Regular Article

Lacosamide in bipolar disorder: A 30-day comparison to a retrospective control group treated with other antiepileptics

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Aim: Bipolar disorder (BD) is often treated with anticonvulsants. Lacosamide has not been tested in BD. We assessed its effects in a hospital setting in patients with BD without epilepsy.

Methods: We treated 102 consecutive hospitalized patients with acute BD with lacosamide 50–300 mg/day. We compared this sample with a retrospective sample treated with other antiepileptics (OAE). We rated patients after 3, 7, 15, and 30 days of treatment with the Brief Psychiatric Rating Scale, Young Mania Rating Scale, Hamilton Depression Rating Scale, Hamilton Anxiety Rating Scale, Clinical Global Impressions – Severity, and Global Assessment of Functioning.

Results: Patients receiving lacosamide were significantly younger and had fewer mixed episodes at intake, and less substance use disorder comorbidity than those receiving OAE. Both groups showed positive effects on all measures. The two groups did not differ on any clinical measure at baseline, but from the 3rd day on, lacosamide patients fared better than OAE patients on the Young Mania Rating Scale and Clinical Global Impressions – Severity and worse on the Hamilton Anxiety Rating Scale. From the 15th day, OAE patients scored better on the Brief Psychiatric Rating Scale. Global Assessment of Functioning scores were significantly more improved in the lacosamide patients. Age, substance use disorder comorbidity, episode type, and educational level significantly affected results. No interactions were found amongst these parameters.

Conclusion: Lacosamide was effective in reducing psychopathology, mania, depression, and anxiety and in improving global functioning in patients with BD-I/II disorder in the short term, with few side-effects. Lacosamide improved mania, clinical severity, and global functioning better than OAE at doses lower than those used in epilepsy.

Key words: bipolar disorder, depression, global functioning, lacosamide, mania.

The chiral functionalized amino acid, lacosamide, is a third-generation antiepileptic drug currently approved as add-on treatment for partial epilepsy. Lacosamide is the R-enantiomer of N-benzyl-2-acetamido-3-methoxypropionamide (Fig. 1) and is endowed with antiepileptic activity, while its S-enantiomer, which is also a neurite outgrowth-promoting collapsin response mediator protein 2 (CRMP2) activity modifier, is devoid of such activity. It has recently received approval for the treatment of partial-onset seizures as monotherapy in the USA (2014) and Europe (2016).

Lacosamide is tolerable and safe with a well-characterized and favorable pharmacokinetic profile, including a fast absorption rate, minimal or no interaction with cytochrome P-450 isoenzymes, and a low potential for drug-drug interactions. Its mechanism of action in not fully understood, but is
suggested to act by enhancing slow inactivation of voltage-gated sodium channels, while leaving fast inactivation unaffected, dissimilarly to other antiepileptics. Furthermore, it inhibits CRMP2 inactivation, thus reducing signaling mediated through tyrosine receptors kinase B/C (trkB/C), like those carried out by neurotrophin 3 (NT-3) and brain-derived neurotrophic factor (BDNF). This site of action is shared with other mood-stabilizing anticonvulsivants. However, the role of lacosamide in modifying CRMP2 activity has been cast into doubt in regard to its effects in epilepsy and a role for CRMP2 in bipolar disorder (BD) is unlikely. Lacosamide was shown to reduce cocaine-induced elevations in reward function in rats, which is considered to be a common feature of manic episodes. It also showed a more beneficial psychotropic profile than other antiepileptic drugs, especially regarding affective symptoms, and caused no impairment of cognitive abilities. However, its off-label use is still limited.

There are few data on lacosamide in psychiatric disorders; however, it is possible that it could prevent substance- and life-event-induced mood elevation. Lacosamide was shown to reduce cocaine-induced mood elevation in an animal model. The main target in the treatment of BD is to suppress mania, since this prevents the subsequent development of depression. In a self-stimulation animal model of mania, low-dose lacosamide significantly reduced cocaine-induced intracranial self-stimulation in the rat, whereas sodium valproate and lamotrigine did this only at the highest dose. High-dose lacosamide increased the threshold of self-stimulation, even in the absence of cocaine. Béguin et al. provided a theoretical basis for using add-on lacosamide in bipolar spectrum disorders (BPSD) and/or substance use disorders (SUD).

