Attenuation of the Effects of Corticosteroids on Declarative Memory with Lamotrigine

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An extensive animal literature suggests that excessive corticosteroid exposure is associated with changes in memory and the hippocampus. Agents that decrease glutamate attenuate corticosteroid effects on the hippocampus. Minimal data are available on preventing or reversing corticosteroid effects on the human hippocampus. We previously reported that open-label lamotrigine was associated with significant improvement in declarative memory in corticosteroid-treated patients. We now examine the impact of 24 weeks of randomized, placebo-controlled lamotrigine therapy on declarative memory (primary aim) and hippocampal volume (secondary aim) in 28 patients ($n = 16$ for lamotrigine, $n = 12$ for placebo) taking prescription corticosteroids. All participants with data from at least one postbaseline assessment ($n = 9$ for lamotrigine, $n = 11$ for placebo) were included in the analysis. Declarative memory was assessed with the Rey Auditory Verbal Learning Test (RAVLT) at baseline and weeks 12 and 24. Hippocampal and total brain volumes were manually traced from MRI scans obtained at baseline and week 24. On the basis of an ANCOVA analysis, total words learned on the RAVLT at exit were significantly greater in the lamotrigine group ($n = 8$, missing data or dropouts $n = 8$) compared to the placebo group ($n = 11$, dropout $n = 1$). RAVLT scores in the lamotrigine group increased from mildly impaired to average range. Hippocampal volume changes were small in both lamotrigine ($n = 7$) and placebo ($n = 7$) groups during the 24-week assessment period and between-group differences were not significant. Results suggest that lamotrigine may improve declarative memory in patients taking prescription corticosteroids although differential dropout rate in the two groups is a concern.
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INTRODUCTION

An extensive literature suggests that stress or excessive corticosteroid exposure is associated with changes in memory and hippocampal structure in animals (Magariños *et al*, 1997; Vyas *et al*, 2002; Uno *et al*, 1989, 1994; Sapolsky *et al*, 1990; Lupien and McEwen, 1997). Leverenz *et al* (1999) did not find overall between-group differences in total hippocampal or subfield volumes, neuronal number, or density in older macaques given oral hydrocortisone for 12 months. However, they found a strong negative correlation between cerebrospinal fluid (CSF) cortisol levels and hippocampal volume ($r = 0.83$, $p \leqslant 0.05$) (Leverenz *et al*, 2003). In animals, agents that decrease glutamate release or enhance serotonin reuptake attenuate the effects of corticosteroids on the hippocampus (Magariños and McEwen, 1995; Magariños *et al*, 1996, 1999; Luine *et al*, 1994; Conrad *et al*, 1996; Watanabe *et al*, 1992). Examining

the effects of corticosteroids on the human hippocampus is challenging since humans cannot ethically be administered corticosteroids for extended periods of time. Therefore, a much smaller human literature on the effects of corticosteroids on the hippocampus is available. Acute administration of exogenous corticosteroids in humans is associated with decline in declarative memory performance (Newcomer *et al*, 1999; de Quervain *et al*, 2000; Brown *et al*, 2006; Bender *et al*, 1988). Patients with Cushing's disease, and cortisol elevations secondary to ACTH-producing pituitary tumors, have memory impairment (Mauri *et al*, 1993; Starkman and Schteingart, 1981) and hippocampal atrophy (Starkman *et al*, 1992) that are at least partially reversible a mean of 17 months after surgery to normalize cortisol levels (Starkman *et al*, 1999, 2003).

We reported that patients receiving long-term corticosteroid therapy had significantly poorer declarative memory performance, lower temporal lobe levels of *N*-acetyl aspartate (NAA), and smaller hippocampal volumes than controls with similar medical histories not taking corticosteroids (Brown *et al*, 2004). However, another report did not find a reduction in NAA levels in patients taking corticosteroids (Khiat *et al*, 2001), and no changes in hippocampal volume (Hajek *et al*, 2006) or post-mortem

histology (Lucassen *et al*, 2001) were found during corticosteroid exposure that was of much shorter duration than in our report (Brown *et al*, 2004).

