RESEARCH ARTICLE

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The effect of memantine on sleep behaviour in dementia with Lewy bodies and Parkinson's disease dementia†

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Objective: Two common and characteristic sleep disturbances have been described in dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD); excessive daytime sleepiness and REM sleep behaviour disorder (RBD). This study is an analysis of a secondary outcome measure of a larger study already reported, aimed to determine whether memantine has an effect on the sleep disturbances in DLB and PDD patients.

Methods: Patients with DLB or PDD were included in a placebo-controlled, randomised controlled study of memantine (20 mg per day) for 24 weeks. The Stavanger Sleep Questionnaire and the Epworth Sleepiness Scale were used to evaluate the effect on sleep disturbances.

Results: Forty two patients started treatment; 20 with memantine and 22 with placebo. The primary analysis was the comparison of change between the two groups during a 24-week period, using the modified ITT population (last observation carried forward). At 24 weeks, patients treated with memantine were less physically active during sleep while patients in the placebo group worsened. Mean difference between the groups (0.5 [0.05–0.90]) was significant ($p = 0.006$). No significant change was observed in severity of excessive daytime sleepiness.

Conclusions: Memantine decreases probable REM sleep behaviour disorder in patients with DLB and PDD. Both diagnostic groups contributed equally to the outcome. Copyright © 2010 John Wiley & Sons, Ltd.

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Introduction

Dementia with Lewy bodies (DLB) accounts for 15–20% of all dementia cases (Lippa *et al*., 2007). Characteristic clinical features include fluctuating cognition, recurrent visual hallucinations, parkinsonism, sensitivity to neuroleptics and prominent disturbances of sleep.

REM sleep behaviour disorder (RBD) is frequently present and distressing to patients with synucleinopathy as the underlying proteinopathy (Boeve *et al*., 2001) such as Parkinson's disease, dementia with Lewy bodies or multi system atrophy (Boeve *et al*., 2003b, 2007b). RBD is thus prevalent in DLB patients, who have more overall sleep disturbances than patients with other neurodegenerative diseases (Grace *et al*., 2000). Normally, muscles are paralysed during REM sleep because of the blockade of motor spinal output, which prevents any motor activity (Arnulf *et al*., 2008). In patients with RBD, this blockade seems to be withdrawn, and they may show a violent behaviour during sleep where they act out their dreams, e.g. by shouting, boxing, kicking and fighting invisible enemies. This

can be dangerous for both the patient and the bedpartner (Mahowald *et al*., 1990; Medicine, 2005). In addition, DLB and PDD patients tend to suffer from other sleep disturbances, which may relate to severity of disease, medications or physical and psychiatric status (Cantor and Stern, 2002; Adler and Thorpy, 2005; Boddy *et al*., 2007) such as excessive daytime somnolence. Sleep disorders have an impact on patient quality of life, functional and cognitive abilities (Tractenberg *et al*., 2005), and efficient treatment is of high pertinence.

In the clinic, treatment of DLB should include treating sleep disturbances experiences by the patient. Therapy should aim towards decreasing the unpleasantness for the patient and the bedpartner by reducing abnormal and violent behaviour and injuries. Currently, pharmacological therapy offered includes melatonin (Kunz and Bes, 1997; Takeuchi *et al*., 2001; Boeve *et al*., 2003a, 2004), mirtazapine (Carley *et al*., 2007; Wiegand, 2008) and most frequently used clonazepam (Sforza *et al*., 1997; Olson *et al*., 2000; Schenck and Mahowald, 2002; Boeve *et al*., 2003a). There has been no prospective placebo-controlled study assessing treatment for RBD associated with DLB or PDD. The identification of a safe and effective treatment is of high priority.

Memantine is a competitive N-methyl-D-aspartate receptor antagonist with moderate affinity. The characteristics of memantine—being neuroprotetective, acting with increased potency with minimal side-effects and acting against excitotoxity—makes memantine a good candidate to use in neurodegenerative diseases. The characteristics of memantine makes it a strong candidate for treating pathology induced by excitotoxicity (Thomas and Grossberg, 2009).

In 2009, Aarsland *et al*. carried out one of the first double-blinded, placebo-controlled studies on memantine in DLB and PDD, and found that the memantine group showed a significantly clinical global improvement compared to the placebo group over 24 weeks. To follow up this study, we have carried out an analysis of secondary outcome measures of sleep disturbances to determine whether memantine affects these characteristic features in DLB and PDD.

