A Three-Country Randomized Controlled Trial of a Psychosocial Intervention for Caregivers Combined With Pharmacological Treatment for Patients With Alzheimer Disease: Effects on Caregiver Depression

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Objective: *To evaluate the effectiveness of a combination of cholinesterase inhibitor therapy for patients with Alzheimer disease (AD) and psychosocial intervention, for their spouse caregivers compared with drug treatment alone in three countries simultaneously.* **Design:** *Randomized controlled trial. Structured questionnaires were administered at baseline and at regular follow-up intervals for 24 months by independent raters blind to group assignment.* **Setting:** *Outpatient research clinics in New York City, U.S., Manchester, U.K. and Sydney, Australia.* **Participants:** *Volunteer sample of 158 spouse caregivers of community dwelling patients with AD.* **Interventions:** *Five sessions of individual and family counseling within 3 months of enrollment and continuous availability of ad hoc* telephone counseling were provided for half the caregivers. Donepezil was prescribed for all patients. **Main Outcome Measure:** *Depressive symptoms of spouse caregivers measured at intake and follow-up assessments for 24 months using Beck Depression Inventory (revised).* **Results:** *Depression scores of caregivers who received counseling decreased over time, whereas the depression scores for caregivers who did not receive counseling increased. The benefit of the psychosocial intervention was significant after controlling for site, gender and country was not accounted for by antidepressant use and increased over 2 years even though the individual and family counseling sessions occurred in the first 3 months.* **Conclusion:** *Effective counseling and support interventions can reduce symptoms of depression in caregivers when patients are taking donepezil. Harmonized multinational psychosocial interventions are feasible. Combined drug and supportive care approaches to the management of people with AD should be a priority.*(Am J Geriatr Psychiatry 2008; 16:893–904)

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As caring for a relative with dementia can have a serious negative impact on a caregiver's mental health[1] creating significantly increased risk for depression,[2–4] interventions have been developed to improve the psychological well-being of caregivers. Randomized controlled trials and meta-analyses have demonstrated that comprehensive individualized psychosocial interventions are effective in reducing symptoms of depression in caregivers of family members with Alzheimer disease (AD).[5–15]

Cholinesterase inhibitors can temporarily improve or slow the rate of progression of symptoms of dementia in people with AD. For example, donepezil has been shown to improve cognitive function[16–18] and reduce aberrant behaviors.[19,20] Cholinesterase inhibitors have also been associated with small but statistically significant reductions in caregiver burden and task oriented time expenditures.[21]

Now that pharmacologic interventions and psychosocial interventions have demonstrated efficacy, it is timely to assess the potential value of combining interventions that target both patients and caregivers. We conducted a study of an intervention which combined counseling and support for spouse caregivers with pharmacologic treatment for their relatives with AD simultaneously in Manchester, U.K., New York City, U.S., and Sydney, Australia. To our knowledge, this is the first longitudinal randomized controlled trial to assess the incremental effectiveness of a psychosocial intervention when combined with a currently established available drug treatment (donepezil) for AD.

The psychosocial intervention replicated the intervention strategy developed at the New York University Aging and Dementia Research Center (NYU-ADRC), which demonstrated significant short and long-term effects on depressive symptomatology in caregivers,[8,9] adding a pharmacologic intervention for patients. The NYU intervention included individual and family counseling sessions tailored to each caregiver's specific situation and additional counseling on request, generally on the phone. All patients, regardless of group assignment, received donepezil from the time of enrollment until they ceased participating, whereas half the spouse caregivers in each country also received the psychosocial intervention.

We hypothesized that the psychosocial intervention would provide significant benefits for caregivers, specifically in reducing depressive symptoms.

PATIENTS AND METHODS

Study Subjects

To be eligible, patients were required to meet National Institute of Neurological and Communicative Disorders and Stroke–AD and Related Disorders Association and *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria for probable AD[22,23]; have a Global Deterioration Scale (GDS)[24] score of 4 to 5, indicating mild to moderate dementia at enrollment; have no contra-indication to donepezil; be stable with other medications; be in good general physical health; be able to give informed consent, or if not able, not object to participating; and be residing in the community with their spouse. Caregivers were required to be the patients' spouses; be self-defined as the primary caregiver and give informed consent. Caregivers who had previously received formal caregiver counseling were excluded. At least one family member other than the caregiver potentially had to be available to participate in family counseling sessions. (On a few occasions in Manchester, family members did not take part in counseling.) The informed consent form and protocol received independent ethics committee/institutional review board approval at each site. Written informed consent was obtained from all patients and caregivers.

Study Design

From the original NYU caregiver intervention study, we estimated that a sample size of 150 would be sufficient to provide a power of at least 0.80 based on Cronbach alpha (α) = 0.05 to detect a medium effect size of the intervention on major outcomes such as depression in analyses that include multiple covariates. A sample of 158 caregiver/patient dyads was enrolled in the study over a 2-year period, from June 1999 to May 2001.

