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

*John R Geddes, Alexandra Gardiner, Jennifer Rendell, Merryn Voysey, Elizabeth Tunbridge, Christopher Hinds, Ly-Mee Yu, Jane Hainsworth, Mary-Jane Attenburrow, Judit Simon, Guy M Goodwin, Paul J Harrison, on behalf of the CEQUEL Investigators and Collaborators**

Summary

Background Depressive symptoms are a major cause of disability in bipolar disorder and there are few safe and effective treatments. The combination of lamotrigine plus quetiapine potentially offers improved outcomes for people with bipolar depression. We aimed 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.

Methods In this double-blind, randomised, placebo-controlled, parallel group, 2×2 factorial trial (CEQUEL), patients with DSM-IV bipolar disorder I or II, who were aged 16 years or older, and required new treatment for a depressive episode, were enrolled from 27 sites in the UK. Patients were randomly assigned (1:1) by an adaptive minimisation algorithm to lamotrigine or placebo and to folic acid or placebo. Participants and investigators were masked to the treatment groups. The primary outcome was improvement in depressive symptoms at 12 weeks with the Quick Inventory of Depressive Symptomatology—self report version 16 (QIDS-SR16). Analysis was by modified intention-to-treat. This trial is registered with EUdraCT, number 2007-004513-33.

Findings Between Oct 21, 2008, and April 27, 2012, 202 participants were randomly assigned; 101 to lamotrigine and 101 to placebo. The mean difference in QIDS-SR16 total score between the group receiving lamotrigine versus the placebo group at 12 weeks was –1·73 ([95% CI –3·57 to 0·11]; p=0·066) and at 52 weeks was –2·69 ([–4·89 to –0·49]; p=0·017). Folic acid was not superior to placebo. There was a significant interaction (p=0·028), 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=0·004) for patients receiving lamotrigine without folic acid compared with 0·12 ([–2·58 to 2·82]; p=0·931) for those receiving lamotrigine and folic acid.

Interpretation Addition of lamotrigine to quetiapine treatment improved outcomes. Folic acid seems to nullify the effect of lamotrigine. CEQUEL should encourage clinicians and patients to consider lamotrigine for bipolar depression, but also to be aware that concurrent folic acid might reduce its effectiveness.

Funding Medical Research Council.

Lancet Psychiatry 2016; 3: 31–39

Published Online December 10, 2015 http://dx.doi.org/10.1016/S2215-0366(15)00450-2

See Comment page 2

*CEQUEL Investigators and Collaborators listed at end of paper

Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, UK (Prof J R Geddes MD, A Gardiner BSc, J Rendell DPhil, E Tunbridge DPhil, C Hinds DPhil, J Hainsworth BSc, M Attenburrow MRCPsych, Prof G M Goodwin FMedSci, Prof P J Harrison DM); **Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK** (A Gardiner, M Voysey MBiostat, L Yu MSc); **and Centre for Public Health, Medical University of Vienna, Vienna, Austria** (Prof J Simon DPhil)

Correspondence to: Prof John Geddes, Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford OX3 7JX, UK

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] Evidence for effective short-term and longer-term treatment options for bipolar depression remain restricted.[3] Recent UK National Institute for Health and Care Excellence guidelines recommend fluoxetine plus olanzapine combination or quetiapine as first-line treatment.[4] The evidence for antidepressant drugs such as fluoxetine in bipolar depression, however, remains controversial, with no consensus that they are either effective or safe.[5] Many patients do not respond to these interventions and the evidence for efficacy and tolerability of longer-term quetiapine is scarce.[3]

Lamotrigine is widely used as an antiepileptic. 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.[6] Clinical observation of a beneficial effect in depression led to investigation in bipolar disorder, which showed efficacy in the prevention of depressive relapse.[7] Lamotrigine is now licensed in the USA and the European Union for the prevention of relapse in patients with bipolar type 1 disorder who have predominantly depressive episodes.[8] There has been considerable uncertainly, however, around the efficacy of lamotrigine monotherapy in the acute phase of bipolar depression. A modest treatment effect was observed in

Research in context

Evidence before this study

During the planning phase of CEQUEL, we conducted a systematic review and individual patient data meta-analysis of randomised trials (Geddes et al, 2009). The pooled analysis found a modest treatment effect for lamotrigine over an 8 week period which was not observed in the individual trials.

Added value of this study

CEQUEL investigated the effect of lamotrigine compared with placebo over a longer time period than previous trials and as add-on therapy to quetiapine. CEQUEL also investigated the effects of folic acid compared to placebo in bipolar depression.

Implications of all the available evidence

Lamotrigine improves depressive symptoms in bipolar depression and the benefits are maintained for 52 weeks. Adding lamotrigine to quetiapine might be an effective and well tolerated option for many patients with bipolar depression. Folic acid may reduce the efficacy of lamotrigine. Lamotrigine also reduced the risk of relapse in patients with bipolar 1 disorder who have predominantly depressive episodes. CEQUEL should encourage clinicians and patients to consider lamotrigine for bipolar depression, but also to be aware that concurrent folic acid might reduce its effectiveness.

pooled analysis, but not seen in individual trials, which could be because the trials were of short (8 week) duration and lamotrigine requires a lengthy 6-week titration period, which means that the participants had been taking a full therapeutic dose for only 2 weeks at the time that the primary outcome was assessed.[9] The LamLit trial noted significant benefit at 8 weeks for the addition of lamotrigine to lithium therapy in patients with bipolar depression.[10]

See Online for appendix

Current monotherapies for bipolar depression remain restricted in terms of both proven efficacy and practical tolerability, but combinations of treatments might lead to improved outcomes. This trial was designed to test the hypothesis that a strategy of combining lamotrigine with quetiapine might lead 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, because 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,[3] leading to a functional synergy between lamotrigine and quetiapine.

