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COMBINED LITHIUM PLUS VALPROATE OR LITHIUM MONOTHERAPY BETTER AT PREVENTING RELAPSE IN BIPOLAR PATIENTS THAN VALPROATE MONOTHERAPY (BALANCE study)

For people with bipolar I disorder*, for whom long-term therapy is clinically indicated, both combination therapy with lithium plus valproate and lithium monotherapy are more likely to prevent relapse than is valproate monotherapy. This benefit seems to be irrespective of baseline severity of illness and is maintained for up to 2 years. These are the conclusions of the BALANCE study, published **Online First** (www.thelancet.com) and in an upcoming Lancet, written by Professor John R Geddes, Clinical Trials Unit for Mental Illness, University of Oxford, UK, and colleagues. However, BALANCE could not confirm or refute an advantage of combined therapy over lithium monotherapy.

Bipolar disorder is a disabling mental illness that is characterised by episodes of both elevated or irritable mood and depression. Although acute episodes can be succeeded by a period of remission, most patients have a recurrent or chronic illness, making bipolar disorder one of the most important causes of disability at ages 15–44 years. Many patients do not respond to monotherapy, and combinations of drugs are often recommended despite little evidence. Lithium plus valproate is often recommended after failure of first-line monotherapy. Should this combination have additive pharmacological effects and prove better than monotherapy, it could be an appropriate first-line therapy

In the randomised BALANCE trial, 330 patients aged 16 years and older with bipolar I disorder from 41 sites in the UK, France, USA, and Italy were allocated to lithium monotherapy, valproate monotherapy, or both agents in combination after an active run-in** of 4–8 weeks on the combination. Patients were followed for up to 24 months, and the primary outcome was initiation of new intervention for an emergent mood episode.

The researchers found that 54% of people in the combination therapy group, 59% in the lithium group, and 69% in valproate

group had a primary outcome event during follow-up. In terms of relative risk, those given combination therapy were 41% less likely to have a primary outcome event versus those given valproate; while those given lithium were 29% less likely to have an event than those given valproate. Both these findings were statistically significant. Patients given combination therapy were also 18% less likely to have an event versus those given lithium monotherapy, but this finding was not statistically significant. A total of 16 participants had serious adverse events after randomisation, that were judged not to be related to the trial treatments: seven receiving valproate monotherapy (three deaths); five lithium monotherapy (two deaths); and four combination therapy (one death). The authors say: "The results of BALANCE show that for people with bipolar I disorder for whom long-term therapy is clinically indicated, combination therapy with lithium plus valproate is more likely to prevent relapse than is monotherapy with valproate. The 41% relative benefit is irrespective of baseline severity of illness, is maintained for up to 2 years, and is most apparent in prevention of manic relapse."

They conclude: "The main BALANCE findings have important implications for clinical decisions about long-term therapy for bipolar disorder. First, valproate monotherapy is recommended by clinical practice guidelines as a first-line option for long-term therapy. Our results suggest that patients should be advised that a better outcome would be likely with combination therapy with lithium plus valproate semisodium or lithium alone. Second, guidelines suggest that patients who have frequent relapses during treatment with lithium monotherapy could switch to valproate monotherapy. The results of BALANCE suggest that these patients would fare better if they changed to combination therapy."

In an accompanying Comment, Dr Rasmus W Licht, Mood Disorders Research Unit, Aarhus University Hospital, Denmark, says that the results of BALANCE, even without a placebo group, confirm the long-term efficacy of lithium, not only for the prevention of mania but also for prevention of depression.

He says: "On the basis of their overall results, the BALANCE group rightly challenges the recommendation by present clinical guidelines that valproate monotherapy is a first-line option for long-term treatment."

He concludes: “By a diligent balance of external and internal validity, BALANCE surely reflects its acronym. It is remarkable indeed that a clear signal could be detected despite the straightforward study procedures, including the allowance of co-medication, and there is no doubt that the trial sets the stage for future large-scale, simple, investigator-sponsored trials."

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