis of primary and secondary outcome measures between the baseline and final visit of patients with behavioral variant frontotemporal degeneration receiving memantine treatment.

Variable	Baseline	6 Months	Z-value	P-value
Primary endpoints				
Clinic dementia rating	1.68±0.125	1.77±0.12	-0.836	0.403
Neuropsychiatric Inventory Questionnaire	15.76±2.250	11.95±1.79	-0.856	0.392
Secondary endpoints				
Neuropsychiatric Inventory Caregiver Distress	8.49±1.420	7.00±1.05	-0.458	0.647
Mini-Mental State Examination	18.10±1.080	16.43±1.03	-3.126	0.002 ^a
Montreal Cognitive Assessment, Chinese version	12.02±1.030	10.33±1.08	-3.026	0.002 ^a
Activity of Daily Life	30.79±1.680	35.07±1.96	-3.878	0.001 ^a
Basic Activity of Daily Life	13.55±0.640	14.86±0.83	-3.181	0.001 ^a
Instrumental Activity of Daily Living	17.17±1.140	20.26±1.23	-3.937	0.001 ^a
Hamilton Depression Rating Scale	9.05±0.890	8.88±0.82	-0.197	0.844

Data are presented as the mean ± standard error. ^aP<0.05 vs. baseline.

Table III. Detailed analysis of Neuropsychiatric Inventory Questionnaire subscale scores between baseline and final visit after 6 months for all patients with bvFTD receiving memantine treatment.

Variable	Baseline	6 Months	Z-value	P-value
Delusions	0.63±0.190	0.59±0.19	-0.419	0.675
Hallucinations	0.63±0.180	0.44±0.18	-1.279	0.201
Agitation	1.98±0.390	1.34±0.29	-2.127	0.033 ^a
Depression	1.24±0.380	0.71±0.22	-1.638	0.101
Anxiety	0.68±0.190	0.73±0.20	-0.241	0.809
Elation	0.24±0.110	0.34±0.17	-0.447	0.655
Apathy	2.83±0.580	1.90±0.43	-1.432	0.152
Disinhibition	1.24±0.450	0.71±0.20	-0.717	0.473
Irritability	2.02±0.380	1.46±0.28	-1.726	0.084
Aberrant motor behavior	1.49±0.370	1.51±0.38	0.000	1.000
Nighttime behavior	1.54±0.410	1.32±0.36	-0.460	0.645
Appetite/eating	1.22±0.370	0.85±0.26	-1.011	0.312
Total scores	15.76±2.250	11.95±1.79	-0.856	0.392

Data are presented as the mean ± standard error. ^aP<0.05 vs. baseline. bvFTD, behavioral variant frontotemporal dementia.

for agitation was an exception, which was significantly different between the baseline and the final visit ($Z=-2.127$, $P=0.033$; Table III).

Of the secondary endpoints analyzed in patients with bvFTD treated with memantine, no statistically significant differences were detected between the total NPI Caregiver Distress (NPI-D) and HAMD scores between the baseline and final visit (Table II). By contrast, significant reductions in the total score of the MMSE ($Z=-3.126$, $P=0.002$) and MoCA, Chinese version ($Z=-3.026$, $P=0.002$) were observed, and a significant increase was observed in ADL ($Z=-3.878$, $P=0.001$), BADL ($Z=-3.181$, $P=0.001$) and IADL ($Z=-3.937$, $P=0.001$) between the baseline and final visit. This indicates the presence of cognitive and functional deterioration in patients with bvFTD treated with memantine.

Subgroup analysis of patients with mild (n=20) and moderate-to-severe (n=22) bvFTD. In order to determine whether the primary endpoints were affected by disease severity, patients with mild (n=20) and moderate-to-severe (n=22) bvFTD were analyzed separately (Table IV). Following 6 months of memantine treatment, the subgroup of patients with moderate-to-severe bvFTD exhibited significantly improved total NPI-Q scores ($Z=-2.488$, $P=0.013$), and significant improvements in the subscales of agitation ($Z=-2.058$, $P=0.04$), depression ($Z=-2.511$, $P=0.012$), apathy ($Z=-2.586$, $P=0.01$) and disinhibition ($Z=-2.047$, $P=0.041$) compared with those at baseline. By contrast, memantine caused no significant changes in patients with mild bvFTD with regard to the total NPI-Q score (14.50±2.82 baseline vs. 15.70±3.00 after 6 months, $P=0.192$) or individual subscale scores. After

Table IV. Detailed analysis of Neuropsychiatric Inventory Questionnaire neuropsychiatric subdomains between mild and moderate-to-severe behavioral variant frontotemporal dementia in patients receiving memantine treatment.