The primary objective 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, we also investigated the effects of addition of folic acid, which is a simple, widely available, over-the-counter treatment, for which there is some evidence of efficacy in unipolar depression.[11] Furthermore, folic acid is often included in vitamin pills as well as being recommended during pregnancy especially when women are taking lamotrigine.[12]

Methods

Study design and participants

CEQUEL was a double-blind, randomised, placebo-controlled, parallel group, 2×2 factorial trial undertaken across 27 sites in the UK (figure 1). The trial protocol is available from JRG. Eligible patients had bipolar disorder I or II diagnosed according to DSM-IV[13] criteria on the basis of clinician interview, required new pharmacological treatment for an acute depressive episode, gave informed consent, and were aged 16 years or older (appendix). Additional criteria for entry to the randomised phase included ability to tolerate quetiapine at a dose of at least 150 mg/day; uncertainty whether quetiapine plus lamotrigine would be more effective than quetiapine monotherapy; acceptable adherence to quetiapine (>90%); and were responding to the prompts to provide outcome data; willing to accept random allocation of treatments; and in the opinion of the investigator, not currently experiencing manic or mixed episode.

Written informed consent was obtained from every patient. The study was approved by each centre.

A number of protocol changes were made during the trial, all of which were approved by the Oxfordshire REC B 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 400 mg/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 randomisation of patients already on quetiapine. Version 06 (May, 2013) included investigation of the effect of the folate hydrolase polymorphism on folic acid.

Randomisation and masking

After 7–14 days run-in on quetiapine, participants were randomly assigned (1:1) to added lamotrigine

