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Authors
Brown, E Sherwood
Sayed, Nasreen
Choi, Changho
et al.

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A randomized, double-blind, placebo-controlled trial of lamotrigine for prescription corticosteroid effects on the human hippocampus

E. Sherwood Brown[a,*], **Nasreen Sayed**[a], **Changho Choi**[c], **Nicholas Tustison**[d], **Jared Roberts**[d,1], **Michael A. Yassa**[d], **Erin Van Enkevort**[a], **Alyson Nakamura**[a], **Elena I. Ivleva**[a], **Prabha Sunderajan**[a], **David A. Khan**[b], **Miguel Vazquez**[b], **Bruce McEwen**[e], **Alexandra Kulikova**[a], **Alan B. Frol**[a], **Traci Holmes**[a]

[a]Department of Psychiatry, The University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas 75390-8849, TX, United States

[b]Department of Internal Medicine, The University of Texas Southwestern Medical Center, Dallas, TX, United States

[c]Department of the Advanced Imaging Research Center, The University of Texas Southwestern Medical Center, Dallas, TX, United States

[d]Department of Neurobiology and Behavior, Center for the Neurobiology of Learning and Memory, University of California, Irvine, United States

[e]The Harold and Margaret Milliken Hatch Laboratory of Neuroendocrinology, Rockefeller University, United States

Abstract

In animals, stress and corticosteroid excess are associated with decreases in memory performance and hippocampal volume that may be prevented with agents that decrease glutamate release. Humans also demonstrate changes in memory and hippocampus with corticosteroids. In this report the effects of glutamate-release inhibitor lamotrigine on hippocampal structure and memory were examined in people receiving medically needed prescription corticosteroid therapy. A total of 54 outpatient adults (n = 28 women) receiving chronic (≥ 6 months) oral corticosteroid therapy were randomized to lamotrigine or placebo for 48 weeks. Declarative memory was assessed using the Rey Auditory Verbal Learning Test (RAVLT); structural magnetic resonance imaging (MRI) as well as single-voxel proton MR spectroscopy (^{1}HMRS) focused on hippocampus were obtained at baseline and week 48. Utilizing a mixed-model approach, structural and biochemical data were examined by separate ANOVAs, and memory was assessed with a multi-level longitudinal model. RAVLT total scores demonstrated significantly better declarative memory performance with lamotrigine than placebo (p = 0.047). Hippocampal subfield volumes were not significantly

*Corresponding author. Sherwood.Brown@UTSouthwestern.edu (E.S. Brown).

[1]Deceased.

Contributors

E. Sherwood Brown designed the study and wrote the protocol. All other authors have provided equal contributions to participant assessment, literature searches and analyses, statistical analysis, and manuscript writing. All authors contributed to and have approved the final manuscript.

different between the treatment groups. In summary, lamotrigine was associated with less decline in declarative memory performance than placebo in corticosteroid-treated patients. Findings suggest that, in humans as well as in animal models, glutamate release inhibitors may attenuate some of the effects on the human memory associated with corticosteroids.

