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Wake up to sleep: The effects of lacosamide on daytime sleepiness in adults with epilepsy

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ABSTRACT

Objective: The objective of the study was to investigate the effects of lacosamide (LCM) on daytime sleepiness ascertained by the Epworth Sleepiness Scale (ESS) in adults with focal epilepsy in a randomized, controlled design.
Methods: Subjects taking ≤2 AEDs for ≥4 weeks underwent polysomnography with EEG followed by the maintenance of wakefulness test (MWT) and completed the ESS and other patient-reported outcomes (PROs) at baseline, LCM 200 mg/day, and LCM 400 mg/day (Visit 4; V4). Primary endpoint was ESS change (V4 to baseline) between LCM and placebo. Noninferiority test on ESS used a one-sided t-test based on a hypothesized difference of 4-point change between groups. Superiority test used a two-sided t-test to investigate the difference in change in PROs and MWT mean sleep latency (MSL) between groups. Fifty-five subjects provided 80% power to show noninferiority of LCM assuming 10% dropout.
Results: Fifty-two subjects (mean age: 43.5 ± 13.2 years, 69% female, median monthly seizure frequency: 1 [0, 4.0]) participated. Baseline group characteristics including age, sex, ethnicity, standardized AED dose, seizure frequency, and ESS were similar. Abnormal baseline ESS scores were found in 35% of subjects. Noninferiority test found a ≤4-point increase in ESS (mean [95% CI]) in LCM subjects vs. placebo (−1.2 [−2.9, 0.53] vs. −1.1 [−5.2, 3.0], p = 0.027) at V4. No significant difference in change in PROs, MSL, seizure frequency, or AED standardized dose was observed between groups.
Significance: Our interventional trial found that LCM is not a major contributor to daytime sleepiness based on subjective and objective measures. Inclusion of sleepiness measures in AED trials is warranted given the high prevalence of sleep–wake complaints in people with epilepsy.

1. Introduction

Excessive daytime sleepiness (EDS) is among the most common complaints of people with epilepsy (PWE), reported in as many as 50% of cases and often attributed to seizures or antiepileptic drugs (AEDs) [1,2]. Primary sleep disorders have been identified as potential contributors [3]. Treatment of sleep disorders in PWE has been shown to reduce seizures [4] and epileptic discharges [5], supporting the view that sleep–wake complaints represent a potential therapeutic target in epilepsy. In addition, EDS and sleep disturbances have been identified as negative predictors of quality of life (QoL) in PWE [1,6,7]. Yet, measures of sleep and wakefulness are not routinely assessed in AED trials even though the effects of epilepsy therapies on these common complaints are apparent in clinical practice. Further, while the newer AEDs have more favorable tolerability profiles than the old, investigations into their effects on sleep–wake complaints and objective sleep measures are limited.

Given the existing knowledge gap and the need for systematic, rigorous studies exploring sleep outcomes in epilepsy, we performed a Phase IV randomized, controlled, single center trial to investigate the effect of lacosamide (LCM) on daytime sleepiness ascertained by the Epworth Sleepiness Scale (ESS), polysomnography (PSG), maintenance of wakefulness tests (MWT), and other patient-reported outcomes (PROs) in adults with focal epilepsy.

2. Methods

2.1. Standard protocol approvals, registrations, and consents

The study was conducted according to US and international standards of Good Clinical Practice and approved by the Cleveland Clinic Institutional Review Board (IRB: 10-518). Subjects reviewed a consent

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form prior to completing study procedures. Written informed consent was obtained from all subjects. The study was registered on ClinicalTrials.gov (NCT01190098).

2.2. Study design

This was a randomized, placebo-controlled, single center trial. Subjects meeting eligibility criteria were randomized in a double-blind 4:1 scheme to LCM or placebo. Lacosamide was titrated to 400 mg/day (200 mg bid) using 50 mg tablets beginning with 50 mg bid at intervals ≥1 week. A 1-step, back-titration of 50 mg bid was allowed in the case of treatment-emergent adverse events (TEAEs). At the end of the Treatment Phase, subjects could enter a 4-week extension phase. Subjects who chose not to extend were tapered off study drug over 2 weeks.

2.2.1. Baseline phase (Visit 1, V1)

The following were collected/performed: 1) medical history and medications; 2) epilepsy, seizure classification, and self-reported seizure frequency over the prior 3 months; 3) neurologic exam; 4) AED serum concentration; 5) PRO measures; 6) ambulatory (in-home) PSG-EEG followed by in-laboratory MWT; and 7) seizure and sleep diary.

2.2.2. Randomization and treatment phase (Visits 2, 3, and 4)

Subjects were randomized at V2 (2 to <8 weeks after V1; median: 34.5 days [21, 49]). Visit 3 (V3) was scheduled 11–21 days after V2, and Visit 4 (V4) 11–21 days after V3. Visit windows accommodated test scheduling and ensured a stable dose for ≥1 week prior to reassessment. Adjustment of concomitant AEDs was permitted only to address disabling seizures and significant TEAEs. During V3 and V4, the following were completed: 1) eligibility confirmation; 2) neurologic exam; 3) medical history, medications, and TEAEs; 4) collection, review, and dispensation of diaries; 5) drug collection, reconciliation, and dispensation (V3: 2 tabs bid for 1 week then 3 tabs bid; V4: 4 tabs bid); 6) AED serum concentration; 7) PRO measures; and 8) PSG-EEG followed by MWT. Median days between V1–V4 and V2–V4 were 31 [28, 38] and 69 [57.5, 78], respectively.