Methods

Patients

The patients were part of a double-blinded, placebo-controlled multicentre trial of memantine conducted in four psychiatric and neurological outpatients clinics in Sweden, Norway and the UK between 2005 and 2008 (Aarsland *et al*., 2009).

To be considered for the study, patients had to fulfil the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria for Parkinson's disease (PD) and subsequently develop dementia according to Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM IV) criteria at least 1 year after the onset of the motor symptoms (PDD), or the consensus criteria for DLB (McKeith *et al*., 2005). In addition, they had to have a mini-mental state examination (MMSE) score of 12 points or more, indicating mild or moderate DLB. Patients with other brain diseases, recent major changes in health status, major depression, moderate-to-severe renal impairment, heart disease, pulmonary disease, hepatic impairment or known allergy to memantine were excluded. Ethics committees at each centre approved the study. All patients and their proxy provided written informed consent, and a spouse or caregiver agreed to assist the study and accompany the patient at all visits for assessments.

An instrument of use in this study, Stavanger Sleep Questionnaire, was only applied in Sweden and Norway. Hence, patients from the original group (Aarsland *et al*., 2009) were only included if they were from the Swedish or the Norwegian centre.

Randomisation

Patients were randomly assigned to receive either the active substance memantine, or the identically looking placebo. Randomisation lists were generated by the study statistician. The groups were matched according to MMSE score of 19 or 20 and cholinesterase inhibitor treatment. The patients were not only randomised overall, they were also randomised according to centres, so that patients from one certain centre could be studied separately. After the study was completed and the data files were verified, the drug codes were broken (Aarsland *et al*., 2009).

Procedures

The initial dose given was 5 mg taken in the morning, with a gradual increase to reach a maintenance dose of 20 mg from week 4, giving 10 mg in the morning and 10 mg in the evening.

Before randomisation, all patients were assessed by a physician carrying out a full medical history and a physical examination, including vital signs and neurological and psychiatric assessment. As part of the diagnostic process structural imaging (MRI or CT)

was done before baseline. In addition, functional imaging (a dopamine transporter single photon emission computed tomography [SPECT]) was recommended but not mandatory for DLB patients.

Other treatments were allowed before and during the trial accordingly; cholinesterase inhibitor for at least 6 months before trial (stable dose 3 months before trial), antiparkinsonian medication (if clinically indicated, dose adjustment allowed), antidepressants, anxiolytics, antipsychotics started at least 4 weeks before and to the end of the trial (if clinically indicated, antipsychotic dose adjustment was allowed). No other NMDA-inhibitor, including amantadine, or anticonvulsant was allowed.

Outcome assessments

Patients were assessed at three instances, baseline, 12 weeks and 24 weeks, which preferably were carried out at the same time of the day. The two main sleep outcome measures in this study were the Stavanger Sleep Questionnaire (SSQ) (Gjerstad *et al*., 2008), and the Epworth Sleepiness Scale (ESS) (Johns, 1991; Boddy *et al*., 2007). Both the SSQ and the ESS were modified to being rated by the carer in an interview by the clinician instead of being rated by the patient herself. The SSQ is designed to obtain information about how the relative was experiencing the patient's sleep during day and night, not formally validated, but used in previous assessments of sleep in PD patients (Tandberg *et al*., 1998; Tandberg *et al*., 1999; Gjerstad *et al*., 2002; Gjerstad *et al*., 2008). One question addressed probable RBD—'Is the patient physically active during sleep?' The answer could be no, mild, moderate or severe, ranging from symptoms like twisting and turning and talking during the night, to uneasy sleep with severe physical and verbal expressions. More severe symptoms were indicated with a higher score. The SSQ is outlined in Figure 1.

The ESS measures excessive daytime somnolence, in other words how likely the patient is to doze off or fall asleep in certain situations such as during a conversation or whilst driving (no, slight, moderate or high chance). The scale consists of eight items, scored from 0 to 3 with a total range from 0 to 24. The normal range is 0–10, borderline is 10–12 and abnormal is 12–24.

Patients were also rated using UPDRS, cognitive tests and NPI. These results have been presented in a previous paper (Aarsland *et al*., 2009).

