Effect of Lamotrigine on Mood and Cognition in Patients Receiving Chronic Exogenous Corticosteroids

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Mood changes, cognitive deficits, and psychosis have been reported during corticosteroid therapy. However, minimal data are available on the treatment of these side effects. This pilot study examined the effect of 12 weeks of open-label lamotrigine treatment (dose: mean = 340 mg/day, SD = 65) on mood and cognition in five patients receiving prescription corticosteroids continuously for at least 6 months before study entry. The participants showed significant improvement in cognition with lamotrigine. Two subjects who met criteria for a current major depressive episode at baseline had baseline-to-exit reductions in scores on the Hamilton Depression Rating Scale of more than 20 points. These pilot data suggest that lamotrigine may be associated with improved mood and performance on cognitive tasks in steroid-treated patients. Larger controlled trials are needed to confirm these preliminary findings.

Corticosteroids are frequently prescribed for a variety of illnesses mediated by the immune system. Mood symptoms appear to be common with corticosteroid treatment and can include both mania and depression. In addition, the cognitive effects of corticosteroids are an area of much interest. Cognitive impairment is associated with even a few days of corticosteroid exposure. Deficits in declarative memory, measured by performance on word-list tests (e.g., the Rey Auditory Verbal Learning Test, the Wechsler Memory Scale paragraph recall), appear to be a particularly common cognitive side effect of corticosteroids. Declarative memory appears to be mediated by the hippocampus, a brain region with a high concentration of glucocorticoid receptors. Emerging data suggest that performance on measures of prefrontal cortex functioning (e.g., the Stroop color-word task) may also be impaired after exogenous corticosteroid exposure in humans and nonhuman primates and in persons with psychiatric illnesses associated with elevated cortisol levels, such as psychotic depression.

Despite the frequency of psychiatric symptoms with corticosteroids, minimal data are available on the treatment of these side effects. Available data suggest that mood stabilizers and antipsychotics may be useful for mood symptoms (for a review, see Brown et al. and Brown and Suppes). A case report has suggested that lamotrigine may be an effective prophylactic agent for steroid-induced mania. No human data are available on the pharmacotherapy of cognitive side effects of corticosteroids, to our knowledge. However, in animals, some agents, including tianeptine, a serotonin reuptake enhancer, and phenytoin, a glutamate release inhibitor, appear to prevent and even reverse hippocampal changes associated with corticosteroid treatment. A study recently reported improved cognition in 13 patients with brain injury after lamotrigine therapy (dose: mean = 250 mg/day), suggesting a potential role for medication as a neuroprotective agent in humans.

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these data and reports of improvement in mood in patients with bipolar disorder who were given lamotrigine, a pilot study using this medication in patients receiving chronic corticosteroid therapy was conducted.

Mood effects of lamotrigine were assessed by using instruments we have used in prior studies of corticosteroid effects, including the Hamilton Depression Rating Scale, the Young Mania Rating Scale (both clinician administered), and the depression subscale of the Internal State Scale (a self-report measure). Cognitive instruments included the total words recalled through five trials on the Rey Auditory Verbal Learning Test, a measure of declarative memory and hippocampal functioning, and the Stroop color-word task, which assesses function of the prefrontal cortex.

METHOD

Ten outpatients were recruited from Parkland Health and Hospital System clinics. Inclusion criteria included oral corticosteroid therapy for at least 6 months and age from 18 to 65 years. Exclusion criteria included neurological diseases (e.g., multiple sclerosis), a history of bipolar disorder or psychotic disorders unrelated to corticosteroid therapy, and allergies or other contraindications to lamotrigine therapy. Each subject signed informed consent that was approved by an institutional review board. At baseline the subjects were administered the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID), the Young Mania Rating Scale (both clinician administered), and the depression subscale of the Internal State Scale (a self-report measure). Cognitive instruments included the total words recalled through five trials on the Rey Auditory Verbal Learning Test, a measure of declarative memory and hippocampal functioning, and the Stroop color-word task, which assesses function of the prefrontal cortex.

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Changes from baseline to completion were examined by using scores on the Young Mania Rating Scale, the Hamilton Depression Rating Scale, the depression subscale of the Internal State Scale, the Rey Auditory Verbal Learning Test, and the Stroop color-word task. Scores on the Rey Auditory Verbal Learning Test and the Stroop color-word task were given as t scores, in which a score of 50 is considered normal or average. Differences between baseline and completion scores were determined with paired, two-tailed Student’s t tests with an a priori alpha of 0.05.

