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The clinical effectiveness and cost effectiveness of lamotrigine for people with borderline personality disorder: A randomized, placebo-controlled trial.

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Conflict of interest

All authors have completed the Unified Competing Interest form (available on request from the corresponding author). All authors declare no other competing interests except Professor Joseph Reilly. Professor Reilly has received project funding from the Drug Safety Research Unit as part of an unrestricted grant provided by Merck Pharmaceuticals.

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The sponsor of the study played no part in the preparation of this paper. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HTA programme, NIHR, or the Department of Health. A more detailed account of the study methods and findings will be published in full in Health Technology Assessment in 2018.

ABSTRACT (252 words)

Objectives

To examine whether lamotrigine is a clinically effective and cost-effective treatment for people with borderline personality disorder.

Method

Multicentre, double-blind, placebo-controlled randomized trial. Between July 2013 to November 2016, we recruited 276 people aged 18 or over, who met diagnostic criteria for borderline personality disorder. We excluded those with co-existing bipolar affective disorder or psychosis, those already taking a mood stabiliser, and women at risk of pregnancy. We randomly allocated participants on a 1:1 ratio to up to 400mg of lamotrigine per day or an inert placebo using a remote web-based randomization service. The primary outcome was total score on the Zanarini Rating scale for Borderline Personality Disorder (ZAN-BPD) at 52 weeks. Secondary outcomes included depressive symptoms, deliberate self-harm, social functioning, health-related quality of life, resource use and costs, side effects of treatment and adverse events.

Results

195 (70.6%) participants were followed up at 52 weeks, at which point 49 (36%) of those prescribed lamotrigine and 58 (42%) of those prescribed placebo were taking it. Mean total ZAN-BPD score was 11.3 (SD = 6.6) among those randomized to lamotrigine and 11.5 (SD = 7.7) among those randomized to placebo (adjusted difference in means = 0.1, 95% C.I = -1.8 to 2.0, p=0.91). There was no evidence of any differences in secondary outcomes. Costs of direct care for those prescribed lamotrigine were similar to those prescribed placebo.

Conclusions

Treating people with borderline personality disorder with lamotrigine is not a clinically effective or cost-effective use of resources.

Trial registration

Current Controlled Trials ISRCTN78923965.

Introduction

Borderline personality disorder is a severe mental disorder that is characterised by sudden distressing changes in mood, unstable relationships and impulsivity (1, 2). Levels of substance misuse and deliberate self-harm and suicide are high among people with borderline personality disorder. The condition occurs globally, with a lifetime community prevalence of over 5% (3). While no drugs have been formally approved for the treatment of borderline personality disorder, people with this condition are prescribed large amounts of medication (4), with as many as 90% being prescribed psychiatric drugs and two-thirds taking long-term antipsychotic drugs (5-7).

Rapid changes in mood are one of the hallmarks of borderline personality disorder (8). This has led to interest in the possibility that mood stabilisers, which improve the mental health of people with bipolar disorder, could also help those with borderline personality disorder (9). Current practice guidelines on the treatment of borderline personality disorder advocate use of mood stabilisers for the treatment of impulsive aggression and self-harming behaviors (10, 11). A systematic review of pharmacotherapy for people with borderline personality disorder concluded that mood stabilisers may be effective in reducing core symptoms of the condition (12). but trials to date have been small and have not examined long term effects (9).

Lamotrigine is an anticonvulsant that is licensed for the treatment of bipolar affective disorder. It is relatively safe in overdose and less teratogenic than some other mood stabilisers (13-15). Evidence that lamotrigine may prevent relapse in rapid-cycling bipolar disorder (16), makes it particularly worthy of testing among people with borderline personality disorder. Two small randomized trials reported reduced impulsivity and affective lability compared to an inactive placebo (17, 18). However both were preliminary studies which only examined short-term effects.

We investigated the clinical and cost-effectiveness of lamotrigine for adults with borderline personality disorder who were using secondary care mental health services. We followed people up 52 weeks after randomization to examine the long-term effects of this treatment.