Lacosamide showed some anxiolytic/antidepressant effects in patients with epilepsy with comorbid anxious/depressive symptoms. A Spanish study found lacosamide to abolish seizures in about 55% of 31 patients with epilepsy, showing also reduced anxiety/depressive symptoms at the 3- and 6-month follow up; symptoms were assessed through the Hospital Anxiety and Depression Scale, a validated self-rated questionnaire. Another study carried out in Ohio, USA, assessed 91 patients with epilepsy with the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E), which detects major depression in patients with epilepsy with a good positive predictive value of 0.62. The study found no significant change after 6 months. However, those 25 patients with elevated scores on the NDDI-E (>15) obtained a significant reduction in depression. Anxiety was not significantly affected by lacosamide, but was measured with a 7-item tool in only 20 of these patients. Lacosamide was found to not deteriorate cognition and in some cases even to improve it in a German study of long-standing adult epilepsy patients. In contrast, a systematic review observed controversial effects on mood and cognition in pediatric populations. In another open, multicenter study of patients with treatment-resistant focal epilepsy, lacosamide improved scores on the Beck Depression Inventory-II in the entire sample of 49 patients aged more than 16 years, and improved anxiety symptoms in patients with anxiety, independently from their improvement in epilepsy. We observed positive mood effects with reduced symptom fluctuation and reduced anxiety in a patient with cyclothymia, post-traumatic stress disorder, and frontotemporal epilepsy. This prompted us to try lacosamide as monotherapy in patients with an acute mood episode in a naturalistic setting, comparing their clinical response to a retrospective group treated with other antiepileptic drugs.

**METHODS**

We included 102 consecutive patients with a DSM-5 bipolar I or II disorder who had been recently hospitalized (during the period from January 2015 to the end of December 2016) for an acute mood episode, aged 18–65 years, both sexes. Patients were administered lacosamide in the range 50–300 mg/day. Usually the starting dose was 50 g/day, switched to 50 mg/12 h according to needs after 2 days, and to the target dose within 1 week. Patients were diagnosed on the basis of the Structured Clinical Interviews for DSM-IV Axis I and Axis II Disorders.
The clinical status was assessed at baseline and 3, 7, 15, and 30 days after initiating lacosamide administration. The instruments used were the 24-item Brief Psychiatric Rating Scale (BPRS), the Young Mania Rating Scale (YMRS), Hamilton’s Rating Scales for Depression (HDRS) and Anxiety (HARS), and the Clinical Global Impressions – Severity (CGI-S) scale. Patients’ global functioning was assessed with the Global Assessment of Functioning (GAF) Scale at baseline and at the 30th day after initiating lacosamide. We compared the clinical and sociodemographic data of patients on lacosamide (L group) with those of a retrospective sample of patients with similar disorders treated with other antiepileptic agents (OAE), evaluated at the same time-points (control group).

Exclusion criteria included treatment other than lacosamide, severe medical or neurological conditions, dementia, and epilepsy in particular, as well as inability to provide informed consent for participation. Patients with significant hepatic or renal impairment were excluded, as these conditions could have affected the pharmacokinetics of lacosamide.

The control group consisted of 123 patients who met inclusion criteria during the period January 2013–April 2017, who provided free, informed consent for treatment received and study participation, and who were receiving treatment with antiepileptics other than lacosamide. Patients were receiving antiepileptic drugs and some of them were receiving benzodiazepines (N = 12) or antipsychotics (N = 23, 21 atypicals). Patients on lithium were not included. No patient in the control or the L group had previously received electroconvulsive therapy. Inclusion and exclusion criteria were the same in both groups.

Side-effects were reported spontaneously by patients and were classified as mild, moderate, and severe. They were subsequently classified as frequent (≥5%) or infrequent (<5%). Included patients signed free, informed consent for participation. The study received approval from the local ethics committee prior to its initiation. It adhered to the Principles of Human Rights, as adopted by the World Medical Association (WMA) at the 18th WMA General Assembly, Helsinki, Finland, June 1964 and subsequently amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013. As the study was observational, we did not apply for a Clinical Trial registration.

Statistical analysis

Percentages, means, and SD were used for descriptive statistics. We used parametric tests to compare the large L (n = 102) and OAE samples (n = 123); that is, the Student’s t-test and Pearson’s correlation coefficient r for continuous variables (i.e., age). We used the χ²-test for categorical variables (i.e., sex, educational level, BD type, episode type, comorbid SUD) or Fisher’s exact test, as appropriate. Effect sizes were calculated with Cohen’s d, adopting Cohen’s original cut-offs (small, about 0.20; medium, about 0.50; and large, about 0.80 or more) and complementing them with Sawilowsky’s corrected threshold for statistical significance, <0.007 (=0.05/7). If splitting the sample for the purpose of analyzing specific subsamples resulted in one with a relatively small size, we subjected it to the Shapiro–Wilks W-test for normality to decide whether to proceed with a parametric test or to shift to a non-parametric one.

The significant differences derived from the comparisons between variables in our descriptive statistics were further examined and confirmed by a forward stepwise logistic regression, which is a semi-automated process of building a model by successively adding variables based solely on the t-statistics of their estimated coefficients. More specifically, sociodemographic variables with a P-value < 0.05 and clinical variables with a P-value < 0.007 at bivariate analysis were included in the multivariate analysis and the most parsimonious set of independent variables was selected through a forward procedure. The latter involves starting with no variables in the model, testing the addition of each variable using a chosen model fit criterion, adding any variable, the inclusion of which provides the most statistically significant improvement of the fit, and repeating this process until none improves the model to a significant extent. The χ²-test with degrees of freedom (d.f.) and P-values were obtained to estimate the size of the association between type of treatment, on one hand, and
patient sociodemographic characteristics (i.e., sex, age, educational level, BD type, episode type, and comorbid SUD), on the other hand, after the confounding effect of covariates was adjusted for, to the extent allowed by the data. Characteristics as ‘predictors’ for treatment type were regarded as potential confounders and considered actual confounders if their distributions were substantially different in the two samples. The cut-off for statistical significance for logistic regression was set at $P < 0.05$. All analyses were two-sided. The Cox–Snell pseudo-$R^2$ was calculated to determine the proportion of the variance in the dependent variable that is predictable from the independent variable(s). We conducted three-way analysis of variance (ANOVA) to investigate whether a three-way interaction existed among age, comorbidity, educational level, and episode type per treatment type in the logistic regression.

