PAPER

Donepezil for cognitive impairment in Parkinson's disease: a randomised controlled study

D Aarsland, K Laake, J P Larsen, C Janvin

J Neurol Neurosurg Psychiatry 2002;**72**:708–712

See end of article for authors' affiliations

Correspondence to: Dr D Aarsland, Section of Geriatric Psychiatry, Psychiatric Hospital of Rogaland, Arm. Hansen v 20, 4095 Stavanger, Norway; aarsland@netpower.no

Received 9 August 2001
In revised form 19 November 2001
Accepted 14 December 2001

Objective: To study the safety and efficacy of the cholinesterase inhibitor donepezil in patients with Parkinson's disease (PD) and cognitive impairment.
Methods: This was a double blind, randomised and placebo controlled, crossover study in which 14 patients with PD and cognitive impairment received donepezil (5 or 10 mg per day) or matching placebo during two sequential periods lasting 10 weeks each. The primary outcome measures were the mini mental state examination (MMSE) score, the clinician's interview based impression of change plus caregiver input (CIBIC+) score, and the motor subscale of the unified Parkinson's disease rating scale (UPDRS).
Results: Two patients on donepezil (14%) dropped out after one and four weeks of the first treatment period because of peripheral cholinergic side effects, otherwise the adverse effects were few and not severe. Carryover or residual effects were not observed. Parkinsonism did not increase during donepezil treatment. After 10 weeks of treatment, the mean MMSE score was increased by 2.1(SD 2.7) points on donepezil and 0.3 (SD 3.2) points on placebo, and the CIBIC+ score was 3.3 (SD 0.9) on donepezil and 4.1 (SD 0.8) on placebo. Statistical analysis of the repeated measurements and crossover study design showed significant effects of donepezil compared with placebo for MMSE (p=0.013) and CIBIC+ (p=0.034). Five (42%) patients on donepezil and two (17%) on placebo were rated as improved on the basis of the CIBIC+ score.
Conclusions: Donepezil improves cognition, and seems to be well tolerated and not to worsen parkinsonism in patients with cognitive impairment.

The prevalence of Parkinson's disease (PD) is nearly 1% in the population 65 years of age and above.[1] Cognitive impairment and dementia often accompany the motor manifestations of the disease. Studies suggest that 25–30% of patients with PD are demented,[2] and the risk of dementia in PD is nearly six times higher than in the general population.[3] Cognitive impairment in patients with PD has important clinical consequences with regard to risk for nursing home placement[4] and caregiver stress.[5]

PD is caused by a progressive degeneration of dopaminergic neurones in the substantia nigra where the principal neuropathological finding is Lewy bodies.[6] These are also found in the cortex of most patients with PD[7] and may contribute to the development of dementia.[8] Neuropathological[9] and imaging[10] studies in patients with PD who have dementia have shown appreciable dysfunction of the cholinergic neurones in the nucleus of Meynert and their cortical terminals, suggesting that cholinergic deficits are also involved in the cognitive impairment in PD.

Cholinergic deficits are typical in Alzheimer's disease,[9] in which treatment with cholinesterase inhibitors improves cognition and activities of daily living.[11] There is also evidence to suggest that cholinergic agents improve cognition in dementia with Lewy bodies (DLB),[12] a disorder with clinical, neurochemical, and pathological similarities to PD.[13] Preliminary results from an open study of treatment of cognitively impaired patients with PD with the cholinesterase inhibitor tacrine[14] suggest that this class of drugs improves cognition in PD, but placebo controlled studies have not yet been reported. The aim of this study was therefore to test the hypothesis that a cholinesterase inhibitor, donepezil, improves cognition in patients with PD and cognitive impairment. Because concern has been expressed that cholinesterase inhibitors may increase parkinsonism, the motor symptoms of PD were monitored during the study.