Methods

The LABILE (Lamotrigine And Borderline personality disorder: Investigating Long-term Effects) trial was a two-arm, parallel group, blinded, randomized trial of lamotrigine versus placebo for adults with borderline personality disorder. Full details of the trial protocol have been published elsewhere (19). We recruited people aged 18 or over who were in contact with mental health services in the United Kingdom. To take part in the study potential participants had to meet DSM-IV diagnostic criteria for borderline personality disorder using the Structured Clinical Interview for Axis II Personality Disorders (20). Potential participants were excluded if they met diagnostic criteria for bipolar affective disorder (type I & II) assessed using the Structured Clinical Interview for Axis I Disorders, or psychotic disorder (21), were prescribed a mood stabiliser currently or within the last four weeks, had a known history of liver or kidney impairment, or had cognitive or language difficulties that prevented them from providing informed consent. We also excluded any pre-menopausal women who were breastfeeding or pregnant at the time of the baseline assessment, contemplating becoming pregnant during the following 12 months, or sexually active and unwilling to take regular contraception. Approval for the research was given by the London Central Research Ethics Committee (Ref: 12/LO/1514) and from the Research and Development departments of the participating provider organizations. The Medicines and Healthcare Products Regulatory Agency (MHRA) gave Clinical Trial Authorisation.

Randomization and blinding

After consenting to participate, eligible patients were asked to complete the Hypomanic Checklist (22), a short screening questionnaire that can distinguish those with bipolar disorder from those

with unipolar depression, and the International Personality Disorder Examination (IPDE) screening questionnaire (23), Local research staff accessed an automated randomization service operated by Nottingham Clinical Trials Unit that randomly allocated participants in a 1:1 ratio to either lamotrigine or placebo. This employed random permuted blocks of varying size, stratified by study centre, severity of personality disorder (using data from the IPDE and criteria developed by Tyrer and Johnson) (24), and extent of bipolarity (using a score of more or less than 14 on the Hypomania Checklist) (22).

The randomization system generated a unique code for each participant corresponding to a predetermined active or placebo allocation. Site pharmacies were unblinded to allocation and would cross-reference the predetermined list held in pharmacy with each trial prescription detailing the participant's randomization code, allowing selection of trial medication from the appropriate arm. Bottles were blinded at the point of dispensing by removal of a tear-off label which contained a code that identified the contents as lamotrigine or placebo in a coded format.

All patients, carers and referring psychiatrists were blinded to treatment assignment until 52 weeks post randomization except in instances where there was an overdose, pregnancy or other adverse event that required disclosure. Researchers collecting follow-up data remained blind in these circumstances. Blinding of researchers, trial manager and trial statistician was maintained until all data entry and processing were completed and the database had been locked. All study researchers, aside from the trial statistician and health economist, remained blind to allocation status until after an initial discussion of trial findings had been completed.

Intervention

All those taking part in the study continued to receive usual treatment which included contact with primary and secondary 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 they were not prescribed lamotrigine (aside from trial medication) or any other antiepileptic mood stabiliser. In addition, those randomized to the active arm of the trial were prescribed up to 200 mg of generic lamotrigine titrated over a six week period depending on how well it was tolerated and clinical response. Treatment dose was titrated according to the established British National Formulary protocol (25) but standardised to 14-day intervals. The starting dose was 25mg per day. Depending on response and tolerance this was increased to 50mg after two weeks, 100mg after four weeks and 200mg thereafter. In keeping with recommendations, the maintenance dose for women taking the combined oral contraceptive pill was increased to 400mg daily (25). Those randomized to control treatment received usual treatment plus a prescription for an inert placebo, which was identical in appearance but contained lactose monohydrate.

In the light of evidence linking adverse skin reactions with patients abruptly starting high doses of lamotrigine, we required participants who had a break in treatment of more than five days to re-titrate medication from 25mg daily.

Outcomes

The primary outcome was symptoms of borderline personality disorder measured at twelve months using total score on the Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD) (26). The ZAN-BPD is a widely used measure of symptoms and behavioural problems experienced by people with this condition. The total range of scores is 0 to 36 with higher scores indicating poorer mental health. The ZAN-BPD has been used in previous studies of pharmacological and psychological treatments for people with borderline personality disorder and is sensitive to change (27). The lead researcher (RS) was trained to use the ZAN-BPD and supervised all other researchers on the project. We examined the degree of agreement between scores on the ZAN-BPD from the pairs of researchers who separately rated 27 participants and found these to be highly correlated (Intraclass Correlation Coefficient = 0.98, 95% CI = 0.95 to 0.99).

