

Treatment of AD with Stabilized Oral NADH: Preliminary Findings

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Abstract.

A pilot randomized, double-blind clinical study of 21 patients with Alzheimer's Disease (AD) evaluated the effects of stabilized oral NADH (reduced nicotinamide adenine dinucleotide; ENADA[®]) 10 mg QD (n=11) or placebo (n=10) on cognitive functions sensitive to changes in severity of dementia. NADH improved verbal recognition memory (p=.011) and verbal fluency (p=.034) from baseline to 6-months compared to placebo. A higher proportion of NADH-treated patients improved, than deteriorated or showed no change, on measures of verbal recognition memory and verbal fluency.

Introduction.

Although cholinergic dysfunction, a primary manifestation of AD, is the main target of current pharmacologic treatment of AD, there is considerable interest in additional approaches.¹ Abnormalities found in AD that may be targets for alternative treatment strategies include decreased protection from free radicals, impaired DNA repair, disruption of electron transport, and reduced levels of noradrenaline, dopamine and serotonin.^{1, 2} NADH can prevent apoptosis, improve free radical scavenging, improve repair of damaged DNA, and increase biosynthesis of dopamine and noradrenaline³. In clinical trials, NADH has been shown to improve cognitive functioning in patients with Parkinson's Disease,³ Chronic Fatigue Syndrome,⁴ and AD.⁵ An open label 8-12 week trial of orally absorbable, stabilized NADH (ENADA[®], Menuco, New York; 10 mg per day) in 17 patients with AD found improvement in the Mini Mental State Examination and Global Deterioration Scale.⁵ Proposed mechanisms of NADH action are elevation of CNS dopamine and adrenaline and possibly enhanced CNS energy production. The present double-blind study tests the effect of NADH on selected cognitive functions in patients with AD. Verbal fluency and word recognition memory were selected as primary outcome measures because of their known sensitivity to changes in level of dementia.

Methods

Patients were recruited from the outpatient clinic of the Neurology Department, Georgetown University Hospital and enrolled in the study if they met the following criteria: diagnosis of probable AD according to NINCDS-ADRDA criteria, 50 years of age or older, MMSE score of between 10 and 25, naive to treatment with NADH, and no use of donezipil or tacrine within six weeks of enrollment in the study. Patients were not required to discontinue other medications. Thirty-three patients were screened and 21 met all inclusion criteria. Informed consent was provided by patients and caregivers before entering into the study. The study was approved by the Georgetown University Medical Center Institutional Review Board.

In this double-blind, placebo-controlled, parallel group pilot study, each patient made nine clinic visits over six months to examine the effects of oral NADH (ENADA[®]) on verbal fluency and verbal recognition memory, primary outcome variables chosen *a priori* (Figure 1). After a two-week drug compliance trial (passed by all patients), participants underwent a neurological examination, routine blood and urine laboratory tests, and baseline neuropsychological tests. Random allocation for two groups was computer-generated off-site; the key was stored at Menuco Corporation (New York) until the end of the study. Patients were randomly assigned to receive either NADH 5 mg, 2 tablets QD (n=11) or matching placebo tablets (n=10). Patients were monitored by neurological examinations at monthly intervals; both patients and caregivers were also queried about adverse effects.

Neuropsychological testing was repeated at 6 weeks and 6 months, using the following measures: Mini Mental State Examination (MMSE),⁶ Mattis Dementia Rating Scale (MDRS),⁶ Hopkins Verbal Learning Test (HVLT),⁷ Verbal Fluency Test (VF),⁸ Fuld Object Memory Test (FOMT),⁶ CogScreen[®] Matching to Sample Test (MTS),⁹ and Clinical Dementia Rating Scale (CDR).¹⁰ Primary outcome measures were the Discrimination Index (words correctly recognized – false positive recognitions) from the Hopkins Verbal Learning Test (i.e., verbal recognition memory) and the total number of words beginning with a specified letter of the alphabet generated in one minute on the Verbal Fluency Test.

We hypothesized that NADH would arrest deterioration and possibly improve cognitive functioning in AD. The analytic approaches employed to test this hypothesis were repeated measures analysis of variance to assess change across sessions and comparison of mean change from baseline to 6 months. The proportions of patients in each group demonstrating improvement, no change or deterioration from baseline to 6 months were also noted.

