Comparative evaluation of quetiapine-lamotrigine combination versus quetiapine monotherapy (and folic acid versus placebo) in bipolar depression: a 2x2 factorial randomised trial. (CEQUEL)

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SUMMARY

BACKGROUND: The combination of lamotrigine plus quetiapine potentially offers better outcomes without inducing mood instability.

METHODS: Double-blind, randomized, placebo-controlled, parallel group, 2x2 factorial clinical trial comparing lamotrigine with or without folic acid versus placebo as add-on to quetiapine in bipolar depression. Patients with DSM-IV bipolar disorder I or II, aged 16 or over, requiring new treatment for a depressive episode, were allocated to lamotrigine or placebo; and folic acid or placebo. The primary outcome was improvement in depressive symptoms at 12 weeks using Quick Inventory of Depressive Symptomatology – self report version (QIDS-SR16).

RESULTS: 202 participants were randomized. The mean difference in QIDS-SR16 total score between groups receiving lamotrigine vs placebo at 12 weeks was -1.73 at 12 weeks (95% CI -3.6 to 0.1; p=0.0657 and -2.69 at 52 weeks (95% -4.9 to -0.5; p=0.0166). Significantly more participants treated with lamotrigine were in remission (QIDS ≤ 5) at 12 weeks (lamotrigine 31%; placebo 16%; relative risk 2.1 [95% CI 1.1-4.1], p=0.0263) and 52 weeks (36%; 13%; RR 3.7 [1.35-10.3], p=0.0117). Folic acid was not superior to placebo. There was a significant interaction (p=0.0282), with folic acid reducing the effectiveness of lamotrigine at 12 weeks. The mean difference on QIDS-SR16 was -4.14 (95% CI -6.90 to -1.37; p = 0.0041) for patients receiving lamotrigine without folic acid, compared to 0.12 (95% CI -2. 58 to 2.82; p=0.93) for those receiving lamotrigine and folic acid.

CONCLUSIONS: Adding lamotrigine to quetiapine treatment improved outcomes. Folic acid appears to nullify the effect of lamotrigine.

INTRODUCTION

Bipolar disorder, an illness characterised by recurrent depressive and manic episodes, is among the most important causes of worldwide disability(1). The burden of depressive, rather than manic, symptoms causes most of the long-term disability and excess mortality in people with bipolar disorder(2)(3). Evidence for effective short- and longer-term treatment

options for bipolar depression remain limited (4). Recent NICE guidelines recommend fluoxetine plus olanzapine combination or quetiapine as first line treatment(5). The evidence for antidepressant drugs like fluoxetine in bipolar depression, however, remains controversial – with no consensus that they are either effective or safe (6). Many patients do not respond to these interventions and the evidence for efficacy and tolerability of longer term quetiapine is limited (4).

Lamotrigine is widely used as an anti-epileptic. It is an inhibitor of voltage-sensitive sodium channels, and is thought to work by reducing presynaptic release of glutamate although its mechanism of action in bipolar disorder remains unclear (7). Clinical observation of a beneficial effect in depression led to investigation in bipolar disorder which demonstrated efficacy in the prevention of depressive relapse (8). Lamotrigine is now licensed in US and EU for the prevention of relapse in patients with bipolar I disorder who experience predominantly depressive episodes (9). There has been considerable uncertainly, however, about the efficacy of lamotrigine monotherapy in the acute phase of bipolar depression. A modest treatment effect observed in pooled analysis but not seen in individual trials which may be because the trials were of limited (8 week) duration and lamotrigine requires a lengthy 6 week titration period which leaves only 2 weeks in which to achieve response (10). The LamLit trial found significant benefit at 8 weeks for the addition of lamotrigine to lithium therapy in patients with bipolar depression (11).

Current monotherapies for bipolar depression remain limited in terms of both proven efficacy and practical tolerability and combinations of treatments may lead to better outcomes. CEQUEL was designed to test the hypothesis that a strategy of combining lamotrigine with quetiapine might lead both to better short-term response *and* longer term outcomes than quetiapine alone. Additive benefits from the combination might, of course, result from their independent mechanisms of action, since the two drugs have entirely different pharmacologies. Further, the rapid onset of the therapeutic effects of quetiapine could make the slow dose titration required for lamotrigine less problematic: more patients would remain on therapy and therefore benefit from the therapeutic potential of lamotrigine in the acute phase. There could also be important advantages in the longer term since patients on the combination who cannot tolerate the known adverse effects of quetiapine would remain on an effective drug following its discontinuation(4), leading to a functional synergy between lamotrigine and quetiapine.

The primary objective of CEQUEL was to determine if combination therapy with quetiapine plus lamotrigine leads to greater improvement in depressive symptoms over 12 weeks than quetiapine monotherapy plus lamotrigine placebo in patients with bipolar depression. By using a factorial design, CEQUEL also investigated the effects of adding folic acid which is a simple, widely available over the counter treatment for which there is some evidence of efficacy in unipolar depression (12) . Furthermore, folic acid is often included in vitamin pills as well as being recommended during pregnancy especially when women are taking lamotrigine(13), Secondary objectives included assessment of longer-term outcomes (up to 52 weeks), quality of life, tolerability, mortality and cost-effectiveness.

