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

John R. Geddes, Joseph R. Calabrese and Guy M. Goodwin

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 QuEtapine-Lamotrigine combination v. quetapine 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 efficacy5 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.8

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

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

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 Depression13 (HRSD) and Montgomery–Åsberg Depression Rating Scale14 (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. 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 $\chi^2=1.80$, 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 $\chi^2=3.12$, 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, 95% CI 0.97–1.25, test of RR=1, $z=1.61$, $P=0.107$) but were statistically significantly higher on MADRS (pooled RR=1.47, 95% CI 1.34–1.61, test of RR=1, $z=4.19$, $P<0.001$).

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk ratio (95% CI)</th>
<th>Number of events</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCA100223</td>
<td>1.26 (0.95–1.67)</td>
<td>59/111</td>
<td>44/109</td>
</tr>
<tr>
<td>SCA30924</td>
<td>1.42 (0.91–1.70)</td>
<td>56/131</td>
<td>44/128</td>
</tr>
<tr>
<td>SCA40910</td>
<td>1.09 (0.81–1.48)</td>
<td>55/133</td>
<td>47/124</td>
</tr>
<tr>
<td>SCAA2010</td>
<td>1.11 (0.83–1.48)</td>
<td>51/103</td>
<td>46/103</td>
</tr>
<tr>
<td>SCAB2001</td>
<td>1.71 (1.08–2.69)</td>
<td>31/63</td>
<td>19/66</td>
</tr>
<tr>
<td>Overall</td>
<td>1.22 (1.06–1.41)</td>
<td>252/541</td>
<td>202/530</td>
</tr>
</tbody>
</table>

**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 $\chi^2=9.03$, 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 $\chi^2=5.86$, d.f.=4, $P=0.210$, test of RR=1, $z=2.20$, $P=0.021$).

On continuous symptom measures, the weighted mean difference on MADRS was $-1.43$ (95% CI $-2.80$ to $-0.06$, $P=0.004$) 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 $\chi^2=4.95$, 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 $\leq 24$ 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=0.39, 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 $-0.06$, $P=0.011$) 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
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, 21 but this is not the case here. Indeed, our search revealed two trials 26,27 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.28 The most common adverse events were headache and nausea.29 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,30 a number of artefacts and biases (such as some consensus that placebo-controlled trials are required for 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 in 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).

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 may actually have underestimated the true efficacy of lamotrigine.

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 as mono- or combination therapy; 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).

The randomised trials included in this analysis were conducted and funded by GlaxoSmithKline, who provided raw data-sets for independent analysis by the authors. J.R.G. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. This analysis was initiated entirely by the authors. No additional support, either scientific or pecuniary, was provided by GlaxoSmithKline. We are grateful to Walter Pastak and Gary Evoniuk of GlaxoSmithKline for their assistance in accessing the individual patient data and for their comments on a draft of the manuscript. We are grateful to Ly-mee Yu and Will Stevens of the Oxford Clinical Trial Unit for Mental Illness for help with the analysis of the continuous data and data processing, and Sarah Stockton of the Centre for Evidence-Based Mental Health for designing and implementing the search strategy.
Table DS1  Summary table of trials included in individual patient data meta-analysis

