Lamotrigine for people with borderline personality disorder: a RCT

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Scientific summary

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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.

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