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Abstract

Lamotrigine for people with borderline personality disorder: a RCT

Mike J Crawford,[1]* Rahil Sanatinia,[1] Barbara Barrett,[2] Gillian Cunningham,[3] Oliver Dale,[4] Poushali Ganguli,[2] Geoff Lawrence-Smith,[5] Verity C Leeson,[1] Fenella Lemonsky,[1] Georgia Lykomitrou-Matthews,[6] Alan Montgomery,[7] Richard Morriss,[7] Jasna Munjiza,[8] Carol Paton,[5] Iwona Skorodzien,[6] Vineet Singh,[9] Wei Tan,[7] Peter Tyrer[1] and Joseph G Reilly[3] on behalf of the LABILE study team

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Background: No drug treatments are currently licensed for the treatment of borderline personality disorder (BPD). Despite this, people with this condition are frequently prescribed psychotropic medications and often with considerable polypharmacy. Preliminary studies have indicated that mood stabilisers may be of benefit to people with BPD.

Objective: To examine the clinical effectiveness and cost-effectiveness of lamotrigine for people with BPD.

Design: A two-arm, double-blind, placebo-controlled individually randomised trial of lamotrigine versus placebo. Participants were randomised via an independent and remote web-based service using permuted blocks and stratified by study centre, the severity of personality disorder and the extent of hypomanic symptoms.

Setting: Secondary care NHS mental health services in six centres in England.

Participants: Potential participants had to be aged ≥ 18 years, meet diagnostic criteria for BPD and provide written informed consent. We excluded people with coexisting psychosis or bipolar affective disorder, those already taking a mood stabiliser, those who spoke insufficient English to complete the baseline assessment and women who were pregnant or contemplating becoming pregnant.

Interventions: Up to 200 mg of lamotrigine per day or an inert placebo. Women taking combined oral contraceptives were prescribed up to 400 mg of trial medication per day.

Main outcome measures: Outcomes were assessed at 12, 24 and 52 weeks after randomisation. The primary outcome was the total score on the Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD) at 52 weeks. The secondary outcomes were depressive symptoms, deliberate self-harm, social functioning, health-related quality of life, resource use and costs, side effects of treatment and adverse events. Higher scores on all measures indicate poorer outcomes.

Results: Between July 2013 and October 2015 we randomised 276 participants, of whom 195 (70.6%) were followed up 52 weeks later. At 52 weeks, 49 (36%) of those participants prescribed lamotrigine and 58 (42%) of those prescribed placebo were taking it. At 52 weeks, the mean total ZAN-BPD score was 11.3 [standard deviation (SD) 6.6] among those participants randomised to lamotrigine and 11.5 (SD 7.7) among those participants randomised to placebo (adjusted mean difference 0.1, 95% CI –1.8 to 2.0; $p = 0.91$). No statistically significant differences in secondary outcomes were seen at any time. Adjusted costs of direct care for those prescribed lamotrigine were similar to those prescribed placebo.

Limitations: Levels of adherence in this pragmatic trial were low, but greater adherence was not associated with better mental health.

Conclusions: The addition of lamotrigine to the usual care of people with BPD was not found to be clinically effective or provide a cost-effective use of resources.

Future work: Future research into the treatment of BPD should focus on improving the evidence base for the clinical effectiveness and cost-effectiveness of non-pharmacological treatments to help policy-makers make better decisions about investing in specialist treatment services.

Trial registration: Current Controlled Trials ISRCTN90916365.

Funding: Funding for this trial was provided by the Health Technology Assessment programme of the National Institute for Health Research (NIHR) and will be published in full in *Health Technology Assessment*; Vol. 22, No. 17. See the NIHR Journals Library website for further project information. The Imperial Biomedical Research Centre Facility, which is funded by NIHR, also provided support that has contributed to the research results reported within this paper. Part of Richard Morriss' salary during the project was paid by NIHR Collaboration for Leadership in Applied Health Research and Care East Midlands.

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List of abbreviations

AD-SUS	Adult Service Use Schedule
AE	adverse event
ASSIST	Alcohol, Smoking and Substance Involvement Screening Test
BDI	Beck Depression Inventory
BPD	borderline personality disorder
CACE	complier-average causal effect
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
DSM-IV	*Diagnostic and Statistical Manual of Mental Disorders*-Fourth Edition
EQ-5D-3L	EuroQoL-5 Dimensions, three-level version
GP	general practitioner
HCL-32	Hypomanic Checklist-32 items
ICER	incremental cost-effectiveness ratio
IPDE	International Personality Disorder Examination
LABILE	Lamotrigine And Borderline personality disorder: Investigating Long-term Effectiveness
NICE	National Institute for Health and Care Excellence
QALY	quality-adjusted life-year
SAE	serious adverse event
SCID-I	Structured Clinical Interview for DSM-IV Axis I Disorders
SCID-II	Structured Clinical Interview for DSM-IV Axis II Personality Disorders
SD	standard deviation
SFQ	Social Functioning Questionnaire
ZAN-BPD	Zanarini Rating Scale for Borderline Personality Disorder

Plain English summary

People with borderline personality disorder (BPD) experience high levels of emotional distress and rapid and upsetting changes in mood. No medications are currently available for people with this condition. 'Mood stabilisers' are known to reduce mood swings in people with bipolar affective disorder and the results of small-scale studies suggest that they may also help people with BPD.

We conducted a clinical trial of the mood stabiliser lamotrigine for people with BPD who were using mental health services. We compared the effects of lamotrigine with those of a placebo (a dummy pill that did not contain any active drug) so that neither the researchers nor the participants knew what treatment they had been given until after we had completed an initial analysis of the results of the study. We assessed mental health, social functioning, quality of life, side effects and use of services in the year after people entered the study.

A total of 276 participants took part and 195 were followed up 1 year later. Fewer than half the participants (39%) were taking trial medication regularly at 1 year. We found no difference in mental health or any of the other outcomes we measured between those who were prescribed lamotrigine and those prescribed the placebo. We checked to see if the results were affected by whether or not people were taking their medication regularly and found no difference between those taking lamotrigine and those taking the placebo. On the basis of the results of this study, we have not shown any benefits of lamotrigine for treating people with BPD. Further research is needed to find out how best to help improve the mental health of people with this condition.

Scientific summary

Background

Borderline personality disorder (BPD) is a severe mental health condition that is associated with poor mental health, rapid and distressing fluctuations in mood and an increased risk of suicidal behaviour. No medication is currently licensed for the treatment of BPD. National guidance on the treatment of people with BPD highlighted the potential value of mood stabilisers but concluded that there was insufficient evidence to recommend the use of any drug in the treatment of this condition. Lamotrigine is a mood stabiliser that reduces fluctuations in mood among people with bipolar affective disorder and prevents episodes of depression in these patients. Compared with other mood stabilisers, lamotrigine is relatively safe in overdose. Two small-scale clinical trials of lamotrigine for people with BPD found improvements in emotional health among those randomised to lamotrigine compared with those randomised to placebo. Neither trial examined the long-term effects of lamotrigine or examined the costs and cost-effectiveness of this approach in trying to help people with BPD.

The Lamotrigine And Borderline personality disorder: Investigating Long-term Effectiveness (LABILE) trial was designed to generate high-quality evidence on the clinical effectiveness and cost-effectiveness of lamotrigine for people with BPD.

Objectives

The main objective of the study was to establish whether or not prescribing lamotrigine to people with BPD provides a clinically effective and cost-effective use of resources. To achieve this objective, we:

1. tested whether or not adding lamotrigine to usual care improves mental health over a 12-month period
2. examined whether or not the addition of lamotrigine to usual care improves social functioning and health-related quality of life, reduces the incidence of suicidal behaviour and lowers the amount of psychotropic medication that people are prescribed
3. examined the cost and cost-effectiveness of adding lamotrigine to the treatment of people with BPD.

Methods

Study design

The study design was a two-arm, parallel-group, double-blind, placebo-controlled, randomised trial with an integrated economic evaluation.

Setting

Study participants were recruited from inpatient units and outpatient clinics in six secondary care mental health services in England: Central and North West London NHS Foundation Trust, Derbyshire Healthcare NHS Foundation Trust, Nottinghamshire Healthcare NHS Foundation Trust, Oxleas NHS Foundation Trust, Tees, Esk and Wear Valleys NHS Foundation Trust and West London Mental Health NHS Trust.

Target population

The target population was people aged ≥ 18 years who were in contact with mental health services and met the *Diagnostic and Statistical Manual of Mental Disorders*-Fourth Edition (DSM-IV) diagnostic criteria for BPD using the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II). We excluded those who met the diagnostic criteria for bipolar affective disorder, those already taking lamotrigine and

those unable to speak sufficient English to complete the baseline assessment. We also excluded any potential participant who was breastfeeding or pregnant at the time of the baseline assessment, planning or contemplating becoming pregnant during the following 12 months or pre-menopausal, sexually active and unwilling to take regular contraception.

Health technologies assessed

All those taking part in the study continued to receive treatment as usual from primary and secondary care services. In addition, those who were randomised to the active arm of the trial were prescribed capsules containing up to 200 mg of generic lamotrigine titrated over a 6-week period, depending on how well it was tolerated and clinical response. In keeping with clinical recommendations, this regime was modified for women taking the combined oral contraceptive pill, who were prescribed up to 400 mg daily.

Those participants randomised to the control arm of the trial were prescribed an inert placebo in capsules that were identical in appearance to the capsules containing lamotrigine but which were backfilled with lactose monohydrate, using the same titration regime as those in the active arm of the trial.

Measurement of costs and outcomes

Our primary outcome was symptoms of BPD measured at 12 months using total score on the Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD). The ZAN-BPD is a widely used measure of the symptoms and behavioural problems experienced by people with BPD.

Our secondary outcomes were measured at baseline and at 3, 6 and 12 months after randomisation: mental health (using ZAN-BPD and the Beck Depression Inventory), deliberate self-harm (using the Acts of Deliberate Self-Harm Inventory), social functioning (using the Social Functioning Questionnaire), health-related quality of life [using the EuroQoL-5 Dimensions, three-level version (EQ-5D-3L)], side effects of treatment, adverse reactions and medication adherence. Resource use and costs were assessed using a modified version of the Adult Service Use Schedule. This questionnaire collects detailed data on use of all hospital and community services, including medication. All assessments were conducted by researchers who were masked to allocation status.

Study logistics

Staff working in mental health services were asked to identify potential participants. Those willing to meet with a researcher were provided with verbal and written information about the study and asked whether or not they would be willing to take part. Those participants who provided written informed consent were assessed for eligibility using the SCID-II to establish if the participant met the criteria for BPD, and the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) to establish whether or not they had coexisting bipolar affective disorder. Those who were eligible were then assessed using study outcome measures, an assessment of their personality (using the International Personality Disorder Examination), hypomanic symptoms [using the Hypomanic Checklist-32 items (HCL-32)] and use of alcohol and other drugs using the Alcohol, Smoking and Substance Involvement Screening Test. Study participants were then randomised centrally by the Nottingham Clinical Trials Unit using a remote web-based system. We used permuted stacked blocks stratified by study centre, severity of personality disorder and extent of hypomanic symptoms. The block size was randomly assigned between 4 and 6.

Sample size

The sample size for the study was calculated on the basis of our primary hypothesis: that, for people with BPD who are in contact with mental health services, the addition of lamotrigine to their usual treatment would reduce the symptoms of their disorder at 52 weeks according to the total score on the ZAN-BPD. We calculated that 214 participants (receiving lamotrigine, $n = 107$; receiving placebo, $n = 107$) would need to be randomised to have 90% power to detect a minimal clinically relevant difference of 3.0 [standard deviation (SD) 6.75] in total score on the ZAN-BPD at 12 months, using a 0.05 level of statistical significance. To take account of 15% loss to follow-up at 6 months, we increased the sample size to 246 participants.

Data analysis

The primary analysis was performed according to the intention-to-treat principle, without imputation of missing data. The analysis was adjusted by site, baseline ZAN-BPD score, severity of personality disorder (simple or complex) and score on the HCL-32 (score of ≥ 14 or < 14). For the secondary analysis of ZAN-BPD scores, groups were compared using a mixed model for repeated outcome measures adjusted by the same stratification variables used for the primary analysis. We investigated whether any treatment effects were sustained or emerged later by including an interaction term between treatment with lamotrigine and time in the model. In the absence of a time effect, the effectiveness parameter was the average difference in mean ZAN-BPD score over the 52-week period, along with 95% confidence interval (CI) and exact *p*-value. Further sensitivity analyses were conducted to adjust for any variable with marked imbalance at baseline and investigate the impact of missing data, using multiple imputation.

We investigated the effect of treatment adherence using complier-average causal effect (CACE) estimation methods according to whether or not the participant has taken medication at a dose of ≥ 100 mg without interruption during the 52 weeks prior to the final follow-up interview. Analyses of secondary outcomes used similar methods to those in the primary analysis. We used general linear models for continuous outcomes and logistic regression models for binary outcomes.

For safety data, including adverse events (AEs), serious adverse events (SAEs) and suspected unexpected serious adverse reactions, we used basic summary statistics, that is, the number of AEs/side effects of different categories and the number and proportion of participants who reported at least one AE or SAE within each treatment arm.

The primary cost-effectiveness analysis involved comparing incremental differences in total costs and incremental differences in mental health assessed using the ZAN-BPD. In a secondary cost–utility analysis, we compared incremental differences in costs with differences in quality of life measured using quality-adjusted life-year (QALYs) derived from the EQ-5D-3L.

Results

Between July 2013 and October 2015, 296 patients were assessed for eligibility, of whom 276 (93.2%) met eligibility criteria and were randomised: 137 to lamotrigine plus usual care and 139 to placebo plus usual care. The mean age of the study sample was 36.1 years (SD 11.0 years) and three-quarters were female. A total of 195 (70.7%) participants completed the 52-week follow-up. A total of 93 (34%) participants reported taking trial medication as per protocol; the proportion was similar in both arms.

There was no difference in adjusted total ZAN-BPD score at 52 weeks between treatment arms (11.3 in the active arm and 11.5 in the control arm of the trial; difference 0.1, 95% CI –1.8 to 2.0). The lack of treatment effect was supported by the results of sensitivity analyses. Differences between groups were not seen for secondary outcomes or at the 12- or 26-week follow-up assessment. The results of the CACE analysis also showed no differences between treatment groups. Regarding AEs, 77 (56%) of those in the lamotrigine arm of the trial experienced one or more events, compared with 93 (67%) of those in the control arm of the trial. The corresponding figures for SAEs were 26 (19%) in the active arm of the trial and 32 (23%) in the control arm.