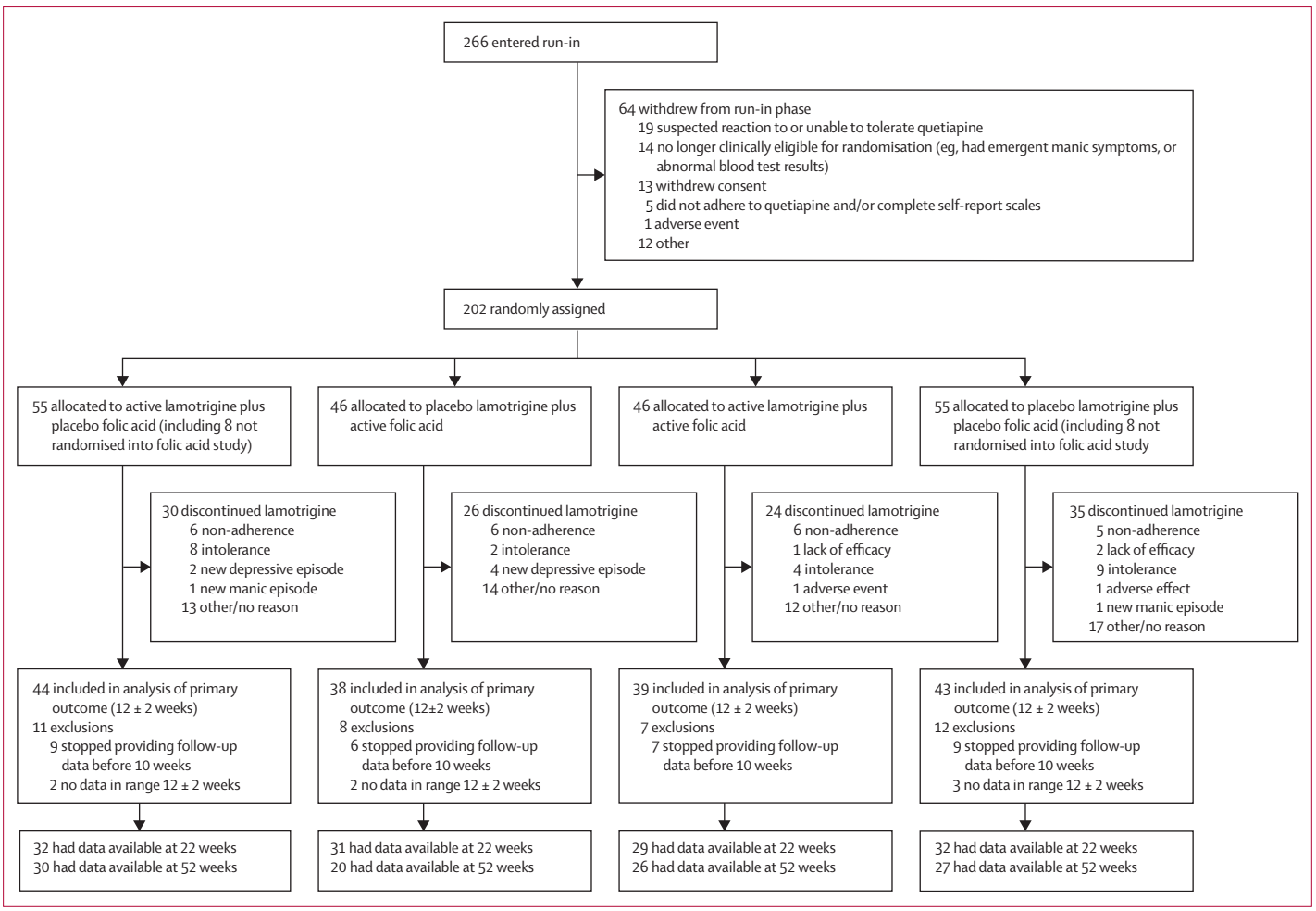

Figure 1: **Trial profile**

200 mg/day (100 mg/day with concurrent valproate and 400 mg/day with concurrent combined oral contraceptives) or placebo by a centralised randomisation service by fax or web-based form. Lamotrigine was commenced at 25 mg daily and increased gradually to 200 mg as in the US FDA prescribing information.[14] Participants, clinicians, and researchers were masked to treatment allocation.

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

Procedures

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 and 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.[15–18] QIDS-SR16 scores are categorised: ≤5 as no depression; 6–10 as mild depression; 11–15 as moderate depression; 16–20 as severe depression; and ≥21 as very severe depression. A minimum level of depressive symptoms was not required for entry to either run-in or randomised phases of the trial

For more on **QIDS** see http://www.ids-qids.org

because the relevant criterion was clinical judgement that new pharmacological treatment was required for a depressive episode. Manic symptoms were assessed with the Altman Self Rating Mania Scale (ASRM).[19] Quality of life was measured at baseline and at 12 weeks and 52 weeks with the EuroQol EQ-5D-3L.[20] Data for symptoms and quality of life were provided by participants by 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 before 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.

	Placebo (n=101)	Lamotrigine (n=101)	Placebo (n=94)	Folic acid (n=92)	NA* (n=16)
Bipolar type					
I	75 (74%)	74 (73%)	67 (71%)	69 (75%)	13 (81%)
II	26 (26%)	27 (27%)	27 (29%)	23 (25%)	3 (19%)
Age (years)					
≤30	17 (17%)	19 (19%)	19 (20%)	17 (19%)	0
31–40	20 (20%)	25 (25%)	25 (27%)	17 (19%)	3 (19%)
41–50	32 (32%)	34 (34%)	26 (28%)	33 (36%)	7 (44%)
>50	32 (32%)	23 (23%)	24 (26%)	25 (27%)	6 (38%)
Sex					
Male	46 (46%)	44 (44%)	41 (44%)	42 (46%)	7 (44%)
Female	55 (55%)	57 (56%)	53 (56%)	50 (54%)	9 (56%)
Dose of quetiapine (mg/day)					
≤150	19 (19%)	19 (19%)	16 (17%)	21 (23%)	1 (6%)
>150–<300	14 (14%)	18 (18%)	20 (21%)	9 (10%)	3 (19%)
300	54 (54%)	55 (54%)	50 (53%)	50 (54%)	9 (56%)
>300	14 (14%)	9 (9%)	8 (9%)	12 (13%)	3 (19%)
Concurrent medication					
Lithium	14 (14%)	12 (12%)	13 (14%)	12 (13%)	1 (6%)
Valproate	18 (18%)	24 (24%)	22 (23%)	18 (20%)	2 (13%)
Other mood stabiliser	2 (2%)	5 (5%)	2 (2%)	3 (3%)	2 (13%)
Olanzapine	4 (4%)	3 (3%)	5 (5%)	1 (1%)	1 (6%)
Other atypical antipsychotic	3 (3%)	4 (4%)	4 (4%)	3 (3%)	0
Conventional antipsychotic	3 (3%)	2 (2%)	1 (1%)	4 (4%)	0
Antidepressant	40 (40%)	29 (29%)	29 (31%)	33 (36%)	7 (44%)
Pretrial quetiapine	22 (22%)	25 (25%)	23 (25%)	21 (23%)	3 (19%)
Pretrial lamotrigine	1 (1%)	1 (1%)	1 (1%)	1 (1%)	0
Participants with mood episodes in past year	27 (27%)	26 (26%)	27 (29%)	24 (26%)	2 (13%)

Data are n (%). Participants were randomised to Lamotrigine or placebo, and additionally randomised to folic acid or placebo if included in that part of the study. Participants are therefore counted twice in this table. NA=not applicable. *Participants who chose not to be randomised into the folic acid component of the study.

Table 1: **Baseline characteristics at randomisation**

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 a response to allocated treatment was considered to be inadequate or if new symptoms emerged. Folic acid (prescribed and over-the-counter preparations) was stopped unless there were reasons why the participant should not be randomised to folic acid or placebo.

All participants initially entered a 7–14 day active run-in with quetiapine monotherapy to screen for adherence to quetiapine and to study procedures, tolerability, and symptom stability. Quetiapine was commenced at 50 mg on days 1 and 2, increased to 100 mg on days 3 and 4, 200 mg on days 5 and 6, and 300 mg on day 7 and beyond. The target dose of quetiapine was 300 mg, but if this was not tolerated a minimum dose of 150 mg was required for at least 3 days to proceed to randomisation. Quetiapine was continued at the established dose throughout the randomised phase unless there were clinical reasons to stop or the patient withdrew consent. Changes to the dose of quetiapine after 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 Oct 21, 2008, and the last patient completed follow-up on April 27, 2013. We also genotyped functional polymorphisms in genes involved in one-carbon pathways, and measured related biochemical indices; these results will be presented separately.

