RESEARCH REPORT

BALANCE: a large simple trial of maintenance treatment for bipolar disorder

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Despite recent developments in the treatment of the acute manic and depressive phases of bipolar disorder, the frequently recurrent nature of the disorder means that ongoing treatment for long-term relapse prevention is often needed. Drugs that are effective in the acute phase are commonly continued in remission to prevent or delay another relapse, but it is unclear which of these drugs is most effective or whether a combination of individually less than ideal drugs may be better than any monotherapy. Lithium effectively halves the relapse rate but it is not effective for all patients and it has a narrow therapeutic index (1). This often leads to low levels of treatment adherence and acute discontinuation may result in new episodes of illness (2). Lower plasma levels improve tolerability and adherence but probably at the cost of optimum efficacy (3). Alternative drug treatments, such as carbamazepine and valproate, have emerged, prompted by the analogy between recurrence in bipolar disorder and the recurrence of seizures in epilepsy (4). Valproate seems to be effective and well tolerated in acute mania (5), although the evidence in maintenance is equivocal, and it is unclear if lithium or valproate is superior (6).

Combinations of drugs, particularly lithium plus valproate, are both recommended and frequently used in clinical practice for mood stabilization, especially for patients who have not responded to monotherapy (7,8). Synergy between lithium and valproate may occur because their putative mechanisms of action converge on signal transduction pathways critical for neurotransmitter function and neuroprotection (9). Clinically, the combination of moderate doses of lithium plus valproate may be more effective than either drug alone.

In the US, use of valproate (both alone and in combination with lithium) for the acute and maintenance treatment of bipolar disorder has increased dramatically since the early 1990s - prescriptions for valproate in bipolar disorder have now overtaken those for lithium (8,10,11). By contrast, in the UK and Europe lithium is still the most frequently used mood stabilizer (12). These variations in clinical practice reflect the absence of evidence, rather than failure to implement it, and highlight the current uncertainty about the appropriate places of lithium and valproate.

THE BALANCE TRIAL

BALANCE (Bipolar Affective disorder: Lithium/ANticonvulsant Evaluation) is a large simple randomised clinical trial designed to test the relative efficacy of the combination of lithium and valproate compared with lithium monotherapy and with valproate monotherapy. Trials commonly fail because: they fail to meet recruitment targets, are too small to detect plausible treatment effects, or are too late and the trial question is overtaken by changing conditions or practice (13,14). Although there is relatively little research on randomized trials in psychiatry, there is rather more in other areas of medicine where large, simple trials have been useful in answering important clinical questions. The main principles that inform the design of such trials are the following:

- The benefits of medical treatments on important outcomes are usually only moderately sized, although clinically worthwhile. This means that the trial needs to be very large to be able to detect the effect reliably.
- Inclusion criteria should be as broad and as unrestrictive as possible. Recruitment has been shown to be adversely affected by the use of strict eligibility criteria (15). Unrestrictive entry criteria make it more likely that the required sample size will be achieved and a broad, heterogeneous range of patients can be recruited, thereby increasing the general applicability of the trial results. The key entry criterion is that both the patient and investigator are substantially uncertain which of the trial treatments would be most appropriate. This is ethical because it effectively excludes patients for whom a specific treatment is known to be most appropriate. It maximizes recruitment by allowing the widest possible eligibility for trial entry. Crucially, the uncertainty principle also makes clinical sense.
- All trial procedures are radically simplified. One of the key barriers to participation in trials by clinicians is time availability. Removing this barrier, by keeping the trial procedures and data collection to an absolute minimum, is essential to achieve the widespread participation and, hence, the required sample size for realising the key objectives of the trial (14,16-18).
- The trial should have adequate support materials, to make sure that patients understand the reasons for the

trial, and patients should be given additional verbal explanations by their physician (19,20).

DESIGN OF BALANCE

BALANCE has been designed using these principles. Patients with bipolar disorder who consent to join the trial enter an active run-in phase during which they will receive combination lithium plus valproate semisodium for up to 8 weeks. Patients will then be randomized to receive lithium monotherapy or valproate semisodium monotherapy or combination therapy with lithium plus valproate semisodium and followed for up to 2 years (Figure 1).

Interventions

Lithium

The dose of lithium in BALANCE will be flexible, but is fixed during the run-in to be *both* tolerated by the patient *and* achieving a plasma level between 0.4 to 1.0 mmol/l.

Valproate

The optimal levels of valproate for maintenance treatment are unclear, but levels between 50 and 150 mcg/ml appear to be optimal for *acute* treatment (21). The dose of valproate semisodium will be 1250 mg/day unless the patient cannot tolerate this dose, in which case 750 mg will be used.

Following randomization, each allocated drug will continue to be prescribed in the dose fixed in the run-in. This will facilitate centralised drug provision and allow the use of time to relapse of mood disorder requiring adjunctive treatment as a primary outcome measure.

Eligibility

The trial is open to any patient with a diagnosis of bipolar disorder who has agreed to commence or continue maintenance therapy, but there is uncertainty about which treatment is likely to be optimal.