After initial screening for eligibility, all assessments were conducted by experienced clinical research staff in face-to-face interviews of caregivers and examination of patients by trained health professionals. After baseline interviews, provision of informed consent, and agreement to randomization, caregiver/patient dyads were randomized by lottery

to the control group, in which patients received donepezil, or the treatment group, in which patients received donepezil and caregivers received the psychosocial intervention. All participating patients received donepezil for up to 24 months free of charge. Caregivers in both groups received resource information, help in an emergency, and the routine services normally provided.

Raters were blind to group assignment. Patients and caregivers were followed for at least 2 years unless the patient entered a nursing home or died, or the caregiver died or dropped out of the study. Family caregivers were scheduled for follow-up interviews every 3 months for the first year and every 6 months for the second year, except that there was no 9-month follow-up visit in Manchester. Follow-up interviews of caregivers included all the instruments administered at baseline.

At each assessment, caregivers were given a 3-month supply of donepezil. Patients not taking donepezil at enrollment began with a dose of 5 mg/day. At the first follow-up, a clinician assessed the response of the patient and increased the dose to 10 mg. This dose was maintained throughout the study unless contraindicated by patient reaction.

Psychosocial Intervention

Within 3 months of enrollment, caregivers who had been randomly assigned to receive the psychosocial intervention participated in five in-person counseling sessions: one individual session, followed by three sessions that included the family members who were invited by the caregiver to participate, and one additional individual session. Ad hoc counseling—counseling on demand by telephone (and/or face-to-face in Australia) was available to spouse caregivers and their family members for the duration of study participation.

Although the structure of the intervention was predetermined, the content depended on the needs of each caregiving family and could include education about AD, information about available resources in the community, or help in understanding how to manage difficult patient behavior. The underlying theme was the importance of emotional support and assistance for the caregiving spouse. Issues discussed included conflicts about how and where to provide care (home/nursing home, etc.), who should provide care, how to ask for and offer help, what kind of help was needed, and who was willing and able to provide help. Changes inpatient status, new symptoms, other family problems, and emergencies often resulted in *ad hoc* calls from caregivers and family members.

Measures

Caregivers completed comprehensive assessments. Demographic characteristics comprised gender, age, race, education, and income. Caregiver depression was measured with the revised Beck Depression Inventory (BDI; $\alpha = 0.92$),[25] a widely used 21-item self-report measure for detecting depression in nonclinical populations. Each item has four statements, arranged in increasing severity, about a specific symptom of depression. The sum of scores on individual items, each ranging from 0 to 3, yield a total score, ranging from 0 to 63. The reliability and validity of the BDI for elderly samples are reasonably good, and it has been adopted widely for use with older adults.[26] The BDI is more sensitive to mild to moderate severity of depression than more biologically weighted scales.[27] The following cut scores have been recommended: minimal (0–13), mild (14–19), moderate (20–28), and severe (29–63) depression.[25]

Social support was assessed with *The Stokes Social Network List* ($\alpha = 0.92$)[28] that measures how satisfied subjects are with their support networks in three areas: general support, tangible assistance, and emotional support, each rated on a 6-point scale (1 = very satisfied, . . . , 6 = very dissatisfied).

Each patient was examined and tested by health care professionals at baseline and during each follow-up visit in the first year after enrollment. The assessment of the patient included a determination by a psychiatrist of the *global* functional status of the patient, measured with the GDS[24] ($\alpha = 0.83$). Cognitive ability was assessed with the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-cog,[29] $\alpha = 0.81$[30]). Ability to perform activities of daily living was measured with the AD Cooperative Study-Activities of Daily Living Inventory[31] ($\alpha = 0.95$; Galasko D: personal communication, 2008). The frequency of behavior problems and the severity of the caregiver's reaction were measured by the Revised Memory and Behavior Problems Checklist ($\alpha = 0.84$ for behavior and $\alpha = 0.90$ for reaction)[32] that consists of 24 questions regarding problem behaviors of the patient that are likely to be

upsetting for the caregiver. The frequency of the behavior and the severity of the caregiver's reactions are each rated on a 5-point scale, ranging from "not at all" to "extremely." The dosage of donepezil, adverse events, concurrent medications, including psychotropic medication and current alcohol intake were recorded at each visit. Use of donepezil at study entry was recorded at baseline.

Statistical Methods

The major aim of the analyses was to estimate the impact of the intervention on caregiver depressive symptoms, taking into account the effects of potential confounders. We conducted descriptive analyses to determine whether there were differences between treatment and control groups and countries at baseline. We then conducted a series of linear regression analyses in which the dependent variable was caregiver depression at baseline and independent variables that were selected on the basis of previous research[9] and the stress process model.[33] The subsequent analyses of the effects of the intervention on depression over time were guided by the results of these preliminary analyses.

