Lack of Association Between Serum Brain-Derived Neurotrophic Factor Levels and Improvement of Schizophrenia Symptoms in a Double-Blind, Randomized, Placebo-Controlled Trial of Memantine as Adjunctive Therapy to Clozapine

To the Editor: We have shown that memantine as adjunctive therapy to clozapine improves negative and positive symptoms in patients with refractory schizophrenia.[1] However, the biologic mechanism for this improvement remains unclear. Meisner et al[2] have reported an interaction between memantine and brain-derived neurotrophic factor (BDNF). An effect of memantine on nonneuronal BDNF-producing cells may explain this interaction by activation of extrasynaptic *N*-methyl-D-aspartate receptors and promotion of neuronal functioning. BDNF is implicated in many psychiatric disorders, such as schizophrenia.[3–6]

We hypothesize that BDNF may play a role in the effect of memantine in patients with schizophrenia. Some studies have evaluated BDNF as a predictor of treatment response[7,8] and as a possible diagnosis biomarker.[9] The aim of this study is to evaluate serum BDNF levels in refractory schizophrenia patients before and after use of memantine as adjunctive therapy to clozapine.

Method. In a double-blind, placebo-controlled trial, 21 outpatients with *DSM-IV*–defined refractory schizophrenia were randomly assigned, from January 2006 through March 2008, to receive either 20 mg/d memantine (n = 10) or placebo (n = 11) adjunctive to clozapine for 12 weeks. Serum BDNF levels were measured at baseline and after 12 weeks of treatment using an ELISA sandwich kit. The primary outcome was total score on the Brief Psychiatry Rating Scale (BPRS)[10] and its subscales of positive and negative symptoms. Response to memantine was defined as a decrease of at least 50% in BPRS score. Comparisons of serum BDNF levels before and after memantine or placebo were assessed by paired Student *t* test. Unpaired Student *t* test was used to assess the difference in serum BDNF levels according to memantine response.

Results. All participants completed the study and were included in the analysis. Significant improvement ($P < .01$) in total BPRS score and positive (effect size = 1.38) and negative (effect size = 3.33) subscales was observed in the active treatment group. Five of 10 patients receiving memantine had a decrease of at least 50% in BPRS total score and were considered as responders. There was no difference in mean ± SD serum BDNF levels before and after memantine (0.30 ± 0.08 and 0.30 ± 0.10, respectively; difference = –0.002, $P = .93$) or placebo (0.35 ± 0.14 and 0.35 ± 0.17, respectively; difference = –0.002, $P = .91$) treatments. In the memantine group, a statistically nonsignificant decrease of serum BDNF levels in responders compared to nonresponders (0.28 ± 0.08 and 0.33 ± 0.06, respectively; $P = .41$) was seen before treatment.

Adjunctive treatment to clozapine with memantine in this cohort was associated with improvement in negative and positive symptoms. There were no differences in serum BDNF levels after memantine treatment. BDNF was identified as a predictor of treatment response.[7,8] However, a difference in serum BDNF levels between responders and nonresponders to memantine was not found in this sample.

There are some limitations in the present study. First, we assessed BDNF in serum. However, a high correlation of serum and cerebrospinal fluid BDNF levels has been reported.[11] Second, the negative results of our comparisons of BDNF levels between responders and nonresponders to memantine may be due to the relatively small sample. Third, all patients were on clozapine treatment before entering the study, and clozapine may increase serum BDNF levels.[4] Therefore, we can hypothesize that an increase in serum BDNF levels had occurred before randomization.

In conclusion, our results do not support the hypothesis that improvement in positive and negative symptoms with adjunctive treatment to clozapine with memantine in patients who have refractory schizophrenia is associated with serum BDNF level variances.

Trial registration: clinicaltrials.gov Identifier: NCT00757978

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