INTERNATIONAL JOURNAL OF GERIATRIC PSYCHIATRY
Int. J. Geriatr. Psychiatry **15**, 713–720 (2000)

DONEPEZIL IN ALZHEIMER'S DISEASE: EIGHTEEN MONTH RESULTS FROM SOUTHAMPTON MEMORY CLINIC

HELEN P. MATTHEWS[1]*, JANE KORBEY[1], DAVID G. WILKINSON[2] AND JENNIFER ROWDEN[1]
[1] *Southampton Memory Clinic, Moorgreen Hospital, Southampton SO30 3JB, UK*
[2] *Thornhill Research Unit, Moorgreen Hospital, Southampton SO30 3JB, UK*

ABSTRACT

The objective of this study was to assess the efficacy of donepezil in patients with mild to moderate Alzheimer's disease (AD) in clinical practice. This was an open-label study in which patients were referred to an elderly mental health clinic in Southampton, UK. Eighty patients with mild to moderate AD received 5 mg/day donepezil for the first 4 weeks, after which, if tolerated, the dose was increased to 10 mg/day. Efficacy and safety assessments were carried out every 3 months. Efficacy was assessed by the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog), Mini-Mental State Examination (MMSE), Neuropsychiatric Inventory (NPI), Neuropsychiatric Inventory-carer Distress Scale (NPI-D). Mean improvements from baseline were observed at the 3-month assessment on all four efficacy measures. At 3 months, 39% of patients showed an improvement of at least 4 points on the ADAS-cog, and 37% of patients had improved by 4 points or more on the NPI. In those patients who showed improvement and were maintained on donepezil, improvements were sustained for 18 months on the MMSE and NPI, 15 months on the NPI-D, and for 6 months on the ADAS-cog. Six per cent of patients discontinued medication due to adverse events. In a typical clinical practice setting, patients with mild to moderate AD tolerated donepezil well. Clinically meaningful improvements in cognitive function and a reduction in neuropsychiatric symptoms were demonstrated in nearly 40% of patients with associated reduction in carer distress. Continued benefit was seen for up to 18 months in the selected group of patients who initially responded to treatment. Copyright © 2000 John Wiley & Sons, Ltd.

KEY WORDS—Alzheimer's disease; donepezil; cholinesterase inhibitors; cognitive function; neuropsychiatric symptoms; carer distress

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia, affecting 500,000 people in the United Kingdom (Alzheimer's Disease Society, 1996). Until the approval of the acetylcholinesterase inhibitor donepezil hydrochloride in February 1997, there was no drug licensed to treat this disorder in the UK. The advent of donepezil led to increased public awareness of AD, promotion of earlier diagnosis and a demand for the provision and assessment of anti-dementia treatments. The difficulty of translating the beneficial effects observed in trials into meaningful clinical comparisons have led to the call for data on patients in more realistic settings (Kelly *et al.*, 1997). Studies supporting the Medicines Control Agency licensing have been criticised (Melzer, 1998), and some clinicians and Health Authorities have questioned the clinical relevance and cost effectiveness of donepezil (Anon, 1997; Stein, 1997). Licensing criteria rely largely on the effect of the treatment on cognitive and global functioning, but the aspects of dementia that carers often find most distressing are changes in behaviour, mood, motivation and personality. These can be difficult to measure, and are not part of licensing requirements other than contributing to the clinician's global assessment.

The Southampton Memory Clinic was set up in October 1997 to manage the introduction of donepezil by ensuring accurate diagnosis and monitoring of efficacy and side effects. The clinic forms part of the Southampton Elderly Mental Health Service which serves a population of 60,000

* Correspondence to: Dr H. P. Matthews, Consultant in Old Age Psychiatry, Southampton Memory Clinic, Moorgreen Hospital, Southampton S030 3JB, UK. Tel: +44-(0)2380-475336. Fax: +44-(0)2380-475346. E-mail: memclin@aol.com

Received 7 September 1999
Accepted 26 November 1999

people over 65 years of age. A shared care protocol was designed which fulfilled the requirements of the subsequently produced Standing Medical Advisory Committee guidelines (1998). Funding and resources were obtained from fundholding general practitioners, Southampton Elderly Mental Health Service, the local Alzheimer's Disease Society and pharmaceutical companies (Pfizer Ltd, Eisai Ltd). All general practitioners in the catchment area were sent information on the diagnosis of AD and other dementias, referral criteria and details of the Memory Clinic. Patients and carers received written information prior to first attendance, and the first 3 months of treatment were presented as a trial period to identify patients who would respond to treatment.