Keywords

Hippocampus; Memory; Corticosteroid; Prednisone; Magnetic resonance imaging

1. Introduction

Preclinical literature suggests that stress or corticosteroid administration is associated with poorer memory performance, as well as epigenetic changes in the hippocampus (Ewald et al., 2014) and reduction in hippocampal dendritic length and number (Magarinos et al., 1997; Vyas et al., 2002) that appear to be most pronounced in the CA3 region (McEwen, 2016). In animal models, glutamate plays an essential role along with glucocorticoids in stress induced remodeling of hippocampal neurons as well as stress- and glucocorticoid-related neurotoxicity (Popoli et al., 2012); and the glutamate release inhibitor, phenytoin, blocks the effects of exogenous corticosteroids on the hippocampus (Magarinos et al., 1996). A much smaller human literature also suggest that chronic (Bender et al., 1988; Brown et al., 2006; Starkman et al., 1992) corticosteroid exposure is associated with a reduction in declarative memory performance, and decreased hippocampal volume (Brown et al., 2004). Hippocampal volume reduction and decreased declarative memory performance in humans exposed to corticosteroids appear to be attenuated by pretreatment with phenytoin (Brown et al., 2013; 2015). Like phenytoin (Mariotti et al., 2010), lamotrigine is an anti-seizure medication that inhibits glutamate release (Deng et al., 2013), at least in part, through modulation of high voltage activated calcium currents (Wang et al., 2001) and sodium channels (Sitges et al., 2007). A small pilot study in humans suggest that lamotrigine therapy may improve declarative memory in medically ill corticosteroid-treated patients (Brown et al., 2008). The current report examines the effects of 48 weeks of lamotrigine or placebo add-on therapy on memory and other cognitive domains, as well as hippocampal biochemistry as assessed with magnetic resonance spectroscopy, and hippocampal subfield volumes in patients with medical illnesses receiving chronic prescription corticosteroid therapy throughout the study. The hypothesis was that lamotrigine would, at least partially, reverse the effects of corticosteroids on memory and the hippocampus in humans. The aims were to determine if lamotrigine add-on therapy was associated with an increase, or less decline, in declarative memory, hippocampal biochemistry and hippocampal subfield volumes, relative to placebo in patients receiving prescription corticosteroids.

2. Experimental procedures

Medically stable outpatients receiving chronic oral corticosteroid therapy were enrolled in a 48-week randomized, double-blind, placebo-controlled, parallel-group, trial of lamotrigine between 5/13/2010 and 4/23/2015 (NCT01142310). Participants provided UT Southwestern IRB-approved written informed consent and were primarily recruited from Parkland

Memorial Hospital and UT Southwestern outpatient clinics. Baseline assessments included a structured clinical interview for DSM-IV (SCID-CV), Rey Auditory Verbal Learning Test (RAVLT) (declarative memory, primary outcome measure); and structural MRI and ^{1}HMRS. The RAVLT consists of 15 nouns read aloud for five consecutive trials followed by a free-recall trial (Schmidt, 1996). RAVLT was selected based on prior research demonstrating its sensitivity to the memory effects of corticosteroids (Brown et al., 2003; 2006; 2008;2015).

Lamotrigine or identical appearing placebo (purchased from Abrams Royal Compounding Pharmacy, Dallas, TX) was initiated at 25 mg/day and titrated to 400 mg/day over 10 weeks using a fixed dosing schedule unless side effects required slower titration or dose reduction. Dose was selected based on previous pilot work (Brown et al., 2003; 2008) and is on the upper end of lamotrigine doses used in mood disorders (Bowden et al., 2003). Medication dose adjustment was managed in a double-blind fashion whereby the physician decreased the dose based on participant report, but was not given information about whether the change was with lamotrigine or placebo. RAVLT was repeated at 12-week intervals using alternative, equivalent versions to minimize learning effects from repeated administration. Neuroimaging was repeated at the end of the study (week 48).

Included were men and women age 18-70 years with physician diagnosis of a chronic medical condition requiring treatment with oral corticosteroids of ≥ 5 mg of prednisone equivalents for ≥ 6 months with anticipated treatment for ≥ 15 additional months. Dose and duration were selected to approximate the lower end at which systemic side effects and adrenal suppression might be expected (Hoes et al., 2007). Excluded were persons with illnesses associated with central nervous system involvement (e.g., multiple sclerosis, seizures, head injury with loss of consciousness of > 30 min) or cognitive impairment (e.g., lifetime substance dependence, schizophrenia, mood disorders) that appeared to be unrelated to corticosteroid use. Participants with systemic lupus erythematosus were allowed if they did not have, based on medical history, SCID results (e.g. meeting DSM-IV criteria for “due to a general medical condition”) and discussion with treating physician, significant central nervous system involvement. Also excluded were vulnerable populations (e.g., intellectual disability, dementia, pregnant or nursing women), those deemed unlikely to attend follow-up appointments, people with severe or life-threatening medical illness that would make completion of study unlikely, contraindications to lamotrigine therapy (severe side effects in the past, taking medications with drug-drug interactions with lamotrigine), high risk or danger to self or others as defined by more than one lifetime suicide attempt or assault, any suicide attempt or assault within the past year, and active suicidal or homicidal ideation that includes a plan and intent, therapy with medications that alter the metabolism of lamotrigine, metal implants, claustrophobia, or other contraindications to MRI or a baseline RAVLT total T score of ≥ 60 (consistent with high memory function and little potential for improvement).