<table>
<thead>
<tr>
<th>Study 1</th>
<th>Study 2</th>
<th>Study 3</th>
<th>Study 4</th>
<th>Study 5</th>
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<tr>
<td>Protocol numbers</td>
<td>GW602/SCAB2001</td>
<td>GW603/SCAA2010</td>
<td>SCA40910</td>
<td>SCA10022</td>
</tr>
<tr>
<td>Participants</td>
<td>Bipolar disorder, type I</td>
<td>Bipolar disorder, type I or II</td>
<td>Bipolar disorder, type I</td>
<td>Bipolar disorder, type II</td>
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<td>Inclusion criteria</td>
<td>HRSD (17 item) ≥ 18 MDE duration 2 weeks to 12 months ≥2 mood episodes in previous 10 years (at least one manic/mixed)</td>
<td>HRSD (17 item) ≥ 18 MDE duration 2 weeks to 12 months if bipolar disorder I ≥2 mood episodes in previous 10 years (at least one manic/mixed) If bipolar disorder II at least one depressive and two hypomanic episodes in previous 10 years</td>
<td>HRSD (17 item) ≥ 18 MDE duration &gt;8 weeks ≥2 mood episodes in previous 10 years (at least one manic/mixed) ≥3 on either HRSD item 1 or 7 at screen and baseline</td>
<td>HRSD (17 item) ≥ 18 MDE duration &gt;8 weeks History of full or partial hospitalisation for a mood episode</td>
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<td>Exclusion criteria</td>
<td>Pregnant, lactating or at risk of becoming pregnant Actively suicidal Rapid cycling (DSM-IV) Epilepsy Abnormal TFTs Panic disorder, bulimia nervosa, obsessive–compulsive disorder, social phobia in 12 months before entry Prior treatment with lamotrigine New course of psychotherapy Any psychoactive drug within 5 half-lives Investigational drug within 30 days</td>
<td>Pregnant, lactating or at risk of becoming pregnant Actively suicidal Rapid cycling (DSM-IV) Epilepsy Abnormal TFTs Panic disorder, bulimia nervosa, obsessive–compulsive disorder, social phobia in 12 months before entry</td>
<td>Pregnant, lactating or at risk of becoming pregnant Actively suicidal Rapid cycling (DSM-IV) Epilepsy Abnormal TFTs Panic disorder, bulimia nervosa, obsessive–compulsive disorder, social phobia in 12 months before entry</td>
<td>Pregnant, lactating or at risk of becoming pregnant Actively suicidal Rapid cycling (DSM-IV) Epilepsy Abnormal TFTs Panic disorder, bulimia nervosa, obsessive–compulsive disorder, social phobia in 12 months before entry</td>
</tr>
<tr>
<td>Treatments and daily dose</td>
<td>Lamotrigine 50 mg or 200 mg (only 200 mg arm included in current analysis) Placebo</td>
<td>Lamotrigine 100–400 mg Placebo</td>
<td>Lamotrigine 200 mg Placebo</td>
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<tr>
<td>Titration schedule for lamotrigine, daily dose</td>
<td>For 200-mg group: Weeks 1 &amp; 2: 25 mg Weeks 3 &amp; 4: 50 mg Week 5: 100 mg Week 6: flexible (100–200 mg) Week 7: flexible (100–300 mg) Weeks 8–10: flexible (100–400 mg)</td>
<td>For 200-mg group: Weeks 1 &amp; 2: 25 mg Weeks 3 &amp; 4: 50 mg Week 5: 100 mg Week 6: flexible (100–200 mg) Week 7: flexible (100–300 mg) Weeks 8–10: flexible (100–400 mg)</td>
<td>For 200-mg group: Weeks 1 &amp; 2: 25 mg Weeks 3 &amp; 4: 50 mg Week 5: 100 mg Week 6: 200 mg</td>
<td>For 100–400-mg group: Weeks 1 &amp; 2: 25 mg Weeks 3 &amp; 4: 50 mg Week 5: 100 mg Week 6: 200 mg Weeks 7: 200 mg</td>
</tr>
<tr>
<td>Number randomised and included</td>
<td>129 total: Lamotrigine 200 mg (n=63) Placebo (n=66)</td>
<td>206 total: Lamotrigine 100–400 mg (n=103; bipolar disorder I=61; bipolar disorder II=41) Placebo (n=103; bipolar disorder I=61; bipolar disorder II=41)</td>
<td>257 total: Lamotrigine 200 mg (n=133) Placebo (n=124)</td>
<td>221 total: Lamotrigine 200 mg (n=111) Placebo (n=109; no post-randomisation primary outcome in 1 participant)</td>
</tr>
</tbody>
</table>
### Table DS1 (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Study 2</th>
<th>Study 3</th>
<th>Study 4</th>
<th>Study 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study completion rate</td>
<td>Lamotrigine: 71% Placebo: 71%</td>
<td>Lamotrigine: 66% Placebo: 67%</td>
<td>Lamotrigine: 61% Placebo: 73%</td>
<td>Lamotrigine: 73% Placebo: 67%</td>
</tr>
<tr>
<td>Duration of double-blind treatment</td>
<td>7 weeks</td>
<td>10 weeks</td>
<td>8 weeks</td>
<td>8 weeks</td>
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<tr>
<td>Primary outcome</td>
<td>17-item HRSD</td>
<td>17-item HRSD</td>
<td>MADRS</td>
<td>MADRS</td>
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<tr>
<td>Secondary outcomes</td>
<td>HRSD item 1, 31-item HRSD, MADRS, CGI–S, CG–I</td>
<td>HRSD item 1, 31-item HRSD, MADRS, CGI–S, CG–I</td>
<td>HRSD item 1, 17-item HRSD, 31-item HRSD, CGI–S, CG–I</td>
<td>HRSD item 1, 17-item HRSD, 31-item HRSD, CGI–S, CG–I</td>
</tr>
</tbody>
</table>

