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Donepezil for the symptomatic treatment of patients with mild to moderate Alzheimer's disease: a meta-analysis of individual patient data from randomised controlled trials

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SUMMARY

Background The objective was to evaluate the efficacy and tolerability of donepezil (5 and 10 mg/day) compared with placebo in alleviating manifestations of mild to moderate Alzheimer's disease (AD).

Method A systematic review of individual patient data from Phase II and III double-blind, randomised, placebo-controlled studies of up to 24 weeks and completed by 20 December 1999. The main outcome measures were the ADAS-cog, the CIBIC-plus, and reports of adverse events.

Results A total of 2376 patients from ten trials were randomised to either donepezil 5 mg/day ($n = 821$), 10 mg/day ($n = 662$) or placebo ($n = 893$). Cognitive performance was better in patients receiving donepezil than in patients receiving placebo. At 12 weeks the differences in ADAS-cog scores were 5 mg/day–placebo: −2.1 [95% confidence interval (CI), −2.6 to −1.6; $p < 0.001$], 10 mg/day–placebo: −2.5 (−3.1 to −2.0; $p < 0.001$). The corresponding results at 24 weeks were −2.0 (−2.7 to −1.3; $p < 0.001$) and −3.1 (−3.9 to −2.4; $p < 0.001$). The difference between the 5 and 10 mg/day doses was significant at 24 weeks ($p = 0.005$). The odds ratios (OR) of improvement on the CIBIC-plus at 12 weeks were: 5 mg/day–placebo 1.8 (1.5 to 2.1; $p < 0.001$), 10 mg/day–placebo 1.9 (1.5 to 2.4; $p < 0.001$). The corresponding values at 24 weeks were 1.9 (1.5 to 2.4; $p = 0.001$) and 2.1 (1.6 to 2.8; $p < 0.001$). Donepezil was well tolerated; adverse events were cholinergic in nature and generally of mild severity and brief in duration.

Conclusion Donepezil (5 and 10 mg/day) provides meaningful benefits in alleviating deficits in cognitive and clinician-rated global function in AD patients relative to placebo. Increased improvements in cognition were indicated for the higher dose.

KEY WORDS — donepezil; Alzheimer's disease; meta-analysis; cognition; global function

INTRODUCTION

The cholinesterase (ChE) inhibitors represent the majority of drugs available for alleviating manifestations of mild to moderate Alzheimer's disease (AD), although memantine, an N-methyl-D-aspartate receptor antagonist, has recently been approved in Europe and the USA for the treatment of moderate to severe AD. Tacrine was the first of the ChE inhibitors to be widely marketed, followed more recently by donepezil, rivastigmine and galantamine, respectively. Individual, randomised controlled trials (RCTs) (Davis *et al*., 1992; Corey-Bloom *et al*., 1998; Rogers *et al*., 1998a; Burns *et al*., 1999; Rösler *et al*., 1999; Raskind *et al*., 2000; Tariot *et al*., 2000; Wilcock *et al*., 2000; Mohs *et al*., 2001; Wilkinson and Murray, 2001; Winblad *et al*., 2001) have demonstrated that these ChE inhibitors, although not curative, can

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provide benefits to patients in terms of cognition, global function, and activities of daily living (ADLs) as well as the neuropsychiatric manifestations of AD that tend to be associated with the more severe stages of AD (Feldman *et al*., 2001; Gauthier *et al*., 2002).

Meta-analyses, conducted by the Cochrane Collaboration (http://www.cochrane.org/cochrane/revabstr/g170index.htm, 2003) and other groups to date (Qizilbash *et al*., 1998; Birks *et al*., 2000a; Birks *et al*., 2000b; Bryant *et al*, 2001; Olin and Schneider, 2001) have strengthened the evidence from the individual trials, demonstrating a similar level of efficacy for the ChE inhibitors on global ratings, cognitive tests, ADLs and behaviour. Whilst the meta-analysis for tacrine has been based on individual patient data from all relevant RCTs, the other meta-analyses have been based on summary data extracted from the published RCTs. Although the latter type of meta-analysis is often a useful initial evaluation, the former, in which details for each participant in every trial are collected and analysed centrally, is considered to be the 'gold standard', providing the most reliable estimates of treatment difference (Stewart and Parmar, 1993; Stewart and Clarke, 1995). For this reason, a meta-analysis using individual patient data from all relevant RCTs of donepezil (5 and 10 mg/day) conducted around the world has been undertaken and is reported in this paper.

