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Review article

Lamotrigine for treatment of bipolar depression: independent meta-analysis and meta-regression of individual patient data from five randomised trials

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Background
There is uncertainty about the efficacy of lamotrigine in bipolar depressive episodes.

Aims
To synthesise the evidence for the efficacy of lamotrigine in bipolar depressive episodes.

Method
Systematic review and meta-analysis of individual patient data from randomised controlled trials comparing lamotrigine with placebo.

Results
Individual data from 1072 participants from five randomised controlled trials were obtained. More individuals treated with lamotrigine than placebo responded to treatment on both the Hamilton Rating Scale for Depression (HRSD) (relative risk (RR)=1.27, 95% CI 1.09–1.47, P=0.002) and Montgomery–Åsberg Depression Rating Scale (MADRS) (RR=1.22, 95% CI 1.06–1.41, P=0.005). There was an interaction (P=0.04) by baseline severity of depression: lamotrigine was superior to placebo in people with HRSD score >24 (RR=1.47, 95% CI 1.16–1.87, P=0.001) but not in people with HRSD score ⩽24 (RR=1.07, 95% CI 0.90–1.27, P=0.445).

Conclusions
There is consistent evidence that lamotrigine has a beneficial effect on depressive symptoms in the depressed phase of bipolar disorder. The overall pool effect was modest, although the advantage over placebo was larger in more severely depressed participants.

Declaration of Interest
J.R.C. is a member of the psychiatry advisory board for GlaxoSmithKline. J.R.G. is Chief Investigator and G.M.G. is a co-investigator on the independent Medical Research Council-funded trial: Comparative Evaluation of QUEtiapine-Lamotrigine combination *v.* quetiapine monotherapy (and folic acid *v.* placebo) in people with bipolar depression (CEQUEL).

Bipolar disorder is among the top causes of worldwide disability and is characterised by both depressive and manic episodes.[1] The depressive symptoms are now recognised to be the predominant cause of disability in the long term for most people with bipolar disorder.[2–4] Prior to 1999, the treatment of bipolar depression had been little studied and there was uncertainty about the treatment of this phase of the disorder. There have long been concerns about the risk of mood destabilisation with antidepressant drugs and there remains uncertainty about efficacy. A meta-analysis found some evidence for efficacy[5] but a subsequent large trial conducted as part of the National Institute of Mental Health funded Systematic Treatment Enhancement Program for Bipolar Disorder (NIMH STEP–BD) found no evidence of benefit for adjunctive therapy with bupropion or paroxetine.[6]

Recent guidelines have suggested a role for lamotrigine, an inhibitor of voltage-sensitive sodium channels in the acute treatment of bipolar depression. Lamotrigine is only licensed in the USA by the Food and Drug Administration and in some European countries for prevention of relapse in bipolar disorder.[7] None the less, it is already in common clinical use for bipolar disorder, particularly in the USA.[8] Although the evidence for the long-term efficacy of lamotrigine is reasonably robust, the five pivotal trials in acute phase therapy have been reported as individually neutral, with no statistically significant benefit from lamotrigine.[9] This apparent lack of acute efficacy sits rather uncomfortably beside evidence for efficacy for relapse prevention. Although lamotrigine may indeed be ineffective in the acute phase, it is possible that the therapeutic effect size of lamotrigine may be smaller than predicted and that the acute trials were consequently underpowered. It is also possible that the need to increase the dose of lamotrigine gradually may have made detection of the acute therapeutic effect more difficult or that any positive effects are confined to a subgroup of individuals and not observable in the full trial samples.

Meta-analysis can increase the statistical power for analysis of the available randomised data. Data can be combined in a variety of ways: pooling individual participant data from several trials is the most informative for meta-analysis because it allows investigation of potential differential effects across participant subgroups.[10,11] We report a meta-analysis of the individual participant data from the five trials conducted by GlaxoSmithKline investigating the efficacy of lamotrigine in acute bipolar depression.