The secondary outcomes were total score on the ZAN-BPD at three, six and twelve months after randomization, together with depression, measured using the Beck Depression Inventory (28), deliberate self-harm using the Acts of Deliberate Self-Harm Inventory (29), social functioning using the Social Functioning Questionnaire (30), use of alcohol and other drugs using the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) (31) and health-related quality of life using the EQ-5D-3L (32). Researchers assessed side effects of trial medication when interviewing participants using a proforma designed to cover the possible effects listed in the British National Formulary entry for lamotrigine (25). Higher scores on all secondary outcomes indicate poorer health or functioning, aside from the EQ-5D-3L for which higher scores indicate lower health-related quality of life. Adverse events were also recorded. Use of health and social care resources and costs were assessed using a modified version of the Adult Service Use Schedule (33). This questionnaire is used to collect detailed data on use of all hospital and community services including medication. All secondary outcomes were assessed three, six, and twelve months after randomization except alcohol and drug use which was assessed at baseline and twelve months later.

Adherence

Researchers maintained regular contact with participants throughout the follow-up period enquiring about side effects and adherence every fortnight, during the initial titration phase, and then monthly once a maintenance dose had been reached. Participants were asked if they had missed doses of medication and a log was made of the dose dispensed on each occasion. We used these logs to record the number of weeks participants reported taking trial medication and the dose of medication they reported taking each week. We defined adherence with medication as the participant taking uninterrupted medication at a dose of 100mg or more throughout the study period after the initial titration phase had been completed. We supplemented these data by asking study participants to complete the Morisky Medication 4-item Adherence Scale at three, six and twelve months (34). This is a four item questionnaire which provides a valid estimate of

adherence with psychotropic medication (35). Total score ranges from 0 to 4 with higher scores indicating higher adherence.

Statistical analysis

The sample size calculation and all data analyses were conducted using Stata versions 13 and 14 (36). In a previous trial of problem solving therapy improvements in mental health and reduced use of emergency medical services were seen among those who had a 3.6 point reduction in total ZAN-BPD score. We needed primary outcome data from 214 participants at 52 weeks to have 90% power to detect a minimal clinically relevant difference of 3.0 (SD = 6.75) in total score on the ZAN-BPD using a 0.05 two-sided level of statistical significance. To take account of 15% loss to follow-up we increased the target sample size to 252.

Details of the statistical analyses were recorded in the Statistical Analysis Plan which was agreed by with the independent Trial Steering Committee prior to completion of data collection, database lock and unblinding of the study.

The primary analysis was performed according to randomized treatment, regardless of adherence with allocation and 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>=14 or <14). For 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 and 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 the participant had taken trial medication at a dose of 100mg or more without interruption during the 52 weeks prior to the final follow-up interview.
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 Years derived from the EQ-5D-3L.

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 and regression models with bootstrapping for cost data.

For safety data including Adverse Events, Serious Adverse Events and Suspected Unexpected Serious Adverse Reactions we used summary statistics, i.e. number of adverse events/side effects of different categories, number and proportion of participants reported at least one Adverse Events or Serious Adverse Events within each treatment arm.
The trial is registered with Controlled Clinical Trials as ISRCTN90916365.

Results

Between July 2013 and October 2015, 296 patients were screened for eligibility. Of these, 276 (93·2%) met eligibility criteria and were randomized (figure 1); 137 to lamotrigine plus usual care and 139 to placebo plus usual care. There were no instances in which researchers were unblinded to the participants' allocation status prior to completion of collection of 52 week outcome data.
Baseline demographic and clinical characteristics of study groups were comparable (table 1). Follow up rates were similar between treatment arms with 195 (71%) participants completing the 52 week

follow up (fig. 1). In total 93 (33.7%) participants took trial medication as per protocol and similar proportions were seen in both arms (table 2). At 12 weeks, 68.8% were taking trial medication regularly, with 38.9% taking it regularly at 12 months.

