Centre for Reviews and Dissemination

THE UNIVERSITY of York

Pharmacological interventions for the prevention of relapse in bipolar disorder: a systematic review of controlled trials

Nerys Woolacott B.Sc., Ph.D.[1], Karla Soares-Weiser M.D., Ph.D.[1], Suzanne Beynon M.Sc.[1], Steven Duffy, B.A. (Hons),Pg.Dip.[1], John Geddes, M.D., F.R.C.Psych.[2]

[1]Centre for Reviews and Dissemination, University of York, UK, [2]Department of Psychiatry, University of Oxford, Oxford, UK

Bipolar disorder (manic-depression) is a complex, recurrent mood disorder associated with significant morbidity and mortality.[1] The use of pharmacological interventions for the management of bipolar disorder is widely accepted, however the effectiveness of the available drugs for maintenance therapy in bipolar disorder is unclear. We sought to determine the effectiveness of the different pharmacological interventions for the prevention of relapse in bipolar disorder by conducting a systematic review of the literature across 14 electronic databases and sources.[2]

Systematic Review Methods

Controlled trials of any pharmacological agents considered relevant to current clinical practice for maintenance treatment in bipolar disorder (I or II). Maintenance treatment was defined as treatment instituted primarily to prevent further episodes of affective illness, after patients were already stabilised, not including treatment of the acute phase of the disease. Treatment could be monotherapy, as adjunct therapy or in combination, compared with placebo, no intervention or with another intervention.

The primary outcomes were:

- All relapses of a bipolar episode using the following three definitions:
  - The number of hospitalisations in each group
  - The number of patients that received an additional intervention
  - As defined by the authors.

The secondary outcomes were:

- Manic relapses using the three definitions
- Depressive relapses using the three definitions
- Drop outs before end of study
- Adverse events leading to discontinuation and other treatment related adverse effects
- Suicide or suicide attempts

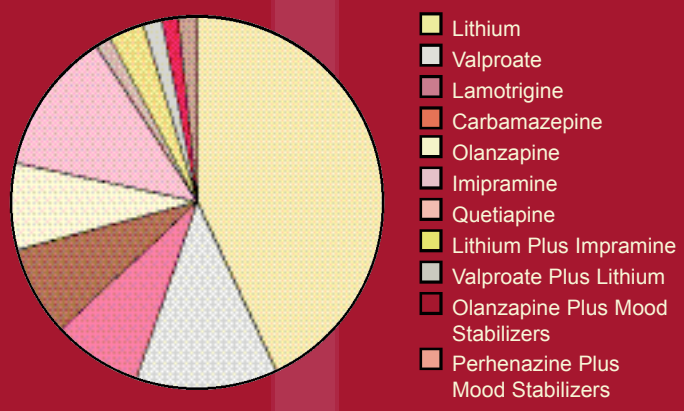
Results

We identified 1,225 potentially relevant references through our search strategy. Of these, 33 examined the effectiveness of pharmacological interventions. The included studies evaluated the effectiveness of 13 different monotherapies and combination therapies (see the figure). The evidence base was dominated by trials involving lithium.

The quality of the studies was variable; sample sizes and length of treatment and follow-up varied across studies and several of the older trials had very small numbers of participants. Poor reporting of methodological details, particularly in terms of randomisation, allocation concealment and blinding made full assessment of study quality difficult.

Lithium, valproate, lamotrigine and olanzapine were significantly better than placebo for preventing relapse. To prevent depressive relapses valproate, lamotrigine and imipramine demonstrated statistically significant benefit compared with placebo. It should be noted that imipramine is not used much in clinical practice due to its adverse effects. To prevent manic relapses lithium and olanzapine demonstrated statistically significant benefit compared with placebo. Of the drugs that have demonstrated some efficacy above that of placebo, only olanzapine demonstrated greater efficacy than lithium, and then for all relapses and manic relapses but not for depressive relapses.

Pharmacological therapies investigated and distribution in the included studies



Conclusions

- There is evidence from placebo controlled trials for the efficacy of lithium, valproate, lamotrigine and olanzapine as maintenance therapy for the prevention of relapse in bipolar disorder.
- For the prevention of manic relapses, olanzapine and lithium are efficacious.