At baseline, costs were, on average, £5618 in the lamotrigine group and £3555 in the placebo group. The average total costs over 52 weeks were £12,244.32 in the lamotrigine group and £8495.41 in the control arm of the trial. The difference in cost was not statistically significant ($p = 0.617$). Group differences between health-related quality of life and the resulting QALYs were also not statistically significant.

Implications for health care

We found no evidence of benefit from prescribing lamotrigine to people with BPD beyond those associated with prescribing an inert placebo. We did not show any beneficial effects of lamotrigine for the treatment of people with BPD. It is important to differentiate emotional instability seen in bipolar disorder with that seen in BPD, as lamotrigine can be an effective treatment for people with bipolar disorder.

Recommendations for future research

1. Future research should examine ways that clinicians can help people with BPD manage at times of crisis without recourse to pharmacotherapy.
2. Further research should test the clinical effectiveness and cost-effectiveness of structured psychological treatments compared with structured clinical care for people with BPD
3. The role of atypical antipsychotic drugs in the treatment of impulsive and self-harming behaviour among people with severe BPD warrants further investigation.

Trial registration

This trial is registered as ISRCTN90916365.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research. The Imperial Biomedical Research Centre Facility, which is funded by the National Institute for Health Research, also provided support that has contributed to the research results reported within this paper. Part of Richard Morriss' salary during the project was paid by NIHR Collaboration for Leadership in Applied Health Research and Care East Midlands.

Chapter 1 Introduction

The importance of borderline personality disorder

Borderline personality disorder (BPD) is a severe mental health condition that is characterised by affective instability, recurrent suicidal behaviour and impaired interpersonal functioning.[1] It is estimated that between 0.5% and 2% of people have BPD.[2] The levels of BPD among people in contact with mental health services are far higher; as many as one-fifth of people who are admitted to inpatient mental health units in the UK have this diagnosis.[3]

People with BPD are more likely to experience other mental health problems such as anxiety, depression and substance misuse. Of those who attend emergency medical services following deliberate self-harm, 1 in 10 have BPD,[4] and the rate of completed suicide among people with this condition is 50 times higher than in the general population.[5] People with this condition have poor social functioning; many are socially isolated and most are unemployed or on long-term sick leave.[6] People with BPD are also more likely to experience poor physical health[7] and mortality due to cardiovascular disease and other physical health problems is higher.[8] The reasons for this are unclear. Although it is possible that the high levels of emotional distress that people with BPD experience are associated with more somatic symptoms,[9] it seems likely that higher levels of smoking and substance misuse are important.[10] People with BPD may neglect themselves, and problems in maintaining interpersonal relationships may make it more difficult for them to obtain the physical health care they need when unwell.[10]

Treatment of borderline personality disorder

Concerns have been expressed about the quality of services for people with BPD.[11] Many people who have this diagnosis report that they are dissatisfied with the treatment they receive,[12,13] and mental health practitioners often find it difficult to work with people with this condition.[14]

Although psychological treatments, such as dialectical behaviour therapy and mentalisation-based therapy, have been shown to improve the mental health of people with BPD,[15] most people with this disorder do not have access to specialist psychological treatment services. Among those who do, many do not engage with psychological treatment, and as many as half of those who do engage drop out before the treatment has been completed.[16] People with the most severe problems are less likely to engage successfully in psychological treatments than those with milder forms of the disorder.[16,17]

No drug treatments are licensed for the treatment of BPD. Despite this, people with this condition are often prescribed large amounts of psychotropic medication.[18] Antidepressants are widely used, despite evidence that they do not improve the mental health or social functioning of people with BPD.[19] The results of randomised trials of antipsychotic medications are equivocal. Although some studies have shown short-term reductions in symptoms of anger and hostility, the longer-term effects of these drugs are not known.[19]

The role of mood stabilisers

Affective instability and higher than expected levels of comorbidity with bipolar disorder among people with BPD have led to considerable interest in the role that mood stabilisers may play in improving the mental health of people with this disorder.[20] Investigation of the role of mood stabilisers was highlighted as a priority for future research in the National Institute for Health and Care Excellence (NICE) guidelines on the recognition and management of BPD.[11] Research into the effects of established mood stabilisers,

such as lithium and carbamazepine, has been limited because of their toxicity in overdose, which is a not infrequent occurrence among people with this condition.[21] Another concern about the use of mood stabilisers in people with BPD is the increased incidence of birth defects among children born to women taking these drugs.[22] Most people with BPD who are in contact with mental health services are women of child-bearing age. Many women with BPD report impulsive behaviour, including unplanned and unprotected sex. Data from women who take these drugs for epilepsy have shown that levels of major congenital malformations are higher among those taking valproate than among those taking lamotrigine.[23] Concerns have also been raised about long-term cognitive impairment among children born to women taking valproate.[24]

Lamotrigine is a mood stabiliser with antiepileptic and analgesic properties.[25,26] The mechanism of action of lamotrigine in patients with bipolar affective disorder is poorly understood but may relate to enhancing the action of the inhibitory neurotransmitters, including gamma-aminobutyric acid.[27]

Evidence in support of the use of lamotrigine for people with BPD comes from three open-label studies and two placebo-controlled trials.[19] The two randomised controlled trials of lamotrigine for people with BPD have reported positive findings. The first trial, by Tritt *et al.*,[28] involved 24 women who were recruited mainly from advertisements placed in primary care practices. In comparison with those women taking the placebo, women taking up to 200 mg of lamotrigine were found to have lower levels of anger 8 weeks later. The second trial, by Reich *et al.*,[29] recruited 28 men and women through websites and television and radio advertisements. Those participants who were randomised to receive up to 225 mg of lamotrigine were subsequently found to have lower levels of affective instability and impulsiveness [assessed using the Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD)] 12 weeks later. A key limitation of both studies is that the degree of severity may have been lower than that seen among people with BPD who are treated in secondary care mental health services. Data on levels of global functioning at the time of the baseline assessment in the trial by Reich *et al.*[29] show that mean levels of impaired social function were in the 'moderate' range. Both studies focused on short-term effects of lamotrigine and neither examined the costs or cost-effectiveness of this intervention.

Lamotrigine is associated with a range of side effects, which include a skin rash that is reported in up to 10% of people taking the drug and a more severe cutaneous reaction, Stevens–Johnson syndrome, which is estimated to occur in $< 0.1\%$ of people taking this drug.[30] The incidence of this problem is reduced by gradual dose escalation and care with interacting agents, such as valproate and oral contraceptives. However, serious events are rare, and the drug is widely used in the UK for the treatment of people with bipolar disorder; therefore, psychiatrists are familiar with its dose titration requirements and the need for vigilance regarding severe cutaneous adverse reactions.

The LABILE study

The Lamotrigine And Borderline personality disorder: Investigating Long-term Effectiveness (LABILE) trial was designed to compare the clinical effectiveness and cost-effectiveness of lamotrigine plus usual care with an inactive placebo plus usual care over a 1-year period. The main aim of the study was to test whether or not prescribing lamotrigine in addition to usual treatment reduces symptoms of this condition, improves social functioning and quality of life, reduces the incidence of suicidal behaviour, reduces the level of alcohol and substance misuse and lowers the amount of antipsychotic and other psychotropic medication that people are prescribed. The trial also examined the cost, cost-effectiveness and cost–utility of adding lamotrigine to usual care for adults with BPD.

Chapter 2 Methods

Design

The LABILE trial was a multicentre, two-arm, parallel-group, double-blind, placebo-controlled, individually randomised trial of lamotrigine versus placebo with 12-, 24- and 52-week follow-up assessments. The trial included an integrated clinical and economic evaluation.

Study setting

Study participants were recruited from secondary care mental health services in England including inpatient units, outpatient clinics and community mental health teams. There were six recruitment centres altogether in London (Central and North West London NHS Foundation Trust, Oxleas NHS Foundation Trust, West London Mental Health NHS Trust), the East Midlands (Nottinghamshire Healthcare NHS Foundation Trust, Derbyshire Healthcare NHS Foundation Trust) and the north-east of England (Tees, Esk and Wear Valleys NHS Foundation Trust).

Participants

To be eligible to take part in the study, potential participants had to be aged $\geq$ 18 years, meet the *Diagnostic and Statistical Manual of Mental Disorders*-Fourth Edition (DSM-IV) diagnostic criteria for BPD and be willing and able to provide written informed consent to take part in the study. Potential participants were excluded if they:

1. had a coexisting diagnosis of bipolar affective disorder (type I and II) or psychotic disorder (schizophrenia, schizoaffective disorder or mood disorder with psychotic features)
2. were already being prescribed a mood stabiliser (lithium, carbamazepine or valproate) or had had one within the past 4 weeks
3. had a known medical history of liver or kidney impairment
4. had cognitive or language difficulties that prevented them from providing informed consent.

In addition to this, women were excluded from the study if they were pregnant, planning a pregnancy or of child-bearing age and not using adequate contraception.

Interventions

Those who were allocated to the active arm of the trial were prescribed encapsulated generic lamotrigine, titrated according to the established *British National Formulary* protocol[30] but with the titration occurring at standardised 14-day intervals. The dose was altered for participants who were taking the combined oral contraceptive pill, which affects the metabolism of lamotrigine. For all participants, the starting dose was 25 mg per day and this was increased to 50 mg after 2 weeks, 100 mg after 4 weeks and 200 mg per day after 6 weeks. The dose was maintained at 200 mg unless the participant was taking the combined oral contraceptive pill, in which case it was further increased to 300 mg after 8 weeks and 400 mg per day after 10 weeks. However, the same dose could be prescribed again for an additional 2 weeks during titration and a lower maintenance dose utilised throughout participation when this was clinically indicated, such as when tolerability or emergent side effects were a concern.

Those who were allocated to the placebo arm of the trial were given capsules identical in appearance to those containing active lamotrigine, but backfilled with lactose monohydrate. This was prescribed in the same regime as that used in the active arm of the trial.

Trial medication was issued to patients fortnightly to cover the dose titration period, with a 17-day supply provided in case the next supply was delayed for any reason, such as a participant not attending a scheduled meeting. Once the maintenance dose was reached, further trial medication was provided either fortnightly or 4-weekly, as decided by the prescriber based on an assessment of risk of intentional overdose. In any instance when a participant had, intentionally or unintentionally, stopped taking trial medication for a period of ≥ 5 consecutive days, they were returned to a prescribed dosage of 25 mg daily and re-titrated gradually to their maintenance dose.

Usual care

Usual care in the trial comprised contact with primary care and secondary care health services, including access to psychological treatment services and inpatient admission if required. No restrictions were imposed on the use of other treatments, except that those who remained in the trial were not to be prescribed lamotrigine (aside from trial medication) or any other mood stabiliser (lithium, carbamazepine or sodium valproate).

Assessments

Assessment of eligibility and for determining randomisation strata

We assessed eligibility using the items on BPD from the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II).[31,32] We planned to use data from other sections of the SCID-II to establish the severity of the participant's personality disorder[33] but, following feedback from researchers and service users, we replaced this with the self-completed International Personality Disorder Examination (IPDE) screening questionnaire (DSM-IV version) to reduce the amount of time that it took to complete the baseline assessment.[34] We used the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)[35] to assess whether or not potential participants had bipolar affective disorder (type I or II) and excluded those who did. Hypomanic symptoms were assessed using the Hypomanic Checklist-32 items (HCL-32),[36] a relatively short screening questionnaire that can distinguish those with bipolar disorder from those with unipolar depression.

Primary outcome

The primary outcome was symptoms of BPD measured using the ZAN-BPD[37] 52 weeks after randomisation. The ZAN-BPD is a widely used measure of the symptoms and behavioural problems experienced by people with BPD. The scale includes four subscores for the domains of affective disturbance, cognitive disturbance, impulsivity and disturbed relationships, which characterise the signs and symptoms of BPD. The ZAN-BPD has been used in previous studies of pharmacological and psychological treatments for people with BPD.[29,38–40] It is reliable (intraclass correlation coefficients for inter-rater reliability = 0.96 and test–retest reliability = 0.93), has high convergent validity with structured clinical ratings of symptoms of BPD and is sensitive to change.[37]

The lead researcher on the study received personal training on the use of the ZAN-BPD from Professor Mary Zanarini (who developed the scale). This researcher then trained the other researchers, initially by using vignettes and then by discussing participants whom they had assessed. In order to test the reliability of the assessment of the primary outcome among researchers, we arranged for 27 participants to be simultaneously rated by two separate researchers and we calculated the extent to which total scores on the scale were correlated.

Secondary outcomes

The following secondary outcomes were assessed:

1. Scores on the ZAN-BPD in the 52 weeks after randomisation using repeated measures analysis of data collected at 12, 24 and 52 weeks' follow-up.
2. Total score on the 21-item Beck Depression Inventory (BDI)[41] at 12, 24 and 52 weeks. The BDI has been widely used as a self-completed questionnaire, provides a valid assessment of the severity of depressive symptoms and can be completed in less than 10 minutes.[42]
3. Incidence and severity of suicidal behaviour and self-harm using the Acts of Deliberate Self-Harm Inventory[43] at 12, 24 and 52 weeks. This structured interview collects detailed information about the number and severity of episodes of self-harm and suicidal acts, and has been used successfully in other trials of treatments for people with BPD.[44]
4. Social functioning using the Social Functioning Questionnaire (SFQ) at 12, 24 and 52 weeks. This questionnaire is an eight-item self-report scale that asks people about problems across a range of settings that people with BPD often experience.[45]
5. Health-related quality of life, using the EuroQoL-5 Dimensions, three-level version (EQ-5D-3L),[46] at 12, 24 and 52 weeks. The EQ-5D-3L provides a brief and reliable measure of health-related quality of life, which is responsive to change in people with BPD.[47]
6. Side effects, using a pro forma designed to cover the possible effects listed in the *British National Formulary* entry for lamotrigine,[30] at 12, 24, and 52 weeks (see *Appendix 1*).
7. Use of alcohol and other drugs at 52 weeks after randomisation, using the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST).[48] This short questionnaire provides a reliable and valid screening test for problem substance use.[49]
8. Use of concomitant psychotropic medication, defined as the proportion of people taking psychotropic medication and the proportion of people taking antipsychotics, at 52 weeks after randomisation.
9. Total cost of health and social services. We collected data on use of resource using the Adult Service Use Schedule (AD-SUS), adapted for use in this trial based on previous research involving people with personality disorders,[50] at 12, 24 and 52 weeks (see *Appendix 2*). This questionnaire collects detailed data on use of all hospital and community health and social care services. At baseline, we used the AD-SUS to record service use over the previous 12 weeks and at the trial follow-up time points we used the AD-SUS to record service use since the previous assessment; thus, the entire study period was covered.