2.1. MR methods

Neuroimaging was performed on a whole-body horizontal bore Philips 3T scanner (Philips Medical Systems; Best, The Netherlands) at the Advanced Imaging Research Center, UT Southwestern Medical Center. The scanner had an integrated body coil for radio-frequency (RF) transmission and an 8-channel phased-array coil for signal reception. Following a

survey scan, sagittal T_1-weighted images of the brain (MP-RAGE: TE/TI/TR = 3.8/875/1360 ms, 256 × 256 × 160 mm^3 field of view, 160 slices, voxel size 1 × 1 × 1 mm^3). MP-RAGE images were subsequently used for hippocampal voxel positioning for MRS (Fig. 1), as well as hippocampal subfield segmentation.

MRS data were acquired using a point-resolved spectroscopy (PRESS) sequence with echo time of 112 ms (TE1 = 32 ms and TE2 = 80 ms), designed for separation of glutamate and glutamine signals between 2.3 and 2.5 ppm. Volume localization was obtained with a 9.8-ms 90° RF pulse and a 13.2-ms 180 ° RF pulse (bandwidths of 4.3 and 1.3 kHz respectively). Following an MP-RAGE imaging scan, a voxel of 40 × 13 × 13 mm^3 (6.8 mL) was positioned along the long axis of the right and left hippocampus, which was the region of interest based on our hypothesis regarding the effects of corticosteroids on the hippocampus and the effect of lamotrigine on declarative memory in our pilot study (Brown et al., 2008). Prior research effectively utilized voxel sizes of similar or larger size for hippocampal MRS data collection (Kroll et al., 2018; Stan et al., 2015). MRS acquisition parameters included TR = 2 s, sweep width = 2.5 kHz, number of sampling points = 2048, and number of signal averages = 256. Water suppression was obtained with a vendor-supplied four-pulse variable-flip-angle sub-sequence. First and second order shimming was carried out, using the fast automatic shimming technique by mapping along projections (FASTMAP) (Gruetter, 1993).

Spectral fitting was performed with LCModel software (Provencher, 1993). Metabolites, including creatine (Cr), NAA, choline (Cho = total choline; glycerophosphocholine (GPC) + phosphocholine (PCho) + free Cho), glutamate (Glu) (primary ^{1}HMRS outcome), and glutamine (Gln) were obtained. Basis spectra were numerically calculated incorporating the slice-selective RF and gradient pulses (Choi et al., 2012). Spectral fitting was conducted between 0.5 and 4.1 ppm. Metabolites were quantified using Cr as an internal reference.

