Effects of Donepezil on Emotional/Behavioral Symptoms in Alzheimer's Disease Patients

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Background: This open-label study examined the effects of the reversible cholinesterase inhibitor donepezil on emotional/behavioral symptoms in Alzheimer's disease (AD) patients.

Method: Patients were diagnosed as having probable/possible AD by National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria. This study used the CERAD Behavior Rating Scale for Dementia (CBRSD) and its subscales to evaluate a group of 25 AD patients treated with donepezil. Dosage was increased at 4 months for most patients from 5 to 10 mg q.h.s. Analysis of variance was used to compare scores over a period of 12 months. These patients were also compared, using t tests, to a reference group that had received no donepezil or other anticholinesterase.

Results: Donepezil administration was associated with improvement in Mini-Mental State Examination (MMSE) and CBRSD total scores at 3-month evaluation ($p \leq .05$). CBRSD depression and behavioral dysregulation scores improved transiently at 4 months ($p \leq .05$). MMSE, CBRSD total, CBRSD depression, and CBRSD behavioral dysregulation scores returned to baseline levels at 12 months, in contrast to the reference group, whose MMSE and CBRSD total scores worsened minimally over the 12 months.

Conclusion: Donepezil has a mildly positive effect on emotional/behavioral symptoms in AD in addition to its effect on cognitive function.

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Evidence that the cholinergic system is important in the encoding of memory,[1] that there is a cholinergic deficit in Alzheimer's disease (AD),[2] and that cholinergic enhancement improves memory in persons with AD[3] is the rationale for treatment of AD patients with drugs that enhance cholinergic function. Of the potential strategies for enhancing cholinergic function, the most successful has been the use of cholinesterase inhibitors. However, the classical cholinesterase inhibitor physostigmine produces little improvement in formal tests of memory[4,5] whether or not combined with its precursor, phosphatidylcholine.[6] The cholinesterase inhibitors tacrine, donepezil, and metrifonate all produce sufficient global improvement for clinicians to recognize.[7–9] Tacrine, donepezil, and metrifonate appear to slow the rate of cognitive decline in AD patients,[10–12] and tacrine has been reported to delay the need for institutional care.[11]

A newly studied aspect of cholinergic enhancement is its possible effect on the emotional/behavioral symptoms associated with AD. Nearly as pervasive as memory disturbance, these symptoms seriously impair quality of life for AD patients and their caregivers[13] and are a primary reason for institutional placement.[14] Support for a possible effect of cholinergic enhancement on psychotic symptoms was provided by a 2-patient crossover study in which the effects of antipsychotic drugs on delusions in AD appeared to be enhanced by the administration of oral physostigmine.[15] In a study of 40 AD subjects,[16] tacrine appeared to reduce anxiety, apathy, hallucinations, aberrant motor behaviors, and disinhibition. Stratification of subjects by dementia severity showed behavioral effects only in the moderately demented group, independent of cognitive response to the drug, and over half of the subjects with cognitive improvement had marked reduction in behavioral symptoms.[16] In a 30-week multicenter study, patients exposed to tacrine 160 mg/day (N = 234) were compared with a placebo group (N = 181).[10] In the tacrine group, there was improvement or stabilization (1-point increase or no change) in the cooperation, delusions, and pacing subscales in the Alzheimer's Disease Assessment Scale (ADAS).[17,18] In a 26-week study, metrifonate was more significantly effective than placebo for symptoms of depression, apathy, and hallucinations.[19]

Thus, it seemed reasonable that the cholinesterase inhibitor donepezil might have similar action.

METHOD

This was an open-label study of persons who were requesting drug treatment of AD. Thus, participants and raters were not blinded. Open-label administration of donepezil 5 mg q.h.s. for 3 months was followed by titration to 10 mg q.h.s. (as suggested by the manufacturer) when deemed clinically feasible. Testing was performed by K.M. at baseline, 1 month, 3 months, 4 months, and 12 months with the Mini-Mental State Examination (MMSE)[20] and the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Behavioral Rating Scale for Dementia (CBRSD).[21] The MMSE, a cognitive screening instrument with scores ranging from 0 (severe impairment) to 30 (little or no impairment), is administered directly to patients. Although a number of scales were available for the assessment of emotional/behavioral symptoms in AD, only a few had been employed in drug studies when this study was initiated in 1997.[22] We chose the CBRSD because of its breadth and ease of administration. This 48-item instrument, which takes about 20 minutes to administer, is a comprehensive assessment of the emotional states and behaviors associated with AD. It has 6 subscales: depression, behavioral dysregulation, inertia, irritability/aggression, psychotic, and vegetative. It is administered to caregivers and is valid and reliable.[23] Scores on the CBRSD range from 0 (no behavioral disturbance) to 167 (severe behavioral disturbance).