Method

Inclusion criteria

We included all the randomised controlled trials conducted by GlaxoSmithKline comparing lamotrigine with placebo in bipolar depression (online Table DS1 and Table 1).

Search strategy

To identify any additional randomised trials, we conducted a search of electronic databases including MEDLINE, EMBASE, CINAHL, PsycINFO, CENTRAL (online Appendix DS1).

Table 1 Participant characteristics of included trials[a]

	Study 1 GW602/SCAB2001	Study 2 GW603/SCAA2010	Study 3 SCA40910	Study 4 SCA10022	Study 5 SCA30924
Age, years: mean (s.d.)					
Lamotrigine	42.2 (11.5)	40.5 (11.3)	37.6 (12.6)	38.1 (11.5)	40.5 (12.5)
Placebo	42.4 (12.7)	40.9 (11.2)	37.3 (11.5)	36.5 (11.9)	38.2 (12.1)
White ethnicity, *n* (%)					
Lamotrigine	57 (90)	90 (87)	113 (88)	70 (64)	94 (74)
Placebo	62 (94)	89 (86)	99 (84)	82 (75)	84 (69)
Female, *n* (%)					
Lamotrigine	35 (56)	66 (64)	74 (57)	70 (64)	69 (54)
Placebo	39 (59)	61 (59)	62 (53)	69 (63)	66 (54)
Duration of current episode, weeks: *n* (%)					
Lamotrigine					
⩽24	49 (78)	79 (77)	104 (81)	76 (70)	83 (65)
>24	14 (22)	24 (23)	25 (19)	33 (30)	43 (34)
Placebo					
⩽24	47 (71)	79 (77)	91 (77)	83 (76)	70 (58)
>24	19 (29)	24 (23)	27 (23)	26 (24)	52 (43)
Intensity of depression based on SCID, *n* (%)					
Lamotrigine					
Mild	2 (3)	8 (8)	0	0	0
Moderate	34 (54)	66 (64)	91 (71)	75 (69)	58 (46)
Severe	27 (43)	29 (28)	38 (29)	34 (31)	69 (54)
Placebo					
Mild	0	6 (6)	0	0	0
Moderate	40 (61)	75 (73)	80 (68)	74 (68)	55 (45)
Severe	26 (39)	22 (21)	38 (32)	35 (32)	67 (55)
Suicide ever attempted, *n* (%)					
Lamotrigine	20 (32)	33 (32)	50 (39)	33 (30)	50 (39)
Placebo	24 (36)	38 (37)	32 (27)	25 (23)	50 (41)

SCID, Structured Clinical Interview for DSM-IV.
a. Numbers may be less than total randomised (see online Table DS1) owing to missing observations.

Data analysis

Individual patient data-sets were compiled from the five GlaxoSmithKline-sponsored trials comparing lamotrigine with placebo. Analyses were of the full intention-to-treat trial populations. The last available observation was used for participants who withdrew from the trial before the end of the study. The *a priori* data analysis plan included analyses of both categorical and continuous outcomes. Trial-specific estimates of the relative risks of response (>50% reduction in baseline score on Hamilton Rating Scale for Depression[13] (HRSD) and Montgomery–Åsberg Depression Rating Scale[14] (MADRS)) and remission (<8 on HRSD and <12 on MADRS) were calculated and pooled using the Mantel–Haenszel fixed effect approach in metan in STATA version 9. The number needed to treat (NNT) was estimated from the inverse of the weighted mean absolute difference in event rates. For continuous measures, separate ANCOVA analyses were conducted of final score (adjusted for baseline) and then pooled using metan.