We previously reported significant improvement in declarative memory in corticosteroid-treated patients given open-label lamotrigine (Brown *et al*, 2003), an antiseizure and mood-stabilizing medication that inhibits glutamate release through modulation of high voltage-activated calcium currents (Stefani *et al*, 1997; Pisani *et al*, 2004; Wang *et al*, 2001) and sodium channels (Stefani *et al*, 1997; Rogawski and Loscher, 2004; Sitges *et al*, 2007; Remy *et al*, 2003). In this report we examined the impact of 24 weeks of randomized, double-blind, placebo-controlled treatment with lamotrigine on declarative memory in patients receiving prescription corticosteroids as the primary aim. A secondary aim was to examine whether between-group differences in hippocampal volume could be detected following 24 weeks of lamotrigine therapy.

METHODS

Participants and Study Medication

A total of 28 medically stable outpatients receiving chronic oral corticosteroid therapy participated in a 24-week randomized, double-blind, placebo-controlled trial of lamotrigine. The enrollment period was from August 2002 through March 2005 with the final week-24 assessment in October 2005. Participants were enrolled from clinics in the UT Southwestern Medical Center that treat patients with chronic oral corticosteroid therapy. Assessments and interventions were conducted at the Psychoneuroendocrine Research Program clinic at UT Southwestern. Inclusion criteria were age of 18–65 years and corticosteroid therapy of at least 7.5 mg of prednisone equivalents daily for at least 6 months. Exclusion criteria were drug or alcohol abuse or dependence, illnesses associated with hippocampal atrophy or with significant CNS involvement (seizures, closed head injury with loss of consciousness, brain tumors, multiple sclerosis), history of a depressive disorder not related to corticosteroid therapy, bipolar disorder, schizophrenia, or posttraumatic stress disorder on a structured clinical interview, mental retardation, dementia or other severe cognitive impairment, pregnant or nursing women, severe or life-threatening medical illness which would make completion of study unlikely, history of allergic reaction or other contraindications to MRI, or lamotrigine therapy. All participants signed an IRB-approved informed consent form. Randomization to treatment group was accomplished using a random number generator at www.randomizer.org by a staff member with no patient contact. Lamotrigine or identical appearing placebo was initiated at 25 mg per day for 2 weeks, increased to 50 mg per day for 2 weeks, and then increased in 50 mg per day increments weekly to a dose of 400 mg per day at week 10 using a fixed dosing schedule unless side effects required a slower titration or dose reduction. To minimize any possibility of rater bias, dose reductions or slower titrations were made by the study physician in a blinded fashion after the research assistant had collected research data for that assessment. The study was registered at clinicaltrials.gov.

Diagnostic and Declarative Memory Assessment

A structured clinical interview for DSM-IV (SCID-CV) (First *et al*, 1995) was administered at baseline to assess past and current psychiatric diagnoses that were exclusionary. The Rey Auditory Verbal Learning Test (RAVLT) (Schmidt, 1996) was administered at baseline and weeks 12 and 24 follow-up, by a blinded staff member, with extensive training and experience to assess declarative memory, using alternate versions (administered in a randomized order) to minimize practice or learning effects. The RAVLT consists of 15 nouns read aloud for five consecutive trials with each trial followed by a free-recall trial. The total score is the total number of words recalled through the five trials. Normative RAVLT *T*-scores controlling for age are reported.

MRI and Procedures

Structural and functional magnetic resonance (MR) images of the brain were obtained at baseline and week 24 follow-up visits. MR images were acquired on a General Electric Horizon LX NV/i 1.5 Tesla scanner (General Electric Medical Systems, Milwaukee, WI) using the standard GE quadrature birdcage RF head coil. To avoid large head motions, each subject's head was immobilized with tightly fitting foam padding and a head strap that was fastened across the forehead. High-resolution T1 images of the entire brain (3D Spoiled Grass (SPGR) pulse sequence: TR = 40 ms; TE = 5 ms; flip angle = 40°; matrix = 256 × 256; FOV = 24; PFOV = 0.75, NEX = 1; slice thickness = 1.7 mm) were acquired during the same scan session for each participant.

