Memantine in patients with Parkinson’s disease dementia or dementia with Lewy bodies: a double-blind, placebo-controlled, multicentre trial

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Summary

Background Dementia with Lewy bodies (DLB) and Parkinson’s disease dementia (PDD) are common forms of dementia that substantially affect quality of life. Currently, the only treatment licensed for PDD is rivastigmine, and there are no licensed treatments for DLB. We aimed to test the safety and efficacy of the N-methyl D-aspartate (NMDA) receptor antagonist memantine in patients with PDD or DLB.

Methods We did a parallel-group, 24-week, randomised controlled study of memantine (20 mg per day) versus placebo at four psychiatric and neurological outpatient clinics in Norway, Sweden, and the UK during 2005–08. Patients were included if they fulfilled the UK Parkinson’s Disease Society Brain Bank clinical diagnostic criteria for Parkinson’s disease (PD) and developed dementia according to the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM IV) criteria at least 1 year after the onset of motor symptoms (PDD) or met the revised consensus operationalised criteria for DLB. Patients were assigned to a computer-generated randomisation list. All physicians who had contact with patients were masked to treatment allocation. The primary outcome measure was clinical global impression of change (CGIC), which ranged from 1 to 7 points, and a low score means a better outcome. Analysis was by intention to treat based on the last observation carried forward. This trial is registered, number ISRCTN89624516.

Findings 72 patients with PDD or DLB were randomly assigned and started treatment: 34 with memantine and 38 with placebo. 56 (78%) completed the study. All withdrawals were owing to adverse events, but the proportion of withdrawals was similar in both groups. At week 24 the patients in the memantine group had better CGIC scores than those taking placebo (mean difference 0·7, 95% CI 0·04–1·39; p=0·03). With the exception of improved speed on attentional tasks in the memantine group (a quick test of cognition [AQT] form: difference 12·4, 95% CI 6·0–30·9; p=0·004), there were no significant differences between the groups in secondary outcome measures.

Interpretation Patients with DLB or PDD might benefit from treatment with memantine, which was well tolerated. Large-scale studies are now required to confirm our preliminary findings.

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Introduction 25 million people worldwide have dementia, including 700 000 in the UK. Dementia with Lewy bodies (DLB) and dementia associated with Parkinson’s disease (PDD) have similar clinical and neuropathological symptoms and account for 15–20% of the global incidence of dementia. The complex courses of DLB and PDD include motor, cognitive, attentional, and psychiatric symptoms, and make these forms of dementia particularly challenging in terms of quality of life for patients and carers, admission to nursing homes, and health-related costs. Modest clinical benefits are seen in cognition, function, and neuropsychiatric symptoms with rivastigmine, but not all patients respond to or can tolerate cholinesterase inhibitors. Better single or combination therapies are, therefore, urgently needed.

Memantine is an N-methyl D-aspartate (NMDA) receptor antagonist that affects glutamatergic neuronal transmission and prevents the toxic effects of raised concentrations of the excitatory neurotransmitter glutamate. Memantine has proven efficacy as a treatment for Alzheimer’s disease. Altered glutamate markers have
been identified in patients with DLB, providing a rationale for therapy with memantine for these individuals. However, preliminary evidence based on case reports has been highly variable and implicates not only the potential for memantine to improve cognitive and motor symptoms in patients with DLB, but also the possibility of adverse events, including worsening in cognition and psychosis. Controlled trials are clearly needed to establish whether memantine has a potential role in the treatment of DLB and PDD; therefore, we did a placebo-controlled study to test the hypothesis that memantine is more effective than placebo for treating the symptoms of patients with PDD or DLB.

