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Effect of lacosamide on depression and anxiety symptoms in patients with focal refractory epilepsy: A prospective multicenter study

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ABSTRACT

Introduction: Depression is the main psychiatric comorbidity in epilepsy with an estimated prevalence between 20% and 55% and one of the main determinants of quality of life. The aim of this study was to investigate the effect of lacosamide (LCM) on mood and anxiety symptoms in patients with focal onset seizures (FOS). The secondary objective was to evaluate if the potential modifications in variables were related to seizure control or to the intrinsic effect of LCM.

Material and methods: We performed a prospective multicenter study in 8 tertiary epilepsy centers in adults with FOS in which LCM was initiated as add-on therapy. Patients' mood and quality of life were evaluated through questionnaires and scales such as the Beck Depression Inventory-II (BDI-II), the State–Trait Anxiety Inventory (STAI-S/T), the Hospital Anxiety and Depression Scale (HADS), and the Quality of Life in Epilepsy-10 (QOLIE-10). Initiation of psychotropic medication was not allowed during the observation period. Patients with diagnosis of major depression or bipolar disorder were excluded. Evaluations were scheduled before LCM treatment, at 3 and 6 months.

Results: Forty-nine patients were included (51% female) with an average age of 39.5 years (range 18–65). At the start of treatment with LCM, 65.3% of the patients were on treatment with one antiepileptic drug (AED). Based on BDI-II, 38.8% of patients had depressive symptoms and 46.9% according to HADS Depression (HADS-D), 63.3% of patients presented pathological levels of anxiety (STAI-S/T), and 44.9% according to HADS Anxiety (HADS-A). Quality of Life in Epilepsy-10 showed that 57.1% of patients had a relevant reduction in their quality of life. After LCM, the score on the BDI-II depression scale decreased significantly ($p < 0.001$). Based on the STAI and HADS-anxiety scales, patients who had a pathological anxiety at baseline, significantly improved. The QOLIE-10 improved significantly over the observation period ($p < 0.001$). At 6 months, 28.3% of patients were seizure-free (67.4% were responders). The improvements on depression and anxiety scores were not statistically related to seizure control.

Conclusion: Lacosamide seems to have a positive effect on depressive and anxiety symptoms. Although the efficacy of LCM in seizure control was demonstrated, the antidepressant and anxiolytic effect on mood and anxiety seems to be an independent factor.

1. Introduction

There is a high prevalence of psychiatric disorders in patients with epilepsy [1]. Among them, depression is the most relevant [2,3]. The reported prevalence of depression in patients with recurrent seizures varies between 20% and 55% [4]. Depression not only severely reduces the quality of life of these patients, but also constitutes a risk of death

Abbreviations: STAI-S/T, A/B State-Anxiety Questionnaire; AEDs, antiepileptic drugs; BDI-II, Beck's Depression Inventory-II; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; FOE, focal onset epilepsy; FOS, focal onset seizures; HADS, Hospital Anxiety and Depression Scale; QOLIE-10, Quality of Life in Epilepsy-10; TLE, temporal lobe epilepsy.

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by suicide. Compared with the general population, patients with epilepsy are twice as likely to suffer from depression and are 3.6–5 times more likely to commit suicide [5–7]. Based on the type of epilepsy, depression is reported more frequently in temporal lobe epilepsy (TLE) [8]. Many patients with refractory epilepsy and depressive symptoms often do not meet the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) standardized criteria for major depression [2,9,10]. In fact, it is considered that within the presentation of affective disorders in epilepsy, an important subgroup of patients develops a syndrome characterized by dysphoric symptoms [11].

In this context, the role of antiepileptic drugs (AEDs) can be crucial, since they constitute the fundamental basis for the treatment of epilepsy. These compounds have complex mechanisms of action with additional effects on mood and behavior. The psychotropic potential of AEDs is related to direct and indirect mechanisms [12]. Various studies have indicated that treatment with certain AEDs is associated with the occurrence of depression symptoms while other compounds are probably antidepressants. Since AEDs are used in the treatment of psychiatric disorders, this may lead to the choice of specific AEDs that address both seizure control and the concomitant treatment of associated comorbid psychopathology [12,13].

Studies of lacosamide (LCM) in this area are currently needed, but there is evidence of the anxiolytic effects in animal models [14]. On the other hand, since the psychiatric pathology is probably the most common comorbidity in epilepsy and certain AEDs may worsen it, it is essential to know their specific effect in this area including potential treatment-emergent suicidal ideation [15–19]. The objective of this study was to evaluate the effect of LCM on mood and anxiety symptoms in a group of patients with drug-resistant focal epilepsy and to determine if this is an independent effect of seizure control.

2. Material and methods

This was a prospective, multicenter observational study in patients over the age of 16 years with focal epilepsy who began adjunctive treatment with LCM. The objective was to determine changes in the symptoms of depression and anxiety.