METHODS

Study design and participants

CEQUEL was a double-blind, randomized, placebo-controlled, parallel group, 2x2 factorial clinical trial with concurrent economic analysis conducted across 27 sites in the UK (Figure 1). Eligible patients (see BOX) were those with bipolar disorder I or II (BDI or II) diagnosed according to DSM-IV (14) criteria on the basis of clinician interview who required new pharmacological treatment for an acute depressive episode, aged 16 or over. The severity of depressive symptoms was assessed with the Quick Inventory of Depressive Symptomatology – self report version (QIDS-SR16) which is a 16 item scale covering the DSM-=IV criteria for depressive episode producing a score between 0-27 (15). The QIDS-SR16 has been shown to agree well with the clinician rated version, in patients with bipolar depression and with other widely used depression rating scales such as the 24-item Hamilton Rating Scale for Depression (15)(16)(17)(18). QIDS-SR16 scores can be categorized: ≤ 5 no depression; 6-10 mild depression; 11-15 moderate depression; 16-20 severe depression; ≥21 very severe depression (www.ids-qids.org). A minimum level of depressive symptoms was not required for entry to either run-in or randomised phases of the trial because the relevant criterion was clinical judgement that new pharmacological treatment was required for a depressive episode. Manic symptoms were assessed using the Altman Self Rating Mania Scale (ASRM) (198). Quality of life was measured at baseline and at 12 and 52 weeks using the EuroQol EQ-5D-3L (20). Data on symptoms and quality of life were provided by participants using the True Colours system via text message, email, or paper(21).

Investigators were encouraged to withdraw any other treatments for mood symptoms that participants were taking prior to entry to the run-in phase but these drugs could be

continued where clinically indicated. Drug treatments that were not withdrawn were continued at the same dose for the duration of the trial unless there was a clinical need for change. All concurrent psychotropic medicines were recorded on the baseline assessment form and any subsequent changes reported. Carbamazepine (which decreases the serum level of lamotrigine) was stopped during the run-in phase or replaced by oxcarbazepine. Additional treatment for depressive symptoms was not allowed during the first 12 weeks of the randomised phase. After 12 weeks, new treatment for depressive symptoms could be initiated as clinically appropriate if response to allocated treatment was considered to be inadequate or if new symptoms emerge. Folic acid (prescribed and over-the-counter preparations) was stopped unless there were reasons why the participant should not be randomised to folate/placebo.

All participants initially entered a 7 to 14 days active run-in with quetiapine monotherapy to screen for adherence to quetiapine and to study procedures, tolerability and symptom stability. Quetiapine was commenced at 50mg on days 1 and 2, increased to 100mg on days 3 and 4, 200mg on days 5 and 6 and 300mg on day 7 and beyond. The target dose of quetiapine was 300mg but if this was not tolerated a minimum dose of 150mg was required for at least 3 days to proceed to randomization. Quetiapine was continued at the established dose throughout the randomized phase unless there were clinical reasons to stop or the patient withdrew consent. Changes to the dose of quetiapine post-randomisation were considered to be protocol non-compliant and when this occured the reason for the change was recorded. The run-in was included both to exclude patients with transient symptoms and to improve efficiency without jeopardising clinical applicability by deploying the combination in a stepped approach comparable with routine clinical practice(22). The first participant was recruited on 21st October 2008 and the last patient completed follow-up on 27th April 2013. We also genotyped functional polymorphisms in genes involved in one-carbon pathways, and measured related biochemical indices; these results will be presented separately.

Randomization and blinding

Following 7 to 14 days run-in on quetiapine, participants were randomized to added lamotrigine 200mg/day (100mg/day with concurrent valproate and 400mg/day with concurrent combined oral contraceptives) or placebo using a centralised randomization service by fax or web-based form. Lamotrigine was commenced at 25mg daily and increased

gradually to 200mg as in the FDA prescribing information http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020241s037s038,020764s030s031lbl.pdf

Participants not currently taking folic acid and with no contraindications to it were separately randomized to folic acid 500µg/day. To enroll a patient, the treating physician faxed the randomization form to the trial office. After establishing eligibility and that informed consent had been obtained, the patient was randomized, assigned a treatment pack number and dispensed medication from the trial pharmacy. Randomization used an adaptive minimisation algorithm balancing for: centre, age, gender, BDI or II, baseline severity of depression, quetiapine dose, concurrent medication, pre-trial use of quetiapine, pre-trial use of lamotrigine and mood episodes in past year (<4; =/>4). The minimisation algorithm was seeded by randomizing the first 60 participants using simple randomization then introducing the minimisation algorithm. Allocated treatment was continued for 52 weeks and follow-up was continued even if trial-allocated treatment was discontinued.

Power and sample size

The sample size was calculated to detect a clinically important effect of lamotrigine on the primary outcome measure, i.e. a 2.0 point difference in the QIDS-SR16 (SD 5.4). The calculation assumed a repeated measures analysis with 3 time points and a correlation between time points of 0.4 and also included a 20% loss to follow-up, yielding a total sample size of 236 (power: 90% and two-sided alpha: 5%).

Primary outcome and analysis

The primary outcome was depressive symptoms score at 12 weeks (±2 weeks) from randomization using QIDS-SR16. The pre-specified primary analysis was assessed via a linear mixed effects model using data at 12 (±2), 22 (±2) and 52 (±2) weeks only. The model fitted time and randomized group as fixed effects and participants as random effect. An interaction between time and randomized group was fitted to allow estimation of treatment effect at each time point. Analysis was by modified intention-to-treat. That is, after randomization, participants were analysed according to their allocated treatment group irrespective of what treatment they actually receive. Assumptions for regression models were assessed using graphically based on residuals. Participants who provided no data within these time windows were excluded. The model was adjusted for folic acid (active/placebo/not allocated), baseline QIDS-SR16, baseline ASRM (>=6), BDI/II, age,

gender, dose of quetiapine (< 300mg/day; 300+ mg/day), concurrent lithium, concurrent valproate, concurrent antidepressant. The primary analysis of the folic acid comparison was conducted in the same way as for the lamotrigine comparison but included only those randomized to the folic acid part of the study. Although an interaction between the interventions was not anticipated, this was investigated by adding an interaction term between the randomized treatments (lamotrigine x folic acid) to the model in the analysis of the primary outcome. The interaction analysis was restricted to participants who were randomized to both lamotrigine/placebo and folic acid/placebo. In line with the primary analysis, a regression based approach adjusting for covariates was applied both for the lamotrigine and folic acid comparisons.