AD patients and caregivers who entered the study were told that the positive drug effects were modest, but that the drug might slow the progression of the disease. No mention was made of potential effects on emotional/behavioral symptoms. Following testing with the MMSE and CBRSD at the baseline visit, the potential side effects of the drug (nausea, vomiting, diarrhea, abdominal cramping, and sweating) were explained, and donepezil 5 mg q.h.s. was prescribed. Patients returned for medical evaluation and for testing at 1 month, 3 months, 4 months, and 12 months. Medical evaluation consisted of a brief interview to inquire about side effects and positive effects of the drug, and measurement of pulse. The decision to increase to 10 mg or to maintain the 5-mg dose was made at the 3-month visit based on the clinician's appraisal of side effects and the patient's general health.

Patient Sample

The sample consisted of AD patients and caregivers seen at the University of Texas (UT) Southwestern Medical Center's Alzheimer's Disease Center (ADC) who wished treatment with a cognitive enhancer and who were willing to cooperate with the regimen of testing. Patients met National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria for probable or possible AD.[24] Initially, all applicants were accepted, but later applicants were excluded whose caregivers reported low levels of emotional/behavioral disturbance (CBRSD scores < 25). This cutoff score was the mean score in a group of largely unmedicated community-dwelling persons with AD.[23] No limitation was imposed on the use of psychotropic medications, but their use was recorded at baseline and throughout the study. We excluded patients with unreliable caregivers, resting pulse below 50 beats/minute, active peptic ulcer disease, diverticulitis, and severe chronic obstructive pulmonary disease. Institutional review board–approved informed consent was obtained from patient or caregiver or both.

Table 1. Characteristics of UT-ADC and ADCS Patients[a]

Variable	UT-ADC (Donepezil-Treated)	ADCS (Untreated)
N	25	153
% Female	60	59
Age, mean ± SD, y	71 ± 8	72 ± 9
Education, mean ± SD, y	14 ± 3	13 ± 3

[a]ADCS = Alzheimer's Disease Clinical Study, UT-ADC = University of Texas Southwestern Medical Center's Alzheimer's Disease Center.

Sample size was based on the pool of eligible applicants seen over the course of 1 year. There were 32 applicants for treatment at the UT-ADC. All were community dwelling. Of these, 4 were excluded owing to lack of emotional/behavioral symptoms (CBRSD score < 25) and 1 was excluded for failure to keep appointments. A total of 27 individuals were enrolled; 25 completed 12 months of donepezil treatment. Of these, 23 were diagnosed as probable AD, 1 was possible AD, and 1 was AD plus small stroke. Patient characteristics are presented in Table 1. We examined data from a reference group of 153 community-dwelling AD patients who completed a 12-month study of assessment instruments by the Alzheimer's Disease Clinical Study (ADCS).[23,25,26] Of these subjects, who had been evaluated semiannually, we selected those who had MMSE and CBRSD scores for both baseline and 12 months. This subgroup of a larger sample omitted the few subjects exposed to cognitive enhancers, but 39% of these ADCS subjects had been exposed to psychotropic drugs during the course of the study. Their characteristics are presented in Table 1.

Donepezil. All UT-ADC patients were started on donepezil 5 mg q.h.s. Of the 25 patients who completed 12 months, 17 were increased to and maintained on a dose of 10 mg q.h.s. and 8 continued on a dose of 5 mg q.h.s. At 5 mg q.h.s., 27% (N = 7) of the 26 persons exposed to this dose reported side effects, including restlessness (N = 1), muscle pain (N = 2), headache (N = 1), nausea (N = 1), and diarrhea (N = 2). At 10 mg q.h.s., 35% (N = 6) of the 17 persons exposed to this dose reported side effects, in-

Table 2. MMSE and CBRSD Scores in 25 Alzheimer's Disease Patients Administered Donepezil for 12 Months[a]