Outcomes

The primary outcome was depressive symptoms score at 12 weeks (±2 weeks) from randomisation using QIDS-SR16. The prespecified primary analysis was assessed via a linear mixed effects model using data at 12 weeks (±2), 22 (±2) weeks, and 52 (±2) weeks only. The model fitted time and randomised group as fixed effects and participants as random effect. An interaction between time and randomised group was fitted to allow estimation of treatment effect at each timepoint. Analysis was by modified intention-to-treat. That is, after randomisation, participants were analysed according to their allocated treatment group irrespective of what treatment they actually received. Assumptions for regression models were assessed graphically based on residuals. Participants who provided no data within these time windows were excluded. The model was adjusted for folic acid (active, placebo, or not allocated), baseline QIDS-SR16, baseline ASRM (≥6), bipolar disorder I or II, age, sex, dose of quetiapine (<300 mg/day or ≥300 mg/day), concurrent lithium, concurrent

valproate, or 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 randomised 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 randomised treatments (lamotrigine x folic acid) to the model in the analysis of the primary outcome. The interaction analysis was restricted to participants who were randomised 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 randomisation and week 52 were analysed with 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 timepoint was derived similarly as described above. To incorporate the noted absence of linearity into the analysis, the regression model was segmented at 12 weeks 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 weeks and 52 weeks; time to new intervention for depressive and manic symptoms; self-harm; mortality; adverse events; 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 or higher at 12 weeks, 22 weeks, and 52 weeks after randomisation, was analysed with log-binomial regression models at each timepoint separately. The models included treatment by lamotrigine, treatment by folic acid (yes, no, or not applicable) and minimisation variables as for the primary analysis.

Statistical analysis

The sample size was calculated to detect a clinically important effect of lamotrigine on the primary outcome measure—ie, a 2·0 point difference (SD 5·4) in the QIDS-SR16. The calculation assumed a repeated measures analysis with 3 timepoints 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 (90% power and two-sided alpha 5%).

Data were analysed with SAS version 9.3 (SAS Institute Inc, Cary, NC, USA).

CEQUEL was registered with EUdraCT, number 2007-004513-33; and approved by REC 08/H0605/39; with a clinical trial authorisation 20584/0234/001-0001 and ISRCTN17054996.

Role of the funding source

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

Results

Between Oct 21, 2008, and April 27, 2012, 202 participants were randomly assigned; 101 to lamotrigine and 101 to placebo (figure 1). Of 266 participants who entered the run-in, 19 (7%) were unable to progress to randomisation due to adverse effects or inability to tolerate quetiapine. Baseline characteristics of randomised participants are summarised in table 1; about three-quarters of patients met criteria for bipolar type I. The aim was to balance groups for bipolar subtype, age, and sex, but some imbalances remained. The largest imbalance was the proportion using antidepressants at randomisation: more participants randomised to placebo were using

	Number of participants	Mean (SD; 95% CI)
Lamotrigine *vs* placebo		
Placebo		
Baseline	101	15·0 (5·4; 13·9–16·0)
Week 12	81	12·5 (6·3; 11·1–13·8)
Week 22	63	11·6 (6·5; 10·0–13·2)
Week 52	47	12·0 (6·1; 10·2–13·8)
Lamotrigine		
Baseline	101	15·3 (5·1; 14·3–16·3)
Week 12	83	10·9 (6·7; 9·4–12·3)
Week 22	61	9·6 (6·4; 7·9–11·2)
Week 52	56	9·2 (6·8; 7·4–11·1)
Folic acid *vs* placebo*		
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)

QIDS-SR16=Quick Inventory of Depressive Symptomatology—self report version 16. *Folic acid versus placebo comparisons restricted to those participants who consented to separate randomisation.

Table 2: **QIDS-SR16 summary statistics**

	Adjusted* mean difference (95% CI)	p value
Placebo *vs* lamotrigine		
12 weeks (±2 weeks)	–1·73 (–3·57 to 0·11)	0·066
22 weeks (±2 weeks)	–1·87 (–3·92 to 0·17)	0·072
52 weeks (±2 weeks)	–2·69 (–4·89 to –0·49)	0·017
Placebo *vs* folic acid		
12 weeks (±2 weeks)	0·75 (–1·16 to 2·66)	0·441
22 weeks (±2 weeks)	0·17 (–1·97 to 2·30)	0·878
52 weeks (±2 weeks)	–0·92 (–3·20 to 1·35)	0·423

*Adjusted for baseline QIDS-SR16, bipolar I or bipolar II, age (classified as <40 years or ≥40 years), sex, dose of quetiapine (<300 mg/day or ≥300 mg/day), concurrent lithium, concurrent valproate, and concurrent antidepressant. Lamotrigine comparisons were adjusted for folic acid (active, placebo, or not applicable). Folic acid comparisons adjusted for lamotrigine (active or placebo). QIDS-SR16=Quick Inventory of Depressive Symptomatology—self report version 16.