METHODS

Searching

All RCTs of the use of donepezil in the treatment of AD were identified from scientific literature searches supplemented by those from Eisai Inc databases.

Selection

All randomised, double-blind, placebo-controlled, parallel-group studies from the donepezil clinical development programme undertaken and completed as of 20 December 1999, in which donepezil was administered for more than one day, were considered for inclusion in this analysis. All patients included in the trials were to have satisfied a diagnosis of probable AD as defined by the validated diagnostic criteria of the International Classification of Diseases (World Health Organization, 1992), Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 1987), and/or the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann *et al*., 1984). Patients were also required to have mild to moderate AD at screening as defined by Mini-Mental State Examination (MMSE) (Folstein *et al*., 1975) scores of between 10 and 26 inclusive, and Clinical Dementia Rating (CDR) (Hughes *et al*., 1982) scores of 1 (mild) or 2 (moderate). While doses other than 5 or 10 mg/day were investigated in some of the trials (i.e. 1 and 3 mg/day), only placebo and donepezil 5 and 10 mg/day doses were considered in the meta-analysis, as regulatory approval was pursued for only these doses in Europe and the USA.

Outcome variables

The primary neuropsychological tests assessed in the studies were the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) (Rosen *et al*., 1984), the Clinician's Interview-Based Impression of Change-plus version (CIBIC-plus) (Knopman *et al*., 1994; Schneider *et al*., 1997), and Clinical Global Impressions Scale (CGI) (Guy, 1976), or a global improvement rating. Because of their similarities, the results of all global assessments were included in the analysis of the CIBIC-plus results. Possible learning effects on the ADAS-cog were minimized by using different word sets in the word recognition and recall components.

Safety was assessed by the monitoring of treatment-emergent adverse events (AEs), clinical laboratory evaluations including haematology, clinical chemistry, and urinalysis, and the recording of vital signs. Reports of AEs were obtained by the investigator at each scheduled evaluation by asking the patient 'How are you feeling?'. In most studies, the following information was recorded for each AE reported: the specific event; date and time of onset and cessation; severity as assessed by the investigator; seriousness of event; relationship to test drug; whether any adjunctive treatment was necessary; and whether hospitalization was necessary. Investigator terms describing adverse events were coded to standard preferred terms using modified Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) dictionaries.

Data extraction

Individual patient data were extracted for all patients randomised into the studies selected for inclusion in the meta-analysis. These related to the efficacy and safety outcome measures from all assessment time points (including baseline). For patients not completing the main randomised part of the study, the reasons for withdrawal were obtained. Data from

the non-randomised follow-on period after the main comparative phase were not used.

Quantitative data synthesis and statistical methods

Analysis of all efficacy variables was performed on the intention-to-treat (ITT) population, defined as patients who took at least one dose of study medication and had at least one post-baseline assessment. Analyses were performed at the weeks of evaluation common to most studies, i.e. weeks 6, 12, 18 and 24. In the main analysis there was no imputation for missing data.

The ADAS-cog assessment (score 0–70, which increases with worsening cognitive status) was treated as a continuous outcome arising from a normal distribution. Fixed effects meta-analysis models were fitted, in which the response variable was change from baseline and the model terms were baseline value, study and treatment. Heterogeneity between studies was tested by including a study-by-treatment interaction term. Random effects models were fitted, in which baseline value, study, and treatment were entered as fixed effects and the study-by-treatment interaction term was included as a random effect in the model. Estimates and 95% confidence intervals (CI) for the mean difference between pairs of treatments for individual studies, and for the overall fixed effects and random effects models, are presented.

The CIBIC-plus was analysed as an ordered categorical variable with five categories, namely, marked or moderate improvement (1 and 2), minimal improvement (3), no change (4), minimal (5) and moderate or marked worsening (6 and 7). A proportional odds model was fitted to each study to provide log-odds ratios for improvement for the 5 mg/day dose relative to placebo, and/or the 10 mg/day dose relative to placebo. The log-odds ratio for the 10 mg/day dose relative to the 5 mg/day dose was also calculated in studies that included all three treatments. The study estimates of the log-odds ratio were combined in a meta-analysis (Whitehead and Whitehead, 1991). Overall fixed effects and random effects estimates were calculated and a test for heterogeneity performed.

