Received: 29 August 2019 | Revised: 3 December 2019 | Accepted: 14 December 2019

DOI: 10.1111/ane.13206

ORIGINAL ARTICLE

Acta Neurologica Scandinavica | WILEY

Clinical experience combined with therapeutic drug monitoring of lacosamide

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Objective: Lacosamide (LCM) is an antiepileptic drug (AED) with insufficient clinical experience in patients with intellectual disability (ID). They often have more severe epilepsy with comorbidities. The objective was to evaluate the efficacy and tolerability of lacosamide (LCM) in patients with refractory epilepsy with and without ID in a real-life setting, taking drug monitoring (TDM) data into account therapeutic.

Methods: Retrospectively, we identified 344 patients using LCM from the TDM service covering the majority of the country, at the National Center for Epilepsy in Norway (2013-2018). Clinical and TDM data were available for 132 patients.

Results: Forty-four of the 132 patients (33%) had ID. The retention rate was significantly higher in the ID vs the non-ID group after 1 year (84% vs 68%, $P < .05$). By combining clinical and TDM data, we demonstrated that 37/38 responding patients had serum concentrations above the lower limit of the reference range (>10 µmol/L), and 16/17 with lower concentrations were non-responders. Mean serum concentration/dose ratios were similar in both groups, 0.06 and 0.07 µmol/L/mg. There were no significant differences regarding efficacy and tolerability. The risk of LCM withdrawal was significantly higher when LCM was added to sodium channel blockers, even if the latter was discontinued.

Significance: Lacosamide was generally well tolerated in patients with drug-resistant epilepsy, where one third had ID, and in these patients the retention rate was higher. The combination of clinical and TDM data could possibly facilitate LCM therapy in these vulnerable patients.

KEYWORDS

antiepileptic drugs, efficacy, epilepsy, intellectual disability, lacosamide, therapeutic drug monitoring, tolerability

1 | INTRODUCTION

Lacosamide (LCM) is one of the most recently introduced antiepileptic drugs (AEDs) and is approved as monotherapy or as add-on treatment in adults, adolescents, and children (from 4 years) with focal epilepsy. In contrast to the majority of sodium channel-blocking AEDs, LCM inhibits slow-activated sodium channels rather than the fast-acting channels.[1-4] Clinical studies have demonstrated a favorable short- and long-term efficacy and tolerability of LCM.[5-7]

Intellectual disability (ID) is present in about 20%-25% of adult patients with epilepsy.[8] In addition to cognitive deficits, many of these patients have behavioral problems often associated with psychiatric and physical comorbidities.[9] The epilepsy is often severe in this population, with a risk of up to 70% of drug-resistant seizures.[10] ID patients often try the newest AEDs soon after approval, usually

as add-on to one or several other AEDs but are usually excluded from randomized controlled clinical trials.[11,12] Thus, there is little evidence-based data concerning the appropriate use of new AEDs in this patient group, where communication barriers make it more difficult to achieve an optimal balance between seizure control and adverse effects.[13] There are some retrospective studies regarding the use of LCM in patients with ID,[14-17] but therapeutic drug monitoring (TDM) was not included as part of the evaluation in these studies.

Therapeutic drug monitoring is an important tool for optimizing drug treatment in epilepsy. In previous studies, we have emphasized the value of TDM in treating patients with LCM.[18-20] In patients with ID and epilepsy, comparative and combined studies of clinical and pharmacokinetic data are lacking. By combining such data, a more comprehensive evaluation of the patient is possible, and pharmacokinetic variability may be accounted for, when it comes to individual factors, drug interactions and polypharmacy in epilepsy or comorbid disorders.[18]

The aim of this study was to evaluate the efficacy and tolerability of LCM in patients with refractory epilepsy with and without ID in a real-life setting, taking TDM data into account.

Highlights

- The retention rate was significantly higher in ID patients (n = 44), and LCM was generally well tolerated in the total study population (n = 132).
- We observed better efficacy of LCM in patients with serum concentrations above 10 μmol/L.
- The combination of clinical evaluation and use of TDM may thus facilitate LCM therapy.