PARTICIPANTS AND METHODS

Patient population

Patients were either referred by general practitioners or by the Southampton Elderly Mental Health Service. In order to be considered for treatment with donepezil, patients were required to satisfy the criteria for possible or probable mild to moderate AD, as defined by the Diagnostic and Statistical Manual of Mental Disorders IV Edition (American Psychiatric Association, 1994), and the National Institute of Neurological and Communicative Disorders and the Alzheimer's Disease and Related Disorders Association (McKhann *et al*., 1984). Patients were excluded if they had contraindications to prescribing donepezil, there were likely compliance issues with medication, or no carer was available who could report on progress. Patients with co-morbid depression were either already on stable treatment, or if identified at the initial assessment, treated appropriately before commencing donepezil.

Design

This was an open-label evaluation of donepezil treatment. Efficacy was measured using the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) (Rosen *et al*., 1984), the Mini-Mental State Examination (MMSE) (Folstein *et al*., 1975), the Neuropsychiatric Inventory (NPI) (Cummings *et al*., 1994), and the Neuropsychiatric Inventory-carer distress scale (NPI-D) (Kaufer *et al*., 1998a). The MMSE and ADAS-cog subscale are tools used extensively in clinical trials to evaluate changes in cognition. The NPI rating scale is a validated clinical rating scale specifically designed to provide a comprehensive evaluation of neuropsychiatric symptomatology in patients with dementia. The NPI-D scale provides a quantitative measure of the distress experienced by carers in relation to the domains assessed by the NPI rating scale. The initial clinic visit involved both patient and carer, who were interviewed by an experienced old age psychiatrist and psychologist. All patients received 5 mg/day donepezil for the first 4 weeks, after which they were reassessed and, if tolerated, the donepezil dose was increased to 10 mg/day. Further efficacy and safety evaluations were undertaken every 3 months.

RESULTS

The results are based on assessments of all new patients referred to the Southampton Memory Clinic between 1 October 1997 and 30 September 1998, and include follow-up assessments until 30 June 1999. A total of 122 new patients (mean age 75 years, range 40–96 years) were assessed, of whom 54% were known to Southampton Elderly Mental Health Service, and 46% were direct general practitioner referrals. Of these patients, 89 (73%) were considered suitable for treatment according to the criteria described above. The main reason for unsuitability (33 patients) was an alternative diagnosis, for example, vascular dementia, depression or no evidence of dementia. A further nine patients declined treatment. Of the 80 patients who commenced treatment with donepezil, three discontinued due to poor compliance, and four were unable to tolerate the medication prior to the 3-month assessment. The outcome of the 80 patients commencing treatment is shown in Table 1. Mean scores at baseline on each of the four efficacy scales for patients receiving treatment for a minimum of 3 months are shown in Table 2.

Identification of response and duration of treatment

Following the first 3-month trial on medication, patients were identified as responders if they showed clinical improvement, as assessed at interview with patient and carer, and also improvement in either cognition or neuropsychiatric symptoms, as measured by the rating scales. The majority of

Table 1. Outcome of 80 patients commencing treatment with donepezil assessed between 1 October 1997 and 30 September 1998, including follow-up data to 30 June 1999

Assessment period (month)	Number of patients		
	Completing treatment period*	Treatment ceased due to lack of efficacy	Treatment ongoing†
3	73	7	
6	44	29‡	
9	36	8	
12	26	7	3
15	14	6	6
18	9	2	3

* Number of patients treated for a minimum of 3, 6, 9, 12, 15 or 18 months.
† Number of patients continuing treatment, but not yet completed 12, 15 or 18 months.
‡ Two patients discontinued due to poor tolerability.

