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The effects of lacosamide on cognition, quality-of-life measures, and quality of life in patients with refractory partial epilepsy

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ABSTRACT

Objective: The objective of this study was to examine cognitive and quality-of-life measures/quality of life outcomes with adjunctive lacosamide therapy in patients with treatment-resistant partial epilepsy.
Methods: This was a prospective, open-label, nonblinded, adjunctive therapy test–retest (within subjects) study of patients with treatment-resistant partial epilepsy in which outcome (cognitive functioning and mood/quality of life) was measured in the same subject before and after adjunctive lacosamide administration for 24 weeks. The cognitive assessment included the following: Controlled Oral Word Association Test, Buschke Selective Reminding Test, Brief Visuospatial Memory Test—Revised, Stroop Color Word Test, Symbol Digit Modalities Test, Digit Span, Digit Cancellation, and Trails A and B. The quality-of-life measures/quality-of-life assessment included the following: Beck Depression Inventory—II, Profile of Mood States, and Quality of Life Inventory—89. Lacosamide was started at 100 mg (50 mg twice daily) and could be titrated as needed up to 400 mg/day (200 mg twice daily). Baseline concomitant AEDs were kept constant. Composite scores were calculated for a pre–post difference score for the cognitive and mood/quality-of-life measures separately and used in regression analyses to correct for the effects of age, education, seizure frequency, seizure severity, dose of lacosamide, and number of AEDs at baseline.
Results: Thirty-four patients were enrolled (13 males, 21 females). Mean age was 38.8 ± 2.43 years. Mean seizure frequency decreased significantly from 2.0 ± 2.55 seizures per week at baseline to 1.02 ± 1.72 seizures per week at posttreatment ($t = 4.59$, $p < .0001$) with a 50% responder rate seen in 18 patients (52.9%). No significant differences were found on the composite scores of the cognitive or the mood/quality-of-life measures after 6 months of lacosamide.
Significance: Lacosamide appeared to have low risks of significant changes in cognition or mood/quality of life. In addition, the present study supports prior studies that have proven lacosamide as an effective adjunctive therapy for the treatment of resistant partial epilepsy.

1. Introduction

Lacosamide is a third-generation antiepileptic drug available in multiple formulations which was approved as adjunct treatment for partial-onset epilepsy in adults by the US Food and Drug Administration (FDA) in 2008 and as monotherapy in 2014. Three randomized, controlled trials (RCTs) of lacosamide as adjunct treatment for medically intractable epilepsy [1–3] and three long-term follow-up studies [4–6] revealed a significant anticonvulsant effect. Lacosamide has also demonstrated a good safety profile with a small degree of adverse events. The most common adverse events reported were diplopia, dizziness, nausea, and headaches [1–6].

Limited data exist regarding the effect of lacosamide on mood and cognition. In the pooled analysis of adverse effects (AEs) from the 3 RCTs [1–3], self-reported rates of "memory impairment" were seen in 2% of the composite treatment arm vs. 1% in the placebo arm, and depression was noted in 2% in the composite treatment arm vs. 1% in the placebo arm. Lacosamide, like all other AEDs, has a warning for suicidality though there are no specific data to suggest an increased risk. Other data regarding mood/cognition have been limited to small prospective uncontrolled or retrospective studies. IJff et al. [7] studied patients with refractory partial-onset epilepsy prospectively before and after lacosamide was added as adjunctive therapy. The authors

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reported that patients had increased subjective complaints but that, objectively, they did not do worse with lacosamide on a computerized task [7]. Helmstaedter and Witt retrospectively studied the impact of adjunctive lacosamide and compared it with that of topiramate and lamotrigine in a naturalistic outpatient setting and concluded that cognitive effects were equivalent to lamotrigine and better than topiramate [8]. As for mood, the effects of lacosamide on depression and anxiety were retrospectively studied in patients with partial-onset epilepsy by Moseley et al. [9]. The authors concluded that lacosamide did not worsen depression or anxiety. Giorgi et al. [10] conducted a small study assessing depression and anxiety on 10 patients and found no changes after the use of lacosamide.

Understanding the cognitive and behavioral side effect profile of AEDs is important to clinical practice since changes in these areas could affect quality of life and adherence with the medication. This study is the first prospective comprehensive study of cognitive and mood/quality-of-life side effects of lacosamide on patients with refractory partial epilepsy using a neuropsychological battery of tests for assessment of attention, concentration, psychomotor speed, verbal and nonverbal learning and verbal fluency, as well as mood/quality-of-life measures and evaluation of adverse/side effects. In contrast to the other two prospective studies, we used a testing battery that was inclusive and sensitive to a range of cognitive functions.

Our study had two objectives: to investigate whether lacosamide affects cognition and mood/quality of life and to determine if any significant changes in cognition or mood/quality of life were dependent on covariates including age, sex, education, number of AEDs, seizure frequency and seizure severity at baseline, and final drug dose at the end of the trial.