A planned subgroup analysis was conducted to investigate whether the treatment effect differed between (a) individuals with bipolar I and bipolar II disorder and (b) individuals with severe depressive illness and moderate illness at randomisation. As there is no universally accepted cut point for the HRSD,[15] we dichotomised the sample around the mean baseline score in the trials. We used meta-regression for the subgroup analysis which is a method that allows the investigation of whether any particular covariates are related to the observed study-specific treatment effects.[16] In STATA, the metareg command uses a random effects iterative method to provide a restricted maximum likelihood estimate of the regression parameters (with their asymptotic variances) and the residual heterogeneity variance.[17] Meta-regression can be a powerful technique but its use in aggregated data is limited to the investigation of study-level variables. The use of individual patient data allows more informative meta-regression analyses of trial data because precisely defined subgroup analyses can be conducted applying consistent definitions across trials.

Discontinuation rates

As a measure of overall acceptability, discontinuation rates from the study arms were compared in each trial using relative risks and pooled using the Mantel–Haenszel fixed effect approach in metan in STATA version 9.

Results

There were five randomised controlled trials (total 1072 participants) conducted by GlaxoSmithKline to compare lamotrigine with placebo in bipolar disorder. Summary details of the trials are presented in online Table DS1 and Table 1, and are reported in detail elsewhere.[9] All five trials compared lamotrigine monotherapy with placebo. Individuals were only included if they had discontinued any other psychoactive drug at least five elimination half-lives before trial entry. Prior treatment with lamotrigine was an exclusion criterion in all trials. Three trials (GW602/SCAB2001, SCA40910, SCA30924) included only people with bipolar I disorder, one trial (SCA10022) included only people with bipolar II disorder and one trial (GW603/SCAA2010) included people with both bipolar I and II disorder. Duration of the trial varied from 7 to 10 weeks. Lamotrigine dose was 50 mg or

200 mg in GW602/SCAB2001, flexible 100–400 mg in GW603/SCAA2010 and 200 mg in SCA40910, SCA30924 and SCA10022. After the initial result from GW602/SCAB2001, the 50 mg dose was considered too low and so was not included in the other trials. We did not therefore include the 50 mg arm in the meta-analysis.

Two non-GlaxoSmithKline sponsored trials were also identified.[18,19] As individual patient-level data were not available from these trials, and the protocols differed substantially from the GlaxoSmithKline trials, these were not included in the main analysis. Both trials, however, reported substantial and statistically significant benefits with lamotrigine compared with placebo; in one case, in combination with lithium.[17]

Primary outcomes

Individuals treated with lamotrigine were more likely to respond to treatment than those treated with placebo on both HRSD (Fig. 1(a)) (pooled RR=1.27, 95% CI 1.09–1.47, heterogeneity χ^2=1.80, d.f.=4 P=0.772, test of RR=1, z=3.13, P=0.002) and MADRS (Fig. 1(b)) (pooled RR=1.22, 95% CI 1.06–1.41, heterogeneity χ^2=3.12, d.f.=4, P=0.538, test of RR=1, z=2.80, P=0.005). The NNT to achieve one more response than would have been observed on placebo was 11 (95% CI 7–25) on HRSD and 13 (95% CI 7–33) on MADRS. Remission rates were not statistically significantly higher for lamotrigine on HRSD (pooled RR=1.10,