We used paired-samples $t$-test to compare, pre- and post-treatment with either lacosamide or OAE, the means of the BPRS, YMRS, HDRS, HARS, CGI-S, and GAF of manic, depressed, or mixed BP patients, respectively. We also used the independent-samples $t$-test to compare the differences (As, calculated by subtracting post-treatment from pre-treatment values), of the means of the BPRS, YMRS, HDRS, HARS, CGI-S, and GAF of manic, depressed, or mixed BP patients treated with lacosamide versus OAE.

All analyses were performed by using SPSS (IBM SPSS Statistics for Windows, Version 24.0 IBM Corporation, Armonk, NY, USA).

RESULTS

There were significant differences between L and OAE patients in sociodemographic characteristics (Table 1). The L sample was significantly younger than the OAE sample ($P = 0.004$), had less SUD comorbidity than OAE patients ($P = 0.000001$), and was of lower educational level than OAE patients ($P = 0.001$). There were no significant differences in marital status (Fisher’s exact test: $P = 0.938$). The $\chi^2$-test showed no significant difference between the L and OAE samples in the proportion of patients with manic, depressed, or mixed episodes on admission ($P = 0.261$). Age and years of education did not correlate with any outcome measure, save for final CGI-S scores, with which both positively correlated weakly ($r = 0.24$ and 0.22, respectively).

Intragroup comparisons

The sample as a whole responded well to the treatment and the two treatment samples, L and OAE, behaved similarly. In both groups and in the entire sample, significant improvements were found at Day 7 on all assessment measures and persisted throughout the entire treatment period. Furthermore, response was significant on the YMRS and on the CGI-S at Day 3 for the L and entire samples, while all groups responded with a similar significance on the GAF (Table S1) and a huge size effect (Table S2).

Intergroup comparisons

The two samples did not differ in number of prior mood episodes ($t = −0.46$, $P = 0.65$) or in the duration of their illness since its onset ($t = 0.21$, $P = 0.83$). Clinical measures showed no differences on any scale at baseline. At the 3rd day of treatment and for the remaining treatment period, L patients fared better than OAE patients on the YMRS and the CGI-S and worse on the HARS, while they did not differ on the HDRS. Furthermore, on the last day of observation (30 days), OAE patients scored lower on the BPRS than L patients (indicating a stronger improvement in psychopathology of the former), and lower on the GAF (indicating that the latter had a better functioning; Table 1; Fig. 2).

Measuring Cohen’s $d$ effect size (baseline vs Day 30) on the considered clinical measures for all groups, we found a very large magnitude (or huge for OAE patients on the BPRS and for the L and the total groups on the CGI-S) for YMRS, HDRS, and HARS in all groups, either considered separately (i.e., L or OAE patients) or together. The magnitude of the effect size for all groups (L, OAE, and total) was huge (Table S2).