2.2.3. Treatment-emergent adverse events

Adverse events were classified according to FDA IND safety reporting standard definitions and reported to UCB Pharma and Cleveland Clinic IRB following established guidelines. A Data Safety and Monitoring Board provided additional safety and oversight.

2.2.4. Study instruments

2.2.4.1. PSG-EEG. Ambulatory 22-channel wireless PSG (Sapphire PSG™ Cleveland Medical Devices, Inc.) included EEG (10–20 system excluding FP1/2 and substituting PZ for P3/P4), chin EMG, airflow, nasal pressure, chest and abdominal respiratory inductance plethysmography, EKG, pulse oximetry, and body position. Scoring was performed according to standard criteria [8]. Hypopneas required a ≥3% desaturation or an arousal.

2.2.4.2. MWT. The MWT is a modification of the multiple sleep latency test (MSLT), the gold standard objective assessment for daytime sleepiness, which measures the ability to stay awake for a defined period. The test's clinical relevance is based on the premise that the volitional ability to remain awake provides important information regarding the ability to stay awake and response to interventions for disorders associated with excessive sleepiness. The study consists of 4 40-min nap trials performed at 2-hour intervals beginning 1.5 to 3 h after the morning awakening performed in the sleep laboratory by a trained technologist. Electroencephalogram (EEG), chin EMG, and EOG are recorded. Time to sleep onset is measured for each trial, and the average is calculated to produce the mean sleep latency (MSL). A MSL <8.0 min is considered abnormal, while 40 min is normal, and values from 8 to <40 min are of uncertain significance [9].

2.2.4.3. Sleep apnea scale of the sleep disorders questionnaire (SA/SDQ). The sleep apnea scale of the sleep disorders questionnaire (SA/SDQ) assesses the likelihood of having obstructive sleep apnea (OSA) based on snoring, age, body mass index, tobacco use, and hypertension [10]. Cutoff scores of ≥32 for women and ≥36 for men correlate with OSA by PSG.

2.2.4.4. Epworth Sleepiness Scale (ESS). The Epworth Sleepiness Scale (ESS) measures daytime sleep propensity by rating one's chance of dozing in 8 soporific situations (sitting and reading, watching TV, sitting inactive in a public place, passenger in a car for an hour without a break, lying down to rest in the afternoon when circumstances permit, sitting and talking to someone, sitting quietly after lunch without alcohol, and in a car while stopped for a few minutes in traffic). Responses range from never to high chance of dozing yielding total scores of 0–24. Normal control scores (5.9 ± 2.2) were significantly lower than those in patients with sleep disorders [11]. The ESS has shown good test–retest reliability with more than 95% of patients showing changes of no more than 4 points [12]. The ESS is unidimensional with internal consistency by factor analysis [12] and superior test–retest reliability and effect size when compared with the MWT [13]. Scores >10 distinguish EDS from normal daytime sleepiness with a sensitivity of 94% and specificity of 100% [14].

2.2.4.5. Fatigue severity scale (FSS). The fatigue severity scale (FSS) assesses fatigue with 9 items rated from 1 to 7 on a Likert scale, where higher scores indicate more severe impairment. The FSS was found to be internally consistent, differentiating controls from chronic disease populations and detecting clinically predicted change in fatigue over time [15].

2.2.4.6. Pittsburgh sleep quality inventory (PSQI). The Pittsburgh sleep quality inventory (PSQI) yields a global score that represents the sum of 7 component scores (0–21), each addressing a specific aspect of subjective sleep quality. The PSQI discriminates between healthy controls (good sleepers, PSQI total score ≤5) and patients with depression and sleep disorders (poor sleepers; PSQI >5), has good internal consistency and test–retest reliability, and has been validated against PSG [16].

2.2.4.7. Functional outcomes of sleep questionnaire (FOSQ). The functional outcomes of sleep questionnaire (FOSQ) is a 30-item instrument measuring functional status related to the impact of EDS on daily activities. Global and subscale scores are produced, which demonstrate its ability to distinguish between normal controls and patients with sleep disorders [17].

2.2.4.8. Adverse event profile (AEP). The adverse event profile (AEP) is an epilepsy-specific, 19-item instrument to monitor TEAEs associated with AEDs. Subjects rate the frequency of problems on a scale from never to always or often [18].

2.2.4.9. Patient health questionnaire-9 (PHQ-9). The patient health questionnaire-9 (PHQ-9) is a 9-item depression scale based on DSM-IV criteria. A score ≥10 indicates moderate-to-severe depressive symptoms. The PHQ-9 discriminates well between individuals with and without depressive disorders [19].

2.2.4.10. Quality of life in epilepsy (QOLIE-31). The quality of life in epilepsy (QOLIE-31) is a 31-item survey of health-related QOL for PWE comprised of 7 subscales covering general and epilepsy-specific domains [20].