2 | MATERIAL AND METHODS

2.1 | Study material

In the period 2013 to 2016, we identified 344 patients using LCM through the TDM service in the Section for Clinical Pharmacology, the National Center for Epilepsy, Oslo University Hospital. The laboratory performs the majority of LCM analyses from the whole country. In 223 of the 344 patients, information from medical records was available at the National Center for Epilepsy, Lillehammer Trust Hospital and St. Olav's Hospital, Trondheim. Data regarding gender, age, epilepsy etiology, epilepsy type, ID, seizure onset, seizure type, previous and current use of AEDs, time of initiation/ discontinuation and efficacy/tolerability were collected. The most recent used dosing of AEDs, serum concentration of AEDs and time of the latest follow-up were noted. To be able to report complete clinical and pharmacological data in a consecutive manner, we excluded 91 patients who had started with LCM before the implementation of TDM-analysis for LCM in routine service (January 2013). Of the remaining 132 patients, 44 (33%) had ID (IQ < 70 points). Patients were grouped into non-ID, mild, moderate or severe ID based on DSM-5 according to information from medical records.

The study patients started LCM therapy in the period January 2013 to May 2016. Date of withdrawal of medication or last visit was used as endpoint in the study. All patients had been followed up for at least 1 year after initiation of LCM treatment (until 2018).

Retention rates were evaluated at 1 year and further estimated through Kaplan-Meier survival analysis up to 44 months. Patients still using LCM were censored in the survival analysis at their last follow-up visit. Efficacy was evaluated from the medical records using a modified Likert scale: (1) no effect, (2) some effect (modest reduction of seizure frequency and/or duration), (3) good effect (defined as >50% reduction of seizure frequency), and (4) complete seizure freedom over a period of at least 1 year. Tolerability was evaluated by the treating clinician, and observed or reported adverse effects were recorded as mild, moderate or severe (ie, leading to LCM discontinuation). In cases of discontinuation of LCM, the reasons were categorized as lack of effect, adverse effects or both. The following AEDs were categorized as predominant sodium channel blockers: eslicarbazepine acetate, oxcarbazepine, carbamazepine, phenytoin, zonisamide, rufinamide, and lamotrigine, according to Hillenbrand et al[21] (but they did not include zonisamide and rufinamide) and more recently by Burns et al.[20] The study was approved by the Regional Ethics Committee.

2.2 | Drug analysis

The serum concentration measurements were performed as routine analysis of validated methods at the National Center for Epilepsy, measured by HPLC-UV with a measuring range of 10-250 μmol/L for LCM, on an Ultimate 3000 HPLC, Dionex (125 × 3 mm, 3 μm Hypersil BDS C-18 column) based on Greenway et al[22] We used the reference range of 10-40 μmol/L based on the results from drug-fasting samples in the morning as suggested by Contin et al[23] and Svendsen et al[19] and confirmed as a national reference range.[24] The most recent analysis of LCM and other AEDs at assumed steady-state conditions were included. Blood samples were drawn drug-fasting in the morning before intake of the morning dose as a standard procedure; otherwise, the samples were excluded.

Serum concentrations, doses, and concentration/dose (C/D) ratios were calculated as means or medians with standard deviation (SD) or minimum-maximum range to express variability.

2.3 | Statistical analyses

For statistical analyses IBM SPSS Statistics version 22 was used. We used Kaplan-Meier survival curves to show how long the duration of treatment was and, furthermore, to estimate statistically the proportion of patients remaining on LCM among those who started treatment after 1 January 2013. To analyze the differences in survival distributions, we

applied the log rank test (estimated duration) and the Breslow test (at 1 year). Student's *t* test and chi-square test were used for testing possible group differences for continuous and categorical variables, respectively. We further applied Hosmer's step-down procedure that permits variables significant at the 0.25 level to be included in the multivariate logistic regression model. Odds ratios and confidence intervals (CI) at a level of 95% were calculated.

