SHORT COMMUNICATION

Effectiveness of Lacosamide on everyday cognitive deficits, psychiatric symptoms and resilience in patients with epilepsy

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Abstract

Lacosamide is a novel antiepileptic with neuroprotective properties. The present study examined the effectiveness of Lacosamide on cognitive functioning, psychiatric symptoms, and resilience in patients of refractory partial epilepsy. This prospective study was conducted at Sheikh Zayed Hospital;Rahim Yar Khan, Nishter Hospital, Multan; and Bahawal Victoria Hospital, Bahawalpur, Pakistan, from November 2017 till May 2018.Thirty-six patients of refractory partial onset epilepsy and 36 healthy individuals particiated in the study.The participants completed brief psychiatric rating scale and brief resilience scale, while their informants completed everyday cognition questionnaire in baseline (pre-treatment) and post-Lacosamide treatment testing sessions. Patients with epilepsy had cognitive deficits, psychiatric symptoms, and lesser resilience in contrast with healthy individuals. Lacosamide treatment improved everyday cognition, reduced psychiatric symptoms and improved resilience in patients with epilepsy. Lacosamide is efficacious in the treatment of everyday cognitive impairment, psychiatric symptoms and resilience in patients with epilepsy.

Keywords: Cognition; Epilepsy; Lacosamide; Psychiatric symptoms; Antiepileptic drugs.

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Epilepsy is the most common neurological disorder affecting 50 million people around the world.Of these, 80 percent are living in middle and low income countries. In Pakistan, over two million people have been affected by epilepsy which is around five percent of the total population living with epilepsy in the world.[1,2] The disorder is characterised by recurrent seizures with partial or generalised onset, neurocognitive deficits and emotional problems.[1-4] Lacosamide is a recommended drug in Pakistan to treat seizures of partial onset.[5] It exerts neuroprotective effects through reducing hyperexcitation of neuronal membranes and altering axonal length, polarity and number.[6] Unlike other antiepileptic drugs, Lacosamide has no negative effects on cognition, mood and quality of life in patients affected by refractory epilepsy.[7] Apart from clinical trials, similar results have been observed in naturalistic out-patient settings with objective and subjective ratings of long-term cognitions, mood and quality of life.[8] Favourable effects of Lacosamide on cognition and neuropsychological functioning has been observed in healthy adults.[9] Recent research has demonstrated that three months of Lacosamide treatment improved cognitive functioning in patients of focal epilepsy with uncontrolled seizures.[10] Epilepsy is comorbid with several psychological disorders and deficient resilience which reduce quality of life.[11] Lacosamide reduces symptoms of anxiety and depression in patients with epilepsy,[12] but its efficacy in other psychological symptoms and resilience is not clear. Resilience is the ability to adapt in response to stress.[13] It is correlated with mental health, well-being and life satisfaction.[14] This study was designed to assess effectiveness of Lacosamide on everyday cognition, psychiatric symptoms, and resilience in patients affected by epilepsy. The hypothesis of this study was that Lacosamide would be efficacious in reducing everyday cognition deficits and psychiatric symptoms in epileptic patients. Further, Lacosamide would be helpful in improving resilience in patients with epilepsy.The rationale of this study was to compare cognitive functioning, psychiatric symptomology and resilience between epileptic patients and healthy individuals. Another objective was to assess the efficacy of Lacosamide to reduce cognitive deficits, psychiatric symptoms and resilience in epileptic patients.

Methods and Results

Approval of the study was received from The Islamia University of Bahawalpur, Pakistan. The study had a test-retest prospective design. Thirty-six patients with diagnosis of refractory partial onset epilepsy participated at Sheikh Zayed Hospital, Rahim Yar Khan; NishterHospital;Multan and Bahawal Victoria Hospital;Bahawalpur, Pakistan, during November 2017 until May 2018. The inclusion criteria was: (i) age range between 50 to 75 years, (ii) must have suffered at least two seizures every month during the last six months at the time of diagnosis, (iii) diagnosed with refractory partial onset epilepsy, (iv) prescribed Lacosamide100-400 mg/day for at least three months and were excluded if they had complaints relating to substance use, psychological or neurological disorder and were on