Adherence

We assessed adherence to study medication at the 12-, 24- and 52-week assessments using the Morisky Medication four-item Adherence Scale.[51] This is a four-item questionnaire that provides a valid estimate of adherence with psychotropic medication.[52] The total score ranges from 0 to 4, with higher scores indicating higher adherence. In addition to this, researchers asked participants about their use of trial medication when each prescription was renewed and any intentional or unintentional treatment breaks were recorded.

Blinding

All patients, carers and referring psychiatrists were blinded to treatment assignment until the participant had left the trial or until 52 weeks post randomisation (whichever was the longer). Blinding of investigators, researchers, the trial manager and the trial statistician was maintained until all data were entered, the database was locked and initial analyses of trial data were complete. The exception to this was for participants whose referring psychiatrist was also the principal investigator, in which case the allocation for that particular participant was revealed following the final assessment.

Site pharmacies were unblinded to trial arm allocation and were provided with a list of the randomisation codes and corresponding trial arm allocation for that site. The trial medication was produced with tear-off labels that identified it as being lamotrigine or placebo in a coded format, so that pharmacy staff could dispense the appropriate medication for a participant. Pharmacy procedures required that the tear-off label

was removed during dispensing and added to trial documents for accountability. The need to maintain the blinding of researchers and other individuals at the site was made clear to those delegated to work on the trial within the pharmacy.

Unblinding at the end of the follow-up period

At 52 weeks after a participant was randomised into the study, regardless of whether or not they withdrew from the study early or completed the participation period in full, a letter was sent to the referring prescriber informing them of the participant's allocation status. When a participant had completed the participation period in full, this allowed the prescriber time to make arrangements for the participant to continue on lamotrigine if appropriate and desired. On completion of the 52-week follow-up assessment, the participant was advised to contact their prescriber to discuss their trial arm allocation and their future treatment.

An individual, who had no other role in the trial, was unblinded for the purpose of informing the referring clinician of the trial arm of the allocation of participants, as part of routine unblinding.

Emergency unblinding

In anticipation of an emergency, such as an overdose of trial medication, Emergency Scientific and Medical Services (ESMS) Global Ltd was contracted to provide a 24-hour emergency unblinding telephone service. All requests for unblinding were recorded.

Study logistics

Recruitment

Potential participants were initially approached about the trial by any health-care professional who was involved in their care, providing that the consultant psychiatrist for the team had agreed in principle to patients under their care taking part in the study.

If a psychiatrist or other health-care professional had a patient under their care who they believed met the eligibility criteria, they then introduced the patient to the trial and provided them with an information sheet.

When the patient provided verbal agreement to discuss their eligibility and possible enrolment into the trial with a member of the research team, a screening number was assigned and contact details passed on to the research team to discuss consent.

Potential participants were given a minimum of 24 hours from receiving the information sheet to consider the information and the opportunity to question the investigator, their general practitioner (GP) or other independent parties regarding participation in the trial.

Screening and baseline

If written informed consent was given and documented, then the referring clinician completed a document to confirm their medical opinion of the participant's eligibility and a researcher completed the screening assessment (*Table 1*) with the participant to assess eligibility. If the participant fulfilled all the eligibility criteria, then the baseline assessment was also completed and they were randomised into the trial. Following randomisation, the participant's GP and consultant were informed of their enrolment into the trial.

Assignment of interventions

Study participants were randomly allocated to the intervention (lamotrigine) or comparator (placebo) arm of the trial by an automated randomisation service operated by Nottingham Clinical Trials Unit. The randomisation sequence was generated using permuted stacked blocks, with block size randomly assigned to 4 or 6. Allocation was 1 : 1, stratified by recruitment site, severity of personality disorder and extent of bipolarity. We used data from the IPDE screening questionnaire to establish whether participants met criteria for probable cluster A or cluster C personality disorders ('complex personality disorder') or whether

TABLE 1 Study assessment schedule[53]

	Time point				
			Follow-up		
Assessments	Screening	Baseline	12-week	24-week	52-week
SCID-II[a]	✗	–	–	–	–
SCID-I[b]	✗	–	–	–	–
IPDE screening questionnaire (DSM-IV version)	✗	–	–	–	–
HCL-32	✗	–	–	–	–
ASSIST	–	✗	–	–	✗
Four-item Morisky Medication Adherence Scale	–	–	✗	✗	✗
ZAN-BPD	–	✗	✗	✗	✗
BDI	–	✗	✗	✗	✗
Acts of Deliberate Self-harm Inventory	–	✗	✗	✗	✗
SFQ	–	✗	✗	✗	✗
EQ-5D-3L	–	✗	✗	✗	✗
Side effects	–	✗	✗	✗	✗
Modified Adult Service User Schedule	–	✗	✗	✗	✗

a Section on BPD.
b Section on bipolar affective disorder (types I and II).

they met only probable criteria for borderline and other cluster B personality disorders ('simple personality disorder') according to the criteria developed by Tyrer and Johnson.[33] We used the extent of bipolarity, measured as total score on the HCL-32, to examine the extent of bipolarity (low, a score of 0–13, or high, a score of ≥ 14).[54]

Follow-up

Prior to providing a new supply of trial medication, the participant was contacted to elicit details of any adverse events (AEs) that occurred, to determine if there had been any intentional or unintentional breaks in their taking of the trial mediation and to ascertain whether or not they wished to continue with the trial.

Participants received an assessment at 12, 24 and 52 weeks. The timing and sequence of all assessments are summarised in *Table 1*.

Data management

Data were entered onto a secure web-based database. Access was restricted by user identifiers and passwords (encrypted using a one-way encryption method). Study data will be archived securely and then safely destroyed after 15 years.

Sample size

We based the sample size calculation for the study on our primary hypothesis: for people with BPD who are in contact with mental health services, the addition of lamotrigine to usual treatment will reduce symptoms of their disorder at 52 weeks' follow-up, according to the total score on the ZAN-BPD.

The ZAN-BPD has been used to examine the clinical effectiveness of a range of psychological and pharmacological treatments for people with BPD. In a randomised trial of a modified form of group-based cognitive behavioural therapy, Blum *et al.*[40] found that there were improvements in mental health and reduced use of emergency medical services among those who were randomised to problem-solving therapy. These improvements were associated with a difference of 3.6 [standard deviation (SD) 6.9] in total ZAN-BPD score. The ZAN-BPD rating scale was also used to examine the clinical effectiveness of lamotrigine for people with BPD in a randomised trial conducted by Reich *et al.*[29] In this small trial ($n = 28$), a non-statistically significant difference of 5.6 (SD 6.75) in total score on the ZAN-BPD was found at 12 weeks. Seventeen (61%) people in the trial completed all 12 weeks of the study and the levels of adherence to trial medications in those that completed the study were judged to be high.

Anticipating that levels of adherence to trial medications would be lower in the LABILE trial than in the study by Reich *et al.*,[29] we powered the study on the basis of a smaller difference in ZAN-BPD score of 3.0 (SD 6.75). The sample size was calculated using Stata® version 13.1 (StataCorp LP, College Station, TX, USA).

A total of 214 participants (107 receiving lamotrigine and 107 receiving placebo) would need to be randomised to have 90% power to detect a minimal clinically relevant difference of 3.0 (SD 6.75) in total score on the ZAN-BPD at 52 weeks, using a 0.05 level of statistical significance. To take account of 15% loss to follow-up at 52 weeks, the sample size was increased to 252. However, this was further revised to 266 during the course of the trial to account for a greater loss to follow-up of 25%.

Statistical analyses

The analysis and reporting of the trial was conducted in accordance with Consolidated Standards of Reporting Trials (CONSORT) guidelines.[55] A detailed statistical analysis plan was developed and agreed with the Independent Data Monitoring and Ethics Committee, and this was finalised prior to the completion of data collection, the database lock and the unblinding of the study. Continuous variables were summarised in terms of the mean, SD, median, lower and upper quartiles, minimum, maximum and number of observations. Categorical variables were summarised in terms of frequency counts and percentages. All data were analysed using Stata, version 13.1.

Preliminary analyses

Descriptive statistics of demographic and clinical measures were used to examine the balance between the randomised arms at baseline.

Primary analysis

The primary analysis was performed according to the intention-to-treat principle on the available case set, without imputation of missing data. The analysis was adjusted by site, baseline ZAN-BPD score, severity of personality disorder (simple or complex) and the extent of bipolarity (score of ≥ 14 or < 14).

Secondary analyses

For secondary analyses of ZAN-BPD scores at 12 and 24 weeks, randomised groups were compared using a mixed model for repeated outcome measures, adjusted by the same stratification variables used for the primary analysis. We investigated whether any treatment effects were sustained or emerged later by including an interaction term between treatment and time in the model. In the absence of a time effect, the effectiveness parameter was the average difference in mean ZAN-BPD score over the 52-week period along with 95% confidence interval (CI) and exact *p*-value.

Sensitivity analyses

Sensitivity analyses of the primary outcome were conducted to:

1. further adjust for any variable with marked imbalance at baseline
2. investigate the impact of missing data, using multiple imputation.

Complier-average causal effect analyses

We investigated the effect of treatment adherence using complier-average causal effect (CACE) estimation methods. Intention-to-treat analysis does not represent treatment effect under non-compliance of treatment; therefore, we used CACE analysis to explore whether or not the treatment effect was directly affected by the level of compliance. The level of compliance was examined using both dichotomous and continuous measures: (1) dichotomous – whether or not the participant had taken medication at a dose of $\geq$ 100 mg without interruption during the 52 weeks prior to the final follow-up interview; and (2) continuous – the percentage of weeks that the patient took the medication at a dose of $\geq$ 100 mg during the 52-week treatment period.

Analyses of secondary outcomes

The secondary outcomes were BDI score, incidence of deliberate self-harm, SFQ score, alcohol and any other substance use, and antipsychotic medication use. The secondary outcomes were analysed in a similar manner to the primary analysis. A generalised linear model was used for continuous outcomes and logistic regression model for binary outcomes.

Safety reporting

For safety data, including AEs, serious adverse events (SAEs) and suspected unexpected serious adverse reactions, we presented basic summary statistics, that is, the number of AEs or side effects of different categories and the number and proportion of participants who reported at least one AE or SAE within each treatment arm.

Health economics analysis

The primary economic evaluation took a NHS/personal social services perspective, including only costs incurred to health and social care services, following guidance from NICE.[56] Although previous studies in people with BPD have found that health and social care are the key cost drivers in this patient group,[44] it is also clear that BPD can have an impact on not only an individual's ability to work but also their absence from work as a result of sickness.[57] Therefore, productivity losses were included in a sensitivity analysis.

Calculation of costs

Costs for the economic evaluation were calculated in three stages: identification, measurement and valuation. The first stage of identification ensures that all relevant resources are included in the evaluation; these are the resources that are particularly relevant for people with BPD and which were identified from published studies,[44,58] meetings with clinicians and discussions with our patient representatives. Resource use was collected in the following areas:

- lamotrigine – drug costs and time with dispensing clinician
- hospital services – inpatient admissions (including admissions for physical and mental health problems), outpatient/day case appointments (for physical and mental health problems), accident and emergency attendances
- community services – GP (in person, on the telephone and at home), practice nurse, mental health care co-ordinator/key worker, psychiatrist, psychologist, community psychiatric nurse, social worker, counsellor/therapist, NHS walk-in clinic, advice service (e.g. Citizens Advice), complementary therapist
- medication.

During data collection there was also an opportunity for respondents to report any other relevant service use, including group therapy, day centre, dietitian, drug and alcohol services, eating disorder services, physiotherapist or podiatrist.

Data on the use of all identified services were collected using a range of methods. Information on the dispensing and dosage of lamotrigine was taken from clinician records. Other data were obtained from participants using a modified version of the AD-SUS, adapted for use in people with BPD on the basis of previous research in this area.[58] The use of community services was collected in interview, in which the study participant was asked to recall which, from a list of community services, they had contacted over the previous period. In addition, researchers used the AD-SUS to collect information on the participant's occupational status (e.g. employed, unemployed, student, retired) and the number of hours and days taken off work as a result of ill-health. The AD-SUS was administered at baseline and at 12, 24 and 52 weeks' follow-up. At baseline, the participant was asked to recall the services that they had used over the previous 12 weeks and at the trial follow-up time points, the participant was asked, using the AD-SUS, about the services that they had used since the previous assessment, so that the entire follow-up period was covered.

The total cost of the resources used by each study participant was calculated by applying a unit cost to each item of resource use. All unit costs were for the financial year 2015/16. The cost of lamotrigine was taken from the *British National Formulary,*[59] using a generic cost from a standard NHS supplier. The cost of time with the dispensing clinician was taken from the *Unit Costs of Health and Social Care*.[60] It was assumed that the clinician was a psychiatrist, who had a 10-minute consultation with the participant during the titration period, followed by 10 minutes every 4 weeks thereafter. All other unit costs were sourced from standard sources and are detailed in *Appendix 3*. Productivity losses were calculated on the basis of days missed from work using information on gross annual pay collected in the AD-SUS. The total cost for each participant was the sum of all their costs. Discounting was not necessary, as costs were collected over a 1-year period only.

Calculation of quality-adjusted life-years

The EQ-5D-3L responses were converted to utility scores using findings from a sample of representative UK adults.[61] These utility scores were then used to calculate quality-adjusted life-years (QALYs) using the area under the curve approach, in which changes in utility scores were assumed to follow a linear path.[62] No discounting of QALYs was necessary.[62]

Data analysis

For the main analysis, complete-case analysis was used in which participants with missing data were excluded. Multiple imputation of missing cases was carried out in a sensitivity analysis. A single missing item from an otherwise complete data set was imputed using mean imputation, so that the participant could be included in the complete-case analysis.

The average use of different types of services by randomised group over 52 weeks' follow-up was tabulated and reported descriptively as the mean number of contacts and the percentage of each group using that service at least once. No statistical comparisons between service uses were completed in order to avoid problems with multiple testing and to keep the focus of the evaluation on costs and cost-effectiveness.