MATERIALS AND METHODS

Consecutive patients with PD and cognitive impairment, diagnosed at the outpatient clinic of the Department of Neurology at the Central Hospital of Rogaland, Stavanger, were invited to participate. The diagnostic evaluation comprised physical and neurological examinations, a clinical interview of the patient and caregiver based on the *Diagnostic and statistical manual of mental disorders*, 4th ed[15] (DSM-IV) criteria for dementia due to PD, neuropsychological examination, routine blood tests, a computed tomography scan of the brain, and a chest radiograph. To exclude patients with a lower probability of idiopathic PD, only patients with clinically definite and probable PD, according to published criteria,[16] were recruited to the study. A diagnosis of clinically definite PD requires that the patient has resting tremor, at least two additional cardinal signs (akinesia, rigidity, or postural abnormalities), unilateral onset and asymmetrical development of the disease, and a good to excellent response to a dopaminergic drug. No atypical features should be present in the history or on the clinical examination. For a diagnosis of clinically probable PD, the patient should have at least two of the four cardinal features of parkinsonism. Resting tremor is not mandatory, and not more than one of the following clinical features may be present: mild dementia or clinically relevant autonomic failure at disease onset; symmetrical disease presentation; no better than a moderate response to a dopaminergic agent; other atypical features.

The inclusion criteria were: mild to severe parkinsonism (Hoehn and Yahr[17] stage less than 5); age 45–95 years; clinical

Abbreviations: PD, Parkinson's disease; MMSE, mini mental state examination; UPDRS, unified Parkinson's disease rating scale; NPI, neuropsychiatric inventory; DLB, dementia with Lewy bodies

evidence of decline in memory and at least one other category of cognitive function; onset of cognitive decline starting one year or more after the onset of parkinsonism; a mini mental state examination (MMSE)[18] score of 16–26. (Patients with more severe cognitive impairment would not be able to complete the neuropsychological battery.) The treatment of the disease should have remained stable during the month preceding the baseline evaluation, and was continued during the study. The spouse or another caregiver accompanied the patient to the hospital for the assessments to act as an informant. Patients with brain disease other than PD or with other severe medical disorders were excluded. The subjects were not be taking anticholinergic drugs or psychotropic agents with anticholinergic effects. All patients provided informed consent, and the study protocol was approved by the committee for ethics in biomedical research of the University of Bergen, Norway.

Design

This was a double blind, placebo controlled, crossover trial with two treatment periods of 10 weeks each. A randomisation list was computer generated according to a randomised block design. The various treatment-placebo and placebo-treatment blocks were then issued with a medication number and assigned to consecutive patients. The principal investigator (DA) was given a sealed envelope containing the individual treatment regimens of each patient. This envelope was to be opened only in case of emergency. All personnel involved in the study remained unaware of the group assignment until all patients had completed the trial.

The assessments took place at baseline and after six and 10 weeks of each treatment period—that is, at week 6, 10, 16, and 20. A previous study of donepezil in patients with Alzheimer's disease showed that cognition declined to baseline level within three weeks of withdrawal.[19] A washout period between the two treatment periods was therefore not considered necessary. The initial dose was donepezil 5 mg or identically appearing placebo tablets taken once a day in the evening. The dose was increased to 10 mg after six weeks if well tolerated. Glasses containing 49 or 35 tablets were given to the patient and caregiver for each six or four week treatment period respectively—that is, one glass for each patient and each dose. The assessments were scheduled at about the same time of the day for each patient, and patients with parkinsonian motor fluctuations were examined in their "on phase"—that is, at their best level of motor functioning. Short acting hypnotics (zolpidem or zopiklon) were allowed, but longer acting benzodiazepines were not allowed to be taken within the 24 hours before testing.

Outcome measures

The primary outcomes were: (*a*) the MMSE score; (*b*) the clinician's interview based impression of change (CIBIC+), which provides a global impression of a patient's cognitive improvement or deterioration over time, scored on the basis of an interview with the patient and a caregiver on a seven point scale (1=very much improved; 4=no change; 7=very much worse) by a clinician, blinded to other assessments; (*c*) the motor subscale of the unified Parkinson's disease rating scale (UPDRS),[20] which assesses the severity of parkinsonism. In addition, psychiatric symptoms such as hallucinations, delusions, agitation, depression, and apathy were rated by the psychiatrist using the neuropsychiatric inventory (NPI).[21] The caregiver and patient also evaluated whether parkinsonism had improved, declined, or remained unchanged during each treatment period using the same seven point scale as the CIBIC+. In addition, the patients completed a battery of neuropsychological tests assessing verbal and visual memory, executive functions, visuospatial abilities, and attention. These results will be described in more detail elsewhere.