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any medication or antiepileptic drugs other than Lacosamide, (v) educated informants. Thirty-six healthy counterparts were included in the study with ages between 50 and 75; those who reported symptoms of psychological or physiological disorder and use of medication were excluded. Patients reported occasional feelings of nausea, dizziness, somnolence, and headache during the treatment period.Purposive sampling technique was used. The sample size was calculated with anticipated effect size f^2= 0.15, desired statistical power level= 0.8, number of predictors=3, probability level=0.05, minimum required sample size=76.[15] Four patients were excluded from the final sample due to the use of other medication during the course of the study. The psychologist who conducted testing sessions and participants were blinded to the objectives of the study.

Everyday cognitive questionnaire[16]

Everyday cognitive questionnaire16 was used to assess cognitive functioning, planning, attention and memory of patients through 39 items rated on 4 point response option with low score showing better cognitive functioning. The questionnaire has good test-retest reliability, external and convergent validity with other measures of cognition.

Brief psychiatric rating scale[17]

Psychiatric symptoms were assessed through Brief psychiatric rating scale.[17] Severity of 24 psychiatric symptoms can be assessed on this scale which has high inter-rater reliability.

Brief resilience scale[18]

The ability to recover from stress was judged on Brief resilience scale.[18] The scale has six items which are responded on 1=strongly disagree to 5=strongly agree. It has good psychometric properties and provides information of coping with health-related stressors. In a pilot study, test-retest reliability was computed with a gap of eight weeks on sample of the current study which showed that the scale was reliable for Pakistani population (patients r = .75, p<.001; healthy individuals r = .63, p<.001).

Procedure

After giving written informed consent, informants of participants completed everyday cognitive questionnaire, while participants completed brief psychiatric rating scale and brief resilience scale in baseline testing session and three months after Lacosamide treatment testing session. Informants of patients were asked about the number of seizures during the last three months at baseline and post-treatment session.

Demographic and clinical information was analysed through descriptive statistics. Patients and healthy individuals were compared on subscales of everyday cognition questionnaire using multivariate test with dependent factors (everyday memory vs language vs visuospatial abilities vs planning vs organisation vs divided attention) x subject groups (patients vs healthy individuals: fixed factor).

Psychiatric symptoms were compared between patients and control group through multivariate test with dependent factors (somatic concern vs anxiety vs depression vs suicidality vs guilt vs hostility vs elevated mood vs grandiosity vs suspiciousness vs hallucinations vs unusual thought content vs bizarre behaviour vs self-neglect vs disorientation vs conceptualisation vs blunted effect vs emotional withdrawal vs motor retardation vs tension vs uncooperativeness vs excitement vs distractibility vs motor hyperactivity vs mannerism and posturing) x subject groups (patients vs healthy individuals: fixed factor).

Group differences were assessed for scores on brief resilience scale with univariate ANOVA with resilience as dependent and group as fixed factor.

Repeated measures analysis of variance was computed to analyse pre-treatment and post-treatment differences on scores of each subscale of everyday cognition questionnaire with treatment (pre vs post)as within subject factor. To assess treatment effects (baseline vs post treatment; within subject) on each psychiatric symptom, repeated measures ANOVAs were conducted. Resilience was assessed with repeated measures ANOVA with treatment (baseline vs post treatment) as within subject factor.

Comparison of performance between patients (baseline) and healthy individuals

Performance of patients and healthy individuals on subscales of everyday cognition questionnaire was compared, which showed that patients had deteriorated everyday memory in contrast with healthy individuals F(1, 70)=1399.76, p<.001, ηp2= 0.95(30.00±2.00 vs. 10.80 ± 2.33), language F (1, 70) =623.31, p<.001, ηp2= 0.89 (29.69 ± 2.91 vs. 12.75 ± 2.84), visuospatial F (1, 70) =693.83, p<.001, ηp2= 0.90 (24.75 ± 2.47 vs. 10.44 ± 2.11), planning F (1, 70) =566.36, p<.001, ηp2= .89 (17.94 ± 1.81 vs. 7.86 ± 1.77), organisation F (1, 70) =2267.37, p<.001, ηp2= 0.97 (22.69 ± 1.09 vs. 9.19 ± 1.30), divided attention F (1, 70) =701.72, p<.001, ηp2= .90 (14.86 ± 1.74 vs. 5.75 ± 1.10).

