Cognitive effects of lacosamide as adjunctive therapy in refractory epilepsy

Background – Lacosamide (LCM) is a novel antiepileptic drug (AED) with potential benefit as adjunctive treatment in patients with partial-onset seizures. As yet, limited information on cognitive effects of LCM is available, especially in real-life settings. *Aims* – In this open clinical prospective study, the cognitive effects of LCM were evaluated when used as adjunctive antiepileptic therapy in patients with refractory epilepsy. *Methods* – We included 33 patients aged between 16 and 74 years (mean: 37 years). All patients had a localization-related epilepsy. Patients were assessed at baseline before starting LCM treatment and during follow-up when the optimal clinical dose was achieved. *Materials* – Subjective complaints were evaluated using the SIDAED; effects on cognition were evaluated using the computerized visual searching task (CVST). *Results* – The CVST showed significant faster information processing reaction times at the second evaluation ($P = 0.013$), which was not correlated with seizure control, type of epilepsy, age, gender, drug load, number of concomitant drugs, dose or duration of LCM treatment. On the SIDAED, patients complained more about their cognitive function at the second evaluation ($P = 0.005$). For the SIDAED, a positive correlation at follow-up was found between the total severity score and higher age ($r = 0.375$, $P = 0.031$), but not with epilepsy factors or treatment characteristics. *Discussion/Conlusion* – Screening of the cognitive effects of LCM showed that LCM does not have negative effects on information processing speed. As this is the most sensitive function for cognitive side effects of AEDs, LCM does not seem to induce the common negative cognitive effects. Remarkably, patients complained more, especially about their cognitive function, which is possible the 'doing better, feeling worse phenomenon'.

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Introduction

Lacosamide (LCM) is a relatively recent introduced antiepileptic drug (AED). It was approved in Europe and USA in 2008 as adjunctive therapy for the treatment of partial-onset seizures in patients with epilepsy aged 16 and older in Europe and in patients 17 and older in the United States (1). LCM is unique among existing AEDs in that it has been shown to exert its anticonvulsant effects predominantly by enhancement of the slow inactivation of voltage-gated sodium channels without effecting fast inactivation (2, 3).The

post hoc analysis of pooled clinical data by Sake et al. (4) suggests that there may be an improved tolerability for LCM in patients not on other sodium channel blockers (SCB's).

The efficacy and safety of adjunctive LCM for partial-onset seizures was established in three multicenter, randomized, double-blind, placebo-controlled trials (5–7). Drug-induced adverse events with an incidence of at least 10% during the treatment period were general CNS and gastrointestinal effects (dizziness, nausea, diplopia, vision blurred, headache, vomiting, ataxia, fatigue, somnolence, vertigo,

nasopharyngitis, abnormal coordination, nystagmus, and tremor). All of these with the exception of headache appeared to be dose related, and four of these adverse effects were greater for LCM than for placebo; dizziness [31% vs 8%], headache [13% vs 9%], nausea [11% vs 4%], and diplopia [11% vs 2%] (7,8). A recent published meta-analysis of all available randomized controlled trials with LCM which included these three trials and seven trials with other disorders (neuropathic pain, migraine, fibromyalgia, knee osteoarthritis) found that these adverse events were more frequent reported in patients with drug-resistant epilepsy compared to other disorders (9). LCM was not associated with any adverse event unambiguously related to cognition in this analysis. However, Doty et al. (10) criticized that no formal cognitive testing was performed in these randomized controlled trials.

In none of the trials, cognitive side effects were recorded as a dominant complaint, which is remarkable given the high incidence of reported cognitive side effects in antiepileptic treatment (11, 12). The only item indicative of cognitive dysfunction reported was memory impairment, but its association with LCM was limited and not significant. However, no formal cognitive testing was performed in any of these trials, and cognitive effects notoriously evade subjective detection, especially in cases where patient use the drug as a 'last resort' (9, 10). In a long-term study rates of adverse events commonly attributed to other AEDS such as changes in cognition were low (13). Recently, the cognitive effects of LCM were compared with lamotrigine and topiramate suggesting a cognitive profile similar to lamotrigine and superior to that of topiramate (14).

