A Simultaneous Comparison of Multiple Treatments for Bipolar I: An Application of Bayesian Statistical Methods

Y Bravo Vergel[1], G Dunn[1], S Palmer[1], S Beynon[2], N Woolacott[2], K Soares-Weiser[2], J Geddes[3], S Gilbody[4]

[1]*Centre for Health Economics, University of York, YO10 5DD York, U.K.*
[2]*Centre for Reviews and Dissemination, University of York, YO10 5DD York, U.K*
[3]*Department of Psychiatry, University of Oxford, OX3 7JX Oxford, U.K.*
[4]*Department of Health Sciences, University of York, YO10 5DD York, U.K.*

BACKGROUND

Bipolar disorder is a recurrent mood disorder associated with significant morbidity and mortality.

Bipolar I is defined as one or more manic or mixed episodes, accompanied by one or more depressive episodes.

Long-term treatment is necessary to **prevent recurrence** and reduce productivity losses & high medical costs associated with treatment of episodes

Lithium has been the mainstay treatment for bipolar for many years. More recently, anticonvulsants, antidepressants and antipsychotics have been used for maintenance. A systematic review of the clinical effectiveness of pharmacological interventions for the prevention of relapse in bipolar I was conducted.[1]

AIM

The relative clinical efficacy of these pharmacological treatments for the prevention of relapse in bipolar I has not been established. In the absence of head-to-head trials comparing all of them, an analysis combining direct and indirect evidence using Bayesian mixed treatment comparison (**MTC**) methods was undertaken.[2,3]

METHODS

As a result of the review, 16 RCTs were included. Trials with patients not stable at randomisation and those that randomised only responders to the treatment of interest were excluded. The trials included placebo and a variety of active treatments as controls, with lithium being the most common one.

Table 1 presents the network of evidence formed by the 8 treatment options object of comparison. Most treatments were linked to the rest of therapies via lithium and placebo control. Carbamazepine was linked only through lithium, olanzapine was linked also through valproate. The base-case analysis included number of relapses as reported by authors and number of patients analysed.

The MTC analysis considered a triple outcome measure (**manic**, **depressive** and "**all" relapses**) for which data is spread across trials. We borrowed strength from data reported on "all" relapses to inform the split manic/depressive relapse when this was not explicitly reported in the individual trials.

To enable indirect comparisons of all the comparators a meta-analysis of all the relapse rates from the RCTs was performed, jointly modelled as a logistic regression. Manic and depressive relapses were specifically modelled (x). The model has a regression-like structure with the response γ_i for trial arm i of study j receiving treatment k derived from a study specific 'baseline' term (μ_j), a treatment effect ($\beta_{x,k}$) and an error term (ε_i):

$$\gamma_i = \mu_j + \beta_{x,k} + \varepsilon_i$$

The model was implemented as a Bayesian hierarchical model using the specialist software WinBUGS. In each trial j we observe $r_{j,k}$ relapses for the comparator treaments k, in a sample of $n_{j,k}$. The likelihood takes the form of:

$$r_{j,k} \sim Bin\,(p_{x,k}\,,\, n_{j,k})$$

Treatment effects were modelled as a fixed treatment-effect model on the log-odds scale, additive to the baseline probability of relapse. Lithium was selected as the baseline treatment.

RESULTS

Table 2 summarises the results of the evidence synthesis in terms of the probability of having a manic, depressive or any type of relapse for the 8 maintenance treatments object of comparison. Results are presented using two different baseline risks, based on representative trials, for patients having experienced a pre-trial manic or depressive episode.

Table 2: Probability of relapse for patients according to type of pre-trial acute episode.

	Pre-trial depressive episode			Pre-trial manic episode		
	Posterior mean	2.5% Cr.I.	97.5% Cr.I.	Posterior mean	2.5% Cr.I.	97.5% Cr.I.
Type relapse: all						
Lithium	0.46	0.37	0.56	0.27	0.22	0.32
Placebo	0.80	0.62	1.0	0.57	0.46	0.69
Divalproex/Valproate	0.42	0.26	0.61	0.29	0.22	0.38
Imipramine	0.64	0.37	0.95	0.64	0.44	0.83
Lamotrigine	0.50	0.27	0.78	0.42	0.26	0.61
Olanzapine	0.58	0.40	0.75	0.23	0.16	0.31
Carbamazepine	0.84	0.51	1.0	0.66	0.30	1.0
Lithium + Imipramine	0.43	0.24	0.68	0.37	0.21	0.57
Type relapse: depression						
Lithium	0.38	0.29	0.47	0.07	0.05	0.10
Placebo	0.62	0.46	0.77	0.18	0.11	0.27
Divalproex/Valproate	0.31	0.17	0.49	0.05	0.03	0.09
Imipramine	0.29	0.13	0.50	0.05	0.02	0.12
Lamotrigine	0.33	0.15	0.55	0.06	0.02	0.13
Olanzapine	0.55	0.37	0.72	0.14	0.08	0.21
Carbamazepine	0.64	0.38	0.92	0.23	0.07	0.62
Lithium + Imipramine	0.28	0.12	0.49	0.05	0.02	0.11
Type relapse: mania						
Lithium	0.08	0.04	0.13	0.20	0.15	0.24
Placebo	0.18	0.08	0.32	0.38	0.29	0.48
Divalproex/Valproate	0.10	0.04	0.19	0.23	0.16	0.32
Imipramine	0.34	0.15	0.59	0.59	0.39	0.77
Lamotrigine	0.17	0.06	0.32	0.36	0.21	0.52
Olanzapine	0.03	0.01	0.06	0.08	0.05	0.12
Carbamazepine	0.24	0.05	0.57	0.43	0.17	0.76
Lithium + Imipramine	0.14	0.05	0.30	0.31	0.16	0.51

