ORIGINAL RESEARCH ARTICLE

Drug Safety 2008; 31 (1): 79-94
0114-5916/08/0001-0079/$48.00/0

Effects of Rivastigmine on Tremor and Other Motor Symptoms in Patients with Parkinson's Disease Dementia

A Retrospective Analysis of a Double-Blind Trial and an Open-Label Extension

Wolfgang Oertel,[1] *Werner Poewe*,[2] *Erik Wolters*,[3] *Peter Paul De Deyn*,[4] *Murat Emre*,[5] *Courtney Kirsch*,[6] *Chuanchieh Hsu*,[6] *Sibel Tekin*[6] and *Roger Lane*[6]

1 Department of Neurology, Philipps University, Marburg, Germany
2 Department of Neurology, Medical University Innsbruck, Innsbruck, Austria
3 Research Institute Neurosciences Vrije Universiteit, Amsterdam, The Netherlands
4 Middelheim Hospital ZNA, University of Antwerp, Antwerp, Belgium
5 Istanbul Faculty of Medicine, Istanbul, Turkey
6 Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA

Abstract

Background and aim: Rivastigmine is now widely approved for the treatment of mild to moderately severe dementia in Parkinson's disease (PDD). However, since anticholinergic drugs have a role in the management of tremor in patients with Parkinson's disease (PD), concerns have been raised that the use of cholinergic drugs might worsen PD. The current analyses were performed to examine the potential of rivastigmine to affect tremor and other motor symptoms in patients with PDD.

Methods: The safety profile of rivastigmine was evaluated using a database from a 24-week, randomized, double-blind, placebo-controlled trial in 541 PDD patients (362 randomized to rivastigmine, 179 to placebo), and 334 PDD patients who subsequently entered an open-label 24-week extension on rivastigmine.

Results: During the double-blind trial, the adverse event (AE) of emerging or worsening tremor was reported in 10.2% of patients in the rivastigmine group, compared with 3.9% in the placebo group ($p = 0.012$). Tremor was most frequently reported during the titration phase of rivastigmine treatment, although this was not reflected in total motor Unified Parkinson's Disease Rating Scale (UPDRS) part III scores. Dose dependence of this AE was not observed. At the end of the double-blind phase, six (1.7%) rivastigmine-treated patients had discontinued the study because of tremor. In the open-label extension in which all patients received rivastigmine, tremor was reported by 6.9% of patients: 3.8% and 12.2% of whom had previously received double-blind rivastigmine and placebo, respectively ($p = 0.006$), suggesting that first exposure to rivastigmine leads to a transient increase in tremor. Three (0.9%) of the 334 patients who entered the

open-label extension phase discontinued because of tremor. Incidences of worsening parkinsonism, bradykinesia and rigidity were all <5% in both treatment groups (all p-values not statistically significant, rivastigmine vs placebo). In the 48-week observation of rivastigmine treatment, there was no evidence of adverse long-term motor outcomes. *Post-hoc* analysis showed that similar improvements in the symptoms of dementia, including the ability to perform activities of daily living, were seen regardless of whether exacerbation of tremor was reported during the study.

Conclusion: Rivastigmine did not induce clinically significant exacerbation of motor dysfunction in patients with PDD. Rest tremor incidence as an AE was a transient phenomenon during dose titration of rivastigmine. There was no indication that exposure to long-term rivastigmine was associated with a worsening of PD.

Background

Parkinson's disease (PD) pathology involves damage to multiple neuronal circuits, including dopaminergic, noradrenergic, serotonergic and cholinergic projection systems.[1] A crucial deficit underlying PD is depletion of dopamine in the striatum caused by loss of mid-brain dopaminergic cells, which is associated with the well recognized motor symptoms of the condition. In addition, in patients with PD dementia (PDD), cholinergic deficits have been shown to occur earlier, be greater in magnitude and more widespread throughout the brain, compared with Alzheimer's disease (AD).[2-4] Evidence of profound cholinergic deficits in PDD raised the question whether cholinesterase inhibitors could be effective in PDD. Early case series and open studies supported this hypothesis.[5-8]

However, since anticholinergic drugs have long had a role in the management of tremor in patients with idiopathic PD,[9] concerns that the use of cholinergic drugs might worsen PD have been raised. However, neurophysiological studies[10,11] suggest that the cholinergic-dopaminergic interaction is complex, and not simply antagonistic. Two major subcortical cholinergic pathways are affected in PDD: a basal forebrain-located pathway that extends from the nucleus basalis of Meynert, the principal source of cholinergic innervation to the cortex[1,12] and a brainstem-located pathway comprising primarily the pedunculopontine nucleus that projects to the thalamus.[13,14] The anatomical distribution of cholinergic and dopaminergic terminals in the striatum overlap extensively, and their coordinated activities seem essential for proper functioning of the basal ganglia. Cholinergic and dopaminergic systems normally modulate brain function in complex feed-forward and feedback loops.[15] A study in rats showed that a marked elevation of acetylcholine following cholinesterase inhibition was associated with a significantly increased release of dopamine in the medial prefrontal cortex or hippocampus.[16] Dependent upon the local regional mix of acetylcholine and dopamine dysfunction, it is possible that cholinesterase inhibitor therapy might have no effect, a positive effect or a negative effect on motor functions in patients with PD.

These early clinical and preclinical findings provided the rational for the first large, double-blind, placebo-controlled study of a cholinesterase inhibitor, rivastigmine, in PDD.[17] Rivastigmine is a sustained inhibitor of butyrylcholinesterase and acetylcholinesterase. In a study of 541 patients with PDD, rivastigmine demonstrated statistically significant efficacy compared with placebo on all evaluated measures of cognition, including executive function and attention, activities of daily living and neuropsychiatric symptoms.[17] Emergence or worsening of tremor was reported as an adverse event (AE) in 10% of patients receiving rivastigmine, but adverse effects on other cardinal symptoms of PD, such as muscle rigidity and bradykinesia, were rare.

The current paper describes a retrospective analysis of this double-blind rivastigmine trial[17] and a further 24-week, open-label extension,[18] which was performed to further evaluate the potential effects of the drug on motor symptoms in patients with PDD.

Methods

Trial Design

A detailed description of the methodology of the double-blind, placebo-controlled, 24-week trial and its long-term, open-label extension has been provided elsewhere.[17,18] Patients with dementia due to PD according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition (DSM-IV) criteria[19] were randomly assigned to receive treatment with rivastigmine (Exelon® [1], Novartis) 3–12 mg/day or placebo in an assignment ratio of 2 : 1. Rivastigmine was started at a dosage of 3 mg/day and increased at 4-weekly intervals to a maximum of 12 mg/day. The highest well tolerated dosage for each patient was maintained during the final 8-week maintenance period. No changes in dopaminergic medications or commencement of new psychotropic medications (except atypical antipsychotics for acute psychosis) were permitted within 4 weeks prior to and throughout the trial. If clinically indicated, a dose increase was permitted in patients already treated with atypical antipsychotics or, in antipsychotic-naive patients, atypical antipsychotics such as clozapine, quetiapine or olanzapine were to be started at very low doses and increased gradually.