Drug doses and clinical response

A total of 102 patients were taking lacosamide: five took 50 mg/day, 28 took 100 mg/day, 18 took 150 mg/day, 45 took 200 mg/day, one took 250 mg/day, and five took 300 mg/day (mean = 161.76; SD, 58.10). Of the 91 (74.0% of the OAE group) patients who were taking valproate, 14 took 600 mg/day, one took 750 mg/day, 16 took 900 mg/day, 39 took 1000 mg/day, one took 1200 mg/day, one took 1250 mg/day, and 19 took 1500 mg/day (mean = 1027.47; SD, 283.75). Of the
| Table 1. Baseline sociodemographic characteristics of the two samples and clinical characteristics across the study |
|--------------------------------------------------|------------------|-----------------|-----------------|------------------|
| **Sociodemographic** | **L (N = 102)** | **OAE (N = 123)** | **Test (Student’s t or χ²)** | **P** |
| Age (mean ± SD)      | 37.75 ± 11.49   | 42.02 ± 10.70   | **t = 2.87548** | **0.004425** |
| Sex, Male/Female, N  | 61/41           | 63/60           | **χ² = 1.661**  | 0.19747        |
| Nationality: Italians/other nationalities, N | 97/5            | 119/4           | **χ² = 0.3953** | 0.529529       |
| Educational level, N |                 |                 |                 |                 |
| No education         | 0               | 0               |                 |                 |
| Primary school       | 16              | 3               |                 |                 |
| Middle school        | 56              | 55              |                 |                 |
| High school          | 29              | 59              |                 |                 |
| College/university   | 1               | 6               |                 |                 |
| PhD/postdoc          | 0               | 0               |                 |                 |
| Marital status       |                 |                 |                 |                 |
| Single/unmarried     | 48              | 55              | **Fisher’s Exact Test P** | 0.93824 |
| Married/cohabitant   | 49              | 60              |                 |                 |
| Divorced, separated  | 4               | 7               |                 |                 |
| Widowed              | 1               | 1               |                 |                 |
| Clinical             |                 |                 |                 |                 |
| Diagnosis BD I/II, N | 51/51           | 65/58           | **χ² = 0.1808** | 0.670711       |
| Episode type on admission |           |                 |                 |                 |
| Manic                | 31              | 39              | **χ² = 2.7783** | 0.261565       |
| Depressive           | 28              | 33              |                 |                 |
| Mixed                | 64              | 52              |                 |                 |
| Duration since onset (years ± SD) | 15.82 ± 9.25   | 15.58 ± 8.16   | **t = 0.2121**  | 0.832222       |
| Number of past mood episodes (N ± SD) | 2.89 ± 1.14   | 2.96 ± 1.05   | **t = −0.45888** | 0.646769       |
| SUD comorbidity/no comorbidity, N | 20/82 | 52/71 | **χ² = 13.1678** | **0.000285*** |
| Other comorbidities, N |               |                 |                 |                 |
| Borderline personality disorder | 3            | 9               | **Fisher’s exact test P** | 0.505495 |
| Personality disorder NOS | 0             | 1               |                 |                 |
| Personality change due to another medical condition | 1 | 0 | | |
| Clinical measures    |                 |                 | Cut-off P < 0.007 |                 |
| Baseline             |                 |                 |                 |                 |
| BPRS                 | 60.20 ± 13.01   | 56.86 ± 10.17   | **t = 2.15771** | 0.032019       |
| YMRS                 | 15.35 ± 7.99    | 17.39 ± 11.11   | **t = −1.54962** | 0.122651       |
| HDRS                 | 18.33 ± 7.29    | 17.90 ± 6.09    | **t = 0.48322** | 0.629416       |
| HARS                 | 20.94 ± 6.87    | 18.73 ± 8.46    | **t = −2.1216** | 0.034975       |
| CGI-S                | 5.07 ± 0.68     | 4.89 ± 0.62     | **t = 2.1105**  | 0.035929       |
| GAF                  | 44.12 ± 7.47    | 45.96 ± 6.61    | **t = 1.96156** | 0.051059       |
| 3 days               |                 |                 |                 |                 |
| BPRS                 | 58.07 ± 12.56   | 54.28 ± 10.54   | **t = 2.46207** | 0.014572       |
| YMRS                 | 9.92 ± 8.70     | 15.45 ± 10.45   | **t = −4.25374** | **0.000031***** |
| HDRS                 | 17.33 ± 6.97    | 16.63 ± 6.12    | **t = 0.80063** | 0.4242         |
| HARS                 | 19.86 ± 7.00    | 16.01 ± 8.38    | **t = 3.64195** | **0.000336*** |
| CGI-S                | 3.94 ± 0.54     | 4.67 ± 0.67     | **t = −8.89201** | **< 0.00001*** |
| 7 days               |                 |                 |                 |                 |
| BPRS                 | 50.35 ± 15.67   | 45.94 ± 11.75   | **t = 2.40958** | 0.016783       |
| YMRS                 | 7.97 ± 7.23     | 12.11 ± 8.43    | **t = −3.90479** | **0.000125*** |
| HDRS                 | 14.31 ± 6.37    | 12.66 ± 5.60    | **t = 2.074**   | 0.039227       |
| HARS                 | 16.63 ± 6.29    | 12.85 ± 7.80    | **t = 3.94462** | **0.000107*** |
| CGI-S                | 3.30 ± 0.61     | 4.19 ± 0.77     | **t = −9.37703** | **< 0.00001*** |

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Table 1. (Continued)

