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The longer-term cognitive effects of adjunctive antiepileptic treatment with lacosamide in comparison with lamotrigine and topiramate in a naturalistic outpatient setting

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ABSTRACT

In this retrospective controlled study, the impact of adjunctive lacosamide (LCM) on cognition in patients with epilepsy was evaluated and compared with that of topiramate (TPM) and lamotrigine (LTG) in a naturalistic outpatient setting. Cognition was investigated by means of objective assessment of executive functions (EpiTrack®) and verbal memory and by subjective ratings of self-perceived side effects (cognition, mood, and vegetative). Quality of life was assessed using the QOLIE-10 questionnaire. Patients underwent assessment at baseline and after a median follow-up interval of 32 weeks. Forty-four patients were treated with LCM, 11 with LTG, and 15 with TPM. Treatment arms differed with regard to the age at onset of epilepsy (LTG > TPM) and to seizure control from baseline to follow-up, which was best in patients whose seizures were treated with LTG (55% vs. 16% in patients whose seizures were treated with LCM and 13% in patients whose seizures were treated with TPM). Groups did not differ in the type of epilepsy, daily drug load or drug load change, nor in baseline seizure frequency. Repeated measures statistics controlling for epilepsy onset and seizure outcome showed deteriorated executive functions with TPM ($F = 7.5$, $p = 0.001$). On an individual level (reliable change indices), 53% of the patients whose seizures were treated with TPM showed losses in this domain (LCM 14%, LTG 27%) and none of the patients showed improvement (LCM 23%, LTG 27%; $\chi^2 = 11.8$, $p = 0.019$). No differences in memory, quality of life, or mood were noted among patients in the three treatment arms. Subjective cognitive complaints increased in 5 of the 9 patients whose seizures were treated with TPM (LCM 1/9, LTG 0/9; $\chi^2 = 11.9$, $p = 0.025$). The findings of this study demonstrate for the first time that the cognitive side effect profile of LCM is comparable to that of LTG and superior to that of TPM. This is indicated by both subjective and objective measures. Given the naturalistic setting and the retrospective nature of the study, a follow-up prospective, randomized trial with larger sample sizes is required to confirm these findings.

1. Introduction

Cognition is an essential domain when evaluating the tolerability of antiepileptic drugs (AEDs). It is well established that adverse cognitive side effects of antiepileptic treatment can negatively affect daily functioning, quality of life (QoL), compliance, and long-term retention of prescribed drugs [1]. Monitoring cognition has recently been introduced as part of routine diagnostics to track the impact of pharmacological treatment.

Lacosamide, a newer AED, was approved in 2008 as adjunctive therapy for the treatment of partial-onset seizures in adults based on results from three large-scale placebo-controlled pivotal (Phase II/III) trials with a total of 1294 patients [2–4]. LCM was generally well tolerated, and no major safety problems were identified. The tolerability of LCM was also evaluated in an analysis of data pooled from the aforementioned trials [5]. While the incidence of treatment emergent adverse events (TEAEs) potentially related to cognition was similar in the placebo and 200 and 400 mg/day LCM groups, it nevertheless increased with higher daily doses of LCM (1.9% in patients with 200, 8.5% in patients with 400, and 13.8% in patients with 600 mg/day). The most frequently reported cognitive TEAE was self-perceived memory impairment, occurring in 5.9% of patients who received the 600 mg/day dose (this dose is not approved). The investigators emphasized the need for studies applying standardized neuropsychological measures in order to further clarify the cognitive profile of LCM. In a recent meta-analysis of 10 randomized controlled trials with LCM, the only item indicative of cognitive dysfunction was memory impairment; however, its association with LCM was limited and not significant. Since formal cognitive testing was not performed in any of these trials, the investigators stated that additional ad hoc studies are required to confirm whether LCM has a favorable cognitive profile [6].

The objective of this study was to evaluate the impact of LCM on cognition by using standardized neuropsychological measures and

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comparing the results with those obtained from comparators with more clearly defined cognitive profiles, notably lamotrigine and topiramate. Both are also newer AEDs, and while LTG generally exhibits a desirable cognitive profile with no apparent cognitive deteriorations [7,8], there is a large body of evidence indicating negative effects of TPM on cognitive functions, especially on frontal-lobe-associated executive functions [9–11]. Two studies in patients with epilepsy [12,13] and one study in healthy volunteers [14] directly compared the cognitive effects of the two comparator drugs and found a clear superiority of LTG over TPM. However, in another study on the cognitive effects of add-on treatment with LTG versus TPM in older adults with epilepsy, therapy with TPM was associated with worse performance in executive functions, but with better performance in selective attention and verbal memory [15].

Another factor determining the choice of LTG and TPM as comparators was their inclusion in the first exercise recent drug trial on AED which was initiated as a first exercise of a law which aims at reducing healthcare costs in Germany (AMNOG, Gesetz zur Neuordnung des Arzneimittelmarktes). When introducing newly developed drugs, pharmaceutical companies are requested to demonstrate their superiority against established generic drugs, otherwise pricing will be fixed at the level of the generic drugs [16]. The first drug that underwent this procedure was retigabine (RTG; trade name Trobalt®), which, at the request of authorities, was compared with LTG and TPM in terms of efficacy and safety.