As a secondary analysis of the primary outcome, all weekly non-missing QIDS-SR16 scores between randomization and week 52 were analysed using a mixed effects linear regression model to account for the repeated measures over time. The mixed effect model contained QIDS-SR16 score as the response variable; and time (week) as a continuous covariate to allow the slope of the regression line representing the change in outcome over time to be assessed. A time by lamotrigine interaction was included as a fixed effect to allow estimation of the slope of the regression line to differ according to treatment allocation. Treatment effect at each time point was derived similarly as described above. To incorporate the observed lack of linearity into the analysis, the regression model was segmented at 12 and 22 weeks and the slope at each point was allowed to vary.

Secondary outcomes included improvement in depressive symptoms at 52 weeks; proportion of participants in remission (QIDS-SR16 ≤ 5) at 12 and 52 weeks; time to new intervention for depressive and manic symptoms; self-harm, mortality, adverse effects and health-related quality of life. EQ-5D utility analyses were based on available cases and following multiple imputation of missing data.

The proportion of participants with manic symptoms, defined as ASRM scores ≥ 6 at 12, 22 and 52 weeks following randomization, was analysed using log-binomial regression models at each time point separately. The models included treatment by lamotrigine, treatment by folic acid (Yes/No/NA) and minimisation variables as for the primary analysis.

Role of the funding source.

CEQUEL was funded by the Medical Research Council. Some study drug was donated by GlaxoSmithKline. Neither funder had any role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

RESULTS

202 participants were randomized (101 lamotrigine; 101 placebo). A CONSORT diagram showing the flow of the participants over the full trial period is presented in Figure 2. Of 266 participants who entered the run-in, 19 (7%) were unable to progress to randomisation due to adverse effects or inability to tolerate it. Baseline characteristics of randomised participants are summarised in Table 1 with approximately three quarters of patients meeting criteria for bipolar type 1. The aim was to balance groups for bipolar subtype, age and gender but some imbalances remain. The largest imbalance was the proportion using antidepressants at randomization: more participants randomized to placebo were using antidepressants, compared with lamotrigine. The direction of imbalance was reversed for the folic acid comparison, with slightly fewer participants using antidepressants at baseline in those who were randomized to placebo compared with folic acid. Analyses were adjusted for these imbalances. Approximately three quarters of participants were diagnosed with BD1 and a quarter were diagnosed BD2 and the mean QIDS-SR16 score indicates moderate depression. The modal daily dose of quetiapine was 300mg/day.

At 12 weeks participants randomized to lamotrigine had lower QIDS- SR16 scores than those randomized to placebo. (see Table 2 and 3). The mean difference between the groups was -1.73 points (95% CI -3.57 to 0.11, p=0.0657). A similar difference was seen at 22 weeks (-1.87 points (-3.92 to 0.17) p=0.0723 (Table 3; Figure 3). At 52 weeks participants randomized to lamotrigine were on average 2.7 points lower on the QIDS scale -2.69 (95% -4.89 to -0.49, p=0.0166) than those randomized to placebo. Thus, mean QIDS-SR16 scores were consistently lower in participants taking lamotrigine compared to placebo. (Table 2). Significantly more participants treated with lamotrigine met criteria for remission (QIDS ≤ 5) at 12 weeks (lamotrigine 31%; placebo 16%; relative risk (RR) 2.11 [95% CI 1.09-4.07], p=0.0236) and 52 weeks (36%; 13%; RR 3.73 [1.35-10.29], p=0.0117). There was no significant interaction of treatment effect by study site.

The secondary analysis of the primary outcome, utilising all submitted scores over the 52 week follow up period resulted in similar findings. Depression scores decreased for those receiving lamotrigine more quickly than those receiving placebo resulting in an estimated difference at 12 weeks of -1.40 (95% CI-2.9 to 0.09, p=0.0661).

One hundred and fifty participants were available for analysis of folic acid vs placebo at 12 weeks. Mean QIDS-SR16 scores were no different in those randomized to folic acid than in those randomized to placebo at 12 weeks or at 22 and 52 weeks (Table 2).

Although an interaction between lamotrigine and folic acid had not been anticipated, it appeared that folic acid was associated with an impaired lamotrigine response in the first 12 weeks.

Due to the interaction observed between treatments the most reliable and unconfounded estimate of the effect of lamotrigine at 12 weeks is the estimate from the group not randomized to take folic acid. At 12 weeks, the mean difference on QIDS-SR16 on lamotrigine compared to placebo with no folic acid was -4.14 (95% CI -6.90 to -1.37; p = 0.0041); with folic acid 0.12 (95% CI -2. 58 to 2.82; p = 0.93). (Figure 4).

There were no significant differences in rates of new treatment (hospital admission or drug treatment) for depression between lamotrigine and placebo (31% vs 39%, adjusted (adj) RR 0.84 (0.58, 1.24) p=0.3789), and marginal for folic acid compared to placebo (27% vs 39%, adj RR 0.67 (0.43, 1.03), p=0.0646). There were no differences observed for new treatments for mania or mixed state between lamotrigine and placebo (9% vs 12% adj RR 0.67 (0.29, 1.56), p=0.3512), or for folic acid compared to placebo (9% vs 12% adj RR 0.79 (0.33, 1.89), p=0.5965). (see Web Table 4). There was no clear increase in clinically significant manic symptoms (manic relapse defined as ASRM>=10) at any time with lamotrigine although the event rate was low and the trial was not powered to evaluate this outcome reliably. (Table 6) More participants on lamotrigine than on placebo reported some manic symptoms (ASRM >= 6) with lamotrigine compared to placebo at 12 weeks (adj RR 2.59 (95% CI 1.24 to 5.41) p=0.0115) but not at 22 or 52 weeks (adj RR 0.98 (0.38 to 2.54) p=09674; 0.94 (0.31 to 2.87) p=0.9153 respectively), reflecting improved mood. Folic acid treatment showed no effect on mania scores.