<table>
<thead>
<tr>
<th></th>
<th>L (N = 102)</th>
<th>OAE (N = 123)</th>
<th>Test (Student’s t or χ²)</th>
<th>P</th>
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<tr>
<td>15 days</td>
<td></td>
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<tr>
<td>BPRS</td>
<td>45.08 ± 14.61</td>
<td>40.41 ± 10.07</td>
<td>t = 2.82804</td>
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<td>YMRS</td>
<td>6.72 ± 5.54</td>
<td>10.66 ± 8.87</td>
<td>t = −3.90166</td>
<td>0.000127**</td>
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<td>HDRS</td>
<td>11.28 ± 5.28</td>
<td>10.74 ± 5.01</td>
<td>t = 0.79256</td>
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<tr>
<td>HARS</td>
<td>13.42 ± 6.05</td>
<td>10.48 ± 6.24</td>
<td>t = 3.57135</td>
<td>0.000435*</td>
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<td>CGI-S</td>
<td>2.51 ± 0.71</td>
<td>3.92 ± 0.94</td>
<td>t = −11.4111</td>
<td>&lt;0.00001***</td>
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<td>30 days</td>
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<td>BPRS</td>
<td>39.70 ± 12.78</td>
<td>35.02 ± 8.79</td>
<td>t = 3.23481</td>
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<td>YMRS</td>
<td>5.14 ± 4.50</td>
<td>7.52 ± 4.69</td>
<td>t = −3.86353</td>
<td>0.000147*</td>
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<tr>
<td>HDRS</td>
<td>8.93 ± 4.85</td>
<td>8.34 ± 3.68</td>
<td>t = 1.03618</td>
<td>0.301239</td>
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<tr>
<td>HARS</td>
<td>10.75 ± 5.94</td>
<td>8.24 ± 5.04</td>
<td>t = 3.42782</td>
<td>0.000724*</td>
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<td>CGI-S</td>
<td>2.14 ± 0.84</td>
<td>3.50 ± 0.80</td>
<td>t = 12.33651</td>
<td>&lt;0.00001***</td>
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<td>GAF</td>
<td>63.16 ± 7.70</td>
<td>59.69 ± 7.05</td>
<td>t = 3.52099</td>
<td>0.000521*</td>
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</table>

*P < 0.05; **P < 0.01; ***P < 0.001. All significant results in bold characters
BD, bipolar disorder; BPRS, Brief Psychiatric Rating Scale; CGI-S, Clinical Global Impressions Scale – Severity; GAF, Global Assessment of Functioning Scale; HARS, Hamilton Anxiety Rating Scale; HDRS, Hamilton Depression Rating Scale; L, lacosamide group; NOS, not otherwise specified; OAE, other antiepileptics group; SUD, substance use disorder; YMRS, Young Mania Rating Scale.

Figure 2. The effect of (—) lacosamide and of (—) other antiepileptics on the scores of assessment instruments across the study period. BL, baseline; BPRS, Brief Psychiatric Rating Scale; CGI-S, Clinical Global Impressions Scale – Severity; HARS, Hamilton Anxiety Rating Scale; HDRS, Hamilton Depression Rating Scale; L, lacosamide group; NOS, not otherwise specified; OAE, other antiepileptics group; SUD, substance use disorder; YMRS, Young Mania Rating Scale.

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19 (15.4% of the OAE group) patients who were taking lamotrigine, one patient took 50 mg/day, four took 100 mg/day, 12 took 200 mg/day, and two took 250 mg/day (mean = 176.32; SD, 56.20). Regarding antiepileptics other than valproate and lamotrigine (N = 13, 10.6% of the OAE group), four patients were taking oxcarbazepine 600 mg/day, four were taking carbamazepine (one took 600 mg/day and three took 800 mg/day), three were taking pregabalin (one took 50 mg/day and two took 450 mg/day), and two were taking gabapentin 1200 mg/day. Six patients were concurrently receiving clonazepam: three patients who were taking 200 mg lamotrigine received oral clonazepam at doses of 0.5–3 mg; and three who were taking 1000–1500 mg valproate received oral clonazepam at doses of 8–9 mg. Correlations between drug doses and clinical measures were not significant or were weak–moderate: inverse correlations between lamotrigine doses and BPRS (r = −0.51), YMRS (r = −0.22), HDRS (r = −0.40), HARS (r = −0.41), and CGI-S (r = −0.50) scores and a curious positive correlation between dose of lacosamide and YMRS scores (r = 0.40).

To address possible confounders, we used forward stepwise logistic regression by entering into the model age, sex, educational level, diagnosis (bipolar I and bipolar II), episode type (depressive, manic, and mixed), and SUD comorbidity. We found age, sex, and educational level to be confounders, resulting in a distortion of the actual relationship between the independent and the dependent (treatment, i.e., L/OAE) variables considered in the model (Table 2). In contrast, BP type and episode type at admission did not affect the relation between the variables.

The Cox–Snell pseudo-$R^2$ was 0.457, meaning that our regression model explains 44.5% of the variance of the dependent variable (L/OAE), that is, our regression model explains only 44.5% of belonging to the L or OAE group.

By performing three-way ANOVA, we found no significant interaction between or among age, educational level, and SUD comorbidity in the determination of our results (Table 3).

Paired-samples $t$-tests showed that all the means, pre- and post-treatment with either lacosamide or OAE, of the BPRS, YMRS, HDRS, HARS, CGI-S, and GAF scales of manic, depressed, or mixed BP patients, respectively, differed significantly and with the same $P$-value (0.00001). Independent-samples $t$-tests showed comparable $\Delta$s BPRS, HDRS, and HARS, scores for manic, depressed, and mixed BP patients treated with lacosamide versus OAE are shown in Table 4. The YMRS improved more in the manic L group, the GAF more in the manic OAE group, and the CGI-S more in the mixed OAE group.