In all analyses, variables with only two categories were coded (0,1): caregiver gender "0" for men and "1" for women; treatment group "0" for usual care and "1" for counseling and support; "began donepezil" "0" for patients who were already taking donepezil at study entry and "1" for those who began taking donepezil at enrollment. Country was recoded into numeric categories: Australia = −1, United States = 0, and England = 1.

Multilevel growth curve analyses were conducted, using hierarchical linear modeling,[34] to estimate longitudinal change in BDI scores. Variations in the patterns of individual change are represented by individual growth curves that indicate individual responses across time (in this case, BDI scores) for each person in the sample. When comparing groups of individuals, common growth patterns within groups and differential growth patterns across groups provide evidence of group differences.[35] Evidence of the extent to which specific variables explain variations in these patterns of group and individual growth can be calculated.[36,37]

Growth curve analyses offer many advantages over more traditional repeated measures analyses. One advantage is that growth curves can be fitted for each subject based on the amount of data provided. Consequently, caregivers who discontinued participation before the 2-year follow-up assessment, or missed an assessment, could be included without imputing data for missing observations. Individual growth curve parameters were modeled as a function of group (treatment versus control) and other predictors of interest. In all models, time was defined as the data collection point, beginning with baseline, defined as Visit 0 and continuing through the sixth follow-up Visit 2 years later (defined as Visit 6).

We began by estimating a reference model (Model 0) in which BDI scores obtained at each follow-up visit (i.e., 3-month, 6-month, . . . , 18-month, 24-month) were modeled as a function of two time-invariant covariates, the baseline BDI score and caregiver gender, as well as two time-dependent covariates, time and a time by gender interaction effect. We then estimated a model in which we added the time-invariant predictor "Group" and the Group by time interaction (Model 1).

We examined several additional models in which there were other potential predictors of change in BDI beyond those in Model 1. The decision about which variables would be included in these subsequent models was based on the results of linear regression analyses of predictors of depression at baseline; variables with a p value less than 0.05 were included in the multilevel models.

Finally, to estimate the size of the effect of the counseling and support intervention on BDI, we calculated the reductions in residual variance left unexplained by several models and the proportions of variance in change in BDI scores over time accounted for by adding gender, the main effect of treatment, and the group by time interaction, to a model in which time was the only predictor.

RESULTS

Demographic Characteristics of Subjects, Subject Accrual, and Follow-Up

Demographic details for patient and caregivers are provided in Table 1. Nearly all patients had mild to moderately severe dementia (GDS 4 or 5). (We inad-

TABLE 1. Characteristics of Caregivers and Patients at Baseline

Characteristic	Treatment (n = 79)	Control (n = 79)	Total (n = 158)	Statistic
Caregiver gender (% female)	46 (58.2%)	43 (54.4%)	89 (56.3%)	$\chi^2_{[2]}$ for gender by country = 4.75, (p = 0.093); $\chi^2_{[1]}$ for group = 0.23 (p = 0.75)
Australia	17 (65.4%)	15 (57.7%)	32 (61.5%)	$\chi^2_{[1]}$ = 0.33 (p = 0.57)
United Kingdom	12 (44.4%)	12 (44.4%)	24 (44.4%)	$\chi^2_{[1]}$ = 0.00 (p = 1.00)
United States	17 (65.4%)	16 (61.5%)	33 (63.5%)	$\chi^2_{[1]}$ = 0.08 (p = 0.78)
Age of caregivers[a] (<50/50–59/60–69/70–79/80–89)	0%/8.9%/26.6%/43%/21.5%	1.3%/8.9%/27.8%/51.9%/10.1%	0.6%/8.9%/27.2%/47.5%/15.8%	$F_{[2,155]}$ = 0.83 (p = 0.44)
Australia	0%/3.8%/19.2%/46.2%/30.8%	0%/19.2%/23.1%/53.8%/3.8%	0%/11.5%/21.2%/50.0%/17.3%	
United Kingdom	0%/3.7%/40.7%/33.3%/22.2%	0%/0%/25.9%/66.7%/7.4%	0%/1.9%/33.3%/50%/14.8%	
United States	0%/19.2%/19.2%/50%/11.5%	3.8%/7.7%/34.6%/34.6%/19.2%	1.9%/13.5%/26.9%/42.3%/15.4%	
Age of patients[a] (<60/60–69/70–79/80–89/90–99)	5.1%/17.7%/49.4%/26.6%/1.3%	1.3%/225.3%/50.6%/21.5%/1.3%	3.2%/21.5%/50.0%/24.1%/1.3%	$F_{[2,155]}$ = 0.72 (p = 0.49)
Australia	0%/11.5%/42.3%/42.3%/3.8%	3.8%/26.9%/50%/19.2%/0%	1.9%/19.2%/46.2%/30.8%/1.9%	
United Kingdom	3.7%/29.6%/55.6%/11.1%/0%	0%/18.5%/63.0%/14.8%/3.7%	1.9%/24.1%/59.3%/13.0%/1.9%	
United States	11.5%/11.5%/50%/26.9%/0%	0%/30.8%/38.5%/30.8%/0%	5.8%/21.2%/44.2%/28.8%/0%	
Severity of dementia of AD patient (GDS 3/GDS 4/GDS 5/GDS 6)	0%/60.8%/36.7%/2.5%	3.8%/53.2%/41.8%/1.3%	1.9%/57.0%/39.2%/1.9%	$\chi^2_{[3]}$ = 3.99 (p = 0.26)
Australia	0%/61.5%/38.5%/0%	0%/50.0%/50.0%/0%	0%/55.8%/44.2%/0%	
United Kingdom	0%/66.7%/29.6%/3.7%	11.1%/59.3%/29.6%/0%	5.6%/63.0%/29.6%/1.9%	
United States	0%/53.8%/42.3%/3.8%	0%/50%/46.2%/3.8%	0%/5551.9%/44.2%/3.8%	
Patient first began taking donepezil when entering study (% yes)	40 (50.6%)	43 (54.4%)	83 (52.5%)	$\chi^2_{[1]}$ = 0.23 (p = 0.63)
Australia	11 (42.3%)	10 (38.5%)	21 (40.4%)	$\chi^2_{[1]}$ = 0.08 (p = 0.77)
United Kingdom	17 (63.0%)	23 (85.2%)	40 (74.1%)	$\chi^2_{[1]}$ = 3.47 (p = 0.06)
United States	12 (46.2%)	10 (38.5%)	22 (42.3%)	$\chi^2_{[1]}$ = 0.32 (p = 0.56)