The following variables were tested in a multivariate logistic regression model: gender, age, years of epilepsy, ID, number of previously tried AEDs, number of AEDs when starting with LCM, number of sodium channel-blocking AEDs at current use, AEDs discontinued, LCM starting dosage, LCM treatment dosage, serum concentration of LCM, and LCM-related efficacy and adverse effects. *P*-values of <.05 were considered statistically significant in all analyses.

3 | RESULTS

3.1 | Patient characteristics

Clinical characteristics of the two populations are shown in Table 1. All patients had drug-resistant epilepsy and used 1-4 AEDs at the time of LCM initiation. The majority of patients were adults, but there were five in the ID group and seven in the non-ID who were below 18 years of age. Most of the patients (95%) had focal epilepsy. Two patients had generalized epilepsy, and three had unclassified epilepsy. The epilepsy etiology was known in 57% of the patients. The most common etiologies included cerebrovascular disorders (n = 14), cerebral tumors (n = 14), and cortical malformations (n = 11). Patients with ID had significantly earlier seizure onset ($P < .005$) and a higher number of previously tried AEDs ($P < .05$). In those patients with ID, nearly 50% (20/44) were categorized as moderate to severe ID (Table 1). One patient in the non-ID group died during the study period. The cause of death was subarachnoid hemorrhage and thus probably not related to the epilepsy.

3.2 | Clinical outcome

Efficacy and tolerability could be assessed in all 132 patients, of whom 38 (29%) were responders (>50% seizure reduction), including five seizure-free patients. In the ID group (n = 44), 15 patients (34%) were responders and two of them became seizure-free. About one third in both patient groups did not experience any improvement of the seizure disorder (Table 2). Mild to moderate adverse effects were reported in 47% of the patients without ID and in 31% in those with ID. In total, 21 (17%) patients discontinued LCM due to adverse effects, 16% (n = 7) in those without ID and 17% (n = 15) with ID.

With the Kaplan-Meier survival analysis, we examined the retention rates at 1 year in the two groups, as all patients had been followed at least 1 year or to LCM withdrawal. At 1 year, the two groups were significantly different; 84% and 68% of the patients with and without ID, respectively, were survivors ($P = .04$). Furthermore, we estimated statistically the total KM "survival" time of LCM to be similar at 42-45 months in the two groups (Figure 1), which was not statistically significant different ($P = .054$).

3.3 | Combining clinical and TDM data

Taking drug monitoring-data from all patients demonstrated pharmacokinetic variability with a distribution of serum concentration and dose relationships which was 5- to 6-fold in both groups (Figure 2B and Table 2). Both groups had a mean dose of LCM of about 300 mg/day (range 25-600 mg/day) (see note in Table 1 about the low dose of 25 mg/day). Almost all patients who were responders had serum concentrations above the lower limit of the reference range (>10 μmol/L); 22/23 non-ID and all 15 ID patients. On the other hand, 17 patients had serum concentrations below 10 μmol/L (12 and 5 in the non-ID and ID group, respectively), of which only one was a responder. Seven of these patients had a daily dosage of 200 mg or more, and thus, the measured serum concentration would be a better marker of efficacy than the dose. This was confirmed, as the responder rate was significantly lower for those with serum concentrations below the lower limit of the reference range, that is ≤10 μmol/L as compared to higher concentrations ($P = .024$), regardless of being ID or non-ID patients.

There were no significant differences between the groups regarding C/D ratios in non-ID vs ID patients, or in efficacy or tolerability measures. The C/D ratios were between 0.06 and 0.07 μmol/L/mg (with a similar SD = 0.02) in all subgroups: seizure-free/good effect, uncertain or no effect, and no/mild or moderate/serious adverse effects. Thus, there were no differences between responders and non-responders, or those who experienced adverse effects or not in the two groups.