There was a decrease in ZAN-BPD at 12 weeks, after which it remained stable throughout the remainder of the follow up. Total scores on ZAN-BPD in the lamotrigine arm of the trial were 11.5 at 12 weeks, 11.9 at 24 weeks and 11.3 at 52 weeks. Corresponding scores among those in the control arm of the trial were 11.5, 11.9 and 11.5 (see figure 2). No difference was found in total ZAN-BPD score at 52 weeks between treatment arms. No difference was found in any of the secondary outcomes, nor in the four sub scores of the ZAN-BPD at any time point (table 3 and supplementary tables S1-S4). The lack of treatment effect was supported by sensitivity analyses. Adjusted difference in mean ZAN-BPD was 0.0 (95% CI = -1.25 to 1.26, p = 0.90) using repeated measures, -0·1 (95% CI = -1.9 to 1.8) using multiple imputation for missing data and 0.3 (95% CI = -3.7 to 4.3) when adjusted for adherence. Regarding adverse events, 77 (56%) of those in the lamotrigine arm of the trial had one or more event, compared to 93 (67%) of those in the control arm of the trial (table 4). The corresponding figures for serious adverse events were 26 (19%) in the active arm of the trial and 32 (23%) in the control arm, including five pregnancies (three in the lamotrigine group and two in the control group).

At baseline, costs were on average $8,160 in the lamotrigine group and $5,163 in the placebo group in the six months prior to randomization. Average total costs over 52 weeks were $17,785 in the lamotrigine group and $12,340 in the control arm of the trial. The difference in cost was not statistically significant (adjusted difference = $931.99, 95% CI = -2,740.44 to 4,604.41, p=0.62). Group differences between health-related quality of life and the resulting Quality Adjusted Life Years were also not statistically significant.

Discussion

In this placebo-controlled randomized trial, we found no evidence that prescribing lamotrigine to people with borderline personality disorder led to improvements in their mental health. The study was large enough to generate a precise estimate of the overall treatment effect, which did not include the minimum clinically important difference of 3.0 on the ZAN-BPD at 12 months (the primary outcome measure). Levels of adherence to trial medication were low with only a third (n = 93, 33.7%) of study participants taking trial medication throughout as specified in the study protocol. Levels of adherence were higher during the first 12 weeks of the study when two-thirds of participants were taking the medication (n = 190, 68.8%), but we did not find differences in study outcomes during this period. In a secondary analysis using Complier Average Causal Effect methods we found no evidence that greater adherence to trial medication was associated with any benefit to patients. Most participants reported one or more adverse effects, but those in the lamotrigine arm of the trial were no more likely to report potential side effects than those in the placebo arm of the trial.

Strengths and limitations of the study

The LABILE trial is the first ever phase III trial of a mood stabiliser for people with borderline personality disorder. One of the main strengths of the study is that we followed participants up over a 12 month period. Borderline personality disorder is a long-term condition but previous drug trials have not examined long-term outcomes (12). We recruited 11% more participants than we originally planned and the study size allowed precision to exclude a minimum clinically significant difference in the severity of symptoms of borderline personality disorder.

In this pragmatic trial we attempted to replicate clinical practice. However one area where we were unable to do this was in the means by which participants obtained their medication. Rather than collecting medication from a local pharmacy most participants had medication delivered to them in person or by post. This meant that participants had more regular contact with staff than they would have done in normal clinical practice. While levels of adherence to medication were low in this trial we believe that the additional contact that participants had with researchers meant that they may have been higher 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 randomized trials of lamotrigine for people with borderline personality disorder both reported positive effects (17, 18). Both trials were smaller, had a larger number of exclusion criteria and followed participants up for a shorter period of time. Several factors may explain differences in the results of the LABILE study and the two previous studies. Randomization does not guarantee that treatment arms are balanced in small trials and it is possible that differences in study outcomes in these previous trials resulted from differences in baseline characteristics of the samples. Secondly, in this pragmatic trial we deliberately kept our exclusion criteria to a minimum. This approach meant that were able to recruit people with the type of complex and severe problems that people with borderline personality disorder who use speciality mental health services generally have. It is possible that lamotrigine reduces symptoms of borderline personality disorder among people who have less complex and severe mental health problems than we recruited to the study. In the LABILE trial we had a rigorous process for maintaining blinding through the use of an automated web-based system that allocated study participants. Methods used to maintain blinding in previous trials are unclear (17).

Implications for clinicians

At present most people with borderline personality disorder who are in contact with mental health services are being prescribed psychiatric drugs (7); with a quarter being prescribed unlicensed mood stabilisers (5). Use of lamotrigine is specifically recommended in some textbooks on the treatment of people with borderline personality disorder (11). Clinicians may feel under considerable pressure to prescribe medication for people with borderline personality disorder especially at times of crisis (6). In the absence of clear evidence suggesting benefits associated with any type of medication, non-pharmacological approaches should be offered (2, 9).