Responder analyses were performed separately for the week 12 and week 24 data, using Fisher's exact test. The change in the ADAS-cog score was used to define a 'responder' in three ways: (a) no change or improvement (change from baseline ≤ 0); (b) improvement of at least 4 points (change from baseline ≤ -4); and (c) improvement of at least 7 points (change from baseline ≤ -7). These values are considered to represent a clinically relevant improvement on the ADAS-cog score by experts as well as the FDA (Peripheral and Nervous System Drugs Advisory Committee Meeting, 1989; Leber, 1990) and CPMP (The European Agency for the Evaluation of Medical Products, 1997).

Analysis of safety variables was performed on the safety population—that is, all randomised patients who took at least one dose of study medication. Abnormal laboratory test values were also investigated. When the overall incidence of a specific AE was $\geq 5.0\%$, Fisher's exact test was used to compare the incidence across the three treatment groups. All analyses were performed using SAS®, Version 6.12.

RESULTS

Study characteristics

A total of 11 trials met the criteria for inclusion in this meta-analysis. One study examining the effect of donepezil on patient function (E2020-A001-312) was excluded because it had a different objective and design from the other ten studies. The design was such that patients left the study once certain criteria relating to functional decline were fulfilled (Mohs *et al*., 2001). Ten trials were therefore included in the analysis, involving 2376 patients randomised to placebo ($n = 893$), donepezil 5 mg/day ($n = 821$), or 10 mg/day ($n = 662$). The studies were conducted in Europe, the USA and Japan, and most were multicentre with either 12- (five studies) or 24- (five studies) week double-blind treatment periods (Table 1). All had similar patient inclusion criteria. Three studies included both 5 and 10 mg/day doses of donepezil and all studies except Study 205 used ADAS-cog as an efficacy assessment. Although all studies collected data on laboratory tests, the specific variables measured varied slightly. Among the ten studies included, eight have been published to date (Rogers *et al*., 1996; Rogers *et al*., 1998a; Rogers *et al*., 1998b; Burns *et al*., 1999; Geldmacher *et al*., 2000; Homma *et al*., 2000; Krishnan *et al*., 2003; Tune *et al*., 2003). The two unpublished studies, J081-134 and X-306, had the same design as the published studies. J081-134 was conducted at 55 sites in Japan, and X-306 was carried out at one centre in Italy.

Patient demographic and background characteristics and concomitant medications

Patient age, MMSE, CDR scores and the percentage of females were similar across all treatment groups

Table 1. Summary of randomised controlled studies included in the meta-analysis

Study	Treatment period (weeks)	Number of patients			
		Total	Placebo	Donepezil (5 mg/day)	Donepezil (10 mg/day)
J081-134 Japanese Phase II study	12	190*	60	64	—
J081-161 (Homma *et al*., 2000) Japanese Phase III study	24	268	132	136	—
A001-201 (Rogers *et al*., 1996) US Phase II study	12	161†	40	39	—
A001-203 (Tune *et al*., 2003) US Phase II study. The PET Study	24	28	14	—	14
A001-204 (Krishnan *et al*., 2003) US Phase II study. The MRS Study	24	67	33	—	34
A001-205 (Geldmacher *et al.*, 2000) US Phase II study. The Visuo-spatial/attention Study	12	12	6	—	6
A001-301 (Rogers *et al*., 1998b) US pivotal Phase III study	12	468	153	157	158
A001-302 (Rogers *et al*., 1988a) US pivotal Phase III study	24	473	162	154	157
EO44-304 (Burns *et al*., 1999) Multinational Phase III study	24	818	274	271	273
X-306 Italian Phase IIIb study. The ApoE Study	12	39	19	—	20

*66 patients received 3 mg/day.
†40 patients received 3 mg/day and 42 patients received 1 mg/day.

at baseline (Table 2). Racial distribution was different between the treatment groups because none of the Japanese studies included the 10 mg/day dose. Approximately 24% of patients received medications prior to the administration of study drug (generally one month before entering a study) and the distribution of the classes of medications was also similar across each treatment group. Over the course of the studies, approximately 77% of patients received at least one concomitant medication and, again, no remarkable differences in the proportion of patients receiving the various classes of medications between the groups were noted. Overall, medications used by more than 10% of patients were analgesics (32.0%), systemic antibacterials (14.8%), psycholeptics (10.2%) and anti-inflammatory and anti-rheumatic products (10.0%).