The total average cost between randomised groups over 52 weeks' follow-up was compared using generalised linear regression models with the following covariates: stratification variables (study centre, severity of personality disorder and extent of bipolarity) and baseline costs. The validity of the results were confirmed by examining the CIs from bias-corrected, non-parametric bootstrapping.[63] The use of parametric tests is recommended for cost data, despite its skewed distribution, because it allows for inferences to be made on the arithmetic mean, which is the most meaningful summary statistic for cost.[64]

Cost-effectiveness analysis

The cost-effectiveness analysis allowed costs and outcomes to be considered together in a decision-making context. The primary cost-effectiveness analysis used QALYs derived from the EQ-5D-3L; a secondary cost-effectiveness analysis used the ZAN-BPD measure. Cost-effectiveness was first assessed through the calculation of incremental cost-effectiveness ratios (ICERs), which are a summary statistic of the difference in mean cost between randomised groups divided by the difference in mean effect.[65] An ICER is calculated from the means of the randomised group, so there remains statistical uncertainty as to the accuracy of the ICER as a summary statistic. Therefore, 5000 resamples (bootstrapping) from the cost and outcomes data were used to generate a new distribution of mean costs and outcomes.[66] These distributions were then plotted onto a cost-effectiveness plane for interpretation.[65] Replications that fall in the south-west quadrant of the plane suggest that lamotrigine is less costly and less effective than the placebo, replications that fall in the south-east quadrant suggest that lamotrigine is less costly and more effective than the placebo, replications in the north-west quadrant suggest that lamotrigine is more costly and less effective than the placebo and replications in the north-east quadrant suggest that lamotrigine is more costly and more effective than the placebo.

Next, the bootstrapped replications were used to calculate the probability that lamotrigine was the 'optimal' choice, depending on the maximum value (willingness to pay, λ) that a decision-maker might be willing to pay for an improvement in outcome. The willingness-to-pay value varied between likely minimum and maximum values, and the results plotted on a graph result in a cost-effectiveness acceptability curve.[67] All cost-effectiveness analyses were adjusted for baseline stratification variables by site, baseline ZAN-BPD score, severity of personality disorder (simple or complex) and score on the HCL-32 (i.e. a score of ≥ 14 or < 14), baseline costs and baseline EQ-5D-3L tariff.

Sensitivity analysis

A number of sensitivity analyses were carried out to test the robustness of the analysis to key assumptions:

1. varying the economic perspective to include productivity losses
2. examining the impact of missing data through multiple imputation of missing cases.

Service user involvement

Plans for the study were presented at a research seminar at the British and Irish Group for the Study of Personality Disorder, which included service user representatives. These discussions, together with feedback from Fenella Lemonsky (an expert by experience and a co-applicant on the study), helped us to decide which mood stabiliser we should examine. We also used feedback from service users and results of a Delphi study of users of personality disorder services to help us decide.[58]

Fenella Lemonsky remained an active member of the project management group throughout the study. Additional input from people with lived experience of using services was provided by Sally Strange and Jennie Parker. Service users reviewed materials for publicising the study and commented on a draft version of the patient information sheet.

Service users also contributed to the communication of study findings; Sally Strange and Jennie Parker helped us interpret study findings and develop our recommendations for services and for future research. Jennie Parker also commented on a draft of the lay summary of the study findings, which we have distributed to study participants, and Fenella Lemonsky presented the results of the study at the annual conference of the British and Irish Group for the Study Personality Disorders in 2017.

An independent service user, Jenny Trite, was an active member of the Trial Steering Group throughout the course of the study.

Ethics approval and governance

The trial was approved by the London-Central Research Ethics Committee (reference number 2/LO/1514). In accordance with the current revision of the Declaration of Helsinki[68] (amended October 2000, with additional footnotes added in 2002 and 2004), a participant had the right to stop trial treatment and to withdraw from the trial at any time and for any reason, without prejudice to his or her future medical care by the physician or at the institution, and was not obliged to give his or her reasons for doing so. The investigator could also withdraw a participant from trial treatment at any time in the interest of the participant's health and well-being or for administrative reasons. Trial follow-up continued after treatment was withdrawn, unless the participant withdrew consent.

All potential participants were provided with written and verbal information about the study before being asked to provide written informed consent to participate in the study.

Progress of the study was overseen by a Trial Steering Committee and a Data Monitoring and Ethics Committee.

Changes to trial design

Change to design between funding proposal and trial commencement

1. Following concerns about the length of time it would take to assess eligibility, we modified our initial plan, which was to assess all aspects of personality disorder using the SCID-II semistructured interview (which can take up to 90 minutes to complete), and instead used only the section of the SCID-II that establishes whether or not a person meets diagnostic criteria for BPD. As we wanted to obtain information about whether or not a person had simple or complex personality disorder, we also used the self-complete IPDE screening questionnaire. This questionnaire takes less than 15 minutes to complete.[69]
2. We added the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST) questionnaire to the 52-week follow-up assessment to enable us to assess whether or not offering study participants lamotrigine had any impact on their use of alcohol and illicit drugs.[48]
3. Initial plans to measure participants' weight at 24 and 52 weeks were removed from the assessment schedule because of problems identifying scales in many of the locations where follow-up assessments were due to be conducted.

Change to design after trial commencement

An additional recruitment site was opened several months into the recruitment period (Derbyshire Healthcare NHS Foundation Trust).

Loss to follow-up during trial participation was expected to be 15%, but an interim assessment of the retention rate showed that it was approximately 20%. Therefore, the target sample size was increased to 266.

Chapter 3 Results

Between July 2013 and October 2015, 413 participants were referred to the study, of whom 296 (71.7%) were screened. Among the potential participants who were screened, 276 (93.2%) met the inclusion criteria and were randomised. Of the 276 participants randomised, 139 were allocated to the placebo plus usual care arm and 137 were allocated to the lamotrigine plus usual care arm. The CONSORT flow diagram for the LABILE trial is presented in *Figure 1*. Follow-up interviews took place between October 2013 and October 2016. The rates of follow-up were similar between treatment arms; overall, 71% of participants attended the 52-week follow-up. There were no instances in which researchers were unblinded to the participant's allocation status prior to completion of collection of 52-week outcome data. Scores on the ZAN-BPD from pairs of researchers who separately rated 27 participants were highly correlated (intraclass correlation coefficient 0.98, 95% CI 0.95 to 0.99).

Baseline characteristics of randomised participants

The demographic and clinical data of each trial arm are summarised in *Table 2*. The results of the outcome assessments at baseline are presented for each arm in *Table 3*. In terms of baseline comparability, the lamotrigine and placebo groups were well matched.

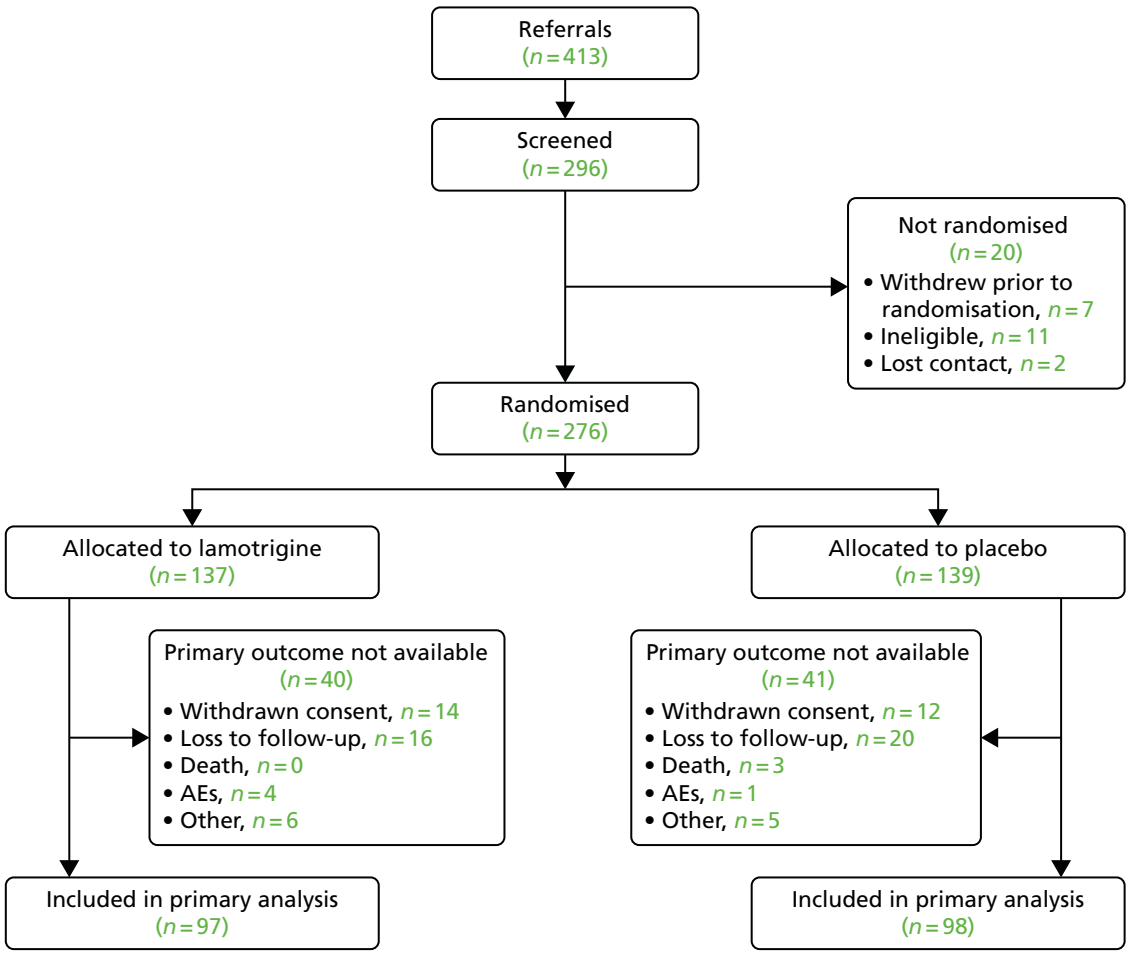

FIGURE 1 The CONSORT flow diagram for the study.

TABLE 2 Baseline demographic and clinical characteristics of study participants

Characteristic	Treatment group	
	Lamotrigine (*N* = 137)	Placebo (*N* = 139)
Age (years) at randomisation		
Mean (SD)	36.0 (11)	36.2 (11)
Sex, *n* (%)		
Male	34 (25)	34 (24)
Female	103 (75)	105 (76)
Ethnicity, *n* (%)		
White	123 (90)	123 (90)
Black	7 (5)	4 (3)
Asian	1 (1)	2 (1)
Mixed	6 (4)	8 (6)
Missing	0	2 (1)
Employment status, *n* (%)		
Employed	34 (25)	26 (19)
Unemployed	95 (69)	105 (76)
Student	4 (3)	1 (1)
Retired	2 (1)	2 (1)
Missing	2 (1)	5 (4)
Total score HCL-32		
Mean (SD)	21.2 (5.5)	22.5 (5.2)
n	72	75
Severity of personality disorder, *n* (%)		
Simple	0	2 (1)
Complex	137 (100)	137 (99)

TABLE 3 Baseline outcome data from study participants

Outcome	Treatment group	
	Lamotrigine (*N* = 137)	Placebo (*N* = 139)
ZAN-BPD		
Mean score (SD)	16.6 (5.8)	17.4 (6.2)
n	135[a]	138[a]
ASSIST,[b] *n* (%)		
Alcohol	53 (39)	54 (39)
Cannabis	35 (26)	27 (19)
Cocaine	11 (8)	15 (11)
Amphetamine-type stimulants	10 (7)	9 (6)
Inhalants	2 (1)	2 (1)

TABLE 3 Baseline outcome data from study participants (*continued*)

Outcome	Treatment group	
	Lamotrigine (*N* = 137)	Placebo (*N* = 139)
Sedatives or sleeping pills	14 (10)	16 (12)
Hallucinogens	1 (1)	4 (3)
Opiates	7 (5)	9 (6)
Other	6 (4)	2 (1)
BDI		
Mean score (SD)	39.8 (11.7)	38.4 (10.2)
n	135	138
SFQ		
Mean score (SD)	15.0 (4.1)	14.9 (4.5)
n	135	137
EQ-5D-3L health state		
Mean score (SD)	42.6 (24)	43.8 (20.9)
n	135	137
Total number of side effects, median (IQR)		
Mild	4 (2–7)	4 (1–7)
Moderate	3 (2–6)	3 (1–6)
Severe	1 (0–3)	1 (0–3)
Deliberate self-harm,[c] *n* (%)		
No	39 (28)	51 (37)
Yes	96 (70)	87 (63)
Unknown	2 (2)	1 (< 0.5)

IQR, interquartile range.
a Three participants withdrew shortly after randomisation and did not complete their baseline assessments.
b Met threshold for brief intervention.
c Any act of intentional self-harm during the previous 6 months.

The ZAN-BPD is a measure of symptoms and behavioural problems and the total score ranges from 0 to 36; a lower score indicates a better outcome. The BDI measures the severity of depression symptoms and the score ranges from 0 to 63; a lower score indicates a better outcome. The SFQ score measures social functioning problems and the score ranges from 0 to 24; a lower score indicates a better outcome.

Adherence to protocol and trial medication

Details of the number of participants who completed each of the follow-up assessments are presented in *Table 4*, broken down by study arm. The median time between randomisation and the completion of these assessments is also presented. In total, 195 (71%) participants completed the 52-week follow-up.

Table 5 summarises the key parameters of trial medication adherence and prescribing over the course of participation for participants in each arm. In total, 93 (34%) participants completed the trial medication per protocol, and similar proportions were shown in both arms. Although 191 (69%) study participants were

TABLE 4 Adherence to follow-up visits

Time point	Treatment group	
	Lamotrigine (*N* = 137)	Placebo (*N* = 139)
12 weeks		
Number of participants who completed the assessment, *n* (%)	111 (81)	104 (74)
Average time in days from randomisation, mean (SD)	13.8 (2.6)	13.7 (1.9)
24 weeks		
Number of participants who completed the assessment, *n* (%)	98 (72)	98 (71)
Average time in days from randomisation, mean (SD)	26 (3.0)	26 (2.5)
52 weeks		
Number of participants who completed the assessment, *n* (%)	97 (71)	98 (71)
Average time in days from randomisation, mean (SD)	51.8 (3.8)	51.6 (2.4)

TABLE 5 Adherence to trial medication among 276 study participants

Outcome	Treatment group	
	Lamotrigine (*N* = 137)	Placebo (*N* = 139)
Was the IMP received as per protocol? [n (%)][a]		
No	93 (68)	90 (65)
Yes	44 (32)	49 (35)
Percentage of the 52-week period that the participant was taking ≥ 100 mg		
Mean (SD)	60 (35)	66 (35)
Range	2–94	2–98
Number of weeks that the participant received IMP		
Median (IQR)	32 (9–52)	46 (7–52)
Minimum, maximum	0, 52	0, 52
Number (%) of participants taking IMP		
At 12 weeks	95 (69)	95 (68)
At 52 weeks	49 (36)	58 (42)
Dose (mg) of IMP taken		
At 12 weeks		
Median (IQR)	200 (200–200)	200 (200–200)
Range	25–400	25–400
At 52 weeks		
Median (IQR)	200 (200–200)	200 (200–200)
Range	100–400	200–400

IMP, investigational medicinal product; IQR, interquartile range.
a Following initial titration participants stayed on a dose of ≥ 100 mg throughout the remainder of the study.

taking the trial medication 12 weeks after randomisation, only 107 (39%) were taking it at the end of the 1-year follow-up period. Self-rated adherence, assessed using the total score on the four-item Morisky Medication Adherence Scale at 12, 24 and 52 weeks' follow-up (*Table 6*), also showed similar levels of compliance with trial medication.