Structural MRI Volumetric Analysis

Anatomical measurements were conducted by two trained and reliable raters and were supervised by one of the authors (MUS), who, following training at Dr MS Keshavan's laboratory at the University of Pittsburgh, has conducted structural imaging analysis at the University of Pittsburgh and UT Southwestern since 2000 (Shad *et al*, 2004, 2006). BRAINS2 software (Magnotta *et al*, 2002) was used to conduct the measurements. Both raters were blind to participant identity, study group assignment, and clinical data. The scans were analyzed in pairs (baseline, week 24) for each participant with the rater unaware of the order. Inter-rater reliabilities (intraclass correlations; $n = 10$) were 0.92 for total brain volume (TBV), 0.91 for right hippocampus, and 0.94 for left hippocampus.

The hippocampus was defined as follows: the superior boundary of the hippocampus is formed by the inferior horn of the lateral ventricle, the inferior boundary by the white matter of the parahippocampal gyrus, the lateral border by the white matter of the temporal stem, and the medial border by the interpeduncular cistern of the white matter. Since it is difficult to differentiate between amygdala and hippocampus complex (Shenton *et al*, 2001, 2002), we used the method described by Keshavan *et al* (2002) which uses the anterior wall of mammillary bodies as the first slice and slice no. 78 (or the slice where the superior and inferior colliculi are fused) as the last slice to measure the hippocampus.

All planes were used to trace the hippocampus with most tracing done in the coronal plane because it had the best resolution. Sagittal and axial planes were used as references (Cook *et al*, 1992; Duvernoy 1999, 2005). Tracing began at the tail of the hippocampus and proceeded rostrally in the coronal plane. The caudal-most extent of the tail of the hippocampus is located where the end of the fornix column is at its greatest length, where it abuts the structure. In this slice, the subsplenial gyrus should be visible immediately superior to the hippocampal formation. The parahippocampal gyrus should be visible immediately inferior to it (Cook *et al*, 1992). Moving anteriorly, the thalamus separates the hippocampal formation from the fornix, and replaces the subsplenial cortex as the structure immediately superior to it. The alveus, a thin lining of white matter, borders the hippocampal formation dorsally and separates it from the hippocampal fissure.

A few slices before the head of the hippocampus come into view, the choroid plexus becomes visible and is superior to the alveus. Moving closer to the head of the hippocampus, the uncal gyrus replaces the choroid plexus as the structure immediately superior to the alveus. Paging rostrally in the coronal plane, the uncal gyrus thickens and blends in with the amygdala. Paging through the coronal slices rostrally, as the head of the hippocampus comes more into view, the amygdala becomes bigger. While tracing the hippocampal head, the alveus continued to be the critical structure that effectively differentiated the hippocampus from the amygdala.

Total brain volume, defined as brain, dura, ventricular and extraventricular CSF, brainstem, and cerebellum, was assessed by manual tracing of coronal slices along the inner border of the inner table of the skull (Gilbert *et al*, 2001).

All hippocampal volumes were adjusted for TBV by using the formula right or left hippocampal volume/TBV $\times$ 100. TBV was measured using protocol described by Gilbert *et al* (2001), which includes combined volume of the cerebral hemispheres, cerebellum, and the brainstem.

Statistical Analyses

In our open-label pilot study a baseline-to-exit change of 10.0 ± 7.8 on the RAVLT was observed (Brown *et al*, 2003). On the basis of these data, a significant level of $p = 0.05$, and assuming the same standard deviation as with lamotrigine but no mean change in the placebo group, a sample of 10 per group would provide 80% power and 13 per group 90% power to detect between-group differences in a randomized, controlled trial. Thus, the current study ($n = 28$) was adequately powered for the primary aim.

