

# Long-Term Use of Rivastigmine in Patients With Dementia With Lewy Bodies: An Open-Label Trial

JANET GRACE, SARAH DANIEL, TIMOTHY STEVENS, K. K. SHANKAR, ZUZANNA WALKER, E. JANE BYRNE, SUSAN BUTLER, DAVID WILKINSON, JAN WOOLFORD, JONATHON WAITE, AND IAN G. McKEITH

**ABSTRACT.** Patients with dementia with Lewy bodies (DLB) have progressive deficits in cognition, parkinsonism, and neuropsychiatric symptoms. Cholinesterase inhibitors have been used to ameliorate cognitive decline and neuropsychiatric symptoms in short-term trials. In this study, patients with DLB were treated with rivastigmine up to 96 weeks. Improvement from baseline was seen in cognitive function as measured by the Mini-Mental State Examination (MMSE), and neuropsychiatric symptoms as measured by the Neuropsychiatric Inventory (NPI) over the first 24 weeks of treatment. By 96 weeks, neither the MMSE scores nor the NPI scores were significantly worse than at baseline.

Dementia with Lewy bodies (DLB) is a progressive condition characterized by cognitive impairment with prominent deficits in attention, frontosubcortical skills, and visuospatial ability. Clinical diagnosis is by consensus criteria, with a diagnosis of probable DLB being made in the presence of a progressive cognitive impairment and two out of three of fluctuating confusion, visual hallucinations, and spontaneous parkinsonism (McKeith et al., 1996). DLB patients have profound dysfunction of cholinergic

neurotransmission, to a greater extent than that seen in Alzheimer's disease (AD; Perry et al., 1993, 1994). Choline acetyl transferase activity is lower than in AD, particularly in the temporal and parietal cortex. DLB patients have fewer neurofibrillary tangles than AD patients, suggesting a preferential response to pro-cholinergic therapy (Perry et al., 1978). The symptoms of DLB are persistent and progressive and there is a need for long-term treatment for the cognitive and noncognitive symptoms.

---

From Newcastle General Hospital (J. Grace, BM BS, MRCPsych; S. Daniel; and I. G. McKeith, MD, FRCPsych), Newcastle upon Tyne, UK, Royal Free and University College London Medical School (T. Stevens, MRCPsych; and Z. Walker, MD, MRCPsych), London, UK, St. Margaret's Hospital (K. K. Shankar), Essex, UK, Department of Old Age Psychiatry, Withington Hospital (E. J. Byrne; and S. Butler), Manchester, UK, Thornhill Research Unit

(D. Wilkinson, MBChR, MRCPGP, FRCPsych; and J. Woolford), Southampton, UK, and University Hospital (J. Waite, BSc, MB ChB, FRCPsych), Nottingham, UK.

*Offprints.* Requests for offprints should be directed to Dr. Janet Grace, Castleside Unit, Newcastle General Hospital, Newcastle upon Tyne, NE4 6BE, UK. e-mail: J.B.Grace@newcastle.ac.uk

Initial open-label data (Aarsland et al., 1999; McKeith et al., 2000b; Shea et al., 1998) demonstrate a response by DLB patients to cholinesterase inhibitors. These trials have been of a short duration (typically 12 weeks) and show a moderate improvement in behavioral symptoms and a small increase in scores on the Mini-Mental State Examination (MMSE; Folstein et al., 1975). A multinational placebo-controlled, double-blind study has recently been completed (McKeith et al., 2000a) showing that rivastigmine at daily doses of 6 to 12 mg was well tolerated and clinically relevant behavioral effects were elicited. Reductions were seen in apathy, anxiety, delusions, and hallucination scores. Tests of attention and memory also showed marked improvement. Beneficial effects disappeared in the withdrawal phase.

This study is a descriptive open-label study, following the progression of 29 patients treated with rivastigmine over a maximum of 96 weeks. Patients were described in terms of change in cognitive function, neurobehavioral problems, and parkinsonism. Improvement was expected in the former two domains.

## METHOD

Twenty-nine patients in three centers were recruited from the placebo-controlled trial of rivastigmine in DLB referred to in the report by McKeith and colleagues (2000a). All patients were recruited after a 3-week open-label washout phase. Patients from the placebo-controlled phase were eligible for inclusion in the open-label phase only in certain centers. All patients enrolled in the open-label trial are reported here. Informed consent was obtained from the patient and the next of kin. The presence or

absence of the core features (fluctuating consciousness, visual hallucinations, and spontaneous parkinsonism) and supporting features of DLB (falls, syncope, loss of consciousness, neuroleptic sensitivity, systematized delusions, and hallucinations in other modalities) was noted. All patients met consensus criteria for DLB at inclusion for the study.