Psychiatric symptoms were compared between patients and healthy individuals on Brief psychiatric rating scale which showed that patients had somatic concern F (1, 70) = 252.19, p<0.001, ηp2= 0.78, anxiety F (1, 70) = 1800.21,

Table-1: Demographic data of patients with epilepsy and healthy individuals.

	Patients with epilepsy (n=36) M ean± SD	Healthy individuals (n=36) Mean ± SD	
Age (50-75 years)	64.14 ± 7.65	64.19 ± 7.80	t (35) =.01, p=.98
Education (10-16 years)	12.19±1.63	12.11±1.78	t (35) =.20, p=.98
Education of informants (10-16 years)	13.50±1.93	13.38±1.84	t (35) =.27, p=.78
	n	n	
Gender (male: female)	18:18	18:18	
Socioeconomic class			
Low	10		
Middle	15		
High	11		
Type of epilepsy			
Frontal lobe	17		
Temporal lobe	19		

p<0.001, ηp2= .96, depression F (1, 70) = 1714.42, p<.001, ηp2= 0.96, suicidality F (1, 70) = 1771.87, p<0.001, ηp2= 0.96, guilt F (1, 70) = 1705.31, p<0.001, ηp2= 0.96, hostility F (1, 70) = 708.26, p<0.001, ηp2= 0.91, elevated mood F (1, 70) = 1772.23, p<0.001, ηp2= 0.96, grandiosity F (1, 70) = 760.13, p<0.001, ηp2= 0.91, suspiciousness F (1, 70) = 631.95, p<0.001, ηp2= 0.90, hallucinations F (1, 70) = 655.57, p<0.001, ηp2= 0.90, unusual thought content F (1, 70) = 611.52, p<0.001, ηp2= 0.89, bizarre behaviour F (1, 70) = 637.87, p<0.001, ηp2= 0.90, self-neglect F (1, 70) = 233.82, p<0.001, ηp2= 0.77, discontinuation F (1, 70) = 694.68, p<0.001, ηp2= 0.90, conceptualisation F (1, 70) = 229.89, p<0.001, ηp2= 0.76, blunted affect F (1, 70) = 271.83, p<0.001, ηp2= 0.79, emotional withdrawal F (1, 70) = 263.60, p<0.001, ηp2= 0.79, motor retardation F (1, 70) = 271.58, p<0.001, ηp2= 0.79, tension F (1, 70) = 231.63, p<0.001, ηp2= 0.76, uncooperativeness F (1, 70) = 248.33, p<0.001, ηp2= 0.78, excitement F (1, 70) = 149.64, p<0.001, ηp2= 0.68, distractibility F (1, 70) = 214.41, p<0.001, ηp2= 0.75, motor hyperactivity F (1, 70) = 86.57, p<.001, ηp2= .55, mannerism and posturing F (1, 70) = 223.70, p<0.001, ηp2= 0.76 in contrast with healthy individuals.

Similarly, performance on Brief resilience scale was compared between patients and healthy individuals which showed that resilience was lesser in patients as compared with healthy individuals F (1, 70) = 78.47, p<0.001, ηp2= 0.52 (Table 2).

Comparison of baseline (pre-treatment) and post-treatment scores of patients with epilepsy

Post-treatment scores of patients showed significant improvement on everyday memory F (1, 35) = 119.96, p<0.001, ηp2= 0.77, language F (1, 35) = 199.53, p<0.001,

Table-2: Mean scores of epileptic patients and healthy controls on everyday cognition questionnaire, brief psychiatric rating scale and brief resilience scale.