responders showed improvements in both cognitive and neuropsychiatric efficacy measures. Continuing response at subsequent 3-month reviews was identified by either no change or improvement in rating scales assessing cognitive and neuropsychiatric symptoms, supported by clinical interview with patient and carer. Medication was only continued if there was evidence of ongoing effectiveness. Of the 73 patients who completed the first 3-month study period, 27 (37%) were discontinued due to lack of initial effectiveness and two due to poor tolerability. At subsequent 6-, 9-, 12-, 15- and 18-month assessments, 18%, 19%, 23%, 14% and 11% of patients who were receiving treatment at these time-points, respectively, were discontinued due to lack of continuing effectiveness. Of the 27 patients who commenced donepezil during the first 3 months of the clinic's operation, eight (30%) were continuing to take donepezil at 18 months.

If effectiveness was in doubt, for example, when there was a disparity noted between the deterioration observed at interview, and that reported by the carer, or identified by the rating scales, donepezil was discontinued for a trial period. Patients were reassessed after 2–4 weeks. Twenty-five patients had such a 'drug holiday', 16 of whom were at the 3-month assessment stage. In 17 patients, this procedure helped to confirm that the drug was no longer benefiting the patient, whereas there was rapid and clinically significant deterioration in the other eight cases, which was reversed when donepezil therapy was reinstated.

EFFICACY OF DONEPEZIL TREATMENT

Cognition

The mean score for the 70 patients who were assessed on the MMSE at 3 months had improved significantly from baseline by 0.96 points ($p = 0.02$) (Table 2). An improvement from baseline in MMSE score of at least 3 points was observed in 24% of these patients at 3 months (mean improvement in these patients, 5.47 points). Overall, 56% of patients had improved at the 3-month assessment, and a further 13% were unchanged. In those patients who continued on treatment, overall mean improvements above baseline on the MMSE scale were observed for the patient cohorts who received donepezil for 6, 9, 12, 15 and 18 months, respectively (Table 2).

The mean improvement from baseline for the 71 patients assessed on the ADAS-cog subscale who received treatment for a minimum of 3 months was 1.07 ($p = 0.18$). An improvement from baseline of at least 4 points in the ADAS-cog subscale scores was observed in 39% of the patients at 3 months (mean improvement in these patients, 7.14 points), whereas 17% of patients improved by 7 or more points. Overall, 58% of patients had improved at 3 months, and a further 6% were unchanged. ADAS-cog subscale scores for those patients who continued on treatment are shown in Table 2. Improvement was maintained at 6 months, whereas the 9- and 12-month patient cohorts showed a slight decline in the mean values on the ADAS-cog, influenced heavily by those non-responders who then discontinued medication. However, when the mean change from baseline was calculated at each time-point for only those patients who were continued on donepezil and completed the subsequent 3-month treatment period, the ADAS-cog scores showed an improvement over baseline continuously up to 15 months.

Neuropsychiatric symptoms

At the 3-month assessment, although 49% of patients showed an improvement from baseline, with 37% showing an improvement of 4 points or greater (mean improvement 13.14; $p = 0.001$), there was a wide variation in response, with no

Table 2. Mean change from baseline in efficacy measures for patients receiving donepezil treatment for 3, 6, 9, 12, 15 and 18 months†

Efficacy measure	MMSE		ADAS-cog		NPI		NPI-D‡	
Mean baseline score (SD)§	19.51 (5.22)		23.78 (9.23)		15.88 (14.41)		9.97 (8.69)	
Period of treatment (months)	*N*¶	Mean change from baseline‖	*N*	Mean change from baseline††	*N*	Mean change from baseline††	*N*	Mean change from baseline††
3	70	0.96*	71	−1.07	68	−0.66	67	−1.91*
6	43	1.90**	44	−1.20	44	−4.49**	43	−2.68**
9	36	1.50*	36	0.42	36	−1.72	35	−2.16
12	26	1.52	26	0.33**	24	−1.17	23	−1.92
15	13	1.81*	14	−2.18	13	−1.46	12	−1.37
18	9	2.50	9	0.34	8	−0.94	7	0.14