At the end of the 24-week, double-blind core trial,[17] all patients were entitled to enter an open-label extension study for a further 24 weeks, during which all patients received rivastigmine.[18] All patients received a starting dosage of 3 mg/day and were re-titrated to their highest tolerated dosage of rivastigmine, in order to maintain blinding. Changes in the dosage of current dopaminergic medications during the extension study were not recommended, but they were permitted. All procedures were in accordance with ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration as revised in 1983.

Primary outcomes of the trial were cognitive performance and clinical impressions of global performance; full efficacy data are reported elsewhere.[17,18] Safety evaluations included recording all AEs reported during the trial (weeks 1–48). Visits were performed at weeks 0, 4, 8, 12, 16, 20 and 24 during the double-blind phase and weeks 28, 32, 36, 40 and 48 during the open-label phase. The safety population consisted of all patients who underwent at least one safety measurement after randomization in the double-blind trial or after entry into the open-label extension study. AEs were coded with a standard glossary (Medical Dictionary for Regulatory Activities [MedDRA], version 7.0).

Changes in symptoms of parkinsonism were assessed with the motor examination section of the Unified Parkinson's Disease Rating Scale (UPDRS part III)[20] at baseline and at weeks 16, 24 and 48. The Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL) scale[21] was used to assess daily functioning in the double-blind trial. ADCS-ADL total and physical scores have been shown to correlate with motor function in patients with PDD,[22] so this provided an additional supportive measure on the potential impact of rivastigmine on motor function. Changes in concomitant dopaminergic and antipsychotic medication were recorded on the case report form.

In-Depth Analysis of Motor Symptoms

The primary focus of the current analysis was to further evaluate the frequency of motor symptoms in PDD patients receiving rivastigmine. Of reported AEs that were considered potentially related to PD exacerbation, tremor was the most common[17,18] and, therefore, the subject of particular attention in the current analysis. Prior to completion of the study, to ensure that all AEs potentially related to an

1 The use of trade names is for product identification purposes only and does not imply endorsement.

exacerbation of PD were captured, a list of these AEs was prospectively compiled (table I).

Changes on the ADCS-ADL in patients who reported tremor were calculated to provide supportive clinical information with regard to the impact of tremor on functional activities.

The incidences and consequences of tremor and other AEs potentially related to PD were investigated in subgroups of patients. These subgroups included patients with moderate to severe dementia and patients who, at baseline, had visual hallucinations and/or were receiving concomitant antipsychotic therapy. Furthermore, if, during the open-label extension study, motor function in patients previously receiving rivastigmine (in the double-blind trial) was similar to or better than that of patients previously receiving placebo, this was considered suggestive of a lack of negative drug effect on the underlying movement disorder (as shown later in the UPDRS section, both groups experienced similar changes in dopaminergic medications in the double-blind study, so such changes were unlikely to confound this interpretation).

Table I. *A priori* list of 22 adverse events of special interest that may be potentially related to Parkinson's disease (PD)[a] and used for the current analysis

Akinesia
Balance disorder
Bradykinesia
Drooling
Dysarthria
Dyskinesia
Dystonia
Fall
Freezing phenomenon
Gait abnormality
Hypertonia
Hypokinesia
Motor dysfunction
Movement disorder
Muscle rigidity
Musculoskeletal stiffness
On and off phenomenon
PD worsening
Parkinsonism worsening
Rigors
Salivary hypersecretion
Tremor

a These adverse events were usually *not* thought to be directly associated with a worsening of PD by the investigators and could be related to conditions other than an exacerbation of underlying PD.

SAS software version 8.2 was used for all analyses. For baseline characteristic comparability, the Wilcoxon rank-sum test was used for continuous variables and the Chi-square test was used for categorical variables. Numbers of patients who experienced AEs or discontinued because of AEs were compared between the treatment groups using Fisher's exact test. The Wilcoxon rank-sum test was used to assess changes from baseline in levodopa use between treatment groups.

Results

Patients

In the 24-week, double-blind core trial,[17] 541 patients entered the study and 433 completed it (figure 1). A total of 334 patients entered, and 273 completed, the 24-week, open-label extension study.[18]

Baseline characteristics of all randomized patients are shown in table II.[17] No statistically significant differences between the treatment groups were observed. The baseline characteristics of the 334 patients electing to participate in the open-label extension were similar to those of the total core trial population.[18]

Adverse Events of Special Interest

During the double-blind core trial, all reported AEs that had been prospectively identified as being potentially related to exacerbation of PD (table I) did not appear to combine to form a pattern suggestive of worsening PD (i.e. the study drug did not appear to contribute to worsening of the underlying pathological disease state), or to be related to conditions other than PD. Tremor occurred in 37 (10.2%) patients in the rivastigmine group, compared with 7 (3.9%) patients in the placebo group ($p = 0.012$) [table III]. Incidences of worsening parkinsonism

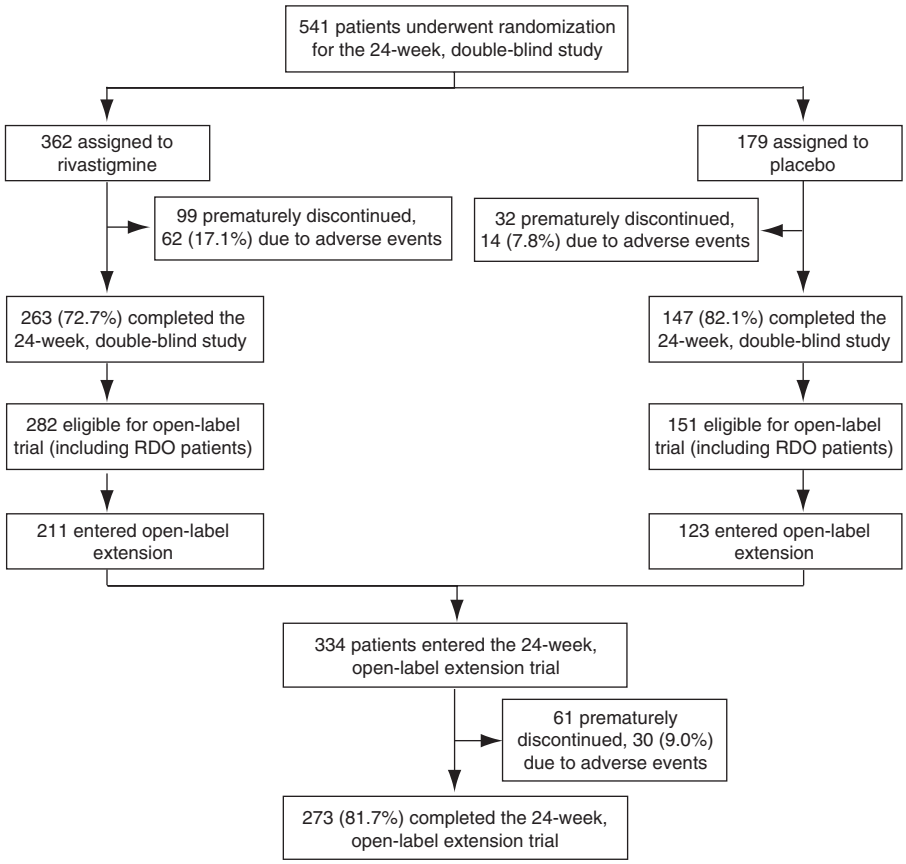

Fig. 1. Assignment of patients in studies.[17,18] **RDO** = retrieved drop out.

and other specific AEs such as bradykinesia and rigidity were all <5% in both treatment groups (all p = not statistically significant [NS]).[17] Rivastigmine was not associated with worsening tremor in patients already reporting this symptom at baseline. In the open-label extension in which all patients received rivastigmine (re-titrated from lowest dose even in patients who had received double-blind rivastigmine, to preserve blinding), tremor was reported by 6.9% of patients: 8 (3.8%) and 15 (12.2%) of whom had previously received double-blind rivastigmine and placebo, respectively (p = 0.006) [table III].