Drug compliance and safety

Dosing compliance was assessed by interviewing the caregiver and tablet counts. Patients were excluded if the number of tablets removed from the bottles divided by the number of treatment days between each visit was outside the range 70–130%. Safety evaluations conducted at each assessment point comprised vital signs and an interview based check list for adverse events based on the Scandinavian society for psychopharmacological scale for side effects.[22]

Statistical analysis

Detailed analysis of the outcome variables were carried out using the general linear model (SYSTAT, SPSS Inc) to encompass the repeated measurement and crossover structure of the design. Subject, treatment, period, and a residual effect (nested with period) of the treatment given in the previous period (coded as none, drug, or placebo) were modelled as categorical. Tests for carryover and period effects were performed. Patients were included in the efficacy analysis if they had both a baseline score and at least one score after the baseline (last observation carried forward). Differences in frequency of side effects were tested with McNemar's test of symmetry using exact methods. Data from patients who had received at least one dose of study drugs were considered for the safety analysis. $p<0.05$ was assumed to be significant.

RESULTS

Thirty three patients were screened, and 14 (13 men, one woman) were randomised (fig 1). Two patients (14%), both male, withdrew from the study because of adverse reactions (dizziness, nausea, and diarrhoea) before the evaluation at week 6 of the first study period; both were receiving donepezil. The remaining 12 all completed the study, assessed according to the protocol, and included in the further analyses. Dose increments were carried out according to the protocol for 11 of the patients. In one patient, the dose was not increased owing to a misunderstanding, and this patient continued on 5 mg donepezil during the final four weeks of the treatment period. Tablet counts showed a high degree of drug compliance (mean 101%, range 83–123%).

Seven subjects were diagnosed as suffering from clinically definite PD and five from clinically probable PD. The mean Hoehn and Yahr stage was 2.4 (range 1–4), age 71.0 (SD 3.9) years, duration of PD 10.8 (SD 5.2) years, baseline MMSE score 20.8 (SD 3.4) (range 16–26), duration of cognitive decline 3.0 (SD 2.6) years, and levodopa dose 485 (SD 256) mg a day. The two treatment groups did not differ with regard to baseline MMSE score, age, or duration of disease. There was a trend towards higher mean UPDRS motor score in the donepezil-placebo group (35.3 (SD 17.0)) compared with the placebo-donepezil group (28.8 (SD 14.0)) ($t=0.7$, $df=10$, $p=0.49$). Eleven patients had impairment of at least two cognitive domains other than memory. Eight patients fulfilled all the DSM-IV criteria for dementia due to PD, while significant functional impairment due to cognitive deficits could not be definitely verified for four.

Effects on primary outcomes

At the end of both treatment periods, patients on donepezil had higher MMSE and lower CIBIC+ scores than those on placebo (table 1), indicating improvement under donepezil treatment. The statistical modelling of the MMSE and the CIBIC+ data showed no significant residual effect nested with treatment period ($p=0.87$ and $p=0.53$ respectively). In the group receiving donepezil first, the MMSE score six weeks after crossover to placebo was 20.3 (SD 3.2), compared with 20.8 (SD 3.9) at baseline. There was thus no indication of a carryover effect. A significant treatment effect of donepezil on the MMSE score compared with placebo was found ($F=9.1$,