During the 12 months follow-up, health-related quality of life improved in all groups generally. No difference was seen for any of the group comparisons (Web Tables 5 and 6).

There were 32 serious adverse events. These included 1 death by suicide (placebo lamotrigine/active folic acid), 15 admissions to hospital for depression involving 10 participants) (5 active lamotrigine, 10 lamotrigine placebo; 6 active folic acid, 9 placebo folic acid); 7 admissions to hospital for mania (4 active lamotrigine, 3 lamotrigine placebo; 2 active folic acid, 5 placebo folic acid); 9 admissions (8 participants) for other reasons. None were considered to be related to trial medication. 4 participants became pregnant three of whom (all allocated placebo lamotrigine and placebo folic acid) miscarried or terminated the pregnancy. There were 16 adverse events that led to withdrawal of treatment, 5 of which were judged to be possible adverse reactions to trial medication (including skin rash; nausea and stomach cramps; musculoskeletal pain; oedema).

The Table 2 show the number of participants included at each time point but there are no data on adherence to treatment.

DISCUSSION

The results of CEQUEL show that adding lamotrigine to quetiapine treatment of acute bipolar depression improved both mean depressive symptoms *and* rates of clinical remission compared to placebo at 12 and 52 weeks. Folic acid was no better than placebo in reducing depressive symptoms. There was a statistically significant interaction between lamotrigine and folic acid at 12 weeks, with folic acid appearing to substantially reduce the effectiveness of lamotrigine. The result of this effect modification was that the mean difference in QIDS-SR16 due to lamotrigine was reduced in the full sample (including participants on both active folic acid and folic acid placebo). Restricting the analysis at 12 weeks to those participants not allocated to folic acid produced an unbiased estimate of the effect of lamotrigine which showed a statistically and clinically significant mean reduction of 4.1 (95% CI 1.37 to 6.90) points on the QIDS-SR16, although the smaller sample size led to greater imprecision around the treatment effect. No benefits due to lamotrigine were observed on the secondary outcome measure of health-related quality of life which may be due to lack of power for these more distal outcomes.

The strengths of CEQUEL include the double –blind design and good retention rates (>80%) at 12 weeks. Almost all the patients recruited into CEQUEL were receiving lamotrigine for the first time, which is a substantial strength of the study because the results are therefore able to inform treatment decisions in patients who have not had experience of the drug. The main weakness is the higher drop-out rate at 52 weeks, although this remains lower than often observed even in double-blind trials maintenance trials in this clinical population (23). Factorial trials, which can be an efficient way to evaluate 2 or more interventions, uncommonly identify interactions between treatments (24)(25). In CEQUEL, there was a statistically and clinically significant interaction which illustrates some of the advantages and disadvantages of this design(26).

The interaction between folic acid and lamotrigine was unexpected and additional research is required to investigate this further. However, there are grounds for considering such an interaction biologically plausible. Lamotrigine was originally synthesized as one of series of folate antagonists on the grounds that folate was thought to be pro-convulsant (7) Hence, it is possible that lamotrigine and folate both bind to a common receptor or enzyme site. Alternatively, it may be a pharmacokinetic effect whereby folic acid reduces absorption of lamotrigine from the gastrointestinal tract. However, there has been surprisingly little research into lamotrigine's mechanism(s) of action to either include or exclude a possible important effect modification by folic acid. We cannot find any prior report of a clinical interaction of the kind we describe here although the summary of product characteristics SmPC for lamotrigine does report an effect on folate levels. Whatever the cause, the interaction is potentially clinically important because folic acid supplementation may be more likely in some patient groups taking lamotrigine, for example pregnant women(13) and as an adjunctive therapy in mood disorder(12). Furthermore, folic acid is present in the doses used in CEQUEL in many over-the-counter vitamin preparations. One clinically important conclusion from CEQUEL is that if a patient with bipolar disorder needs folic acid therapy, then lamotrigine should be avoided (and vice versa). Furthermore, the result raises an intriguing question about the likely efficacy of lamotrigine in countries which fortify wheat flower with folic acid: the US programme has been estimate to provide 100-200 micrograms of folic acid per day in women of childbearing age (27). It is unclear if this amount is sufficient to reduce the treatment effect.

CEQUEL confirms the efficacy, in the absence of folic acid, of adding lamotrigine to quetiapine in bipolar depression and that the benefits persist for 52 weeks. These findings complement another independent trial, which showed clinical benefit for lamotrigine combination therapy, although in that case in combination with lithium (11). Together with the pooled data of lamotrigine vs placebo(10), it appears that lamotrigine is an effective treatment in bipolar depression. Guidelines have varied in their recommendation of lamotrigine as a first choice option for treating bipolar depression because of the uncertainties remaining from the industry sponsored trials. They either suggest using lamotrigine monotherapy as a first line treatment option (28) or as a second line option or following non-response to initial therapy (5). CEQUEL is an important addition to the evidence base that informs clinical practice because it suggests that adding lamotrigine to quetiapine may be an effective and well tolerated option for many patients with bipolar depression.

Research in context

Systematic review

During the planning phase of CEQUEL we conducted a systematic review and individual patient data meta-analysis of randomised trials

Geddes JR, Calabrese J, Goodwin GM. Lamotrigine for treatment of bipolar depression: an independent meta-analysis and meta-regression of individual patient data from 5 randomized trials British Journal of Psychiatry 2009 194: 4-9

We included all the randomised controlled trials conducted by GlaxoSmithKline comparing lamotrigine with placebo in bipolar depression and to identify any additional randomised trials, we conducted a search of electronic databases including MEDLINE, EMBASE, CINAHL, PsycINFO, CENTRAL

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).