	Patients with epilepsy[a] (n=36)		Healthy individuals (n=36)	
	Mean±SD	95% CI[b]	Mean±SD	95% CI[b]
Every day memory	30.00±2.00	29.27-30.72	10.80±2.33	10.08-11.52
Language	29.69±2.91	28.73-30.65	12.75±2.84	11.79-13.70
Visuospatial	24.75±2.47	23.98-25.51	10.44±2.11	9.67-11.21
Planning	17.94±1.81	17.34-18.54	7.86±1.77	7.26-8.45
Organisation	22.69±1.09	22.29-23.09	9.19±1.30	8.79-9.59
Divided attention	14.86±1.74	14.37-15.34	5.75±1.10	5.26-6.23
Somatic concern	3.50 ± 0.50	3.33-3.66	1.63 ± 0.48	1.47-1.80
Anxiety	6.50 ± 0.50	6.33-6.66	1.44 ± 0.50	1.27-1.61
Depression	6.33 ± 0.47	6.17-6.41	1.52 ± 0.50	1.36-1.69
Suicidality	6.55 ± 0.50	6.38-6.72	1.55 ± 0.50	1.38-1.72
Guilt	6.44 ± 0.50	6.27-6.61	1.52 ± 0.50	1.36-1.68
Hostility	4.52 ± 0.50	4.36-4.69	138 ± 0.49	1.22-1.55
Elevated mood	6.50 ± 0.50	6.33-6.66	1.47 ± 0.50	1.30-1.64
Grandiosity	5.77 ± 0.76	5.56-5.99	1.61 ± 0.49	1.39-1.82
Suspiciousness	4.47 ± 0.50	4.30-4.64	1.47 ± 0.50	1.30-1.64
Hallucinations	4.52 ± 0.50	4.35-4.69	1.46 ± 0.50	1.30-1.64
Unusual thought content	4.38 ± 0.49	4.22-4.55	1.45 ± 0.50	1.30-1.63
Bizarre behaviour	4.55 ± 0.50	4.38-4.72	1.55 ± 0.50	1.38-1.72
Self-neglect	3.69 ± 0.70	3.48-3.89	1.47 ± 0.50	1.26-1.67
Disorientation	4.61 ± 0.08	4.44-4.77	1.50 ± 0.50	1.33-1.66
Conceptualization	4.02 ± 0.77	3.80-4.25	1.63 ± 0.54	1.41-1.86
Blunted affect	3.80 ± 0.66	3.60-4.00	1.50 ± 0.50	1.30-1.69
Emotional withdrawal	3.69 ± 0.74	3.48-3.90	1.30 ± 0.46	1.09-1.51
Motor retardation	3.91 ± 0.73	3.70-4.12	1.47 ± 0.50	1.26-1.68
Tension	3.72 ± 0.70	3.51-3.92	1.52 ± 0.50	1.32-1.73
Uncooperativeness	3.58 ± 0.69	3.38-3.78	1.36 ± 0.48	1.16-1.50
Excitement	3.30 ± 0.70	3.10-3.51	1.52 ± 0.50	1.32-1.73
Distractibility	3.75 ± 0.76	3.53-3.96	1.50 ± 0.50	1.28-1.71
Motor hyperactivity	3.02 ± 0.84	1.79-3.25	1.50 ± 0.40	1.26-1.73
Mannerism & posturing	3.77 ± 0.76	3.56-3.99	1.49 ± 0.50	1.28-1.71
Resilience	1.44 ± 0.50	1.27-1.61	2.50 ± 0.50	2.33-2.66

[a]Baseline scores; [b]Confidence interval lower bound-upper bound.

ηp2= 0.85,visuospatial F (1, 35) = 193.58, p<0.001, ηp2= 0.84, planning F (1, 35) = 346.94, p<0.001, ηp2= 0.90,organisation F (1, 35) = 479.59, p<0.001, ηp2= 0.93, and divided attention F (1, 35) = 398.58, p<0.001, ηp2= 0.91 compared with baseline scores. Post-treatment scores showed significant reduction in somatic concern F (1, 35) = 445.78, p<0.001, ηp2= 0.92, anxiety F (1, 35) = 209.15, p<0.001, ηp2= 0.85, depression F (1, 35) = 331.63, p<0.001, ηp2= 0.90, suicidality F (1, 35) = 258.42, p<0.001, ηp2= 0.88, guilt F (1, 35) = 232.87, p<0.001, ηp2= 0.86, hostility F (1, 35) = 343.00, p<0.001, ηp2= 0.90, elevated mood F (1, 35) = 360.00, p<0.001, ηp2= 0.91, grandiosity F (1, 35) = 65.89, p<0.001, ηp2= 0.65, suspiciousness F (1, 35) = 267.68,

Table-3: Mean treatment scores of epileptic patients (n=36)on everyday cognition questionnaire, brief psychiatric rating scale and brief resilience scale.