† The change in score from baseline was calculated for each individual patient in each of the six cohorts (patients receiving treatment for at least 3, 6, 9, 12, 15 and 18 months, respectively), and the mean change from baseline obtained for each cohort.
‡ Carer assessment.
§ Based on number of patients receiving treatment for a minimum of 3 months.
¶ Number of patients assessed at each time-point.
‖ A positive value indicates clinical improvement.
†† A negative value indicates clinical improvement.
* $p \leqslant 0.05$.
** $p \leqslant 0.01$.

significant improvement in mean NPI scores (mean improvement 0.66, $p = 0.68$). For those patients who continued on treatment, mean total NPI scores showed sustained improvement from baseline at 6, 9, 12, 15 and 18 months (Table 2). Changes in the individual NPI symptom domains at the 3-month assessment in patients treated with donepezil are shown in Table 3. In over 50% of patients, these symptoms had cleared or reduced by the 3-month assessment. The most commonly reported symptoms were apathy, anxiety, depression and agitation.

Carer distress

At the 3-month review, 51% of the 67 carers assessed showed an improvement from baseline on the NPI-D scale and 13% were unchanged. The mean improvement from baseline for carers at 3 months was 1.91 ($p = 0.02$). For those patients continuing on donepezil at 6, 9, 12 and 15 months, the overall mean improvement amongst their carers was maintained (Table 2).

Clinical effects

In order to equate these improvements observed on the efficacy scales with clinical change, a selection of brief anecdotal reports from individual patient case histories are included here.

Case 1. After 6 months' treatment, JB had returned to going into town alone on the bus, and her carer reported a considerable improvement in her conversational skills, and that she had no further word finding difficulty. (At 6 months, improvement in MMSE = 5 points, improvement in ADAS-cog = 4 points.)

Case 2. At 6 months, ED now recalls his children and grandchildren, although he remains a little confused about his great grandchildren (MMSE improvement = 4 points; ADAS-cog improvement = 5 points).

Case 3. 'JL has taken up knitting again; she hasn't done it for years.' Her GP commented, 'She is more outgoing, chatty and happy as opposed to being withdrawn and confused. I am sure the drug has been worthwhile.' (Baseline NPI [8] and NPI-D [1] both reduced to 0 by 3 months, and maintained at 6 months).

Case 4. VW's carer commented, 'It's a lot easier.

Table 3. Changes in the individual Neuropsychiatric Inventory domains at the 3-month assessment in patients treated with donepezil

Neuropsychiatric symptom	Number reported	Symptom cleared	Symptom reduced	Symptom unchanged	Symptom increased	Patients (%) with symptom cleared or reduced
Delusions	6	5		1		83
Hallucinations	1	1				100
Agitation and aggression	8	4	2	1	1	75
Depression and dysphoria	9	3	2	3	1	56
Anxiety	15	8	3	2	2	73
Elation and euphoria	3	3				100
Apathy	15	11	3		1	93
Disinhibition	6	4	1		1	83
Irritability and lability	6	3	3			100
Aberrant motor behaviour	6	5	1			100
Night-time disturbance	3	2			1	67
Appetite	6	3	2		1	83

I am phoned once or twice a week instead of four or five times a day at work.' She has also remembered how to use her electric kettle. (Baseline NPI [5] and NPI-D [3] both reduced to 0 at 6 months.)

Case 5. AS commented, 'Made me feel more alive. I was a bit foggy. I am much clearer thinking now, I'm not so forgetful, things don't pass me by.' His carer said, 'He is not so forgetful. He can remember more and start a conversation and talk to people again.' (Baseline NPI [8] and NPI-D [15] both reduced to 0 at 3 months.)

Adverse events

Donepezil was well tolerated, with 95% of patients maintained on 10 mg/day. There was a low incidence of treatment-emergent adverse events, and only five patients (6%) withdrew from treatment because of these. Adverse events usually occurred within the first few weeks, the most common being nausea and abdominal cramps. Most symptoms were of mild intensity, generally resolving without the need for dose modification. There were no serious adverse events.