	Baseline		1 Month		3 Months		4 Months		12 Months	
Scale	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
MMSE	13.84	7.77	15.2	7.48[b]	15.8	7.71[b,c]	15.4	7.77[b]	12.74	7.54
CBRSD total	35.9	17.7	29.3	13.1	29.9	13.0[c]	29.2	14.8[c]	30.8	15.5
Depression	7.76	7.25	4.92	3.80[c]	6.36	4.06	5.08	5.45[c]	5.48	4.34
Behavioral dysregulation	5.60	3.76	4.44	2.64	4.20	2.89	3.64	2.71[c]	5.04	3.44
Inertia	2.08	0.86	2.20	0.76	2.12	1.05	2.28	0.89	2.00	1.00
Irritability/ aggression	5.52	4.03	5.24	3.78	5.40	3.77	5.16	3.79	5.36	3.84
Psychotic	2.08	4.41	1.72	3.14	1.56	3.11	1.48	3.23	2.92	4.76
Vegetative	1.96	1.24	1.56	0.92	1.72	0.89	2.80	2.53[b]	1.64	1.35

[a] Abbreviations: CBRSD = CERAD Behavioral Rating Scale for Dementia, MMSE = Mini-Mental State Examination.
[b] Statistically different from 12 months (Tukey) ($p \leq .05$).
[c] Statistically different from baseline (Tukey) ($p \leq .05$).

cluding restlessness (N = 2), syncope (N = 1), increased irritability (N = 1), nausea (N = 3), and diarrhea (N = 1).

Psychotropic drugs. Of the 25 UT-ADC patients completing the study, 10 did not have psychotropic drugs during the course of the study, 7 had no dosage change in their use of psychotropic drugs, and 8 had either drug changes or dosage increases. The psychotropic medications, which were largely prescribed by M.F.W., included antidepressants (total of 11, 9 on selective serotonin reuptake inhibitors [SSRIs]), benzodiazepines (N = 1), antipsychotics (N = 2), and buspirone (N = 1). Changes in psychotropics included addition or increase of SSRI antidepressants (N = 4), trazodone (N = 2), and antipsychotics (N = 2).

Other drugs. Female UT-ADC patients were questioned about estrogen use. Eight of the 15 females were taking estrogen and 7 were not. Although not prescribed, the use of vitamin E was also determined, as vitamin E at a dose of 2000 IU has been reported to slow symptomatic progress of AD.[27] There were 3 patients taking vitamin E at baseline, and 6 began taking the vitamin during the study. None exceeded 800 IU/day.

Statistical Methods

Standard descriptive statistics were obtained for current age, age at onset of dementia, and years of education. Frequencies were obtained for gender, race, and current diagnosis. The mean, standard deviation, and range were determined for each of the scales and subscales used in the study. The same descriptive measures were also obtained for the following UT-ADC groups: (1) women taking estrogen and those not taking estrogen, (2) patients who were taking no psychotropic drugs (or were on stable dosage throughout the study) and patients whose psychotropic drugs were changed in type or dosage, and (3) patients taking 5 mg of donepezil and those taking 10 mg of donepezil. Group 2 also had descriptive statistics through 1 year.

Three preliminary studies were performed on the UT-ADC group comparing MMSE and CBRSD scores. We performed t tests comparing women taking estrogen to those not taking estrogen. There were no statistically significant differences between the 2 groups at baseline so they were not studied separately.

Differences were examined between UT-ADC patients taking psychotropic drugs and those not taking any of these drugs. Repeated measures analyses of variance (ANOVAs) were performed on MMSE and CBRSD scores across the visits with drug usage as the between-subjects factor. There was no statistical evidence of a difference between psychotropic drug use versus no psychotropic drug use, nor was there an indication of any interaction between drug use and visits on any of the 3 ANOVAs.

Differences on the MMSE and CBRSD total scores were also evaluated between the use of 5 mg and 10 mg of donepezil. Repeated measures ANOVAs were performed across the visits with dosage as the between-subjects factor. There was no statistical evidence of a difference between dosage, nor was there an indication of any interaction between dosage and visits. Consequently, data for the 2 groups were analyzed together.