Statistical analysis

Statistical analysis was carried out using the Statistical Package for Social Sciences (SPSS) software (version 17.0 .1 for Windows, SPSS Inc., Chicago, IL, USA). To compare continuous non-normally distributed data Mann–Whitney *U*-test was used. Pearson's χ^2 test was used to analyse categorical variables in the baseline characteristics such as gender. The primary analysis was the comparison of change between the two groups during the 24-week period, using the modified ITT population (i.e. all patients with at least one follow-up assessment, and using LOCF). The Mann–Whitney test was used for this analysis. In a secondary analysis, the change within the two non-parametric related samples was analysed using Wilcoxon signed-rank test. In addition, the proportions with RBD and EDS in the two groups at the three assessment points were compared using χ^2 test. All *p*-values were two-tailed and unadjusted for multiple comparisons. Statistical significance was set at $p \leq 0.05$.

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.

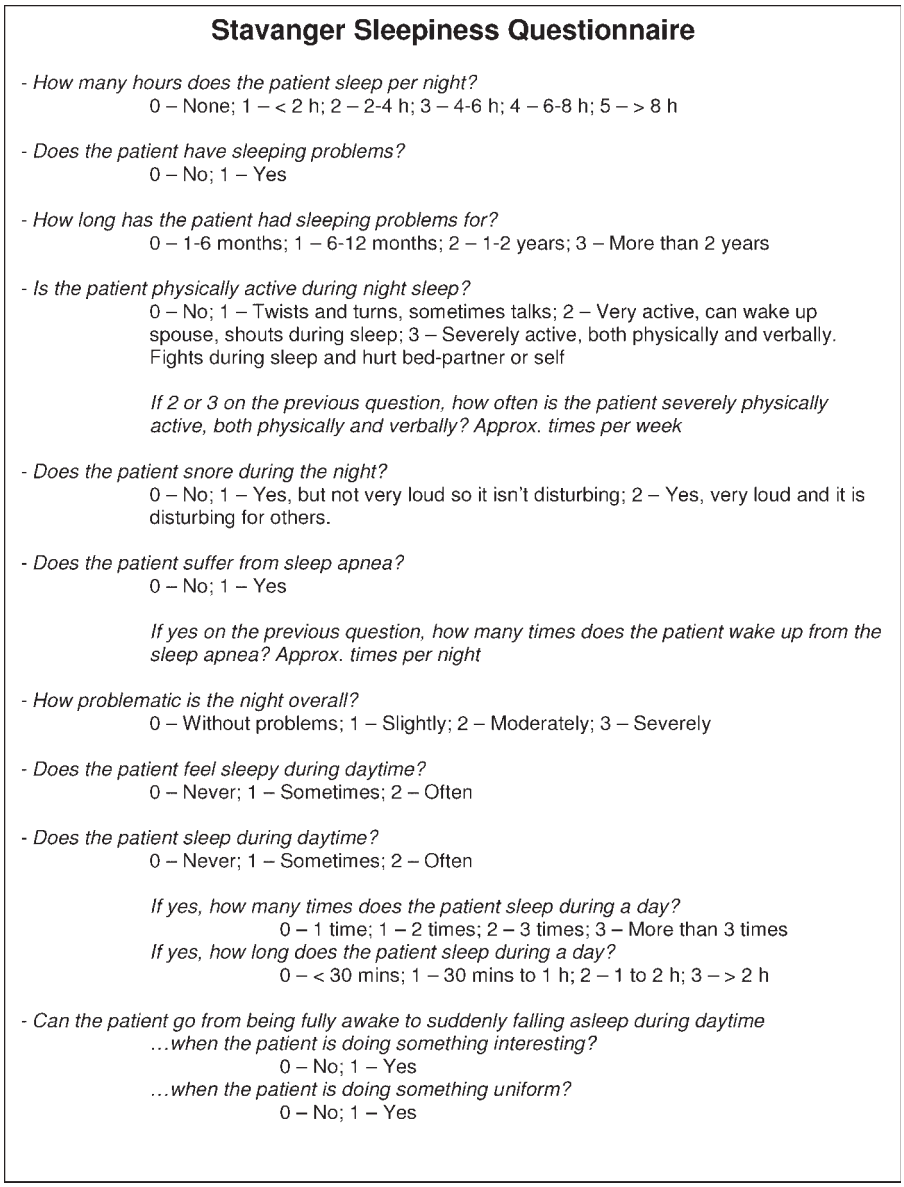
Results

Fifty seven patients from the research centres in Malmö, Sweden, and Stavanger, Norway, started the study. Twenty seven patients were randomly assigned to memantine, and 30 to placebo. Out of these, 2 from the memantine group and 7 from the placebo group withdrew before the 24 weeks. One patient from the placebo group dropped out before the first study drug was administered. Forty seven patients completed the 24 weeks (Figure 2).

