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


CRD summary
The review assessed the clinical effectiveness and cost effectiveness of pharmacological and/or psychosocial interventions for the prevention of relapse in people with bipolar disorder. For bipolar patients with predominantly depressive symptoms, lithium, valporate or lamotrigine, or a combination of lithium with an antidepressant is the treatment of choice. For bipolar patients with predominantly symptoms of mania, lithium and olanzapine are preferred. However, there was insufficient data on adverse events. Overall, this was a well conducted review and the authors' conclusions are likely to be reliable.

Authors' objectives
To determine the clinical effectiveness and cost-effectiveness of pharmacological and/or psychosocial interventions for the prevention of relapse in people with bipolar disorder.

Searching
MEDLINE, PREMEDLINE, EMBASE, CINAHL, BIOSIS Previews, PsycINFO, Science Citation Index, the Cochrane Central Register of Controlled Trials (CENTRAL), LILACS, Inside Conferences (DIALOG), ISI Proceedings, National Research Register and the National Technical Information Service were searched up to September 2005 for relevant studies. Search terms were reported. In addition, internet searches including specific organisation websites and abstracts from the Society of Biological Psychiatry (1999), Affective Disorders/European Psychiatry (2005) and the Biennial Schizophrenia Winter Workshop (2002) were checked.

Study selection
Randomised or quasi-randomised controlled trials with at least three months of follow-up that compared pharmacological or psychosocial interventions with placebo, no intervention or with another intervention in people with a diagnosis of bipolar I disorder or bipolar II disorder were eligible for inclusion in the review. Bipolar I or bipolar II disorder were defined according to explicit diagnostic criteria (DSM-IV or ICD-10) through use of structured interview or otherwise were included. Patients treated only in an acute manic or depressive phase were excluded. The interventions included: lithium salts, anticonvulsants, antipsychotics, antidepressants, cognitive behaviour therapy (CBT), psychoeducation, family intervention, case management and integrated care therapy. Only trials of interventions used for maintenance were eligible (defined as treatment given primarily to prevent further episodes of affective illness after patients were already stabilised). Crossover trials in which the length of treatment before crossover was less than three months were excluded. All but one of the included studies was of adults. The proportion of females ranged from 23 per cent to 100 per cent. Most included studies included: participants diagnosed as having only bipolar I disorder; participants with bipolar I and II; or not specified. Three studies included only participants with bipolar II disorder. The percentage of patients with rapid cycling ranged from 2.5 per cent to 100 per cent. The primary outcome was all relapses. Secondary outcomes were also listed.

A minimum of 30 per cent of the papers were screened independently by two reviewers. Any disagreements were resolved by consensus or with the decision of a third reviewer.

Assessment of study quality
The quality of the included studies was assessed according to the following criteria: study design, random assignment, sequence generation, allocation concealment, groups similar at baseline, eligibility criteria specified, blinding (assessors, care provider, and patient), point estimates and variability presented for primary outcome, intention-to-treat (ITT) analysis and reporting of sample size calculation.

Quality assessment was carried by one reviewer and checked independently by a second reviewer. Any disagreements were resolved by consensus or with the decision of a third reviewer.
Data extraction
Dichotomous data were extracted as the number of individuals with the outcome of interest and the total number of individuals in the intervention and control groups. Odds ratios (OR) were calculated for each trial for dichotomous data. The mean and standard deviation (SD) were extracted for continuous outcomes. If the mean and SD were unavailable, the median, standard error or range were extracted. For studies that presented data for more than one length of follow-up, data from the longest-follow-up were used. For the crossover studies only data from the first period before crossover were extracted.

Data were extracted by one reviewer and checked independently by a second reviewer. Any disagreements were resolved through consensus or with the decision of a third reviewer.