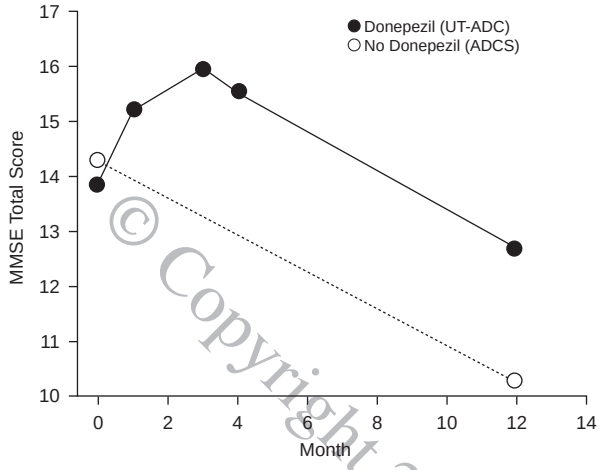
Because of the small sample sizes involved, the effects of vitamin E on MMSE and CBRSD scores could not be analyzed.

Since psychotropic treatment, estrogen use, and donepezil dosage had no effect on MMSE and CBRSD scores, repeated measures ANOVAs were performed with all the subjects. Where the omnibus ANOVA was statistically significant ($p \leq .05$), a Tukey multiple comparison test was performed to determine which visits were different.

RESULTS

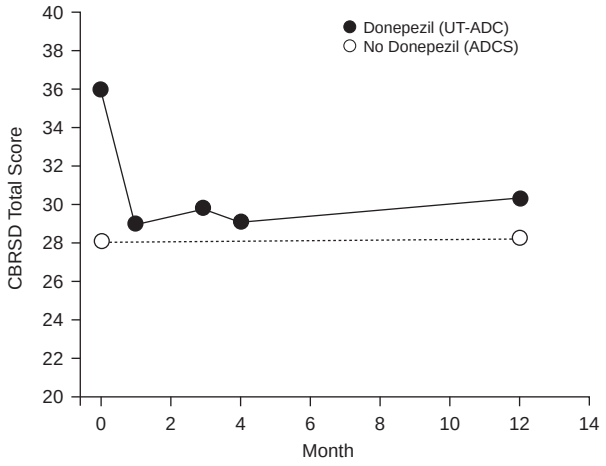
The total UT-ADC group (N = 25) had statistically significant omnibus ANOVAs for MMSE and CBRSD total,

Figure 1. Comparison of Mean Mini-Mental State Examination(MMSE) Total Scores for Patients on Donepezil (UT-ADC) and Patients Not on Donepezil (ADCS)[a]



[a]Abbreviations: ADCS = Alzheimer's Disease Clinical Study, UT-ADC = University of Texas Southwestern Medical Center's Alzheimer's Disease Center.

Figure 2. Comparison of Mean CERAD Behavioral Rating Scale for Dementia (CBRSD) Total Scores for Patients on Donepezil (UT-ADC) and Patients Not on Donepezil (ADCS)[a]



[a]Abbreviations: ADCS = Alzheimer's Disease Clinical Study, UT-ADC = University of Texas Southwestern Medical Center's Alzheimer's Disease Center.

Table 3. Baseline and 12-Month MMSE and CBRSD Scores for UT-ADC Patients Administered Donepezil and ADCS Patients Not Administered Donepezil[a]

	UT-ADC Patients (N = 25)					ADCS Patients (N = 153)				
	Baseline		12 Months			Baseline		12 Months		
Scale	Mean	SD	Mean	SD	Δ	Mean	SD	Mean	SD	Δ
MMSE	13.84	7.77	12.74	7.54	–1.10	14.21	7.93	10.3	8.08	–3.91
CBRSD total	35.9	17.7	30.8	15.5	–5.1	28.0	19.0	28.2	17.2	0.2
Depression[b]	7.76	7.25	5.48	4.34	–2.28	4.40	4.78	4.22	4.73	–0.18
Behavioral dysregulation[b]	5.60	3.76	5.04	3.44	–0.56	4.27	3.68	4.36	3.48	0.09
Inertia[b]	2.08	0.86	2.00	1.00	–0.08	1.88	0.98	1.89	0.99	0.01
Irritability/ aggression[b]	5.52	4.03	5.36	3.84	–0.16	4.04	4.51	4.54	4.75	0.50
Psychotic[b]	2.08	4.41	2.92	4.76	0.84	1.89	3.57	2.46	3.85	0.57
Vegetative[b]	1.96	1.24	1.64	1.35	–0.32	1.34	1.18	1.40	1.21	0.06