Reductions in symptoms of borderline personality disorder during the course of the trial are in keeping with the results of longitudinal studies showing that the mental health of people with this condition improves over time (37, 38). However the pattern of improvement among study participants, with reductions in symptoms during the first 12 weeks of the trial, suggests that regression to the mean or general factors such as instillation of hope may have been responsible for this improvement.

In the LABILE trial we took great care not to recruit women who were pregnant, wanting to become pregnant or were pre-menopausal, sexually active and unwilling to take regular contraception. Despite the assurances that participants gave us, five subsequently became pregnant during the trial. While lamotrigine has been shown to be relatively safe in pregnancy, this is not true of all mood stabilisers – notably sodium valproate (39). Warnings have been issued about the use of off-licence sodium valproate to women of child bearing age (40). Despite this a recent national audit showed that over 10% of women with borderline personality disorder who are in contact with secondary care mental health services in the UK are currently being prescribed this drug (5). Data from the LABILE trial emphasises the importance of avoiding use of unlicensed medications that are potentially teratogenic for women with borderline personality disorder who are of child bearing age.

Conclusions

Based on the results of this trial we do not recommend that people with borderline personality disorder are prescribed lamotrigine. While pharmacological treatment of coexisting mental health conditions is important, we did not find evidence to support the use of lamotrigine for treatment the core symptoms of borderline personality disorder.

Contributors

MJC, RS, BB, FL, VL, RM, CP, PT and JGR were involved in all parts of the study. WT, AAM, BB and PG were involved in data analysis and revising the manuscript. RS, GC, GL, JM and IS were involved in recruiting study participants and revising the manuscript. OD, GL-WS and VS were principle investigators and were also involved in revising the manuscript. All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. MJC is the guarantor.