[a]Age is presented in categories for presentation purposes only. *t* tests were based on original continuous age data.

TABLE 2. Number of Caregivers Providing Beck Depression Scale Data at Indicated Time Points

Assessment	Treatment (n = 79)	Control (n = 79)	Total (n = 158)	Percent
Intake	79	77	156	98.7
3 Month	70	65	135	85.4
6 Month	69	70	139	88.0
9 Month[a]	39	44	83	52.5
12 Month	64	59	123	77.8
18 Month	45	44	89	56.3
24 Month	40	42	82	51.9

[a]The 9-month follow-up evaluation was not conducted in the United Kingdom.

vertently included two patients in the treatment group and one in the control group with GDS 6 ratings and three patients in the control group with GDS 3 ratings.) Subjects did not differ significantly in caregiver gender or age, patient age or severity of patient dementia between countries, or treatment groups.

Table 2 shows the number of subjects included in the analyses during each of the follow-up assessments. At baseline, 3 of the 158 participants were missing essential baseline data. At the end of 1 year, 123 (77.8%) of the original 158 caregivers supplied Beck Depression Scale data and 82 (51.9%) did so at the end of 2 years. The causes of missing data at the end of 2 years included 21 patients (13.3%) who had been placed in nursing homes and 20 (12.7%) who had died before being placed in nursing homes, three caregivers (1.9%) who had died, 28 (17.7%) who refused to continue or moved out of the area and were no longer able to participate, and four (2.5%) for whom the reason was unknown. Caregivers who did not complete the 2-year follow-up were similar to completers in age ($t(156) = 1.16$, $p = 0.25$) and baseline Beck depression scale scores ($t(156) = 0.81$, $p = 0.42$). Significantly more female caregivers (N = 53, 59.6%) than males (N = 29, 42%) completed the 2-year follow-up ($\chi^2_{[1]} = 4.10$, $p = 0.043$). Participant flow through the study is illustrated in Fig. 1. There were no adverse events attributable to the study interventions.

Caregiver Depression at Baseline

Relatively large standard deviations of caregiver depression in comparison with means suggested a wide variation in the number of symptoms of depression reported by caregivers. Almost 20% of caregivers in all three countries had BDI scores above 13, indicating at least mild depression (Table 3). Differences in BDI scores between treatment and control groups and between countries were not significant ($F_{[lsqb]2,155[rsqb]} = 0.48$, $p = 0.49$).