For the RAVLT (primary aim) a one-way ANCOVA, using baseline RAVLT scores, current corticosteroid dose, duration of corticosteroid therapy, and years of education as covariates and gender as a fixed factor, was conducted to compare total scores between groups at exit on the intent-to-treat sample (those with week 12 or week 24 assessments). For hippocampal volume/TBV ratio (secondary aim) a one-way ANCOVA, using baseline hippocampal volume, current prednisone dose, duration of corticosteroid therapy, and years of education as covariates, and gender as a fixed factor was conducted to assess exit left and right

hippocampal volume/TBV between groups in those with exit MRI data (week 24). Based on the Kolmogorov–Smirnov test, the data were normally distributed.

Correlations between baseline and baseline-to-exit change in RAVLT scores and hippocampal volume and age, current corticosteroid dose, duration of corticosteroid therapy, and level of education were explored using Pearson's correlation coefficient.

RESULTS

A total of 28 participants were randomized ($n = 16$ lamotrigine and $n = 12$ placebo) with 20 participants ($n = 9$ lamotrigine and $n = 11$ placebo) returning for at least one postbaseline RAVLT assessment (week 12 and/or 24) (intent-to-treat sample). One participant had missing RAVLT data leaving 19 participants ($n = 8$ lamotrigine and $n = 11$ placebo) in the sample used for the analysis. Data at the week 24 assessment (end of study) were available on 18 participants ($n = 8$ lamotrigine and $n = 10$ placebo). Early dropouts and the intent-to-treat sample were similar at baseline, with the exception of percentage of men and left hippocampal volumes that showed trends toward between-group differences (Table 1). The lamotrigine and placebo groups were similar on demographic and other baseline characteristics (Table 2). Concomitant medications were numerous in both early dropouts and those who returned for at least one postbaseline assessment (Table 1), and consisted of immunosuppressants (7 (88%) *vs* 16 (80%)), antihypertensives (6 (75%) *vs* 16 (80%)), antacids (6 (75%) *vs* 18 (90%)), analgesics (1 (13%) *vs* 8(40%)), antidepressants (3 (38%) *vs* 4 (20%)), vitamin/mineral supplements (4 (50%) *vs* 13 (65%)), sedative/hypnotic/anxiolytics (1 (13%) *vs* 1 (5%)), antipsychotics (for sleep and other adjunctive therapy, not psychosis) (1 (13%) *vs* 1 (5%)), muscle relaxants (1 (13%) *vs* 2 (10%)), anticonvulsants (not prescribed for seizures) (0 (0%) *vs* 1 (5%)), antiemetics (1 (13%) *vs* 0 (0%)), xanthine oxidase inhibitors (1 (13%) *vs* 1 (5%)), statins (2 (25%) *vs* 5 (25%)), antimicrobials (2 (25%) *vs* 5 (25%)), antihyperglycemics (4 (50%), *vs* 2 (10%)), antihistamines (1 (13%) *vs* 3 (15%)), estrogen supplementation (0 (0%) *vs* 1 (5%)), carbonic anhydrase inhibitor (0 (0%) *vs* 1 (5%)), and erectile dysfunction medication (0 (0%) *vs* 1 (5%)). Concomitant medications in the treatment groups (lamotrigine *vs* placebo) in the intent-to-treat sample were also similar in number (Table 2) and consisted of immunosuppressants (7 (78%) *vs* 9 (82%)), antihypertensives (8 (89%) *vs* 10 (91%)), antacids (5 (56%) *vs* 3 (27%)), analgesics (4 (44%) *vs* 4 (36%)), vitamins/mineral supplementation (5 (56%) *vs* 8 (73%)), antidepressants (3 (33%) *vs* 1 (9%)), muscle relaxant (2 (22%) *vs* 0 (9%)), sedative/hypnotic/anxiolytic (1 (11%) *vs* 0 (0%)), statins (1 (11%) *vs* 4 (36%)), antihyperglycemic (0 (0%) *vs* 2 (18%)), antihistamines (1 (11%) *vs* 2 (18%)), estrogen supplementation (0 (0%) *vs* 1 (9%)), antipsychotic (1 (11%) *vs* 0 (0%)), xanthine oxidase inhibitor (0 (0%) *vs* 1 (9%)), anticonvulsant (1 (11%) *vs* (0 (0%)), estrogen supplementation (0 (0%) *vs* 1 (9%)), antimicrobial (2 (22%) *vs* 3 (27%)), carbonic anhydrase inhibitor (0 (0%) *vs* 1 (9%)), and erectile dysfunction medication (1 (11%) *vs* 0 (0%)). Changes in concomitant medications defined as any

