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

Health Technology Assessment 2007; Vol. 11: No. 39

Health Technology Assessment
NHS R&D HTA Programme
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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.
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.
• 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**

The Health Technology Assessment (HTA) programme, now part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the costs, effectiveness and broader impact of health technologies for those who use, manage and provide care in the NHS. ‘Health technologies’ are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

The research findings from the HTA Programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the ‘National Knowledge Service’.

The HTA Programme is needs-led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, the public and consumer groups and professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA Programme then commissions the research by competitive tender.

Secondly, the HTA Programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Thirdly, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

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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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Published by Gray Publishing, Tunbridge Wells, Kent, on behalf of NCCHTA.

Printed on acid-free paper in the UK by St Edmundsbury Press Ltd, Bury St Edmunds, Suffolk.