Figure 2 shows the incidence rates of tremor in (i) all rivastigmine-treated patients in the double-blind trial; (ii) rivastigmine- and placebo-group patients who completed the double-blind trial; and (iii) rivastigmine-treated double-blind trial patients who also completed the open-label extension study (i.e. received 48 weeks of rivastigmine treatment). Tremor was most frequently reported (in 4.6% of patients) during weeks 8–12 of the double-blind study titration phase, when patients were scheduled to titrate from 6 mg/day to 9 mg/day. Of 37 patients who reported tremor as an AE during the double-blind study, six discontinued the double-blind trial prematurely because of tremor (1.7% of patients in the rivastigmine group and 0.0% of patients in the placebo group; p = 0.19).[17] Other parkinsonian events were reported in 3.3% of rivastigmine-treated patients (table III), and discontinuation rates due to these events were low (1.4%). No single parkinsoni-

Table II. Baseline characteristics of all randomized patients (n = 541). There were no statistically significant differences between groups at baseline (Wilcoxon rank-sum test for continuous variables, Chi-square test for categorical variables)

Characteristic	Rivastigmine (n = 362)	Placebo (n = 179)
Age in years [mean (SD)]	72.8 (6.7)	72.4 (6.4)
CNS medications[a] [n (%)]		
antipsychotic agents	100 (27.6)	47 (26.3)
levodopa	346 (95.6)	169 (94.4)
dopamine agonists	165 (45.6)	83 (46.4)
Duration of PD in years[b] [mean (SD)]	8.7 (5.7)	9.5 (5.9)
Baseline modified Hoehn and Yahr staging (UPDRS part V) [n (%)]		
0	1 (0.3)	0 (0.0)
1–2.5	181 (50.0)	85 (47.5)
3	114 (31.5)	63 (35.2)
4	51 (14.1)	28 (15.6)
5	15 (4.1)	2 (1.1)
Baseline UPDRS part III motor score [mean (SD)]		
all patients	34.0 (14.6)	32.2 (13.2)
tremor-dominant PD patients only[c]	26.0 (14.4)	39.8 (17.6)
akinetic-rigid PD patients only[c]	34.6 (14.4)	31.7 (12.8)
Duration of dementia in years[b] [mean (SD)]	1.1 (1.3)	1.4 (1.8)
Severity of dementia in MMSE score [mean (SD)]	19.4 (3.8)	19.2 (4.1)
mild PDD (MMSE 18–24) [n (%)]	253 (71.1)	126 (70.4)
moderate PDD (MMSE 10–17) [n (%)]	103 (28.9)	50 (27.9)
Visual hallucinations [n (%)][d]	118 (33.1)	70 (39.1)

a Medications taken within 4 weeks prior to the start of the study.

b Time since first diagnosis by a physician.

c Twenty-four and nine rivastigmine- and placebo-treated patients, respectively, had tremor-dominant PD; 138 and 170 rivastigmine- and placebo-treated patients had akinetic-rigid PD.

d Baseline data on visual hallucinations were available for 536 patients.

MMSE = Mini-Mental State Examination; **PD** = Parkinson's disease; **PDD** = Parkinson's disease dementia; **SD** = standard deviation; **UPDRS** = Unified Parkinson's Disease Rating Scale.

an symptom accounted for >0.6% of withdrawals in either group. Three (0.9%) of the 334 patients who entered the open-label extension phase discontinued because of tremor.[18]

In 12 patients, tremor resolved spontaneously (based on AE reports; i.e. the worsening or exacerbation had ended) with continued use of rivastigmine (9 during the double-blind trial, 3 after entry into the open-label extension). Among 19 patients for whom the dose of rivastigmine was decreased following tremor onset, tremor resolved in 13 (68%) patients; the other 6 (32%) remained in the study with persistent tremor. The mean duration of reported emerging or worsening tremor was 12.4 days. Twenty-one patients experiencing tremor during the double-blind trial continued into the open-label extension, and 19 of these 21 patients completed the open-label extension; reasons for patients electing not to enter the open-label extension were not recorded.

Reports of tremor decreased during the extension study in the group receiving rivastigmine for the full 48 weeks (3.8% during the open-label extension study, in patients who had received rivastigmine in the core double-blind trial). However, patients who were exposed to rivastigmine for the first time during the open-label extension study (who had received placebo during the double-blind trial) experienced more tremor, compared with extension study patients previously exposed to rivastigmine. Similar findings were seen with other predefined AEs of special interest that were potentially related

Table III. Numbers (%) of patients reporting predefined adverse events (AEs) of special interest, potentially related to an exacerbation of Parkinson's disease (PD), with >2% incidence

AEs reported	Double-blind trial			Open-label extension[a]		
	double-blind rivastigmine (n = 362)	double-blind placebo (n = 179)	p-values	double-blind rivastigmine (n = 211)	double-blind placebo (n = 123)	p-values
Any predefined AE of special interest	99 (27.3)	28 (15.6)	0.003	28 (13.3)	32 (26.0)	0.005
Tremor	37 (10.2)	7 (3.9)	0.012	8 (3.8)	15 (12.2)	0.006
Fall	21 (5.8)	11 (6.1)	NS	7 (3.3)	9 (7.3)	NS
PD (worsening)	12 (3.3)	2 (1.1)	NS	7 (3.3)	5 (4.1)	NS
Parkinsonism	8 (2.2)	1 (0.6)	NS	2 (0.9)	0 (0.0)	NS
Bradykinesia	9 (2.5)	3 (1.7)	NS	1 (0.5)	0 (0.0)	NS

a All patients received rivastigmine in the open-label extension study.

NS = not significant.

to an exacerbation of PD. Reports of these AEs in rivastigmine-treated patients decreased after completion of the double-blind trial titration phase and remained low during the double-blind trial maintenance phase and during the extension study, but showed a slight increase during rivastigmine dose re-titration in the extension study.

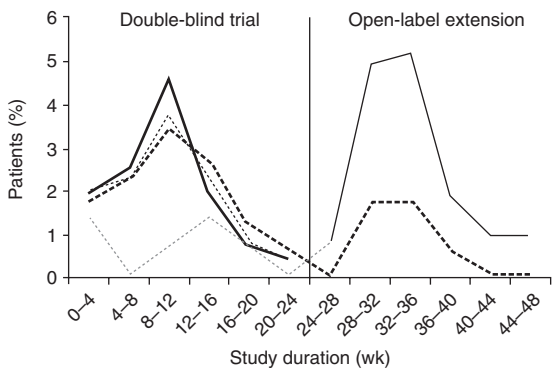

Fig. 2. Percentage of patients reporting the adverse event of tremor over time.