Results

Twenty-one patients were enrolled in this study. Four patients did not complete the study, 2 in each treatment group: 3 patients were unable to cooperate with the cognitive testing procedures at baseline, and one patient dropped out after 10 weeks due to inability of the caregiver to transport the patient to the study site. Of the 17 patients who completed the study, the age range was from 57 to 84 years; median age 77.5. The duration of illness ranged from 13 months to 83 months; median 26 months. The MMSE scores at baseline ranged from 12 to 24; with a median of 18.

At baseline, the randomized groups were not statistically different with respect to age, gender, months since diagnosis, total dementia scores (MDRS and MMSE), or on the two primary endpoints (HVLТ discrimination index, VF total words in one minute). However, at baseline, in spite of randomization, patients in the NADH group recalled 4.3 more words than patients in the placebo group in one measure of verbal learning (HVLТ Recall, $p=0.022$), .

Results for the two groups at baseline, 6 weeks and 6 months are shown in Table 1. Repeated measures analysis of variance revealed a significant group by visit interaction effect for the verbal recognition memory test (HVLТ discrimination index; Wilks' Lambda=0.47, $p=0.01$). Placebo patients deteriorated across sessions, making 1.8 more recognition errors at 6 months compared to baseline. In contrast, NADH patients made an average of 2.6 fewer recognition errors at 6 months compared to baseline ($t=2.61$, $df=13$, $p=0.01$). Analysis of the proportion of patients demonstrating improvement, no change, or deterioration, showed a deterioration in verbal recognition memory (i.e., HVLТ discrimination index) for 5 of the 8 placebo patients. By comparison, no NADH patients deteriorated on this measure and 3 showed improvement.

There was a similar, though non-significant group by visit interaction trend seen for the VF test (Wilks' Lambda=0.78, $p=0.199$). Analysis of change from baseline to 6-months shows a significant difference between groups on verbal fluency ($t=-1.99$, $df=14$, $p=0.0335$). Placebo patients generated an average of 3.6 fewer words per minute at 6-months compared to baseline, whereas NADH patients generated an average increase of 1.5 words per minute. Decrease in

verbal fluency was seen in 6 of the 8 placebo patients. In contrast, while 2 of the NADH patients showed deterioration, 4 were unchanged and 3 showed improvement in verbal fluency at 6 months.

Other secondary measures supported the primary endpoint findings by showing either no difference or better performance for patients in the NADH group. The only secondary measure showing a significant group by visit interaction effect ($p=0.02$) was the accuracy score from the Matching to Sample test (MTS acc). Placebo patients showed a marked decline in MTS acc from baseline to week 6 (from 61.3% to 50.6%), which remained low at 6 months, while there was a 6.1% increase in accuracy for the NADH group ($t=-3.01$; $p=.005$). Procedural errors in administration of the CDR resulted in a failure to obtain valid data for that particular measure. No patients in either the NADH or placebo groups reported adverse effects and their laboratory values remained normal.

Discussion

AD patients receiving stabilized orally absorbable NADH showed significantly better performance on measures of verbal recognition memory and verbal fluency following six months of double-blind treatment than patients receiving placebo. These measures are among the most sensitive to changes in dementia severity;⁷ however, no inferences can yet be drawn about the effect of NADH on other cognitive functions or behaviors impaired by AD. At this point, it is difficult to directly compare the present findings with those reported in AD clinical trials using other therapies and outcome measures,¹ or to determine the clinical significance of the fluency and memory improvements found with NADH.

In spite of randomization, there was a significant difference on one measure of memory at baseline between treatment groups. It is possible that the lower functioning patients in the placebo group may have deteriorated more rapidly than the patients in the NADH group, independent of treatment. Cognitive tests that are sensitive at one level of dementia may not be sensitive at another stage of dementia.

Nonetheless, the results of this double-blind pilot study are encouraging and are consistent with the results of the earlier open label study with a different group of patients in showing a beneficial effect of NADH on cognitive functioning in AD. Furthermore, the small number of patients in this pilot study may have been insufficient to detect other potentially significant differences between treatment groups, thus these preliminary results will require replication and extension.

Table 1. Mean cognitive test scores (SD) for patients diagnosed with AD (n=17).