2.2. Structural MRI volumetric analysis

Hippocampal subfield segmentation was performed using a consensus labeling approach based on a set of 19 T2-weighted images acquired with an optimized hippocampus-specific acquisition protocol (image resolution: 0.47 × 0.47 mm^2 in-plane, 2.0 mm slice thickness) from cognitively normal subjects that were manually labeled using a highly reliable anatomical protocol used in prior published work for hippocampal subfields (Yassa et al., 2011; Yassa and Stark, 2011). Anatomical labeling of the atlas set comprises separate labels for right and left dentate gyrus (DG)/CA3, CA1, and subiculum. Scans were coupled with corresponding T1-weighted images (image resolution: 0.75 × 0.75 × 0.75 mm^3) which were acquired for multi-spectral atlas-based registration. To propagate a weighted consensus labeling from the expertly labeled atlas set to the unlabeled T1-weighted images of our study cohort, we spatially normalized the atlas set to the unlabeled subject and applied the joint label fusion technique. Advanced Normalization Tools (ANTs) package was used for both spatial normalization (Avants et al., 2011) and consensus-based labeling (i.e., joint label fusion) (Wang et al., 2013). First, the intra-subject atlas T1/T2 rigid transforms were calculated. To minimize total number of deformable registrations, a “pseudo-geodesic” approach to align the data was used (Tustison and Avants, 2013). This required construction of an optimal T1-weighted template (Avants et al., 2010) representing

the average shape/intensity information of the T1 component of the atlas set. Deformable transformations between each T1-weighted image of the study cohort and the T1 atlas template were calculated. Transformation between the atlas labels and unlabeled study cohort image was then computed by concatenating the $T1_{atlas}/T2_{atlas}$ rigid transformation, the $T1_{atlas}$ /T1 template deformable transformation, and the T1 template/and $T1_{subject}$ deformable transforms. Once the atlas set was normalized to the unlabeled subject, regional labeling was determined using weighted averaging where the weighting takes into account the unique intensity information contributed by each atlas member. After visual quality assessment to confirm the output of the labeling procedures, voxels within the labeled regions were counted and multiplied by the voxel resolution to calculate volumes in cubic millimeters.

2.3. Statistical analysis

The sample size was based on the effect size observed in a pilot data with $d = 0.35$. The trial was randomized by the study statistician without participant contact using a random number generator. Hierarchical linear modeling (HLM) was used to analyze the longitudinal data because it allows modeling of both within- and between-individual variations and can include individuals who only have data for a single occasion (e.g., only at week 12) (Maxwell and Delaney, 2004). Individual data are weighted by number of data points and the reliability of their regression. At level-1 time points were nested under each participant (weeks 12, 24, 36, 48). At level-2, treatment and baseline RAVLT scores were included in the model as between-participant variables. We also considered controlling for corticosteroid dose and duration, but they were not significant covariates, and were removed from the model. Time and treatment were added to the model uncentered because they were coded with a zero-value (0 = placebo, 0 = week 12) and baseline RAVLT scores were grand mean centered. Variance and covariance components in HLM are estimated through maximum likelihood procedures (Raudenbush and Bryk, 2002). The treatment by time interaction indicated the treatment influence on participants' change over the course of the study.

Structural MRI and ^{1}HMRS data, collected at baseline and week 48, were analyzed using a mixed model ANOVA. Treatment was included in the model as a between-subjects variable, time (baseline and week 48) were included as a within-subject variable, and the interaction between treatment and time was included to examine the influence of treatment on hippocampal volume at week 48.

3. Results

3.1. Baseline characteristics

A total of 54 participants were randomized and received lamotrigine or placebo. In the lamotrigine group, $n = 6$ were lost to follow-up, $n = 2$ discontinued due to symptoms of their medical illness and $n = 1$ due to study drug side effects. In the placebo group, $n = 4$ were lost to follow-up, $n = 3$ discontinued due to symptoms of their medical illness, $n = 2$ due to study drug side effects, $n = 1$ due to treatment non-adherence, $n = 1$ changed their mind about study participation and $n = 1$ died for reasons unrelated to study participation, resulting in a completer sample of 33 ($n = 17$ lamotrigine, $n = 16$ placebo). The intent-to-

treat sample ($n = 38$, $n = 17$ lamotrigine, $n = 21$ placebo) included participants with post-baseline (week 12 or later) RAVLT data. Baseline characteristics of participants receiving lamotrigine and placebo with at least one post-baseline assessment (intent-to-treat sample) are provided in Table 1. The categorical variables were compared using the chi-square test, while the continuous variables were compared using the independent samples *t*-test. The two groups were similar in age, sex, race, mean prednisone therapy duration, premorbid intelligence estimates, and medical conditions; however, the lamotrigine group, on average, was receiving a higher prednisone dose.