Cr.I. = Bayesian Credible Interval

Table 1: Treatment comparisons forming the network of evidence

Trial	Placebo	Lithium	Valproate	Lamotrogine	Olanzapine	Carbama-zepine	Imipramine	Imipramine + lithium
Bowden 2000	■	■	■					
Bowden 2003	■	■		■				
Calabrese 2000	■			■				
Fieve 1976	■	■						
Prien 1973	■	■					■	
Prien 1974	■	■						
Calabrese 2003	■	■		■				
Coxhead 1992		■				■		
Calabrese 2005		■	■					
Kane 1981		■						■
Kleindienst 2000		■				■		
Prien 1984		■					■	■
Simhandl 1993		■				■		
Tohen 2005		■			■			
Hartong 2003		■				■		
Altamura 2004			■		■			

References

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For depressive relapse, results indicate that for patients with a pre-trial acute depressive episode, the lowest probability of relapse is achieved by the combination lithium plus imipramine (0.28, 95% CrI 0.12-0.49), followed by imipramine monotherapy, valproate and lamotrigine with very similar results. The ranking of the treatments is the same for patients with a pre-trial manic episode.

Olanzapine shows the lowest probability of experiencing a manic relapse for patients with manic symptoms (0.08, 95% CrI 0.05-0.12), followed by lithium (0.20, 95% CrI 0.15-0.24) and valproate (0.23, 95% CrI 0.16-0.32). The ranking of treatments is the same for patients with a pre-trial depressive episode.

These results are reflected in the posterior probabilities that each treatment is best (Table 3).

Table 3: Percentage of relapse and posterior probability that each treatment is best

	Pre-trial depressive episode		Pre-trial manic episode	
	% Relapse	Probability best	% Relapse	Probability best
Type relapse: all				
Lithium	46.7	0.06	27.7	0.09
Placebo	80.8	0.0	57.2	0.0
Divalproex/Valproate	42.3	0.39	29.8	0.10
Imipramine	64.2	0.01	64.6	0.0
Lamotrigine	50.8	0.14	42.9	0.0
Olanzapine	58.5	0.01	23.2	0.74
Carbamazepine	84.7	0.0	66.5	0.0
Lithium + Imipramine	43.7	0.37	37.4	0.04
Type of relapse: depression				
Lithium	38.3	0.0	7.7	0.0
Placebo	62.2	0.0	18.6	0.0
Divalproex/Valproate	31.9	0.16	5.9	0.19
Imipramine	29.5	0.29	5.6	0.30
Lamotrigine	33.4	0.19	6.6	0.16
Olanzapine	55.1	0.0	14.5	0.0
Carbamazepine	64.0	0.0	23.1	0.0
Lithium + Imipramine	28.9	0.32	5.4	0.33
Type of relapse: mania				
Lithium	8.3	0.0	20.0	0.0
Placebo	18.7	0.0	38.6	0.0
Divalproex/Valproate	10.4	0.0	23.9	0.0
Imipramine	34.7	0.0	59.0	0.0
Lamotrigine	17.4	0.0	36.3	0.0
Olanzapine	3.4	0.99	8.6	0.99
Carbamazepine	24.1	0.0	43.9	0.0
Lithium + Imipramine	14.8	0.0	31.9	0.0

For the prevention of a manic relapse, independently of the existence of previous symptoms, olanzapine was by far the best treatment option (0.99). For the prevention of a depressive relapse, lithium and imipramine showed the highest probability of being the best (0.32, 0.33), followed closely by imipramine (0.29, 0.30) and lamotrigine (0.19, 0.16).

For the prevention of any type of relapse, results differed between groups of patients: valproate (0.39) and lithium plus imipramine (0.37) were the best options for patients with depressive symptoms, whilst olanzapine (0.74) and valproate (0.10) were the best for patients with manic symptoms.

CONCLUSIONS

Most systematic reviews focus on pair-wise, direct comparisons of treatments, which makes it difficult to draw an overall conclusion about which treatment is best when several possible treatments are available. The use of MTC methods allowed us to form an internally consistent summary of the relative effects of the 8 drugs under comparison, and also obtain the posterior probability of each drug being the best (i.e. lowest relapse). Meta-analyses comparing simultaneously multiple treatments are feasible, the combination of all available data using MTC methods allows relevant treatments to be compared while respecting randomisation, providing the efficacy parameter estimates required to inform cost-effectiveness analysis.

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