Run-in phase

The run-in will increase the likelihood that patients who cannot tolerate the drugs, or who will not comply, withdraw before randomization, enhancing the validity and efficiency of the trial (22). Ensuring that participants are tolerant under normal clinical conditions during the active run-in phase should also facilitate recruitment of patients and increase the general applicability of the results of the trial, since, in normal clinical practice, patients would undergo a trial of a proposed medication before long-term treatment was recommended.

At the end of the run-in phase, if there remains uncertainty, the participant is allocated to trial therapy using telephone randomization with minimization. If allocated to monotherapy, the discontinued drug will be withdrawn gradually over 28 days to reduce the likelihood of withdrawal relapses (2,23,24).

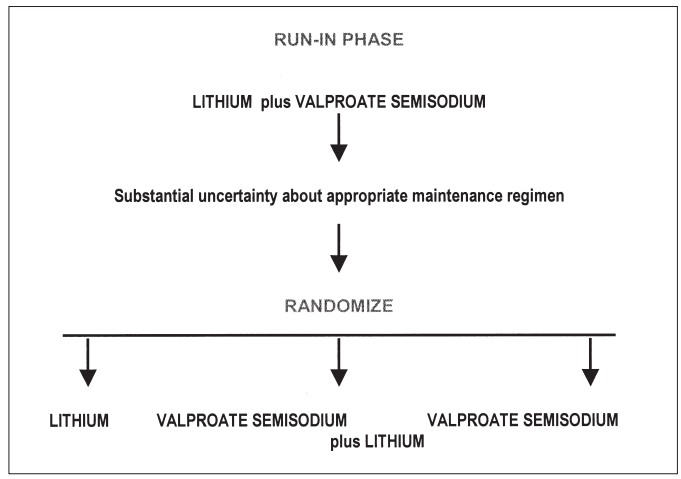

Figure 1 Design of BALANCE

Primary outcomes

The principal primary outcome will be the time to hospital admission during the scheduled randomized treatment period. Although there is general agreement that admission to hospital is a clinically meaningful and measurable outcome, it is a potentially insensitive measure of the less severe mood fluctuations that cause considerable disability in bipolar disorder. Furthermore, manic episodes are more likely than depressive episodes to result in hospital admission. The use of adjunctive antidepressant and antipsychotic medication and of mood stabilizers other than lithium and valproate semisodium will provide another measure of the occurrence of mood episodes that are not severe enough to lead to admission.

Secondary outcomes

Secondary outcomes will include the Global Assessment of Functioning, deliberate self-harm, quality of life, treatment-emergent adverse events, withdrawal from allocated treatment and adherence.

Open design

An open design has been selected to improve recruitment and because the principal primary outcome is objective and so the risk of ascertainment bias is relatively low. Performance bias will be reduced by the use of fixed post-randomization doses and the use of the pragmatic outcome to use additional treatment as co-primary outcome.

Maximizing follow-up

In BALANCE, a high follow-up rate on the principal outcome will be achieved by the use of hospital admission as primary outcome, the pre-randomization run-in phase and the minimization of the burden on patients and investigators imposed by the trial procedures.

Sample size and power

Recent trials suggest a 70% admission-free survival rate on lithium monotherapy during the trial (24 months), with a 30% rate of lapse from treatment (25,26). A 10% improvement in the absolute survival rate in the combination group is both feasible and clinically important. Power calculations have included an adjustment for a 30% rate of withdrawal from study treatment. To achieve 90% power, a 2-sided significance level of $2p<0.05$, and assuming a 5% loss to follow-up rate, 878 participants will be needed in each treatment group. The target total sample size for BALANCE will be 3000 participants. This sample size will have >95% power to detect a 10% absolute improvement in the prescription-free survival for antidepressants or antipsychotics.

Planned analyses

The primary analysis (by full intention-to-treat) will be a survival analysis of time to hospital admission during the scheduled treatment period of patients allocated to lithium plus valproate vs. those allocated to valproate monotherapy; patients allocated to lithium plus valproate vs. those allocated to lithium monotherapy, and those allocated to lithium monotherapy vs. those allocated to valproate monotherapy. These analyses will be repeated for time to use of adjunctive drug treatment.

CURRENT STATUS OF BALANCE

The start-up phase of BALANCE is currently in progress in seven centres in the UK. The trial will be extended across the UK during the next 2 years.

Acknowledgements

BALANCE is a collaborative UK trial. The Principal Investigators are: Doug Altman, John Geddes, Guy Goodwin, Ed Juszczak, Ian Anderson, John Cookson, Nicol Ferrier, Allan Young, Sophia Frangou, Peter Jones, Chris Kelly, Glyn Lewis, Keith Lloyd, Richard Morriss, Malcolm Peet, Ian Reid, Jan Scott, Peter Tyrer. The BALANCE Trial is funded by the Stanley Foundation. Sanofi-Synthelabo have generously contributed supplies of valproate semisodium and lithium for the trial.

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