3.2. Declarative memory findings

Of the 54 participants, 38 had at least one post-baseline (week 12) visit and were included in the clinical trial data analysis (intent-to-treat sample). RAVLT total scores (primary outcome measure) demonstrated a significant interaction between treatment group and time [b = 0.096 (SE = 0.048), t(70) = 2.017, $p = 0.047$]. Although both groups showed decreasing RAVLT scores over time, the lamotrigine group decreased less than the placebo group and had higher scores at week 48 (Fig. 2). Specifically, at week 48, the lamotrigine group had average RAVLT t-scores that were 5 point higher than the average of those given placebo, which is equivalent to the effect size of approximately half of a standard deviation higher.

3.3. Spectroscopy findings

With ^{1}HMRS, there was a significant treatment by time interaction on the Cho/Cr ratio in the left hippocampus [F(1,26) = 4.893, $p = 0.036$]. The Cho/Cr ratio in the placebo group significantly decreased from baseline to week 48 [F(1,26) = 5.612, $p = 0.026$], whereas in the lamotrigine group it did not. At week 48, the Cho/Cr ratio was marginally higher with lamotrigine [F(1,26) = 4.083, $p = 0.054$] (Table 3). No other within- or between-group differences in biochemistry outcomes were found.

3.4. Structural MRI findings

Structural MRI analyses examined three hippocampal subfields: DG/CA3, CA1, and subiculum (Table 2). None of the subfields showed a statistically significant between-group difference in volume.

3.5. Adherence, safety and tolerability

The side effects were obtained via self-report and the overall number of reported side effects was not significantly different between groups ($p = 0.50$). In the Lamotrigine group, the most common side effects were headache (35%), diarrhea (29%), nausea (29%), vomiting (18%), dizziness (12%), and rash (12%). A total of 73.1% reported greater than 80% study adherence by pill counts with lamotrigine as compared to 57.1% with placebo ($\chi^2(1) = 1.50$, $p = 0.22$).

4. Discussion

Lamotrigine was associated with a reduction in amount of decline in declarative memory over 48-weeks as compared to placebo in patients receiving chronic prednisone therapy. As illustrated in Fig. 1, a smaller decline in declarative memory performance was observed

over 48 weeks in the lamotrigine group than in the placebo group. This finding suggests that lamotrigine attenuates the effects of corticosteroids on memory, and is consistent with literature in animal models suggesting that agents that decrease glutamate release block the effects of stress or corticosteroids on the hippocampus.

The mechanism by which lamotrigine was associated with attenuation of the effects of corticosteroids on memory in the present study is not clear. Since corticosteroids are known to lead to dendritic shortening, one possibility is that lamotrigine is reversing this process. For example, lamotrigine reportedly increases hippocampal dendritic outgrowth in cell cultures (Park et al., 2015).

None of the examined hippocampal subfields demonstrated a statistically significant difference in volume with lamotrigine as compared to placebo. Thus, at least in the timeframe of a 48-week observation period, the difference between the lamotrigine and placebo groups in the clinical domain of declarative memory was not accompanied by a change in hippocampal subfield volume. These observations are similar to those in our pilot study in which lamotrigine or placebo were administered at the same dose as in this report for 24 weeks in 28 prednisone-treated patients. The findings are also consistent with other research in people receiving chronic exogenous corticosteroids (Coluccia et al., 2008) or with Cushing's Disease (Resmini et al., 2012) that suggest that memory may be a more sensitive marker of the effects of corticosteroids on the hippocampus than volume.

The implications of the declarative memory findings are as follows. First, lamotrigine may potentially be a useful medication to attenuate the effects of prescription corticosteroids on declarative memory. If the findings generalize to people with elevated levels of the endogenous corticosteroid cortisol, then this medication might be useful in people with Cushing's disease and to a subset of people with mood disorders who have elevated cortisol levels. Second, this report replicated our previously reported pilot study, suggesting that lamotrigine attenuates the effects of corticosteroids on declarative memory (Brown et al., 2008).

