

## Donepezil in the Treatment of Dementia With Lewy Bodies

**S**IR: Cholinomimetics effectively treat cognitive decline in Alzheimer disease (AD). Dementia with Lewy bodies (DLB), characterized by cognitive impairment, significant motor rigidity, and visual hallucinations,<sup>1</sup> is characterized by greater cholinergic impairment than AD.<sup>2</sup>

Rivastigmine benefits behavior and cognition in DLB.<sup>3</sup> However, no published double-blinded placebo-controlled study of DLB exists for donepezil. We studied the cognitive response of DLB to donepezil in a double-blinded, double-crossover study. The double-crossover design allowed greater sensitivity with a smaller sample size because we used within-subject comparison.

The hypothesis was that cognition, as measured by the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), would be significantly better on donepezil than on placebo. Secondary measures assessed specific cognitive domains and activities of daily living. We did not expect an effect on extrapyramidal function, since that would be predominantly due to dopaminergic dysfunction.

All subjects consented in accordance with the human-subjects committee. Eight patients who met the consensus guidelines for the diagnosis of DLB<sup>4</sup> were recruited from the Memory Disorders Clinic at the Ohio State University.

Subjects were evaluated at baseline and every 4 weeks on the Mini-Mental State Exam (MMSE), the ADAS-Cog, the Unified Parkin-

son's Disease Rating Scale (UPDRS), the Boston Naming Test (BNT), the Hopkins Verbal Learning Test (HVLT), and a 12-item visuospatial copying battery (VSB; items were the following: rectangle, triangle, hexagon, cross, bidirectional arrow, five-pointed star, intersecting pentagons, embedded squares connected at corners, four-directional arrow, lightning bolt, cube, and complex figure [square inside a hexagon inside an elongated hexagon with two circles on the right corner and a triangular flag on the bottom left corner]).

Functional ability was assessed at the same time by caregivers using the Physical Self-Maintenance Scale (PSMS) and the Instrumental Activities of Daily Living (IADL) scale. Caregivers were also asked to chart the incidence of hallucinations during the final week of each treatment block. After baseline, patients were randomized to start either donepezil 5 mg daily or placebo in a double-blinded manner (10 mg was not used because of brevity of the treatment phase). At the end of the fourth week of treatment, subjects were switched to the opposite condition for another 4 weeks. These two 4-week blocks were then repeated. Therefore, the crossover period was 16 weeks in duration, with two blocks of 4 weeks each on both drugs (donepezil and placebo), with each subject getting either placebo-donepezil-placebo-donepezil or donepezil-placebo-donepezil-placebo. Investigators were unblinded at the end of statistical analysis.

For each assessment, we fit an ANOVA model with group (treatment order: placebo-donepezil-placebo-donepezil versus donepezil-placebo-donepezil-placebo); test

session (post-treatment Visits 1-4) and treatment (donepezil versus placebo) as fixed effects and subjects within groups as random effects. Significance of the model was established before testing the hypothesis of interest.

One subject was lost to follow-up before initiation (moved to a nursing home where caregiver could not coordinate study visits). Average age of the remaining seven subjects was 65 years (standard deviation [SD]: 3.47; three men, four women). Three received placebo first; four received donepezil first. One of these seven subjects was unable to complete the last two visits (8 weeks) because she was moved to a nursing home and was unable to be transported without sedation. As predicted, patients while on donepezil had a significantly better performance on the ADAS-Cog and MMSE (Table 1). The effect size (Cohen's *d*) of the difference between donepezil and placebo was 0.20 for the ADAS-Cog and 0.28 for the MMSE. Differences on VSB, BNT, HVLT, PSMS, IADL, and UPDRS did not reach significance (Table 1). Caregivers did not complete hallucination logs reliably enough for analysis. Six of seven patients did hallucinate during the study, and the seventh had a history of hallucinations. There was no significant difference on any of the measures between the group starting on placebo and the group starting on donepezil. Overall change over time also did not reach significance for any of these measures during the 16 weeks.

Despite a relatively small sample size, donepezil was effective for treatment of cognition in DLB in this double-blind, placebo-controlled, double-crossover study us-

## Letters

ing well-established, standardized measures of global cognitive functioning. Effects on specific cognitive domains, measures of functional ability, and extrapyramidal impairment did not reveal significant results. Our study suggests that donepezil is a treatment option for cognitive impairment in DLB.

This study detected change in cognitive performance with only 4 weeks per drug condition. Other cholinesterase inhibitor studies used longer time periods. Possible carryover into the placebo phase could result from the short time period selected, but this would have only served to decrease the magnitude of effect of our findings. Experience in our clinic has suggested that patients' families will commonly report early changes

in "concentration" after initiation of cholinesterase inhibitors. Since acetylcholine modulation is primarily believed to affect the attentional system,<sup>5</sup> it may be of future interest to assess attentional performance by use of short treatment periods in order to detect early improvement.