	Pre-treatment[a]		Post-treatment	
	Mean ± SD	95% CI[b]	Mean ± SD	95% CI[b]
Every day memory	30.00 ± 2.00	29.27-30.72	24.69 ± 2.43	23.87-25.51
Language	29.69 ± 2.91	28.73-30.65	21.55 ± 2.38	20.74-22.36
Visuospatial	24.75 ± 2.47	23.98-25.51	17.80 ± 1.84	17.18-18.43
Planning	17.94 ±1.81	17.34-18.54	12.41 ± 1.15	12.02-12.80
Organisation	22.69 ± 1.09	22.29-23.09	16.19 ± 2.05	15.50-16.88
Divided attention	14.86 ± 1.74	14.37-15.34	9.44 ± 0.50	9.27-9.61
Somatic concern	3.50 ± 0.50	3.33-3.66	5.94 ± 0.82	5.66-6.22
Anxiety	6.50 ± 0.50	6.33-6.66	4.69 ± 0.46	4.53-4.85
Depression	6.33 ± 0.47	6.17-6.41	4.44 ± 0.50	4.27-4.61
Suicidality	6.55 ± 0.50	6.38-6.72	4.41 ± 0.50	4.24-4.58
Guilt	6.44 ± 0.50	6.27-6.61	4.63 ± 0.48	4.47-4.80
Hostility	4.52 ± 0.50	4.36-4.69	6.47 ± 0.50	6.30-6.64
Elevated mood	6.50 ± 0.50	6.33-6.66	4.50 ± 0.50	4.32-4.67
Grandiosity	5.77 ± 0.76	5.56-5.99	4.49 ± 0.50	4.32-4.67
Suspiciousness	4.47 ± 0.50	4.30-4.64	6.52 ± 0.50	6.35-6.69
Hallucinations	4.52 ± 0.50	4.35-4.69	6.58 ± 0.50	6.41-6.75
Unusual thought content	4.38 ± 0.49	4.22-4.55	6.50 ± 0.50	6.31-6.67
Bizarre behaviour	4.55 ± 0.50	4.38-4.72	6.51 ± 0.50	6.32-6.67
Self-neglect	3.69 ± 0.70	3.48-3.89	5.94 ± 0.75	5.68-6.20
Disorientation	4.61 ± 0.08	4.44-4.77	6.00 ± 0.12	5.75-6.24
Conceptualization	4.02 ± 0.77	3.80-4.25	6.27 ± 0.70	6.04-6.51
Blunted affect	3.80 ± 0.66	3.60-4.00	6.19 ± 0.70	5.95-6.43
Emotional withdrawal	3.69 ± 0.74	3.48-3.90	6.11 ± 0.78	5.84-6.37
Motor retardation	3.91 ± 0.73	3.70-4.12	5.91 ± 0.80	5.64-6.18
Tension	3.72 ± 0.70	3.51-3.92	5.88 ± 0.82	5.61-6.16
Uncooperativeness	3.58 ± 0.69	3.38-3.78	6.02 ± 0.81	5.75-6.30
Excitement	3.30 ± 0.70	3.10-3.51	5.86 ± 0.86	5.56-6.15
Distractibility	3.75 ± 0.76	3.53-3.96	5.88 ± 0.82	5.61-6.16
Motor hyperactivity	3.02 ± 0.84	1.79-3.25	6.33 ± 0.67	6.10-6.56
Mannerism & posturing	3.77 ± 0.76	3.56-3.99	5.80 ± 0.82	5.52-6.08
Resilience	1.44 ± 0.50	1.27-1.61	3.61 ± 0.49	3.44-3.77

[a]Baseline scores; [b]Confidence interval lower bound-upper bound.