No statistical differences were found in the demographics (Table 1). The baseline characteristics showed that male DLB and PDD subjects were more common than female. The baseline frequency of 'physically active during sleep' overall was 54%. There were no statistical differences between the patients in the memantine and placebo group or in the DLB and PDD group.

The results using SSQ are shown in Table 2.

Probable RBD, expressed as a physically active behaviour during sleep, decreased significantly within the memantine group decreased significantly during treatment, illustrated in Figure 3. The number of



Stavanger Sleepiness Questionnaire

- *How many hours does the patient sleep per night?*
  0 – None; 1 – < 2 h; 2 – 2-4 h; 3 – 4-6 h; 4 – 6-8 h; 5 – > 8 h

- *Does the patient have sleeping problems?*
  0 – No; 1 – Yes

- *How long has the patient had sleeping problems for?*
  0 – 1-6 months; 1 – 6-12 months; 2 – 1-2 years; 3 – More than 2 years

- *Is the patient physically active during night sleep?*
  0 – No; 1 – Twists and turns, sometimes talks; 2 – Very active, can wake up spouse, shouts during sleep; 3 – Severely active, both physically and verbally. Fights during sleep and hurt bed-partner or self

  If 2 or 3 on the previous question, how often is the patient severely physically active, both physically and verbally? Approx. times per week

- *Does the patient snore during the night?*
  0 – No; 1 – Yes, but not very loud so it isn't disturbing; 2 – Yes, very loud and it is disturbing for others.

- *Does the patient suffer from sleep apnea?*
  0 – No; 1 – Yes

  If yes on the previous question, how many times does the patient wake up from the sleep apnea? Approx. times per night

- *How problematic is the night overall?*
  0 – Without problems; 1 – Slightly; 2 – Moderately; 3 – Severely

- *Does the patient feel sleepy during daytime?*
  0 – Never; 1 – Sometimes; 2 – Often

- *Does the patient sleep during daytime?*
  0 – Never; 1 – Sometimes; 2 – Often

  If yes, how many times does the patient sleep during a day?
  0 – 1 time; 1 – 2 times; 2 – 3 times; 3 – More than 3 times
  If yes, how long does the patient sleep during a day?
  0 – < 30 mins; 1 – 30 mins to 1 h; 2 – 1 to 2 h; 3 – > 2 h

- *Can the patient go from being fully awake to suddenly falling asleep during daytime*
  …when the patient is doing something interesting?
  0 – No; 1 – Yes
  …when the patient is doing something uniform?
  0 – No; 1 – Yes

Figure 1 Outline of the Stavanger Sleepiness Questionnaire (SSQ).

patients with no or mild probable RBD increased over time (40 to 57% and 16 to 30%, respectively), whilst patients with moderate probable RBD decreased (44 to 13%). The same pattern was not seen in the placebo group (Figure 3). Separate statistical analysis of DLB and PDD patients concerning these results showed that both groups contributed equally to the significant outcome.

The results have been analysed further using logistic regression. Adjustments for age, gender, disease duration, MMSE, neuroleptic, cholinesterase inhibitors, total neuropsychiatric inventory (NPI), hallucinations of NPI, basal Disability Assessment for Dementia scale (DAD), instrumental DAD and Epworth Sleepiness Scale all showed to be non-significant in the model.

Evaluation of baseline subjective hypersomnolence in the ESS showed that 46% of the patients scored within the normal range, 10% were borderline and 44% had abnormal scores, and mean ESS score was 11.6 (SD = 5.9). Mean ESS scores in the DLB group and PDD group were 12.9 and 10.6, respectively (ns). No significant improvement or worsening was shown with or without memantine treatment (Table 3).