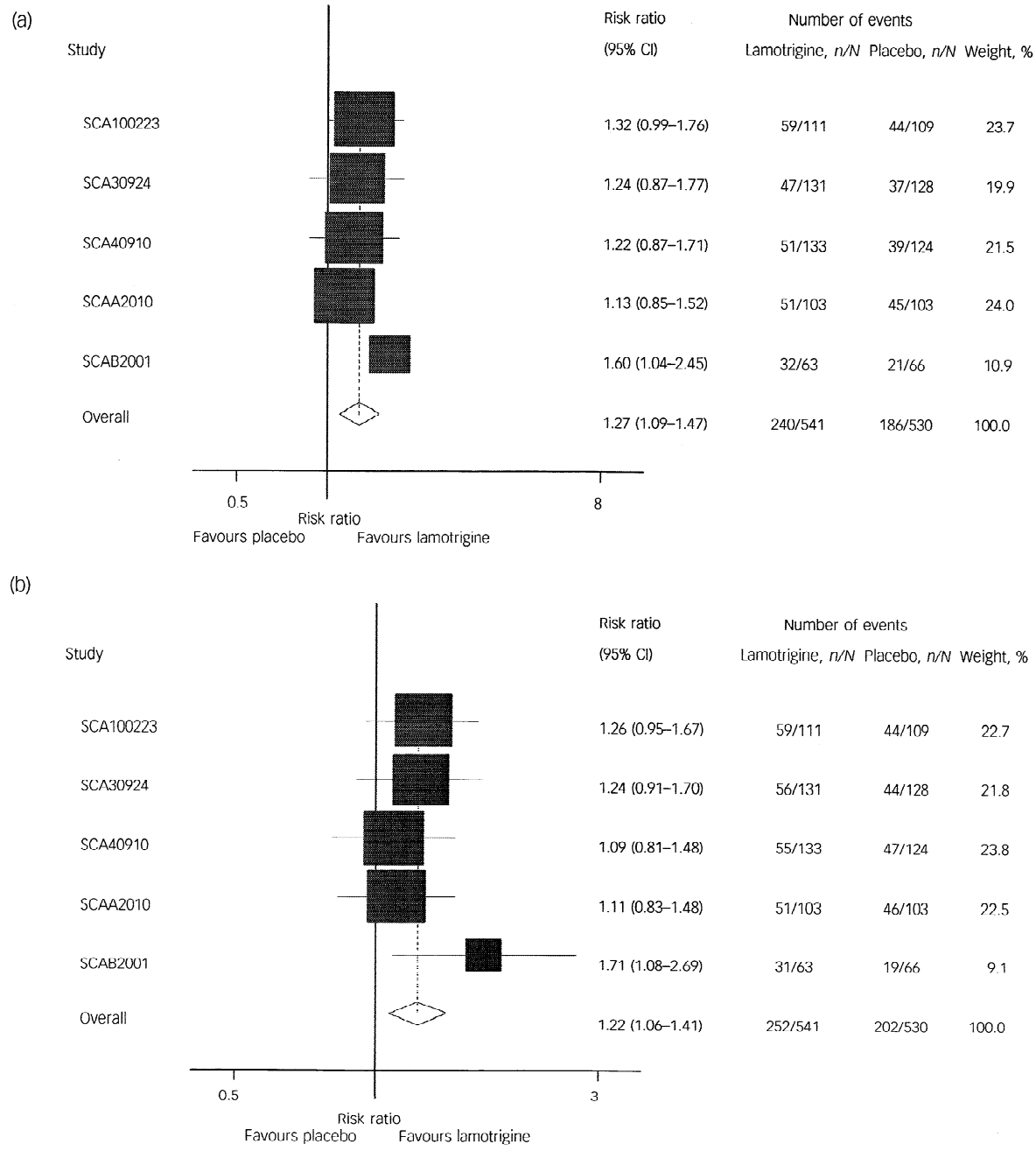

Fig. 1 Lamotrigine compared with placebo: meta-analysis of randomised trials: (a) >50% reduction on Hamilton Rating Scale for Depression and (b) >50% reduction on Montgomery–Åsberg Depression Rating Scale.

95% CI 0.90–1.36, heterogeneity χ^2=9.03, d.f.=4, *P*=0.060, test of RR=1, *z*=0.93, *P*=0.351) but were on MADRS (pooled RR=1.21, 95% CI 1.03–1.42, heterogeneity χ^2=5.86, d.f.=4, *P*=0.210, test of RR=1, *z*=2.30, *P*=0.021).

On continuous symptom measures, the weighted mean difference on MADRS was −1.43 (95% CI −2.80 to −0.06, *P*=0.04) and −1.01 (95% CI −2.17 to 0.14, *P*=0.084) on HRSD. The standardised mean difference on MADRS was −0.12 (95% CI −0.24 to −0.00, *P*=0.04) and −0.11 (95% CI −0.23 to 0.01, *P*=0.084) on HRSD.