3.4 | Use of concomitant AEDs

Polytherapy with a mean of two other AEDs at initiation of LCM was seen in both groups (90% and 98% of patients, range 1-3 and 1-4 in non-ID and ID groups, respectively), and with 5-7 previously tried AEDs (Table 2). The most commonly used AEDs in combination with LCM were non-interacting drugs: levetiracetam, valproate, lamotrigine, and clobazam (Figure 2A). There were more users of clobazam in the ID group than in the non-ID group, but this was not associated with improved efficacy, as only one out of nine patients had a good clinical response and two had some effect in combination with LCM. In both groups, 27% used concomitant enzyme-inducing drugs: carbamazepine, phenobarbital, or phenytoin (n = 12 in the ID vs 24 in the non-ID patients). The C/D ratio of LCM decreased by 21%; the mean C/D ratio of LCM was 0.054 with enzyme-inducing vs 0.069 μmol/L/mg with non-enzyme-inducing comedication ($P < .001$). Non-AEDs were not included in the analysis.

For the whole group of patients, we found that those who used a sodium channel-blocking AEDs at start of LCM treatment

TABLE 1 Clinical characteristics of patients using lacosamide (n = 132)

Characteristics	Non-ID patients	ID patients
Number	88 (49 w, 39 m)	44 (25 w, 19 m)
Age (y)	38 (10-79)	31.5 (4-68)
Epilepsy onset (mean age, y)	18	5.4
Duration of epilepsy (y)		
Mean	18	23.9
Type of epilepsy		
Focal onset	84	41
Generalized onset	1	1
Unknown onset	3	2
Etiology		
Known	53 (60%)	23 (52%)
Genetic	4	5
Cortical malformation	7	4
Hippocampal sclerosis	5	0
Vascular	12	2
Trauma	3	4
Tumor	10	4
Infection	7	1
Other	5	3
Unknown	35 (40%)	21 (48%)
Antiepileptic drugs (AEDs)		
Number of AEDs at start	1-3 (mean 1.9)	1- 4 (mean 2.1)
Mean number of previous AEDs	5.7	7.4
Reason for start		
Poor seizure control	43	32
Poor seizure control + adverse effects	29	9
Adverse effects	16	3
Intention to discontinue another AEDs	71	25
Lacosamide monotherapy	10 (11%)	1 (2%)
Polytherapy (1-4 other AEDs)	79 (89%)	43 (98%)
Doses and serum concentrations		
Mean dose (SD) mg/d	304 (116)	284 (106)
Median (range) mg/d	300 (100-600)	300 (25-500)[a]
Mean serum concentration (SD) μmol/L	21.3 (9.3)	21.2 (9.3)
Median serum concentration (range) μmol/L	17.8 (8.1-44.3)	19.5 (10-47)
C/D ratio (μmol/L/mg)	0.07 (0.02)	0.07 (0.02)

Abbreviations: C/D ratio, concentration/dose-ratio; M, men; W, women.
[a]One patient on 25 mg/d with multifocal epilepsy, severe ID, and very sensitive to medication.

TABLE 2 Efficacy and tolerability of lacosamide (n = 132)

Characteristics	Patients without ID (88)	Patients with ID (44)
Discontinuation		
Total	36 (41%)	12 (27%) (P = .125)
Adverse effects	15	7
Lack of effect	5	2
No effect and/or adverse effects	15	3
Deceased[a]	1	0
Efficacy		
Seizure-free/responder[b]	3/23 (26%)	2/15 (34%)
Uncertain efficacy	34 (39%)	16 (36%)
Lack of effect	31 (35%)	13 (30%)
Tolerability		
No adverse effects	38 (43%)	24 (55%)
One or more effects	50 (57%)	20 (45%)
Mild effects	27 (31%)	9 (20%)
Moderate	14 (16%)	5 (11%)
Severe	9 (10%)	6 (14%)
Most commonly reported		
Dizziness	10 (11%)	4 (9%)
Headache	1 (1%)	2 (5%)
Sedation	14 (16%)	5 (11%)
Gastrointestinal	6 (7%)	4 (9%)
Cognitive impairment	9 (10%)	2 (5%)
Behavioral	1 (1%)	5 (11%)
Visual disturbances	5 (6%)	0
Other	9 (10%)	4 (9%)

[a]Subarchnoidal hemorrhage.
[b]Responders were defined as >50% seizure reduction.

significantly more often withdrew LCM than those who used other AEDs (P < .01), even if the sodium channel blocker had been withdrawn after the initiation of LCM.