For our specific patient group (i.e., patients with refractory epilepsies in a tertiary epilepsy referral and care center), data about the cognitive effects of LCM are important for clinical decision making. Cognitive complaints of the epilepsy, the seizures and the drugs may be confusingly entangled, limiting evaluation of the effectiveness of a drug in an individual patient. Preferably, cognitive effects of LCM would be studied in a randomized clinical trial. However, rarely cognition is an outcome (primary or secondary) of the industry driven RCT's. The alternative reports of clinical experience (often case reports) have led, however, to a substantial delay in detecting and understanding some behavioral effects of AEDs (15). Our study must therefore be seen as a systematic clinical audit, collecting information on the cognitive effects in the naturalistic clinical setting.

Methods

Subject selection

Patients who were scheduled to start with LCM between March 2009 and September 2011 were included. They were investigated before this drug was added to their current treatment and when they were using LCM. The study was approved by the local medical ethical committee.

Assessment procedures

Cognitive effects of LCM were assessed at two different times: at baseline before starting with this drug and at follow-up. The intervals between baseline and follow-up are variable because data were collected as part of normal clinical practice. The patient characteristics (age and sex), type of epilepsy, comedication, drug load, average dose of LCM, length of treatment with LCM at follow-up, efficacy, and reasons for discontinuation of LCM were included in the database. Efficacy was evaluated by change in seizure frequency from baseline to follow-up using a 3-point scale; reduction in seizure frequency, seizure remission, or increase in seizure frequency.

Instruments

Patients were tested with two measurements: a standardized inventory to evaluate subjectively perceived cognitive side effects and a neuropsychological test to assess possible effects independent of subjective complaints. Complaints were assessed using a list of 46 items with possible AED-related complaints, the SIDAED (16, 17). A complete overview of the SIDAED is provided in the Appendix A. The included items form 10 categories: general CNS, behavior (increased irritability), depressive symptoms, cognitive function, motor problems and coordination, visual complaints, headache, cosmetic and dermatological complaints, gastrointestinal complaints, and sexuality and menses. For each item, the patient rates the severity of the complaint on a four-point Likert scale (no problem, mild, moderate, or serious problem). In addition, the duration of the complaints is scored (since a few weeks, since months or half a year or longer). A total subjective complaints score was calculated for each patient from

the SIDAED complaints questionnaire, consisting of the number of mentioned complaints, weighing a mild score as 1, moderate as 2, and severe as 3 points. Thus, the range of the total severity complaints score could vary from 0 to 138. This questionnaire can be analyzed in different ways: regarding the total reported complaints, the different categories and the different items. The SIDAED is chosen because the psychometric properties have been established (16–18) and cognitive complaints can be measured relative to other domains.

The computerized visual searching task (CVST), an adaptation of Goldstein's visual searching task gives an indication of the visual (complex) information processing speed (19). A target grid pattern in the centre of the computer screen has to be compared with 24 surrounding patterns. Only one of them is identical to the target pattern. An example of this test is provided in the Appendix B. The patient is asked to react as fast as possible; reaction times are recorded. After each correct response, the central target pattern changes. The test consists of 24 different patterns, and after 12 presentations, the surrounding grids change. This task was included as slowing of central information processing is observed to be the dominant cognitive effect of most AED's and also the first sign of cognitive adverse effects (11, 12).

Dosing and titration

The initial dose of 50 mg was increased at weekly intervals by 50 mg up to the recommended maintenance dose of 200–400 mg/day. However, the titration schedule was individualized in response to patient complaints and seizure frequency.