**Methods**

**Patients**

Patients with mild or moderate PDD or DLB (ie, a mini-mental state examination [MMSE] score of 12 points or higher) were recruited at four psychiatric and neurological outpatient clinics in Norway, Sweden, and the UK during 2005–08. Patients were included if they fulfilled the UK Parkinson’s Disease Society Brain Bank clinical diagnostic criteria for Parkinson’s disease (PD) and subsequently developed dementia according to the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM IV) criteria at least 1 year after the onset of motor symptoms (PDD) or they met the revised consensus operationalised criteria for DLB.

Operationalised diagnoses were made by a licensed psychiatrist or neurologist with experience in assessing patients with dementia and parkinsonism. Standardised rating scales were used to identify the symptoms required for a diagnosis of DLB: parkinsonism (unified Parkinson’s disease rating scale [UPDRS]; hallucinations (neuro-psychiatric inventory [NPI]); and cognitive fluctuations [Mayo fluctuation scale]). Exclusion criteria included other brain disease, recent major changes in health status, major depression, moderate-to-severe renal impairment, heart disease, pulmonary disease, hepatic impairment, results of laboratory tests deemed to be clinically relevant by the study physician that were higher than the normal values, or a known allergy to memantine. The study was approved by the ethics committees at each participating centre. All patients gave written informed consent, and a spouse or other responsible caregiver who had frequent contact with the patient was required to accompany them to all study visits.

**Randomisation and masking**

Patients were randomly assigned to receive either memantine or an identically looking placebo. The randomisation lists were generated by the study statistician in the statistical program package R. A randomisation list was forwarded to the study pharmacist at each centre. After enrolment and baseline tests, a signed enrolment form was then faxed to the study pharmacist at each centre to confirm that appropriate consent had been obtained, that the participant met the entry criteria for the study, and to provide the information for stratification: a MMSE score of 19 or 20 points, the use of a cholinesterase inhibitor, and treatment centre. The pharmacist assigned each participant to a treatment group on the basis of the generated randomisation list. Randomisation data were kept strictly blinded; access was restricted to only authorised individuals (eg, the study pharmacist) who had no contact with patients before unblinding. The drug codes were broken and made available for data analysis only when the study was completed and the data files had been verified.

**Procedures**

The initial dose was 5 mg taken in the morning, with a planned gradual increase to the maintenance dose of 20 mg (10 mg in the morning and 10 mg in the evening) from week 4. Compliance was assessed by counting unused tablets and checking for regular intake of study medication (ie, medication was taken regularly and not missed for 5 consecutive days).

Before randomisation, a full medical history and physical examination, which included vital signs and neurological and psychiatric assessments, were done by a physician (EL, CB, DA, GA, FB, and ZW). Electrocardiography (ECG) and laboratory tests were done as clinically indicated. Structural imaging (MRI or CT) was done within 1 year before baseline. Functional imaging (a dopamine transporter single photon emission computed tomography [SPECT] scan) was recommended for patients with DLB but was not mandatory.

Stable treatment with the following drugs was allowed before and during the trial: any cholinesterase inhibitor for at least 6 months before enrolment (current cholinesterase inhibitors at a stable dose for at least 3 months before and during the trial); antiparkinsonian treatment (dose adjustment was allowed if clinically indicated); or antidepressants, anxiolytics, and anti-psychotics for 4 weeks before enrolment and to the end of the study (dose adjustment or starting anti-psychotic treatment was allowed if clinically indicated). Treatment with other NMDA receptor antagonists, including amantadine, and anticonvulsant drugs was not allowed.

Participants were assessed at baseline, at week 12, and at week 24, preferably at the same time of the day at each visit. The primary outcome variable was the clinical global impression of change (CGIC), which was rated after a clinical interview with the patient and their caregiver. The CGIC is a seven-point categorical scale that gives a global rating of change in symptoms from baseline: a score of 1 indicates substantial improvement; a score of 2 indicates a moderate improvement; a score of 3 indicates a minimum improvement; a score of 4 indicates no change; a score of 5 indicates minimum worsening; a score of 6 indicates moderate worsening; and a score of 7 indicates substantial worsening. The scoring instruction included all the relevant clinical domains in this assessment, such as cognition, attention and wakefulness, psychiatric symptoms, motor symptoms, and daily functioning, independent of the clinical rating scales. The CGIC ratings were assigned by study clinicians (EL, CB, DA, GA, ZW, and FB). The protocol specified that the same rater should
do all assessments for each patient, which was the case for most assessments. Before the study, detailed discussions were held to ensure consistent rating between the study clinicians. The CGIC was chosen as the primary outcome owing to the heterogeneity in clinical presentation of this group of patients and the absence of validated rating scales that cover all the key clinical domains.