The allocation of a patient in the study was determined by medical practice and was clearly unrelated to the decision of including the patient in the study, as it is stated in the SAS-3470-2009 regulation by the Ministry of Health, Equality and Social Policy and The Spanish Agency of Medicines and Medical Devices (AEMPS) postauthorization observational studies.

2.1. Hypothesis and objectives

The study's primary hypothesis was to demonstrate that LCM (200–400 mg/day), through its mechanism of action, could have antidepressant and anxiolytic effects. The inclusion criteria were patients over the age of 16 years diagnosed with focal epilepsy with an indication for an add-on treatment who agreed to participate in the study and signed an informed consent. Exclusion criteria were historical or current diagnosis of major depressive or bipolar disorder according to the DSM-IV, risk of suicide, concomitant use of psychotropic or psychotherapeutic treatment, vagus nerve stimulation carrier or undergoing epilepsy surgery, cardiac conduction disorder, any clinically relevant medical condition, and degenerative neurological disease. Neither the use of antidepressants, antipsychotics, anxiolytics, antihistamines, opiates, itraconazole, or rifampin were allowed during the study; nor was the use of any investigational drug within 1 month prior to the screening visit.

2.2. Efficacy measures

Beck Depression Inventory-II (BDI-II), State–Trait Anxiety Inventory (STAI-S/T), Hospital Anxiety and Depression Scale (HADS), and Quality of Life in Epilepsy-10 (QOLIE-10) have been validated for the Spanish population [20–23]. The HADS and BDI-II are 2 of the 3 instruments endorsed by the National Institute for Health and Clinical Excellence (NICE) for use in measuring baseline depression severity and responsiveness to treatment.

2.3. Study design

Four assessments were conducted: screening, medical history, inclusion criteria, and exclusion criteria. Visit 1 (1 day before starting LCM treatment): questionnaires. Until visit 2, the doses of other AEDs are maintained. Visit 2 (3 months after starting LCM): dose in steady-state and questionnaire completion. Visit 3 (6 months after starting LCM): questionnaire completion and end of study.

2.4. Ethics committee

The AEMPS Regulatory with code RRO-LAC-2012-01 approved the current research project in 2012. The protocol, the informed consent, and any related relevant documents were examined and approved by the Clinical Research Ethics Committee (CEIC-Parc de Salut Mar). The study met the international and national good clinical practice as required by the principles of the Declaration of Helsinki of 2008 of the World Medical Association and the current legislation on protection of personal data (law 15/1999 of 13 December [Data Protection Act]).

2.5. Statistical methods

A descriptive analysis of the qualitative and quantitative variables collected was conducted. The last observation carried forward procedure was used for managing missing data. The level of statistical significance was established at 5%. The progression of depressive symptoms (BDI-II and HADS-D), anxiety levels (STAI-S/T and HADS-A), and quality of life (QOLIE-10) of patients was assessed using the Friedman's test. To determine changes from baseline in the scales, the Mann–Whitney's test and Spearman's coefficient of correlation (ρ) were used. Clinical efficacy was measured by the number of seizure-free patients and responders (reduction in the number of seizures ≥ 50%). For this analysis, the percentage of patients in each situation and its 95% confidence interval (CI) were provided. Analyses were performed with the statistical package IBM SPSS version 19.0.

3. Results

Forty-nine patients (51% female) included in this study started on treatment with LCM as add-on therapy in eight epilepsy tertiary care centers in Spain. The mean age of the sample was 39.5 years (range 18–65), with an average epilepsy duration of 17.1 years; 59.2% of epilepsies were cryptogenic. In 51% of cases, the location was in the temporal lobe. The median number of seizures was three per month. At the start of treatment with LCM, 65.3% of the patients were on treatment with one AED (Table 1). In 71.4% of patients, 2 or more AEDs had been used prior to starting with LCM. The median number of previous AEDs was 3 drugs (range 1 to 8). The most frequent concomitant AED was levetiracetam (LEV) (57.1% of patients).

From the initial 49 patients enrolled, three withdrew the study before 3 months because of adverse events (two patients) or lack of efficacy (one patient). At 3 months, 46 patients (93.9%; 95% CI: 83.1–98.7%) remained in the study and completed visit 2 (efficacy population). After 3 months, another five patients withdrew the study because of adverse events. Therefore, 41 patients (83.7%; 95% CI 72.3–95.0) achieved 6 months of treatment.

At baseline, according to the BDI-II scale of the initial 49 patients, 10.2% of patients (n = 5) had mild depression, 18.4% (n = 9) moderate, and 10.2% (n = 5) severe (total 38.8%). In the HADS Depression (HADS-D) scale, 24.5% of patients (n = 12) had moderate depression and 22.4%