Table 3: **QIDS-SR16 adjusted mean differences from mixed effects regression model by time**

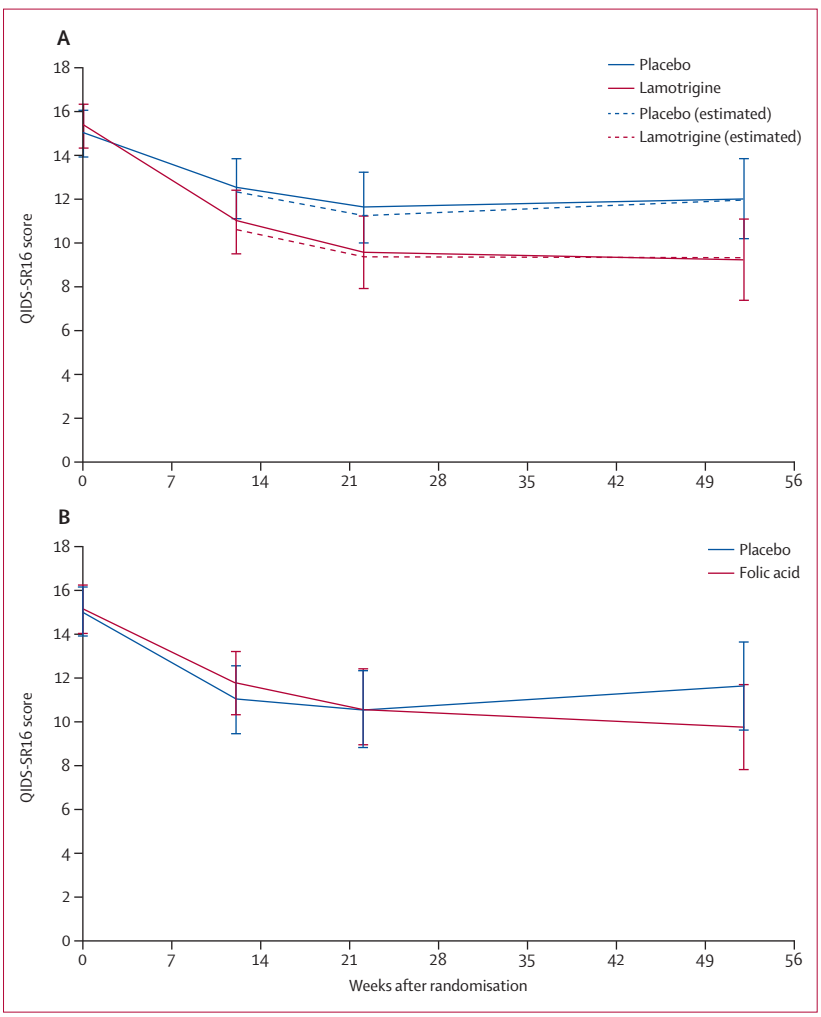

Figure 2: **Observed and estimated mean QIDS-SR16 scores at key timepoints by comparisons for lamotrigine (A) and folic acid (B)**
Error bars show 95% CI. QIDS-SR16=Quick Inventory of Depressive Symptomatology—self report version.

antidepressants compared with those randomised to lamotrigine. The direction of imbalance was reversed for the folic acid comparison, with slightly fewer participants using antidepressants at baseline in those who were randomised to placebo compared with those randomised to folic acid. Analyses were adjusted for these imbalances. About three quarters of participants were diagnosed with bipolar disease I and a quarter were diagnosed with bipolar disease II and the mean QIDS-SR16 score indicates moderate depression. The modal daily dose of quetiapine was 300 mg/day.

At 12 weeks, participants randomised to lamotrigine had lower QIDS- SR16 scores than those randomised to placebo (table 2; table 3; figure 2A). The mean difference between the groups was –1·73 points ([95% CI –3·57 to 0·11]; p=0·066). A similar difference was seen at 22 weeks (–1·87 points [–3·92 to 0·17]; p=0·072; table 3; figure 2B). At 52 weeks, participants randomised to lamotrigine were on average 2·7 points lower on the QIDS scale (–2·69 ([95% CI –4·89 to –0·49]; p=0·017) than those randomised to placebo. Thus, mean QIDS-SR16 scores were consistently lower in participants taking lamotrigine than in those taking placebo (table 3).

Significantly more participants treated with lamotrigine met criteria for remission (QIDS ≤5) at 12 weeks (26 [31%] in lamotrigine group *vs* 13 [16%] in placebo group; relative risk (RR) 2·11 [95% CI 1·09–4·07]; p=0·026) and at 52 weeks (20 [36%] in lamotrigine group vs six [13%] in placebo group; RR 3·73 [1·35–10·29]; p=0·012).

The secondary analysis of the primary outcome, using all submitted scores over the 52 week follow up period resulted in similar findings (data not shown). 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=0·066).

150 participants (all those available who were randomly assignedto folic acid study) were available for analysis of folic acid versus placebo at 12 weeks. Mean QIDS-SR16 scores were no different in those randomly assigned to folic acid than in those randomly assigned to placebo at 12 weeks or at 22 weeks and 52 weeks (table 2; figure 2B).