Cognitive impairment was assessed using the MMSE. Behavioral disturbance was assessed using the Neuropsychiatric Inventory (NPI; Cummings et al., 1994) and parkinsonism was assessed using the Unified Parkinson's Disease Rating Scale (UPDRS). An NPI subscore was defined as a sum of the scores for delusions, hallucinations, agitation, and apathy. All assessments were made at baseline and at 12-weekly intervals. The dose of rivastigmine was titrated at 2-weekly intervals to the maximum tolerated dose, with a starting dose of 1.5 mg twice a day to a maximum allowed dose of 6 mg twice a day.

Data were analyzed using SPSS for Windows version 9.0. The data were treated as being normally distributed with no assumptions made as to direction of effect.

## RESULTS

Twenty-nine patients were recruited, 9 women and 20 men. The average age of the sample was 75.76 years (*SD* 6.42, range 63 to 87). At the start of the trial, 14 patients had all three core diagnostic symptoms and the remainder had two. Twenty-four had visual hallucinations, 28 had fluctuations of consciousness, and 19 patients had spontaneous symptoms of parkinsonism (Table 1).

The mean MMSE score at baseline was 18.6 (*SD* 4.79, range 7-27). The mean total NPI score was 25.1 (*SD* 7.58, range 0-52)

and the mean NPI subscore was 11.8 (*SD* 8.19, range 0-31). The mean total UPDRS score was 28.7 (*SD* 11.60, range 9-55) with a subscore UPDRS of 12.5 (*SD* 4.46, range 2-19).

**Discontinuation Rates**

The maximum number of weeks of treatment was 96. Of the 29 patients started on treatment, 9 discontinued treatment in the course of the trial; 4 were discontinued because of side effects (2 with nausea and vomiting, 1 with nausea, vomiting, and

“flu-like symptoms,” and 1 with electrocardiographic changes suggesting a serious cardiac arrhythmia following a myocardial infarction), and 4 were discontinued because they were nonresponders. One patient died while on medication because of unrelated causes. The mean length of time on treatment for those discontinued due to side effects was 24 weeks. Two of the patients who discontinued due to side effects were considered by the clinical team to be showing a clinical response to treatment. The mean length of time on treatment for those discontin-

**TABLE 1. Frequency of Supportive Features of DLB**

Features Supportive of DLB	Present (%)
Falls	9/29 (31.0)
Syncope	2/29 (6.8)
Transient loss of consciousness	4/29 (13.7)
Systematized delusions	11/29 (37.9)
Neuroleptic sensitivity	6/29 (20.7) <sup>a</sup>
Hallucinations in other modalities	8/29 (27.6)

*Note.* DLB = dementia with Lewy bodies.

<sup>a</sup>Not all patients had previous exposure to neuroleptics.

**TABLE 2. A Comparison of Patients Who Continued and Discontinued Medication**

	Continued Medication	Discontinued Medication
Number	20	9
Age	76.3	74.5
Gender	5 female	4 female
Parkinsonism	13/20	6/9
Visual hallucinations	17/20	7/9
Fluctuating	19/20	9/9
MMSE at start	19.2	15.6
NPI at start	24.21	27.4
NPI subscore at start	11.00	13.86
UPDRS at start	27.89	30.86
UPDRS5 at start	12.69	12.14

*Note.* MMSE = Mini-Mental State Examination; NPI = Neuropsychiatric Inventory; UPDRS = Unified Parkinson’s Disease Rating Scale; UPDRS5 = Unified Parkinson’s Disease Rating Scale-Subscale.

ued due to nonresponse was 30.5 weeks. A comparison of patients who discontinued medication versus patients who continued on medication is given in Table 2.

**Efficacy Rates**

The changes in scores over the treatment period are shown in Figure 1. The mean MMSE scores at Weeks 12 and 24 ( $p = .016$  and  $.007$ , respectively) were significantly higher than those at baseline (Figure 1).

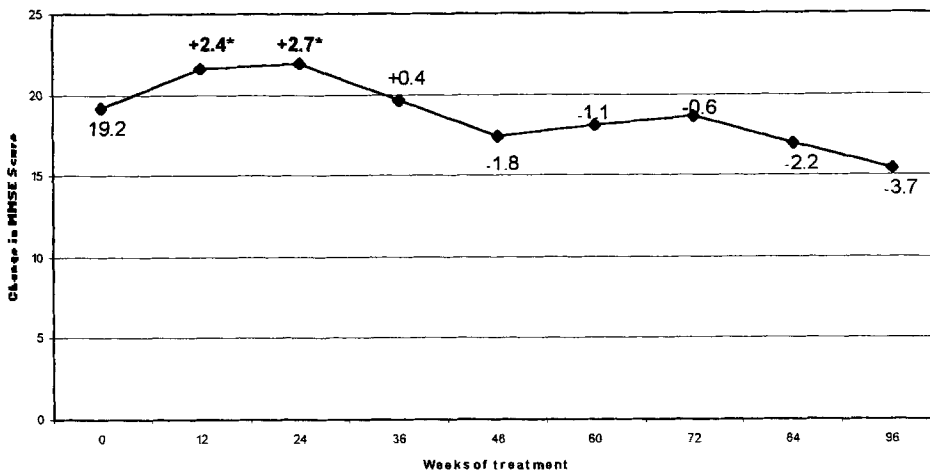
Total NPI score was significantly lower at Week 12 than at baseline ( $p = .016$ ) and there was a trend toward a lower NPI score at Week 24 ( $p = .070$ ) (Figure 2). NPI subscore showed a similar pattern with significantly lower scores at Weeks 12 and 24 than at baseline ( $p = .0001$  and  $.003$ , respectively). Scores for Weeks 36 to 96 were not significantly higher than at baseline (i.e., there was no