Table 2. Summary of patient characteristics by treatment group

	Placebo ($n = 893$)	Donepezil	
		5 mg/day ($n = 821$)	10 mg/day ($n = 662$)
Mean age, yrs (SD) (range)	71.5 (8.5) (44–93)	72.1 (8.1) (46–94)	72.8 (7.8) (50–94)
Female patients, %	60	64	61
Race, %			
Caucasian	76	73	97
Japanese	22	24	0
Other	2	3	3
Screening MMSE score (SD) (range)	19.5 (4.4) (9–26)	19.4 (4.6) (9–26)	19.6 (4.3) (8–27)
Screening CDR score, %			
0.5	< 1	1	1
1.0	77	75	81
2.0	22	24	18
3.0	< 1	< 1	0

Primary efficacy variables

The individual study and overall pairwise treatment differences (and 95% CI) of the ADAS-cog at weeks 12 and 24 for the donepezil 5 and 10 mg/day groups relative to placebo and the donepezil 10 *vs* 5 mg/day groups are presented in Table 3. There was little evidence of heterogeneity between the studies at weeks 12 and 24. Based on the results from the overall fixed effects analysis, patients who received 5 or 10 mg/day donepezil demonstrated a statistically significant ($p < 0.001$) better ADAS-cog score at all time points compared with placebo (Figure 1). In addition, the magnitude of improvement with donepezil 10 mg/day was greater than that achieved with donepezil 5 mg/day at all evaluations, and reached statistical significance at weeks 18 and 24 ($p = 0.015$; $p = 0.005$). The results from the overall random effects analysis were similar, although the improvement of donepezil 10 mg/day compared with donepezil 5 mg/day at week 24 was not statistically significant ($p = 0.10$). Similar results were observed on the analysis after imputation of missing values at all time points. The percentages of patients responding to treatment according to any improvement or no change from baseline on ADAS-cog scores, or improvements of at least 4 or 7 ADAS-cog points at weeks 12 and 24 are presented in Table 4.

There was a beneficial effect of donepezil (5 mg/day and 10 mg/day) over placebo in terms of the ADAS-cog scores across all patients irrespective of

Table 3. ADAS-cog assessments (estimates [95% confidence intervals] of treatment difference) and odds ratios for a better CIBIC-plus score (95% confidence intervals), at weeks 12 and 24, from individual studies and overall for donepezil (5 and 10 mg/day) compared with placebo, and donepezil 10 mg/day compared with donepezil 5 mg/day