Interpretation

CEQUEL extends the results of the systematic review by investigating the effect of lamotrigine over a longer time period than the industry-sponsored trials and by investigating its efficacy as add-on therapy to quetiapine. The results confirm that lamotrigine improves depressive symptoms in bipolar depression and suggests that adding lamotrigine to quetiapine may be an effective and well tolerated option for many patients with bipolar depression.

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JRG, JR, LY, GMG, ET, PH, JS designed the trial; JRG, MJA, AG, JH, JR, CH coordinated the study, oversaw patient recruitment and trial procedures and finalised the dataset. ET, PH, AG, JR and JRG oversaw collection and analysis of biological samples. MV, LY, and JS conducted the statistical and economics analyses. JG and MV drafted the paper which was reviewed by all authors

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Trial Steering Committee: Chair – Prof Shôn Lewis; John Geddes, Guy Goodwin, Hugh Gazzard, Neil Armstrong, Andrea Cipriani, Alex Gardiner, Jennifer Rendell, Jane Sinclair
Data Monitoring Committee: Chair – Prof Thomas Barnes; Deborah Ashby, Vivien Curtis, Ly-Mee Yu, John Geddes in attendance during open session.
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DISCLOSURES

GMG holds shares in P1vital and has served in the last 2 years as consultant, advisor or CME speaker for AstraZeneca, Abbvie , Cephalon/Teva, Convergence, Eli Lilly, GSK, Lundbeck, Medscape, Merck, Otsuka, P1Vital, Servier, Sunovion, Takeda. EMT has served as a consultant for UCB Pharma. PJH reports grants from MRC, grants from Wellcome Trust, during the conduct of the study; personal fees from Sunovion Pharmaceuticals, personal fees from Roche Pharmaceuticals, personal fees from Boehringer Ingelheim, personal fees from Teva, Accord, and Sandoz, grants from Takeda (Cambridge) , outside the submitted work; .

Eligibility criteria for entry to run-in phase:

Inclusion criteria:

1. Primary diagnosis of bipolar disorder type I or II (based on DSM-IV criteria for a hypomanic or manic episode),
2. Consent to participate in the trial,
3. Aged 16 or over,
4. Current depressive episode requiring new pharmacological treatment (either as add-on therapy or as a change of treatment).

Exclusion criteria:

1. Definite indications or contraindications to lamotrigine, quetiapine or folic acid[1] (Including pregnancy and planned pregnancy),
2. New course of a specific psychosocial intervention[2] started in the past 4 weeks,
3. First appointment for a specific psychosocial intervention[2] booked within the next 14 weeks,
4. In the opinion of the investigator, currently experiencing manic or mixed episode,
5. Primary diagnosis of schizophrenia.

Plus, for women of child-bearing potential:

6. Currently breast feeding or not using adequate contraception.

[1] Participants who have active cancer, a diagnosed pre-malignant condition, a strong family history of cancer or are unwilling to stop taking folic acid supplements can, where clinically appropriate, be randomized to the lamotrigine/placebo arm.

[2] Defined as Cognitive Behaviour Therapy (CBT), Group Psychoeducation, Family-focused Therapy and Interpersonal and Social Rhythm Therapy (IPSRT)

Additional criteria for entry to the randomized phase:

Patients must satisfy the eligibility criteria above plus all the following criteria to be eligible for entry to the randomized phase:

1. Able to tolerate quetiapine at a dose of at least 150mg/day
2. Uncertainty whether quetiapine plus lamotrigine would be more effective than quetiapine monotherapy
3. Acceptable adherence to quetiapine (>90%) and self-report satisfactory
4. Willing to accept random allocation of treatments
5. In the opinion of the investigator, not currently experiencing manic or mixed episode.

Box: Eligibility criteria

TABLE 1 BASELINE CHARACTERISTICS AT RANDOMIZATION

	Placebo		*Lamotrigine*		*Placebo*		*Folic Acid*		*N/A**	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
Bipolar Type										
bipolar1	75	74.3	74	73.3	67	71.3	69	75.0	13	81.3
bipolar2	26	25.7	27	26.7	27	28.7	23	25.0	3	18.8
Age										
≤ 30 Years	17	16.8	19	18.8	19	20.2	17	18.5	0	0
31-40 years	20	19.8	25	24.8	25	26.6	17	18.5	3	18.8
41-50 years	32	31.7	34	33.7	26	27.7	33	35.9	7	43.8
> 50 years	32	31.7	23	22.8	24	25.5	25	27.2	6	37.5
Gender										
male	46	45.5	44	43.6	41	43.6	42	45.7	7	43.8
female	55	54.5	57	56.4	53	56.4	50	54.4	9	56.3
Quetiapine dose (mg/day)										
<150	19	18.8	19	18.81	16	17.0	21	22.8	1	6.3
>150 - < 300	14	13.9	18	17.82	20	21.3	9	9.8	3	18.8
300	54	53.5	55	54.46	50	53.2	50	54.4	9	56.3
> 300	14	13.9	9	8.91	8	8.5	12	13.0	3	18.8
Concurrent Medication										
Lithium	14	13.9	12	11.9	13	13.8	12	13.0	1	6.3
Valproate	18	17.8	24	23.7	22	23.4	18	19.6	2	12.5
Other mood stabiliser	2	2.0	5	5.0	2	2.1	3	3.3	2	12.5
Olanzapine	4	4.0	3	3.0	5	5.3	1	1.1	1	6.3
Other atypical antipsychotic	3	3.0	4	4.0	4	4.3	3	3.3	0	0
Conventional antipsychotic	3	3.0	2	2.0	1	1.1	4	4.4	0	0
Antidepressant	40	39.6	29	28.7	29	30.9	33	35.9	7	43.8
Pre-trial quetiapine	22	21.8	25	24.8	23	24.5	21	22.8	3	18.8
Pre-trial lamotrigine	1	1.0	1	1.0	1	1.1	1	1.1	0	0
Participants with mood episodes in past year	27	26.7	26	25.7	27	28.7	24	26.1	2	12.5