p<0.001, ηp2= 0.88, hallucinations F (1, 35) = 243.22, p<0.001, ηp2= 0.87, unusual thought F (1, 35) = 287.15, p<0.001, ηp2= 0.89, bizarre behaviour F (1, 35) = 299.82, p<0.001, ηp2= 0.89, self-neglect F (1, 35) = 238.45, p<0.001, ηp2= .87, disorientation F (1, 35) = 98.98, p<0.001, ηp2= 0.73, conceptualisation F (1, 35) = 307.41, p<0.001, ηp2= 0.89, blunted affect F (1, 35) = 142.23, p<0.001, ηp2= 0.80, emotional with drawal F (1, 35) = 145.00, p<0.001, ηp2= 0.80, motor retardation F (1, 35) = 132.63, p<0.001, ηp2= 0.79, tension F (1, 35) = 115.98, p<0.001, ηp2= 0.76, uncooperativeness F (1, 35) = 260.61, p<0.001, ηp2= 0.88, excitement F (1, 35) = 211.60, p<0.001, ηp2= 0.85, distractibility F (1, 35) = 79.72, p<0.001, ηp2= 0.69, motor hyperactivity F (1, 35) = 498.12, p<0.001, ηp2= 0.93, mannerism & posturing F (1, 35) = 157.13, p<0.001, ηp2= 0.81 compared with pre-treatment scores.Resilience improved after treatment among patients F (1, 35) = 134.61, p<0.001, ηp2= .79. (See Table 3 for mean scores)

Discussion

The objective of this study was to compare everyday cognition, psychiatric symptoms and resilience between epileptic patients and healthy controls. Moreover, the objective was to assess the effectiveness of Lacosamide in the treatment of cognitive deficits, psychiatric symptoms and resilience in patients with epilepsy. It was found that patients with epilepsy had impaired everyday cognition in contrast with healthy individuals. There were higher psychiatric symptoms and lesser resilience in contrast with their healthy counterparts. Patients showed psychiatric symptoms of anxiety, depression, suicidality, guilt, hostility, elevated mood, grandiosity, suspiciousness, hallucination, unusual thought, bizarre behaviour, self-neglect, disorientation, conceptualisation, blunted affect, emotional withdrawal, motor retardation, tension, uncooperativeness, excitement, distractibility, motor hyperactivity, mannerism and posturing. Resilience is the ability to recover from illness and overcome adverse circumstances of one's life.[19] Resilient individuals have better coping skills and are more likely to deal successfully with challenging situations.[20] Results of the present study show that Lacosamide treatment was beneficial for improving resilience in patients with epilepsy. It was also found that psychiatric symptoms and cognitive deficits were reduced post-Lacosamide treatment in epileptic patients. These findings are consistent with previous literature showing that Lacosamide is efficacious in treating psychiatric disorders associated with epilepsy. For instance, in a study with epileptic patients, anxiety and depression were reduced without psychotropic medication when Lacosamide was given solely as an add-on therapy it rather improved the quality of life.[21] A previous study with rodents also demonstrated that apart from being an antiepileptic drug, Lacosamide has anxiolytic properties.[22] Further studies have demonstrated positive effects of Lacosamide treatment on cognition.[9,10] Lacosamide has high oral bioavailability, neuroprotective effects, and potential efficacy for central nervous system-related disorders such as schizophrenia and anxiety.[23] Animal studies show that Lacosamide improved memory in Alzheimer's disease through reducing the level of histone deacetylase inhibitor in cerebral cortex.[24] Long-term use of lacosamide improved executive functioning and memory as observed in naturalistic outpatient setting.[25] Though few studies have shown that Lacosamide has no side effects related to cognition, mood stability and quality of life,[8,9] this study for the first time examined efficacy of Lacosamide on everyday

cognition, psychiatric status and resilience in epileptic patients. This study had few limitations such as randomised, placebo and blinded study design could have yielded more reliable results. Another limitation was the short sample size.Therefore,results should be considered as preliminary evidence.

Conclusion

Results of this study suggest that Lacosamide is effective in reducing cognitive deficits, psychiatric symptoms and improving resilience in patients with refractory partial epilepsy.

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