Study	Study week	ADAS-cog			CIBIC-plus		
		5 mg/day *vs* placebo	10 mg/day *vs* placebo	10 mg/day *vs* 5 mg/day	5 mg/day *vs* placebo	10 mg/day *vs* placebo	10 mg/day *vs* 5 mg/day
J081-134	12	−1.16 (−2.99 to 0.68)	—	—	1.35 (0.66 to 2.77)	—	—
J081-161	12	−2.16 (−3.49 to −0.83)	—	—	3.53 (2.14 to 5.88)	—	—
	24	−2.94 (−4.37 to −1.50)	—	—	3.14 (1.93 to 5.11)	—	—
A001-201	12	−3.20 (−5.20 to −1.20)	—	—	1.18 (0.49 to 2.81)	—	—
A001-203	12	—	−1.03 (−3.70 to 1.65)	—	—	—	—
	24	—	−2.09 (−5.09 to 0.92)	—	—	—	—
A001-204	12	—	−3.38 (−5.75 to −1.02)	—	—	—	—
	24	—	−3.99 (−7.14 to −0.83)	—	—	—	—
A001-301	12	−2.59 (−3.81 to −1.38)	−3.07 (−4.32 to −1.81)	−0.47 (−1.72 to 0.78)	1.97 (1.27 to 3.05)	2.05 (1.31 to 3.22)	1.04 (0.67 to 1.62)
A001-302	12	−2.19 (−3.40 to −0.98)	−2.73 (−3.98 to −1.48)	−0.54 (−1.78 to 0.70)	1.60 (1.03 to 2.48)	1.76 (1.11 to 2.78)	1.10 (0.7 to 1.73)
	24	−2.75 (−4.11 to −1.39)	−3.23 (−4.67 to −1.80)	−0.48 (−1.93 to 0.96)	1.93 (1.24 to 3.01)	2.39 (1.48 to 3.85)	1.24 (0.77 to 1.99)
A001-304	12	−1.91 (−2.75 to −1.08)	−2.27 (−3.11 to −1.42)	−0.35 (−1.21 to 0.50)	1.46 (1.04 to 2.03)	1.91 (1.35 to 2.68)	1.31 (0.93 to 1.84)
	24	−1.12 (−2.15 to −0.09)	−2.83 (−3.88 to −1.78)	−1.71 (−2.76 to −0.65)	1.45 (1.02 to 2.05)	1.90 (1.34 to 2.71)	1.31 (0.92 to 1.87)
X-306	12	—	−0.86 (−3.72 to 2.01)	—	—	—	—
Overall (fixed)	12	−2.11 (−2.61 to −1.61) $p<0.001$	−2.54 (−3.09 to −1.98) $p<0.001$	−0.42 (−1.00 to 0.15) $p=0.15$	1.77 (1.45 to 2.14) $p<0.001$	1.90 (1.51 to 2.41) $p<0.001$	1.17 (0.93 to 1.48) $p=0.17$
Test for heterogeneity	12		$p=0.85$		$p=0.07$	$p=0.89$	$p=0.69$
Overall (random)	12	−2.11 (−2.61 to −1.61) $p<0.001$	−2.54 (−3.09 to −1.98) $p<0.001$	−0.42 (−1.00 to 0.15) $p=0.15$	1.79 (1.32 to 2.39) $p<0.001$	1.90 (1.51 to 2.41) $p<0.001$	1.17 (0.93 to 1.48) $p=0.17$
Overall (fixed)	24	−1.98 (−2.69 to −1.27) $p<0.001$	−3.13 (−3.91 to −2.36) $p<0.001$	−1.15 (−1.96 to −0.35) $p=0.005$	1.89 (1.49 to 2.40) $p<0.001$	2.05 (1.55 to 2.75) $p<0.001$	1.28 (0.97 to 1.70) $p=0.08$
Test for heterogeneity	24		$p=0.33$		$p=0.04$	$p=0.45$	$p=0.85$
Overall (random)	24	−2.08 (−3.32 to −0.83) $p=0.01$	−3.16 (−4.44 to −1.89) $p=0.001$	−1.09 (−2.51 to 0.33) $p=0.10$	2.01 (1.30 to 3.13) $p=0.002$	2.05 (1.55 to 2.75) $p<0.001$	1.28 (0.97 to 1.70) $p=0.08$

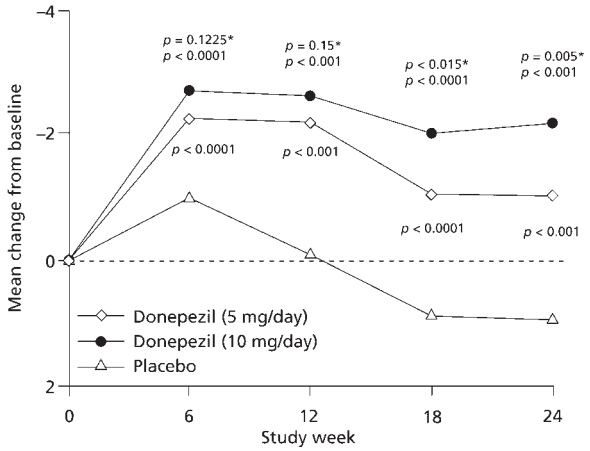

Figure 1. Mean change from baseline in ADAS-cog scores for 5 and 10 mg/day donepezil- and placebo-treated patients with mild to moderate Alzheimer's disease (fixed effects meta-analysis)