Table 1 Demographic Information for Those with a Week 12 or Week 24 Assessment (N = 20) and Early Dropouts (N = 8)

Treatment group	Study survival to at least week 12 (N = 20)	Discontinuation prior to week 12 (N = 8)	p-value
Mean age (SD, range)	46.1 (12.1, 24–64)	46.1 (5.6, 37–53)	0.994
Males, N (%)	15 (75.0)	3 (37.5)	0.061
Ethnicity, N (%)			0.118
Caucasian	11 (55.0)	1 (12.5)	
African-American	6 (30.0)	4 (50.0)	
Hispanic	2 (10.0)	3 (37.5)	
Other	1 (5.0)	0 (0.0)	
Education, N (%)			0.463
High school, graduation, or less	7 (35.0)	4 (50.0)	
Some college or more	13 (65.0)	4 (50.0)	
Medical condition requiring prednisone, N (%)			0.864
Renal transplant	17 (85.0)	7 (87.5)	
Rheumatic disease	3 (15.0)	1 (12.5)	
Current prednisone dose (mg per day)	13.8 (10.0)	14.3 (8.2)	0.901
Duration of prednisone therapy (months)	63.0 (73.4)	88.6 (77.1)	0.418
RAVLT total *T*-score	38.2 (12.3)	36.4 (13.2)	0.732
Hippocampal volume/TBV × 100			
Left	0.1734 (0.01882)	0.1906 (0.01436)	0.057
Right	0.1795 (0.02242)	0.1929 (0.02125)	0.219
Concomitant medications			
Number of medications/patient	5.75 (2.25)	5.0 (2.29)	0.442

Abbreviations: RAVLT, Rey Auditory Verbal Learning Test; SD, standard deviation; TBV, total brain volume

addition, discontinuation or change in dose or frequency were similar in the two groups (Table 2).

The mean baseline dose of corticosteroids was numerically, but not statistically significantly, higher in the lamotrigine group (Table 2). Exit corticosteroid dose (16.7 ± 16.7 mg per day for lamotrigine *vs* 9.4 ± 3.8 mg per day for placebo) was not significantly different between groups ($p = 0.175$). The baseline-to-exit difference in corticosteroid dose was also not significant (based on paired *t*-tests) in the lamotrigine ($p = 0.563$) or placebo ($p = 0.186$) groups. The mean exit dose of lamotrigine was 388.9 ± 22.0 mg per day in the group receiving active medication and the equivalent of 377.3 ± 51.8 mg per day (based on number of pills dispensed) in the placebo group ($p = 0.512$).

Participants discontinued before week 24 for the following reasons: gastrointestinal symptoms, present before the study, that participants felt became worse (week 2), rash that resolved, problems with recent hair transplant and ear infection (week 12), lack of child care (week 10), dizziness (week 2), worsening of gout symptoms, participant felt study procedures were too time consuming and she was already taking too much medication (week 6), itching around mouth and shoulders (week 4), work schedule conflicts (week 2), chest pain in participant with history of

coronary artery disease (week 2) (lamotrigine group); no side effects at last assessment but participant did not return to clinic or return phone calls (week 8), dizziness, tremor, and poor coordination (week 16) (placebo group).