Discontinuation rates

Discontinuation rates for each study are shown in online Table DS1. Overall, there was no difference between lamotrigine and placebo (RR=1.02, 95% CI 0.93–1.11, *P*=0.731, heterogeneity χ^2=4.95, d.f.=4, *P*=0.292).

Subgroup analyses

Diagnostic subgroup

There was no statistically significant interaction (regression coefficient −0.06, 95% CI −0.35 to 0.24, *P*=0.705) between diagnostic subgroup and treatment effect (bipolar type I RR=1.24, 95% CI 1.04–1.46; bipolar type II RR=1.15, 95% CI 0.90–1.47).

Baseline severity of depression

The mean HRSD score at randomisation was 24.37 (s.d.=3.83, range 18–37). We therefore dichotomised the HRSD at ⩽24 and >24. There was a significant interaction by severity of depressive symptoms at randomisation (regression coefficient=0.30, 95% CI 0.14–0.60, *P*=0.04). Lamotrigine was superior to placebo in individuals with severe depressive symptoms at randomisation (baseline HRSD score >24, RR=1.47, 95% CI 1.16–1.87, *P*=0.001, NNT=7, 95% CI 4–17) but not in people with moderate symptom severity (RR=1.07, 95% CI 0.90–1.27, *P*=0.445) (Fig. 2). This interaction was replicated in a secondary meta-regression using the continuous MADRS score as the independent variable (regression coefficient=3.99, 95% CI 1.02–6.94, *P*=0.008). Lamotrigine was superior to placebo in individuals with severe depressive symptoms at randomisation (baseline HRSD score >24, standardised mean difference=−0.24, 95% CI −0.42 to −00.06, *P*=0.011) but not in those with moderate symptom severity (standardised mean difference=−0.02, 95% CI −0.19 to 0.14, *P*=0.442).

In the severe group, the response to lamotrigine rate was 110/242 (45.5%) compared with 71/236 (30.1%) in the placebo group. In the moderate group, the response to lamotrigine rate was 142/299 (47.5%) compared with 131/294 (44.6%) in the placebo group. Thus, the interaction by severity was because of a higher response rate in the moderately ill placebo-treated group, rather than, for example, a higher response rate in the severely ill lamotrigine-treated group.

Discussion

Meta-analysis of the individual patient data from five manufacturer-sponsored randomised trials found consistent evidence of an overall modest benefit for lamotrigine. About 11 people would need to be treated to achieve one more response