Variable	Mild (n=20)			Moderate-to-severe (n=20)		
	Baseline	6 Months	P-value	Baseline	6 Months	P-value
Delusions	0.35±0.20	0.65±0.33	0.109	0.90±0.32	0.52±0.20	0.113
Hallucinations	0.45±0.25	0.55±0.34	0.414	0.81±0.27	0.33±0.17	0.068
Agitation	2.10±0.57	1.40±0.34	0.233	1.86±0.54	1.29±0.48	0.040 ^a
Depression	1.35±0.70	1.00±0.41	0.595	1.14±0.37	0.43±0.16	0.012 ^a
Anxiety	0.65±0.25	1.20±0.37	0.077	0.71±0.29	0.29±0.12	0.071
Elation	0.10±0.10	0.40±0.31	0.317	0.38±0.19	0.29±0.17	0.317
Apathy	2.50±0.69	3.15±0.77	0.305	3.14±0.93	0.71±0.23	0.010 ^a
Disinhibition	1.15±0.70	0.90±0.26	0.382	1.33±0.57	0.52±0.30	0.041 ^a
Irritability	2.00±0.55	1.95±0.49	0.862	2.05±0.55	1.00±0.24	0.073
Aberrant motor behavior	1.50±0.61	1.80±0.63	0.180	1.48±0.43	1.24±0.44	0.354
Nighttime behavior	1.60±0.52	1.80±0.65	0.684	1.48±0.64	0.86±0.33	0.498
Appetite/Eating	0.75±0.33	0.90±0.39	0.655	1.67±0.65	0.81±0.34	0.173
Total scores	14.50±2.82	15.70±3.00	0.192	16.95±3.52	8.38±1.76	0.013 ^a

Data are presented as the mean ± standard deviation; ^aP<0.05 vs. baseline.

Table V. Changes in Neuropsychiatric Inventory Questionnaire scores in memantine-treated patients with mild and moderate-to-severe behavioral variant frontotemporal dementia.

Observation	Mild ^{a,b}	Moderate-to-Severe ^{a,b}
Improved	5	12
No change	3	4
Worsened	12	4

^aχ²-value = 7.131, ^bP-value = 0.028.

6 months, the comparison of NPI-Q scores between groups demonstrated that 5 patients improved, 3 patients remained stable and 12 patients worsened in the mild bvFTD group; whereas 12 patients improved, 4 patients remained stable and 4 patients worsened in the moderate-to-severe bvFTD group (Table V). The outcome proportions of the patients, on the basis of improved, unchanged or worsened NPI-Q scores, was found to differ significantly between the mild and moderate-to-severe bvFTD groups (P=0.028; Fig. 1).

Discussion

The present study compared the changes in cognitive function, and neuropsychiatric and behavioral symptoms, in patients with mild and moderate-to-severe bvFTD using standardized tests after 6 months of memantine treatment. Analysis of the combined cohort of 42 patients with bvFTD demonstrated that cognitive performance worsened, indicated by changes in MoCA and MMSE scores, and ability to perform activities in daily living deteriorated, indicated by changes in ADL, during the 6-month period of memantine treatment. Although

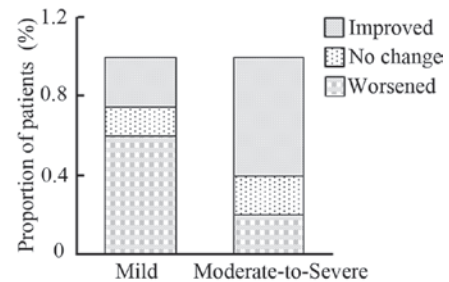


Figure 1. Neuropsychiatric Inventory Questionnaire (NPI-Q) values obtained at the final visit following 6 months of memantine treatment. In the mild behavioral variant frontotemporal degeneration (bvFTLD) group, the NPI scores worsened in 12 patients, remained stable in 3 patients and improved in 5 patients; in the moderate-to-severe bvFTD group, 4 patients worsened, 4 patients remained stable and 12 patients improved. (P=0.028). The P-value was used to analyze the proportion of patients that have shown improvement, no change and worsening of symptoms between the mild and moderate-to-severe groups.

memantine had no beneficial effects on the total or subscale NPI-Q scores of the combined cohort of 42 patients with bvFTD, the moderate-to-severe patient subgroup performed significantly better than the mild patient group in their response to memantine treatment. This was demonstrated by changes to the total NPI-Q score, and subscale scores for agitation, depression, apathy and disinhibition. Memantine appeared to be safe and well-tolerated, and no patient withdrew from the trial as a result of adverse reactions.