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Figure 1 CONSORT diagram

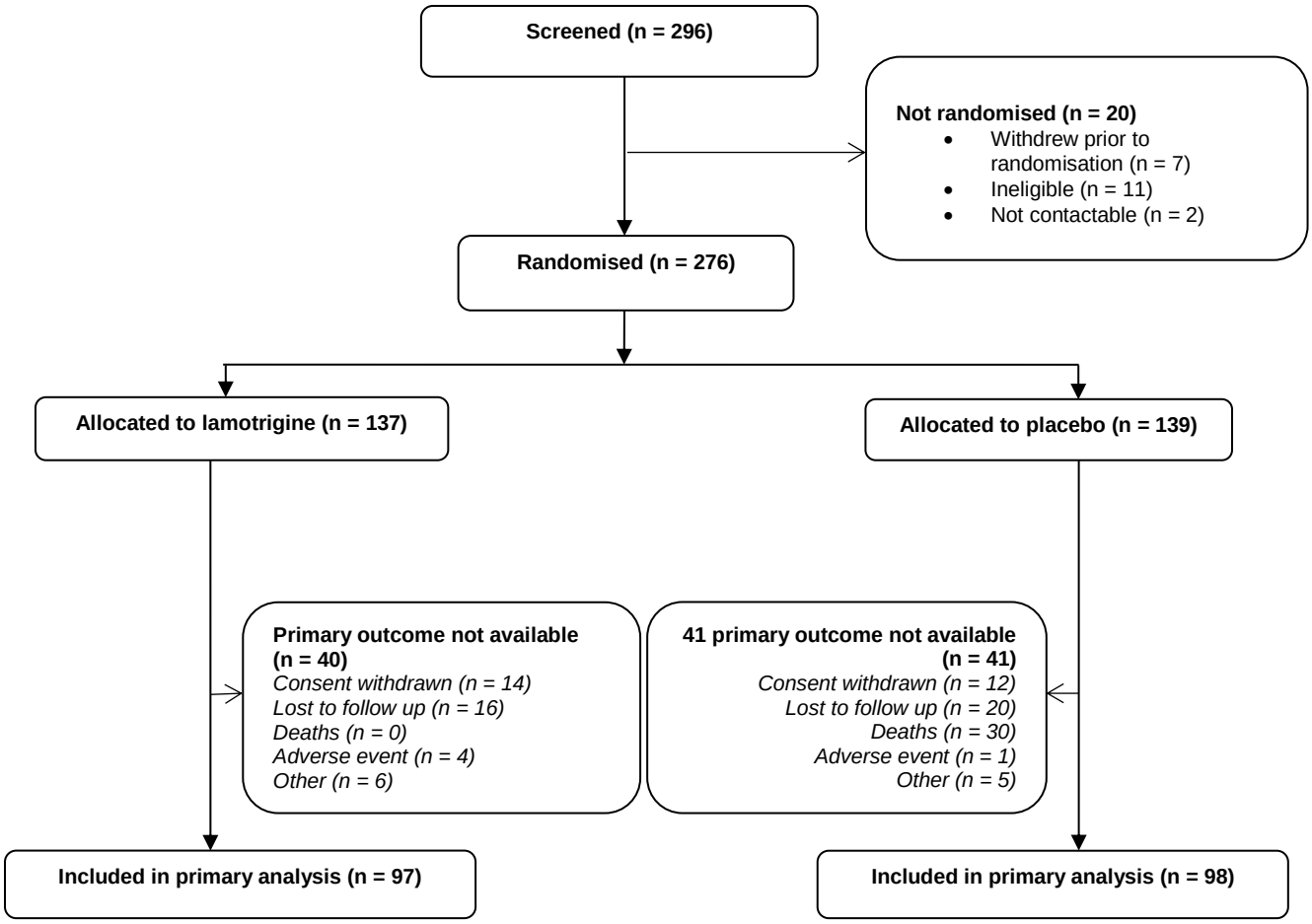

Table 1: Summary characteristics of study participants by intervention group

Characteristic		**Lamotrigine**		**Placebo**	
		N/ mean	%/ SD	N/ mean	%/ SD
Mean age in years at randomization (SD)		36.0	11	36.2	11
Gender:	Male	34	25	34	24
	Female	103	75	105	76
Ethnicity:	White	123	90	123	90
	Black	7	5	4	3
	Asian	1	1	2	1
	Other	6	4	10	7
Employment status*:	Employed	34	25	26	19
	Unemployed	95	69	105	76
	Student	4	3	1	1
	Retired	2	1	2	1
Severity of personality disorder:	Simple	0	0	2	1
	Complex	137	100	137	99
ZAN-BPD* (mean, SD)		16.6	5.8	17.4	6.2
Beck Depression Inventory* (mean, SD)		39.8	11.7	38.4	10.2
Deliberate self-harm in previous six months		96	70	51	37
Current alcohol misuse: yes		53	39	54	39
Current drug misuse: yes		54	39	47	34
Social functioning score* (mean)		15.0	4.1	14.9	4.5

ZAN-BPD - Zanarini rating scale for Borderline Personality Disorder
SD = Standard deviation
*Missing data: n = 137 lamotrigine and 134 placebo
Missing data: n = 72 lamotrigine and 75 placebo

Table 2: Adherence to trial medication

	Lamotrigine		Placebo	
	N/ mean	%/ IQR	N/ mean	%/IQR
Study medication received per protocol*	44	32	49	35
Morisky Rating scale at 12 month[#] Median [IQR]	3	2,4	3	2,4
Number of weeks participants received study medication Median [IQR]	32	9, 52	46	7,52
Number receiving medication throughout first 12 weeks	95	69	95	68
Number receiving medication 40 to 52 weeks	49	36	58	42
Dose of medication at 12 weeks in mg Median [IQR]	200	200, 200	200	200, 200
Dose of medication at 52 weeks in mg Median [IQR]	200	200,200	200	200,200

IQR = Inter quartile range

*Following initial titration participant stayed on a dose of 100mg or more throughout the remainder of the study

[#] Missing data: n = 88 lamotrigine and 82 placebo

Figure 2. Change in total ZAN-BPD score at 12, 26 and 52 weeks.