*Participants who chose not to be randomized into the folic acid component of the study

TABLE 2 QIDS-SR16 SUMMARY STATISTICS

Trial arm			*N*	*Mean*	*Std Dev*	*Lower 95%* CL for Mean	*Upper 95%* CL for Mean
Lamotrigine Comparison	Placebo	Baseline	101	15	5.4	13.9	16
		Week 12	81	12.5	6.3	11.1	13.8
		Week 22	63	11.6	6.5	10	13.2
		Week 52	47	12	6.1	10.2	13.8
	Lamotrigine	Baseline	101	15.3	5.1	14.3	16.3
		Week 12	84	11	6.7	9.5	12.4
		Week 22	61	9.6	6.4	7.9	11.2
		Week 52	56	9.2	6.8	7.4	11.1
Folic Acid Comparison*	Placebo	Baseline	94	15.0	5.5	13.9	16.1
		Week 12	73	11.0	6.6	9.4	12.5
		Week 22	52	10.5	6.2	8.8	12.3
		Week 52	47	11.6	6.9	9.6	13.6
	Folic Acid	Baseline	92	15.1	5.4	14.0	16.2
		Week 12	77	11.8	6.3	10.3	13.2
		Week 22	60	10.6	6.8	8.9	12.4
		Week 52	46	9.8	6.5	7.8	11.7

***Folic acid vs placebo comparisons restricted to those participants who consented to separate randomization**

TABLE 3 QIDS-SR16 ADJUSTED MEAN DIFFERENCES FROM MIXED EFFECTS REGRESSION MODEL

Time	***Group***	***Adjusted Mean Diff***	***95% LCL***	***95% UCL***	***P value***
12 weeks (±2 weeks)	Placebo				
	Lamotrigine	-1.73	-3.57	0.11	0.0657
22 weeks (±2 weeks)	Placebo				
	Lamotrigine	-1.87	-3.92	0.17	0.0723
52 weeks (±2 weeks)	Placebo				
	Lamotrigine	-2.69	-4.89	-0.49	0.0166
12 weeks (±2 weeks)	Placebo				
	Folic acid	0.75	-1.16	2.66	0.4405
22 weeks (±2 weeks)	Placebo				
	Folic acid	0.17	-1.97	2.30	0.8780
52 weeks (±2 weeks)	Placebo				
	Folic acid	-0.92	-3.20	1.35	0.4230

**Adjusted baseline QIDS-SR$_{16}$, bipolar I or bipolar II, age (classified as <40 years; 40+ years), gender, dose of quetiapine (< 300mg/day; 300+ mg/day), concurrent lithium, concurrent valproate, concurrent antidepressant. Lamotrigine comparisons adjusted for folic acid (active/placebo/NA); Folic acid comparisons adjusted for lamotrigine (active/placebo).*

WEB TABLE 4 SUMMARY OF SELF RATED MANIC SYMPTOM SCORES BY RANDOMIZATION TO LAMOTRIGINE OR PLACEBO

	ASRM >=10				*ASRM >=6*			
	Placebo		**Lamotrigine**		**Placebo**		**Lamotrigine**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Baseline	3/101	3%	0/101	0%	10/101	10%	12/101	12%
Week 12	2/81	2%	4/83	5%	9/81	11%	23/83	27%
Week 22	8/62	8%	3/60	8%	9/62	9%	9/60	9%
Week 52	2/47	4%	4/54	7%	6/47	13%	8/54	15%

WEB TABLE 5 EQ-5D UTILITY ADJUSTED MEAN DIFFERENCES BY RANDOMIZATION TO LAMOTRIGINE OR PLACEBO

	Group	*Mean*	*StdErr*	*95% LCL*	*95% UCL*	*Mean Diff*	*95% LCL*	*95% UCL*	*P value*
Available case analysis									
12 weeks	Placebo	0.64	0.03	0.58	0.71				
	Lamotrigine	0.65	0.03	0.59	0.72	0.01	-0.08	0.10	0.848
52 weeks	Placebo	0.67	0.04	0.59	0.74				
	Lamotrigine	0.68	0.03	0.61	0.75	0.01	-0.09	0.12	0.807
Imputed full dataset									
12 weeks	Placebo	0.64	0.03	0.59	0.69				
	Lamotrigine	0.65	0.03	0.60	0.70	0.01	-0.06	0.08	0.838
52 weeks	Placebo	0.67	0.02	0.63	0.71				
	Lamotrigine	0.66	0.02	0.62	0.70	-0.01	-0.06	0.04	0.653

**Adjusted for folic acid (active/placebo/NA), baseline EQ-5D-3L utility, age (classified as <40 years; 40+ years), gender. Available case analysis: N = 152 (12 weeks), N = 92 (52 weeks); imputed dataset: N = 202 (12 weeks), N = 202 (52 weeks).*

WEB TABLE 6 EQ-5D UTILITY ADJUSTED MEAN DIFFERENCES BY RANDOMIZATION TO FOLIC ACID OR PLACEBO

	Group	*Mean*	*StdErr*	*95% LCL*	*95% UCL*	*Mean Diff*	*95% LCL*	*95% UCL*	*P value*
Available case analysis									
12 weeks	Placebo	0.66	0.03	0.60	0.73				
	Folic acid	0.66	0.03	0.59	0.73	-0.01	-0.10	0.09	0.905
52 weeks	Placebo	0.63	0.04	0.56	0.71				
	Folic acid	0.73	0.04	0.65	0.80	0.10	-0.01	0.20	0.085
Imputed full dataset									
12 weeks	Placebo	0.67	0.03	0.62	0.72				
	Folic acid	0.64	0.03	0.58	0.69	-0.03	-0.11	0.04	0.417
52 weeks	Placebo	0.64	0.02	0.60	0.68				
	Folic acid	0.69	0.02	0.65	0.73	0.05	-0.01	0.10	0.095