Multivariate logistic regression analysis of possible factors associated with efficacy and tolerability was performed. This did not demonstrate any significant findings for any of the following variables: gender, age, years of epilepsy, ID, number of previously tried AEDs, number of AEDs when starting with LCM, number of sodium channel-blocking AEDs at current use, AEDs discontinued, LCM starting dosage, LCM treatment dosage, serum concentration of LCM, and LCM-related efficacy and adverse effects (data not shown).

4 | DISCUSSION

In the present study, efficacy, tolerability, and TDM data in ID patients as compared to non-ID patients were similar. The retention

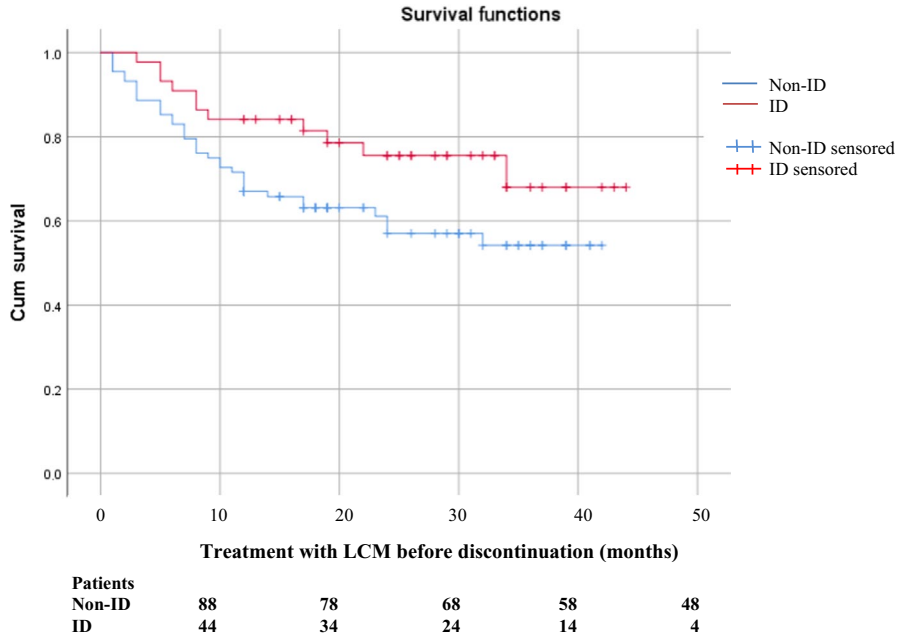

FIGURE 1 Kaplan-Meyer plot showing the predicted retention rate of lacosamide (LCM) in 132 patients who started with lacosamide after 1 January 2013, 88 without ID and 44 with ID. In the group without ID, 36 had discontinued lacosamide (blue curve) while 11 had discontinued the medication in the ID group (red curve). For 52 and 33 in the two groups, respectively, it was uncertain whether they still use lacosamide after the latest follow-up (defined as censored marked with a cross). All patients had been followed for at least 1 y, and furthermore, the statistical analyses defined the predicted values for discontinuation. At 1 y, the ID group has a significantly higher retention rate (P = .04), but the difference was not significant at the further predicted values toward >40 mo

rate of LCM after 1-year follow-up was, however, significantly higher in patients with ID than in the non-ID group (84% vs 67%). The predicted time to discontinuation of more than 40 months was, however, not significantly different. Retention rates of LCM in patients with ID have previously been investigated in several studies[14-17] with similar results as in our study, but this is the first study that directly compares ID patients with a non-ID group, also including TDM data. The results show a similar exposure of LCM in both groups, pointing to the same degree of follow-up and monitoring, which increases the impact of the study. Retention rates are considered a marker for effectiveness, which expresses the joint outcome of both efficacy and tolerability. However, neither efficacy nor tolerability appeared to be different in the two groups, although there was a slight predominance of more responders and less recorded adverse effects in the ID group, which conceivably had an impact on the retention rate. As compared to other recently approved AEDs, we previously demonstrated a retention rate of 83%, 72%, and 63% of eslicarbazepine acetate in patients with refractory epilepsy after 1, 2, and 3 years of treatment, respectively.[19] In another study with patients with refractory epilepsy and ID, the retention rate of perampanel was 46% and 42%, after 1 and 2 years, respectively.[25]