DISCUSSION

Today it is rare in medicine to be presented with the first available specific treatment for a common disease, as was the case when donepezil was introduced in the United Kingdom for the treatment of mild to moderate AD. As one might expect, those not involved in the clinical trials treated the early findings with scepticism. Even after publication of results from double-blind, placebo-controlled, randomized Phase II and Phase III trials (Rogers *et al*., 1996, 1998a, b; Burns *et al*., 1999) reporting clear benefits in cognitive and global function with donepezil treatment, a negative perception persisted. One key criticism was that the patients in these studies were highly selected. More recently, however, one open-label study in the United States in 1000 unselected AD patients showed similar efficacy and good tolerability with donepezil treatment (McRae *et al*., 1998).

The findings presented here, which constitute one of the first reports of the use of donepezil in a United Kingdom clinical setting, confirm and supplement the results from controlled clinical trials (Rogers *et al*., 1996, 1998a, b; Burns *et al*., 1999), and help bridge the gap between the trial data and clinical practice. The severity of dementia in this patient cohort is similar to that reported in the clinical trials and it is interesting that comparative results were achieved despite differences in patient recruitment.

A significant improvement of 0.96 points in the mean MMSE score was observed at the 3-month assessment, and for the patients who continued on medication, mean MMSE scores remained above baseline throughout the 18-month study period. This test is simple to administer and widely used

in clinical practice and the results are relevant in view of the expected deterioration of 3–4 points per year in the MMSE score (Teri *et al*., 1990; Burns *et al*., 1991). The results are in accordance with those of the 1000 patient study carried out in the United States (McRae *et al*., 1998), and data published by Kaufer *et al*. (1998b). In addition, they provide evidence of efficacy beyond the 24-week period reported in shorter-term clinical trials (Rogers *et al*., 1998b; Burns *et al*., 1999).

Mean scores on the ADAS-cog subscale for those patients who responded to donepezil and completed the subsequent 3-month treatment period showed improvement above baseline for 15 months. These findings are, therefore, in agreement with the results from a long-term, open-label extension trial, where improvements in the ADAS-cog subscale above baseline were reported for up to 38 weeks following donepezil treatment (Rogers and Friedhoff, 1998). In contrast, the expected mean annual deterioration in the ADAS-cog subscale score is 9–11 points per year in untreated patients with moderate AD (Stern *et al*., 1994), although the deterioration in the placebo groups in clinical trials is usually in the range of 4–8 per year.

Although the benefits in cognitive function observed in the present study are modest for many patients, a considerable proportion of them showed much more marked cognitive improvement. When assessed at 3 months by the ADAS-cog subscale, 39% of patients showed an improvement of at least 4 points, the value which the panel of experts convened by the US Food and Drug Administration advised could be considered a clinically meaningful effect (FDA, 1989).

On the NPI total score, mean improvements above baseline were maintained for 18 months in patients who continued on medication. The expected decline without treatment on the NPI total scale in patients with mild to moderate AD has been shown to be 3.9 points in 6 months (Morris *et al*., 1998). When assessed at 3 months, 37% of the patients in the present study had improved by at least 4 points. This clearly affirms that a proportion of patients achieved substantial improvements in neuropsychiatric symptoms with donepezil treatment. These results support those of Kaufer *et al*. (1998b), who reported improvements in neuropsychiatric symptoms from a more mildly disturbed group with a mean baseline NPI total score of 8, compared with 16 in this study.

Although, in AD, cognitive function influences quality of life for both patient and carer, it is now well documented that aspects of behaviour and mood have an even greater impact on well-being (Brodaty, 1996). Hence, the observed improvements in neuropsychiatric symptoms in this study are very relevant, especially as they were associated with an observed reduction in carer distress. As behavioural and psychiatric symptoms are risk factors for the requirement for domiciliary support or residential care (Steele *et al*., 1990), these findings have obvious beneficial implications for overall spending on health and social care budgets. If it were demonstrated that treatment with donepezil or other cholinesterase inhibitors reduced spending on social support, or delayed institutionalisation, the costs to the United Kingdom National Health Service could potentially be offset against savings made by Social Services. This would be in accord with the adoption of the 'whole systems' approach to managing care, currently encouraged by the United Kingdom Department of Health.