	Treatment group (n=9)			Placebo group (n=8)		
	Baseline	6 weeks	6 months	Baseline	6 weeks	6 months
VF †	14.22 (10.56)	17.44 (11.18)	15.75 (12.12)	12.88 (12.70)	12.63 (17.30)	9.25 (12.96)
HVLT disc * †	6.00 (3.12)	6.67(3.57)	8.57(2.64)	4.38 (2.67)	4.88 (2.85)	2.63 (3.20)
FOMT recog	6.22 (2.54)	6.22 (2.11)	5.25 (2.60)	4.38 (2.33)	6.13 (1.96)	4.00 (2.16)
MTS acc *	51.67 (15.81)	57.78 (22.65)	53.75 (11.57)	61.25 (19.41)	50.63 (24.41)	50.13 (30.66)
HVLT 1-3 ‡	9.44 (3.71)	10.44 (3.94)	10.38 (4.69)	5.13 (2.9)	7.38 (2.67)	5.75 (2.55)
VF categ	7.67(4.80)	6.67 (3.61)	5.50 (3.34)	4.88 (2.23)	5.63 (3.07)	4.75 (2.12)
MMSE	18.44(4.13)			16.00 (4.50)		
MDRS	105.22(13.60)			91.38 (17.86)		

† Significant group difference in change from baseline to 6 months (p<0.05)

* Significant group x session effect (p<0.05)

‡ Significant group difference at baseline (p<0.05)

Abbreviations: FOMT, Fuld Object Memory recognition test; HVLT disc, Hopkins Verbal Learning Test discrimination index; HVLT 1-3, Hopkins Verbal Learning Test total words recalled, trials 1-3; MDRS, Mattis Dementia Rating Scale, total score; MMSE, Mini Mental State Examination; MTS acc, Matching to Sample accuracy; VF, Verbal Fluency phonemic rule; VF categ, Verbal Fluency semantic rule.

Figure 1. Flow chart of pilot NADH study.

Thirty-three patients were screened at the Neurology Department, Georgetown University Hospital. Twenty-one met all inclusion criteria stated in Methods. Patients were then randomly assigned to receive either NADH 5 mg, 2 tablets QD (n=11) or matching placebo tablets (n=10). Four patients did not complete the study, 2 in each treatment group. The remaining patients were assessed at the end of 6 months for changes in the primary and secondary efficacy variables as described in Methods. A neuropsychological assessment at the end of 6 weeks also gave secondary efficacy variable data.

References

1. Mayeux R, Sano M. Treatment of Alzheimer's disease. *N Engl J Med* 1999;341:1670-1679.
2. Aisen PS, Davis KL. The search for disease-modifying treatment for Alzheimer's disease. *Neurology* 1997;48:S35-S41.
3. Birkmayer JG, Vrecko C, Volc D, Birkmayer W. Nicotinamide adenine dinucleotide (NADH)--a new therapeutic approach to Parkinson's disease. Comparison of oral and parenteral application. *Acta Neurol Scand Suppl* 1993;146:32-35.
4. Forsyth LM, Preuss HG, MacDowell AL, Chiazze L, Jr., Birkmayer GD, Bellanti JA. Therapeutic effects of oral NADH on the symptoms of patients with chronic fatigue syndrome. *Ann Allergy Asthma Immunol* 1999;82:185-191.
5. Birkmayer JG. Coenzyme nicotinamide adenine dinucleotide: new therapeutic approach for improving dementia of the Alzheimer type. *Ann Clin Lab Sci* 1996;26:1-9.
6. Lezak MD. *Neuropsychological assessment*. New York: Oxford University Press, 1995.
7. Brandt J. The Hopkins verbal learning test: development of a new verbal memory test with six equivalent forms. *Clinical Neuropsychologist* 1991;5:125-142.
8. Borkowski J, Benton A, Spreen O. Word fluency and brain damage. *Neuropsychologia* 1967;5:135-140.
9. Kay G. *CogScreen - Aeromedical edition: professional manual*. Odessa, FL: Psychological Assessment Resources, 1995.
10. Berg L, Hughes CP, Coben LA, Danziger WL, Martin RL, Knesevich J. Mild senile dementia of Alzheimer type: research diagnostic criteria, recruitment, and description of a study population. *J Neurol Neurosurg Psychiatry* 1982;45:962-968.