Secondary outcomes included the 24-week scores for five instruments: the MMSE, a global test of cognition with scores that range from 0 to 30, on which a high score means better cognition; a quick test of cognitive speed (AQT), consisting of three separate tests that require the rapid naming of 40 repeated single-dimension stimuli (colours or forms) followed by dual-dimension stimuli (ie, colour–form combinations) to test executive–attentional systems, such as divided attention, shifting attention, and processing speed, on which the score for each test is the time taken for completion; the NPI, a structured clinical interview of the caregiver (scores can range from 0 to 144, for which a high score means more neuropsychiatric symptoms); the disability assessment for dementia (DAD), which measures activities of daily living (scores range from 0 to 52, and high scores mean better function); and the modified UPDRS motor subscale (scores range from 0 to 32 points, and high scores mean more severe parkinsonism).

**Statistical analysis**

An improvement of 0·6 points on the CGIC would be deemed clinically significant. In a previous pilot study of a cholinesterase inhibitor in patients with PDD, a standard deviation of the CGIC of 0·9 was reported, giving a standardised difference of 0·67. By use of a two-sided test, and a two-tailed significance level of 0·05, 72 patients needed to be enrolled to have 80% power to detect a difference between groups of at least 0·6 points in the CGIC.

The primary efficacy population was predefined as all patients who were randomised and received at least one dose of study medication and who were assessed with the CGIC at least once, whether or not they received the study drug at that time (intention-to-treat population). Patients who discontinued treatment prematurely were encouraged to attend assessments at predefined times; when available, the results of these assessments were used for efficacy analysis; the last observation carried forward (LOCF) method was used to impute values that were not available at the final assessment.

Statistical analyses were done with the SPSS software, version 17.0 (SPSS, Chicago, IL, USA). The predefined analysis plan stipulated the primary outcome as CGIC scores at week 24, based on the Mann–Whitney, or ANCOVA if there were significant differences on key demographic or clinical variables at baseline despite the stratification procedure. Standardised effect sizes were calculated using Cohen’s d method. For the secondary outcome variables, measures at week 24 that used the LOCF method were compared with baseline performance (paired Student’s t test) for normally distributed continuous variables and a non-parametric test (Wilcoxon signed-rank test) for skewed variables. The changes between the two groups were calculated with the Mann–Whitney test. Because this was a phase II study, no adjustment was made for multiple com-parisons of the secondary outcomes. Comparisons of the baseline variables were made, as appropriate, with the Student’s t test, the Mann–Whitney U test, or the χ² test, respectively. Two-sided p values of less than 0·05 were deemed statistically significant.

**Role of the funding source**

The sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, or the writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

**Results**

75 patients were randomly assigned, and 72 (40 with PDD and 32 with DLB) started study medication (figure 1). Of these, 34 were assigned to memantine and 38 to placebo. 16 withdrew before the end of the study owing to adverse events, although five of these attended the 12-week visit, and 56 completed 24 weeks. There were no significant differences in any of the demographic or clinical variables or treatment characteristics between the treatment groups for the randomised (table 1) or LO CF populations (webappendix). In the placebo group, one patient had their dose of antipsychotic drugs decreased during the study and two patients had their doses increased or initiated, whereas no changes were made to the antipsychotic medication of patients in the memantine group. The dose of dopaminergic drugs was decreased during the study in one patient in the placebo group and increased or initiated in two patients in the memantine group and two patients in the placebo group.