Statistical analysis

Data were analyzed with SPSS version 21.0, Chicago, IL, USA. For analyzing the neuropsychological data, paired sample t-tests were used. Pearson correlations were used to exclude for influential effects on the neuropsychological results. Patients characteristics (gender and age), epilepsy factors (seizure control and type of epilepsy), and treatment characteristics (number of concomitant drugs, drug load, dose and duration of LCM treatment) were taken into account. Because the SIDAED consisted of 10 different categories, a P-value ≤ 0.005 was considered significant for the subscales of the SIDAED. This more stringent criterion of significance was based on the Bonferroni adjust-

ment for multiple tests. For the items of the SIDAED, a Bonferroni corrected P-value ≤ 0.001 was considered significant.

Results

Patient characteristics

A total of 33 patients were included in this study. Most patients (73%, $n = 24$) were female. Mean age at baseline was 37 years (SD: 14.5). Most patients (58%, $n = 19$) had a symptomatic localization-related epilepsy, and 42% ($n = 14$) had a cryptogenic localization-related epilepsy.

Five patients (15%) discontinued their LCM treatment before the second evaluation and were excluded for further analysis. Reasons for discontinuation were unsatisfactory therapeutic effect in two patients and side effects in three patients. These side effects were tiredness, dizziness, coordination, and balance problems.

The 28 remaining patients were using LCM treatment with a mean daily dose at follow-up of 298.2 mg/day (SD: 120.6). LCM was added to the anticonvulsant regimen. Twenty-one of 28 patients (75%) were taking LCM in addition to a SCB. Concurrent AED's ranged from 1 to 4 (mean: 1.9, SD: 0.8). The majority of the patients were taking carbamazepine (43%), clobazam (32%), lamotrigine (25%), and levetiracetam (21%).

Mean follow-up time was 7 months (SD: 6, range 1–24). In nine patients (28%), comedication was changed at follow-up; in five patients, only the dose of comedication was optimized, and in four patients, there was a medication switch in which LCM was added in exchange for one other anticonvulsant.

Seizure frequency was reduced in 50% ($n = 14$) of the patients. In 12 patients (43%), LCM did not have an effect on seizure frequency. Two patients (7%) had more seizures than before treatment with LCM was started.

Patients characteristics and their clinical date are provided in Table 1.

Neuropsychological findings

The CVST showed significant faster information processing speed at the second evaluation ($t = 2.644$, $P = 0.013$). At follow-up, patients showed an average increase of speed of more than 3-s (18%) on this task at follow-up (mean at baseline: 18.67 s; SD: 8.9; mean at follow-up: 15.40 s; SD: 7.5).