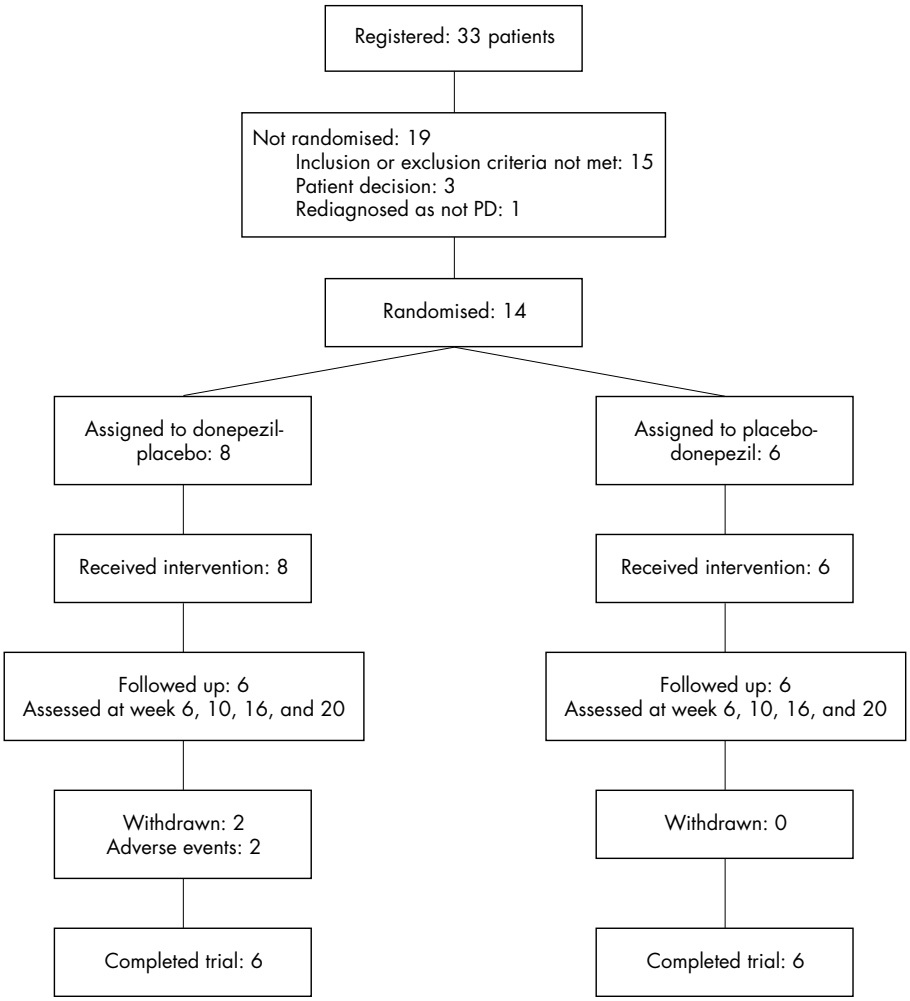

Figure 1 Progress of the patients throughout the 20 weeks of the crossover trial. Intervention was the administration of donepezil or placebo during two treatment sequences of 10 weeks each.

df=1, p=0.013). On donepezil, the mean MMSE score difference from baseline to week 10 was 2.1 (SD 2.7) points and on placebo 0.3 (SD 3.2) points. Figure 2 shows the mean MMSE scores by group. There were negative, but non-significant, correlations between baseline MMSE scores and change during donepezil treatment at week 6 (Pearson r=–0.01) and week 10 (r=–0.38, p=0.22).

Three patients had missing data on the CIBIC+ (two at week 6 and one at week 16). These data points were coded as no change. After 10 weeks of treatment, five (42%) patients on donepezil and two (17%) on placebo were rated as improved—that is, a CIBIC+ score of 3 or lower. The mean CIBIC+ score at week 10 was 3.3 (SD 0.9) during donepezil treatment and 4.1 (SD 0.8) during placebo treatment. Statistical modelling showed a significant treatment effect in favour of donepezil on this outcome also (F=6.0, df=1, p=0.034). Reanalysis of the data without recoding the missing CIBIC+ data points, thereby excluding data from three cases from the analysis, resulted in a p value of 0.079.

The scores on the UPDRS motor subscale disclosed no deterioration in parkinsonian symptoms after 10 weeks of treatment with donepezil (p=0.37). Similarly, neither the caregivers nor the patients reported worsening of parkinsonism (p=0.20) (table 1). Few of the 12 patients had positive NPI scores on delusions (n=3), hallucinations (n=2), agitation (n=1), depression (n=6), or apathy (n=5) at baseline, and

Table 1 Scores on efficacy measures at baseline and after treatment with donepezil and placebo

		After 6 weeks		After 10 weeks	
	Baseline	Donepezil	Placebo	Donepezil	Placebo
MMSE score	20.8 (3.4)	22.7 (3.6)*	19.9 (4.0)	22.8 (3.7)*	21.0 (5.0)
CIBIC+ score	–	3.1 (0.9)*	3.7 (0.5)	3.3 (0.9)*	4.1 (0.8)
UPDRS motor score	32.1 (15.2)	–	–	31.8 (15.4)	35.1 (8.1)
Subjective impression of parkinsonism	–	3.6 (1.2)	3.8 (1.4)	3.7 (1.1)	4.2 (1.5)

Values are mean (SD) or number (%) of patients with at least one score after the baseline.
*p<0.05 compared with placebo (repeated measurements analysis of variance).
MMSE, Mini-mental state examination; UPDRS, unified Parkinson's disease rating scale; CIBIC+, Clinician's interview based impression of change based on carer information.