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This study was supported by an unrestricted educational grant from Pfizer/Eisai. Dr. Nagaraja is supported by an NIH grant (M01-RR-00034) awarded to The Ohio State University. Dr. Scharre has grants from Janssen, Forest, and Pfizer; he is a consultant for Novartis, Janssen, and Pfizer; he is on the speakers' bureau for Janssen, Pfizer, Eisai, Abbott, and AstraZeneca. Dr. Beversdorf has grants from Pfizer, Eisai, and Repligen; he is a consultant for Janssen and Pfizer; he is on the speakers' bureau for Janssen, Pfizer, and Eisai. Dr. Beversdorf is also supported by NIH grants NS045222 and DA15734.

**TABLE 1. Summary of baseline performance and average results in dementia-with Lewy-body (DLB) patients within drug condition, and repeated-measures ANOVAs comparing donepezil and placebo conditions, accounting for time across visits and treatment order (donepezil first or placebo first)**

Test	Baseline mean (SD)	Donepezil mean (SD) <sup>a</sup>	Placebo mean (SD) <sup>a</sup>	ANOVA
General cognitive tasks				
MMSE	18.7 (10.7)	20.7 (7.4)	19.0 (8.6)	$F_{[1, 16]} = 7.583$ p = 0.014
ADAS-Cog	25.4 (20.1)	23.5 (18.1)	27.2 (19.2)	$F_{[1, 15]} = 11.315$ p = 0.004
Tasks for specific cognitive domains				
BNT	36.4 (19.3)	39.4 (15.8)	40.1 (15.0)	$F_{[1, 15]} = 0.805$ p = 0.384
HVLT recall	6.3 (3.8)	10.0 (5.3)	10.0 (6.2)	$F_{[1, 15]} = 0.087$ p = 0.772
recognition	5.3 (4.5)	6.5 (3.8)	7.1 (4.0)	$F_{[1, 15]} = 0.557$ p = 0.467
VSBS	4.9 (3.7)	5.6 (3.7)	5.0 (3.5)	$F_{[1, 14]} = 1.464$ p = 0.246
Functional ability				
PSMS	11.0 (5.7)	11.5 (6.4)	12.0 (6.6)	$F_{[1, 16]} = 2.551$ p = 0.130
IADL	19.7 (7.9)	19.6 (7.4)	20.4 (8.4)	$F_{[1, 16]} = 3.923$ p = 0.065
Extrapyramidal function				
UPDRS	31.6 (7.3)	32.1 (6.3)	30.3 (6.9)	$F_{[1, 14]} = 0.376$ p = 0.550

<sup>a</sup> Averaged across visits (donepezil versus placebo).

Note: SD: standard deviation; MMSE: Mini-Mental State Exam; ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale; BNT: Boston Naming Test; HVLT: Hopkins Verbal Learning Test; VSBS: visuospatial copying battery; PSMS: Physical Self-Maintenance Scale; IADL: Instrumental Activities of Daily Living; UPDRS: Unified Parkinson's Disease Rating Scale.

## Letters

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## Diminished Stress Resilience in Institutionalized Elderly Patients: Is Hypovitaminosis D a Factor?

**S**IR: Epidemiological research suggests that hypovitaminosis D has reemerged as a problem in climatically diverse regions worldwide, even in mid-latitude, temperate regions such as California and Australia.<sup>1,2</sup> Thomas et al.<sup>1</sup> have provided strong evidence for an increased risk of hypovitaminosis D even among inpatients whose dietary intake of vitamin D meets or exceeds national standards. Although hypovitaminosis D contributes to the still surprisingly high incidence of rickets in the United States,<sup>2</sup> its greatest impact is among elderly persons and medical inpatients.<sup>1</sup> Initial symptoms of hypovitaminosis D are diminished re-

silience to psychosocial stress, generalized muscle pain, and nonspecific fatigue.<sup>1,2</sup> The classic symptom of hypovitaminosis D, osteomalacia (and the associated increased risk of hip fracture), usually only becomes evident in later stages.<sup>1,2</sup>

Ultraviolet (UV) light is an essential factor in the production of the active form of Vitamin D (Vitamin D hormone; VDH).<sup>1</sup> Therefore, low sun exposure is a major risk factor for hypovitaminosis D.<sup>1,2</sup> Other risk factors include advanced age, chronic liver and renal diseases, and a low-fat diet.<sup>1</sup> The increased risk of hypovitaminosis D in elderly and chronically mentally ill persons may be largely a result of their overrepresentation in housebound and institutionalized populations.<sup>1</sup>

Current medical recommendations, such as avoiding sunlight to lower the risk of skin disease and decreasing fat intake to lower the risk of coronary heart disease, may also be contributing to the reemergence of hypovitaminosis D.<sup>1,2</sup> Although these standard recommendations should not be reversed, such preventive health measures may be contributing to an increased incidence of hypovitaminosis D.