The low incidence of side effects observed with donepezil in this study (only 6% of patients discontinued medication due to adverse events, and no serious adverse events were experienced), is in accordance with published trial data (Rogers *et al*., 1996, 1998a, b; Burns *et al*., 1999). Further, the good tolerability profile observed in these Memory Clinic patients was similar to that of the patients

KEY POINTS

- Clinically meaningful improvements in cognitive function and a reduction in neuropsychiatric symptoms were demonstrated in nearly 40% of patients, with associated reduction in carer distress.
- In a typical clinical practice setting, patients with mild to moderate Alzheimer's disease tolerated donepezil well.
- These findings reflect practical experience in a 'real world' patient population, and suggest that the selection and monitoring of patients offers an effective way of ensuring the appropriate use of anti-dementia drugs.
- The prescribing of drug treatments should always be seen as one aspect of comprehensive, multi-disciplinary service for patients with Alzheimer's disease.

in the United States study (McRae *et al*., 1998), where 97% of patients had prior or co-morbid medical histories and 94% were taking concomitant medications. These findings, therefore, support the lack of drug interactions with donepezil reported in formal pharmacokinetic and pharmacodynamic evaluations (Tiseo *et al*., 1998).

The main limitation of any naturalistic study is the lack of a placebo control, and, as published, randomised, controlled trials do show benefits in placebo-treated patients, it is not possible to be certain that all of the improvements in our patients are drug-related. However, donepezil has already been shown in clinical trials to have efficacy against placebo, and our aim in this study was to evaluate the effect of the drug when it is used in open clinical practice and to demonstrate the utility of controlled prescribing within the Memory Clinic setting described. A degree of fluctuation in individual patients would be expected, but the numbers are large enough to minimise such effects. The improvements noted for patients continuing for 15 and 18 months may be due in part to these patients having a disease which is progressing more slowly, and thus the results should be interpreted accordingly.

In the typical clinical setting of this study, over 50% of patients with mild to moderate AD treated with donepezil showed improvements in cognitive function at 3 months, and almost 50% showed reductions in neuropsychiatric symptoms, with associated decrease in carer distress. Therefore, the clinical trial results are echoed by this clinical practice experience in the United Kingdom, where doubts about cost effectiveness and fears of profligate prescribing have been prevalent. Health Authorities and Primary Care Groups can be reassured that drugs such as donepezil can produce cognitive, behavioural, and global benefits to patients and reduce carer distress, and that careful selection and monitoring can help ensure that any additional costs relate to genuine benefit. The prescribing of drug treatments should, however, always be seen as one aspect of a comprehensive, multidisciplinary service for patients with AD.

ACKNOWLEDGEMENT

The Authors would like to thank P.P.S. International, Worthing, for their assistance in developing this manuscript.

CONFLICT OF INTEREST STATEMENT

Southampton Memory Clinic has received funding from Pfizer Ltd and Eisai Ltd. Dr Wilkinson directs a psychopharmacology unit running Phase II and Phase III trials of anti-dementia compounds. He has received grants from all major pharmaceutical companies including Pfizer Ltd and Eisai Ltd.

REFERENCES

Alzheimer's Disease Society. 1996. *Opening the Mind: New Frontiers in Alzheimer's Research*. Alzheimer's Disease Society: London.

Anon. 1997. New dementia drug. *Bandolier* **40**: 2–3.

American Psychiatric Association. 1994. *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn. American Psychiatric Association: Washington, DC.

Brodaty H. 1996. Caregivers and behavioural disturbances: effects and interventions. *Int. Psychogeriatr*. **8**(Suppl. 3): 455–458.

Burns A, Jacoby R, Levy R. 1991. Progression of cognitive impairment in Alzheimer's disease. *J. Am. Geriatr. Soc*. **39**: 39–45.

Burns A, Rossor M, Hecker J, Gauthier S, Petit H, Möller HJ, Rogers SL, Friedhoff LT and the International Donepezil Study Group. 1999. The effects of donepezil in Alzheimer's disease—results from a multinational trial. *Dement. Geriatr. Cogn. Disord*. **10**: 237–244.

Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. 1994. The Neuropsychiatric Inventory: comprehensive assessment of psychotherapy in dementia. *Neurology* **44**: 2308–2314.