**Adjusted for lamotrigine (active/placebo), baseline EQ-5D-3L utility, age (classified as <40 years; 40+ years), gender. Available case analysis based on N = 140 (12 weeks), N = 84 (52 weeks); imputed dataset based on: N = 186 (12 weeks), N = 186 (52 weeks).*

Figure 1. CEQUEL design

Patient with bipolar I/II disorder with depressive episode

Active run-in with quetiapine:

1- 2 weeks

Lamotrigin	Folic Acid	
	Yes	**No**
Yes	*Group 1* Lamotrigine plus folic acid plus quetiapine	*Group 2* Lamotrigine plus folic acid placebo plus quetiapine
No	*Group 3* Lamotrigine placebo plus folic acid plus quetiapine	*Group 4* Lamotrigine placebo plus folic acid placebo plus quetiapine

Follow-up for 52 weeks post-randomisation

Figure 2. CONSORT Diagram

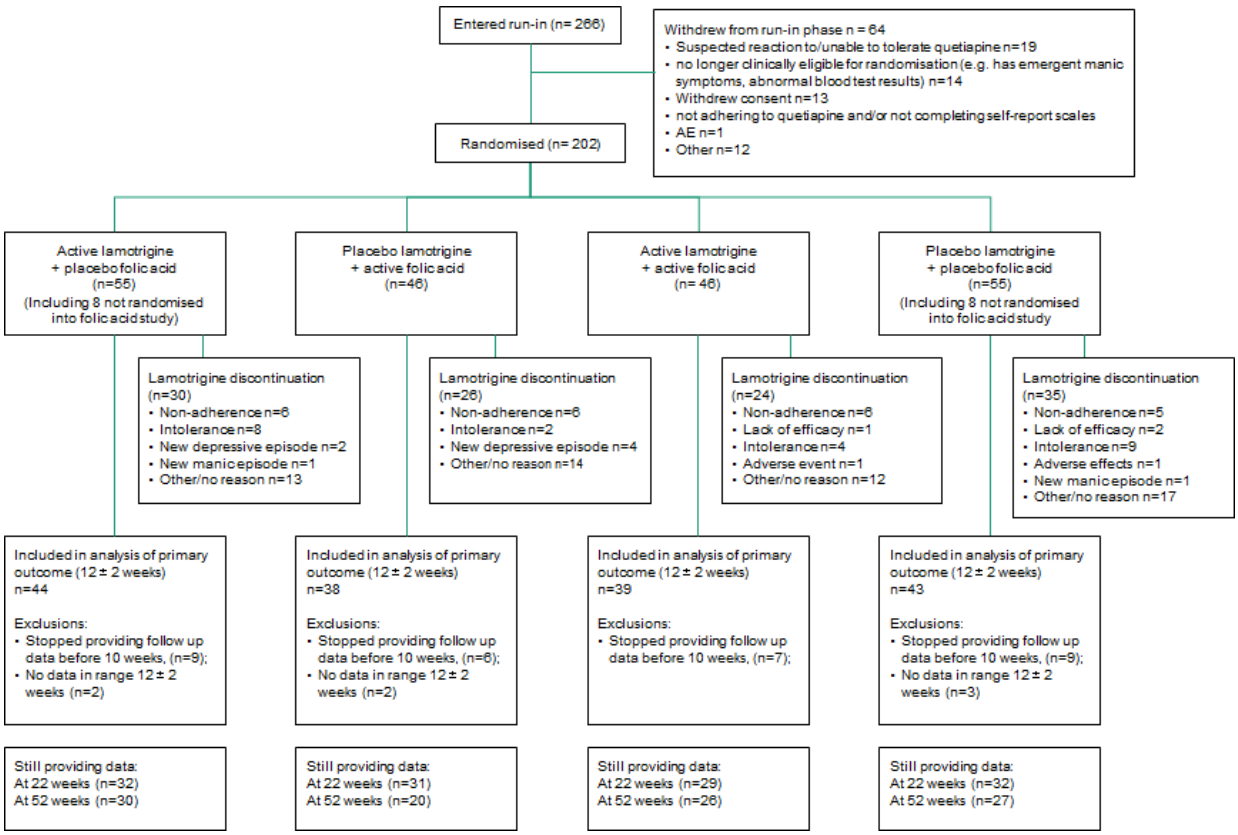
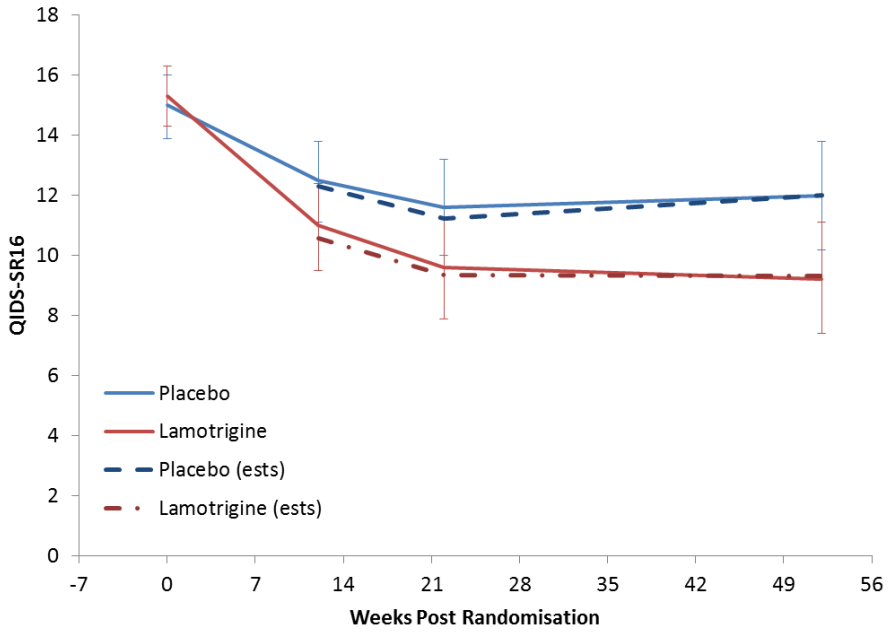