Table 1 Clinical characteristics of patients

Patient	Sex	Age	Type of localization-related epilepsy	Dosage LCM (mg) at second evaluation	Concurrent AED	Effect on seizure frequency	Treatment duration (LCM) at second evaluation (months)	Reason for discontinuation
1	F	74	Cryptogenic	200	PB 25 CLB 30	=	4	
2	F	44	Symptomatic	300	CBZ 600 CZP 1	−	5	
3	F	28	Symptomatic	200	PHT 350 OXC 1800 CLB 20	+	3	
4	F	62	Symptomatic	250	VPA 300 CLB 10	=	3	
5	F	59	Cryptogenic	400	CBZ 1000	=	3	
6	F	16	Symptomatic	Discontinued	−		Discontinued	Ineffectiveness
7	F	62	Cryptogenic	200	LEV 200 LTG 300 CLB 40	=	2	
8	F	45	Cryptogenic	100	LEV 500	−	24	
9	F	25	Cryptogenic	200	VPA 2250	−	1	
10	M	34	Symptomatic	300	LEV 3000 OXC 1200 LTG 500	=	3	
11	M	35	Symptomatic	Discontinued	−		Discontinued	Adverse events
12	F	19	Symptomatic	300	LTG 150	−	3	
13	M	18	Cryptogenic	400	OXC 2700 PGB 225	−	4	
14	F	37	Symptomatic	300	CBZ 1600 LTG 200	=	3	
15	F	50	Cryptogenic	200	GBP 1200 CBZ 600	−	4	
16	M	24	Symptomatic	600	LTG 550 TPM 200	=	10	
17	F	23	Symptomatic	400	AZM 500 CZP 3	=	12	
18	F	45	Symptomatic	250	CBZ 800 LTG 600	=	3	
19	F	19	Cryptogenic	300	VPA 1200 CBZ 1100	−	10	
20	M	47	Symptomatic	Discontinued	−		Discontinued	Ineffectiveness
21	M	25	Symptomatic	500	LEV 3000 CBZ 800 CLB 30	−	6	
22	M	51	Symptomatic	Discontinued	−		Discontinued	Adverse events
23	F	42	Cryptogenic	550	LEV 2000 PB 150	−	7	
24	F	44	Symptomatic	400	−	−	22	
25	M	29	Cryptogenic	150	CBZ 100 TPM 200	−	2	
26	F	29	Symptomatic	Discontinued	−		Discontinued	Adverse events
27	F	41	Cryptogenic	300	CBZ 1000	−	4	
28	F	22	Cryptogenic	200	LTG 175 CLB 20	=	17	
29	F	44	Symptomatic	400	CLB 20	−	8	
30	F	24	Cryptogenic	300	CBZ 800 CLB 10	+	2	
31	F	36	Symptomatic	250	PHT 187.5	−	3	
32	M	35	Symptomatic	200	CBZ 1400	=	10	
33	F	24	Cryptogenic	200	LEV 1000 CBZ 800 CLB 20	=	14	

PB, phenobarbital; CLB, clobazam (Frisium); CBZ: carbamazepine (Tegretol); CZP, clonazepam (Rivotril); PHT, phenytoin (Diphantoine); OXC, oxcarbazepine (Trileptal); VPA, valproate (Depakine); LEV, levetiracetam (Keppra); LTG, lamotrigine (Lamictal); PGB, pregabalin (Lyrica); GBP, gabapentin (Neurontin); AZM, acetazolamide (Diamox), seizure frequency; −, reduction; +, increase; =, seizure remission, no effect; AED, antiepileptic drug; LCM, lacosamide.

On the SIDAED, none of the patients mentioned zero complaints at baseline or follow-up. At baseline, before the start of treatment with LCM, the distribution of subjective complaints as measured by the SIDAED ranged from 3 to 36 (maximal range on the scale is 0–46), with a mean number complaints of 15.8 (SD: 7.0). At second evaluation, the average rate of subjective complaints did not differ from baseline ($P = 0.431$) with a mean number of complaints of 16.8 (SD: 8.5; range: 1–35).

A statistically significant effect was only found for the subscale cognitive complaints. For the other subscales, results did not yield statistical significance (see Fig. 1). Both the severity of the cognitive complaints ($t = -3.367$, $P = 0.002$) as the number of the cognitive complaints ($t = -2.992$, $P = 0.005$) increased in the treatment phase. The mean severity score on the subscale

cognitive function per item increased from 0.78 to 1.11 (see Table 2). At baseline, patients reported to experience on average 4.2 (SD: 1.9) of the nine possible cognitive complaints. In the treatment phase, this was increased to an average of 5.3 (SD: 2.4).

When analyzing the 46 items, a significant higher severity score was found at the second evaluation for the following items from the cognitive function category; 'I have difficulty remembering names' ($t = -4.917$, $P < 0.000$), 'I notice I sometimes have difficulty expressing myself' ($t = -3.783$, $P < 0.000$), and 'I have difficulty finding the right words' ($t = -3.475$, $P = 0.001$).