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

Due to the interaction noted between treatments, the most reliable and unconfounded estimate of the effect of lamotrigine at 12 weeks is the estimate from the group not randomised to take folic acid. At 12 weeks, the mean difference in QIDS-SR16 on lamotrigine compared with placebo was –4·14 ([95% CI –6·90 to –1·37]; p=0·004) with no folic acid and 0·12 ([–2·58 to 2·82]; p=0·931) with folic acid (figure 3).

There were no significant differences in rates of new treatment (hospital admission or drug treatment) for depression between the treatment groups (31 [31%] in

lamotrigine group *vs* 39 [39%] in placebo group; adjusted RR 0·84 [95% CI 0·58–1·24]) p=0·380) or folic acid compared with placebo (25 [27%] in folic acid group *vs* 37 [39%] in placebo group; adjusted RR 0·67 [0·43–1·03]; p=0·065). There were no differences noted for new treatments for mania or mixed state between treatment groups (nine [9%] in lamotrigine group *vs* 12 [12%] in placebo group; adjusted RR 0·67 [95% CI 0·29–1·56]; p=0·35) or for folic acid compared with placebo (eight [9%] in folic acid group *vs* 11 [12%] in placebo group; adjusted RR 0·79 [0·33–1·89]; p=0·60). 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 (appendix p 2). More participants on lamotrigine than on placebo reported some manic symptoms (ASRM ≥ 6) at 12 weeks (adjusted RR 2·59 [95% CI 1·24–5·41]; p=0·012), but not at 22 weeks (adjusted RR 0·98 [0·38–2·54]; p=0·967) or at 52 weeks (0·94 [0·31–2·87]; p=0·92), reflecting improved mood. Folic acid treatment showed no effect on mania scores (data not shown).

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 (appendix pp 3–4).

There were 32 serious adverse events in 24 randomised participants. These included one death by suicide (in the folic acid only group), 18 admissions to hospital for depression, mania, or other mood disorders involving 15 participants (six participants allocated placebo only, three participants allocated lamotrigine only, two participants allocated folic acid only, and four participants allocated lamotrigine plus folic acid); and 13 admissions to hospital in nine participants for other reasons; (three participants allocated placebo only, two participants allocated lamotrigine only, one participant allocated folic acid only, and three participants allocated lamotrigine plus folic acid). None were judged to be related to trial medication.

There were 17 non-serious adverse events that led to withdrawal of treatment in 17 participants. Five were judged to be possible adverse reactions to trial medication (one participant allocated placebo only, two participants allocated lamotrigine only, one participant allocated folic acid only, and one participant allocated lamotrigine plus folic acid). Symptoms included nausea and stomach cramps, musculoskeletal pain, and oedema. For 12 participants, the adverse event was judged to be unrelated to trial medication (five participants allocated placebo only, three participants allocated lamotrigine only, two participants allocated folic acid only and two participant allocated lamotrigine plus folic acid.

Table 2 shows the number of participants included at each timepoint but there are no data for adherence to treatment.

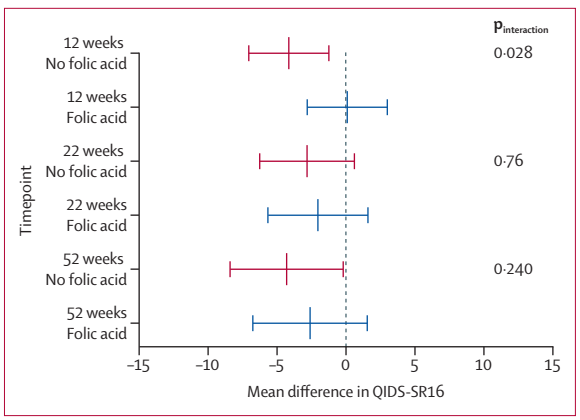

***Figure 3*: Forest plot showing within-group model estimates by timepoint and folic acid group**
QIDS-SR16=Quick Inventory of Depressive Symptomatology—self report version.

Discussion

The results of CEQUEL show that addition of lamotrigine to quetiapine for treatment of acute bipolar depression improves both mean depressive symptoms and rates of clinical remission compared with placebo at 12 weeks 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 seeming 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 points (95% CI 1·37–6·90) 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 might be due to lack of power.

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 maintenance trials in this clinical population.[23] Factorial trials, which can be an efficient way to evaluate two or more interventions, uncommonly identify interactions between treatments.[24,25] In CEQUEL, there was a statistically and clinically significant interaction, which shows 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 to consider such an interaction biologically plausible. Lamotrigine was originally synthesised as one of a series of folate antagonists on the grounds that folate was thought to be pro-convulsant.[6] Hence, it is possible that lamotrigine and folate both bind to a common receptor or enzyme site. Alternatively, it could be a pharmacokinetic effect whereby folic acid reduces absorption of lamotrigine from the gastrointestinal tract. There has been surprisingly little research into the mechanism(s) of action of lamotrigine to either include or exclude a possible important effect modification by folic acid. We cannot find any previous report of a clinical interaction of the kind we describe here, although the summary of product characteristics for lamotrigine does report an effect on folate levels. Whatever the cause, the interaction is potentially clinically important because folic acid supplementation might be more likely in some patient groups taking lamotrigine, for example pregnant women[12] and as an adjunctive therapy in mood disorder.[11] 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). 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 estimated to provide 100–200 µg 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.[10] Together with the pooled data of lamotrigine versus placebo,[9] it seems 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.[4] 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.

