Combo Therapy Best at Averting Bipolar Relapse

BY BRUCE JANCIN

FROM THE ANNUAL INTERNATIONAL CONGRESS OF THE ROYAL COLLEGE OF PSYCHIATRISTS

EDINBURGH – Long-term combination therapy with lithium plus valproate in patients with bipolar I disorder proved to be markedly more effective than valproate monotherapy in the randomized BALANCE trial.

BALANCE (Bipolar Affective Disorder: Lithium Anticonvulsant Evaluation) will be a practice-changing study, both in the United States and in the United Kingdom, where it originated, study coordinator and chief investigator Dr. John R. Geddes predicted at the congress.

"As valproate monotherapy is substantially the most commonly used treatment in the United States, BALANCE should probably lead to some change in practice over there. …. I think BALANCE would suggest that for a majority of patients, combination therapy would be a better bet than valproate monotherapy. And even lithium might be better as a first-line therapy," commented Dr. Geddes, professor of epidemiological psychiatry and a senior clinical research fellow at the University of Oxford (England).

BALANCE included 330 patients aged 16 and older with bipolar I disorder at 41 sites in the United Kingdom, France, the United States, and Italy who were randomized to open-label lithium monotherapy at a target dose of 0.4-1.0 mmol/L, valproate monotherapy at 750-1,250 mg/day, or both agents in combination.

The primary outcome was emergence of a new mood episode requiring further intervention (defined as either another medication or hospitalization) during 2 years of follow-up. This occurred in 69% of the valproate group, 59% of those taking lithium, and 54% on combination therapy (Lancet 2010;375:385-95).

Thus, combination therapy resulted in a 41% relative risk reduction in the primary end point compared with valproate monotherapy, and an 18% reduction compared with lithium. Lithium monotherapy achieved a 39% relative risk reduction compared with valproate.

The time to a 10% hospitalization rate averaged 4.7 months in the valproate group, 7.7 months with lithium, and 11.3 months with combination therapy.

"You may well want to put patients on combination therapy before they've had the chance to fail on monotherapy, in the same way that in cancer therapy we often use combination therapy right from day 1. It really gives you the best chance of controlling the condition," he said.

In terms of numbers needed to treat (NNT), BALANCE showed that seven bipolar patients would need to receive combination therapy for 2 years instead of valproate in order for there to be one fewer relapse; that's a very favorable NNT, Dr. Geddes observed. The NNT was 10 for lithium vs. valproate, and 20 for combination therapy vs. lithium monotherapy.

"We can neither refute nor confirm an added benefit for combination therapy over lithium alone," Dr. Geddes said. "The trial would have to be quite a lot larger to pick up any added benefit."

No baseline predictors of individual treatment response could be identified. Genotype data are now being analyzed. "The results so far aren't overly impressive, so don't hold your breath on that one," he advised.

Lithium proved to be better than valproate for prevention of depressive as well as manic relapses in BALANCE, contrary to the conventional wisdom that holds that valproate is the more effective agent against depressive symptoms. However, this finding is consistent with the results of a recent meta-analysis by Dr. Geddes and his colleagues, which he said showed "quite convincingly" that lithium was more effective than valproate in preventing depressive symptoms.

The BALANCE trial was funded by the Stanley Medical Research Institute, with donation of drugs by Sanofi-Aventis. Dr. Geddes disclosed having received research funds from the Medical Research Council, the Economic and Social Research Council, and the National Institute for Health Research, as well as the Stanley Medical Research Institute. ■