Correlational analysis

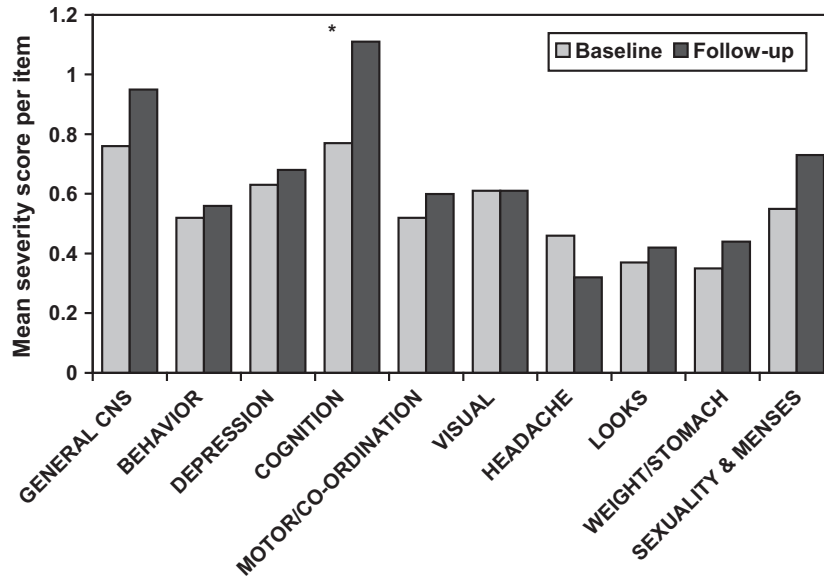A significant positive correlation was found at follow-up between processing speed and the

Figure 1. Differences in the subscales of the SIDAED between baseline and follow-up. *$P \leq 0.05$.

Table 2 The mean reported severity score per item per subscale

Subscale	Baseline	Follow-up
General CNS	0.80	0.94
Behavior (increased irritability)	0.55	0.56
Depressive symptoms	0.65	0.70
Cognitive function	0.78	1.11*
Motor problems and coordination	0.54	0.60
Visual complaints	0.69	0.61
Headache	0.52	0.30
Cosmetic and dermatological complaints	0.40	0.41
Gastrointestinal complaints	0.35	0.38
Sexuality and menses	0.59	0.70

*$P \leq 0.05$.

SIDAED cognitive items 'I notice my reaction to others is slow' ($r = 0.465$, $P = 0.013$) and 'I notice my speech is slow' ($r = 0.467$, $P = 0.012$). Improvement of processing speed was associated with a decrease of complaints. No other cognitive complaints were correlated with the information processing task.

The improved information processing speed could not be explained by patient characteristics such as gender ($P = 0.712$) or age ($P = 0.771$), or by epilepsy factors such as seizure control ($P = 0.332$) or type of epilepsy ($P = 0.494$), or by treatment characteristics such as number of concomitant drugs ($P = 0.359$), drug load ($P = 0.927$), or dose ($P = 0.830$) and duration of LCM treatment ($P = 0.659$).

For the SIDAED, a positive correlation at follow-up was found between the total severity score and age ($r = 0.375$, $P = 0.031$). The older the patients, the more complaints were reported. Gender, epilepsy factors or other treatment characteristics did not affect the results.

Discussion

Lacosamide is a relatively recent introduced AED with potential benefit as adjunctive treatment in patients with partial-onset seizures (20). In this open clinical prospective study, the cognitive effects of LCM when used as adjunctive antiepileptic therapy in adolescent and adult patients with refractory epilepsy were evaluated in the real-life setting.

During LCM treatment, we found a statistically significant improvement of information processing speed (increase of 18%). This function is generally impaired in individuals taking other AEDs (9, 11, 12). Speed of information processing is the most sensitive function affected by AED treatment; therefore, this result is remarkable. However, activating effects have also been reported for lamotrigine (11, 12, 21, 22). Ketter et al. (23) divided AEDs in activating and sedating drugs, and our results suggest that LCM may be classified as a cognitive activating drug. The results were not biased by interfering factors. The significant improvement of central information processing speed was not correlated with change in seizure frequency, type of epilepsy, age, gender, drug load, number of concomitant drugs or dose and duration of LCM treatment. Therefore, our

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