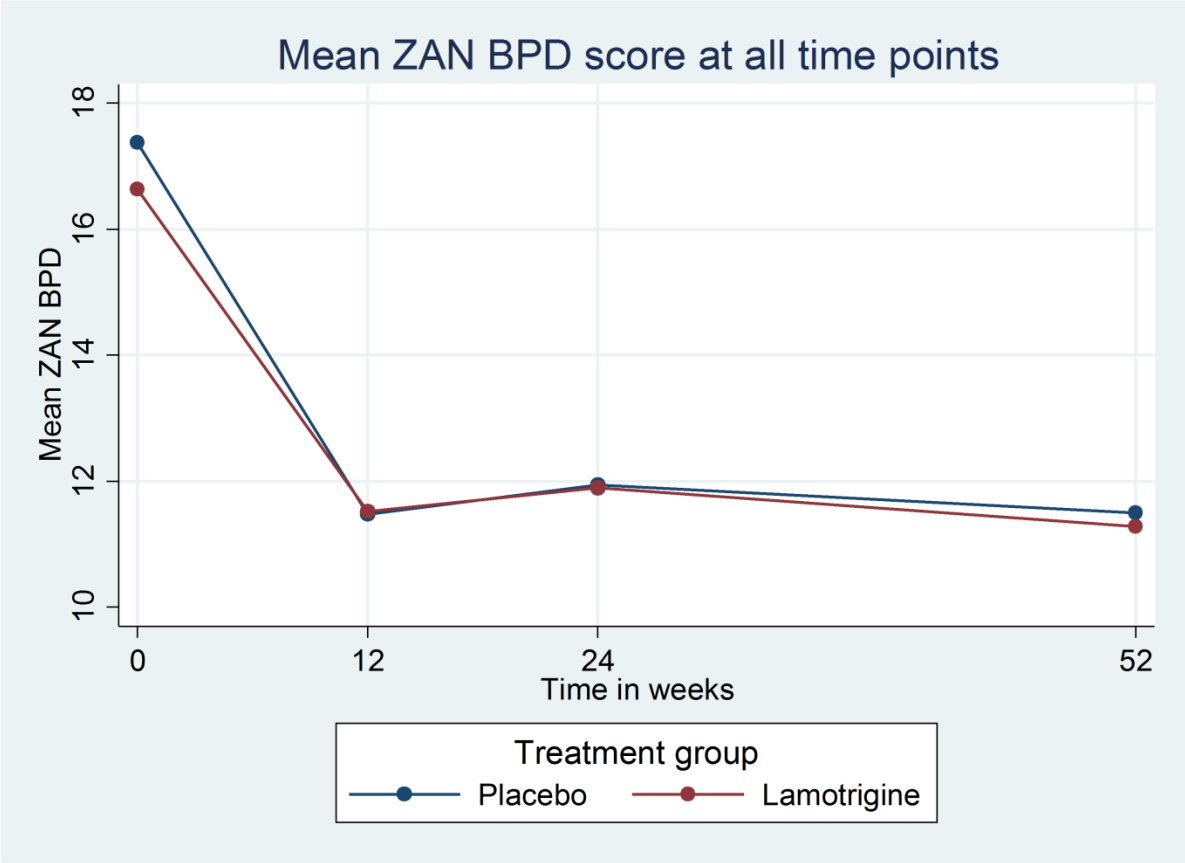

Table 3: Primary and secondary outcomes at 52 weeks

	Lamotrigine		Placebo		*Adjusted difference	95% Confidence Intervals	p-value
	N/ mean	%/ SD	N/ mean	%/ SD			
Zanarini Scale for Borderline Personality Disorder	11.3	6.6	11.5	7.7	0.1	-1.8, 2.0	0.906
Beck Depression Inventory [SD]	28.8	16.1	28.7	15.5	-0.2	-4.5,4.1	0.937
Deliberate self-harm in last 6m (n, %)	45	46	8	39	1.25	0.68, 2.28	0.464
Social Functioning Questionnaire	12.4	4.3	12.3	4.9	0	-1.2, 1.2	0.987
Alcohol use[#]	28	31	22	25	1.4	0.7, 2.7	0.354
Any other drug use[#]	27	30	23	26	1.2	0.6, 2.3	0.598
Total cost	12244.3	17442.8	8495.4	11349.1	641.6	-1886.6, 3169.8	0.617
Quality Adjusted Life Years	0.467	0.300	0.511	0.269	-0.012	-0.057, 0.034	0.612

*Adjusted by site and other stratification factors. Estimate is 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 due to collinearity.

Summary statistics is mean [SD] for continuous outcomes and N (%) for binary outcomes.

*Missing data: n = 83 lamotrigine and 77 placebo

Table 4: Summary of adverse events among study participants by intervention group by Medical Dictionary for Regulatory Activities (MedDRA) classifications

	Lamotrigine	**Placebo**
Total number of adverse events	246	285
Total number of participants with at least one adverse event	77	93
Total number of adverse events 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