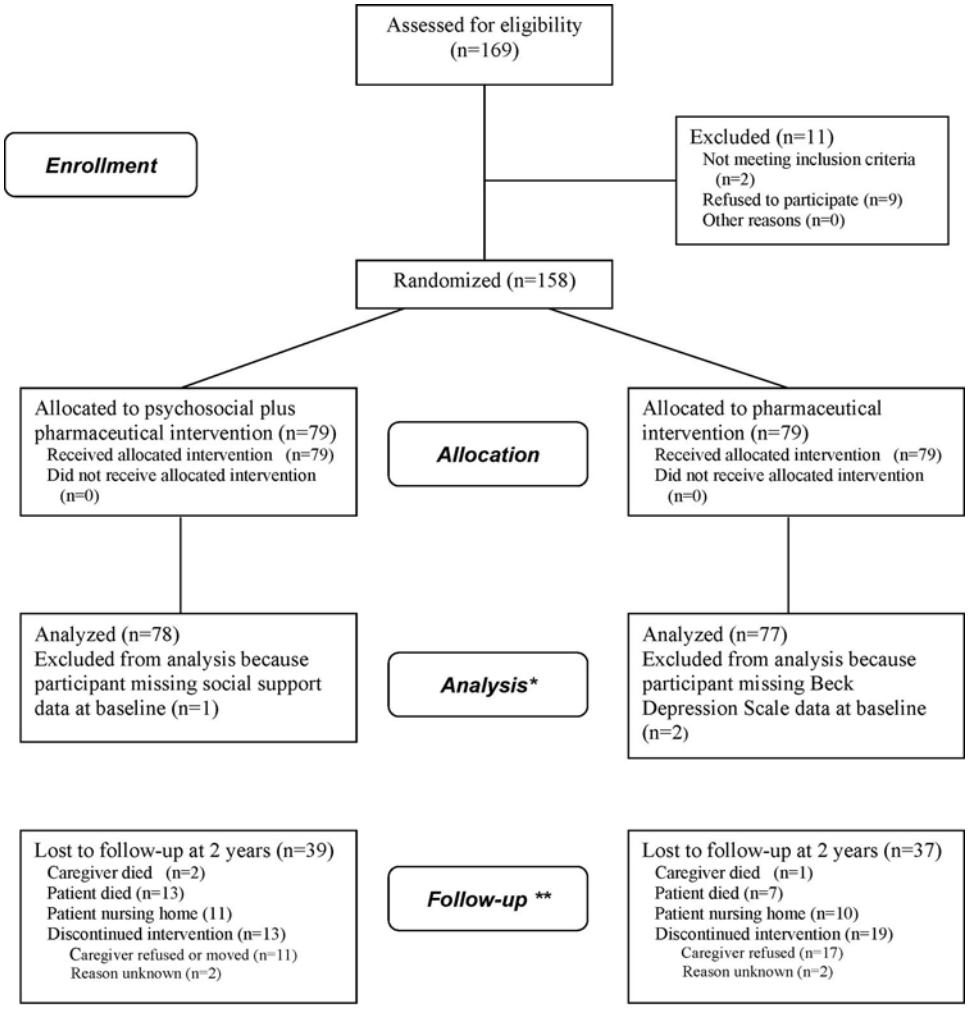
The linear regression analyses suggested that caregiver characteristics were much more important than patient characteristics in predicting caregiver depression at baseline. Female caregivers had significantly more symptoms of depression than male caregivers (Table 4). Caregivers of patients who were taking donepezil at study entry were significantly more depressed than those whose spouses were not yet taking donepezil. As in the NYU study, caregivers who were less satisfied with the emotional support they received from family and friends[38] and those who had more severe reactions to troublesome patient behaviors[39] had significantly more symptoms of depression.

Severity of dementia did not predict number of symptoms of depression but most patients were in the early stages of dementia. Although frequency of problem behaviors did not predict caregiver depression, severity of reaction to the behaviors did. Caregiver depression at baseline was not related to their spouses' problems with activities of daily living or their scores on the ADAS-cog. Finally, there was no significant difference in symptoms of depression at baseline among caregivers by country (Table 4).

The Effect of the Intervention on Change in Caregiver Depression Over Time

The results of the longitudinal analyses predicting change in BDI are displayed in Table 5. Model 0 shows that the main effect for time was not significant, indicating that overall, BDI did not change significantly over the 2 years of the study for participants when undifferentiated by group. There was a significant gender difference, with female caregivers endorsing more symptoms of depression than males. The change in depression over time was unrelated to gender. The coefficient associated with BDI at baseline merely reflects the fact that, on average, the BDI scores were significantly different from 0.

FIGURE 1. Trial Profile



Notes

* The statistical analysis used, hierarchical linear modeling, made it possible to include information from any subject who provided at least two data points of information on key variables, whether or not they were subsequently lost to follow-up.

** We report loss to follow-up as subjects no longer participating at the 2-year follow-up. It should be noted that all but 3 of these subjects were included in the data analysis, as they provided at least two data points of information on all variables included in the data analysis.

TABLE 3. Beck Depression Scale Scores of Caregivers at Baseline

Characteristics	Treatment (n = 79)	Control (n = 77)[a]	Total (n = 156)	Statistic
Mean (SD)	8.98 (7.02)	8.25 (5.93)	8.62 (6.49)	$F_{[2,155]} = 0.48$ ($p = 0.49$)
Minimal depression (0–13)	64 (81.0%)	63 (81.8%)	127 (81.4%)	
Mild depression (14–19)	8 (10.1%)	11 (14.3%)	19 (12.2%)	
Moderate depression (20–28)	5 (6.3%)	3 (3.9%)	8 (5.1%)	
Severe depression (29–63)	2 (2.5%)	0 (0%)	2 (1.4%)	

[a]Two subjects in the control group did not provide complete BDI scores at baseline.