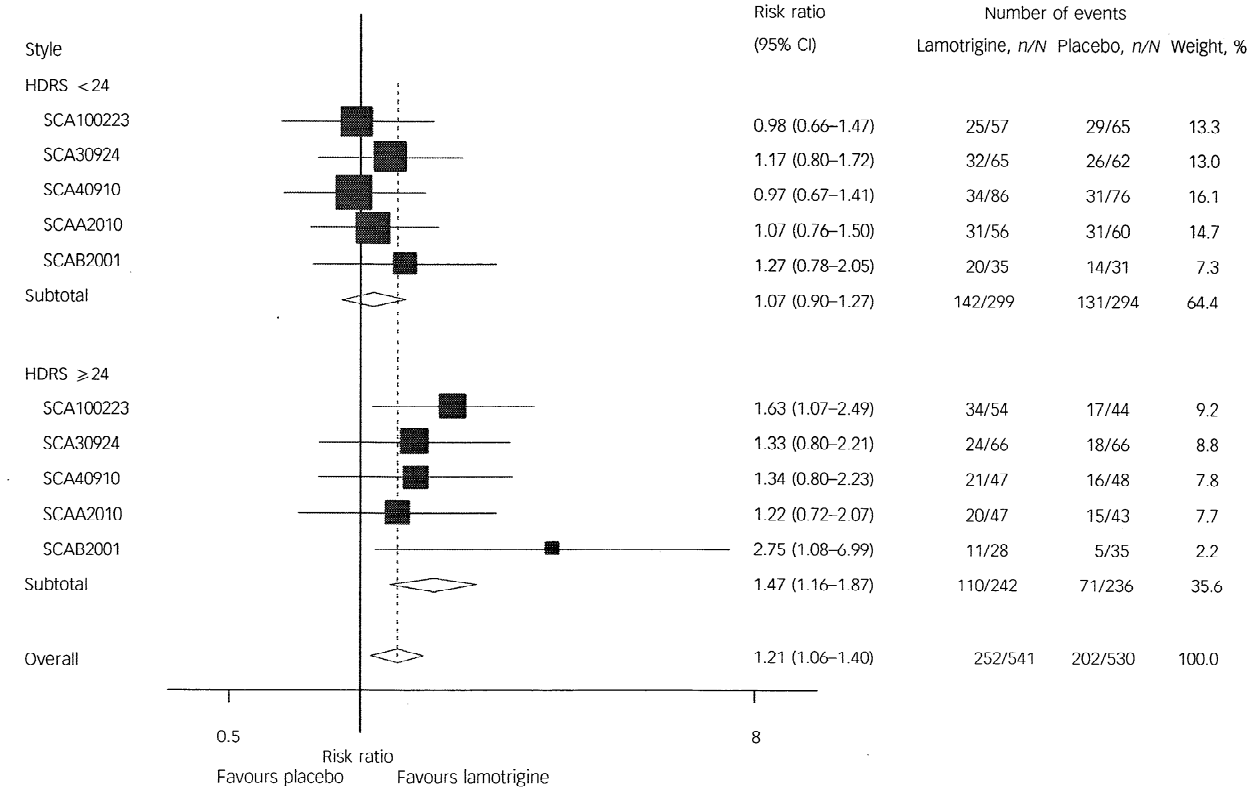

Fig. 2 Randomised trials comparing lamotrigine with placebo stratified by baseline severity of Hamilton Rating Scale for Depression (17-item version).

than would be achieved on placebo: this is at the margins of being clinically worthwhile. The magnitude of the treatment effect in the main analysis was reduced by the high placebo response rate in the moderately ill subgroup of participants. Consequently, the treatment effect appears to be more substantial in participants who are more severely ill (NNT=7) but the actual response rate on lamotrigine is very similar in both subgroups.

As with all quantitative reviews, this review is subject to a number of limitations. Publication bias, or the tendency for trials with negative or neutral findings not to be published, can seriously limit the reliability of meta-analysis. Moreover, studies from which individual data can be obtained may not represent an unbiased sample of all the trials. In this analysis, the bipolar depression trials included in the main analysis are the total of the acute studies conducted by GlaxoSmithKline, the manufacturer of lamotrigine. There is some evidence that trials conducted by the manufacturer of a drug may be more likely to detect and report results that favour their drug,[20] but this is not the case here. Indeed, our search revealed two trials[18,19] conducted independently of GlaxoSmithKline that both reported substantial benefits with lamotrigine compared with placebo in acute bipolar depression. This probably increases the confidence that we can have in the overall results.

This review was highly focused on the effect of lamotrigine on depressive symptoms and we did not request access to data on specific adverse events. Withdrawal rates were similar for participants allocated to lamotrigine and placebo. A comprehensive analysis of the rates of adverse events in these trials has been recently published.[9] The most common adverse events were headache and nausea.[9] The incidence of non-serious rash was low and there were no reports of serious rash in any of the five trials.