Primary outcome

The total score on the ZAN-BPD decreased for study participants as a whole between baseline and 12 weeks and then remained fairly stable throughout the remainder of the follow-up. This pattern was seen in both arms. No difference was seen in adjusted mean total ZAN-BPD score at 52 weeks (*Table 7*).

The lack of treatment effect was supported by the results of the sensitivity analyses (*Table 8*), which included the following:

- using repeated measures analysis to include ZAN-BPD scores at all visits
- adjusting baseline variable with imbalance (no formal statistical testing for differences)
- multiple imputation of missing data using chained equations
- CACE analysis to investigate the impact of compliance level on treatment effect.

Secondary outcomes

Comparison of secondary outcomes at 52 weeks between those in the two treatment arms of the trial revealed no statistically significant differences (*Table 9*). The proportion of people who were prescribed psychotropic medication in the year following randomisation was 93% of those in the lamotrigine arm and 95% of those in the placebo arm of the trial, of whom 16% in the lamotrigine arm and 17% in the placebo arm of the trial were prescribed antipsychotic medication. We also found no evidence of clinically important differences in secondary outcomes at 12 or 26 weeks (see *Appendix 4*). No differences were seen on any of the subscores of the ZAN-BPD at 52 weeks. The adjusted mean difference for those

TABLE 6 Total score on the four-item Morisky Medication Adherence Scale at 12, 24 and 52 weeks

	Treatment group	
Time point	Lamotrigine ($N = 137$)	Placebo ($N = 139$)
12 weeks		
Median score (IQR)	3 (2–4)	3 (2–4)
n	109	99
24 weeks		
Median score (IQR)	3 (2–4)	3 (2–4)
n	89	91
52 weeks		
Median score (IQR)	3 (2–4)	3 (2–4)
n	88	82

IQR, interquartile range.
Note
The Morisky Medication Adherence Scale score measures the participants/adherence to trial medication. Total score ranges from 0 to 4, with higher scores indicating better adherence.

TABLE 7 Total ZAN-BPD score at baseline and at 12, 24 and 52 weeks

Time point	Treatment group		Adjusted difference[a] (95% CI); *p*-value
	Lamotrigine (*N* = 137)	Placebo (*N* = 139)	
Baseline			
Mean score (SD)	16.6 (5.8)	17.4 (6.2)	–
n	135	138	
12 weeks			
Mean score (SD)	11.5 (5.7)	11.5 (7.1)	–
n	111	104	
24 weeks			
Mean score (SD)	11.9 (6.1)	11.9 (7.0)	–
n	98	98	
52 weeks			
Mean (SD)	11.3 (6.6)	11.5 (7.7)	0.1 (–1.8 to 2.0); $p = 0.91$
n	97	98	

a Adjusted by site, baseline ZAN-BPD score, severity of personality disorder and extent of bipolarity. Data from 195 participants were included in the primary analysis model.

TABLE 8 Sensitivity analyses of primary outcome

Treatment group	Adjusted difference in means[a]	95% CI	Analysis scenario
Lamotrigine	0.0	–1.25 to 1.26	Repeated measure[b]
Placebo	–	–	–
Lamotrigine	0.0	–1.90 to 1.90	Further adjustment of baseline data[c]
Placebo	–	–	–
Lamotrigine	–0.1	–1.90 to 1.80	Multiple imputation of missing data[d]
Placebo	–	–	–
Lamotrigine	0.3	–3.70 to 4.30	Using dichotomous treatment adherence indicator[e]
Placebo	–	–	–
Lamotrigine	0.0	0.02 to 0.03	Using continuous treatment adherence indicator[e]
Placebo	–	–	–

a Adjusted by site, baseline ZAN-BPD score, severity of personality disorder and extent of bipolarity.
b The interaction between treatment arm and visits was tested and found to be non-significant. Therefore, the final model did not have this interaction term. Data from 234 participants were included in the model.
c Analysis was further adjusted by proportion of participants with inpatient admission at baseline.
d The multiple imputation model using chained equations includes baseline and follow-up ZAN-BPD scores, age, sex, ethnicity, severity and extent of bipolarity.
e The definitions of dichotomous and continuous treatment adherence indicators are detailed in *Data analysis*.

TABLE 9 Analysis of secondary outcomes at 52 weeks

Outcome measure, treatment group	Time point		Adjusted difference[a] (95% CI)	*p*-value
	Baseline	52-week follow-up		
Depression score (as measured by the BDI) (*N* = 180), mean score (SD)				
Lamotrigine	39.8 (11.7)	28.8 (16.1)	–0.2 (–4.5 to 4.1)	0.937
Placebo	38.4 (10.2)	28.7 (15.5)	–	
Deliberate self-harm[b] (*N* = 179), *n* (%)				
Lamotrigine	96 (70)	45 (46)	1.25 (0.68 to 2.28)	0.464
Placebo	87 (63)	38 (39)	–	
Social functioning (as measured by the SFQ) (*N* = 179), mean score (SD)				
Lamotrigine	15 (4.1)	12.4 (4.3)	0 (–1.2 to 1.2)	0.987
Placebo	14.9 (4.5)	12.3 (4.9)	–	
Alcohol use (as measured by ASSIST) (*N* = 178), *n* (%)				
Lamotrigine	53 (39)	28 (31)	1.4 (0.7 to 2.7)	0.354
Placebo	54 (39)	22 (25)	–	
Other substance misuse (as measured by ASSIST) (*N* = 178), *n* (%)				
Lamotrigine	54 (39)	27 (30)	1.2 (0.6 to 2.3)	0.598
Placebo	47 (34)	23 (26)	–	

a Adjusted by site and other stratification factors. The estimate is the difference in means for continuous outcomes, and odds ratio for binary outcomes. Severity was not included in the model for self-harm, alcohol use and any other substance use because of collinearity.
b Any act of intentional self-harm in the 6 months prior to the baseline and 52-week interviews.

prescribed lamotrigine was –0.1 (95% CI –0.9 to 0.7) on the affective disturbance subscore, 0.1 (95% CI –0.4 to 0.7) for cognitive disturbance, –0.1 (95% CI –0.6 to 0.5) for impulsivity and 0.0 (95% CI –0.5 to 0.5) for disturbed relationships compared with those in the placebo arm of the trial (see *Appendix 4*, *Table 22*).

Safety

Tables 10 and *11* show that there was an excess of AEs in the placebo group but the incidence of those classified as serious did not differ across treatment arms. There were three deaths in the trial, all of which occurred in the placebo arm. No suspected unexpected serious adverse reactions were recorded.

Using a pro forma to enquire about the presence of specific known side effects of lamotrigine revealed no difference between the groups at any assessment time points (*Table 12*).

TABLE 10 Summary of AEs by *Medical Dictionary for Regulatory Activities*[70] codes

AE	Treatment group	
	Lamotrigine ($N = 137$)	Placebo ($N = 139$)
Total number of AEs	246	285
Total number of participants with at least one AE, *n* (%)	77 (56)	93 (67)
Total number of AEs by system organ class		
Blood and lymphatic system disorders	2	3
Cardiac disorders	0	1
Endocrine disorders	0	1
Eye disorders	1	6
Gastrointestinal disorders	38	55
General disorders and administration site conditions	14	14
Hepatobiliary disorders	1	0
Immune system disorders	1	1
Infections and infestations	23	38
Injury, poisoning and procedural complications	17	39
Investigations	7	3
Metabolism and nutrition disorders	2	1
Musculoskeletal and connective tissue disorders	8	7
Nervous system disorders	32	31
Pregnancy, puerperium and perinatal conditions	3	2
Psychiatric disorders	37	40
Renal and urinary disorders	1	0
Reproductive system and breast disorders	3	1
Respiratory, thoracic and mediastinal disorders	16	9
Skin and subcutaneous tissue disorders	35	31
Social circumstances	1	1
Surgical and medical procedures	4	1

Note
Adverse events data are all events reported including the SAEs.

TABLE 11 Summary of SAEs by *Medical Dictionary for Regulatory Activities*[70] codes

SAE	Treatment group	
	Lamotrigine ($N = 137$)	Placebo ($N = 139$)
Total number of SAEs	36	48
Total number of participants with at least one SAE, *n* (%)	26 (19)	32 (23)
Total number of SAEs by system organ class		
Eye disorders	0	1
Gastrointestinal disorders	1	3

TABLE 11 Summary of SAEs by *Medical Dictionary for Regulatory Activities*[70] codes (*continued*)

SAE	Treatment group	
	Lamotrigine ($N = 137$)	Placebo ($N = 139$)
General disorders and administration site conditions	2	1
Immune system disorders	1	0
Infections and infestations	0	1
Injury, poisoning and procedural complications	6	19
Metabolism and nutrition disorders	1	0
Musculoskeletal and connective tissue disorders	1	0
Nervous system disorders	1	0
Pregnancy, puerperium and perinatal conditions	3	2
Psychiatric disorders	16	20
Renal and urinary disorders	1	0
Respiratory, thoracic and mediastinal disorders	1	0
Social circumstances	1	0
Surgical and medical procedures	1	1

TABLE 12 Summary of side effects at baseline and at 12, 24 and 52 weeks

Time point, side effect level	Treatment group, median number of side effects (IQR)	
	Lamotrigine ($n = 137$)	Placebo ($n = 139$)
At baseline		
Mild	4 (2–7)	4 (1–7)
Moderate	3 (2–6)	3 (1–6)
Severe	1 (0–3)	1 (0–3)
At 12 weeks		
Mild	9 (5–13)	7.5 (4–14)
Moderate	6 (3–9)	6 (4–9)
Severe	2 (0–5)	1 (0–4)
At 24 weeks		
Mild	11.5 (7.5–18)	13 (6–20)
Moderate	9 (5.5–12.5)	8.5 (4–14.5)
Severe	2.5 (0–7.5)	2 (0–6)
At 52 weeks		
Mild	17 (11–24.5)	16 (8–25)
Moderate	12 (6–19)	11 (4.5–17)
Severe	3 (0–10)	3 (1–8.5)

IQR, interquartile range.

Chapter 4 Economic evaluation

The availability of service-use data at each follow-up period is summarised in *Table 13*, which shows that full service-use information was available for 61% of participants in the lamotrigine group and 57% of participants in the placebo group.

Service use

All resources used by study participants over the 52-week follow-up are summarised in *Table 14*. There are some noticeable differences in the use of hospital services over the follow-up period; participants in the lamotrigine group had an average of 12 nights of inpatient care compared with six nights of inpatient care in the placebo group. The SDs and ranges reported alongside the means in the table suggest that this difference in mean costs was because of a small number of participants who had long stays in hospital. Outpatient appointments and accident and emergency attendances were similar between groups.

TABLE 13 Availability of service-use data at follow-up

	Treatment group, *n* (%)	
Time point	Lamotrigine	Placebo
Baseline	135 (100)	137 (100)
12 weeks	110 (80)	104 (77)
24 weeks	98 (72)	97 (72)
52 weeks	91 (66)	88 (65)
All periods	83 (61)	77 (57)

TABLE 14 Use of services per participant over the 52-week follow-up period

	Treatment group					
	Lamotrigine ($n = 83$)			Placebo ($n = 77$)		
Service	Mean (SD)[a]	Range	%[b]	Mean (SD)[a]	Range	%[b]
Inpatient nights	12.66 (34.59)	0–239	46	6.37 (17.95)	0–127	35
Outpatient contacts	4.47 (7.26)	0–39	67	5.36 (9.69)	0–66	77
A&E contacts	3.86 (8.47)	0–69	70	3.52 (5.90)	0–28	61
General practice	20.43 (24.13)	0–157	98	17.16 (16.57)	1–83	100
Health care	28.90 (23.19)	0–85	95	21.23 (25.60)	0–167	95
Mental health services	12.65 (15.13)	0–84	96	13.29 (19.56)	0–148	96
Social care	13.88 (49.36)	0–429	73	12.25 (36.37)	0–291	70
Complementary services	1.02 (9.33)	0–85	1	0.08 (0.68)	0–6	1
Any medication	–	–	93	–	–	95
Any antipsychotic medication	–	–	16	–	–	17

A&E, accident and emergency department.
a The mean refers to the number of visits to the service.
b The percentage refers to the proportion of participants using each of these services at least once.

In general, the use of community health services was similar in both groups. Between 98% and 100% of participants saw their GP at least once over the period of follow-up, and, on average, the number of times a participant saw their GP was between 17 and 20. Use of other health-care services (practice nurse, walk-in clinic, dietitian, physiotherapist, podiatrist) and community mental health services (psychiatrist, psychologist, care co-ordinator/key worker, psychiatric nurse, counsellor/therapist, group therapy, day centre, drug and alcohol services, eating disorder services) was equally high.

Cost

At baseline, on average, costs were £5618 in the lamotrigine group and £3555 in the placebo group. The adjusted difference of £2376 was not statistically significant (95% CI –£108.13 to £4860.37; $p = 0.061$). The mean average cost differences between the groups are detailed in *Table 15*. The average drug and prescribing cost of lamotrigine was £242.69. The difference in hospital costs between the lamotrigine and placebo groups (£7294.09 vs. £4711.22) reflects the different average duration of inpatient stays. Other medication costs were also higher in the lamotrigine group (£674.10 vs. £302.64), resulting in higher average total costs in the lamotrigine group (£12,244.32) than in the placebo group (£8495.41), although this difference in cost was not statistically significant (95% CI –£1886.61 to £3169.83; $p = 0.617$).