4.1 | Efficacy and tolerability

One third of patients with ID were considered as responders, whereas one out of four of patients was responder in the non-ID group (Table 2). The responder rates are lower than in previous randomized controlled trials[6] and in the pooled analysis by Biton et al[5] This may be due to more severe and difficult-to-treat epilepsies in our cohort. Adverse effects were reported in 45% in those with ID and in 57% in those without ID. Such a tolerability profile is similar to another clinical study.[21] There was a significant increased risk of withdrawal of LCM among those who used other sodium channel-blocking AEDs. This is in line with other studies, where this possible pharmacodynamic interaction resulted in an increased burden of CNS-related adverse effects in the patients using such combination.[16,21]

Our study also indicates that patients being less tolerant or experience poorer efficacy of other sodium channel blockers were more likely to stop their medication with LCM. This is probably due to the epileptogenesis and a group of patients that are sensitive to sodium channel blockers.

A higher long-term retention rate in subjects with ID can be influenced by a number of factors. It is well known that inadequate intake of medication is a common cause of poor seizure control in the general epilepsy population,[26] whereas it is a less common obstacle in subjects with strictly supervised drug intake.[27] On the other hand, unwitnessed seizures may sometimes occur undetected in independent people, whereas people with intellectual handicaps are surrounded by staff most of the time. The quality of self-reporting in subjects with intact cognition is fundamentally different from information obtained from caregivers of ID patients. Hence, less reported adverse effects in those with ID are not surprising. Subjects with pre-existing brain dysfunction may be more vulnerable to CNS-related adverse effects which sometimes may be differently expressed in these people.[28] Mild to moderate adverse effects may not always be noticed by the caregivers, but