Since the most frequent comorbidity was SUD and differed in distribution between the L and OAE samples, while other comorbidities were distributed equally between them (Fisher’s exact test: $P = 0.505$), we conducted separate analyses to compare the effects in non-comorbid and comorbid patients. Interestingly, OAE patients were significantly older in the SUD non-comorbid group (Table S3), thus indicating that the effects of age were mainly driven by this subgroup. No age differences were found between the SUD comorbid and SUD non-comorbid subsamples, the comparison being carried out through the Student’s $t$-test, since Shapiro–Wilks $W$ was 0.933 and normality was accepted. The L group at baseline was characterized by higher baseline anxiety levels in the SUD non-comorbid group (mean = 21.85 ± 6.27 vs mean = 17.2 ± 8.05; $t = 2.81; P = 0.006$), but such differences disappeared in the course of the study. In contrast, in the OAE group, anxiety was higher in the SUD comorbid group at baseline and all

<table>
<thead>
<tr>
<th>Table 2. Forward stepwise logistic regression</th>
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<td>2</td>
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<td>3</td>
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</table>

†$\chi^2$ for data entry is based on the likelihood ratio test. Stepwise method: Forward entry.
considered time-points (Supplementary Table 3), while at Day 15, CGI-S scores were worse in the SUD comorbid subgroup, compared to the SUD non-comorbid subgroup (SUD comorbid, mean = 4.23 ± 1.00 vs SUD non-comorbid, mean = 3.69 ± 0.82; \( t = -3.28; P = 0.0013 \)).

### Table 3. Three-way analysis of variance

<table>
<thead>
<tr>
<th>Origin</th>
<th>Type III sum of squares</th>
<th>d.f.</th>
<th>Mean square</th>
<th>( F )</th>
<th>( P )</th>
</tr>
</thead>
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<td>Correct model</td>
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<td>7</td>
<td>1.142</td>
<td>5.189</td>
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<td>(Intercept)</td>
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<td>0.000</td>
</tr>
<tr>
<td>Age</td>
<td>0.256</td>
<td>1</td>
<td>0.286</td>
<td>1.431</td>
<td>0.002</td>
</tr>
<tr>
<td>Educational level</td>
<td>2.021</td>
<td>1</td>
<td>2.527</td>
<td>12.417</td>
<td>0.003</td>
</tr>
<tr>
<td>Comorbidity × Age</td>
<td>0.718</td>
<td>1</td>
<td>0.762</td>
<td>3.986</td>
<td>0.081</td>
</tr>
<tr>
<td>Comorbidity × Educational level</td>
<td>0.000</td>
<td>1</td>
<td>0.002</td>
<td>0.003</td>
<td>0.998</td>
</tr>
<tr>
<td>Age × Educational level</td>
<td>0.035</td>
<td>1</td>
<td>0.034</td>
<td>0.129</td>
<td>0.687</td>
</tr>
<tr>
<td>Comorbidity × Age × Educational level</td>
<td>0.005</td>
<td>1</td>
<td>0.006</td>
<td>0.021</td>
<td>0.893</td>
</tr>
<tr>
<td>Error</td>
<td>48.629</td>
<td>217</td>
<td>0.240</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>115.000</td>
<td>225</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted total</td>
<td>51.372</td>
<td>224</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\( ^† R^2 = 0.132 \) (adjusted = 0.126).

### Table 4. Independent-samples \( t \)-tests of the Deltas of the means of the clinical measures of manic, depressed, or mixed BP patients treated with lacosamide vs OAE