Outcomes

The EQ-5D-3L scores at baseline and all follow-up points are detailed in *Table 16*. There were very few between-group differences in EQ-5D-3L scores and the resulting QALYs. The QALYs in the lamotrigine group were 0.287 and in the placebo group were 0.299, not significantly different (95% CI –0.057 to 0.034; $p = 0.612$).

Cost-effectiveness analysis

The ICER for the QALY outcome using adjusted mean differences is not reported. As it was negative, the lamotrigine treatment was dominated by the placebo. The ICER for ZAN-BPD using adjusted mean differences was £641.61/0.22 = £2916 per unit change in ZAN-BPD score.

The uncertainty around the ICER for QALYs is shown in *Figure 2*. The bootstrapped replications are present in all four quadrants of the plane: 44% appear in the less effective, more costly, quadrant; 23% in the more costly, more effective, quadrant; 21% in the less effective, less costly, quadrant; and 12% in the less costly, more effective, quadrant. The green line denotes the willingness-to-pay value of £20,000 per QALY.

TABLE 15 Total costs (£) per participant over the 52-week follow-up period

	Treatment group, mean cost (SD)				
Cost item	Lamotrigine ($n = 83$)	Placebo ($n = 77$)	Difference[a]	95% CI[a]	*p*-value[a]
Intervention	242.69 (95.99)	0.00 (0.00)	244.78	222.71 to 266.84	
Hospital	7294.09 (15,894.87)	4711.22 (10,057.64)	416.76	–1798.50 to 2632.01	
Community	4033.44 (3599.40)	3481.54 (3090.88)	158.94	–437.91 to 755.79	
Medication	674.10 (2457.12)	302.64 (971.04)	23.73	–302.89 to 350.35	
Total	12,244.32 (17,442.80)	8495.41 (11,349.10)	641.61	–1886.61 to 3169.83	0.617

a Adjusted for by site, baseline ZAN-BPD score, severity of personality disorder (simple or complex) and score on the HCL-32 (a score of ≥ 14 or < 14).

TABLE 16 EQ-5D-3L utility scored and QALYs over the 52-week follow-up period

	Treatment group			
	Lamotrigine		Placebo	
Time point	*n*	Mean score (SD)	*n*	Mean score (SD)
Baseline	135	0.424 (0.336)	137	0.446 (0.343)
12 weeks	109	0.488 (0.365)	104	0.509 (0.344)
24 weeks	93	0.473 (0.366)	91	0.525 (0.341)
52 weeks	86	0.47 (0.355)	80	0.516 (0.353)
All-period QALY[a]	83	0.287 (0.023)	77	0.299 (0.292)

a Adjusted for by site, baseline ZAN-BPD score, severity of personality disorder (simple or complex) and score on the HCL-32 (a score of ≥ 14 or < 14).

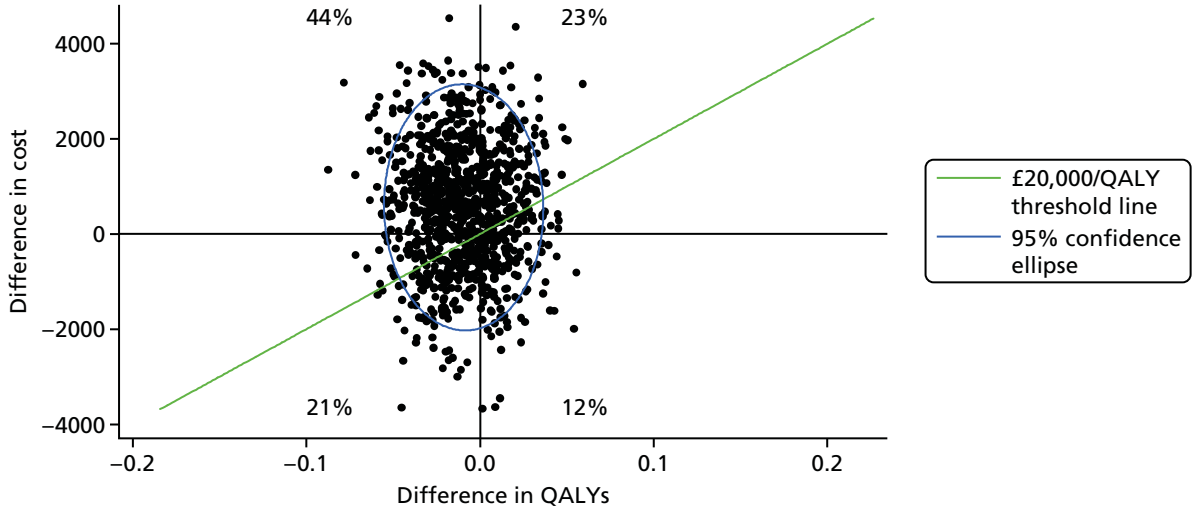

FIGURE 2 Scatterplot on a cost-effectiveness plane of differences in costs vs. differences in QALYs.

As there are only relatively few replications below this line, it suggests that lamotrigine treatment is not cost-effective in terms of QALYs. The cost-effectiveness acceptability curve in *Figure 3* gives a clear representation of the cost-effectiveness plane. There are no willingness-to-pay values at which the probability of lamotrigine treatment being cost-effective is > 35%.

The bootstrapped replications for the ZAN-BPD outcomes are shown in *Figure 4*. Here, the replications are mainly to the right of the *y*-axis, suggesting that outcomes were slightly better in the lamotrigine treatment group; however, the lack of a difference in cost between the groups is reflected in 54% of replications being in the more costly, more effective, quadrant. The resulting cost-effectiveness acceptability curve in *Figure 5* can only be indicative, as we do not know the willingness-to-pay values for a unit change in ZAN-BPD score. The curve suggests that there is a probability of > 60% that lamotrigine treatment is cost-effective, but only when willingness-to-pay values for a unit change in ZAN-BPD score are greater than £1000.

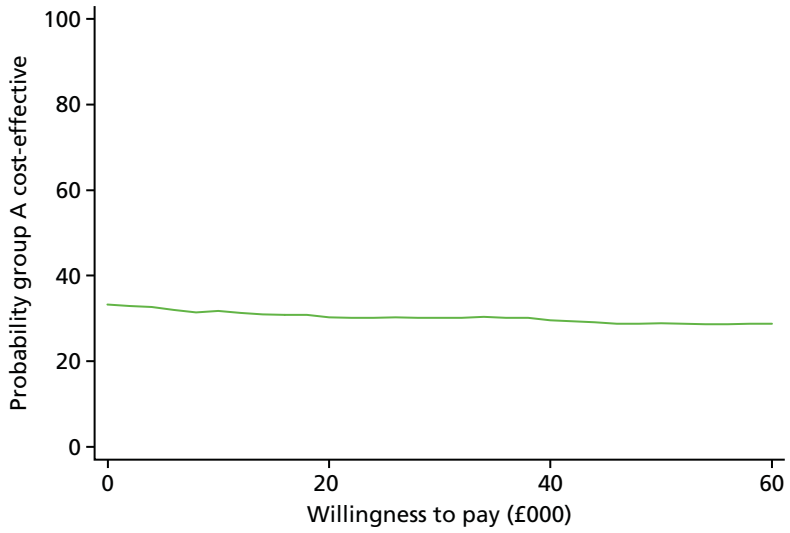

FIGURE 3 Cost-effectiveness acceptability curve showing the probability that lamotrigine treatment is cost-effective compared with placebo at different values that a decision-maker might be willing to pay for increases in QALYs.

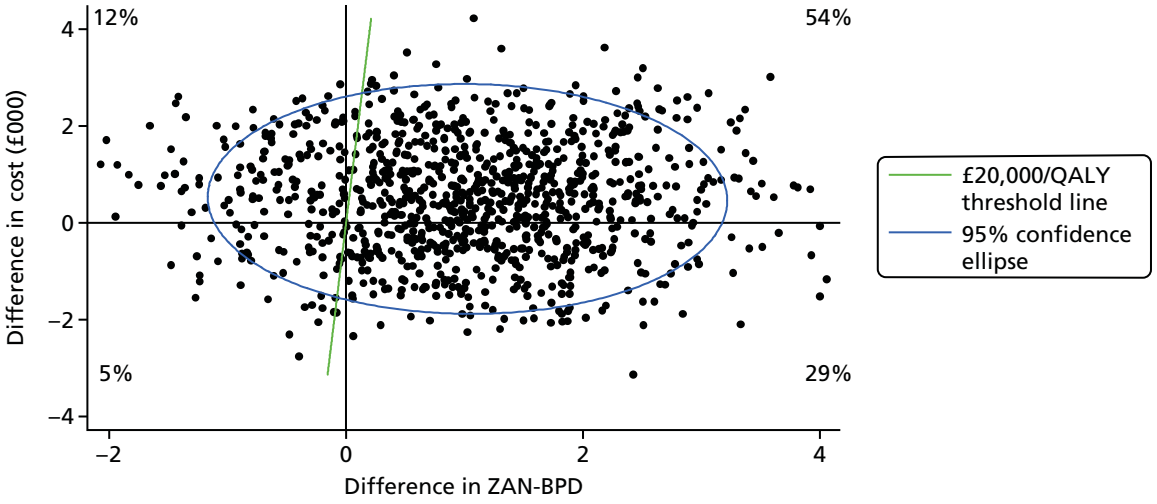

FIGURE 4 Scatterplot on a cost-effectiveness plane of differences in costs vs. differences in ZAN-BPD.

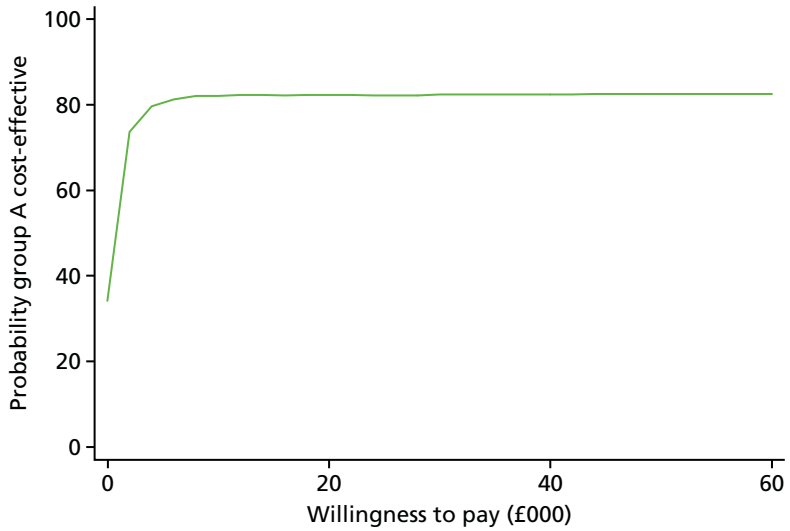

FIGURE 5 Cost-effectiveness acceptability curve showing the probability that lamotrigine treatment is cost-effective compared with placebo at different values that a decision-maker might be willing to pay for decreases in ZAN-BPD scores.

Sensitivity analysis

The sensitivity analyses are presented in *Table 17* and show that varying the economic perspective to include productivity losses and examining the impact of missing data through multiple imputation of missing cases have no impact on the finding that lamotrigine treatment is not cost-saving and thus it is unlikely to be cost-effective compared with placebo.

TABLE 17 Sensitivity analysis of differences in costs (£)

	Treatment group, mean cost (SD)				
Type of analysis	Lamotrigine	Placebo	Cost difference[a]	95% CI[a]	*p*-value[a]
Main analysis ($n = 160$)	12,244.32 (17,442.80)	8495.41 (11,349.10)	641.61	–1886.61 to 3169.83	0.617
Total cost including productivity losses ($n = 160$)	12,378.70 (17,410.19)	8634.52 (11,299.95)	661.31	–1877.68 to 3200.30	0.608
Multiple imputation of missing cases	12,655.64 (1822.07)	7209.06 (1283.66)	1773.42	–76.94 to 3623.77	0.06

a Adjusted by site, baseline ZAN-BPD score, severity of personality disorder (simple or complex) and score on the HCL-32 (a score of ≥ 14 or < 14).

Chapter 5 Discussion

Data from this randomised trial of adding lamotrigine treatment to usual care for people receiving secondary care mental health services for BPD show that the effect of this intervention was no different from that of offering an inert placebo in addition to usual care. Follow-up data collected from 195 (70.7%) out of 276 participants at 12 months showed no difference in score on the ZAN-BPD (adjusted mean difference 0.1, 95% CI –1.8 to 2.0). When differences in the primary outcome were compared over the course of the 12-month follow-up period, among the 234 participants who completed at least one follow-up assessment, no difference was observed in the adjusted ZAN-BPD score (0.0, 95% CI –1.9 to 1.9). Although costs associated with prescribing lamotrigine were small compared with those of inpatient and community care, we did not find evidence that offering patients with BPD lamotrigine was a cost-effective use of resources, given the large number of resources needed to be invested for very small changes in the ZAN-PD score outcome.

Levels of adherence to trial medication were low, with only one-third ($n = 93$, 33.7%) of study participants taking trial mediation throughout the 1-year follow-up period, as specified in the study protocol. Levels of adherence were higher during the first 12 weeks of the study, at which point two-thirds of participants were taking trial medication ($n = 190$, 68.8%). However, differences between the treatment arms in the severity of symptoms of BPD were not found at the 12-week assessment, despite medication compliance being higher during this period. In a secondary analysis using CACE methods, we found no evidence that greater adherence to medication was associated with any benefit to patients in the lamotrigine treatment arm of the trial.

In addition to there being no difference in the scores on ZAN-BPD between the treatment arms, treatment with lamotrigine was no better than placebo in terms of improvement on any other measures of mental health. Levels of depression, likelihood of self-harming or suicidal behaviour and likelihood of problem drug or alcohol use were all comparable across the groups at follow-up. Social functioning was also equivalent across groups. There were no deaths in the lamotrigine arm of the trial over the 12-month follow-up period, but three among those in the placebo arm of the trial. Quality of life, assessed using the EQ-5D-3L, was poor in both groups, a finding which is consistent with other studies in people with BPD.[47]

The number of AEs reported was higher in the placebo arm than in the lamotrigine treatment arm, and more participants in the placebo arm than in the lamotrigine treatment arm had at least one AE (67% vs. 56%). Serious AEs were comparable across treatment arms. A pro forma to elicit information about the known side effects of lamotrigine at each assessment showed that these were comparable across the treatment arm. Taken together, these data suggest that lamotrigine was well tolerated in participants in the active arm of the trial.