TABLE 4. Linear Regression Analysis of Predictors of Caregiver Depression at Baseline

Variables	Unstandardized Coefficients		Standardized Coefficients		
	B	SE	[β]	t^a	p
Caregiver gender (1 = female, 0 = male)	2.627	1.032	0.201	2.546	0.012
Caregiver age	−0.070	0.062	−0.090	−1.121	0.264
Dementia severity (GDS)	0.747	0.920	0.065	0.812	0.418
Highest education level achieved	0.024	0.380	0.005	0.064	0.949
Years of education	−0.140	0.153	−0.075	−0.913	0.263
Patient started taking donepezil at intake (1 = yes, 0 = no)	−2.122	1.030	−0.164	−2.061	0.041
Country	−0.492	0.637	−0.062	−0.772	0.441
Satisfaction with support in general	−0.534	0.632	−0.064	−0.525	0.601
Satisfaction with assistance from social network	0.531	0.522	0.107	1.017	0.311
Satisfaction with emotional support	1.413	0.663	0.237	2.130	0.035
Average satisfaction	2.211	0.501	0.357	4.361	<0.001
Frequency of troublesome patient behavior	−0.063	0.063	−0.111	−0.998	0.320
Reaction to troublesome patient behavior	0.227	0.058	0.436	3.938	<0.001
ADAS-Cog	0.064	0.046	0.117	1.403	0.163
Activities of daily living (ADCS-ADL)	−0.048	0.052	−0.098	−0.911	0.364

Highest education level achieved was coded in six categories, similar in all three countries, with graduate school coded as 1 and primary or junior high school or equivalent coded as 6 (education level was missing in seven cases).

[a] *t* tests. Degrees of freedom for *t* tests = 153, except in the case of highest education level achieved, where *t* = 146.

Model 1 included group and time main effects, the group by time interaction, and caregiver gender as a covariate. This group main effect indicates the average treatment effect over all time points, from baseline to the 2-year follow-up. The treatment group entered the study with somewhat higher average BDI scores than the control group, but the difference at baseline was not significant (Table 3). The BDI scores of the two groups changed in opposite directions over time. Because this was a disordinal (or crossover) interaction, the main effects for time and group were not significant. There was, however, a significant group by time interaction effect (Table 5); the predicted BDI scores decreased for treatment caregivers and increased for control caregivers. Figure 2 illustrates the covariate adjusted predicted means using Model 1, indicates that 6 months after baseline, the model predicted scores for the treatment group crossed over and became lower than those for the control group.

We examined the reductions in residual variance associated with certain key predictors from Model 1. With only caregiver gender and time in the model (Model 0) to predict change in depression scores there was a significant residual variance of 0.218 ($\chi^2_{[127]}$ = 174.64, N = 155, p <0.003). When the main effect of group was added, the unexplained variance decreased only slightly, to 0.216, ($\chi^2_{[127]}$ = 174.55, N = 155, p <0.004). However, when the treatment by time interaction was added to the model, the variance in change in depression over time was reduced significantly, to 0.181 ($\chi^2_{[126]}$ = 167.76, N = 155 p <0.008). Thus, 16.5% of the variance in the between person change over time (21.645 − 18.068/21.645) was due to the effect of the counseling and support intervention.

In Model 2, we included an additional covariate to indicate whether the patient had been taking donepezil before entering the study or began taking it on entry. There was a significant (negative) main effect of donepezil (Table 5). The group by time interaction is still significant in this model and virtually unchanged from Model 1, which suggests that donepezil status at baseline had little or no impact on the effect of the intervention.

In Model 3, we included the severity of the caregiver's reaction to the patient's problem behavior as a time-varying covariate, in addition to the predictors in Model 2. We found a significant main effect of caregiver reaction on changes in symptoms of depression (Table 5). The group by time interaction became slightly smaller and was no longer significant in this model.

Model 4 included satisfaction with emotional support as a time-varying covariate in addition to group, the group by time interaction, caregiver gender, and

TABLE 5. Model of Change in Depressive Symptoms (Beck Depression Inventory, BDI) from Baseline to Year 2