Scores on the RAVLT total words learned in trials 1–5 were in the mildly impaired range in both groups at baseline. In these 20 participants ($n = 8$ lamotrigine, $n = 11$ placebo, and $n = 1$ missing data) with baseline and at least one postbaseline visit, the exit RAVLT scores were significantly higher ($p = 0.028$) in the lamotrigine group as compared to the placebo group (Table 3).

Postbaseline structural MRI data were available for 14 participants ($n = 7$ lamotrigine and $n = 7$ placebo). Data at week 24 were not available for 14 participants due to study discontinuation prior to week 24 ($n = 10$), or claustrophobic reaction due to MRI scanner environment, body habitus too large for the scanner, or excessive motion during imaging ($n = 4$). Hippocampal volumes did not differ significantly between groups (Table 4).

Baseline scores on the RAVLT ($n = 27$) correlated significantly with amount of education ($r = 0.633$, $p < 0.001$). Baseline left and right hippocampal volume/ TBV ratios ($n = 22$) correlated significantly with each other ($r = 0.705$, $p < 0.001$). In the lamotrigine group, baseline-to-exit (week 24) change in left hippocampal volume/TBV ratio

($n = 7$) correlated negatively with duration of corticosteroid therapy ($r = -0.868$, $p = 0.011$), and change in right hippocampal volume/TBV ratio correlated negatively with age ($r = -0.773$, $p = 0.042$). Change in RAVLT ($n = 8$) also correlated negatively with age ($r = -0.750$, $p = 0.032$) in the lamotrigine group. In the placebo group, changes in left and right hippocampal volume/TBV ratios ($n = 7$) correlated with each other ($r = 0.954$, $p = 0.001$), and change in RAVLT ($n = 11$) correlated negatively with age ($r = -0.616$, $p = 0.044$).

Table 2 Demographic Information at Baseline for the Intent-To-Treat Sample ($N = 20$)

Treatment Group	Lamotrigine ($N = 9$)	Placebo ($N = 11$)	p-value
Mean age (SD, range)	44.6 (11.2, 25–62)	47.4 (13.3, 24–64)	0.620
Males, N (%)	7 (77.8)	8 (72.7)	0.795
Ethnicity, N (%)			0.404
Caucasian	6 (66.7)	5 (45.5)	
African-American	3 (33.3)	3 (27.3)	
Hispanic	0 (0)	2 (18.2)	
Other	0 (0)	1 (9.1)	
Education, N (%)			0.423
High school, graduation, or less	4 (44.4)	3 (27.3)	
Some college of more	5 (55.6)	8 (72.7)	
Medical condition requiring prednisone, N (%)			0.413
Renal transplant	7 (77.8)	10 (90.9)	
Rheumatic disease	2 (22.2)	1 (9.1)	
Current prednisone dose (mg per day)	18.4 (13.4)	10.1 (3.6)	0.103
Duration of prednisone therapy (months)	85.3 (97.9)	44.7 (41.7)	0.272
RAVLT total	37.0 (13.2)	39.1 (12.2)	0.726
Hippocampal volume/ TBV × 100			
Left	0.1662 (0.0142)	0.1748 (0.0122)	0.246
Right	0.1699 (0.0957)	0.1800 (0.0225)	0.297
Concomitant medications			
Number of medications/patient	5.11 (2.37)	4.91 (2.34)	0.851
Any change in a concomitant medication	5/9 (56%)	4/11 (36%)	0.391

Abbreviations: RAVLT, Rey Auditory Verbal Learning Test; SD, standard deviation; TBV, total brain volume.