Strengths and weaknesses of the study

The LABILE trial is the first ever UK-based study of a medical treatment for people with BPD. Data were collected from participants receiving secondary care from NHS mental health services in six large mental health trusts in the north, south and centre of England. The study was designed to maximise internal validity. This included using independent remote randomisation to avoid unmasking researchers and adhering to an analysis plan that was finalised and shared with the Independent Data Monitoring and Ethics Committee and Trial Steering Group prior to the start of data analysis. Members of the research team drafted their conclusions and recommendations while still masked to treatments received by the two trial arms.

We used a validated measure of severity of BPD that is acceptable to patients and sensitive to change.[37,40] All researchers were trained to use the measure, and inter-rater reliability between researchers was high.

One of the main strengths of the LABILE trial is that participants were followed up over a 12-month period. BPD is a long-term condition, but previous drug trials have not conducted double-blind assessments beyond 12 weeks.

We recruited 11% more participants than we originally planned and the study was sufficiently powered to detect a minimum clinically significant difference in the severity of symptoms of BPD. We over-recruited, as it became clear that we were not going to achieve our ambitious target of following up 85% of participants to 12 months after randomisation. The 71% rate of follow-up that we achieved was very similar to that achieved in a UK study of problem-solving therapy for people with personality disorder[71] and may represent a more realistic target for studies that aim to follow up people with personality disorder in community-based studies. A planned secondary analysis using multiple imputation to account for missing data found no difference between the study arms.

In this pragmatic trial, we attempted to replicate clinical practice in the NHS. However, one area in which we were unable to do this was in the means by which participants obtained their medication. Most participants typically had medication delivered to them in person or by post, rather than collecting medication from a local pharmacy as required by this study. This meant that participants had more regular contact with staff than they would have done in normal clinical practice (once every 2 weeks during titration and once a month for the majority of participants once the recommended dose was achieved). Although levels of adherence to medication were low, we believe that the additional contact that participants had with study researchers meant that the level of adherence may have been higher in the trial than would be seen in routine clinical practice.

Comparison with results of previous trials

In contrast to the results of the LABILE study, the two previous randomised trials of lamotrigine treatment for people with BPD both reported positive effects.[28,29] Both trials were smaller, had a larger number of exclusion criteria and followed up participants for a shorter period of time. There are a number of other differences between the LABILE study and these other trials, which are summarised in *Table 18*.

In their trial of 24 women with BPD recruited from advertisements in primary care clinics, Tritt *et al.*[28] reported statistically significant reductions in four out of five scales of the State–Trait Anger Expression Inventory at 8 weeks. Reich *et al.*[29] randomised 28 men and women with BPD who were recruited from websites and advertisements on local television and radio stations. Although a statistically significant difference was not seen in total score on the ZAN-BPD at 12 weeks, the team reported differences in two out of the four subscales of this measure (affective lability and impulsivity).[29]

The primary outcome of the LABILE study was assessed at 1 year, but in exploring the reasons for differences in outcomes between these trials, we have focused on data from the 12-week follow-up assessment for comparison. We believe that a number of factors may have resulted in the differences in the results between the LABILE study and the two previous randomised trials. First, we cannot rule out the possibility that apparent differences between groups in the two earlier trials result from chance. Randomisation does not guarantee that treatment arms are balanced in small-scale trials and it is possible that differences in study outcomes resulted from confounding.

The LABILE study was designed to generate evidence that can be used by secondary care mental health services. We therefore limited our exclusion criteria and recruited people who had high levels of contact with mental health services and major impairments in social functioning. This approach meant that we were able to recruit people with the type of complex and severe problems that people with BPD who use NHS secondary care mental health services generally have. A commonly used marker of severity is whether or not people have other coexisting personality problems in addition to BPD.[33] It is of note that all but one of the people who took part in the LABILE trial met criteria for other personality disorders and had the

TABLE 18 Comparison of the methods, design and results of the LABILE study with two previous trials of lamotrigine for people with BPD

Characteristics of study and sample	Trial		
	LABILE study[a]	[a]Reich *et al.*[29]	[a]Tritt *et al.*[28]
Total sample size	276	27	24
Source of study participants	Clinical referral from inpatient and community secondary care mental health services	Members of the public who responded to websites and adverts on television and radio	Advertisements placed in primary care clinics
Exclusion criteria	• Psychosis • Bipolar disorder • Mood stabiliser • Pregnancy	• Substance dependence (past 60 days)[a] • Actively suicidal • Unstable medical condition • Psychotherapy started within past 30 days	• Abusing alcohol or drugs[b] • Actively suicidal • Somatically ill • Any psychotropic medication • Major depression • Current psychotherapy
Randomisation	Independent	Prearranged random number sequence	In-house
Age (years), mean	36	32	29
Female (%)	75	89	100
Employed (%)	22	Not stated	100
Mean ZAN-BPD score	17.0	18.8	Not assessed
Previous mental health hospitalisation	34.4% in the last 6 months	51.9% lifetime	19% lifetime
Mean dose	200 mg	93.3 mg	200 mg
Adherence (% taking trial medication)	66.7	80	Not stated
Funding	Public	Industry	No funding declared

a To facilitate comparison of data from these three studies we have used 12-week data from the LABILE study and presented these alongside 12-week data from the trial by Reich *et al.*[29] and 8-week data from the trial by Tritt *et al.*[28]
b In addition to exclusion criteria that were used in the LABILE study (psychosis, use of a mood stabiliser or pregnant/at risk of pregnancy).

types of complex personality-related problems that people in contact with NHS secondary services generally have. In contrast, the two previous trials of lamotrigine treatment for people with BPD excluded people who were misusing alcohol or other drugs, were actively suicidal or were receiving inpatient treatment. Therefore, there are important differences in the sample that we recruited compared with those in the two previous trials. For instance, 73% of participants in the trial conducted by Tritt *et al.*[28] were employed, compared with only 22% in the LABILE trial, and none of those recruited by Tritt *et al.* had a recent history of deliberate self-harm, compared with two-thirds of participants in the LABILE trial. It is possible that lamotrigine treatment reduces the symptoms of BPD among people who have less complex mental health problems, higher level of social functioning and lower levels of substance misuse than those we recruited to the LABILE trial.

Previous research has shown that people with more complex and severe personality problems are less likely to adhere to treatment.[17] It is possible that participants in the LABILE study were less adherent to trial medication than those in the two previous trials. Tritt *et al.*[28] did not report data on adherence. Reich *et al.*[29] did not provide detailed information about adherence but did note that 3 (20%) out of the 15 participants in the active arm of the trial were no longer taking medication at 12 weeks, compared with 86 (31%) of 276 participants in the LABILE trial who were no longer taking lamotrigine at 12 weeks. Although we cannot rule out the possibility that differences in levels of adherence are responsible for differences in

outcomes between these trials, the results of the CACE analysis do not suggest that higher levels of adherence to lamotrigine result in greater improvements in mental health.

It is possible that other aspects of the design of previous trials contributed to their positive effects. For instance, in the LABILE trial we had a rigorous process for maintaining blinding through the use of a computerised system, managed by an independent team that allocated study participants. In contrast, Tritt *et al.*[28] used an internal group to oversee treatment allocation. Insufficient information is provided in the paper by Reich *et al.*[29] to establish the process they used to randomise participants.

The LABILE trial is the only one of the three studies to be publicly funded. The trial by Reich *et al.*[29] was funded by a manufacturer of Lamictal® (a proprietary form of lamotrigine; GlaxoSmithKline UK Ltd, Brentford, UK) and the trial by Tritt *et al.*[28] was self-funded.

Finally, we are not aware of any unpublished trials of lamotrigine for people with BPD, but we cannot rule out the possibility that publication bias helps to explain the absence of previous negative trials of this treatment approach.

Implications for clinical practice

People with BPD experience high levels of emotional distress at times of crisis and may behave in an erratic or impulsive way that puts their health at risk. Emotional distress, suicidal behaviour or thoughts of suicide may lead people into contact with mental health services at such times. Interpersonal problems and negative experiences of previous contact with services often make it difficult for people with BPD to trust health-care professionals or feel reassured by their attempts to provide support and advice. In such circumstances, the prescription of medication can provide a clear signal to the patient that they are being taken seriously and health-care staff may also feel reassured that they are 'doing something' under difficult circumstances. Data from a national audit of prescribing practice suggest that one-quarter of people who are in contact with mental health services are being prescribed a mood stabiliser.[72] Some patients report that prescribing medication during a crisis can help bring about short-term reductions in emotional distress. The results of the LABILE study support the clinical impression that prescribing lamotrigine can lead to improvements in mental health but suggest that this benefit is no greater than would be found if a placebo were to be prescribed.

Current NICE guidelines[73] for the treatment of BPD recommend that future research should be conducted to examine the impact of mood stabilisers on people with the condition, but they conclude that there was insufficient evidence to recommend any drug treatment at the time of publication. The results of the LABILE trial provide evidence to support current NICE recommendations and emphasise the need to use alternative approaches to help people with BPD cope with crises and take steps to improve their mental health. The two best-established treatments for BPD are dialectical behaviour therapy and mentalisation-based treatment.[74] More recently, evidence has begun to emerge that Systems Training for Emotional Predictability and Problem Solving (STEPPS),[40] schema-focused therapy[75] and day therapeutic community treatment[76] can also improve the health of people with BPD. Clinicians who are working with people in secondary care mental health services should be aware of how they can help support people through mental health crises and how to access evidence-based psychological treatments when these are available.

In the LABILE trial, we took great care not to recruit women who were pregnant, wanting to become pregnant or having regular unprotected sex. Despite the assurances that potential recruits gave us, six participants subsequently became pregnant during the course of the trial. Although lamotrigine treatment has been shown to be relatively safe in pregnancy, this is not true of all mood stabilisers – notably sodium valproate.[23] In January 2015, the Medicines and Healthcare products Regulatory Agency issued a warning advising clinicians to avoid prescribing sodium valproate to women of child-bearing age when possible.[77] Despite this, a recent national audit showed that 11% of women with BPD who are in contact with

secondary care mental health services are currently being prescribed this drug.[72] The data from the LABILE study showing the high level of unplanned pregnancies among women with BPD emphasise the importance of avoiding the use of unlicensed medications, such as sodium valproate, that are potentially teratogenic.

Future research

Existing evidence-based psychological treatments for BPD are lengthy, intensive and expensive. Previous research has demonstrated that, when compared with treatment as usual, these interventions are associated with reduced levels of deliberate self-harm and contact with health-care services.[74] However, studies that compare the effects of these interventions with high-quality control treatments delivered in a consistent manner show less, if any, additional benefit.[78,79] Reductions in self-harm and contact with health-care services raise the possibility that specialist psychological treatment for BPD provides an effective use of available resources, but very few data on the costs and cost-effectiveness of these treatments exist. Further research is needed to examine the costs and cost-effectiveness of specialist psychological treatment for people with BPD compared with high-quality structured general psychiatric management. Such research is needed to help policy-makers make better decisions about investing in specialist treatment services, which many patients are currently unable to access in the NHS.

Even were such services to become more widely available, a substantial minority of people with BPD would be unwilling or unable to use these group-based treatments. There is a pressing need for new research to examine alternative psychological approaches to helping people with BPD cope better with emotional crises and improve their mental health. Computer-assisted self-help interventions and training and support for friends and family of people with BPD are all areas worthy of further exploration.[80]

An area of particular concern is how best to help people with severe BPD who are treated in inpatient mental health units. Following a number of open-label studies of clozapine treatment for people with BPD,[81,82] the use of this atypical antipsychotic drug is becoming more widespread. Evidence from cohort studies suggests that this type of medication may help reduce impulsive self-harming behaviour and reduce the need for inpatient treatment.[82] However, this drug is also associated with potential harms, including blood dyscrasia,[82] which have the potential to be fatal if not properly monitored and treated. The large number of potential benefits and harms of clozapine for the treatment of inpatients with severe BPD provides a strong case for a placebo-controlled randomised trial of this drug. Given the high rate of drop-out in this and other Phase III trials of community-based interventions for people with BPD, consideration should be given using primary outcomes that do not require direct patient contact.

Conclusions

Based on the results of this trial, we have not shown any benefits of prescribing lamotrigine for people with BPD. These results provide further support for current NICE guidelines, which state that medication should not be used specifically for BPD and consideration should be given to referring people for specialist psychological treatment when these services are available.

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Mike J Crawford (Professor of Mental Health, Centre for Psychiatry, Imperial College London) was the chief investigator of the study, and contributed to the design of the study and the study protocol and the preparation of this manuscript.

Rahil Sanatinia (Research Associate, Centre for Psychiatry, Imperial College London) provided clinical leadership, supported recruitment of study participants and contributed to the preparation of this manuscript.

Barbara Barrett (Reader, King's College London) developed plans for the economic evaluation, contributed to the design of the study and the study protocol and preparation of this manuscript.

Gillian Cunningham (Research Associate, Tees, Esk and Wear Valleys NHS Foundation Trust) recruited and followed up study participants and contributed to the preparation of this manuscript.

Oliver Dale (Consultant Psychiatrist, West London Mental Health NHS Trust) was a principal investigator and contributed to the conduct of the study and the preparation of this manuscript.

Poushali Ganguli (Research Associate, King's College London) contributed to the management, analysis and interpretation of economic data and to the preparation of this manuscript.

Geoff Lawrence-Smith (Consultant Psychiatrist, Oxleas NHS Foundation Trust) was a principal investigator, and contributed to the conduct of the study and the preparation of this manuscript.

Verity C Leeson (Clinical Trials Manager, Centre for Psychiatry, Imperial College London) co-ordinated the trial, contributed to the development of the study protocol and preparation of this manuscript.

Fenella Lemonsky (Expert by Experience, Centre for Psychiatry, Imperial College London) oversaw service user involvement in the study and contributed to the design of the study protocol and preparation of this manuscript.

Georgia Lykomitrou-Matthews (Research Associate, University of Nottingham) recruited and followed up study participants and contributed to the writing of this manuscript.

Alan Montgomery (Professor, University of Nottingham) contributed to the development of the analysis plan for the study and the study protocol and the preparation of this manuscript.

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All authors read and approved the final manuscript.