One patient in the memantine group and one patient in the placebo group dropped out due to adverse events. One patient in the memantine group

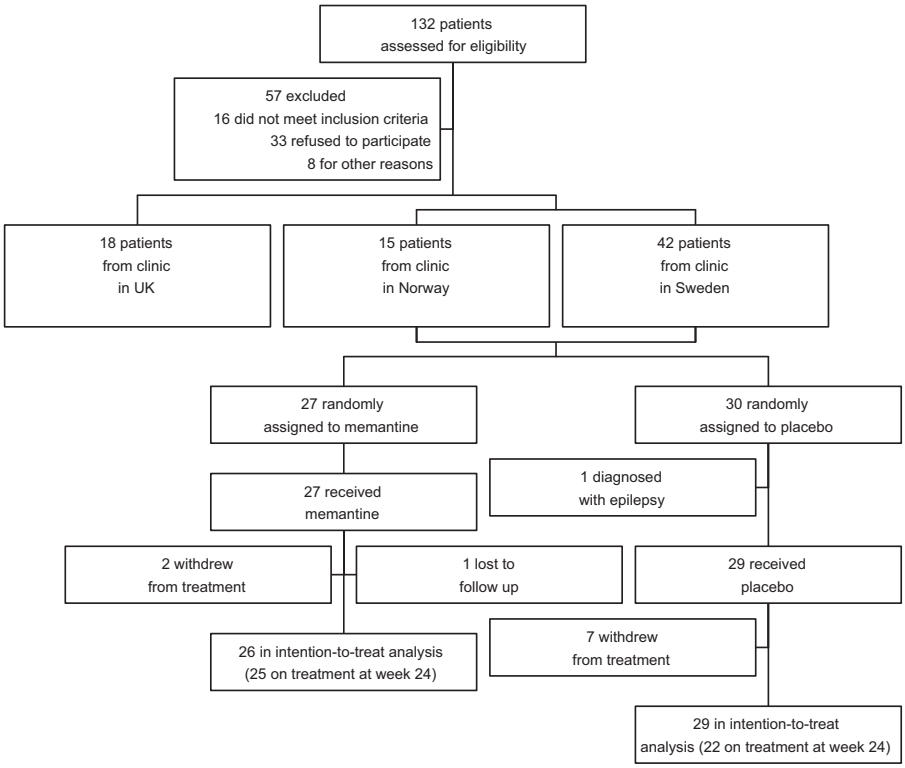


Figure 2 Trial profiles.

Table 1 Demographical and clinical characteristics of patients

	Memantine ($n = 27$)	Placebo ($n = 30$)	p-value
Age (years)	76.4 (6.5)	76.3 (5.0)	0.961
Men/women	20:7	20:10	0.550
Duration of disease (years)	6.0 (3.0–8.0)	7.0 (3.0–9.5)	0.359
DLB/PDD	14:13	13:17	0.529
Duration of PD before onset of dementia (years)	3.0 (1.0–7.0)	3.0 (1.0–6.5)	0.426
MMSE score	20.2 (3.7)	19.6 (4.4)	0.596
Cholinesterase inhibitors	10 (37%)	19 (63%)	0.058
Antiparkinsonian medication	20 (74%)	27 (90%)	0.119
Levodopa dose (mg/day)[a]	500 (200–750)	500 (300–700)	0.342
Antipsychotics	5 (19%)	9 (30%)	0.323
Antidepressants	12 (44%)	12 (40%)	0.740

Data are mean (SD), median (IQR) or number (%). PDD, Parkinson's disease dementia; DLB, dementia with Lewy bodies; MMSE, mini-mental state examination.
[a]Memantine $n = 35$; Placebo $n = 39$.

Table 2 Effect of memantine on probable REM sleep behaviour disorder over 24 weeks using Stavanger Sleep Questionnaire

Physically active during sleep (prob RBD)	n	Baseline	24 weeks (LOCF)	Within-group p value	Change at 24 weeks	Between-group difference[a]
Memantine	26	1.0 (0.0–2.0)	0.0 (0.0–1.0)	0.005	0.44 (0.70)	0.5 (0.05–0.90)*
Placebo	29	0.0 (0.0–2.0)	0.5 (0.0–2.0)	0.660	−0.04 (0.90)	

Data are mean (SD) or median (IQR). LOCF, last observation carried forward. Scores are continuous or scaled (0–3).
[a]Mann–Whitney U test.
*p value = 0.006.