DISCUSSION

The hippocampus is sensitive to the effects of corticosteroids. Unlike dexamethasone, which appears to penetrate the CNS rather slowly, prednisolone (De Kloet and McEwen, 1976), the active metabolite of prednisone, readily crosses the blood–brain barrier (Bannwarth *et al*, 1997). We previously reported improvement in declarative memory in patients receiving long-term corticosteroid therapy who were given open-label lamotrigine (Brown *et al*, 2003). Our current study attempted to replicate these findings using a randomized, double-blind, placebo-controlled design.

Baseline RAVLT scores were in the mildly impaired range in the patient sample. In the lamotrigine group, RAVLT scores increased to the average range while scores in the placebo group remained mildly impaired. Our data suggest that lamotrigine was associated with statistically significant improvement in declarative memory in patients receiving long-term corticosteroid therapy. The observed change in RAVLT scores with lamotrigine seems to confirm our previous findings. To our knowledge, data are not available relating to functional change with degree of change in the RAVLT. However, the categorical improvement, in the lamotrigine group, from the mildly impaired to average range suggests that the findings may be of clinical as well as statistical significance. Of note, the RAVLT mean actually decreased from baseline to week 12 but then increased by week 24 in the lamotrigine group. This decrease at week 12 appears to be due to one participant with a RAVLT *T*-score of 6 at week 12. The next lowest RAVLT score by any participant at any assessment was 20. If this participant is excluded the mean at week 12 for the lamotrigine group is 40.0 ± 8.6, which is slightly higher than the baseline mean.

Significant changes in hippocampal volume were not observed. The changes in hippocampal volume, not unexpectedly during the 24-week assessment period, were small in both groups. To our knowledge this is the first study that has looked at the impact of a medication on hippocampal volume in a group of patients exposed to high levels of corticosteroids. Prior studies have looked at

Table 3 Mean RAVLT Scores at Baseline, Week 12, Week 24 and Exit (Includes Subjects that Dropped Out Prior to Week 24) in Patients Receiving Corticosteroids and Given Lamotrigine or Placebo

Treatment Group	Baseline (Mean ± SD)	Week 12 (Mean ± SD)	Week 24 (Mean ± SD)	Exit[a] (Mean ± SD)
Lamotrigine	37.0 ± 13.2	35.8 ± 14.4	46.1 ± 15.0	45.3 ± 15.5
Placebo	39.1 ± 12.2	38.5 ± 10.8	40.1 ± 11.0	39.8 ± 10.5

[a]ANCOVA comparing the exit scores of the two groups (lamotrigine *vs* placebo), using baseline RAVLT scores, current corticosteroid dose, duration of corticosteroid therapy, and years of education as covariates and gender as a fixed factor, with *B* (difference in adjusted means) $= -10.63$, 95% confidence interval (based on difference in adjusted means) $= (-19.90, -1.35)$, d.f. $= 1$, F $= 6.13$, $p = 0.028$.

Table 4 Baseline and Exit Right and Left Hippocampal Volumes in Participants Receiving Corticosteroid Therapy Given Lamotrigine or Placebo

	Baseline		Week 24*	
	Lamotrigine (Mean ± SD)	Placebo (Mean ± SD)	Lamotrigine (Mean ± SD)	Placebo (Mean ± SD)
Right hippocampal/total brain volume × 100	0.1691 ± 0.0096	0.1800 ± 0.0225	0.1704 ± 0.0184 (+0.8% from baseline)	0.1798 ± 0.0202 (−0.1% from baseline)
Left hippocampal/total brain volume × 100	0.1662 ± 0.0142	0.1748 ± 0.0127	0.1654 ± 0.0163 (−0.5% from baseline)	0.1723 ± 0.0160 (−1.4% from baseline)

[a]ANCOVA comparing the exit scores of the two groups (lamotrigine *vs* placebo), baseline hippocampal volume, current prednisone dose, duration of corticosteroid therapy, and years of education as covariates, and gender as a fixed factor, with B (difference in adjusted means) = −0.00, 95% confidence interval (based on difference in adjusted means) = (0.00, 0.00), d.f. = 1, F = 0.036, *p* = 0.852.

