Memantine May Improve Cognition in Bipolar Disorder
Fran Lowry  |  Jun 19, 2013

MIAMI — A drug that for years has been approved to treat moderate to severe Alzheimer's disease may have a role in improving the cognitive deficits associated with bipolar disorder.

In a randomized, controlled, parallel-arm clinical trial of adjuvant memantine vs placebo in euthymic patients with bipolar disorder, memantine improved several cognitive domains and also demonstrated increased hippocampus neuronal viability on imaging scans of the brain.

The trial was presented in a rapid communication session here at the 10th International Conference on Bipolar Disorders (ICBD).

"Subjects with bipolar disorder have significant cognitive and functional deficits, even when they are euthymic," lead author Dan Iosifescu, MD, director, Mood and Anxiety Disorders Program, Icahn School of Medicine at Mount Sinai, New York City, told Medscape Medical News.

"This is something that is not usually recognized, and it is important because it has a direct impact on the individual's ability to function in real life, even when their symptoms of depression are somewhat controlled," Dr. Iosifescu said.

Problems with attention, short-term memory, and executive functioning exist, but there is little understanding about what will be helpful to improve or compensate for such deficits, he added.

"For a very long time, these cognitive deficits were interpreted as having some residual symptoms, depression or mania, and that these needed to be better controlled, perhaps with increased doses of mood stabilizers. But as it turns out, this is not the right answer, and a lot of people continue to have cognitive problems," he said.

In the study, which was conducted at the Massachusetts General Hospital, Boston, Mount Sinai, and Northwestern University in Chicago, Illinois, 72 euthymic bipolar patients (mean age, 47 years; range, 37 - 57 years), 53% female, were randomly assigned in a 2:1 fashion to receive memantine or placebo for 12 weeks.

At the end of the 12 weeks, all patients were given memantine for another 12 weeks. The doses of memantine were flexible and ranged from 5 to 20 mg/day.

Fifty-five percent of the patients had type I bipolar disorder, and 45% had bipolar II disorder. All had reported subjective cognitive deficits, scoring higher than 17 on the Massachusetts General Hospital (MGH) Cognitive and Physical Functioning Questionnaire (CPFQ).

The patients underwent a number of tests that measured attention (the Rapid Visual Information Processing Task [RVIP] of CANTAB); short-term working memory (the Spatial Working Memory [SWM of the CANTAB]); verbal and episodic memory (the California Verbal Learning Test [CVLT-II] and the Delayed Matching to Sample (DMS of the CANTAB); social functioning (the Social Adjustment Scale-Self Report [SAS-SR]); and the Repeatable Battery for the Assessment of Neuropsychological States (RBANS), which includes 5 subscales of attention, immediate memory, visuospatial construction skills, delayed memory, and language.

In addition, proton magnetic resonance spectroscopy (MRS) was performed in 11 of the study patients.

The researchers found that in the first 12 weeks of the study, patients who received memantine showed significant improvements compared with patients receiving placebo in spatial and working memory, verbal and episodic memory, total RBANS score, and improved attention, language, and delayed memory.
However, there were no significant differences in social functioning between the placebo and memantine groups, Dr. Iosifescu said.

"We would have liked to hear that they were better able to find a job or that their interpersonal relationships got better, that their improvements in cognition translated into something useful, but this wasn't the case. But perhaps we will see a benefit in the life functioning of these patients further down the line," he said.

Memantine Positively Affects Brain Chemistry

The MRS studies showed that memantine increased levels of N-acetylaspartate, a measure of neuronal viability, in the left hippocampus, and increased choline in the right hippocampus.

"We only did the MRS studies in 9 of our study population, 3 who took placebo and 6 who took memantine, so it's a very small group. Still, we were encouraged to see an objective signal that memantine was doing something positive for brain function," Dr. Iosifescu said.

"So we saw that people did better on tests of cognition, and also saw biological changes occurring at the same time in the brain. That increased our confidence that the drug's effect is real and something that we should be paying attention to," he said.

Memantine was well tolerated, and retention in the study was excellent, he added.

The expectation currently is that memantine might be a useful addition to cognitive training programs to help people with bipolar disorder improve their cognition.

"If you can help people pay better attention and have better retention when they are trying to learn, they would improve their ability to participate successfully in cognitive remediation strategies," Dr. Iosifescu said.

Medscape Medical News asked Charles L. Bowden, MD, clinical professor at the University of Texas Health Science Center, San Antonio, for his comments about this study.

Dr. Bowden noted that there is evidence that overactive glutamate is "probably" present in recurrent depression.

"The problem is that the efforts to come up with a strategy that will turn down the glutamate message hasn't been very productive. Will this work? I don't know," he said.

The fact that the researchers found objective evidence from MRS that memantine was doing something favorable "is encouraging, not so much because it shows a change in the clinical state, but it's a signal based on the imaging in the brain," Dr. Bowden said.

"This is an encouraging report. Is it going to help any patient tomorrow or the next day? No. But it's as interesting a report as I've seen."

The study was sponsored by Forest Laboratories Inc. Dr. Iosifescu and Dr. Bowden report no relevant financial relationships.