FTLD is a clinically, anatomically and histopathologically heterogeneous disorder (3), making it difficult to design a therapeutic trial that could accommodate all possible therapeutic outcome measures. This, therefore, creates particular challenges for determining an optimal management model with a single pharmacological agent. Although memantine is an FDA-approved AD medication, it is not indicated for FTLD treatment. Furthermore,

a recent randomized controlled trial discouraged the prescription of memantine to FTLN patients (16,17). Despite this, the evidence-based clinical practices guidelines, clinical experience indicates that a high percentage of patients with FTLN are treated with AChEI, memantine or both. A cross-sectional design using 1,092 cases with AD and 64 cases with FTLN were registered by the Registry of Dementias of Girona. Memantine was used by 17.2% and 10.9% of patients with AD and FTLN, respectively. There is a discrepancy regarding clinical practice and the recommendations based upon clinical evidence (32).

The aggregate analysis of neuropsychological, cognitive and functional performance across a cohort of patients with bvFTD in the present study indicated that treatment with memantine worsened a patient's cognitive function and ability to perform activities in daily living, and this is consistent with a previously reported randomized controlled clinical trial (16). Notably, each enrolled subject in the present study had significant neuropsychiatric disturbances, as assessed by NPI-Q and NPI-D scores. The high prevalence of neuropsychiatric symptoms in patients with bvFTD has been previously reported in other community-based studies (33,34). Patients with moderate-to-severe bvFTD had a higher NPI-Q total score than patients with mild bvFTD. In the current study, it was observed that behavioral disturbances improved markedly in patients with moderate-to-severe bvFTD, in comparison with patients with mild bvFTD, after 6 months of memantine treatment. Detailed analysis of behavioral subscales demonstrated that the most notable improvements were observed in agitation, depression, apathy and disinhibition. Despite the relatively small sample size included in the present study, this is a potentially important finding.

Different responses to memantine treatment in patients with mild and moderate-to-severe bvFTD may be attributed to the heterogeneous profile of preserved and/or impaired brain regions, or selective functional systems in different stages of the disease. Neuropathological and imaging studies of early FTLN suggest that the disease begins in the anterior cingulate cortex (ACC) and frontoinsula (FI) before spreading throughout a circumscribed network of brain regions (35,36). ACC and FI are the exclusive location of the von Economo neuron (VEN) that is specifically and selectively attacked in the early stages of bvFTD; these are implicated in several neuropsychiatric illnesses, in particular in disturbances of empathy, social awareness and self-control (37,38). In addition, the VEN somatodendritic compartment appears to primarily express dopamine (D3), serotonin (5HT-1b, 2b) and vasopressin (1a) receptors, but does not respond to glutamic acid (39). VEN damage in early-stage bvFTD may explain why selective serotonin reuptake inhibitors, such as paroxetine (40) or 5-hydroxytryptamine 2A (5-HT2A) antagonists (41), but not NMDA receptor antagonists, have modest benefits in improving the behavioral symptoms of patients with mild FTLN.

In more advanced stages of bvFTD, the loss of frontal and temporal neurons becomes more severe with greater deep layer involvement as the disease spreads throughout the white matter to more posterior regions and the subcortex (42). Moreover, presynaptic proteins such as α -synuclein and neurofilament proteins would be lost during severe cases of bvFTD; these two proteins are relatively preserved in a number of mild cases of bvFTD (43). A previous study demonstrated that memantine

treatment can stimulate dendritic spine maturation and promote excitatory synapse formation, restoring excitatory synapses to a normal range in mice with fragile X syndrome (44). Based on these findings, it can be suggested that memantine exerts its therapeutic capacity by alleviating behavioral disturbances through promoting synapse formation and modulating glutamate neuronal excitability in later stages of bvFTD.

Chow *et al* demonstrated using ¹⁸F-FDG PET analysis that patients with mild FTLN (mean CDR score, 1.35) who were treated with memantine displayed increased cortical metabolic activities in the frontal and temporal brain regions, and in the salience network hubs, although no improvements in clinical symptoms were detected (14,15). This suggests that the curative effect of memantine is too weak to be detected at a heterogeneous clinical symptom level; however, the results demonstrated that memantine induces metabolic changes in patients with early stage FTLN. It remains to be tested whether pharmaceutical effects on cortical metabolic activities would lead to clinical improvements as the disease progresses from mild to moderate-to-severe stage bvFTD.

In conclusion, to the best of our knowledge, the present study is the first to evaluate the effect of memantine on detailed longitudinal changes assessed by behavioral, cognitive and functional scales in patients with mild and moderate-to-severe bvFTD. The results demonstrate that memantine improves neuropsychiatric symptoms observed in patients with moderate-to-severe bvFTD, in particular the symptoms of agitation, depression, apathy and disinhibition. However, the current data must be interpreted carefully due to the relatively small number of patients with FTLN involved in the study. In the future, larger-scale, randomized, controlled studies with hierarchical design for subtype and severity of dementia are required in order to further evaluate the efficacy of memantine in patients with moderate-to-severe bvFTD.

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