Contributors

JRG, JR, LY, GMG, ET, PH, and JS designed the trial. JRG, MJA, AG, JH, JR, and 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.

CEQUEL Study Group

Trial Steering Committee: Shôn Lewis (chair), John Geddes, Guy Goodwin, Hugh Gazzard, Neil Armstrong, Andrea Cipriani, Alex Gardiner, Jennifer Rendell, and Jane Sinclair.
Data Monitoring Committee: Thomas Barnes (chair), Deborah Ashby, and Vivien Curtis.
Avon and Wiltshire Mental Health Partnership NHS Trust: Jonathan Evans (principal investigator), William Bruce-Jones, Daniel Meron, Linda Heaney; *Barnet, Enfield and Haringey Mental Health NHS Trust:* Laurence Ratna (principal investigator); *Berkshire Healthcare NHS Foundation Trust:* Elizabeth Clifford (principal investigator), James Jeffs, Yousuf Rahimi, Saima Arshad; *Cambridgeshire and Peterborough NHS Foundation Trust:* Neil Hunt (principal investigator); *Central & North West London NHS Foundation Trust:* Maria Clarke (principal investigator); *Coventry and Warwickshire Partnership NHS Trust:* Ashok Jainer Kumar (principal investigator), Colin Campbell, Cath Dumughn, Bettahalasoor Somashekar; *Devon Partnership NHS Trust:* Charles Antwi (principal investigator), Sherin Mehany; *Dorset Primary Care Trust:* Jonathan Godfrey (principal investigator), Ian Rodin; *Dudley & Walsall Mental Health Partnership NHS Trust:* Panayiotis Zikis (principal investigator), Muhammad Naeem Khan; *Greater Glasgow and Clyde Health Board:* Jacqui Anderson (principal investigator); *Hertfordshire Partnership NHS Foundation Trust:* Jeremy Chase (principal investigator); *Lancashire Care NHS Foundation Trust:* Graham Ash (principal investigator), Mithilesh Jha, Muhammad Iqbal Naeem, Vinod Rao, Paul Reed; *Leeds Partnerships Foundation NHS Trust:* Tariq Mahmood (principal investigator),Tom Hughes, Yasir Abbasi; *Leicestershire Partnership NHS Trust:* Gary Drybala (principal investigator); *Lincolnshire Partnership NHS Foundation Trust:* Ashok Singh (principal investigator); *Lincolnshire Partnership NHS Foundation Trust:* Rudresh Pathak (principal investigator); *Lothian Health Board:* Elizabeth Hare (principal investigator), Donald James MacIntyre, Andrew McIntosh; *Northumberland, Tyne and Wear NHS Foundation Trust:* Iain Macmillan (principal investigator), David Cousins; *Norfolk and Waveney Mental Health NHS Foundation Trust:* Jon Wilson (principal investigator), Poornima Chandrappa, Obianuju Ugochukwu, Sumita Prabhakaran; *Northamptonshire Healthcare NHS Foundation Trust:* Husni Al-Robb (principal investigator), Mamdouh El-Adl, Manar Shaheen; *Nottinghamshire Healthcare NHS Trust:* Richard Morriss (principal investigator), Obi Okoye, Corinne Lewis; *Oxford Health NHS Foundation Trust:* John Geddes (principal investigator), Mary Jane Attenburrow, Rob Bale, Theodore Bargiotas, Philip Davison, Svetlana Hemsley, Emma Henderson, Alan Ogilvie, Digby Quested, Peter Sargent, Hugh Series, Matthew Taylor, Nicola Crowley, Pramod Kumar, Larissa Ryan, Rajiv Sharma, Olga Tsatalou, Philip Wilkinson; *Sheffield Health & Social Care NHS Foundation Trust:* Subha Thiyagesh (principal investigator); *South Staffordshire & Shropshire Healthcare NHS Foundation Trust:* Rubina Anjum (principal investigator), Ignasi Agell, Venkat Ramaswamy; *Southern Health NHS Foundation Trust:* Nicola Foster (principal investigator), Georgina Prentice; *Tees Esk & Wear Valleys NHS Foundation Trust:* Heinz Grunz (principal investigator), Ronnie Browne, Lenny Cornwall, Raj Kumar, Baxi Sinha; *West London Mental Health NHS Trust:* Peter Tyrer (principal investigator), Mohammed Al-Rawi, Syed Faisal Haq, Chris Bench.

Declaration of interests

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, and Takeda. EMT has served as a consultant for UCB Pharma. PJH reports grants from the Medical Research Council and the Wellcome Trust during the conduct of the study; and personal fees from Sunovion Pharmaceuticals, Roche Pharmaceuticals, Boehringer Ingelheim, Teva, Accord, and Sandoz, and Takeda (Cambridge) outside of the submitted work. JRG, AG, MV, ET, CH, L-MY, and JS declare no competing interests.

Acknowledgments

This study was funded by the Medical Research Council and managed by NIHR on behalf of the MRC-NIHR partnership. The views expressed in

this publication are those of the author(s) and not necessarily those of the MRC, NHS, NIHR or the Department of Health. We thank Orla Macdonald for managing the trial medication.