<table>
<thead>
<tr>
<th>Clinical measures</th>
<th>L (N = 102) ( \Delta ) mean ± SD</th>
<th>OAE (N = 123) ( \Delta ) mean ± SD</th>
<th>Independent-samples ( t )-test</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPRS</td>
<td>23.0 ± 11.1</td>
<td>11.1 ± 9.6</td>
<td>1.914</td>
<td>0.171</td>
</tr>
<tr>
<td>YMRS</td>
<td>11.5 ± 12.2</td>
<td>10.1 ± 8.0</td>
<td>10.836</td>
<td>0.002**</td>
</tr>
<tr>
<td>HDRS</td>
<td>8.4 ± 6.3</td>
<td>8.9 ± 5.1</td>
<td>1.624</td>
<td>0.207</td>
</tr>
<tr>
<td>HARS</td>
<td>9.9 ± 9.1</td>
<td>11.4 ± 6.3</td>
<td>0.265</td>
<td>0.265</td>
</tr>
<tr>
<td>CGI-S</td>
<td>1.7 ± 1.2</td>
<td>3.2 ± 0.9</td>
<td>0.584</td>
<td>0.584</td>
</tr>
<tr>
<td>GAF</td>
<td>14.5 ± 8.7</td>
<td>21.1 ± 12.5</td>
<td>6.143</td>
<td>0.016*</td>
</tr>
<tr>
<td>Depressed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPRS</td>
<td>21.1 ± 9.3</td>
<td>18.1 ± 10.4</td>
<td>0.289</td>
<td>0.593</td>
</tr>
<tr>
<td>YMRS</td>
<td>4.9 ± 5.4</td>
<td>10.1 ± 6.9</td>
<td>0.656</td>
<td>0.421</td>
</tr>
<tr>
<td>HDRS</td>
<td>11.9 ± 6.9</td>
<td>9.8 ± 5.2</td>
<td>1.667</td>
<td>0.202</td>
</tr>
<tr>
<td>HARS</td>
<td>11.9 ± 6.9</td>
<td>9.7 ± 5.4</td>
<td>1.403</td>
<td>0.241</td>
</tr>
<tr>
<td>CGI-S</td>
<td>1.3 ± 0.5</td>
<td>2.7 ± 0.9</td>
<td>6.692</td>
<td>0.012*</td>
</tr>
<tr>
<td>GAF</td>
<td>11.5 ± 5.9</td>
<td>15.9 ± 9.1</td>
<td>3.511</td>
<td>0.066</td>
</tr>
<tr>
<td>Mixed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPRS</td>
<td>21.6 ± 11.3</td>
<td>21.9 ± 14.0</td>
<td>0.748</td>
<td>0.389</td>
</tr>
<tr>
<td>YMRS</td>
<td>11.2 ± 9.3</td>
<td>10.8 ± 7.9</td>
<td>1.806</td>
<td>0.182</td>
</tr>
<tr>
<td>HDRS</td>
<td>9.1 ± 5.9</td>
<td>8.4 ± 5.2</td>
<td>1.209</td>
<td>0.274</td>
</tr>
<tr>
<td>HARS</td>
<td>10.1 ± 7.8</td>
<td>8.3 ± 5.8</td>
<td>2.930</td>
<td>0.090</td>
</tr>
<tr>
<td>CGI-S</td>
<td>1.2 ± 1.1</td>
<td>2.0 ± 1.3</td>
<td>1.094</td>
<td>0.298</td>
</tr>
<tr>
<td>GAF</td>
<td>14.3 ± 9.5</td>
<td>17.8 ± 11.5</td>
<td>1.999</td>
<td>0.160</td>
</tr>
</tbody>
</table>

*\( P < 0.05 \); **\( P < 0.01 \). All significant results in bold characters

BPRS, Brief Psychiatric Rating Scale; CGI-S, Clinical Global Impressions Scale – Severity; GAF, Global Assessment of Functioning Scale; HARS, Hamilton Anxiety Rating Scale; HDRS, Hamilton Depression Rating Scale; L, lacosamide group; OAE, other antiepileptics group; YMRS, Young Mania Rating Scale.
Side-effects were uncommon in the L group, while they were more common in the OAE group. Headache was reported by about 10% of patients in the L group and 15% of patients in the OAE group, dizziness in 6% of L patients and 8% of OAE patients, and nausea in 5% of L patients and 18% of OAE patients. Confusion and cognitive symptoms were reported by 1% of L patients and 20% of OAE patients ($\chi^2 = 50.44, P < 0.0001$). All side-effects in the L group were mild and self-limited, while cognitive disturbances in the OAE group tended to persist. No liver or kidney function alterations were reported in the L group.

**DISCUSSION**

In this study, we observed that lacosamide administration in individuals with a depressive or manic episode in the course of BD was associated with a good clinical response similar to that of other antiepileptics. Improvement did not depend on type of episode or of BD. Furthermore, lacosamide more vigorously improved the clinical global impression of patients and showed a better antimanic response than other antiepileptics. The effect on global functioning was similar in the two groups.

There are nine currently known human neuronal $\alpha$ subunit-bearing voltage-gated sodium channels, ranging from Na\textsubscript{v}1.1 to Na\textsubscript{v}1.9. These are encoded by genes termed SCN1A to SCN5A for Na\textsubscript{v}1.1 to Na\textsubscript{v}1.5, respectively, and SCN8A to SCN11A for Na\textsubscript{v}1.6 to Na\textsubscript{v}1.9. Lacosamide stabilizes the slow-inactivated state of neuronal Na\textsubscript{v}1.1 and Na\textsubscript{v}1.7 channels,\textsuperscript{34} but was shown also to act on Na\textsubscript{v}1.2,\textsuperscript{35} Na\textsubscript{v}1.3, and Na\textsubscript{v}1.8,\textsuperscript{36,37} but not on Na\textsubscript{v}1.6, whose gene SCN8A was found to be possibly associated with BD.\textsuperscript{38} One possible connection with lacosamide-influenced processes is indirect, stemming from the fact that lithium, an effective antimanic agent, normalizes the pCRMP2-to-CRMP2 ratio and restores aberrant neuronal spine densities in human-induced pluripotent stem cells from lithium-responsive BD patients.\textsuperscript{39} CRMP2, which is known to regulate responses to Na\textsubscript{v}1.7 channels\textsuperscript{40} is a target of lacosamide, but how much this is relevant to its action in BD is still to establish. We found differences in the action of lacosamide versus other antiepileptics that we currently cannot explain in terms of slow versus fast inactivation of voltage-gated sodium channels, that is, a stronger antimanic effect, a stronger effect on CGI-S-rated psychopathology, and on quality of life, and a weaker effect on anxiety and BPRS-rated psychopathology. A possible mechanism could involve a differential influence on amplitude and latency of the evoked compound action potential of neurons, that lacosamide reduced at higher-than-therapeutic levels, while phenytoin reduced acutely even at higher-than-therapeutic levels,\textsuperscript{41} but this leaves open the question about its molecular underpinnings. A recently added possible mechanism of the action of lacosamide is enhancement of GABA\textsubscript{A} currents.\textsuperscript{42}