Variables in Model	B	SE	*t*	*df*	p > *t*
Model 0					
BDI at baseline	6.38	0.70	9.11	153	<0.001
Time	−0.04	0.09	−0.48	153	0.631
Caregiver gender (F = 1, M = 0)	3.52	1.01	3.47	153	0.001
Caregiver gender by time	0.12	0.16	0.71	152	0.481
Model 1					
BDI at baseline	5.96	0.81	7.37	152	<0.001
Group (treatment = 1, usual care = 0)	0.88	1.02	0.86	152	0.391
Time	0.12	0.12	1.02	152	0.312
Group × time	−0.38	0.17	−2.18	152	0.031
Caregiver gender (F = 1, M = 0)	3.46	1.01	3.42	152	0.001
Caregiver gender by time	0.16	0.16	0.99	152	0.323
Model 2					
BDI at baseline	7.10	0.94	7.55	151	0.000
Group (treatment = 1, usual care = 0)	0.71	1.00	0.71	151	0.479
Time	0.19	0.12	1.56	153	0.121
Group × time	−0.34	0.17	−2.00	153	0.047
Caregiver gender (F = 1, M = 0)	3.70	0.89	4.18	151	<0.001
Began donepezil at baseline (1 = yes, 0 = no)	−2.22	0.90	−2.46	151	0.015
Model 3					
BDI at baseline	8.19	0.80	10.22	151	0.0001
Group (treatment = 1, usual care = 0)	0.63	0.90	0.70	151	0.483
Time	0.17	0.11	1.51	153	0.133
Group × time	−0.26	0.16	−1.69	153	0.092
Caregiver gender (F = 1, M = 0)	2.31	0.81	2.84	151	0.006
Began donepezil at baseline	−2.40	0.79	−3.02	151	0.003
Reactions to troublesome patient behaviors	0.18	0.03	5.87	154	<0.001
Model 4					
BDI at baseline	7.36	0.92	8.03	151	0.0001
Group (treatment = 1, usual care = 0)	0.71	0.92	0.77	151	0.443
Time	0.17	0.12	1.34	153	0.183
Group × time	−0.41	0.18	−2.26	153	0.025
Caregiver gender (F = 1, M = 0)	3.50	0.84	4.16	151	<0.001
Began donepezil at baseline (1 = yes, 0 = no)	−2.09	0.85	−2.46	151	0.015
Satisfaction with emotional support (6 = very dissatisfied, 1 = very satisfied	0.94	0.22	4.30	154	<0.001
Model 5					
BDI at baseline	8.34	0.82	10.17	151	<0.001
Group (treatment = 1, usual care = 0)	1.03	0.78	1.32	151	0.190
Time	0.18	0.11	1.56	153	0.122
Group × time	−0.36	0.16	−2.27	153	0.024
Caregiver gender (F = 1, M = 0)	1.71	0.72	2.36	151	0.020
Began donepezil at baseline (1 = yes, 0 = no)	−2.17	0.71	−3.07	151	0.003
Reactions to troublesome patient behaviors	0.19	0.03	6.20	154	<0.001
Satisfaction with emotional support	0.77	0.24	3.26	154	0.002

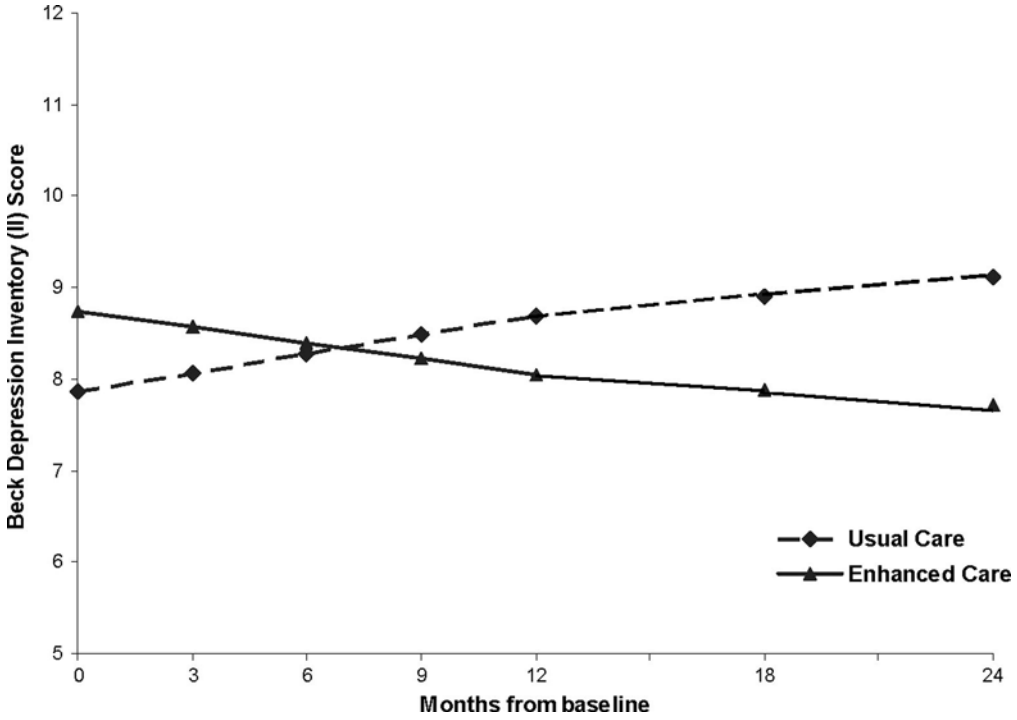
donepezil status of the patient at enrollment. A significant main effect was found for satisfaction with emotional support, indicating that caregiver depression was higher when the caregiver was less satisfied with his or her emotional support (Table 5).