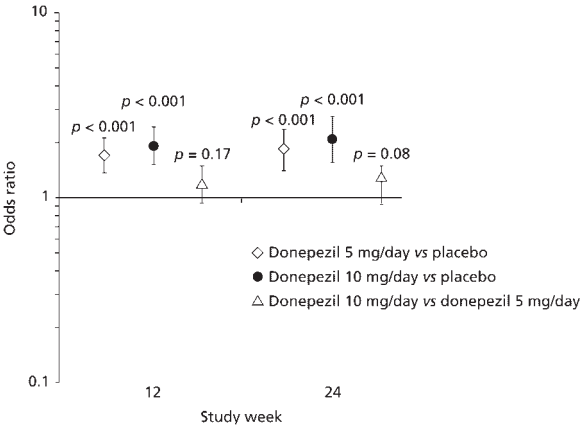

Figure 2. Overall odds ratios and 95% confidence intervals for improvement in the CIBIC-plus assessment for donepezil 5 and 10 mg/day *vs* placebo and donepezil 10 mg/day *vs* donepezil 5 mg/day at weeks 12 and 24 based on the proportional odds model (fixed effects meta-analysis)

MMSE score, CDR score, age, gender or use of nicotine. Statistically significant differences between donepezil and placebo were found in most subgroups, with the exception of the subgroup of patients over 80 years of age. The lack of statistical significance in the subgroup over 80 years of age is most likely due to the smaller sample size and lack of decline in those receiving placebo.

The odds of improvement in CIBIC-plus scores from the overall fixed effects analysis were approximately twice as great with donepezil 5 or 10 mg/day as with placebo at each evaluation, as shown in Figure 2 and Table 3. These results were statistically significant ($p < 0.001$) at all time points evaluated. The odds of improvement were 1.2 to 1.3 times as great with donepezil 10 mg/day as with donepezil 5 mg/day at weeks 12 and 24, but this was not statistically significant ($p = 0.17$ and $p = 0.08$, respectively). There was a suggestion of heterogeneity between the studies for the comparison of the 5 mg/day dose and placebo, but this had no major impact on the results.

Table 4. Percentage of patients classified as responders according to reductions in ADAS-cog scores from baseline at weeks 12 and 24

Study week	Treatment group	Reduction in ADAS-cog from baseline		
		≥0 points	≥4 points	≥7 points
12	Placebo	51	19	5
	Donepezil 5 mg/day	66	31	13
	Donepezil 10 mg/day	70	31	14
24	Placebo	42	15	5
	Donepezil 5 mg/day	59	27	10
	Donepezil 10 mg/day	64	31	14

All values were statistically significant ($p < 0.001$) for 5 and 10 mg/day donepezil compared with placebo.

Secondary efficacy variables

Significant improvements in the secondary efficacy variables MMSE and CDR-Sum of Boxes scores were also observed. However, assessments of patient quality of life (QoL) scores showed extensive inter- and intra-patient variability and the pairwise differences between the treatment groups were not statistically different.

Safety and tolerability

A total of 2376 patients with AD received at least one dose of study medication in the ten clinical trials that were included in the meta-analysis. Overall, 83.8%, 76.1% and 83.9% of patients treated with 5 or 10 mg/day donepezil or placebo, respectively, completed the trials (Table 5). The rates of completion of double-blind therapy were similar within each study, regardless of the treatment group, and did not vary widely across studies. The percentage of patients who discontinued for any specific reason was generally similar across treatment groups. The most common reason for discontinuation was AEs.

Table 5. Patient disposition and most common adverse events occurring in ≥ 5% of donepezil patients (listed by decreasing order of incidence)

Number of subjects (%)	Placebo ($n = 893$)	Donepezil	
		5 mg/day ($n = 821$)	10 mg/day ($n = 662$)†
Patients completing study	749 (83.9)	688 (83.8)	504 (76.1)
Most common reasons for withdrawal:‡			
Adverse event (AE)	52 (5.8)	52 (6.3)	92 (13.9)
Patient or investigator request	24 (2.7)	26 (3.2)	19 (2.9)
Protocol violation	26 (2.9)	20 (2.4)	21 (3.2)
Subjects with at least one AE	541 (62)	535 (65)	533 (83)**¶
Nausea	42 (5)	47 (6)	132 (21)**¶
Diarrhoea	36 (4)	61 (7)**	102 (16)**¶
Headache	75 (9)	67 (8)	82 (13)**¶
Insomnia	36 (4)	43 (5)	74 (12)**¶
Vomiting	23 (3)	24 (3)	71 (11)**¶
Dizziness	37 (4)	47 (6)	54 (8)**§
Pain	40 (5)	45 (5)	52 (8)**
Rhinitis	43 (5)	39 (5)	52 (8)*§
Anorexia	11 (1)	25 (3)	44 (7)
Urinary tract infection	50 (6)	40 (5)	41 (6)
Accidental injury	35 (4)	35 (4)	39 (6)
Cramp	10 (1)	26 (3)	36 (6)
Infection	35 (4)	42 (5)	30 (5)
Agitation	31 (4)	18 (2)	29 (5)
Confusion	29 (3)	27 (3)	30 (5)

†Safety database unavailable for Protocol 306.
‡Over 3% of patients in any group.
*$p < 0.05$ compared with placebo.
**$p < 0.01$ compared with placebo.
§$p < 0.05$ compared with donepezil 5 mg/day.
¶$p < 0.01$ compared with donepezil 5 mg/day.