The study has several limitations. The sample size was relatively modest. The clinical population used was very complex with chronic and severe medical illnesses. The vast majority of the participants were receiving corticosteroids to prevent kidney transplant rejection in some cases secondary to Systemic Lupus Erythematosus (SLE). However, the proportion of the sample with SLE and with renal transplants were similar in the two treatment groups. Prednisone dose and duration also varied among the participants, but these variables were controlled for in the analysis and the two treatment groups were generally demographically similar. Nonetheless, the reduction in decline in memory could be due to neuroprotective mechanisms other than simply attenuation of corticosteroid-induced glutamate release by lamotrigine. The analysis focused only on declarative memory, which is related to the hippocampus. At 48 weeks, the duration of treatment was long for a randomized, placebo-controlled clinical trial, but perhaps relatively short for a study examining reversibility of changes in the hippocampus due to corticosteroids. A longer study might have demonstrated larger between-group differences. The response of the medical illness to prednisone might influence the findings. While no formal

assessment of prednisone response was included in the study, most participants were renal transplant patients who were medically quite stable, suggesting a good response to the immunosuppressive regimen. The participants had low mean levels of depression. This is likely both a strength and limitation of the study. The low levels of depression minimize the potential confounding or additive effects of depression on the hippocampus. On the other hand, the low levels of depression preclude a meaningful analysis of the effects of lamotrigine on depressive symptoms. Other strengths of the study were the translational nature and the potential clinical applications. The findings suggest that medications, such as lamotrigine, that reduce glutamate release may be able to reverse the effects of prescription corticosteroids on declarative memory. Thus, the findings have significance in that they both translate preclinical research to humans and suggest potential clinical treatments for people with corticosteroid-excess.

To summarize, in the largest study to date exploring a medication to block the effects of corticosteroids on the human brain, lamotrigine administration was associated with a reduction in decline on a declarative memory task. These findings suggest attenuation of the effects of corticosteroids on the human hippocampus with this medication.

Conflict of Interest

Dr. Brown has ongoing funding from NIAAA, NIA, NHLBI, Stanley Medical Research Institute, and Otsuka Pharmaceutical. Dr. Ivleva has ongoing support from NIMH. Dr. Yassa is supported by NIMH R01MH102392 and NIA R01AG053555. All other authors have no conflicts to declare.

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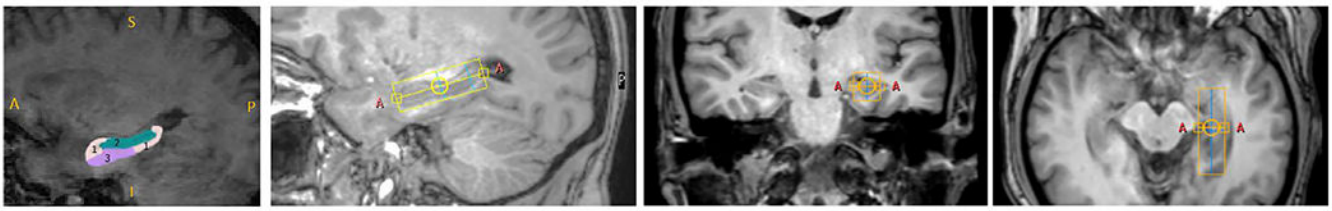

Fig. 1.

MRS voxel placement and structural MRI image from the hippocampus of a participant on lamotrigine.

From left to right: structural MRI of hippocampal subfields, saggital view (1 - left CA1, 2 - left DG/CA3, 3 - left subiculum); saggital, coronal, and horizontal views demonstrate placements of the MRS voxel of interest in hippocampus.