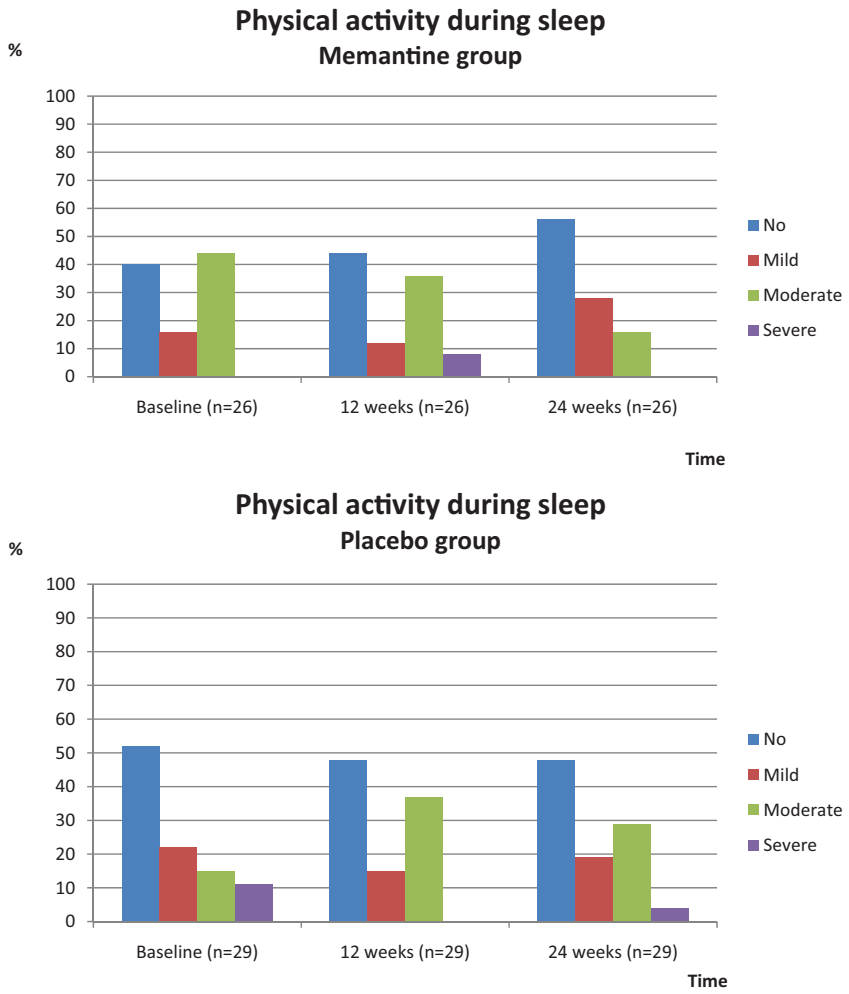


Figure 3 Frequency (%) of probable RBD in memantine group and placebo group over time.

and six patients in the placebo group withdrew from the study owing to worsening of the disease.

Discussion

As a part of the first randomised placebo-controlled study on memantine, we researched the effect of memantine on probable RBD as measured from a question about physically active behaviour during sleep and excessive daytime somnolence. The prevalence of probable RBD within the study group was 60%. By comparison, the prevalence of RBD is estimated to be 0.38–0.5% (Ohayon *et al.*, 1997; Chiu *et al.*, 2000) in the general population and sleep-related violent behaviour in general is about 2% (Ohayon *et al.*, 1997). We found that probable RBD decreased significantly within the memantine group over 24 weeks ($p = 0.005$) whilst increasing in the placebo group. The difference between the two groups was significant ($p = 0.006$). DLB and PDD patients contributed equally to the significant results, indicating that both diagnostic groups were positively affected by the treatment. Memantine showed no significant effect on excessive daytime sleepiness.

The major advantage of this study was the randomised, double-blinded, placebo-controlled study design. In addition, although RBD have been included in the

Table 3 Effect of memantine on daytime drowsiness using Epworth Sleepiness Scale

	n	Baseline	24 weeks (LOCF)	Within-group *p* value
ESS total				
Memantine	32	11.7 (5.9)	11.8 (5.8)	0.552
Placebo	28	11.5 (5.4)	11.2 (5.7)	0.776

Data are mean (SD). ESS, Epworth Sleepiness Scale; LOCF, last observation carried forward.

diagnostic criteria for DLB since 2005 (McKeith *et al*., 2005), this is the first study to research treatment for probable RBD in patients with synucleinopathies. The major disadvantage was that RBD was not confirmed with polysomnography. Physical activity during sleep is not necessarily indicative of RBD but could also reflect movement unrelated to RBD such as periodic leg movements, arousal movements or arousal-related talking, movement that may be frequent in the patient group.