Discontinuations due to AEs were higher in the donepezil 10 mg/day group (13.9%) than in the donepezil 5 mg/day (6.3%) or placebo (5.8%) groups (Table 5).

AEs occurred in 65% and 83% of patients treated with 5 or 10 mg/day donepezil, respectively, compared with 62% of placebo-treated patients. The majority of AEs that occurred with a significantly higher incidence in the donepezil-treated groups relative to placebo and considered possibly related to study drug were mainly cholinergic in nature, as anticipated from donepezil's known mode of action. Indeed, of the AEs that occurred in ≥5% of patients, only diarrhoea, nausea, vomiting and dizziness were considered related to study medication in a majority of the patients in each treatment group. Insomnia was also reported as a treatment-related AE and is an expected side effect of the cholinomimetic action of donepezil. The incidence of insomnia is thought to be related to the administration of this medication just before retiring, with peak plasma concentrations therefore more likely to occur during the night. In patients experiencing insomnia, it has been reported that switching to morning dosing may eliminate this (Ross and Shua-Haim, 1998).

Most AEs were mild, only occasionally moderate in intensity and generally transient in nature. Most other non-cholinergic induced AEs were considered unrelated to study drug. Headache was considered related to study medication in approximately half of the patients in each treatment group who experienced such an AE, but pain, rhinitis and urinary tract infections were considered unrelated to study medication in most patients. There were no clinically significant differences in abnormal laboratory test parameters, vital signs or cardiovascular parameters between the study groups.

DISCUSSION

This meta-analysis of individual patient data, from all appropriate individual RCTs using statistically robust assessments of cognition and global function over periods of up to 24 weeks, has confirmed and strengthened the evidence for the clinical benefits provided by donepezil (5 and 10 mg/day). Comparisons of the overall and individual study pairwise treatment differences demonstrate the consistency between the results of the individual studies and those of the pooled data for all of the efficacy variables included in the meta-analysis. In line with the previously reported dose-response effect (Burns *et al*., 1999), the results of the meta-analysis indicate a greater sustained benefit in cognition and global function with the 10 mg/day donepezil dose compared with the 5 mg/day dose. The overall fixed effects analysis of ADAS-cog at 24 weeks showed a significant difference between the two doses at the 0.5% level. When allowance was made for heterogeneity between the studies in the overall random effects analysis, significance was found at the 10% level. For the CIBIC-plus analysis at 24 weeks, both the fixed and the random effects analyses showed significance at the 8% level.

Although the beneficial effect of donepezil in terms of ADAS-cog was not statistically significant at the 5% level in the subgroup of patients who were over 80 years of age, this cannot be taken as evidence that patients over 80 will not benefit from donepezil treatment. A more likely explanation is that there was insufficient power to detect treatment differences in this subgroup due to a smaller sample size and also a lack of decline in patients over 80 receiving placebo. No association was found between age and change in

ADAS-cog from baseline when age was included as a covariate in the fixed effects meta-analysis model.

It is recognised that the response to treatment with ChE inhibitors varies among different patients over a two-year period. In particular, representation of results by group mean scores only may lead to an inaccurate perception of the value of treatment owing to this heterogeneity of response. The use of responder analyses, however, can assist in the interpretation of treatment effects. For example, using conventionally designated definitions for patient responses to ChE inhibitors (Peripheral and Central Nervous System Drugs Advisory Committee Meeting, 1989; Leber, 1990; The European Agency for the Evaluation of Medical Products, 1997), approximately twice the number of patients treated with either 5 or 10 mg/day donepezil improved by either 4 or 7 points on the ADAS-cog from baseline levels compared with placebo. In addition, at least two-thirds of patients demonstrated no change or stabilisation compared with 50% of placebo-treated patients.