The finding of an interaction between the severity of depressive symptoms at randomisation and the size of the treatment effect appeared to be because of a larger placebo response in individuals who are less severely ill. This suggests that the finding should be interpreted cautiously clinically as it probably does *not* mean that only people who are severely ill are likely to respond to lamotrigine. The finding is, however, of considerable methodological importance, especially for the design of placebo-controlled monotherapy trials. Although there is still some consensus that placebo-controlled trials are required for regulatory purposes,[21] a number of artefacts and biases (such as inflation of baseline scores to meet eligibility criteria) can result from the difficulties of conducting placebo-controlled trials when existing standard treatments are available.[15,22] These problems can inflate placebo response making it difficult to detect drug effects but they are often overlooked in the interpretation of the results of such trials. We believe that our results suggest that it is essential to ensure a reliable and sufficient severity of illness at baseline in participants in clinical trials to minimise such artefacts. This methodological challenge is likely to increase in importance because the increasing number of drugs for which an indication for bipolar disorder is being sought has made recruitment of more participants who are severely ill into placebo-controlled trials in bipolar disorder more difficult.[23] Although placebo control remains a regulatory requirement for the development of new antidepressants, an adequate severity of symptoms at the point of randomisation will remain a challenging prerequisite for success.

There was no difference in response to lamotrigine between bipolar disorder type I and II subgroups. This parallels the findings in the BOLDER (BipOLar DepRession) trials of quetiapine.[24,25] and supports the idea that depressive episodes arising in an illness course characterised by mania or hypomania are probably very similar in terms of treatment response.

The effect of lamotrigine compared with placebo only became statistically significant when data from five randomised controlled trials were pooled by meta-analysis. This might mean that the true effect of lamotrigine is too small to be reliably detected by individual studies and, possibly, too small to be clinically important. However, the interaction by baseline severity suggests that the trial may actually have underestimated the true efficacy of lamotrigine. It is worth noting that a simple 'vote counting' analysis (as is often used by regulatory authorities) would fail to quantify the treatment effect at all. None of the individual trials reported a statistically significant effect on the primary outcome:[9] this meta-analysis suggests that there is a modest but consistent effect across the trials. The current regulatory approach of requiring two 'successful' pivotal trials may encourage the conduct of multiple, underpowered trials. Conversely, there may be an unjustified focus on unrepresentatively large effects from one or two trials that meet criteria for statistical significance, ignoring (and failing to publish) any trials that do not produce a statistically significant result.[26,27] The vote-counting approach does not make the most efficient or reliable use of the total randomised data and routinely risks bias in the estimation of true treatment effects. In this case, vote counting would have failed to detect a positive treatment effect of uncertain clinical significance.

Finally, in addition to their clear methodological importance, the results of this meta-analysis are potentially of clinical importance for people with bipolar disorder and their doctors because they provide some solid empirical support for a commonly used drug treatment in a disorder with few proven therapies. It suggests that lamotrigine may be an effective treatment for acute bipolar depression arising in a bipolar disorder of type I or II as well as for prevention of relapse. Further trials are warranted to clarify the size of the treatment effect of lamotrigine both as monotherapy and in combination: the ongoing CEQUEL (Comparative Evaluation of QUEtiapine–Lamotrigine combination *v.* quetiapine monotherapy (and folic acid *v.* placebo) in people with bipolar depression) trial will provide further knowledge of the effectiveness of lamotrigine as add-on therapy to quetiapine in 'real world' people with bipolar disorder (www.cequel.org).

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References

1 Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. *Lancet* 1997; **349**: 1436–42.

2 Judd LL, Akiskal HS, Schettler PJ, Coryell W, Endicott J, Maser JD, et al. A prospective investigation of the natural history of the long-term weekly

symptomatic status of bipolar II disorder. *Arch Gen Psychiatry* 2003; **60**: 261–9.

3 Judd LL, Akiskal HS, Schettler PJ, Endicott J, Maser J, Solomon DA, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry* 2002; **59**: 530–7.

4 Kupfer DJ, Frank E, Grochocinski VJ, Luther JF, Houck PR, Swartz NA, et al. Stabilization in the treatment of mania, depression and mixed states. *Acta Neuropsychiatrica* 2000; **12**: 110–4.

5 Gijsman HJ, Geddes JR, Rendell JM, Nolen WA, Goodwin GM. Antidepressants for bipolar depression: a systematic review of randomized, controlled trials. *Am J Psychiatry* 2004; **161**: 1537–47.