FIGURE 3 OBSERVED AND ESTIMATED MEAN QIDS-SR16 SCORES (95% CI) AT KEY TIME POINTS BY COMPARISONS

2a. Lamotrigine comparison



2b. Folic Acid comparison

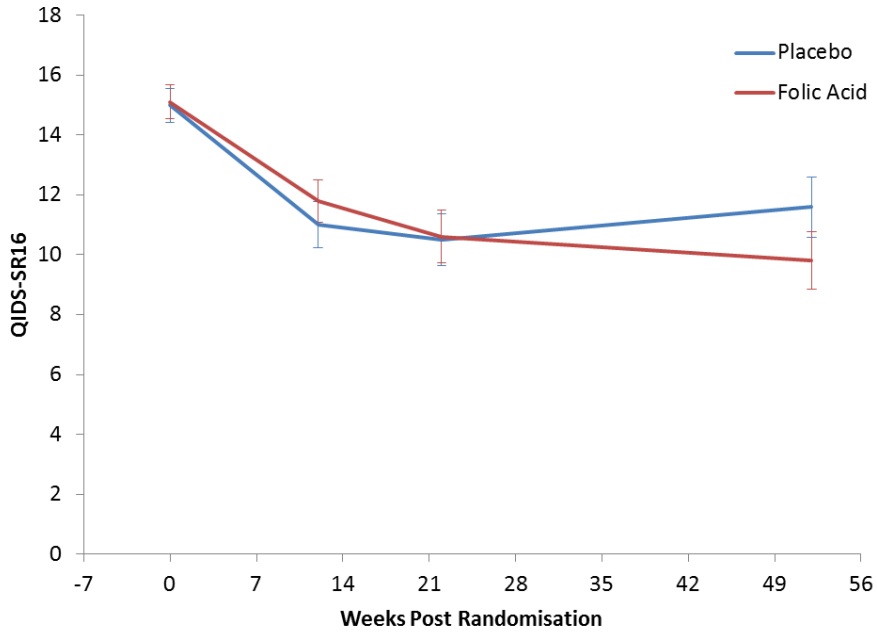
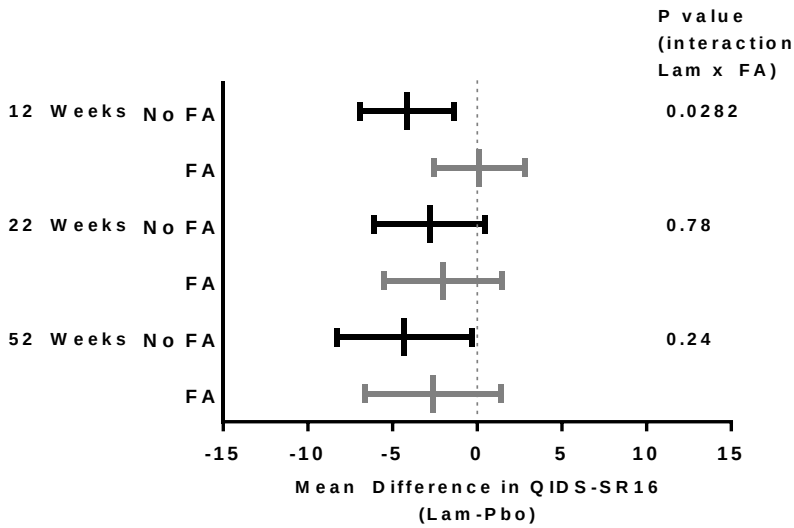


Figure 4 Forest plot – within group model estimates by time point and folic acid group – participants randomized in the folic acid study



Time	*Folic Acid*	*Mean Diff (Lam-Pbo)*	*Lower*	*Upper*	*P value*	*P value (interaction)*
12 weeks	No FA	-4.136	-6.904	-1.368	0.0041	0.0282
	FA	0.118	-2.583	2.819	0.9307	
22 weeks	No FA	-2.814	-6.114	0.487	0.0926	0.7767
	FA	-2.011	-5.501	1.479	0.2521	
52 weeks	No FA	-4.303	-8.276	-0.331	0.0346	0.2398
	FA	-2.594	-6.606	1.417	0.1973	

Adjusted for baseline QIDS-SR$_{16}$, baseline Altman, age, bipolar I or bipolar II, gender, dose of quetiapine (< 300mg/day; 300+ mg/day), concurrent lithium, concurrent valproate, concurrent antidepressant.

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Regulatory and ethical issues

A number of protocol changes were made during the trial., all of which were approved by the ethics committee. The protocol initially approved was version 02. Protocol version 03 (December 2008) included changes to procedures for distributing the investigational medicinal product. Protocol version 04 (March 2009) included the addition of questions relating to use of health and social care resources and dose of lamotrigine 400mg/day for women taking oral contraceptives. Version 05 included a change to primary outcome from binary - "remission at 12 weeks" to continuous - "greater improvement in depressive symptoms over 12 weeks", a consequent reduction in sample size from 584 to 236 and to allow immediate randomization of patients already on quetiapine. Version 06 (May 2013) included investigation of the effect of the folate hydrolase polymorphism on folic acid. Plus a number of amendments to sites, etc. CEQUEL was registered with EUdraCT No.: 2007-004513-33; and approved by REC 08/H0605/39; with a clinical trial authorization 20584/0234/001-0001 and ISRCTN17054996.