In the double-blind core trial, AEs potentially associated with parkinsonian symptoms were generally mild or moderate in severity, with only four severe events in the rivastigmine group (1.1%; one tremor, two worsening parkinsonism, one muscle rigidity) and one severe event in the placebo group (0.6%; one muscle rigidity).

Of rivastigmine-treated patients experiencing tremor as an AE, 21 (57%, compared with 58% of all rivastigmine-treated patients) entered the extension study. Of rivastigmine-treated patients who experienced AEs potentially related to an exacerbation of PD in the double-blind trial, 53 (54%) entered and 47 (89%) completed the extension study. Total discontinuations due to these AEs in the extension study were 1.2%.

Because of the small numbers of tremor-dominant patients at baseline (<15%), findings for this group are not presented separately, because the subpopulation was considered too small to provide meaningful or reliable data.

Additional analyses of subpopulations at possible increased risk for exacerbation of PD gave no indication that rivastigmine differentially affected these groups. Patients with mild (Mini-Mental State Examination [MMSE] 18–24; n = 253) or moderate (MMSE 10–17; n = 103) dementia at baseline reported emerging or worsening tremor that was not significantly different between severity groups (11.1% vs 8.7% for rivastigmine and 4.8% vs 2.0%

Table IV. Effects of baseline antipsychotic use on outcomes (double-blind trial, all randomized patients)

Outcomes measured	Antipsychotic users at baseline		Antipsychotic non-users at baseline	
	rivastigmine	placebo	rivastigmine	placebo
ADCS-ADL score				
No. of patients	94	45	239	120
Baseline score	34.9 ± 16.6	34.4 ± 15.0	44.2 ± 18.7	43.8 ± 17.7
Change at week 24	−1.2 ± 13.0	−3.5 ± 10.5	−1.1 ± 12.4	−3.6 ± 10.2
UPDRS part III score				
No. of patients	71	37	192	109
Baseline score	33.9 ± 14.9	32.3 ± 12.9	32.5 ± 13.9	32.6 ± 13.0
Change at week 24	−0.5 ± 9.3	−1.2 ± 8.9	−0.3 ± 9.6	−0.1 ± 8.4
Adverse events [n (%)]				
Tremor	8 (7.8)	1 (2.1)	29 (11.2)	6 (4.6)
Bradykinesia	4 (3.9)	1 (2.1)	5 (1.9)	2 (1.5)
Muscle rigidity	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)

ADCS-ADL = Alzheimer's Disease Cooperative Study – Activities of Daily Living; **UPDRS** = Unified Parkinson's Disease Rating Scale.

for placebo in mild vs moderate dementia patients, respectively), and similar incidences of bradykinesia (1.6% vs 4.9% and 1.6% vs 2.0%, respectively) and muscle rigidity (0.4% vs 0.0% and 0.0% vs 0.0%, respectively). Patients reporting visual hallucinations at baseline (n = 188) and non-hallucinators (n = 348) also reported similar incidences of tremor in the rivastigmine and placebo groups (10.2% vs 2.9% in visual hallucinators and 10.5% vs 4.6% in non-hallucinators, respectively),[23] and similar incidences of bradykinesia (2.5% vs 0.0% and 2.5% vs 2.8%, respectively), and muscle rigidity (0.0% vs 0.0% and 0.4% vs 0.0%, respectively). The use of antipsychotics at baseline, relative to those not receiving antipsychotics at baseline, appeared to be associated with a slightly decreased risk of reported tremor in both the rivastigmine (7.8% vs 11.2%) and placebo (2.1% vs 4.6%) groups (table IV). Over the course of the double-blind study, changes in antipsychotic use in the rivastigmine group were comparable to those seen with placebo.[17]

Unified Parkinson's Disease Rating Scale Motor Subscale Scores

Despite differences in AE rates between the treatment groups during the double-blind trial, total UPDRS motor scores were not significantly different between the rivastigmine and placebo groups (p = 0.83), including subscores for tremor items (p = 0.84). Rivastigmine-treated patients showed similar mean changes from baseline on UPDRS part III scale scores (total, tremor at rest and postural tremor scores) to patients in the placebo group (table V). Mean changes in total UPDRS part III scores in rivastigmine-treated patients in the double-blind and extension studies were less than the expected annual change of 1.5–3.3 points reported in community-based studies[24,25] (table V, figure 3). Table VI shows detailed findings from the UPDRS part III item scores during the double-blind study. First reports of tremor did not appear to be dose related, but rather occurred most frequently in patients receiving rivastigmine ≤6 mg/day (table VII).

Within a subpopulation (necessarily defined post baseline) of patients who reported the AE of tremor during the double-blind trial and also provided UPDRS scores, rivastigmine-treated patients (n = 27) showed comparable total score changes to the overall population who received rivastigmine, except for more marked deterioration in their 'tremor at rest' sub-item scores. Patients with the AE of tremor who received placebo (n = 7) showed a large improvement in UPDRS part III scores (–9.3 points), but this result is difficult to interpret, because of the small sample size in this group.

In the 48-week observation of rivastigmine treatment there was no evidence that rivastigmine adversely affected the long-term motor outcome. In

Table V. Mean (± SD) Unified Parkinson's Disease Rating Scale (UPDRS) part III motor scores at baseline and changes from baseline at weeks 24 and 48[a]

Patient group	Baseline UPDRS scores (week 0)		Change from baseline to week 24 (end of double-blind trial)		Change from week 24 to week 48 (end of open-label extension)	
	rivastigmine	placebo	rivastigmine	placebo	rivastigmine-rivastigmine	placebo-rivastigmine
All randomized patients						
No. of patients	263	146	263	146	171	196
Total score[b]	32.9 ± 14.2	32.5 ± 13.0	−0.3 ± 9.5	−0.4 ± 8.5	1.5 ± 8.8	2.3 ± 10.9
Tremor at rest[c]	2.0 ± 2.8	1.7 ± 2.6	0.1 ± 2.6	0.0 ± 2.1	−0.1 ± 2.0	0.5 ± 2.7
Postural tremor[c]	1.3 ± 1.4	1.1 ± 1.5	−0.1 ± 1.4	0.0 ± 1.2	0.1 ± 1.2	0.0 ± 1.3
Subpopulation reporting AEs potentially related to an exacerbation of PD during the double-blind trial						
No. of patients	69	22	69	22		
Total score[b]	35.5 ± 13.5	38.0 ± 14.2	0.8 ± 10.6	−1.2 ± 12.9		
Tremor at rest[c]	2.3 ± 2.9	2.9 ± 3.8	0.4 ± 2.6	−1.5 ± 3.8		
Postural tremor[c]	1.5 ± 1.7	1.3 ± 1.8	−0.1 ± 1.6	−0.3 ± 1.9		
Subpopulation reporting AEs of tremor during the double-blind trial						
No. of patients	27	7	27	7		
Total score[b]	36.8 ± 11.6	43.7 ± 14.3	−0.6 ± 8.9	−9.3 ± 8.7		
Tremor at rest[c]	3.1 ± 2.8	5.9 ± 4.7	0.7 ± 2.2	−2.1 ± 5.0		
Postural tremor[c]	2.1 ± 1.6	2.4 ± 2.8	−0.1 ± 2.2	−0.6 ± 2.4		

a Positive change scores indicate worsening of PD motor symptoms on UPDRS part III scale.

b Total scores at baseline have been calculated only for patients who had a week 24 evaluation.

c Some patients may not have both baseline and endpoint assessments.