cognitive and hippocampal volume changes in patients with Cushing's disease before and after treatment of the hypercortisolemia. Adults with Cushing's disease demonstrate improvement in some, but not all, cognitive domains following normalization of cortisol levels (Hook *et al*, 2007). An increase in hippocampal volume of approximately 3% is reported 17 months after surgical excision of the ACTH-secreting tumor in patients with Cushing's disease (Starkman *et al*, 1999, 2003). Some, but not all, neurocognitive assessments showed correlations with change in hippocampal volume in Cushing's disease patients (Starkman *et al*, 2003). In children with Cushing's disease, no changes in a declarative memory task were observed, and some other cognitive measures actually worsened 1 year following treatment (Merke *et al*, 2005). Hippocampal volume increased by about 5% in these patients at 1-year follow-up ($p = 0.08$). Our study may have failed to observe a significant change in hippocampal volume due to the observation period of only 24 weeks as compared to 12–17 months in the studies of patients with Cushing's disease.

The negative correlation between change in left hippocampal volume and duration of corticosteroid therapy in the lamotrigine group suggests that patients with longer corticosteroid exposure continued to show a decline in hippocampal volume. In the lamotrigine group, change in right hippocampal volume and change in RAVLT both correlated negatively with age. A similar negative relationship between age and change in RAVLT scores was observed in the placebo group. These findings suggest that older age is associated with further decline in RAVLT scores in both groups, and is consistent with literature suggesting greater sensitivity of the aging hippocampus to corticosteroid effects in animal models (Hassan *et al*, 1996). The correlational data from our study suggest that future research should target the use of lamotrigine in younger patients with relatively brief duration of corticosteroid therapy.

The study has several limitations. The sample size is modest which may increase the risk of Type I error for memory and Type II error for hippocampal volume. The assessment period of only 24 weeks or less is also a limitation. Changes in hippocampal volume may take a longer period of time to observe. The changes in memory might also increase more with longer treatment. The patient population is complex with serious medical illnesses, multiple concomitant medications, and differences in corticosteroid dose and duration. This limitation is inherent in human research on the long-term effects of corticosteroids. However, the two treatment groups were similar demographically and we controlled for potentially important patient characteristics (eg corticosteroid dose) in the data analysis. The study, while showing improvement in declarative memory, does not prove that the memory improvement was related to an interaction with the corticosteroids. In patients with seizures, lamotrigine appears to have a more benign effect on cognition than some other antiseizure medications (Pressler *et al*, 2006). In healthy controls (Aldenkamp *et al*, 2002) and in animal models (Shannon and Love, 2004) lamotrigine appears to be associated with no significant changes in cognitive performance. In patients with bipolar disorder, both improvement (Daban *et al*, 2006) and worsening of cognitive performance (Osuji *et al*, 2007, in press) have been reported with lamotrigine. A study in HIV-positive patients with cocaine use reported no change in RAVLT performance with lamotrigine (Margolin *et al*, 1998). Thus, while the effects of lamotrigine on memory may not be specific to patients taking corticosteroids, studies in other populations suggest neutral or mixed effects of lamotrigine on cognition. The differential dropout rate between treatment groups is a concern and could lead to bias if this is not a random occurrence. Early dropouts and the subjects used in the analysis (intent-to-treat sample) were similar demographically as were the two treatment groups. The higher discontinuation rate in the lamotrigine group may suggest poor tolerability using the dosing and titration schedule employed in this study. Thus, our findings are only generalizable to the subgroup of corticosteroid-treated patients who are able to remain on lamotrigine therapy for at least 12 weeks.

In summary, lamotrigine was associated with improvement in declarative memory potentially consistent with partial reversal of the effects of corticosteroids on hippocampal functioning. Additional research with a longer assessment period is needed to determine if declarative memory continues to improve with lamotrigine compared to placebo and whether differences in hippocampal volume are observed.

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DISCLOSURE/CONFLICTS OF INTEREST

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