detectable deterioration in NPI score over the 96-week treatment period, with a significant improvement in function over the first 24 weeks).

The total UPDRS and UPDRS subscale scores were lower in Week 12 than at baseline ( $p = .009$  and  $.026$ , respectively), indicating a reduction in severity of parkinsonian symptoms (Figure 3). Total UPDRS score was also lower at Week 24 ( $p = .009$ ). UPDRS total and subscale scores were not significantly increased from baseline in Weeks 36 to 96, showing no detectable deterioration in parkinsonism over the treatment period.

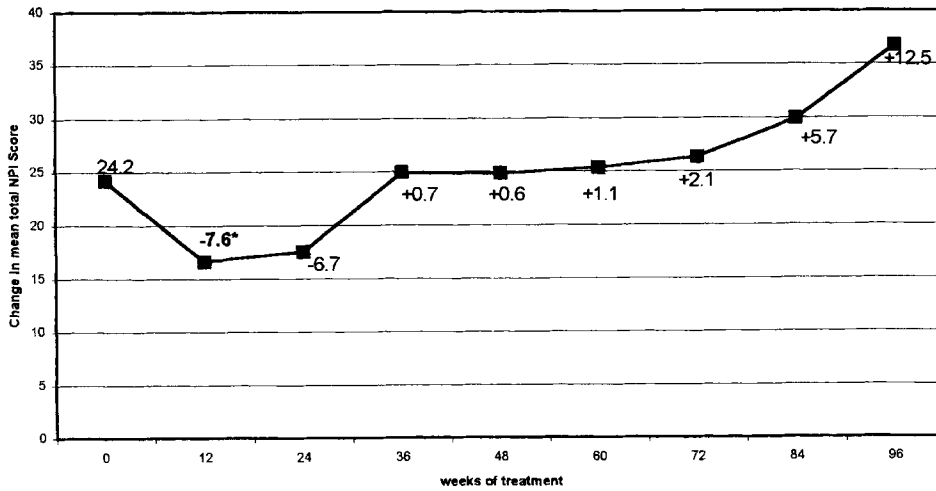
**DISCUSSION**

Interpretation of data from this trial is limited because it was of an open-label design and there was no control group.



week	12	24	36	48	60	72	84	96
t	<b>-2.637</b>	<b>-3.052</b>	-0.617	1.4431	0.745	0.319	1.757	1.710
2 tailed sig	<b>0.016</b>	<b>0.007</b>	0.545	0.177	0.475	0.757	0.122	0.148

Figure 1. Change in MMSE in nondiscontinued group over treatment period.



week	12	24	36	48	60	72	84	96
t	<b>2.662</b>	1.953	-0.108	2.308	0.666	0.542	-0.024	-1.677
2 tailed sig	<b>0.016</b>	0.070	0.916	0.054	0.522	0.607	0.981	0.154

Figure 2. Change in total NPI score in nondiscontinued group over treatment period.

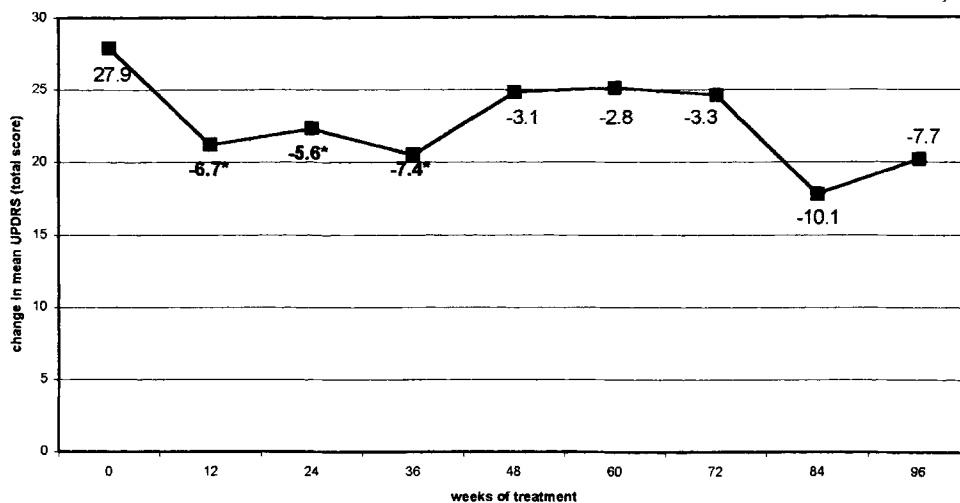
Despite these failings, it is the longest trial of the use of cholinesterase inhibitors in DLB to be published.