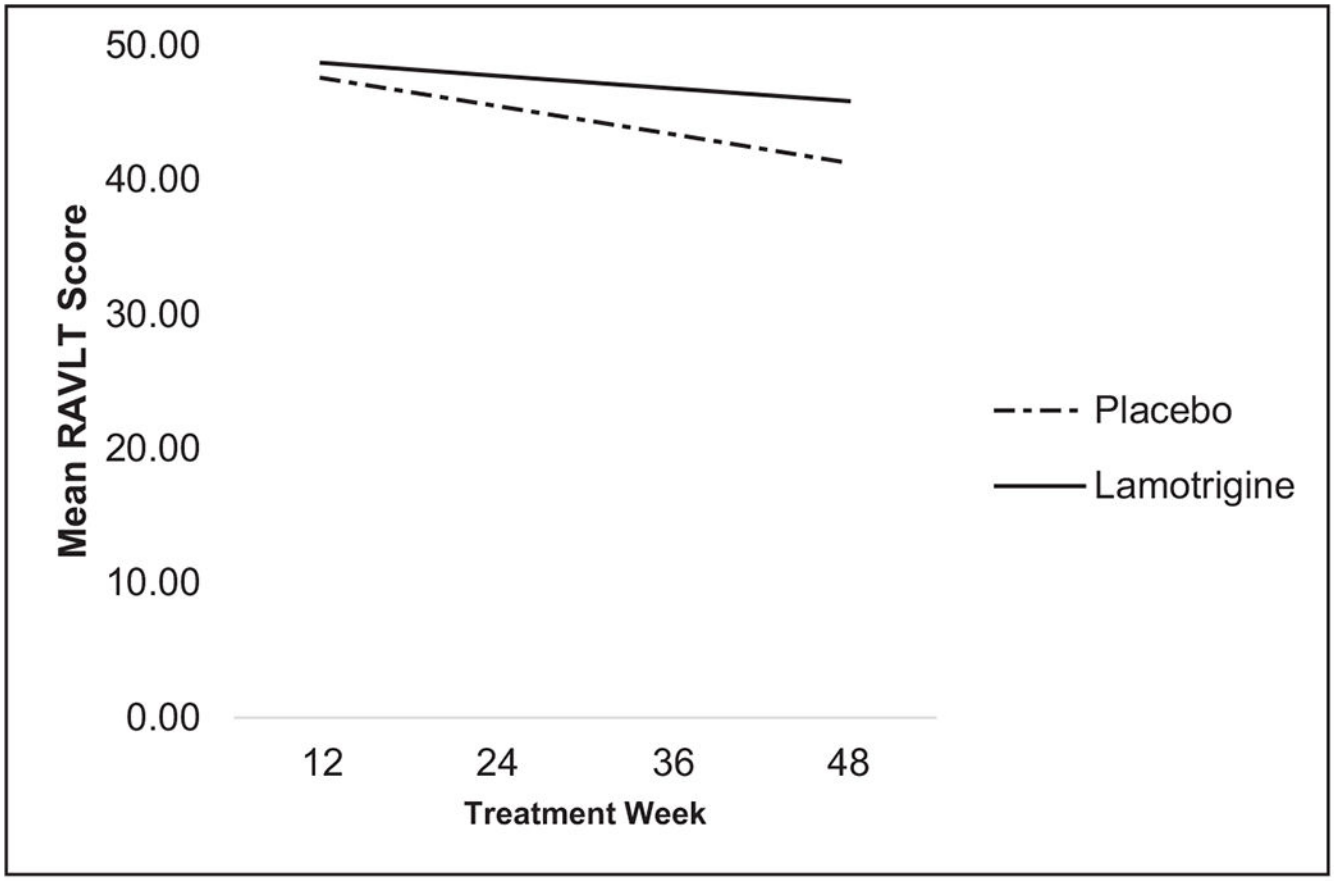

Fig. 2.
Change in mean RAVLT scores in the lamotrigine and placebo groups. RAVLT - Rey Auditory Verbal Learning Test.