AEs = adverse events; **PD** = Parkinson's disease.

Table VI. Mean (±SD) Unified Parkinson's Disease Rating Scale (UPDRS) part III individual item scores at baseline and changes from baseline at week 24[a][20]

UPDRS individual item	Baseline scores (week 0)		Change from baseline to week 24 (end of double-blind trial)	
	rivastigmine (n = 263)	placebo (n = 146)	rivastigmine (n = 263)	placebo (n = 146)
Speech	1.6 ± 0.9	1.5 ± 0.8	0.0 ± 0.7	0.1 ± 0.6
Facial expression	1.8 ± 0.9	1.9 ± 0.8	0.0 ± 0.8	−0.1 ± 0.8
Tremor at rest	2.0 ± 2.8	1.7 ± 2.6	0.1 ± 2.6	0.0 ± 2.1
Action or postural tremor of hands	1.3 ± 1.4	1.1 ± 1.5	−0.1 ± 1.4	0.0 ± 1.2
Rigidity	6.6 ± 4.0	6.2 ± 3.5	−0.3 ± 2.7	−0.3 ± 3.2
Finger taps	3.3 ± 1.8	3.2 ± 1.6	0.0 ± 1.4	−0.1 ± 1.3
Hand movement	2.9 ± 1.6	2.7 ± 1.6	0.0 ± 1.4	0.1 ± 1.4
Rapid alternating movements of hands	3.2 ± 1.6	3.1 ± 1.6	0.0 ± 1.5	0.0 ± 1.3
Leg agility	3.2 ± 1.9	3.0 ± 1.8	−0.1 ± 1.6	0.0 ± 1.5
Arising from chair	1.5 ± 1.2	1.4 ± 1.2	0.1 ± 0.9	0.1 ± 0.9
Posture	1.7 ± 0.9	1.6 ± 0.8	0.0 ± 0.8	0.1 ± 0.7
Gait	1.6 ± 0.9	1.6 ± 0.8	0.0 ± 0.7	0.0 ± 0.7
Postural stability	1.5 ± 1.0	1.4 ± 0.9	0.0 ± 0.8	0.0 ± 0.7
Body bradykinesia and hypokinesia	2.0 ± 0.9	1.9 ± 0.8	0.0 ± 0.8	0.0 ± 0.6

a Positive change scores indicate worsening of Parkinson's disease motor symptoms on UPDRS part III scale.

fact, 'delayed start' analysis showed that patients who received rivastigmine treatment throughout the double-blind and open-label extension studies tended to have superior UPDRS motor scores at completion of the extension study, relative to patients who initially received placebo during the double-blind trial. This trend towards delayed start worsening was more apparent in patients whose dementia was more severe at baseline, defined by lower baseline MMSE scores.

UPDRS part III scores in the subpopulation reporting any of the predefined AEs potentially related to an exacerbation PD during the double-blind trial showed that baseline scores in this subpopulation were higher (worse) than those of the overall population (table V). Rivastigmine-treated patients in this subpopulation showed a slight deterioration in their total and 'tremor at rest' sub-item scores and a slight improvement in the 'postural tremor' sub-item score, during the double-blind study (table V). Patients who reported these AEs and received placebo had an improvement in total scores and tremor-related sub-item scores over the duration of the trial.

Alzheimer's Disease Cooperative Study – Activities of Daily Living Motor Scale Scores

During the double-blind trial, deterioration was observed in total ADCS-ADL scores in the rivastigmine and placebo groups at the week-24 endpoint, but decline was significantly less in rivastigmine-treated patients than in patients receiving placebo (−1.10 vs −3.60; p = 0.023).[17] These effects appeared to be maintained during the open-label extension, for up to 48 weeks (figure 4). The mean slight improvement was maintained in the subgroup of patients with more advanced dementia (MMSE scores 10–17) at baseline (figure 5).

Table VII. Doses of rivastigmine received by patients reporting their first adverse event of tremor during the double-blind study

Dose (mg/day)	Rivastigmine (n = 362)	Placebo (n = 179)	Total (n = 541)
≤3	10	3	13
>3 to 6	12	1	13
>6 to 9	6	1	7
>9 to <12	2	0	2
12	7	2	9
Total	**37**	**7**	**44**

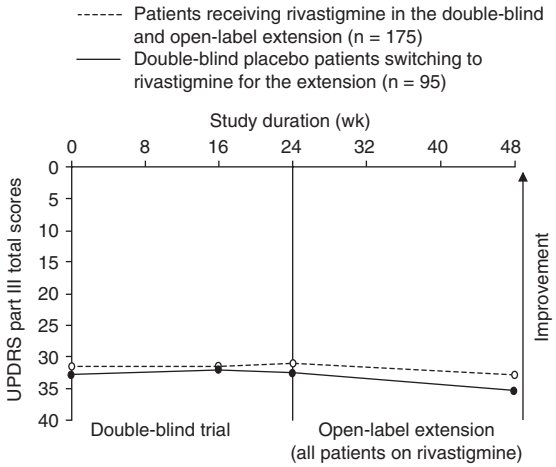

Fig. 3. Unified Parkinson's Disease Rating Scale (UPDRS) part III total scores for all patients completing the double-blind trial and open-label extension study, based on patients providing data at each timepoint.

In the subpopulation of patients who reported tremor during the double-blind trial, ADCS-ADL scale scores showed an improvement with rivastigmine treatment at week 24 (+1.43 points), while patients who received placebo showed a decline (−3.50 points). In this subpopulation, the changes in mean ADCS-ADL scores in both the rivastigmine and placebo groups, and the difference between treatment groups, was at least comparable to that seen in the overall core study population. The same was true for a subpopulation of patients with AEs potentially related to an exacerbation of PD, who showed changes of −0.90 points in the rivastigmine group and −3.50 points in the placebo group. Thus, tremor or AEs potentially related to an exacerbation of PD did not appear to have a meaningful impact on functional outcome.

Concomitant Dopaminergic Medications

Reports of tremor and other events potentially related to an exacerbation of PD in rivastigmine-treated patients were rarely severe, usually transient and infrequently led to dose changes of concomitant dopaminergic medications.

In the double-blind trial, similar numbers of patients in the rivastigmine and placebo groups received newly introduced (10.5% vs 9.5%; p = NS) or increased doses (6.4% vs 4.5%; p = NS) of dopaminergic medications. Increases in daily doses from baseline to week 24 were calculated as 17.5 mg of levodopa in the rivastigmine group and 7.2 mg of levodopa in the placebo group (p = NS). Considering that the usual minimum starting dose of levodopa treatment is 375–500 mg/day, these dose increases were not considered clinically significant.