Similarly to Alfaro et al.,\textsuperscript{43} we observed improved depression and anxiety, as well as quality of life (assuming that GAF provides to some extent a measure of quality of life) in patients with BD receiving lacosamide. This study observed also an improvement of impulsiveness, which we did not investigate. However, we obtained improvement on all mood measures and on anxiety in patients with no epilepsy, while the above study was conducted only on patients with epilepsy. The fact that Alfaro et al.\textsuperscript{43} did not have a control group prevents us from making further comparisons. We should mention here that although both treatments reduced anxiety, as assessed with HARS, the effect of lacosamide was inferior to that of OAE, from Day 3 to the end of the study. We have no key to interpret this, as anxiety is increased during manic bouts and lacosamide had a greater effect than OAE at the same time-points.

We observed a strong effect on global functioning of patients with BD and no epilepsy receiving lacosamide after 1 month of treatment. Other studies did not investigate specifically global functioning, but showed no effect of lacosamide on quality of life in patients with epilepsy\textsuperscript{14,44} however, another study on patients with brain-tumor-related epilepsy did not observe with lacosamide, compared to levetiracetam, the expected decay in quality of life.\textsuperscript{45} Furthermore, all these studies investigated mood through nonspecific tools or with self-rated depression scales in patients with epilepsy, finding positive\textsuperscript{13,44} or no effects\textsuperscript{45} after long-term treatment, while we used specific instruments for each affective dimension and found prominent improvement of mood measures in acute treatment (30 days) of patients with BD and no epilepsy. This explains the only partial overlaps of the results we obtained, compared to previous literature.

Separately analyzing SUD comorbid versus SUD non-comorbid subsamples, we found that the effects...
of age could have been mediated through the OAE SUD non-comorbid subgroup. Furthermore, we found opposite baseline levels of anxiety in the L versus OAE subgroups according to their SUD comorbidity, that is, L patients with no SUD comorbidity were less anxious than those with SUD comorbidity; conversely, in the OAE group, SUD comorbid patients were more anxious at baseline than SUD non-comorbid patients and remained more anxious throughout the study. Moreover, the former were more ill at Day 15 than the latter, showing that comorbidity confers resistance to the improvement of anxiety and general psychopathological status to OAE, in line with literature findings of poorer response of SUD comorbid BD patients to treatment,46,47 something that we did not encounter in our L group. Lacosamide is now tested for its efficacy in neuropathic pain, in which its S-enantiomer is more likely to carry out the analgesic effect,48 and is now a fourth-line recommendation in the Canadian Pain Society’s guidelines for chronic neuropathic pain,49 even though its analgesic effect is overall considered to be limited.50 Our study backs the preclinical suggestion by Béguin et al.7 to test lacosamide in BD and in substance addiction.

Common side-effects of lacosamide include dizziness, headache, confusion, diplopia, nausea, nasopharyngitis, and vomiting; however, other symptoms, like psychosis51 and reduced sexual activity,52 have also been described. A reversible, short-lasting increase in suicidal ideation subsided after discontinuation and a switch to another antiepileptic.53 In our study, we observed few side-effects and no suicidal ideation, psychosis, or diminished libido or sexual function. Side-effects were mild and transient. The L group fared better in side-effects compared to OAE patients. In particular, we observed significantly fewer cognitive side-effects in L patients compared to OAE patients, thus matching other findings.54 Our choice to exclude patients with significant renal and liver impairment was supported by later findings.55

Conclusions

We found lacosamide to be effective in reducing symptoms in patients with bipolar I and II disorder, with few side-effects. Lacosamide had an advantage over other antiepileptics in improving mania and the general clinical picture, as well as global functioning. Dosages at which these effects were obtained were generally lower than those used to treat epilepsy. The mechanisms whereby lacosamide improved BD are unclear and should be further studied.

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Disclosures

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Author Contributions

I.C., S.D.F., and G.D.K. designed the study and wrote the first draft; I.C. and S.D.F. treated and evaluated patients; G.D.K., L.L., and D.P. carried out literature searches; D.P. and G.D.K. carried out statistical analyses; L.L. conducted biochemical examinations; and S.D.F. supervised the writing of
the manuscript. All authors wrote extensive portions of the manuscript and all approved its final form.

REFERENCES


**SUPPORTING INFORMATION**

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site:

**Table S1.** Intragroup comparisons of effects of treatments vs baseline at the different time-points considered (cut-off $P < 0.007$).

**Table S2.** Effect sizes of treatments on all considered measures for all groups.

**Table S3.** Intragroup comparisons for substance use disorders (SUD) comorbid vs SUD non-comorbid subsamples (cut-off $P < 0.007$, save for age, $P < 0.05$).