In the memantine group, the mean CGIC score at week 24 was 3·5 (SD 1·5; median 3·0), compared with 4·2 (1·2; 4·0) in the placebo group (table 2). In the intention-to-treat analysis with LOCF, the mean difference was 0·70 (95% CI 0·04–1·36; p=0·03), with effect size of 0·52. At week 12, the mean difference in CGIC score was 0·59 (0·01–1·18; p=0·02). Figure 2 shows the distribution of CGIC scores in the two groups. A moderate or substantial clinical improvement was noted in eight (27%) patients in the memantine group compared with none in the placebo group. Moderate worsening was noted in five (17%) patients in the memantine group and six (18%) in the placebo group. In a preliminary descriptive subgroup analysis, there were no differences in the mean CGIC LOCF between the memantine and placebo treatments in patients with DLB (4·0 vs 3·9, mean difference – 0·1, –1·1 to 1·3). The mean score in the PDD group was 4·3 in the placebo group and 2·9 in the memantine group (mean difference 1·4, 0·6 to 2·2), suggesting a more pronounced global response in patients with PDD.
Table 2 shows the results of the analyses of the secondary efficacy variables. With the exception of the AQT form condition (Mann–Whitney test Z score 2·0; p=0·045), for which the memantine group had an improved score and the placebo group had a worse score, there were no significant differences between the memantine and placebo groups between baseline and week 24 for any of the secondary outcomes. There were, however, significant differences within the groups for two of the secondary outcome measures: the mean MMSE score in the memantine group improved from 20·1 to 21·5 (Wilcoxon paired test Z score 2·3; p=0·02), compared with a non-significant decrease in MMSE score from 20·6 to 20·0 in the placebo group (mean difference 1·9, 95% CI 0·06–3·8; Mann–Whitney test Z score 1·7; p=0·09). In the placebo group, there was a significant worsening of the DAD scores (mean change 2·5 [SD 4·6]; p=0·004), compared with a non-significant worsening in the memantine group (mean change 1·0 [6·4]; p=0·42).

Seven (20%) of 35 patients in the memantine group and nine (23%) of 40 patients in the placebo group dropped out owing to adverse events. Seven patients withdrew from the placebo group and four patients withdrew from the memantine group owing to worsening of the disease. Five withdrawals were deemed unrelated to PDD or DLB: stroke (one memantine and one placebo); delirium after urinary tract infection (two memantine); and diarrhoea and vomiting (one placebo). 35 (47%) patients (20 on placebo and 15 on memantine) reported incident adverse events during the study. Table 3 shows the most frequently reported adverse events.

Discussion
The main finding of this study is that the patients who received memantine improved more than the patients who received placebo. A moderate-to-substantial improvement was reported by eight (27%) patients in the memantine group; no patients in the placebo group reported more than a slight improvement. The difference in CGIC scores between the groups was 0·7, and the effect size was 0·52, which is usually thought to be a medium-sized effect.26 This difference compares favourably with the results reported in previous studies of cholinesterase inhibitors in Alzheimer’s disease23 and PDD.2 Preliminary descriptive subgroup analyses suggested a more pronounced global response in PDD than in DLB, highlighting the need for further assessment in larger trials. Although adverse events were common, and 21% (16 of 75) of this frail elderly population withdrew owing to adverse events, the proportions who withdrew or reported adverse events did not differ between treatment groups, suggesting that memantine was well tolerated. This compares favourably with previously reported studies of cholinesterase inhibitors, in which a higher proportion of withdrawals owing to adverse events (mainly peripheral cholinergic effects) were reported in the active group than in the placebo group.6

With the exception of one cognitive speed item, none of the secondary outcome measures in this preliminary study showed a significant between-group difference. However, there were additional indications of an improvement in overall cognitive functioning: the mean difference between the change in MMSE score from baseline and the study end was 1·9 in favour of memantine. This difference is larger than that reported in key trials of cholinesterase inhibitors in Alzheimer’s disease and PDD.2,24 A significant worsening in activities of daily living (DAD) was seen in the placebo group between baseline and week 24, whereas the decline was less pronounced and non-significant in the memantine group, indicating a potential difference in the worsening of activities of daily living. There was no difference in motor and psychiatric symptoms, suggesting that the effects on attention and executive function, global cognition, and ADL led to the changes in CGIC score.

