Effectiveness of interventions for preventing relapse in people with bipolar disorder

A systematic review and economic model of the clinical effectiveness and cost-effectiveness of interventions for preventing relapse in people with bipolar disorder

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Executive summary

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Executive summary

Background

Bipolar disorder is a recurrent mood disorder associated with significant morbidity and mortality that places a considerable economic burden on UK society. Long-term treatment of bipolar disorder is necessary to prevent recurrence and reduce the loss of productivity and increased medical costs associated with this illness. Lithium has been the mainstay treatment for bipolar disorder for many years, but more recently, anticonvulsants, antidepressants, antipsychotics and adjunctive psychosocial therapies have been used in the maintenance treatment of bipolar disorder. However, the evidence for the effectiveness of these treatments is unclear.

Objective

The aims of this review were to determine the clinical effectiveness and cost-effectiveness of pharmacological and/or psychosocial interventions for the prevention of relapse in people with bipolar disorder.

Methods

This technology assessment comprised the following research.

- A systematic review of the clinical effectiveness of pharmacological and psychosocial interventions for the prevention of relapse in bipolar disorder. Randomised or quasi-randomised controlled trials of maintenance therapy that provided data on rate of relapse were reviewed.
- An analysis using the methods of mixed treatment comparison (MTC) to enable indirect comparisons to be made between the treatments for the prevention of relapse in bipolar disorder.
- A systematic review of existing economic evaluations of treatments for the prevention of relapse in bipolar disorder.
- Development of an economic model of treatments for the prevention of relapse in bipolar disorder.

Results

Clinical effectiveness

The review of clinical effectiveness included 45 trials; all but one tested the intervention or comparator in adults. They were placebo- or active controlled trials of lithium, valproate, lamotrigine, carbamazepine, olanzapine, imipramine, quetiapine, amitriptyline, perphenazine, flupenthixol and psychosocial interventions [cognitive behaviour therapy (CBT); psychoeducation; family intervention; care management; and integrated group therapy].

For the prevention of all relapses, lithium, valproate, lamotrigine and olanzapine were statistically significantly better than placebo. The evidence was strongest for lithium and lamotrigine; that for olanzapine may be unreliable as only responders to olanzapine were studied.

For the prevention of depressive relapses, valproate, lamotrigine and imipramine were statistically significantly better than placebo. The evidence is probably strongest for lamotrigine; the evidence base for imipramine is very weak (two very small trials). For manic relapses, lithium and olanzapine were statistically significantly better than placebo, but again for olanzapine only responders to olanzapine were studied.

Only olanzapine demonstrated greater efficacy than lithium, and then for all relapses and manic relapse, but not for depressive relapse.

In order to investigate the relative efficacy of the treatments, an MTC was performed. The purpose of an MTC is to bring together the clinical evidence regarding the efficacy of all treatments for a specified indication in a 'network of evidence' linked by common comparators. Of all the treatments included in the systematic review, lithium, valproate, lamotrigine, carbamazepine, olanzapine, imipramine and lithium plus imipramine could be linked in a network of evidence. None of the psychosocial interventions could be linked into the network of evidence.

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The results of the MTC indicate that carbamazepine is not an effective maintenance treatment for bipolar I disorder. In patients with mainly depressive symptoms the treatment with the highest probability of being the best for the prevention of all relapses appears to be valproate, followed by lithium plus imipramine. In patients with mainly manic symptoms, olanzapine is by far the best option for the prevention of all relapses, followed by valproate and lithium.

From the studies investigating psychosocial interventions, there were few data for each comparison and outcome. The evidence suggests that CBT, in combination with usual treatment, is effective for the prevention of relapse. Group psychoeducation and possibly family therapy may also have roles as adjunctive therapy for preventing relapse.

Cost-effectiveness

Following the review of economic evidence from the literature, a new decision analytic model was developed. This focused on the cost-effectiveness of long-term maintenance treatments of bipolar I patients with a range of alternative pharmacological treatments.

The results from the model suggest that the choice between alternative pharmacological treatments based on cost-effectiveness considerations is dependent upon a number of factors: the previous episode history of a patient (i.e. whether manic or depressive) and the mortality benefit assumed for lithium strategies.

The results from the base-case analysis for patients with a recent history of depression suggest that valproate, lithium and the combination of lithium and imipramine are potentially cost-effective depending upon the amount that a decision-maker is willing to pay for additional health gain [assessed here using quality-adjusted life-years (QALYs)]. Using conventional amounts that the NHS is prepared to pay for health gain (£20,000–40,000 per QALY), the lithium-based strategies appear to be potentially cost-effective for this group.

For patients with a recent history of mania, the choice of pharmacological intervention appears to be between olanzapine and lithium monotherapy. Again using conventional threshold as a reference point, the results suggest that lithium is the most cost-effective therapy.

Excluding the additional mortality benefit associated with lithium-based strategies resulted in all treatments for patients with a recent history of a depressive episode being dominated by valproate and, in the case of patients with a recent history of a manic episode, by olanzapine.

Conclusions

Lithium, valproate, lamotrigine and olanzapine are effective as maintenance therapy for the prevention of relapse in bipolar disorder. Olanzapine and lithium are efficacious for the prevention of manic relapses and valproate, lamotrigine and imipramine for the prevention of depressive relapse. Carbamazepine is not an effective maintenance treatment. There is no trials evidence for the efficacy of combination therapy.

Psychosocial therapies have not been investigated thoroughly. There is some evidence that CBT, group psychoeducation and family therapy might be beneficial as adjuncts to pharmacological maintenance treatments.

There is insufficient information to permit any meaningful assessment of the relative tolerability of the treatments or their relative effects on suicide rate and mortality.

For patients with a recent depressive episode, valproate, lithium monotherapy and the combination of lithium and imipramine are potentially cost-effective. For patients with a recent manic episode, olanzapine and lithium monotherapy are potentially cost-effective.

The cost-effectiveness estimates in both groups of patients were shown to be sensitive to the assumption of a reduced suicidal risk associated with lithium-based strategies.

Research recommendations

The following areas are recommended for further research:

- A comprehensive review of, and further primary research into, the adverse effects of all treatments is required.
- Further investigation is needed of the differential effects in bipolar I, bipolar II and in rapid cycling and of the effects of treatments on suicide rates.

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- A trial of a combination of lithium plus a selective serotonin reuptake inhibitor antidepressant is warranted.
- Good-quality trials of valproate are needed.
- Better and larger trials of psychosocial interventions, particularly CBT, are needed.
- Good-quality trials in children are required.

It is very important that future trials should be good-quality randomised controlled trials, involving an adequate number of participants and have sufficient duration of follow-up. Ideally, this research should be conducted via a properly resourced trial network.

Publication

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The research reported in this monograph was commissioned by the HTA Programme as project number 05/35/01. The contractual start date was in September 2005. The draft report began editorial review in May 2006 and was accepted for publication in February 2007. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme or the Department of Health.

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