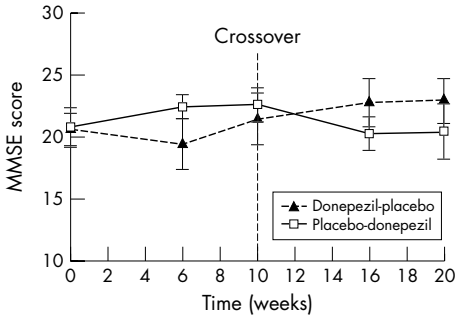

Figure 2 Change in mini mental state examination (MMSE) score from baseline over the two treatment sequences. Values are mean (SE).

Table 2 Number with adverse events reported during treatment with donepezil and placebo

	Any degree (moderate/severe)	
	Donepezil (n=14*)	Placebo (n=12)
Nausea	4 (3)	2 (1)
Headache	4 (3)	3 (1)
Tiredness	7 (6)	6 (5)
Insomnia	2 (1)	2 (1)
Increased dreaming	3 (2)	5 (2)
Dizziness	7 (3)	3 (1)
Increased sweating	6 (5)	3 (2)
Increased salivation	6 (4)	4 (1)
Dry mouth	4 (2)	5 (2)
Diarrhoea	2 (2)	2 (1)
Constipation	5 (2)	4 (0)
Urinary retention	0	0
Rash	3 (0)	0
Any adverse event	12 (11)	9 (7)
Number of adverse events per person, mean (SD)	4.2 (3.2)	2.8 (1.0)

*14 patients received donepezil treatment, but only 12 received placebo treatment because two patients dropped out.

mean NPI scores were low at baseline. No significant treatment effects were observed with regard to any of the NPI items (results not shown).

Adverse events

Table 2 shows the proportion of patients reporting adverse events. The number of patients reporting any adverse events while taking donepezil was 10 out of 14 (71%) and while taking placebo nine out of 12 (75%) (14 patients entered the donepezil condition, and only 12 the placebo condition). Most specific examples of adverse events were more common during donepezil than during placebo treatment, but statistical significance (McNemar's test) was not reached. However, owing to the few patients in the study, the power of detecting significant differences was low.

DISCUSSION

This study shows that donepezil improves performance on the MMSE and the clinician's interview based impression of cognition in patients with PD and cognitive impairment. Clinical improvement was reported for 42% of the patients receiving donepezil compared with 17% receiving placebo. To the best of our knowledge, this is the first placebo controlled trial reporting a benefit of a cholinesterase inhibitor in patients with PD and cognitive impairment. We found no indication that such treatment worsens parkinsonism. Two of 14 patients withdrew because of typical side effects of donepezil. The remaining 12 did not report significantly more side effects in the donepezil than the placebo condition. However, the power of this small study is evidently too low to give precise estimates for the prevalence of side effects of donepezil in patients with PD and cognitive impairment.

The small sample size and the skewed sex distribution may raise concern about the representativeness of the patients. However, age, disease duration, stage of parkinsonism, and level of cognitive impairment as measured by the MMSE score were similar to that of a representative community based sample of patients with PD and mild to moderate dementia previously reported.[2] Eight patients fulfilled the DSM-IV criteria for dementia due to PD, and another three fulfilled the dementia criteria suggested by Cummings and Benson.[23] This suggests that the results are generalisable to patients with PD and mild to moderate dementia.