References

1 Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; **386:** 743–800.

2 Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry* 2002; **59:** 530–37.

3 Geddes JR, Miklowitz DJ. Treatment of bipolar disorder. *Lancet* 2013; **381:** 1672–82.

4 National Collaborating Centre for Mental Health. Bipolar disorder: the management of bipolar disorder in adults, children and young people, in primary and secondary care. London: National Institute for Health and Clinical Excellence; 2014. https://www.nice.org.uk/guidance/cg185 (accessed Nov 13, 2015).

5 Sidor MM, MacQueen GM. An update on antidepressant use in bipolar depression. *Curr Psychiatry Rep* 2012; **14:** 696–704.

6 Brodie MJ. Lamotrigine. *Lancet* 1992; **339:** 1397–400.

7 Weisler RH, Calabrese JR, Bowden CL, Ascher JA, DeVeaugh-Geiss J, Evoniuk G. Discovery and development of lamotrigine for bipolar disorder: a story of serendipity, clinical observations, risk taking, and persistence. *J Affect Disord* 2008; **108:** 1–9.

8 Goodwin GM, Bowden CL, Calabrese JR, et al. A pooled analysis of 2 placebo-controlled 18-month trials of lamotrigine and lithium maintenance in bipolar I disorder. *J Clin Psychiatry* 2004; **65:** 432–41.

9 Geddes JR, Calabrese JR, Goodwin GM. Lamotrigine for treatment of bipolar depression: independent meta-analysis and meta-regression of individual patient data from five randomised trials. *Br J Psychiatry* 2009; **194:** 4–9.

10 Van der Loos MLM, Mulder PGH, Hartong EGTM, et al. Efficacy and safety of lamotrigine as add-on treatment to lithium in bipolar depression: a multicenter, double-blind, placebo-controlled trial. *J Clin Psychiatry* 2009; **70:** 223–31.

11 Taylor MJ, Carney SM, Goodwin GM, Geddes JR. Folate for depressive disorders: systematic review and meta-analysis of randomized controlled trials. *J Psychopharmacol* 2004; **18:** 251–56.

12 Harden CL, Pennell PB, Koppel BS, et al. Management issues for women with epilepsy-focus on pregnancy (an evidence-based review): III. Vitamin K, folic acid, blood levels, and breast-feeding. *Epilepsia* 2009; **50:** 1247–55.

13 American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (4th edn). Washington DC: American Psychiatric Association, 1994.

14 LAMICTAL prescribing information. US Food and Drug Administration. http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020241s037s038,020764s030s031lbl.pdf (accessed Nov 13, 2015).

15 Rush AJ, Trivedi MH, Ibrahim HM, et al. The 16-Item quick inventory of depressive symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry* 2003; **54:** 573–83.

16 Trivedi MH, Rush AJ, Ibrahim HM, Carmody TJ, Biggs MM, Suppes T. The inventory of depressive symptomatology, clinician rating (IDS-C) and self-report (IDS-SR), and the quick inventory of depressive symptomatology, clinician rating (QIDS-C) and self-report (QIDS-SR) in public sector patients with mood disorders: a psychometric evaluation. *Psychol Med* 2004; **34:** 73–82.

17 Bernstein IH, Rush AJ, Suppes T, Kyotoku Y, Warden D. The quick inventory of depressive symptomatology (clinician and self-report versions) in patients with bipolar disorder. *CNS Spectr* 2010; **15:** 367–73.

18 Bernstein IH, Rush AJ, Suppes T, et al. A psychometric evaluation of the clinician-rated Quick Inventory of Depressive Symptomatology (QIDS-C16) in patients with bipolar disorder. *Int J Methods Psychiatr Res* 2009; **18:** 138–46.

19 Altman EG, Hedeker D, Peterson JL, Davis JM. The Altman self-rating mania scale. *Biol Psychiatry* 1997; **42:** 948–55.

20 EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. *Health Policy* 1990; **16:** 199–208.

21 Bopp JM, Miklowitz D, Geddes JR, Goodwin GM, Rendell J, Stevens W. Text messaging based mood charting for individuals with bipolar disorder. Association for Behavioral and Cognitive Therapies. Orlando, FL; 2008.

22 Pablos MA, Barr RG, Shea S. Run-in periods in randomized trials: implications for the application of results in clinical practice. *JAMA* 1998; **279:** 222–25.

23 Suppes T, Vieta E, Liu S, Brecher M, Paulsson B, Trial I. Maintenance treatment for patients with bipolar I disorder: results from a north American study of quetiapine in combination with lithium or divalproex (Trial 127). *Am J Psychiatry* 2009; **166:** 476–88.

24 ISIS-2 (Second International Study of Infarct Survival) Collaborative Group Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988; **2:** 349–60.

25 McAlister FA, Straus SE, Sackett DL, Altman DG. Analysis and reporting of factorial trials: a systematic review. *JAMA* 2003; **289:** 2545–53.

26 Lubsen J, Pocock SJ. Factorial trials in cardiology: pros and cons. *EurHeart J* 1994; **15:** 585–88.

27 Crider KS, Bailey LB, Berry RJ. Folic acid food fortification—its history, effect, concerns, and future directions. *Nutrients* 2011; **3:** 370–84.

28 Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. *Bipolar Disord* 2013; **15:** 1–44.