Publications

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Data sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it is important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Pro forma for recording possible side effects of trial medication

Symptom	Source		Severity			
	Patient report	Case-notes, investigation or examination	Absent (0)	Mild (1)	Moderate (2)	Severe (3)
1. Headache (b)						
2. Back pain						
3. Joint pain and swelling (d, e)						
4. Blurred vision						
5. Nystagmus (voluntary or involuntary eye movements)						
6. Conjunctivitis (pink, blood-shot white of eye)						
7. Dry mouth						
8. Palpitations (irregular heart-beat)						
9. Dizziness						
10. Unsteadiness						
11. Ataxia (coordination problems)						
12. Tremor						
13. Other movement disorders						
14. Nausea/vomiting (a, b, e)						
How often?						
Do you have an explanation for this?						
15. Loss of appetite (a, e)						
16. Loss of weight (a, c, e)						
17. Diarrhoea (a, e)						

Symptom	Source		Severity			
	Patient report	Case-notes, investigation or examination	Absent (0)	Mild (1)	Moderate (2)	Severe (3)
18. Constipation						
19. Abnormal Colour Stools (a, e)						
20. Drowsiness (a, e)						
21. Insomnia						
22. Disorientation/confusion (b, e)						
23. Rash (a, b, c, d, e)						
Where?						
Do you have an explanation for this?						
24. Jaundice (a, e)						
25. Pruritis (a, d ,e)						
Where?						
Do you have an explanation for this?						
26. Skin lesions (d)						
Where?						
27. Blisters (d)						
Where?						
28. Mouth ulcers (d)						
29. Facial swelling (a)						
30. Lymphadenitis – swollen glands (a, c)						
31. Swollen/painful abdomen (e)						
32. Photophobia – intolerance or discomfort in response to light (b)						

Symptom	Source		Severity			
	Patient report	Case-notes, investigation or examination	Absent (0)	Mild (1)	Moderate (2)	Severe (3)
33. Breathlessness						
34. Fever (a, b, c, d)						
35. Aggression						
36. Agitation						
37. Suicidal thoughts Did you have these before taking the medication? Would you ever think of acting on these?						
38. Anaemia (f)						
39. Bruising (f)						
Other side effects						

Items labelled:	Total Number
Absent	
Mild	
Moderate	
Severe	

Appendix 2 Modified version of the Adult Service Use Schedule as used in this trial

Reproduced with permission from Dr Barbara Barrett (2018, King's College London, personal communication).

Instructions

Sections A to D should be completed in interview with the service user.

Section E should be completed using the hospital computer database.

At baseline, the schedule covers the patient's use of services for the six months preceding the interview.
At follow-up, the schedule covers the patient's use of services since the previous interview.

Use circles to select options from lists.

Numbers, zeros or missing data codes should be placed in every cell.

See Appendix 1 for Code List

Period(s) covered (tick all that apply)	
Baseline	
Baseline to 12-week	
12 to 24-week	
24 to 52-week	
If previous interviews missed, this schedule should cover the entire period from previous to current interview date. Please tick all periods that apply.	
DO NOT REPRODUCE WITHOUT PERMISSION. CONTACT Barbara.m.barrett@kcl.ac.uk	

Section A: Employment

A01 – What is your current occupational status?

01	Full-time employment (30+ hours per week)	Go to A02
02	Part-time employment (<30 hours per week)	Go to A02
03	Employed & currently unable to work	Go to A02
04	Full-time student	Go to B01
05	Voluntary worker	Go to B01
06	Unemployed & looking for work	Go to B01
07	Unemployed & not looking for work (e.g. housewife/husband)	Go to B01
08	Unemployed & unable to work for medical reasons	Go to B01
09	Medically retired	Go to B01
10	Retired	Go to B01
555	Not applicable	Go to B01
666	Research worker unable to evaluate	Go to B01
999	Not completed	Go to B01

A02 – What is your approximate gross pay per year (current or most recent employment)?

1	Under £5,000	Go to A03
2	£5,001-£10,000	Go to A03
3	£10,001-£15,000	Go to A03
4	£15,001-£20,000	Go to A03
5	£20,001-£25,000	Go to A03
6	£25,001-£30,000	Go to A03
7	£30,001-£35,000	Go to A03
8	£35,001-£40,000	Go to A03
9	£40,001-£45,000	Go to A03
10	£45,001-£50,000	Go to A03
11	£50,001+	Go to A03
555	Not applicable	Go to A03
666	Research worker unable to evaluate	Go to A03
999	Not completed	Go to A03

A03 – How many HOURS have you worked per week on average over the last six months/since the previous interview?

		HOURS	Go to A04
555	Not applicable		Go to B01
666	Research worker unable to evaluate		Go to B01
999	Not completed		Go to B01

A04 – How many DAYS have you been absent from work due to illness over the last six months/since the previous interview?

		DAYS	Go to B01
555	Not applicable		Go to B01
666	Research worker unable to evaluate		Go to B01
999	Not completed		Go to B01

Section B: Hospital Services (FROM PATIENT REPORT)

B01 – Have you had a hospital admission during the last six months/since the previous interview?

1	Yes	Go to B02
0	No	Go to B03
555	Not applicable	Go to B03
666	Research worker unable to evaluate	Go to B03
999	Not completed	Go to B03

B02 – If yes, record details below.

Mental health admission (code 1) or other reason (code 2)	Was the admission planned (code 1) or unplanned (code 2)?	Brief details if other reason (coded 2)	Number of nights

B03 – Have you been to hospital for an outpatient/day patient appointment during the last six months/since the previous interview?

1	Yes	Go to B04
0	No	Go to B05
555	Not applicable	Go to B05
666	Research worker unable to evaluate	Go to B05
999	Not completed	Go to B05

B04 – If yes, record details below.

Speciality (use code if possible)	Details if speciality code='other'	Number of appointments

B05 – Have you attended an accident and emergency (A&E) department in the last six months/since the previous interview?

1	Yes	Go to B06
0	No	Go to C01
555	Not applicable	Go to C01
666	Research worker unable to evaluate	Go to C01
999	Not completed	Go to C01

B06 - If yes, record details below.

Detail reason	Admitted	Ambulance	Number of contacts
	Yes / No	Yes / No	
	Yes / No	Yes / No	
	Yes / No	Yes / No	
	Yes / No	Yes / No	
	Yes / No	Yes / No	
	Yes / No	Yes / No	
	Yes / No	Yes / No	
	Yes / No	Yes / No	
	Yes / No	Yes / No	
	Yes / No	Yes / No	

Section C: Community services

C01 – Which of the following community based professionals or services have you had contact with over the last six months/since the previous interview?

		Number of contacts	Average duration (minutes)
01	General practitioner – home		
02	General practitioner – practice		
03	General practitioner – telephone		
04	Practice nurse (in GP surgery)		
05	Care Co-ordinator		
06	Psychiatrist		
07	Psychologist		
08	Community Psychiatric nurse		
09	Occupational therapist		
10	Social worker		
11	District nurse		
12	Home help/support working		
13	Counsellor/therapist		
14	NHS Walk-in clinic		
15	Advice service e.g. citizen's advice bureau, housing association		
16	Helpline e.g. Samaritans		
17	NHS Direct (telephone)/111		
18	Self-help groups e.g. AA		
19	Complementary therapist		
20	Other – give details		
21	Other – give details		
22	Other – give details		
23	Other – give details		

Section D: Medication

D01 – Have you been prescribed any medication in the last six months/since the previous interview?

Please record psychotropic medication only. For current medication ask for current dose; for medication no longer taken ask for final dose.

Name of Medication	Date Started	Dose	Units (see codes below)	Frequency (see codes below)	Date Stopped	Continuing at interview?
e.g. Citalopram	01/04/2007	30	1	1	555 - NA	Yes
						Yes / No
						Yes / No
						Yes / No
						Yes / No
						Yes / No
						Yes / No
						Yes / No
						Yes / No
						Yes / No
						Yes / No
						Yes / No
						Yes / No
						Yes / No

Section E: DATA COLLECTION FROM HOSPITAL DATABASES

E01 – Did the patient have a hospital admission during the last six months/since the previous interview?

1	Yes	Go to E02
0	No	End questionnaire.
555	Not applicable	End questionnaire.
666	Research worker unable to evaluate	End questionnaire.
999	Not completed	End questionnaire.

E02 – If yes, record details below.

Admission code (see below)	Reason (if coded other)	Date of admission	Date of discharge

1	Intensive care	3	Rehabilitation
2	Acute care	4	Other - specify

APPENDIX 1: MODIFIED ADULT SERVICE USER SCHEDULE CODE LIST

Code missing data as follows:

555	Not applicable
666	Research worker unable to evaluate
999	Not completed

Speciality codes for B04

1	Mental Health	22	Medical Oncology
2	Allergy	23	Nephrology
3	Audiology	24	Neurology
4	Blood Test	25	Obstetrics
5	Cardiology	26	Occupational Therapy
6	Dental Specialties	27	Ophthalmology
7	Dermatology	28	Orthoptics
8	Diabetic Medicine	29	Pain Management
9	Diagnostic Imaging	30	Palliative Medicine
10	Dietetics	31	Physiotherapy
11	Endocrinology	32	Podiatry
12	ENT	33	Rehabilitation
13	Gastroenterology	34	Respiratory Medicine
14	General Medicine	35	Rheumatology
15	General Surgery	36	Sexual and Reproductive Health Clinic (previously referred to as Family Planning Clinic)
16	Genito-Urinary Medicine	37	Speech & Language Therapy
17	Geriatric Medicine	38	Trauma & Orthopaedics
18	Gynaecology	39	Tropical Medicine
19	Hepatology	40	Urology
20	HIV/ AIDS	41	X-Ray
21	Infectious Diseases	42	Other

Medication units for Section D01

1	Milligrams (mg)	5	Depot
2	Microgram (mcg)	6	Patch
3	Grams (g)	7	Other – give details
4	Millilitres (ml)		

Medication frequency for Section D01

1	Once daily	7	As needed, about three times a week
2	Twice daily	8	As needed, about twice a week
3	Three times daily	9	As needed, about once a week
4	Four times daily	10	As needed, about once a fortnight
5	Once weekly	11	As needed, about once a month
6	Once per fortnight	12	Other – give details

Appendix 3 Unit costs and sources for economic evaluation

Cost item	Unit cost (£)	Source
Inpatient stay, per night	538–587	*NHS Reference Costs 2015*[83]
Outpatient, per appointment	42–298	*NHS Reference Costs 2015*[83]
Accident and emergency, per attendance	114–192	*NHS Reference Costs 2015*[83]
Ambulance, per call	96	*NHS Reference Costs 2015*[83]
GP contact, per minute of contact	2.82–3.60	Curtis and Burns[60]
Practice nurse, per minute of contact	0.72	Curtis and Burns[60]
Community mental health services, per minute of contact	0.68–4.35	Curtis and Burns[60]
Community health services, per minute of contact	0.50–2.53	Curtis and Burns[60]

Appendix 4 Secondary outcomes at secondary time points

TABLE 19 Beck Depression Inventory score at baseline and at 12, 24 and 52 weeks' follow-up

	Treatment group	
Time point	Lamotrigine (*N* = 137)	Placebo (*N* = 139)
Baseline		
Mean score (SD)	39.8 (11.7)	38.4 (10.2)
Median score (IQR)	41 (31–49)	39 (30–46)
n	135	138
12 weeks		
Mean score (SD)	29.9 (15.7)	29 (14.5)
Median score (IQR)	30 (19–42)	31 (17–40)
n	110	104
24 weeks		
Mean score (SD)	30.7 (15.1)	29.9 (15.1)
Median score (IQR)	32 (20–42)	31 (17–42)
n	98	97
52 weeks		
Mean score (SD)	28.8 (16.1)	28.7 (15.5)
Median score (IQR)	29 (14–42)	29 (16–41)
n	92	88

IQR, interquartile range.

TABLE 20 Deliberate self-harm at baseline and at 12, 24 and 52 weeks' follow-up

	Treatment group, *n* (%)	
Time point	Lamotrigine (*N* = 137)	Placebo (*N* = 139)
Baseline		
No	39 (28)	51 (37)
Yes	96 (70)	87 (63)
Unknown	2 (2)	1 (< 0.5)
12 weeks		
No	59 (54)	62 (60)
Yes	51 (46)	41 (40)
Unknown	1 (< 0.5)	1 (< 0.5)

continued

TABLE 20 Deliberate self-harm at baseline and at 12, 24 and 52 weeks' follow-up (*continued*)

	Treatment group, *n* (%)	
Time point	Lamotrigine (*N* = 137)	Placebo (*N* = 139)
24 weeks		
No	56 (57)	60 (62)
Yes	42 (43)	37 (38)
Unknown	0	1 (< 0.5)
52 weeks		
No	46 (47)	50 (51)
Yes	45 (46)	38 (39)
Unknown	6 (7)	10 (10)

Note
Denominators are the total number of participants who completed the individual follow-up.

TABLE 21 Social Functioning Questionnaire at baseline and at 12, 24 and 52 weeks' follow-up

	Treatment group	
Time point	Lamotrigine (*N* = 137)	Placebo (*N* = 139)
Baseline		
Mean score (SD)	15 (4.1)	14.9 (4.5)
Median score (IQR)	15 (12–18)	15 (12–18)
n	135	137
12 weeks		
Mean score (SD)	12.6 (4.5)	12.6 (5.2)
Median score (IQR)	12 (9–16)	12 (9–17)
n	110	104
24 weeks		
Mean score (SD)	11.8 (4.3)	12.2 (4.9)
Median score (IQR)	12 (9–14)	12 (9–15)
n	98	97
52 weeks		
Mean score (SD)	12.4 (4.3)	12.3 (4.9)
Median score (IQR)	13 (10–15)	12 (8–15)
n	91	88

IQR, interquartile range.

TABLE 22 Total score on ZAN-BPD subscores at baseline and at 52 weeks' follow-up

Subscore	Time point		Adjusted difference in means (95% CI)[a]	*p*-value
	Baseline	52 weeks' follow-up		
Affective disturbance				
Lamotrigine	6.9 (2.2)	4.7 (2.8)	–0.1 (–0.9 to 0.7)	0.850
Placebo	7.2 (2.4)	4.9 (3.1)	–	
Cognitive disturbance				
Lamotrigine	4 (2)	2.7 (2.2)	0.1 (–0.4 to 0.7)	0.615
Placebo	4.3 (2)	2.6 (2.1)	–	
Impulsivity				
Lamotrigine	3 (2.1)	2.1 (2)	–0.1 (–0.6 to 0.5)	0.824
Placebo	3 (1.8)	2.1 (2.1)	–	
Disturbed relationship				
Lamotrigine	2.7 (1.9)	1.7 (1.8)	0 (–0.5 to 0.5)	0.982
Placebo	2.9 (2)	1.8 (2)	–	

a Adjusted by site and other stratification factors.

EME
HS&DR
HTA
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