In addition, medication adherence is not available in the NHIRD. Therefore, these points should be considered as limitations of our study.

Finally, we defined the use of carbamazepine, valproic acid, lithium or lamotrigine as the use of any mood stabiliser. Guidelines have suggested that combination therapy is an acceptable strategies for treating bipolar disorder.[4] Similar to the results of our prior study,[5] we believe that combination therapy for bipolar disorder may have contributed to the gap between the number of patients receiving any mood stabiliser and the sum of patients as per the numbers given separately for carbamazepine, valproic acid, lithium and lamotrigine in our study.

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Timing of onset of lithium relapse prevention - how early, how late?

In a recent paper, Dr Taylor raises an important issue: how long does it take for people with bipolar disorder to respond to lithium treatment?[1] In meta-analysis of data from three clinical trials, he found that patients randomised to lithium had significantly lower relapse rates than those receiving placebo, even in the first 2 weeks of treatment. This conclusion, however, does not answer the more relevant question as to how long a treatment trial should last before it can be established whether it is effective. In other words, is it worth waiting for let us say a year before switching to another option?

Clinical experience would suggest that there is a great range of time to response, which may relate to diagnostic and genetic heterogeneity.[2] Some patients respond within a few weeks whereas others may continue having major mood symptoms during the first year of treatment. Patients in the latter group will be inevitably categorised as 'non-responders' if even a single relapse is the criterion of treatment failure.

In Dr Taylor's study all three trials were based on discontinuation designs and were enriched for acute response to quetiapine or lamotrigine. However, enriched discontinuation designs with time to relapse as the outcome variable are less than ideal for evaluation of treatments of an illness that runs a lifelong course that is often highly unpredictable. Furthermore, most recent studies of long-term treatment of bipolar disorder (including the three trials discussed here) evaluate continuation treatment rather than recurrence prevention.

With respect to the minimal necessary length of treatment trial, there is practically no systematic data and the existing bipolar treatment guidelines stay away from the subject as well. In an earlier study, Ahrens *et al* attempted to estimate the time needed for patients to benefit from the suicide-reducing effect of lithium; they concluded that a treatment period of at least 2 years was necessary to return suicide risk to population baseline.[3] Given this, a more realistic design of maintenance studies might consider different outcome criteria such as affective morbidity assessed periodically over a sufficiently long observation period. As for a practical decision as to how long a treatment trial needs to last, it may become easier with advances in personalised treatment and discoveries about predictors of treatment response. Then it should be possible to individualise the length of a treatment trial – longer in those people expected to benefit from a specific treatment and abandon unsuccessful treatment earlier in those where the likelihood of response is equivocal.

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Author's reply

Corbett & Alda raise the interesting question of how long a treatment trial should last before it can be established whether lithium is effective for a specific individual. As they note, existing experimental studies are not necessarily designed to address that particular question, which raises significant conceptual and analytic challenges.

Their interesting suggestion of assessing maintenance treatments through comparison of cumulative morbidity over long periods may be becoming a more feasible prospect through the combination of electronic health records analysis[1] with the increased availability of longitudinal mood monitoring outside experimental studies.[2]

Pending these new data, the available evidence indicates that lithium is likely to reduce the risk of manic relapse rapidly, whereas full effects against depressive relapse probably develop over a longer period.[3]

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