In Model 5, we included both severity of reaction and satisfaction with emotional support and found that both of these predictors were significant, but that the group by time interaction was relatively unaffected (Table 5), suggesting that the effects of these predictors were largely independent of and did not account for the effect of the intervention on symptoms of depression.

Effects of Caregiver Utilization of Antidepressants and Patients Beginning Donepezil Treatment on Caregiver Depression

Caregiver utilization of antidepressants did not differ by intervention group. The percentages of caregivers taking antidepressants at intake, at 1 year and at 2 years were as follows: in the treatment

FIGURE 2. Predicted Beck Depression Inventory (BDI-II) Scores by Time and Treatment Group, Controlling for Caregiver Gender



group 11.4%, 10%, and 8.3%, respectively; and 14.3%, 15.4%, and 8.3% in the control group. These differences are not statistically significant.

DISCUSSION

In this study, the first to examine the combined effects of a caregiver intervention and pharmacotherapy, we demonstrated that five sessions of counseling based on the NYU model[40] reduced depression scores in spouses of persons with AD taking donepezil. This benefit was significant in analyses that controlled statistically for caregiver gender and country and was not accounted for by antidepressant use.

Although the difference in change in depressive symptoms between the two groups was small, it is remarkable that the trend continued over the 2 years of the study, and the gap between the two groups continued to widen (approximately 1.5 points at 24 months), even though the formal intervention occurred within 3 months of enrollment. In the NYU study, differences in depression scores were apparent for up to 5 years after enrollment.[9]

We note that in this first multinational psychosocial intervention study, benefits were independent of country, suggesting its generalizability, at least for spouse caregivers in Anglophonic cultures. The intervention strategy was effective despite differing approaches to counseling—more responsive to expressed caregiver needs in the United States and Australia and more structured in content in the United Kingdom. Future studies should be designed to identify more clearly the mechanisms of action of such interventions, so that they could be even more cost-effective.

Depression scores at baseline were higher among caregivers of patients who were already taking donepezil when they entered the study than among caregivers of patients who commenced donepezil at intake, suggesting that enrollment may have been differentially motivated. Perhaps caregivers of existing donepezil patients were more likely to be seeking help for themselves, whereas caregivers of newly

commencing donepezil patients were more interested in obtaining access to medication.

Although the attrition of almost half the sample at the 2 years follow-up might be viewed as a limitation to our findings, BDI scores of caregivers leaving the study were not significantly different at baseline from completers, and we employed statistical analyses that were able to include information about participants even when they did not complete all follow-up evaluations. Future studies are needed to evaluate the applicability of this intervention to populations that are more diverse with respect to language, culture, relationship of caregiver to person with dementia, type and severity of dementia, and presence of comorbidities.

A possible limitation to the study arises from concern that the assessment scales were not used in the same way in the three countries. This is the first reported multinational study of a psychosocial intervention for people with dementia and their family caregivers. However, there have been numerous trials of pharmaceutical agents for people suffering from dementia in which the two coauthors from the United Kingdom and Australia have participated. Although scales such as the GDS and ADAS-cog have not been validated in each of the three countries, they are originally in English, pose no difficulty in interpretation in practice and are used extensively in international trials (e.g., see Brodaty et al.[41]). In this trials, these measures have been sensitive to pharmacologic interventions, some of which have been approved in all three countries and elsewhere.

A meta-analysis and review of caregiver research and the deleterious consequences of caregiving a few years ago in this *journal*[42] concluded that geriatric psychiatrists are uniquely qualified to care simultaneously for caregivers and care-recipients and urged further study of interventions for caregivers. Our study provides further evidence that psychosocial interventions can have long lasting effects and are cost-effective,[43] requiring only modest expenditure. Other studies demonstrated preserved caregiver health[44] and delay in nursing home admission[6,45,46] for several years after completion of the formal components of psychosocial interventions. These studies provide a persuasive argument for widespread availability of support and counseling for family caregivers.

We conclude that a model that includes five sessions of counseling, two with the primary caregiver and three with the extended family, supplemented by counseling and information by telephone (or occasionally face-to-face) as requested, provides added benefits to caregivers of persons with dementia taking cholinesterase inhibitors. Previous reports indicate that information per se is relatively ineffective[11,47]; that it is important to attend to caregivers' emotional needs before information and skills training can be effective[5]; that a sufficient "dose" of intervention is required; and that relationship to a key person, here the counselor, is important.[12] Our study suggests that a fairly modest intervention by skilled personnel can pay handsome dividends which continue over at least 2 years.

This study has also demonstrated that harmonized multinational psychosocial intervention studies are feasible and that effective psychosocial interventions for caregivers are achievable and practical and can provide significant benefits when the patient is taking drugs such as donepezil. Combining drug and supportive care approaches in the treatment of people with Alzheimer disease should be a priority.

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