In the subpopulation of patients with tremor, mean daily doses of levodopa and other dopamimetics increased by 24.9 mg and 8.9 mg (calculated as levodopa-equivalent doses) in the rivastigmine and placebo groups, respectively. In the subpopulation of patients with AEs potentially related to an exacerbation of PD, the mean daily dose of levodopa and dopamimetics in the placebo group was higher than that in the rivastigmine-treated patients (833.6 mg vs 665.2 mg; p = NS) at baseline. Figure 6 shows mean daily doses of levodopa and dopamimetics in patients who experienced AEs potentially related to an exacerbation of PD, throughout the double-blind study. There was no significant change in the mean doses of levodopa and dopamimetics, particularly in response to increased incidence rates of AEs poten-

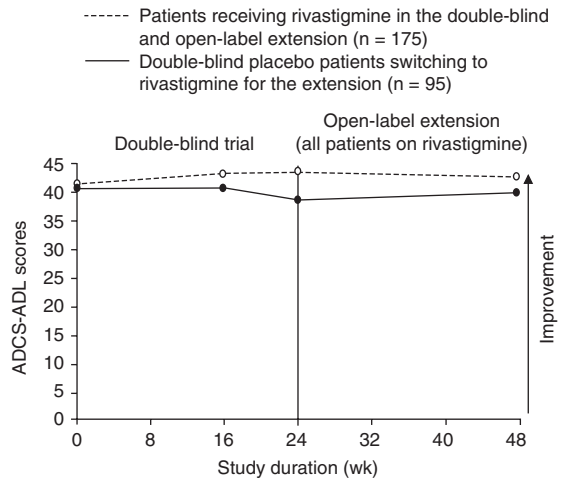

Fig. 4. Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL) scores for all patients completing the double-blind trial and open-label extension study, based on patients providing data at each timepoint.

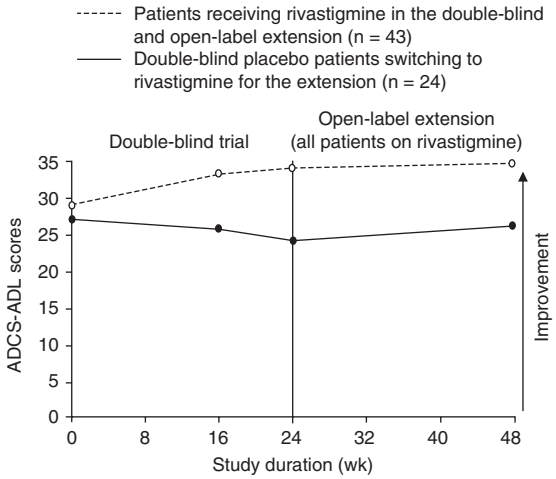

Fig. 5. Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL) scores for patients with moderate dementia (Mini-Mental State Examination scores 10–17) at baseline, who completed the double-blind trial and open-label extension study, based on patients providing data at each timepoint.

tially related to an exacerbation of PD that peaked during weeks 8–12 of the dose-titration period.

There were 177 patients who received a total of 48 weeks of rivastigmine treatment. Amongst these patients, 4.5% initiated new dopaminergic medications, indicating that dopaminergic medications tended to be stable during long-term treatment. There was a slight increase in mean doses of levodopa and dopamimetics (67.3 mg) in patients who received double-blind rivastigmine treatment and who also completed the extension study.

Discussion

The classical hypothesis for tremor alleviation by anticholinergic drugs in PD is that dopamine inhibition of acetylcholine effects is reduced in the striatum of PD patients; therefore, the normal cholinergic system is operating in relative excess, causing tremor.[26,27] This hypothesis predicts that PD motor symptoms should worsen with cholinomimetic drugs such as the cholinesterase inhibitors, and the data obtained by this study at first glance appear to offer partial confirmation of this hypothesis. However, the current analysis suggests that rivastigmine therapy has no serious effect on motor function in most PD patients. Although increased tremor was reported by one in ten patients during the double-blind trial, incidences of other specific AEs such as bradykinesia and rigidity were less common and reported in similar rates in the rivastigmine and placebo groups. Moreover, rest tremor was not a problem over the longer term, with the majority of cases appearing to resolve following the completion of rivastigmine dose up-titration or dose reduction. These findings were supported by UPDRS part III motor scores, which showed similar changes from baseline in the rivastigmine and placebo groups during the double-blind trial.

Reports of tremor and other less common events potentially related to an exacerbation of PD were associated with the week 8–12 titration period (in the rivastigmine group in the double-blind trial, and in the former placebo group in the open-label extension), which corresponded to the scheduled titration from 9 to 12 mg/day of rivastigmine. Once past this titration step, newly emergent tremor was less commonly reported. These data suggest that the transient increase in rest tremor under rivastigmine may be related to the first exposure to and up-titration of this compound. Decreasing the dose of rivastigmine appeared to decrease or abolish tremor. Moreover, these events were usually mild, seldom severe (a single report) and had few meaningful clinical consequences in terms of increases in dopaminergic therapy, treatment discontinuation or increased

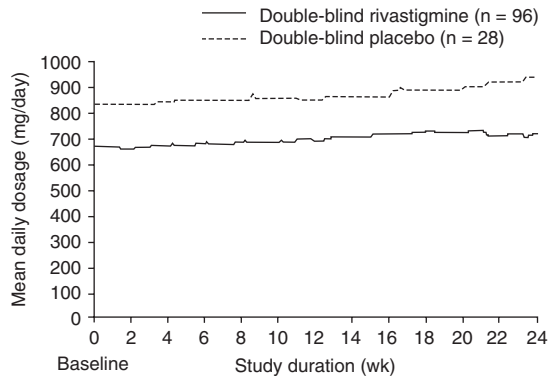

Fig. 6. Mean daily dosages of levodopa and dopamimetics in patients who experienced adverse events potentially due to a worsening of Parkinson's disease during the 24-week, double-blind trial.

motor dysfunction at week 16 or study endpoint assessments, or impaired performance of activities of daily living.

PDD is a chronic degenerative disorder with an expected decline in functional activity. However, in the double-blind trial, rivastigmine not only provided a beneficial effect on activities of daily living relative to placebo in the overall population,[17] but also showed similar effects in subpopulations who reported tremor or who reported any of the predefined AEs potentially related to an exacerbation of PD. Importantly, patients who reported these events did not have significant overall deterioration in their PD motor symptoms. Dopaminergic medication intake was stable during long-term treatment. Thus, the decreased incidence of tremor or of AEs potentially due to an exacerbation of PD seen in rivastigmine-treated patients during the maintenance phase and extension study does not appear to be due to increased doses of dopaminergic medications.

According to the Exelon® product label, more treatment-emergent tremor was seen in rivastigmine-treated patients with AD than in those receiving placebo (4% vs 1%). In a recent large, 2-year, randomized, double-blind study, more AEs of tremor were seen in rivastigmine-treated moderate AD patients with symptoms suggestive of concomitant Lewy body disease (12%) than in AD patients without such symptoms (4.7%).[28] These findings are consistent with previous studies of rivastigmine in patients with PDD or dementia with Lewy bodies (DLB), in which tremor was the only parkinsonian symptom to show significant exacerbation.[29,30] More recently, tremor amplitude was measured using accelerometers in a small study (n = 19) of rivastigmine-treated PDD patients during the 'on' state.[31] Accelerometric assessments showed an increase in average tremor amplitude in the right hand ($p = 0.02$), though left-hand tremor was reported not to change. The authors concluded that rivastigmine caused only slight worsening of tremor in patients with PDD, while improving cognition.[31] Resting tremor, if exacerbated or emergent, is obvious to the patient, family, and treating physician. Thus, patients requiring dose reductions, or even discontinuation of rivastigmine treatment, can be easily identified, monitored and managed appropriately.