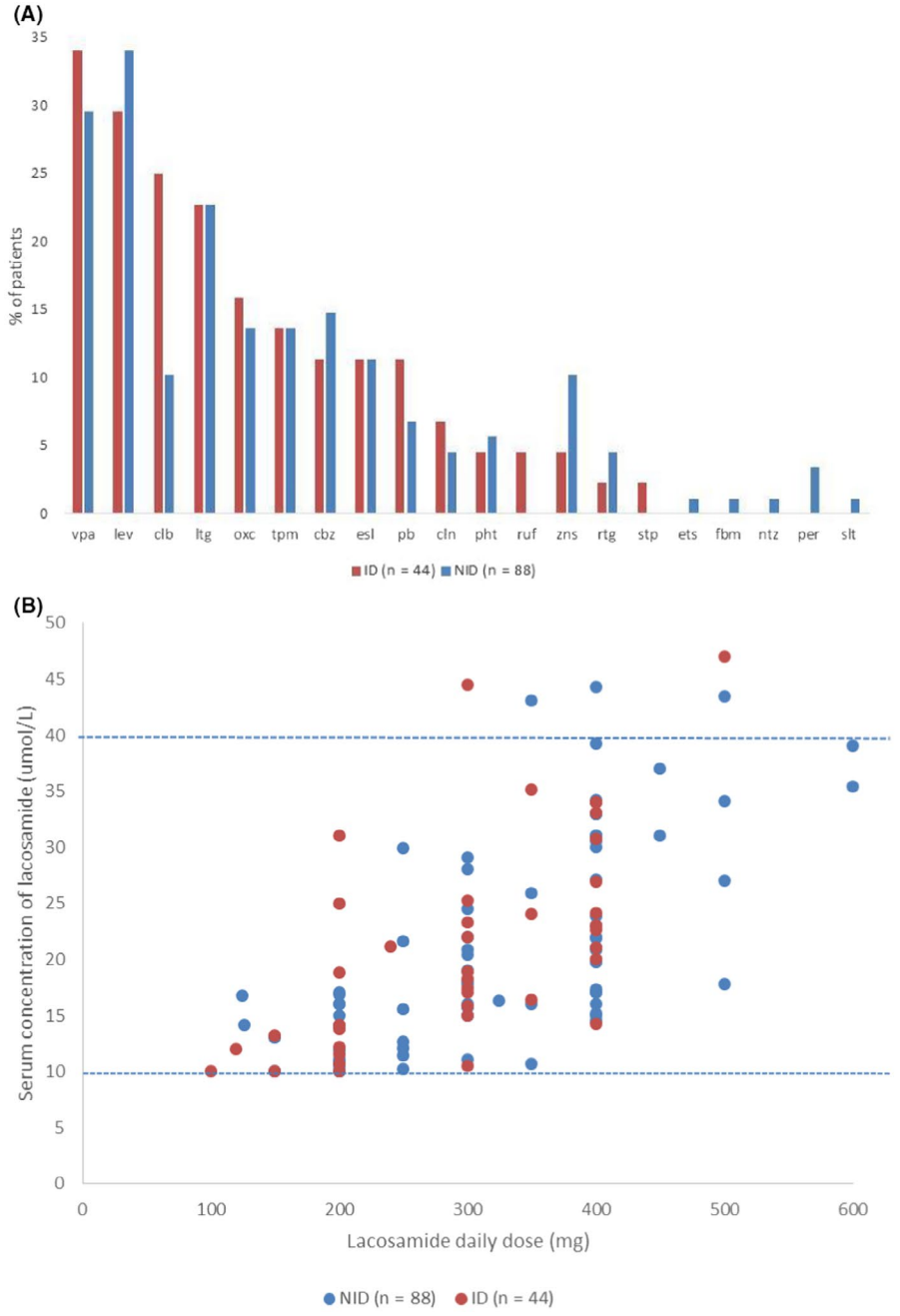

FIGURE 2 Pharmacological data on lacosamide in 132 patients. A, Use of concomitant antiepileptic drugs among patients with intellectual disability (ID) and patients without intellectual disability (NID) and patients using lacosamide. (CBZ, carbamazepine; CLB, clobazam; CLN, clonazepam; ESL, eslicarbazepine acetate; ETS, ethosuximide; FBM, felbamate; LEV, levetiracetam; LTG, lamotrigine; NTZ, nitrazepam; OXC, oxcarbazepine; PB, phenobarbital; PER, perampanel; PHT, phenytoin; RTG, retigabine; RUF, rufinamide; SLT, sulthiame; STP, stiripentol; TPM, topiramate; VPA, valproic acid; ZNS, zonisamide). B, Dose and serum concentration relationships of lacosamide in NID (n = 88) and ID (n = 44) patients. The reference range is marked with horizontal lines (10-40 µmol/L). Seventeen of the patients had serum concentrations below 10 µmol/L that was given as a value of <10, and these values are therefore excluded from the figure

they may occasionally be converted to behavioral reactions, which is frequently misunderstood. These pitfalls should receive attention in surveillances of AED treatment in the ID population. A high retention rate of a new drug does not always signify that the treatment is of clear benefit to the patient. Particular care should be taken to discontinue redundant drugs and to avoid overmedication in people with reduced abilities to express their own preferences.

In contrast to some other newer AEDs, psychiatric and behavioral adverse effects do not appear to limit the use of LCM. However, in one study in patients with ID aggression/agitation was reported in one fourth of patients.[15] In the present study, behavioral effects were rare but occurred more frequently in patients with ID. Meta-analyses have shown that the occurrence of adverse effects of LCM increases with dose, and withdrawals were often caused by symptoms as dizziness, vertigo, ataxia, and nausea. Such effects are not easily detected by the caregivers of patients with ID.[5,29] In the search for predictors of efficacy, a recent study concluded that there were no genetic predictors of LCM response identified, but patients with refractory generalized genetic epilepsies might benefit from treatment with LCM.[30] There were, however, few patients with generalized epilepsies in the present study.

