Published in final edited form as:

Alzheimer Dis Assoc Disord. 2010 ; 24(3): 308. doi:10.1097/WAD.0b013e3181cf468d.

Pilot Trial of Memantine in Primary Progressive Aphasia

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To the Editor:

Primary progressive aphasia (PPA) is a clinical syndrome characterized by a progressive language disorder with preservation of memory, visuospatial skills, and reasoning functions in the initial stages.¹ There are currently no Food and Drug Administration approved treatments for PPA or other forms of non-Alzheimer dementia. We previously showed that bromocriptine did not produce significant effects on language measures during a 15-week double-blind cross-over study.² A trial of galantamine was also mostly negative despite a trend suggesting that aphasia scores were more stable in the treatment than the placebo group.³ Boxer et al⁴ recently published an open-label study of memantine in 3 non-Alzheimer clinical dementia syndromes, including 2 PPA subtypes known as progressive nonfluent aphasia and semantic dementia.⁵ The progressive nonfluent aphasia patients showed relative stability on the Alzheimer Disease Assessment Scale-Cognitive over the 52 weeks of the study, whereas the semantic dementia patients declined.

We conducted a double-blind, placebo controlled trial with 18 PPA subjects with mild-to-moderate disease severity (mean Western Aphasia Battery⁶ aphasia quotient=72.4). Patients were randomly assigned to receive memantine or placebo for 26 weeks and were then crossed over to the other arm. Subjects received 5mg memantine daily (or placebo) for the first week and were titrated up by 5mg memantine per day every week over the next 3 weeks until reaching the target dose of 20mg memantine in 2 divided doses per day. Subjects remained at 20mg/d for the next 5 months. Assessment of language, behavior, and activities of daily living was performed at baseline and at the end of the 6-month period. The washout phase consisted of reducing the memantine dose by 5mg/d/wk over a 4-week period followed by 2 weeks of no medication. Subjects were then crossed over to the other arm of the study. Nine subjects completed the entire trial. Of the 9 subjects who discontinued, 7 were unable to return for follow-up testing because of living out of state and 2 wanted to receive a prescription for memantine. None of the subjects experienced any adverse events related to the study drug.

All data were analyzed using a repeated measures analysis of variance to determine whether the change from baseline to endpoint was different between the drug and placebo phases. Although none of the measures showed a significant difference in change between placebo and drug phases, there was a trend for a smaller degree of decline on the Western Aphasia Battery total aphasia quotient in the drug group (-2.13) than in the placebo group (-6.42), a mean difference in change of 4.29. Power calculations based on these data indicate that a sample of size 14 has 80% power to detect a mean difference in change of 4.0 units on the aphasia quotient in future trials. Consistent with the Boxer et al study, these results provide support for the consideration of larger-scale randomized controlled trials in PPA.

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