6 Sachs GS, Nierenberg AA, Calabrese JR, Marangell LB, Wisniewski SR, Gyulai L, et al. Effectiveness of adjunctive antidepressant treatment for bipolar depression. *N Engl J Med* 2007; **356**: 1711–22.

7 American Psychiatric Association. Practice guideline for the treatment of patients with bipolar disorder (revision). *Am J Psychiatry* 2002; **159** (suppl 4): 1–50.

8 Marangell LB, Martinez JM, Ketter TA, Bowden CL, Goldberg JF, Calabrese JR, et al; for the STEP-BD Investigators. Lamotrigine treatment of bipolar disorder: data from the first 500 patients in STEP-BD. *Bipolar Disord* 2004; **6**: 139–43.

9 Calabrese JR, Huffman RF, White RL, Edwards S, Thompson TR, Ascher JA, et al. Lamotrigine in the acute treatment of bipolar depression: results of five double-blind, placebo-controlled clinical trials. *Bipolar Disord* 2008; **10**: 323–33.

10 Stewart LA, Clarke MJ. Practical methodology of meta-analyses (overviews) using updated individual patient data. Cochrane Working Group. *Stat Med* 1995; **14**: 2057–79.

11 Clarke MJ, Stewart LA. Obtaining data from randomised controlled trials: how much do we need for reliable and informative meta-analyses? *BMJ* 1994; **309**: 1007–10.

12 First MB, Gibbon M, Spitzer RL, Williams JBW. *Structured Clinical Interview for DSM–IV Axis I Disorders Research Version (SCID–I)*. Biometric Research, New York State Psychiatric Institute, 1996.

13 Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960; **23**: 56–62.

14 Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979; **134**: 382–9.

15 National Collaborating Centre for Mental Health. *Depression: Management of Depression in Primary and Secondary Care*. National Institute for Health and Clinical Excellence, 2004 (http://www.nice.org.uk/page.aspx?o=235213).

16 Thompson SG, Higgins JPT. How should meta-regression analyses be undertaken and interpreted? *Stat Med* 2002; **21**: 1559–73.

17 Sharp SJ. Meta-analysis regression. *Stata Technic Bull* 1998; **42**: 16–22.

18 Frye MA, Ketter TA, Kimbrell TA, Dunn RT, Speer AM, Osuch EA, et al. A placebo-controlled study of lamotrigine and gabapentin monotherapy in refractory mood disorders. *J Clin Psychopharmacol* 2000; **20**: 607–14.

19 van der Loos M, Nolen WA, Vieta E. Lamotrigine as add-on to lithium in bipolar disorder. *Bipolar Disord* 2007; **9** (suppl 1): 107.

20 Montaner JS, O'Shaughnessy MV, Schechter MT. Industry-sponsored clinical research: a double-edged sword. *Lancet* 2002; 358: 1893–5.

21 Charney DS, Nemeroff CB, Lewis L, Laden SK, Gorman JM, Laska EM, et al. National Depressive and Manic-Depressive Association consensus statement on the use of placebo in clinical trials of mood disorders. *Arch Gen Psychiatry* 2002; **59**: 262–70.

22 Geddes JR, Cipriani A. Selective serotonin reuptake inhibitors. *BMJ* 2004; **329**: 809–10.

23 Calabrese JR, Rapport DJ, Shelton MD, Kimmel SE. Evolving methodologies in bipolar disorder maintenance research. *Br J Psychiatry* 2001; **178** (suppl 41): s157–63.

24 Calabrese JR. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. *Am J Psychiatry* 2005; **162**: 1351–60.

25 Thase ME, Macfadden W, Weisler RH, Chang W, Paulsson B, Khan A, et al; for the BOLDER II Study Group. Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo-controlled study (the BOLDER II study). *J Clin Psychopharmacol* 2006; **26**: 600–9.

26 Chalmers TC, Lau J. Meta-analytic stimulus for changes in clinical trials. *Stat Methods Med Res* 1993; **2**: 161–72.

27 Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR. Publication bias in clinical research. *Lancet* 1991; **337**: 867–72.