[a]Abbreviations: ADCS = Alzheimer's Disease Clinical Study, CBRSD = CERAD Behavioral Rating Scale for Dementia, MMSE = Mini-Mental State Examination, UT-ADC = University of Texas Southwestern Medical Center's Alzheimer's Disease Center.
[b]ADCS Sample sizes varied for the subscales from 132 to 153.

depression, and dysregulation ($p < .05$) (Table 2). As expected, there was an elevation (improvement) of MMSE scores ($p = .001$) that started at 1 month, was maintained through 4 months, but declined to baseline by 12 months (Figure 1). Further, a significant reduction ($p = .01$) in emotional/behavioral disturbance as measured by the CBRSD was found at the third- and fourth-month visits but also returned to baseline by 12 months (Figure 2). The CBRSD subscales that showed significant reduction were behavioral dysregulation ($p = .003$) and depression ($p = .02$). Dysregulation included items such as *restless or overactive, does things with no clear purpose, more confused at particular part of the day, wanders,* and *tries to leave home or caregivers.*

The UT-ADC and ADCS groups were virtually identical in demographic characteristics (Table 1) and in baseline MMSE scores (Table 3). The baseline CBRSD total was significantly different between the UT-ADC and ADCS samples ($t = 1.95$, $df = 176$, $p = .05$), as was the depression subscale ($t = 3.00$, $df = 176$, $p = .002$), confirming that the UT-ADC sample had greater emotional/behavioral symptomatology. Table 3 provides the descriptive statistics for both groups of patients at baseline and 12 months. The UT-ADC sample had a 1.1-point MMSE decrease, while the untreated ADCS reference group had a 3.9-point decrease. On the CBRSD, the UT-ADC sample had a 5.1-point decrease, while the untreated ADCS sample had a 0.2-point increase. Table 3 shows

the difference between 12-month and baseline scores for the 2 groups. Although the differences could not be evaluated statistically, behavioral dysregulation scores decreased slightly in the UT-ADC sample and increased slightly in the untreated ADCS sample. For the depression subscale, the UT-ADC sample had a small decrease while the ADCS sample had a minimal decrease. In both samples, the psychotic subscale showed approximately the same small increase.

DISCUSSION

The results are limited by the study's nonblind condition to families and to the rater and the lack of a placebo-control group. The small but transient increase in MMSE scores in the donepezil-treated group was similar to that found in other cholinesterase inhibitor studies.[7–9] The CBRSD revealed an additional possible anticholinesterase benefit of decrease in overall behavioral disturbance. Others have suggested the use of cholinesterase inhibitors for psychotic symptoms in AD,[15] but the low frequency of psychotic symptoms in our group precluded testing this hypothesis. We found a reduction in overall CBRSD, depression, and behavioral dysregulation scores that was significant only up to 4 months. Nevertheless, this may be important, in that behavioral disturbance with AD tends to increase with worsening cognition,[28,29] although, as found in our UT-ADC sample and the ADCS reference group, it probably does not increase appreciably over the course of 12 months.[30] It seems unlikely that the apparent emotional/behavioral effects of donepezil were due to the use of concomitant psychotropics because the effect appeared in a subgroup whose medications were qualitatively and quantitatively unchanged over the study period. However, this group was small. It is also possible that change might have been shown in the CBRSD domains of inertia, vegetative symptoms, and psychotic symptoms had not the initial scores been so low. Indeed, the overall CBRSD scores do not suggest a severe level of behavioral disturbance in the UT-ADC group. Thus, study of a cholinesterase inhibitor in a more disturbed group seems warranted as a means to deal with this issue and to replicate the present findings.

CONCLUSION

Alzheimer's disease patients treated with donepezil showed a small, but significant 3-month increase in MMSE scores and less deterioration on this scale at 1 year than a reference group of untreated patients. The CBRSD showed an additional possible donepezil benefit of reduction in overall behavioral symptoms to the level of the reference group. Further studies on treatment of individuals with greater emotional/behavioral disturbance need to be undertaken before a definitive statement can be made about the emotional/behavioral impact of anticholinesterase agents in AD.

Drug names: buspirone (BuSpar), donepezil (Aricept), phosphatidylcholine (PhosChol), physostigmine (Antilirium), tacrine (Cognex), trazodone (Desyrel and others).

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