RESULTS

Ten subjects were enrolled in the study. However, three dropped out and were lost to follow-up. One subject started taking venlafaxine from another physician between the week 6 and 8 study assessments and was, thus, not included in the analysis. This subject’s Hamilton Depression Rating Scale score decreased from 23 at week 4 to 15 at week 6. Thus, the addition of venlafaxine was for residual depressive symptoms and was not due to lack of improvement with lamotrigine. One subject had a reduction in corticosteroid dose during the study and was not included in the analysis. Thus, a total of five subjects completed all 12 weeks of the study and were included in the analysis. A completers analysis was used in order to examine only subjects who had received a dose of lamotrigine considered therapeutic for other illnesses, including seizures and bipolar disorder. The dropouts consisted of two men and three women. The dropouts and completers did not differ significantly in current corticosteroid doses or baseline scores on the Hamilton depression scale, the depression subscale of the Internal State Scale, the Rey Auditory Verbal Learning Test, or the Stroop color-word task. However, the dropouts had significantly higher baseline scores on the Young Mania Rating Scale than the completers (mean = 6.8, SD = 2.7, versus mean = 2.8, SD = 1.3, respectively) (p = 0.02). One subject dropped out because of nausea, diarrhea, and headaches that may have been secondary to the medication; another dropped out to participate in another research study; and one was lost to follow-up.

The five subjects included in the analysis consisted of one man and four women with a mean age of 42.6 years (SD = 11.2). Three of these subjects had asthma, two had rheumatoid arthritis, and one had dermatomyositis and received a mean prednisone dose of 19.8 mg/day (SD = 12.9). The mean final lamotrigine dose was 340 mg/day (SD = 65). Two subjects were taking stable doses of psychotropic drugs at baseline for sleep and/or mood symptoms, including amitriptyline (25 mg/day) and olanzapine (2.5 mg/day). Concomitant nonpsychotropic drugs included oral hypoglycemics, methotrexate, diuretics, hydroxychloroquine, montelukast sodium (one subject each), calcium supplements, folic acid, antihistamines, β-agonists
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(two subjects each), nonsteroidal anti-inflammatory agents, and steroid inhalers (three subjects each).

Psychiatric diagnoses on the SCID included one case each of panic disorder (current), specific phobia of heights (current), and generalized anxiety disorder (current). In addition, substance-induced mood disorder (three past and two current cases and all secondary to corticosteroid therapy) was found in five subjects. Thus, only two of the five participants met current criteria for a mood disorder. Baseline cognitive performance was low-average on the Rey Auditory Verbal Learning Test (t score = 45.4) and mildly impaired on the Stroop color-word task (t score = 36.8).

Overall, mood measures showed nonsignificant reductions, with mean Hamilton Depression Rating Scale scores decreasing from 14.4 (SD = 10.7) to 5.6 (SD = 4.0) (p = 0.23), depression subscale scores of the Internal State Scale decreasing from 75.8 (SD = 61.8) to 25.0 (SD = 25.6) (p = 0.09), and Young Mania Rating Scale scores increasing very slightly from 2.8 (SD = 1.3) to 3.4 (SD = 2.8) (p = 0.65) (Table 1). However, in the two subjects with baseline Hamilton depression scale scores above 20 (both meeting criteria for a substance-induced mood disorder related to corticosteroid therapy), substantial improvement in depression was observed (Figure 1).

During 12 weeks of lamotrigine therapy, normative scores on the Rey Auditory Verbal Learning Test (total words recalled) increased significantly, from 45.4 (SD = 8.0) to 55.8 (SD = 5.3) (p = 0.04). Normative scores on the Stroop color-word task also increased significantly, from 36.8 (SD = 6.4) to 53.2 (SD = 7.3) (p = 0.003). Lamotrigine was well tolerated. To our knowledge, only one subject dropped out because of possible medication side effects.