Methods of synthesis
Where more than one study was available for comparison, data were pooled using a fixed-effect model. Subgroup analysis was performed for the primary outcome measure 'all relapses': studies in which patients were randomised during the acute phase; studies in which patients were only randomised to treatment after they had shown a positive response to the study agent; and the effect of bipolar II disorder. Statistical heterogeneity was assessed using the $\chi^2$ test. The potential impact of missing data was assessed through sensitivity analyses. In studies with more than two treatment arms, data were analysed for different combinations within the same trial. A mixed treatment comparison (MTC) was also conducted using the outcomes 'all relapse', manic relapse and depressive relapse. The MTC analysis excluded trials that were purely bipolar II. Assessment of publication bias was planned, but the small number of trials for each treatment comparison precluded this.

Results of the review
Forty-five trials (n=5,333) were included in the review; forty-two RCTs and three quasi-randomised trials. The sample sizes ranged from 12 to 463. The generation of allocation sequence was clearly reported in 15 studies.

Lithium, valporate lamotrigine and olanzapine were found to be significantly better than placebo for the prevention of all relapses; evidence was strongest for lithium and lamotrigine. Valporate, lamotrigine and imipramine found to be significantly better than placebo for the prevention of depressive relapses; evidence was strongest for lamotrigine. Lithium and olanzapine were found to be significantly better than placebo for the prevention of manic relapses; evidence was strongest for lithium strategies.

Mixed treatment comparisons indicated that valporate followed by lithium plus imipramine was the best treatment for the prevention of all relapses in patients with mainly depressive symptoms; olanzapine followed by valporate and lithium was the best treatment for prevention of all relapses in patients with mainly manic symptoms. Carbamazepine was not an effective maintenance treatment for bipolar I disorder. None of the psychosocial interventions could be linked (by use of common comparators) into this model.

CBT in combination with usual treatment was found to be effective for the prevention of relapse. Group psychoeducation and possibly family therapy may also have roles as adjunctive therapy in prevention relapse. Studies of psychosocial interventions reported few relevant data and outcomes.

Cost information
Results indicated that the choice between alternative pharmacological treatments in terms of cost-effectiveness is dependent on the previous episode history of a patient and the mortality benefit assumed for lithium strategies. Results from the base-case analysis found that valporate, lithium and the combination of lithium and imipramine are potentially cost-effective (depending on how much the decision maker is willing to pay for additional health gain) for patients with a recent depressive episode, and that olanzapine and lithium are potentially cost-effective for patients with a recent manic episode. The cost-effectiveness for these patient groups was found to be sensitive to the assumption of a reduced suicidal risk associated with lithium-based strategies.

Authors' conclusions
Lithium, valporate, lamotrigine and olanzapine are effective as maintenance therapy for the prevention of relapse in bipolar disorder. Olanzapine and lithium are effective for the prevention of manic relapses. Valporate, lamotrigine and imipramine are effective for the prevention of depressive relapse. There is some evidence that CBT, group psychoeducation and family therapy might be effective as an adjunct to pharmacological treatments. However, there is not enough information regarding the relative tolerability of these treatments or their relative effects on suicide rate and mortality. Valporate, lithium monotherapy and the combination of lithium and imipramine are cost-effective in patients with a recent depressive episode. Olanzapine and lithium monotherapy are potentially cost-effective for patients with a recent manic episode.

CRD commentary
The review question was supported by clear inclusion and exclusion criteria. Several sources were searched for relevant studies unrestricted by language and the authors attempted to locate unpublished studies, minimising the likelihood of language and publication bias. Steps were taken to minimise reviewer error and bias. Validity was assessed using specified criteria and the results reported. Data were pooled where possible and statistical heterogeneity assessed. Overall, this was a well-conducted review and the authors’ conclusions are likely to be reliable.

Implications of the review for practice and research
Practice: the authors suggested that the polarity of the most recent episode (depressive/manic) was a useful way of guiding therapy for patients.

Research: Further studies were needed on the adverse effects of all treatments, the differential effects of agents in bipolar I and II and rapid cycling, and the effects of lithium with SSRI (selective serotonin reuptake inhibitor). In addition, good quality trials of valporate, combination therapy, psychosocial interventions and the disorder in children were required.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.