Quantitative mental status assessments of cognition such as the ADAS-cog and MMSE may fail to detect changes in affect, social skills, and executive function discernible by an independent clinician as being clinically important (Krishnan *et al*., 2003). In addition to these quantitative assessments, clinical trials of antidementia drugs have used a variety of clinician-rated impression of change scales, each different in terms of depth and structure. The CIBIC-plus is a fully validated scale used for the majority of donepezil trials, developed by an academic consortium, the Alzheimer's Disease Co-operative Study Units (ADCS) Global Scales Committee (Schneider *et al*., 1997). The CIBIC-plus is not an instrument but a semi-structured interview of the patient and carer performed by a clinician barred from knowledge of all psychometric test scores, laboratory values and AE reports. It provides a global rating score that reflects patient function in four areas: ADLs, behaviour, general and cognition, through the probing of 15 separate domains. Since the deficits in AD are heterogeneous, this tool allows the interviewer to establish baseline anchor points specific to each patient. The lack of structure is intended to provide autonomy to the interviewer while ensuring that all patients are evaluated with the same depth and breadth.

Consistent with the results of the individual RCTs, the results from the CIBIC-plus assessment observed in this meta-analysis demonstrate that clinical improvement was observed in a significantly greater number of donepezil-treated patients than in placebo-treated patients. These results were supported by the CDR-Sum of Boxes assessment, a global measure that is linear over time and used to follow disease progression (Guy, 1976), and further support a delay in the decline in global functioning in donepezil-treated patients for at least six months.

Finally, it was not possible to interpret the QoL results of this meta-analysis reliably because of the nature of the scale itself and the wide variation in individual assessments. Although these data may indicate a lack of effect of donepezil on QoL, there are inherent difficulties in assessing QoL in an AD population in response to drug therapy. Cognitive impairment can result in a lack of insight and patients may therefore offer somewhat unreliable opinions regarding their own QoL. Carer-based assessments are equally unreliable, since some patients may not receive care from a single carer, and those who do will still be evaluated based on a subjective opinion. Thus, no appropriately validated, reliable and sensitive instruments of QoL are available to date, as acknowledged in the European Medicines Evaluation Agency guidelines for clinical trials in AD. Therefore it is likely that the scale used in these studies was not appropriate for assessment of QoL in this patient population.

As expected from the results of RCTs completed to date, donepezil (5 and 10 mg/day) was well tolerated, with a high proportion of patients with mild to moderate AD from all treatment groups completing the trials. The majority of AEs that did occur were related to the well-known cholinergic activity of this class of drug, being mainly gastrointestinal in nature. Such AEs generally occurred on increasing the dose of donepezil from 5 to 10 mg/day after just one week, and were generally of mild to moderate severity and transient in nature. In subsequent studies, a similar frequency of AEs in donepezil-treated patients to that of placebo has been demonstrated after increasing the dose after at least four weeks (Feldman *et al*., 2001; Winblad *et al*., 2001). In addition, there were no clinically significant differences in abnormal laboratory test parameters, vital signs or cardiovascular parameters between the study groups.

In summary, the results of this meta-analysis demonstrate that donepezil is a well-tolerated, effective symptomatic treatment for patients with AD. All studies included in the meta-analysis indicated a positive effect of donepezil, with some individual study results reaching statistical significance. While both doses of donepezil are effective, maximal benefits are likely to be gained from the 10 mg/day donepezil dose after initial treatment with 5 mg/day donepezil for 4–6 weeks. This initial dosing period

KEY POINTS

- Donepezil (5 and 10 mg/day) provides clinically meaningful benefits in alleviating deficits in cognition and global function in AD patients relative to placebo.
- This meta-analysis, using robust assessments of cognition and global function over periods of up to 24 weeks, confirmed and strengthened the evidence for the clinically relevant benefits provided by donepezil.
- While both doses were clinically effective, increased improvements in cognition and global function were indicated for donepezil 10 mg/day over donepezil 5 mg/day.
- Donepezil was well tolerated; AEs were mainly cholinergic in nature, brief and mild in intensity.

is used to minimise the development of cholinergic side effects. Thus, the physician and caregiver, in conjunction with the patient if possible, should determine the benefits of therapy on the basis of improvement, stabilisation or a slowing of deterioration in cognition, global function, ADLs and/or behaviour.

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