On the other hand, repeated measurements using a sleep questionnaire not commonly encountered in everyday practice is known from our clinical experience to lead to a form of habituation and increased awareness of symptoms over time. This can thus lead to a higher reporting of symptoms by the caregiver after the baseline visit, which is possible to be the reason behind the increase in symptoms seen in Figure 3. In spite of any practice effects from the repeated measurements, probable RBD decreased within the memantine group after 24 weeks, which supports the outcome.

DLB and PDD patients are fragile, and withdrawals from studies are common. However, the patients that dropped out were mainly in the placebo group (seven out of nine), suggesting that memantine was well tolerated.

A disadvantage shared with other treatment studies was the small sample size. Also, the SSQ is a secondary variable from the original RCT (Aarsland *et al*., 2009) and this study was not originally powered to assess sleep disturbances in particular. The majority of patients were treated with cholinesterase inhibitors during the study. Concerns that this might have affected the outcome (Emre, 2009) were addressed using statistical analysis. Comparing treatment groups, cholinesterase inhibitors and the RBD results did not yield any significant differences that could have influenced the results. Administration of antidepressants, known to sometimes worsen RBD, is similar in both treatment groups (Table 1) and should thus not influence the outcome. In regards to further studies, more attention should be directed towards a better powered study and a more sensitive instrument.

Whereas the generators of REM sleep are believed to be in the brainstem, underlying pathology involved in RBD is not established (Boeve *et al*., 2003b). Locus ceruleus (LC) has been shown to have a role in regulation of sleep as well as in attention (Sara, 2009), and the LC involvement in RBD has been discussed and questioned (Schenck *et al*., 1996; Boeve *et al*., 2003b, 2007a). However, there are no large studies assessing the underlying pathology of RBD in human subjects to our knowledge. An animal study in rats investigated the effects of anti-dementia drugs on sleep patterns and found that memantine increased sleep latency, increased total awake time and decreased total REM sleep time. The findings were thought to be due to the effect of memantine leading to a release of dopamine into the prefrontal cortex (Ishida and Kamei, 2009). In regards to possible dopaminergic effects from L-dopa treatment on sleep patterns, we looked for a correlation between changes in REM sleep behaviour to total L-dopa dose in our patients. We found no significant results in either of the groups. Perhaps there is another aspect of memantine affecting sleeping patterns of DLB and PDD patients, as the differences in L-dopa therapy did not affect the RBD.

Previous studies have not addressed treatment of RBD in DLB and PDD. Overall, there are few studies assessing treatment for DLB, and DLB currently lacks an FDA approved treatment. Sixteen randomised controlled trials can be found regarding DLB. Most are on different cholinesterase inhibitors. Rivastigmine has been shown to have a symptomatic effect in both PDD (Emre *et al*., 2004) and DLB (McKeith *et al*., 2000) patients. However, the effect of rivastigmine on sleep patterns is inconclusive, although several studies have shown rivastigmine producing sleep disturbances (Ishida and Kamei, 2009), and Schredl *et al*. found that rivastigmine increased the number of awakenings in elderly subjects, as well as advanced the REM sleep (Schredl *et al*., 2000).

Following one of the first placebo-controlled study of memantine (Aarsland *et al*., 2009), our results support and add to the finding that patients treated with memantine improves more than patients treated with placebo. In this study, memantine showed to improve probable REM sleep behaviour disorder. RBD is frequent, affects the patient and relative on both a physical and emotional level and often predates other symptoms of DLB and PDD (Schenck *et al*., 1986; Boeve *et al*., 2001; Arnulf *et al*., 2008; De Cock *et al*., 2008). It is therefore imperative to recognise and provide efficient treatment for RBD.

Conclusion

Memantine decreases probable REM sleep behaviour disorder in patients with DLB and PDD. Both diagnostic groups contributed equally to the outcome. These findings contribute to the current knowledge of memantine (Aarsland *et al*., 2009; Leroi *et al*., 2009) as well as treatment of REM sleep behaviour disorder in DLB and PDD patients. It indicates the effectiveness of

Key points

- Treatment with memantine significantly improves probable RBD in DLB and PDD patients
- Memantine has no significant effect on excessive daytime somnolence
- Memantine is well tolerated in DLB and PDD patients

memantine in clinical practice and shows an attempt to target a prevalent symptom in DLB and PDD patients. The studies on memantine are encouraging and suggest the need for further research.

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 Seirien Pharmaceuticals and research grants from H Lundbeck A/S. EL has received honoraria from H Lundbeck A/S, Novartis for lectures. VL has no conflicts of interest.

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