As patients with parkinsonism and dementia may also fulfil criteria for possible DLB,[24] there was a possibility that patients with DLB erroneously diagnosed as suffering from PD were included. Care was therefore taken to exclude patients who might fulfil clinical criteria for DLB. According to an international panel of experts, the main clinical feature distinguishing PD from DLB is the sequence of the development of symptoms. In particular, if dementia[24] or hallucinations[25] develops within one year of onset of parkinsonism, such patients should be diagnosed with DLB and not PD. This type of patient was excluded from this study. In our study, the mean duration of parkinsonism was nearly 10 years before cognitive decline started to become evident, strongly indicating that the patients included would have been diagnosed as PD and not DLB using modern diagnostic criteria.[26] On the other hand, patients with PD often have some Lewy bodies in their cerebral cortex,[7] and recent studies suggest that cortical Lewy bodies contribute to dementia in PD.[8] Thus, DLB and PD with dementia may be neuropathologically indistinguishable. Further studies are needed to clarify the exact clinical, pathological, and nosological distinction between DLB and PD.

The advantage of a crossover design is that comparison can be made within subjects rather than between subjects, and the sample size needed will therefore be smaller.[27] However, the disadvantage is the risk of confounding caused by carryover and period effects, and that patients may be withdrawn during the first treatment period and therefore not receive the second treatment. The results in our study did not indicate any carryover effect. This is consistent with studies on Alzheimer's disease showing that the effect of donepezil had disappeared three weeks after withdrawal.[19]

Neocortical cholinergic activity is reduced in PD and at least as severe in patients with PD and dementia as in patients with Alzheimer's disease.[9 28] Choline acetyltransferase activity in the temporal cortex of patients with PD and dementia correlates with the number of cholinergic neurones in the nucleus of Meynert and with cognition, but not with the extent of plaques or tangles.[29] There are indications that postsynaptic muscarinic receptors are better preserved and are more functionally intact in patients with PD and dementia than in those with Alzheimer's disease.[9] Accordingly, cholinergic drugs may be more effective in demented patients with PD than in those with Alzheimer's disease. This may explain why the differences between active drug and placebo on the MMSE and CIBIC+ scores seemed more pronounced in our study than in trials on patients with Alzheimer's disease.[11] This is also in line with previous reports suggesting a better response to cholinergic treatment in DLB than in Alzheimer's disease.[30] However, given the crossover design and the limited number of patients, our findings must be confirmed in larger parallel group trials before donepezil can be recommended for cognitive impairment in patients with PD.

ACKNOWLEDGEMENTS

The study received partial support from Pfizer Norway Inc. We thank N G Lim and H R Marianayagam for assistance with patient assessment.

Authors' affiliations

D Aarsland, C Janvin, Section of Geriatric Psychiatry, Psychiatric Hospital of Rogaland, Stavanger, Norway
K Laake, Department of Geriatric Medicine, Ullevål Hospital, Oslo, Norway
J P Larsen, Department of Neurology, Central Hospital of Stavanger, Norway

Competing interests: DA, JPL, and KL have been reimbursed by Pfizer Inc, the manufacturer of donepezil, for attending several conferences, and have received fees for speaking, consulting, and organising education. The present study was partially funded by a grant from Pfizer Inc. None of the authors have been employed by, or hold any stocks or shares in, Pfizer.