Tremor is believed to have a cholinergic basis, with anticholinergic agents being used successfully to control tremor in PD.[9] The more frequent reports of tremor associated with rivastigmine are thought to be due to a symptomatic response to enhanced cholinergic stimulus and a complex cholinergic-dopaminergic interaction, especially in the striatum. This region expresses acetylcholinesterase predominantly over butyrylcholinesterase,[32] although it is fed by a number of feedback loops from other brain regions in which butyrylcholinesterase may be predominantly expressed.[33] The current trial evaluated rivastigmine, a dual inhibitor of both acetylcholinesterase and butyrylcholinesterase. In another randomized controlled trial of the acetylcholinesterase-inhibitor donepezil (n = 550), about 7% of patients with PDD reported tremor.[34] Probably both acetylcholinesterase and butyrylcholinesterase contribute to elevations in acetylcholine that, in turn, lead to increased tremor. The severity of the motor impairment in PD is correlated with cognitive impairment.[35] However, tremor in particular has little association with cognitive decline,[36-39] and there is no evidence that increased tremor is associated with the progression of bradykinesia, rigidity or the overall motor disability, symptoms that have themselves been associated with progression of PD.[40]

Patients who received placebo from the beginning of the double-blind trial did not do as well on assessments of motor symptoms (UPDRS part III) or functioning (ADCS-ADL) in the open-label extension as patients who received rivastigmine from the beginning. Thus, the 'delayed start' analysis showed that patients who received rivastigmine-treatment throughout the double-blind and extension studies tended to have better motor symptom scores at the completion of the extension study, relative to patients who initially received placebo in the double-blind trial. The worsening in the placebo group was more apparent in PDD patients with moderate dementia. Thus, there was no evidence to suggest

that rivastigmine increased the progression of motor disability of PD.

Rivastigmine is currently the only agent approved by regulatory agencies for the treatment of PDD, and therefore this is a timely and important review of long-term safety and tolerability. Other cholinesterase inhibitors have also demonstrated cognitive benefits in PDD. A small study (n = 7) using tacrine (another inhibitor of both acetylcholinesterase and butyrylcholinesterase) provided the first evidence of cognitive benefits in this population.[5] Subsequently, two small studies (n = 14 and 22) suggested that the acetylcholinesterase-inhibitor donepezil may provide cognitive benefits in patients with PDD,[41,42] although a larger (n = 550), double-blind, placebo-controlled study of donepezil in PDD patients failed to reach statistical significance on its primary cognitive endpoint, the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog).[34] Safety and tolerability data from this larger donepezil study are not yet publicly available. However, available data suggest that the use of cholinesterase inhibitors may offer clinical benefits in many PDD patients, and may encourage the use of licensed agents in this condition.

The current analysis is limited by its *post-hoc* nature, and the findings must therefore be interpreted with caution. Patients were allowed to take a range of concomitant drugs, reflective of normal clinical practice. However, some psychotropic drugs are known to impact motor symptoms,[43] and these effects were not controlled in the current analyses (changes in antipsychotic use in the rivastigmine group were comparable with those seen with placebo, and therefore this was not considered necessary). Early discontinuations due to AEs may have had the potential to bias the results. It is feasible that patients withdrawing from the study due to AEs may leave a population of patients better able to tolerate rivastigmine and therefore bias the tolerability data in favour of rivastigmine in remaining patients. This may be particularly true in long-term studies in which patients less able to tolerate treatment are more likely to discontinue at an earlier stage. The fact that the reasons for some patients not entering the open-label extension phase were not recorded may also limit interpretation as it is not known whether these reasons might bias the results. In addition, a possible worsening effect on the UPDRS motor subscale may have been masked by the level of variance in scoring. A large number of centres participated in the study, and this may have contributed to the large standard deviations seen on this assessment. Nevertheless, the UPDRS scores provide the most comprehensive data to date on the effects of a cholinesterase inhibitor on motor symptoms in a well defined, prospectively studied population of patients with PDD. The patients taking part in this study were carefully selected, with at least a 2-year delay (mean 6.8 years) between the diagnosis of PD and the onset of symptoms of dementia, to differentiate them from patients with DLB. A range of concomitant medications were permitted, as were various concurrent illnesses.

Conclusions

In conclusion, although emergent or worsening tremor was reported in approximately one in ten rivastigmine-treated patients during the double-blind trial, a 2- to 3-fold higher rate than in the placebo group, rivastigmine did not induce clinically significant exacerbation of motor dysfunction in patients with PDD. Emerging or working rest tremor as an AE was usually a transient phenomenon during up-titration of the drug, did not result in substantially increased use of dopaminergic medication, and resulted in few discontinuations. In particular, the AE of tremor in rivastigmine-treated patients was not reflected in worse overall UPDRS motor scale scores, although slight deterioration was seen on the resting tremor item. Similar improvements in the symptoms of dementia, including the ability to perform activities of daily living, were seen regardless of whether exacerbation of tremor was reported during the study. There was no indication that long-term exposure to rivastigmine was associated with a worsening of PD. When treating PDD patients with rivastigmine, clinicians should remain vigilant, especially at the time of rivas-

tigmine initiation and dose titration. However, the risk of a clinically significant exacerbation of motor symptoms, notably tremor, appears to be low.

Acknowledgements

This research was funded by Novartis Pharmaceuticals. The sponsor has provided Professors Oertel and Emre with grant support, and personal honoraria. Professors Wolters, De Deyn and Poewe have received personal honoraria from the sponsor during their careers. Dr Kirsch was an employee of the sponsor during the development of the manuscript. Dr Hsu is an employee of the sponsor. Drs Tekin and Lane are employees of the sponsor and have equity or ownership interest.

