# Treatment Trial of Oxiracetam in Alzheimer's Disease

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**• Twenty-four carefully assessed patients with probable Alzheimer's disease were enrolled in a double-blind, placebo-controlled treatment study of oxiracetam, a nootropic agent reported to improve memory performance in patients with dementia. A broad battery of neuropsychological tests failed to reveal any improvement in the treated group or in any treated patient when individual test scores were analyzed. These findings indicate that oxiracetam is ineffective in reducing cognitive impairment due to Alzheimer's disease.**

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Cyclic derivatives of γ-aminobutyric acid, termed *nootropics*, have been investigated as potential pharmacologic treatments for dementia. Oxiracetam (4-hydroxy-2-oxo-1-pirrolidine-acetamide) is a hydroxylated analogue of the nootropic agent piracetam and has been reported to improve target symptoms in patients diagnosed with multi-infarct dementia,[1] dementias of mixed causes,[2-4] and dementia of the Alzheimer type.[5] In this double-blind, placebo-controlled investigation, we evaluated the effects of oxiracetam on memory, language, and visuospatial/visuomotor performance in Alzheimer's disease.

## PATIENTS AND METHODS

The 24 patients (mean [±SD] age, 71.7±6.4 years; educational level, 13.3±3.5 years) were referred to the Emory University/Wesley Woods Memory Assessment Clinic, Atlanta, Ga, for evaluation of dementia. All had appropriate neurologic, neuropsychological, laboratory, and imaging studies to determine a diagnosis of probable Alzheimer's disease[6] with mild to moderate impairment (mean Mini-Mental State Examination[7] score, 21.3±2.8). Previous approval was provided by appropriate review boards, and informed consent was obtained from subjects or caregivers.

After baseline neuropsychological tests were administered, 11 patients received 800 mg of oxiracetam twice daily, and 13 patients received placebo on the same schedule. All patients were reassessed after 1 month, and 15 patients (seven receiving oxiracetam and eight receiving placebo) remained in the study to be retested after 3 months. Treatment durations of 1 and 3 months were selected because previous reports of nootropic agents were conducted within this time frame.[5,8,9] Memory and language were measured with the Selective Reminding Test,[10] Benton Visual Retention Test,[11] Boston Naming Test,[12] Controlled Oral Word Association,[13] and Token Test.[14] Visuospatial and visuomotor functions were assessed with Block Design[15] and the Rey-Osterreith Complex Figure.[16] Three parallel forms were available on all tests except the Block Design and Rey-Osterreith, and the order of test administration was counterbalanced across patients and across testing sessions.

Two-sample *t* tests were used to compare the treated and placebo groups for demographic measures, baseline cognitive performance, and change scores during the course of treatment. Repeated-measures analyses of variance with group (drug or placebo) as the between-subjects factor and testing occasion (baseline, 1 month, or 3 months) as the within-subjects factor were performed. On the basis of a power of 80% and a type I error rate of 0.05, sufficient sample sizes were determined for each of the neuropsychological measures after estimating score changes that would be clinically important. An overall sample size of 24 subjects met these conditions for the following measures: Block Design, Boston Naming Test, Controlled Oral Word Association, Selective Reminding, and Benton Visual Retention. Statistical tests for the clinically important changes in the Rey-Osterreith and Token Test had slightly lower power on the basis of this sample size.

## RESULTS

Two-sample *t* tests indicated that drug- and placebo-treated groups of patients were not significantly different ($P>.05$) in age, education, Mini–Mental State examination scores, or baseline performance on neuropsychological measures. Scores on each of the neuropsychological measures for baseline and 1 month after treatment are presented in the Table.