Table 1

Baseline characteristics of the study participants intent-to-treat sample.

Characteristics	Treatment group			
	Placebo		Lamotrigine	
	Mean	SD	Mean	SD
Age	44.05	9.77	43.58	11.90
Prednisone dose (mg)	5.76	1.79	9.34	7.06
Prednisone duration (years)	5.18	5.52	4.63	4.10
QIDS-SR baseline	4.57	3.26	4.21	2.92
	N	%	N	%
Sex				
Male	11	52.4	10	52.6
Female	10	47.6	9	47.4
Ethnicity				
Caucasian	3	14.3	3	15.8
African American	12	57.1	10	52.6
Hispanic	5	23.8	4	21.1
Other	1	4.8	2	10.5
Diagnosis at baseline				
Kidney transplant	18	85.7	14	73.7
SLE	5	9.0	6	11.0
Other	3	14.3	5	26.3

Note: QIDS-SR - Quick Inventory of Depressive Symptomatology Self-Report; SLE - Systemic Lupus Erythematosus.

Table 2

Mean hippocampal subfield volume (mm^3) at Baseline and Week 48 in lamotrigine and placebo groups.

Hippocampal subfield			Baseline		Week 48		Effect size Cohen's *d*
			Mean	SD	Mean	SD	
DG/CA3	Left	Placebo	645.68	93.92	647.69	85.78	0.022
		Lamotrigine	594.23	98.38	569.00	123.01	0.231
	Right	Placebo	708.00	101.66	725.31	100.95	0.171
		Lamotrigine	644.59	122.72	660.00	127.50	0.124
CA1	Left	Placebo	1615.19	238.06	1618.12	236.26	0.012
		Lamotrigine	1587.00	203.00	1575.06	218.92	0.057
	Right	Placebo	1656.25	242.06	1658.56	224.15	0.010
		Lamotrigine	1570.76	170.39	1599.18	172.31	0.166
SUB	Left	Placebo	755.62	136.65	738.00	138.38	0.128
		Lamotrigine	752.53	164.66	783.12	109.56	0.212
	Right	Placebo	765.75	119.72	753.75	121.55	0.100
		Lamotrigine	734.18	117.70	699.18	124.42	0.290

Note: DG - Dentate gyrus; CA - Cornu ammonis; SUB - Subiculum.

Table 3

[1]HMRS-based metabolites at baseline and week 48 in the lamotrigine and placebo groups.

Metabolite			Baseline		Week 48		Effect size Cohen's *d*
			Mean	SD	Mean	SD	
Glu/Cr	Left	Placebo	0.89	0.13	0.84	0.10	0.420
		Lamotrigine	0.86	0.11	0.86	0.13	0.000
	Right	Placebo	0.92	0.15	0.94	0.12	0.144
		Lamotrigine	0.92	0.13	0.98	0.20	0.369
Gln/Cr	Left	Placebo	0.56	0.17	0.44	0.20	0.658
		Lamotrigine	0.50	0.16	0.56	0.22	0.321
	Right	Placebo	0.60	0.23	0.57	0.22	0.133
		Lamotrigine	0.47	0.18	0.59	0.26	0.554
NAA/Cr	Left	Placebo	1.36	0.12	1.30	0.16	0.437
		Lamotrigine	1.31	0.18	1.28	0.17	0.170
	Right	Placebo	1.38	0.20	1.35	0.17	0.159
		Lamotrigine	1.38	0.23	1.35	0.18	0.142
Cho/Cr	Left	Placebo	0.20	0.02	0.18	0.02	1.000
		Lamotrigine	0.19	0.03	0.22	0.08	0.534
	Right	Placebo	0.20	0.02	0.20	0.02	0.000
		Lamotrigine	0.19	0.02	0.20	0.02	0.500

Note: [1]HMRS - proton magnetic resonance spectroscopy; Glu - glutamate; Cr - creatine; Gln - glutamine; NAA - N-acetylaspartate; Cho - choline.