FDA. 1989. Peripheral and Central Nervous System Drugs Advisory Committee Meeting, 7 July 1989. Dept of Health and Human Services, Public Health Service, Food and Drug Administration 227: Rockville, MD.

Folstein MF, Folstein SE, McHugh PR. 1975. "Mini-Mental State": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr. Res*. **12**: 189–198.

Kaufer DI, Cummings JL, Christine D, Bray T, Castellon S, Masterman D, MacMillan A, Ketchel P, DeKosky ST. 1998a. Assessing the impact of neuropsychiatric symptoms in Alzheimer's disease: the neuropsychiatric inventory caregiver distress scale. *JAGS* **46**: 210–215.

Kaufer DI, Catt K, Pollock BG, Lopez OM, DeKosky ST. 1998b. Donepezil in Alzheimer's disease: relative cognitive and neuropsychiatric responses and impact on caregiver distress. *Neurology* **50** (Suppl. 4): A89: P02.013.

Kelly CA, Harvey RJ, Cayton H. 1997. Drug treatment for Alzheimer's Disease. *BMJ* **314**: 693.

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. 1984. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services task force on Alzheimer's disease. *Neurology* **34**: 939–944.

McRae TD, Relkin N, Knopman D. 1998. A large-scale trial of donepezil in the treatment of Alzheimer's disease. *Neurology* **50**(Suppl. 4): A90: P02.017.

Melzer D. 1998. New drug treatment for Alzheimer's disease: lessons for healthcare policy. *BMJ* **316**: 762–764.

Morris JC, Cyrus PA, Orazem J, Mas J, Bieber F, Ruzicka BB, Gulanski B. 1998. Metrifonate benefits cognitive, behavioral, and global function in patients with Alzheimer's disease. *Neurology* **50**: 1222–1230.

Rogers SL, Friedhoff LT. 1998. Long term efficacy and safety of donepezil in the treatment of Alzheimer's disease: an interim analysis of the results of a US multicentre open label extension study. *Eur. Neuropsychopharmacol.* **8**: 67–75.

Rogers SL, Friedhoff LT, Donepezil Study Group. 1996. The efficacy and safety of donepezil in patients with Alzheimer's disease; results of a US multicenter, randomized, double-blind, placebo-controlled trial. *Dementia* **7**: 293–303.

Rogers SL, Doody RS, Mohs RC, Friedhoff LT, Donepezil Study Group. 1998a. Donepezil improves cognition and global function in Alzheimer's disease: a 15-week, double-blind, placebo-controlled study. *Arch. Intern. Med.* **158**: 1021–1031.

Rogers SL, Farlow MR, Doody RS, Mohs F, Friedhoff LT, and the Donepezil Study Group. 1998b. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. *Neurology* **50**: 136–145.

Rosen WG, Mohs RC, Davis KL. 1984. A new rating scale for Alzheimer's Disease. *Am. J. Psychiatry* **141**: 1356–1364.

Standing Medical Advisory Committee. 1998. *The Use of Donepezil for Alzheimer's disease*. NHS Executive, London, U.K.

Steele C, Rovner B, Chase GA, Folstein M. 1990. Psychiatric symptoms and nursing home placement of patients with Alzheimer's disease. *Am. J. Psychiatry* **147**: 577–587.

Stein K. 1997. Donepezil in the treatment of mild to moderate senile dementia of the Alzheimer's type (SDAT). *Wessex Institute for Health Research and Development*, DEC report no. 69.

Stern RG, Mohs RC, Davidson M, Schmeider J, Silverman J, Kramer-Ginsberg E, Searcey T, Bierer L, Davis KL. 1994. A longitudinal study of Alzheimer's disease: measurement, rate and predictors of cognitive deterioration. *Am. J. Psychiatry* **151**(3): 390–396.

Teri L, Hughes JP, Larson EB. 1990. Cognitive deterioration in Alzheimer's disease: behavioural and health factors. *J. Gerontol.* **45**: 58–63.

Tiseo PJ, Rogers SL, Friedhoff LT, Perdomo CA, Foley K, Vargas R. 1998. The pharmacokinetics of donepezil. *Br. J. Clin. Pharmacol.* **46**(Suppl. 1): 1–60.