CG–I, Clinical Global Impression–Improvement; CGI–S, Clinical Global Impression–Severity; HRSD, Hamilton Rating Scale for Depression Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; MDE, major depressive episode; TFT, thyroid function test.

### References


### Search history (January 2005 to November 2006)

1. exp bipolar disorder/
2. ((bipolar OR bi?polar OR bi polar) adj5 (disorder$ OR depress$)).tw.
3. (mania$ OR manic$ OR hypomania$).tw.
4. (((cyclothymi$ OR rapid OR ultradian) adj5 cycl$) OR RCBD).tw.
5. OR/1-4
6. (lamotrigin$ OR lamictal OR lamictin OR labileno).mp.
7. (Bw 430 C OR Bw 430c OR Bw 430c78 OR Bw430c OR Bw430c78).tw.
8. 84057-84-1.rn.
9. OR/6-8
10. exp clinical trials/ OR exp clinical trial/ OR exp controlled clinical trials/
11. exp crossover procedure/ OR exp cross over studies/ OR exp cross-over design/
12. exp double blind procedure/ OR exp double blind method/ OR exp single blind procedure/ OR exp single blind method/ OR exp double blind study/ OR exp single blind study/ OR exp double blind randomized trial/ OR exp single blind randomized trial/ OR exp double blind randomized controlled trial/ OR exp single blind randomized controlled trial/ OR exp crossover randomized trial/ OR exp crossover randomized controlled trial/ OR exp crossover controlled clinical trial/ OR exp crossover trial/ OR exp parallel randomized trial/ OR exp parallel randomized controlled trial/ OR exp parallel controlled clinical trial/ OR exp parallel trial/ OR exp randomized crossover trial/ OR exp randomized controlled trial/ OR exp randomized controlled clinical trial/ OR exp randomized parallel trial.
13. OR/10-19
14. NOT (animals/ AND human$)
15. (animals NOT (animals AND human)).po.
16. limit 24 to yr='2005–2007'
17. remove duplicates from 25
18. Total number of hits: 202

2a. Lamotrigine OR lamictal OR lamictin OR labileno mp.
2b. 84057-84-1 rn.
2c. OR/6-8
2d. OR/10-19
2e. NOT (animals AND human mp.)
2f. limit 24 to yr='2005–2007'
2g. remove duplicates from 25
2h. Total number of hits: 202
Lamotrigine for treatment of bipolar depression: independent meta-analysis and meta-regression of individual patient data from five randomised trials
John R. Geddes, Joseph R. Calabrese and Guy M. Goodwin
Access the most recent version at DOI: 10.1192/bjp.bp.107.048504

Supplementary Material
Supplementary material can be found at:
http://bjp.rcpsych.org/content/suppl/2009/01/06/194.1.4.DC1

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