References

1. Lang AE, Lozano AM. Parkinson's disease: first of two parts. N Engl J Med 1998; 339: 1044-53
2. Perry EK, Curtis M, Dick DJ, et al. Cholinergic correlates of cognitive impairment in Parkinson's disease: comparison with Alzheimer's disease. J Neurol Neurosurg Psychiatry 1985; 48: 413-21
3. Tiraboschi P, Hansen LA, Alford M, et al. Cholinergic dysfunction in diseases with Lewy bodies. Neurology 2000; 54: 407-11
4. Bohnen NI, Kaufer DI, Ivanco LS, et al. Cortical cholinergic function is more severely affected in parkinsonian dementia than in Alzheimer disease: an in vivo positron emission tomographic study. Arch Neurol 2003; 60: 1745-8
5. Hutchinson M, Fazzini E. Cholinesterase inhibition in Parkinson's disease. J Neurol Neurosurg Psychiatry 1996; 61: 324-6
6. Bullock R, Cameron A. Rivastigmine for the treatment of dementia and visual hallucinations associated with Parkinson's disease. Curr Med Res Opin 2002; 18: 258-64
7. Reading PJ, Luce AK, McKeith IG. Rivastigmine in the treatment of parkinsonian psychosis and cognitive impairment: preliminary findings from an open trial. Mov Disord 2001; 16: 1171-95
8. Fogelson N, Kogan E, Korczyn AD, et al. Effects of rivastigmine on the quantitative EEG in demented parkinsonian patients. Acta Neurol Scand 2003; 107: 252-5
9. Romrell J, Fernandez HH, Okun MS. Rationale for current therapies in Parkinson's disease. Expert Opin Pharmacother 2003; 4: 1747-61
10. Grady SR, Salminen O, Laverty DC, et al. The subtypes of nicotinic acetylcholine receptors on dopaminergic terminals of mouse striatum. Biochem Pharmacol 2007; 74: 1235-46
11. Millan MJ, DiCara B, Dekeyne A, et al. Selective blockade of dopamine D(3) versus D(2) receptors enhances frontocortical cholinergic transmission and social memory in rats: a parallel neurochemical and behavioural analysis. J Neurochem 2007; 100: 1047-61
12. Zarow C, Lyness SA, Mortimer JA, et al. Neuronal loss is greater in the locus coeruleus than nucleus basalis and substantia nigra in Alzheimer and Parkinson diseases. Arch Neurol 2003; 60: 337-41
13. Jellinger K. The pedunculopontine nucleus in Parkinson's disease, progressive supranuclear palsy and Alzheimer's disease. J Neurol Neurosurg Psychiatry 1988; 51: 540-3
14. Rub U, Del Tredici K, Schultz C, et al. Parkinson's disease: the thalamic components of the limbic loop are severely impaired by alpha-synuclein immunopositive inclusion body pathology. Neurobiol Aging 2002; 23: 245-54
15. Glowinski J. Recent finding on dopaminergic transmission in the basal ganglia. Adv Neurol 1990; 53: 67-73
16. Liang YQ, Tang XC. Comparative studies of huperzine A, donepezil, and rivastigmine on brain acetylcholine, dopamine, norepinephrine, and 5-hydroxytryptamine levels in freely-moving rats. Acta Pharmacol Sin 2006; 27: 1127-36
17. Emre M, Aarsland D, Albanese A, et al. Rivastigmine for the dementia associated with Parkinson's disease. N Engl J Med 2004; 351: 29-38
18. Poewe W, Wolters E, Emre M, et al. Long-term benefits of rivastigmine in dementia associated with Parkinson's disease: an active treatment extension study. Mov Disord 2006; 21: 456-61
19. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association, 1994
20. Fahn S, Elton RL and Members of the UPDRS development committee. Unified Parkinson's disease rating scale. In: Fahn S, Marsden CD, Calne DB, et al., editors. Recent developments in Parkinson's disease. Florham Park (NJ): MacMillan Healthcare Information, 1987: 153-64
21. Galasko D, Bennett D, Sano M, et al. An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord 1997; 11 Suppl. 2: S33-9
22. Brønnick K, Ehrt U, Emre M, et al. Attentional deficits affect activities of daily living in dementia associated with PD. J Neurol Neurosurg Psychiatry 2006; 77: 1136-42
23. Burn D, Emre M, McKeith I, et al. Effects of rivastigmine in patients with and without visual hallucinations in dementia associated with Parkinson's disease. Mov Disord 2006; 21: 1899-907
24. Jankovic J, Kapadia AS. Functional decline in Parkinson disease. Arch Neurol 2001; 58: 1611-5
25. Alves G, Wentzel-Larsen T, Aarsland D, et al. Progression of motor impairment and disability in Parkinson disease: a population-based study. Neurology 2005; 65: 1436-41
26. Barbeau A. The pathogenesis of Parkinson's disease: a new hypothesis. Can Med Assoc J 1962; 87: 802-7
27. Duvoisin RC. Cholinergic-anticholinergic antagonism in parkinsonism. Arch Neurol 1967; 17: 124-36
28. Touchon J, Bergman H, Bullock R, et al. Response to rivastigmine or donepezil in patients with Alzheimer's disease and symptoms suggestive of concomitant Lewy body pathology. Curr Med Res Opin 2006; 22: 49-59
29. Giladi N, Shabtai H, Gurevich T, et al. Rivastigmine (Exelon) for dementia in patients with Parkinson's disease. Acta Neuro Scand 2003; 108: 367-73
30. McKeith I, Del Ser T, Spano P, et al. Efficacy of rivastigmine in dementia with Lewy bodies: a randomized double-blind, placebo controlled international study. Lancet 2000; 356: 2031-6
31. Gurevich TY, Shabtai H, Korczyn AD, et al. Effect of rivastigmine on tremor in patients with Parkinson's disease and dementia. Mov Disord 2006; 21: 1663-6
32. Darvesh S, Hopkins DA, Geula C. Neurobiology of butyrylcholinesterase. Nat Rev Neurosci 2003; 4: 131-8
33. Bullock R, Lane R. Executive dyscontrol of dementia, with emphasis on subcortical pathology and the role of butyrylcholinesterase. Curr Alzheimer Res 2007; 4: 277-93

34. Dubois B, Tolosa E, Kulisevsky J, et al. Efficacy and safety of donepezil in the treatment of Parkinson's disease patients with dementia [poster presentation]. 8th International Conference on Alzheimer's and Parkinson's Diseases; 2007 Mar 14-18; Salzburg
35. Richards M, Stern Y, Marder K, et al. Relationships between extrapyramidal signs and cognitive function in a community-dwelling cohort of patients with Parkinson's disease and normal elderly individuals. Ann Neurol 1993; 33: 267-74
36. Wilson RS, Schneider JA, Bienias JL, et al. Parkinsonian like signs and risk of incident Alzheimer disease in older persons. Arch Neurol 2003; 60: 539-44
37. Wilson RS, Bennett DA, Gilley DW, et al. Progression of parkinsonian signs in Alzheimer's disease. Neurology 2000; 54: 1284-9
38. Fleischman DA, Wilson RS, Bienias JL, et al. Parkinsonian signs and cognitive function in old age. J Int Neuropsychol Soc 2005; 11: 591-7
39. Alves G, Larsen JP, Emre M, et al. Changes in motor subtype and risk for incident dementia in Parkinson's disease. Mov Disord 2006; 21: 1123-30
40. Deuschl G, Raethjen J, Baron R, et al. The pathophysiology of parkinsonian tremor: a review. J Neurol 2000; 247 Suppl. 5: V33-48
41. Aarsland D, Laake K, Larsen JP, et al. Donepezil for cognitive impairment in Parkinson's disease: a randomised controlled study. J Neurol Neurosurg Psychiatry 2002; 72: 708-12
42. Ravina B, Putt M, Siderowf A, et al. Donepezil for dementia in Parkinson's disease: a randomized, double-blind, placebo controlled, crossover study. J Neurol Neurosurg Psychiatry 2005; 76: 934-9
43. Lahti AC, Holcomb HH, Weiler MA, et al. Functional effects of antipsychotic drugs: comparing clozapine with haloperidol. Biol Psychiatry 2003; 53: 601-8

Correspondence: Prof. *Wolfgang Oertel*, Klinik für Neurologie, Philipps-Universität, Rudolf-Bultmann Strasse 8, D 35033 Marburg, Germany.
E-mail: oertelw@med.uni-marburg.de