REFERENCES

1 **Tandberg E**, Larsen JP, Nessler EG, *et al*. The epidemiology of Parkinson's disease in the county of Rogaland, Norway. *Mov Disord* 1995;**10**:541–9.
2 **Aarsland D**, Tandberg E, Larsen JP, *et al*. Frequency of dementia in Parkinson's disease. *Arch Neurol* 1996;**53**:538–42.
3 **Aarsland D**, Andersen K, Larsen JP, *et al*. Risk of dementia in Parkinson's disease: a community-based, prospective study. *Neurology* 2001;**56**:730–6.
4 **Aarsland D**, Larsen JP, Karlsen K, *et al*. Mental symptoms in Parkinson's disease are important contributors to caregiver distress. *Int J Geriatr Psychiatry* 1999;**14**:866–74.
5 **Aarsland D**, Larsen JP, Tandberg E, *et al*. Predictors of nursing home placement in Parkinson's disease: a population-based, prospective study. *J Am Geriatr Soc* 2000;**48**:938–42.
6 **Forno LS**. Neuropathology of Parkinson's disease. *J Neuropathol Exp Neurol* 1996;**55**:259–72.
7 **Hughes AJ**, Daniel SE, Blankson S, *et al*. A clinicopathologic study of 100 cases of Parkinson's disease. *Arch Neurol* 1993;**50**:140–8.
8 **Hurtig HI**, Trojanowski JQ, Galvin J, *et al*. Alpha-synuclein cortical lewy bodies correlate with dementia in Parkinson's disease. *Neurology* 2000;**54**:1916–21.
9 **Perry E**, Irving D, Kerwin JM, *et al*. Cholinergic transmitter and neurotrophic activities in Lewy body dementia: similarity to Parkinson's and distinction from Alzheimer disease. *Alzheimer Dis Assoc Disord* 1993;**7**:69–79.
10 **Kuhl DE**, Minoshima S, Fessler JA, *et al*. In vivo mapping of cholinergic terminals in normal aging, Alzheimer's disease, and Parkinson's disease. *Ann Neurol* 1996;**40**:399–410.
11 **Rogers SL**, Farlow MR, Doody RS, *et al*. A 24-week, double-blind,placebo-controlled study of donepezil in patients with Alzheimer's disease. *Neurology* 1998;**50**:136–45.
12 **McKeith I**, Del Ser, Spano PF, *et al*. Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind placebo-controlled international study. *Lancet* 2000;**356**:2031–6.
13 **McKeith IG**, Burn D. Spectrum of Parkinson's disease, Parkinson's dementia, and Lewy body dementia. *Neurol Clin* 2000;**18**:865–83.
14 **Hutchinson M**, Fazzini E. Cholinesterase inhibition in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1996;**61**:324–6.
15 **American Psychiatric Association**. Diagnostic and statistical manual of mental disorders. 4th ed. Revised. Washington DC: American Psychiatric Association.
16 **Larsen JP**, Dupont E, Tandberg E. The clinical diagnosis of Parkinson's disease: proposal of diagnostic subgroups classified at different levels of confidence. *Acta Neurol Scand* 1994;**84**:242–51.
17 **Hoehn MH**, Yahr MD. Parkinsonism: onset, progression, and mortality. *Neurology* 1967;**17**:427–42.
18 **Folstein MF**, Folstein SE, McHugh PR. "Mini-Mental State": a practical method for grading the mental state of patients for the clinician. *J Psychiatr Res* 1975;**12**:189–98.
19 **Greenberg SM**, Tennis MK, Brown LB, *et al*. Donepezil therapy in clinical practice. A randomized cross-over study. *Arch Neurol* 2000;**57**:94–9.
20 **Fahn S**, Elton RL. Members of the UPDRS Development Committee. Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Calne DB, *et al*, eds. *Recent development in Parkinson's disease*. Florham Park, NJ: Macmillan Health Care Information, 1987:153–63.
21 **Cummings JL**, Mega M, Gray K, *et al*. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology* 1994;**44**:2308–14.
22 **Lingjærde O**, Ahlfors UG, Bech P, *et al*. The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side-effects in neuroleptic-treated patients. *Acta Psychiatr Scand* 1987;**76**(suppl):334.
23 **Cummings JL**, Benson DF. *Dementia: a clinical approach*. 2nd ed. Boston: Butterworth-Heinemann, 1992.
24 **McKeith IG**, Galasko D, Kosaka K, *et al*. Consensus guidelines for the clinical diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. *Neurology* 1996;**47**:1113–24.
25 **Litvan I**, MacIntyre A, Goetz CG, *et al*. Accuracy of the clinical diagnoses of Lewy body disease, Parkinson's disease, and dementia with Lewy bodies. *Arch Neurol* 1998;**55**:969–78.
26 **Gelb DJ**, Oliver E, Gilman S. Diagnostic criteria for Parkinson's disease. *Arch Neurol* 1999;**56**:33–9.
27 **Altman DG**. *Practical statistics for medical research*. London: Chapman & Hall/CRC, 1991:447.
28 **Tiraboschi P**, Hansen LA, Alford M, *et al*. Cholinergic dysfunction in diseases with Lewy bodies. *Neurology* 2000;**54**:407–11.
29 **Perry E**, Curtis M, Dick DJ, *et al*. Cholinergic correlates of cognitive impairment in Parkinson's disease: comparisons with Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 1985;**48**:413–21.
30 **Samuel W**, Caligiuri M, Galasko D, *et al*. Better cognitive and psychopathologic response to donepezil in patients prospectively diagnosed as dementia with Lewy bodies: a preliminary study. *Int J Geriatr Psychiatry* 2000;**15**:794–802.