DISCUSSION

Overall, no significant changes in mood were observed, although we found a less-than-significant decrease in self-reported depressive symptoms on the depression subscale of the Internal State Scale. Although Hamilton Depression Rating Scale scores were somewhat elevated at baseline (mean = 14.4, SD = 10.7), Young Mania Rating Scale scores were within the normal range (mean = 2.8, SD = 1.3). Thus, in our group of subjects taking corticosteroids for the long term at relatively low doses, we did not see the hypomanic mood symptoms reported in patients taking brief courses of higher doses of corticosteroids. Although no improvement in group mean depression scores was observed, in the two subjects with current mood disorders secondary to corticosteroid therapy at baseline, an impressive reduction in depressive symptoms was noted. In these two participants, the reduction in Hamilton depression scale scores continued until approximately week 6 and was sustained throughout the 12-week clinical trial. We know of no previous studies that have examined lamotrigine for the treatment of depression associated with corticosteroid therapy. Thus, these cases are of interest; we suggest that this agent may be useful in treating corticosteroid-induced depression as well as bipolar depression.

At baseline the participants showed low-average performance on the declarative memory task of the Rey Auditory Verbal Learning Test and mild impairment in cognition related to the prefrontal cortex on the Stroop color-word task, consistent with prior reports on patients receiving corticosteroids. Improvement in declarative memory, as measured with the Rey Auditory Verbal Learning Test total score, was found in the five subjects who completed the 12-week study. This finding suggests that this form of memory, which is sensitive to hippocampal functioning, improved with lamotrigine therapy. Given the open design of the study, we cannot rule out practice or learning effects from repeated testing as an explanation for this improvement. However, we used alternative forms of the Rey Auditory Verbal Learning Test with different words to minimize practice effects. The available literature supports significant practice effects with repeated testing when using the same version of the Rey Auditory Verbal Learning Test in a time frame similar to that of the current report but no practice effects when using alternate versions. In addition, a report from a trial of lamotrigine in patients with HIV and cocaine abuse found no change in Rey Auditory Verbal Learning Test scores, even with repeat testing with the same version. The literature also suggests that corticosteroid-treated patients do not appear to exhibit normal practice effects on measures of declarative memory. Three studies have reported no improvement in performance on repeated administration of the Wechsler Memory Scale paragraph recall test in subjects receiving corticosteroids. In contrast, the comparison subjects in these studies, who were not taking corticosteroids, showed improvement in scores with repeated testing. Thus, the improvement in scores observed in the present study is not likely secondary to practice effects. As memory sometimes improves when mood symptoms resolve in patients with major depressive disorder (for a review, see Brown et al.), the improvement in cognition could be related to the antidepressant effect of lamotrigine. However, given the small group size in this study, we were not able to explore
TABLE 1. Outcome Measures for Five Patients With Corticosteroid-Induced Mood Symptoms Who Were Given Lamotrigine for 12 Weeks

<table>
<thead>
<tr>
<th>Subject</th>
<th>Depressive Subscale of the Internal State Scale</th>
<th>Hamilton Depression Rating Scale</th>
<th>Young Mania Rating Scale</th>
<th>Rey Auditory Verbal Learning Test</th>
<th>Stroop Color-Word Task</th>
<th>Brief Psychiatric Rating Scale Depression Subscale of the Internal State Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Man, age 43, with dermatomyositis</td>
<td>2</td>
<td>5</td>
<td>10</td>
<td>21</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Woman, age 64, with asthma</td>
<td>1</td>
<td>2</td>
<td>28</td>
<td>3</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Woman, age 43, with rheumatoid arthritis</td>
<td>4</td>
<td>4</td>
<td>24</td>
<td>3</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Woman, age 22, with asthma</td>
<td>4</td>
<td>2</td>
<td>28</td>
<td>3</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Woman, age 41, with asthma and rheumatoid arthritis</td>
<td>4</td>
<td>2</td>
<td>28</td>
<td>3</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

FIGURE 1. Depression Scores Before and During 12 Weeks of Lamotrigine Therapy for Two Patients With Baseline Mood Disorders Who Were Receiving Corticosteroids

In summary, in our group of subjects receiving corticosteroid therapy and given open-label lamotrigine for 12 weeks, improvement in cognition was observed. In depressed subjects, improvement in mood was also seen. These findings are from a preliminary pilot study but suggest that lamotrigine may be useful for patients reporting depressive symptoms or memory loss during corticosteroid therapy. Larger controlled trials are needed to confirm these preliminary observations.

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