A dropout rate of 9 of 29 (31.0%) is similar to that seen in other trials of cholinesterase inhibitors. Statistical analysis of the characteristics of the group that discontinued medication is not possible due to the small sample size. The mean MMSE score of the group who discontinued medication was lower than that of the nondiscontinued group and the NPI scores were higher, possibly suggesting a more profoundly demented group.

Both cognitive and noncognitive symptoms, as measured by the MMSE and the NPI, improved from baseline at Weeks 12 and 24. MMSE score increased from a baseline score of 19.2 to a maximum of 21.9 at Week 24. The mean MMSE score did not fall to baseline levels until Week 36. There is a possibility of a placebo response, but the improvement in MMSE score and the

length that it was sustained militate against this. Total and subscore NPI scores followed a pattern similar to MMSE scores, with total scores returning to baseline at Week 36. DLB is a progressive illness and a substantial reduction in MMSE scores and worsening of behavioral symptoms would be expected over a 96-week period, although there are no longer studies of change in behavior over time. The changes in UPDRS scores were variable, with a fluctuating picture being seen over time. It is possible that this was due to the fluctuating nature of this disease or changes in antiparkinsonian medication over the treatment period.

Over the 96-week treatment period, these measurements of cognitive function, behavioral disturbance, and parkinsonism did not deteriorate to become statistically worse than at baseline. These findings suggest that rivastigmine is effective in improving cognition and reducing neurobehavioral



week	12	24	36	48	60	72	84	96
t	2.930	2.998	2.141	0.564	0.000	0.770	0.455	0.000
2 tailed sig	0.009	0.009	0.049	0.590	1.000	0.467	0.665	1.000

Figure 3. Change in total UPDRS score in nondiscontinued group.

disturbances over the initial period of treatment. This is confirmed by the recently published double-blind trial (McKeith et al., 2000a).

REFERENCES

Aarsland, D., Bronnick, K., & Karlsen, K. (1999). Donepezil for dementia with Lewy bodies: A case study. *International Journal of Geriatric Psychiatry, 14*, 69-72.

Cummings, J. L., Mega, M., Gray, K., et al. (1994). The Neuropsychiatric Inventory: Comprehensive assessment of psychopathology in dementia. *Neurology, 44*, 2308-2314.

Folstein, M. F., Folstein, F. E., & McHugh, P. R. (1975). Mini-Mental State: A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12*, 189-201.

McKeith, I. G., Del Ser, T., Spano, P., Emre,

M., Wesnes, K., et al. (2000a). Efficacy of rivastigmine in dementia with Lewy bodies: A randomised double blind placebo controlled international study. *Lancet, 356*, 2031-2036.

McKeith, I. G., Galasko, D., Kosaka, K., et al. (1996). Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): Report of the consortium on DLB international workshop. *Neurology, 47*, 1113-1124.

McKeith, I. G., Grace, J., Walker, Z., Wilkinson, D., & Stevens, T. (2000b). Rivastigmine in the treatment of dementia with Lewy bodies: Preliminary findings from an open trial. *International Journal of Geriatric Psychiatry, 15*, 387-392.

Perry, E. K., Haroutinian, V., & Davis, K. L. (1994). Neocortical cholinergic activities differentiate Lewy body dementia from classical Alzheimer's disease. *Neuroreport, 5*, 747-749.

Perry, E. K., Irving, D., & Kerwin, J. M. (1993). Cholinergic neurotransmitter and neu-

rotrophic activity in Lewy body dementia. *Alzheimer Disease and Associated Disorders*, 7, 62-79.

Perry, E. K., Tomlinson, B. E., Blessed, G., Bergmann, K., Gibson, P. H., et al. (1978). Correlation of cholinergic abnormalities with senile plaques and mental test scores in dementia. *British Medical Journal*, Suppl. 2, 1457-1459.

Shea, C., MacKnight, C., & Rockwood, K. (1998). Aspects of dementia—Donepezil for treatment of dementia with Lewy bodies: A case series of nine patients. *International Psychogeriatrics*, 10, 229-238.

*Acknowledgments.* Janet Grace and Sarah Daniel have been supported by funding from Novartis Pharmaceuticals.