4.2 | Evaluation of the combination of clinical- and TDM data

Taking drug monitoring was used as a part of the comprehensive follow-up in all patients. The pharmacokinetic variability in our study

was moderate and similar in both groups, and there were no differences in doses used and serum concentrations obtained in ID vs non-ID patients. This is an interesting finding as it is often claimed that patients with ID have a lower threshold for experiencing especially behavioral adverse effects.[29] Almost all patients with a good clinical efficacy had serum concentrations above the lower limit of the reference range, whereas those with low concentrations were non-responders. Our findings indicate that serum concentrations of LCM below 10 µmol/L (ie, the lower limit of the reference range) result in poor efficacy. Some of these patients with low concentrations seemed to have relevant therapeutic daily dosages above 200 mg, which underlines the importance of using TDM when experiencing lack of efficacy.[19-21,31,32] Concomitantly used AEDs contributed only moderately to variability between patients.

4.3 | Study limitations

Retrospective studies have a number of limitations, as medical records and TDM databases may be incomplete. Nevertheless, we recently compared the data from TDM request forms and found that the given information about AEDs and dosages was in accordance with the medical records.[19] Retrospective, uncontrolled studies may be a valuable supplement to prospective studies by the possibility to identify rare adverse effects in subgroups of patients as they represent a real-life setting.[11] There might be a selection bias regarding the patients included for clinical evaluation, since they all were included based on the TDM database, and we were not able to reach patients starting with LCM not registered in the database. In a realistic and retrospective setting, adherence could not be controlled for, but it is assumed to be satisfactory, especially in ID patients where often healthcare professionals or caregivers are responsible for the daily drug intake.

5 | CONCLUSION

The use of LCM in patients with refractory epilepsy with and without ID was compared regarding clinical efficacy in combination with TDM data. LCM was generally well tolerated in patients with drug-resistant epilepsy, where one third had ID. The retention rate was higher in ID than in non-ID patients after 1 year of follow-up. Responders had serum concentrations above the lower limit of the reference range. The combination of clinical and TDM data could possibly facilitate LCM therapy in these vulnerable patients. Although the balance between efficacy and tolerability in subjects with and without ID is difficult to compare, the present study suggests that LCM has a favorable pharmacological profile for the treatment of refractory epilepsy in patients with ID.

ACKNOWLEDGEMENTS

None.

CONFLICT OF INTEREST

The authors have no conflicts of interest or any financial disclosures regarding this manuscript. Torleiv Svendsen has received honoraria for attending advisory boards and/or for speaker's honoraria from Eisai, GlaxoSmithKline, and UCB. Eylert Brodtkorb has received honoraria and/or financial support for attending conferences from Eisai, GlaxoSmithKline, and UCB. Svein I. Johannessen has received honoraria for attending the advisory board of GW Pharma. Morten I Lossius has received honoraria for attending advisory boards and/or for speaker's honoraria from Eisai and UCB. Cecilie Johannessen Landmark has received speaker's honoraria from Eisai, GW Pharma, and Labor Krone.

AUTHOR CONTRIBUTIONS

The contribution of the authors of this manuscript has been as follows: Torleiv Svendsen and Cecilie Johannessen Landmark has planned and designed the study, written the first draft of the manuscript, and been responsible for revisions. Torleiv Svendsen was responsible for clinical evaluation of patients from the National Center for Epilepsy and Innlandet Hospital Trust, and clinical data handling. Eylert Brodtkorb has performed the clinical evaluation of patients from St. Olav's University Hospital and contributed to the data handling. Arton Baftiu and Svein I. Johannessen has contributed to data handling, discussion, and statistical analyses. Karl Otto Nakken and Morten I. Lossius has contributed to clinical evaluation and discussion. All authors have contributed to writing and revising the manuscript and have approved the final manuscript.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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How to cite this article: Svendsen T, Brodtkorb E, Baftiu A, et al. Clinical experience combined with therapeutic drug monitoring of lacosamide. *Acta Neurol Scand*. 2020;00:1–8. https://doi.org/10.1111/ane.13206