Evaluation of the effects of oxiracetam on verbal memory entailed analyses of two measures from the Selective Reminding Test: the total number of words recalled and the number of words recalled on at least two consecutive trials without reminding by the examiner ("long-term storage"). No effects of patient group, testing session, or interactions were significant for these variables. Analysis of performance on the Benton Visual Retention Test also did not indicate any significant effects or interactions. The potential benefit of oxiracetam on other cognitive abilities apart from memory was examined. There were no group effects, session effects, or significant interactions for measures of expressive language (Boston Naming Test, Controlled Oral Word Association), language comprehension (Token Test), or visuospatial abilities (Block Design, Rey-Osterreith).

The medication trial was discontinued by its corpo-

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| Neuropsychological Measures* | Placebo (n=13) | | Oxiracetam (n=11) | |
|---|---|---|---|---|
| | Baseline | 1 Month | Baseline | 1 Month |
| Selective Reminding | | | | |
| Total words recalled (72)† | 23.2±7.6 | 23.1±8.7 | 22.2±10.3 | 23.9±7.8 |
| Long-term storage (72) | 7.5±6.8 | 6.4±5.3 | 6.5±7.7 | 6.5±4.0 |
| Benton Visual Retention Test, total pictures recalled (10) | 1.8±1.5 | 2.2±1.9 | 1.5±1.0 | 1.8±1.3 |
| Boston Naming Test, No. correct (15) | 10.8±3.5 | 11.0±3.7 | 8.0±3.3 | 8.5±3.9 |
| Controlled Oral Word Association, No. of words for 2 letters | 13.2±7.5 | 13.9±8.7 | 18.7±8.9 | 15.5±5.7 |
| Token Test, No. of points (22) | 19.0±2.3 | 18.3±2.6 | 19.6±2.5 | 19.6±2.2 |
| Block Design, No. of points (51) | 7.0±7.7 | 8.8±7.9 | 10.4±7.7 | 10.3±7.8 |
| Rey-Osterreith, No. of points (36) | 22.9±12.4 | 21.1±12.4 | 22.2±9.9 | 21.5±13.0 |

*Values expressed as mean±SD.
†Total possible in parentheses.

rate sponsors, and so not all patients could be followed up past 1 month. However, seven patients treated with oxiracetam and eight patients receiving placebo underwent additional testing at 3 months. There were again no significant differences in the age, education, or Mini–Mental State examination scores of these groups. Measures of verbal and visual memory, expressive language, and visuospatial/visuomotor abilities revealed no significant differences between oxiracetam- and placebo-treated patients. A repeated-measures analysis of variance on the change in scores on the Token Test, however, indicated a significant effect of occasion ($P<.05$). Scores at 3 months (mean±SD, 17.1±3.8) were significantly lower than those at 1 month (18.4±2.7), but the effect was comparable for both groups.

## COMMENT

Preclinical studies of oxiracetam have documented improvement of memory deficits in rats exposed to scopolamine[17] or electroshock[18] and in aged rats.[19] In human trials, treatment with oxiracetam has been associated with improved neuropsychological test scores in patients with mixed dementia syndromes.[1-4] However, these studies were not always double blinded and placebo controlled. Some failed to match control groups on pretrial assessments, and none of these specifically excluded vascular dementias in which some spontaneous improvement over time might well be expected to occur. Recent studies of other nootropic agents have also failed to show improvement in Alzheimer's disease.[8,9]

Since Alzheimer's disease is the most common form of dementia in the general community,[20] agents that have potential for improving cognitive function deserve careful study. Our results are based on a 1-month double-blind, placebo-controlled treatment trial of oxiracetam in highly selected patients with probable Alzheimer's disease by research criteria. Experimental groups were carefully matched, and a broad battery of neuropsychological tests were administered, most with alternative forms to reduce the contribution of learning effects. Although small, our sample size was sufficient to detect clinically important changes in several of the neuropsychological measures with a power of 80%. Although we cannot rule out the possibility that a larger sample or a longer treatment trial might have detected subtle improvements, these results suggest that oxiracetam does not offer meaningful clinical improvement of cognitive function in patients with Alzheimer's disease.

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