All relapses in trials comparing an active treatment with placebo for the prevention of relapse in bipolar disorder

Comparison (number of trials)	OR (95% CI)	Test for heterogeneity if pooled estimate
All relapses as stated by authors		
Lithium versus placebo (6)	0.35 (0.24, 0.5)	X^2=15.86, df=4, p=0.003
Valproate versus placebo (1)	0.51 (0.30, 0.87)	
Lamotrigine versus placebo (1)	0.48 (0.24, 0.99)	
Olanazapine versus placebo (1)	0.22 (0.13, 0.36)*	
Imipramine versus placebo 2	0.53 (0.09, 3.02)	X^2=0.02, df=1, p=0.88
Imipramine + lithium versus placebo	0.08 (0.01, 0.98) (bipolar II only)	
All relapses admission to hospital		
Lithium versus placebo (3)	0.23 (0.13, 0.39)	X^2=0.84, df=2, p=0.66
Olanzapine versus placebo (1)	0.17 (0.04, 0.71*	
All relapses institution of additional treatment		
Lithium versus placebo (3)	0.6 (0.41, 0.87)	X^2=4.58, df=2, p=0.10
Lamotrigine versus placebo (3)	0.69 0.49, 0.95)	X^2=3.14, df=2, p=0.21

* Responders only

All relapses in trials comparing two active treatments for the prevention of relapse in bipolar disorder

Comparison (number of trials)	OR (95% CI)	Test for heterogeneity if pooled estimate
All relapses as stated by authors		
Lithium versus valproate (2)	1.37(0.84, 2.24)	X^2=0.02, df=1, p=0.88
Lithium versus lamotrigine (1)	1.09 (0.59, 2.01)	
Lithium versus carbamazepine (4)	0.48 (0.27, 0.84)	X^2=4.54, df=3, p=0.21;
Lithium versus olanzapine (1)	1.56 (1.02, 2.40)	
Lithium versus imipramine (3 trials)	0.25 (0.11, 0.59)	X^2=0.22, df=2, p=0.90
Lithium versus lithium + imipramine (1)	0.89 (0.46, 1.72)	X^2=1.40, df=2, p=0.50
Valproate versus olanzapine (1)	1.02 (0.32, 3.23)†	
Olanzapine + mood stabilizers versus mood stabilizers (1)	0.92 (0.39, 2.14) *	
Imipramine versus imipramine + lithium (2)	4.46 (1.67, 11.92)	X^2=0.15, df=1, p=0.70
All relapses admission to hospital		
Lithium versus carbamazepine (3)	0.63 (0.33, 1.2),	X^2=4.3, df=2, p=0.12
Lithium versus olanzapine (1)	1.78 (1.08, 2.93)	
All relapses institution of additional treatment		
Lithium versus lamotrigine (2)	0.83 (0.55, 1.24)	X^2=0.11, df=1, p=0.74
Perphenazine + mood stabilizers versus mood stabilizers (1)	2.86 (0.53, 14.73)*	

† Randomised in the acute treatment phase * responders only

- For the prevention of depressive relapses, valproate and lamotrigine are efficacious.
- Despite widespread use in clinical practice, there is little evidence to support the efficacy of combination therapy.
- The results suggest that a combination of lithium with an antidepressant may be effective for the prevention of relapses. Controlled trials of combination therapies, such as lithium plus a SSRI antidepressant, are warranted.
- There is insufficient information regarding the relative effects of the treatment on suicide rate and mortality.
- A comprehensive review of the long-term adverse effects profiles of those treatments considered to be the best (lithium, valproate, lamotrigine and olanzapine) is required to properly inform decisions about their relative effectiveness and clinical use.

References

1. Muller-Oerlinghausen B, Berghofer A, Bauer M. Bipolar disorder. *Lancet* 2002;359:241-47.
2. Soares-Weiser K, Bravo Vergel Y, Beynon B, Dunn G, Barbieri M, Duffy S, Geddes J, Gilbody S, Palmer S, Woolacott N. A Systematic Review And Economic Model Of The Clinical Effectiveness And Cost Effectiveness Of Interventions For Preventing Relapse In People With Bipolar Disorder. Health Technol Assess. In press.

This project was funded by the NIHR Health Technology Assessment Programme (project number 05/35/01) and will be published in full in Health Technology Assessment. See the HTA programme web site for further project information. **www.hta.ac.uk**

The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.