For the present study, cognition was the primary outcome parameter. Subjective side effect ratings and QoL served as secondary outcome parameters. Due to the naturalistic setting, seizure control was not an outcome parameter but was controlled for when subjective and cognitive changes in the three treatment arms were compared. We hypothesized a superior cognitive outcome in patients whose seizures are treated with LCM compared with patients whose seizures are treated with TPM, but not with patients whose seizures are treated with LTG.

2. Methods

2.1. Study design and participants

This retrospective longitudinal study was conducted at the polyclinic of the Department of Epileptology at the University of Bonn, where a program of routine cognitive monitoring along with pharmacological treatment changes has been put in place. Records from outpatients with epilepsy who underwent standardized cognitive assessment before and during adjunctive treatment with LCM, LTG, or TPM were identified and included in the analysis.

2.2. Neuropsychological assessments

The diagnostic package for monitoring the impact of AEDs on cognition comprises objective measures of executive function and memory as well as subjective scales on self-perceived side effects and QoL. Retest intervals are not fixed but follow individual plans for follow-up visits for a given patient. Hence longer-term rather than short-term follow-up visits are the consequence.

2.2.1. Executive function

The EpiTrack® (second edition with recently extended and revised norms) is a screening tool dedicated to the tracking of adverse cognitive effects of antiepileptic medication [17]. The test includes six subtests: response inhibition, visuo-motor speed, mental flexibility, visual motor planning, verbal fluency, and working memory. Based on the subtest results, an age-corrected total score is calculated. Application and evaluation of this test are simple and, thus, enhance objectivity. Age-corrected norms from 689 healthy individuals (age range of 16–87 years) and reliable change indices (RCIs, $p<0.1$) for reassessments after 3–5 months are provided. Patients can achieve a maximum score of 49 points. The interval for mild impairment is 29–31 points, and the cutoff for significant impairment is ≤ 28 points. Practice corrected RCIs indicate a significant change with a gain of >3 points and a loss of >2 points. Studies demonstrated the usefulness of the EpiTrack with regard to cognitive monitoring of the impact of pharmacological treatments [18,19] and its sensitivity in regard to the overall drug load, i.e., the number of concurrent AEDs and different substances [20].

2.2.2. Verbal memory

Episodic memory was assessed via a shortened version of the Verbaler Lern- und Merkfähigkeitstest (VLMT) [21], the German adaption of the Rey Auditory Verbal Learning Test (RAVLT) and the most commonly applied verbal learning and memory test in German epilepsy centers [22]. The applied version consists of two consecutive trials of learning and immediate recall of a 15-item word list before performing the EpiTrack. Delayed free recall of the learned items is requested after the EpiTrack. Thus, the Epitrack represents the distraction condition for memory testing. Memory performance was normalized with results from 383 healthy individuals. Scores for learning (learning trials $1+2$), memory (delayed recall trial 3), and loss of learned items over time (trial 2 minus trial 3) were each converted into a scale ranging from 1 to 7 according to the norm data of the healthy subjects and merged into a total memory score ranging from 3 to 21. After age correction, total memory scores from 14 to 18 were rated as normal, scores greater than 18 as above average, scores from 11 to 13 as mild impairment, and scores of ≤ 10 as significant impairment. According to practice corrected RCI ($p<0.1$), a change was considered significant when there was a gain of >3 points and a loss of >5 points. This short version of the VLMT had recently been applied together with EpiTrack in a study on the cognitive effects of levetiracetam vs. carbamazepine monotherapy [19].

2.2.3. Subjective measures

Self-perceived side effects of AEDs were assessed by a rating scale covering three domains: cognition (vigilance, psychomotor speed, attention, verbal fluency, verbal comprehension, word finding, remote memory, recent memory, and visuo-spatial memory), behavior (energy, depression, anxiety, aggression, and irritability), and physical/physiological symptoms (dizziness, nausea, weight gain or loss, sexual dysfunction, and libido). Patients are asked to rate the presence and strength of impairments which they explicitly attribute to drug treatment on a four-tiered scale ranging from not at all (0) to strong (3).

2.2.4. Quality of life

QoL was assessed via the German adaptation of the Quality of Life in Epilepsy (QOLIE)-10 questionnaire, which is a widely used and validated instrument developed specifically to screen aspects of health-related QoL in individuals with epilepsy [23]. The QOLIE-10 covers different epilepsy- and treatment-related issues including energy, mood, mobility, work and social limitations, cognitive problems, physical and cognitive treatment effects, seizure worries, and general quality of life. In contrast to the original version, the German adaptation comprises 13 items. Each item includes a 5-tiered rating scale (1–5) so that total scores between 13 and 65 can be achieved with greater values reflecting worse QoL. Since item level values of 1 indicate no impairment and values of 2 indicate the mildest form of impairment, total scores exceeding half of the possible maximum were arbitrarily defined as impaired QoL (cutoff: ≥ 33). Change in QoL was rated as significant when a patient's scores changed more than one standard deviation (>11 points) with reference to a sample of 892 patients with epilepsy.

2.3. Statistical analyses

With the exception of the side effect rating scale, all behavioral data were analyzed on group and individual levels. Baseline characteristics