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Evaluating the longer-term cognitive effects of adjunctive perampanel compared to lacosamide in a naturalistic outpatient setting

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ABSTRACT

Purpose: This retrospective longitudinal study aims to compare the longer-term cognitive and behavioral side effects of adjunctive antiepileptic treatment with perampanel (PER) and lacosamide (LCM), two third generation antiepileptic drugs with suggested favorable cognitive profiles. The two drugs were monitored according to a previously established routine diagnostic protocol (Helmstaedter et al. E&B 2013;26:182-7) which facilitates the retrospective comparison of antiepileptic drug tolerability in a naturalistic outpatient setting.
Methods: Records from 94 patients were evaluated who underwent neuropsychological assessment before and under adjunctive treatment with either PER (n = 57) or LCM (n = 37). Cognition was assessed using the EpiTrack screening for executive functions and a VLMT short form for verbal memory. Subjective assessments included a German QOLIE-10 adaptation (quality of life) and an extended Adverse Events Profile (AEP). The median follow-up interval was 36 weeks.
Results: Multivariate repeated measures statistics revealed a non-significant trend towards an interaction effect "time – treatment arm" on both executive function and memory. When analyzed separately executive functions and memory scores significantly improved under LCM ($t = -2.76$ $p < 0.01$ and $t = -2.44$ $p < 0.05$ respectively). Subjectively, PER was associated with improvements in 2/18 physiological domains and in the LCM group 1/9 cognitive domains deteriorated. Seizure freedom was achieved for five patients treated with LCM (14%) and 15 treated with PER (26%, $\chi^2 = 2.2$, n.s.).
Conclusion: In a naturalistic outpatient setting, chronic adjunctive treatment with PER and LCM did not negatively affect cognition and LCM may even improve cognition. Neither drug increased self-reported irritability or aggression. This suggests favorable longer-term tolerability.

1. Introduction

About 60% of patients with epilepsy become seizure-free with the first or second antiepileptic drug (AED). Adding more AED only marginally increases the seizure free rate [1]. In order to improve treatment for the remaining patients, development of AED with new mechanisms of action is crucial. Additionally, newer AED generally exhibit fewer cognitive and behavioral side effects [2]. These belong to the least tolerated side effects [3], they can affect drug retention more than lack of seizure control [4], and they have been shown to be associated with lower subjective quality of life [5]. Some new AED have even been associated with cognitive improvement [6]. The current study aims to compare cognitive side effects of treatment with two newer AED, perampanel (PER) and lacosamide (LCM) in a naturalistic outpatient setting.

PER is a selective, noncompetitive antagonist to α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, a class of ionotropic glutamate receptors [7]. It was licensed as adjunctive medication for partial-onset and generalized seizures in 2012 and is in the evaluation process for monotherapy in Europe [8]. In Germany, PER was withdrawn from the market in 2013 following the implementation of a law to reduce healthcare costs (AMNOG, Gesetz zur Neuordnung des Arzneimittelmarktes). After pricing disputes have been settled, it has been reintroduced to the German market in 2018.

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The efficacy of PER in the treatment of partial-onset seizures has been demonstrated in three randomized controlled studies with a total of 1331 patients [7,9,10]. In these three trials, the most frequently reported adverse events were generally mild or moderate such as dizziness or somnolence.

Cognitive effects of PER have been investigated by Meador and colleagues [11] in adolescents with epilepsy. This study provided no evidence for a change in the global cognitive score but suggested possible benefits and disadvantages in individual scores, though effect sizes were small. Data from the extension phase also did not show an effect of long-term adjunctive treatment with PER on the global cognitive score [12]. Psychiatric adverse events seemingly arose more frequently [13]. A dose-dependent increase in hostility and aggression became apparent in the randomized controlled trials [14]. Recently the FDA demanded a boxed warning for "serious psychiatric and behavioral adverse reactions" including homicidal ideation and threats in the US prescribing information [15]. In one retrospective analysis of clinical experience with PER, 10% of the participants discontinued treatment because of behavioral reactions including suicidal ideation and aggressive behavior [16], while in another, PER showed similar clinical efficacy and a higher retention rate than levetiracetam (LEV) [17].

Lacosamide (LCM) is believed to take effect by increasing the number of voltage-gated sodium channels (VGSC) in the cell membrane that enter into the slow inactivated state. This does not influence normal synaptic transmission (fast inactivation of VGSC) but reduces the overall availability of VGSC. It may therefore selectively inhibit pathological activity [18]. LCM was approved in 2008 as adjunctive and monotherapy for patients with partial-onset seizures with or without secondary generalization. Three placebo-controlled trials with a total of 1308 patients demonstrated the efficacy of LCM in reducing seizures as well as its tolerability [19–21].