Our results must be interpreted with caution. Although there was no difference in attrition between the groups, the number of patients who withdrew from the study was substantial; therefore, in light of the small sample size, the study did not have adequate statistical power to detect significant differences in scores on the rating scales that were used as secondary efficacy variables. Although improved speed and a non-significant improvement on a global cognitive scale were detected in the memantine group, which of the key symptom domains are most sensitive to changes during treatment with memantine is still unknown. There were no differences in the change in NPI total score; however, the total NPI score includes a wide range of different symptoms and, thus, a difference on some of the NPI sub-items might occur without it being apparent on the total score. A recent similar, but smaller, study25 showed a numerical but non-significant improvement on the CGIC in favour of memantine in patients with PDD with a similar effect size to the one reported here. Tolerability was good in this study; only one of 25 patients withdrew from the study. Therefore, in neither of the studies was the dropout rate higher in the memantine group than it was in the placebo group. In the current study, the patients were recruited from psychiatric and neurology clinics and their characteristics are typical of PDD and DLB, which supports the generalisability of the trial findings.

Previous studies have shown that rivastigmine has a symptomatic effect in patients with PDD2 or DLB,3 whereas the results of case reports and preliminary reports from controlled studies of memantine in PDD and DLB have been inconclusive.5–9,22 We have shown an effect of memantine in this population. Previous reports of severe psychosis in patients with DLB during treatment with memantine9 were not confirmed in the current study. There was no change in the modified UPDRS motor score in either of the two groups, suggesting that motor symptoms do not worsen in patients with PDD or DLB during treatment with memantine.

In conclusion, we show that memantine is safe in patients with DLB or PDD and we provide a preliminary indication of its clinical effectiveness. Owing to the small size of our patient group, the absence of available treatments, and the poor prognosis in terms of quality of life, health-related costs, institutionalisation, and mortality, the development of treatments for these patients must be a priority. Our current findings are encouraging and indicate the need for large multicentre studies.
Contributors
DA designed the study, assessed and analysed the data, and wrote the draft of the manuscript. CB contributed to the study design, recruitment at one of the sites, and writing of the manuscript. ZW contributed to recruitment and assessment of patients in the UK and the writing of the manuscript. FB participated in the planning and design of the study, data collection, and the writing of the manuscript. GA participated in the design and implementation of the study and the interpretation of the data, KK collected and prepared the data for analysis and reviewed the manuscript. IL participated in the planning, design, collection, data analysis, and writing of the manuscript.

Conflicts of interest
DA has received honoraria and research support from H Lundbeck A/S, Novartis, GE Healthcare, and Merck–Serono. During the past 5 years, CB has received honoraria from Novartis, Eisai, Shire, H Lundbeck A/S, Myriad, Arcadia, and Serien Pharmaceuticals and research grants from H Lundbeck A/S. ZW has received funding for travel, speaker and consultancy fees, and research support from GE Healthcare, consultancy fees from Bayer Healthcare, and research support from H Lundbeck A/S. GA has received speaker’s honoraria from H Lundbeck A/S and Orion Pharma, and research support from GSK. IL has received unrestricted grants from Eisai/Pfizer and has received speaker’s honoraria from H Lundbeck A/S, Shire, Pfizer, and Novartis. EL has received honoraria from H Lundbeck A/S for lectures. FB, FJP-R, LM, and KK have no conflicts of interest.

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