Accumulating evidence in animal models suggests that hypovitaminosis D increases the risk for glutamate excitotoxicity during acute activation of the fear circuitry and that systemic vitamin D attenuates oxidative injury to the locus coeruleus.<sup>3</sup> These results suggest that hypovitaminosis D may be linked to lower resilience to acute psychosocial stress in humans. This vulnerability may also extend to the effects of chronically elevated allostatic load.

Drugs such as phenytoin, carbamazepine, and rifampin have been shown to interfere with vitamin D activation or clearance, and research is examining whether newer mood stabilizers, such as valproate and lamotrigine, interfere with vitamin D activation.<sup>2,4</sup> Supplementation should be considered in any high-risk group. Laboratory assays for VDH are widely available but rarely utilized and can easily be included in psychiatric research protocols alongside glucocorticoid and mineralocorticoid levels.

In summary, hypovitaminosis D may interact negatively with the stress response, and institutionalized and housebound elderly patients are at higher risk for low VDH levels. If confirmed, this idea is especially noteworthy because, unlike many other risk factors affecting stress-related morbidity, treatment of hypovitaminosis D is simple, inexpensive, and likely to have high patient acceptance.

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*This material is based on work supported, in part, by the Office of Re-*

## Letters

search and Development, Medical Research Service, Department of Veterans Affairs, VA Pacific Islands Health Care System, Spark M. Matsunaga Medical Center. Support was also provided by a National Alliance for Research on Schizophrenia and Depression (NARSAD) Independent Investigator Award and the VA National Center for PTSD.

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## Repeat Cognitive Screening of Initially Normal, Older Primary-Care Patients

**S**IR: There is emerging evidence that patients with Alzheimer disease (AD) may benefit from early detection and early initiation of therapy;<sup>1</sup> therefore, effective screening strategies for AD are of increasing importance. Currently, mild cognitive impairment and early AD often go undiagnosed by primary care physicians. Although patients who "screen positive" may receive further evaluation, the majority of outpatient elderly persons will have negative initial screens.<sup>2</sup> Multiple organizations, including the American

Academy of Neurology, have noted that there are insufficient data to recommend for or against routine screening for dementia, and there are no data to suggest how "screen-negative" patients should be followed over time.<sup>3</sup> We conducted a pilot study to determine the rate of undetected cognitive impairment among older patients with a history of normal cognitive screening.

Patients from a geriatric primary care clinic where all patients received a baseline screening Mini-Mental State Exam (MMSE) upon entry were recruited for follow-up cognitive screening that included the Folstein MMSE.<sup>4</sup> Subjects were at least 65 years old, had a normal baseline MMSE ( $\geq 24$ ) upon entry to the clinic at least 1 year earlier, and had no dementia diagnosis. The study was approved by the University of Washington Human Subjects Review Committee, and informed consent was obtained from participating subjects. Demographic data were extracted by chart review. The mean (standard deviation) age of subjects was 76.1 (5.5) years, and 16 of 25 subjects were women.

Of 25 eligible subjects with initially normal MMSE scores, 6 (24%; 95% confidence interval: 6%–42%) subjects had an abnormal MMSE ( $\leq 23$ ) at follow-up. Subjects received their follow-up screening at varying time-points relative to their initial MMSE (range: 1.1 to 5.0 years), but all abnormal follow-ups occurred within 3 years of the initial MMSE. Multivariate logistic regression revealed that none of the following correlated with abnormal MMSE: age, gender, ethnicity, education, baseline MMSE, ADLs at baseline, or psychiatric or medical comorbidity.

In this small, cross-sectional study, nearly a quarter of elderly patients who had been cognitively intact upon entry to a primary care clinic were found to have an abnormal MMSE between 1 and 3 years later. Although the confidence intervals for this rate of positive screening are wide because of the small sample, the data suggest that even patients with normal cognitive screen scores should be monitored closely for the development of cognitive impairment in order to facilitate early detection and treatment. Power to detect clinical associations with abnormal follow-up MMSE was limited by the small sample size.

A larger, prospective study of screening that also incorporates diagnostic evaluations will be needed to determine the optimal timing of these periodic screens, but, on the basis of these preliminary results, between 1 and 3 years would seem a logical start. Ultimately, research linking screening with treatment outcomes and cost-effectiveness measures will be needed to better inform practice guidelines for primary-care cognitive screening.

*This work was previously presented at the American Association for Geriatric Psychiatry Annual Meeting, 2002, Orlando, Florida.*

*The authors thank Kersten Sato for her assistance with the preparation of the manuscript.*

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## Letters

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