LCM has been associated with signs of vestibulocerebellar dysfunction such as dizziness, vertigo, and ataxia which emerge with increased dosage [22]. Up to now there is little evidence for any cognitive side-effects, though a pooled analysis of adverse events from randomized controlled trials suggests a dose-dependent increase of self-reported memory problems [23]. When objective measures are employed, LCM does not seem to induce negative effects on cognition in patients with epilepsy [24]. In a randomized, double-blind, two-period crossover study Meador and colleagues [25] found that healthy adults experienced fewer cognitive side effects when treated with LCM compared to carbamazepine (CBZ). LCM seems to exhibit a favorable cognitive profile similar to lamotrigine (LTG) and LEV. Similarly, Liguori et al. found that executive functions as assessed by the EpiTrack actually improve after introduction of LCM as compared to CBZ in a series of 16 cases [26].

When directly comparing PER and LCM, clinical outcomes showed relatively high responder rates in patients with refractory epilepsies [27]. The present study aimed to compare the longer-term cognitive and behavioral effects of adjunctive treatment with PER or LCM. According to the literature, we hypothesized no particular cognitive side effects. In addition, following recent reports on negative behavioral effects of PER, the behavioral outcomes were of special interest.

The study followed a retrospective, observational, controlled protocol which had been applied before when comparing LCM, topiramate, and LTG in a natural outpatient setting [24]. Following the experience with this and previous studies [6,28], an ongoing routine diagnostic screening protocol has been established at the epilepsy center in Bonn which facilitates monitoring of the efficacy as well as objective and subjective side effects on cognition and behavior of the longer-term use of all new AED [29].

2. Method

2.1. Study design and participants

This retrospective longitudinal study is based on records from patients who were tested before and during the longer-term treatment with PER or LCM at the epilepsy center in Bonn. Here, physicians can make use of a neuropsychological service to monitor cognition and behavior along with pharmacological treatment changes [29]. Since examinations are scheduled by the physician according to individual treatment concerns, follow-up intervals can be relatively long. Additionally, some patients decide against trying new medication or discontinue it after consulting in-house or local physicians, some did not return to the clinic within the observation interval and in some cases a follow-up examination was impossible because of logistic difficulties. A summary of the drop-out rates can be found in Supplementary Table 1.

2.2. Neuropsychological assessment

The standardized diagnostic screening package used has been described in more detail in a previous publication [24]. It contains measures of attention and executive functioning, verbal memory, quality of life and subjective side effects.

The EpiTrack [30] is a screening tool for executive function which is especially sensitive to drug effects and therefore uniquely appropriate for monitoring ongoing treatment [31]. It consists of six subtests that contribute to an age-corrected total score. Patients can achieve a maximum score of 49 (after age-correction). A total score of 29–31 points indicates mild impairment and the cutoff for significant impairment is $\leq$28 points. Significant change is indicated by a gain of $>$3 points or loss of $>$2 points.

Verbal memory was examined using a shortened version of the Verbaler Lern- und Merkfähigkeitstest (VLMT) [32], the German adaptation of the Rey Auditory Verbal Learning Test (RAVLT). According to normative data of 383 healthy subjects, scores for learning, memory and loss over time were converted into a total score and corrected for age [24]. 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 $\leq$10 as significant impairment. Changes were considered significant when there was a gain of $>$3 points or loss of $>$5 points.

Self-perceived side effects of AED were assessed by an extended Adverse Event Profile (AEP). The self-rating scale considers nine cognitive, five behavioral and 18 physiological symptoms [24]. Patients were 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).

Quality of life (QoL) was assessed via the German adaptation of the Quality of Life in Epilepsy (QOLIE)-10 questionnaire [33]. In the German version, 13 items covering epilepsy- and treatment related issues are rated from 1 to 5 with greater values reflecting worse QoL. As in previous publications, total scores exceeding half of the possible maximum were arbitrarily defined as indicating impairment (cutoff: $>$32). Change in QoL was rated as significant when a patient's baseline score changed by more than eleven points.

2.3. Statistical analyses

Baseline characteristics of the study groups were compared by T-tests and frequency statistics (χ^2) of categorical data. Changes in objective test performance and QoL were evaluated by repeated measures analysis of covariance (MANCOVA) with time as within- and treatment arm as between-subjects factor. Performance