2. Methods

2.1. Patient population and study design

This was a prospective, open-label, nonblinded, adjunctive therapy test–retest (within subjects) study of patients with uncontrolled partial epilepsy in which outcome (cognitive functioning and mood/quality of life) was measured in the same subject before and after adjunctive lacosamide administration. This design was chosen since it best emulates what occurs in clinical practice. All procedures were done with prior approval from the Copernicus Group IRB (CGIRB; Durham, NC) #: MLA1-10-124.

The inclusion criteria were as follows: (1) ages 18–70 years; (2) able and willing to provide written informed consent in accordance with the International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines; (3) a native English speaker or balanced bilingual; (4) diagnosis of refractory partial-onset epilepsy; and (5) historical mean seizure frequency of at least 2 seizures per month for the 6 months prior to the first visit.

The exclusion criteria were as follows: (1) subjects with a history of drug or alcohol abuse; (2) pregnant females or those using an unreliable method of contraception; (3) diagnosis of a major psychiatric disorder (bipolar disorder, schizophrenia, psychotic disorder, major depression) requiring hospitalization in the past 2 years or the presence of other psychological or behavioral conditions that the investigator judged should grounds for exclusion from the study; (4) currently using an antidepressant, anxiolytic, or antipsychotic agent; (5) active suicidal plan or suicidal thoughts in the past 6 months; (6) presence of a progressive, demyelinating, or degenerative neurological condition; (7) diagnosis of psychogenic nonepileptic seizure disorder; (8) a history of traumatic brain injury or of cardiac arrhythmia; and (9) impaired intelligence quotient (estimated Full Scale IQ < 70).

Withdrawal criteria included the following: (1) subjects who endorsed suicidality, (2) any episode of status epilepticus, (3) need for use of rescue benzodiazepine more than once per week, (4) any laboratory abnormalities which were deemed by the investigator to be clinically significant, (5) any clinically significant objective clinical signs or symptoms that were intolerable or incapacitating to the patient and/or pose a serious threat to well-being, (6) nonadherence with study protocol (<80% compliance with study medication), (7) females who became pregnant during the study, (8) and voluntary withdrawal by the patient.

Study subjects were referred by a Northeast Regional Epilepsy Group neurologist in New York and New Jersey between August 2010 and March 2015.

2.2. Study visits

The study was spread over 28 weeks and was divided into three phases: screening (visit 0), titration/treatment phase (visits 1, 2, 3), and termination phase (visit 4) (Fig. 1). Screening duration was 4 weeks, visit 1 was at 4 weeks after screening, visit 2 at 6 weeks, visit 3 at 18 weeks, and visit 4 (termination phase) at 28 weeks. Telephone calls were made 2 weeks after screening and at weeks 6, 10, 14, 22, and 26 to obtain seizure frequency and seizure severity data to assess compliance with the daily diary and to monitor adverse events and changes in concomitant medications.

At the screening visit (visit 0), eligibility assessment was performed, and written informed consent was obtained. Baseline demographic data included seizure history, type and frequency, AED use history, medical history, and psychiatric history collected. Measurement of vital signs, body weight, and height and physical and neurological examination were performed. Laboratory safety studies (urinalysis, hematology, chemistries, and serum or urine pregnancy tests as appropriate) and urine pregnancy tests were obtained. Subjects were trained in maintenance of a seizure diary to be kept throughout the study. After the screening visit, laboratory testing was done only if clinically indicated.

Over a 4-week baseline period, subjects were assessed on compliance with the daily diary, and screening test results were reviewed with a telephone call from the study coordinator at week 2. All concomitant AEDs were kept stable during the 4-week baseline period.

During visit 1 (week 4), inclusion and exclusion criteria and seizure diaries were reviewed. If the subject still met the eligibility criteria, the drug was dispensed as described below (Section 2.3). During all visits after the screening visit (visits 1, 2, 3, 4), physical and neurological examinations were performed, and vital signs, seizure frequency, seizure severity, and adverse events data were collected.

After completion of the study, subjects were given an option to taper off the drug after visit 4 (i.e., after a minimum of 28 weeks into the study). In this study, 3 out of the 34 subjects elected to taper off medication. Subjects who wished to remain on the drug continued to receive it as a prescription medication. A summary of the protocol can be seen in Table 1.

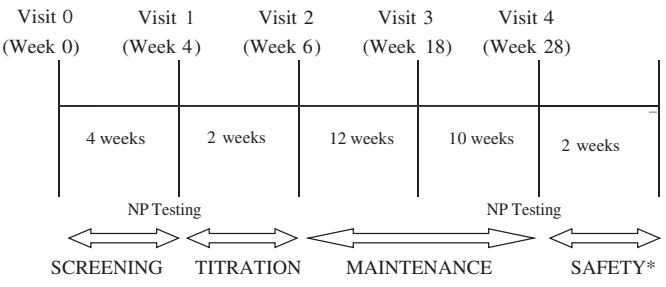

Fig. 1. Schematic diagram showing the flow of the study (* refers to an optional safety visit after the study was completed. Subjects could choose to stop taking the drug at this point; the subjects that elected to stay on lacosamide received it as a prescription medication). NP = neuropsychological testing.