Lithium Augmentation of Nortriptyline for Subjects Resistant to Multiple Antidepressants

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Abstract: Lithium augmentation, the most studied augmentation strategy for depression, has not been evaluated in patients with a history of non-response to multiple antidepressants. The objective of this study was to assess the efficacy of lithium augmentation for patients with a history of treatment resistant depression who also failed a prospective trial of nortriptyline. We enrolled 92 subjects with treatment resistant depression. Treatment resistance was defined by at least one, but no more than five, adequate trials of antidepressants during the current episode. Subjects were treated with nortriptyline (NT) for 6 weeks. Those subjects who tolerated NT for 6 weeks and whose depression did not respond (n=35) were randomized to receive either lithium (n=18) or placebo (N=17) augmentation of nortriptyline for an additional 6 weeks. Response was defined as an equal to or greater than 50% decrease in HAM-D-17 scores. After 6 weeks of double-blind augmentation, 12.5% of subjects responded to lithium and 20.0% to placebo. Our results revealed no significant difference between lithium and placebo augmentation. While lithium augmentation seems to be useful in depression refractory to a single medication in some studies, our data suggest limited usefulness of this option for patients refractory to multiple treatments. More definitive data await the outcome of the NIMH Sequential Treatment Alternatives to Relieve Depression (STAR*D) study. (J Clin Psychopharmacol 2003;23: 92–95)

Even though it is difficult to define treatment resistant depression (TRD), at any given time TRD accounts for 10% to 30% of depressive episodes and 15% to 30% of psychiatric outpatients.1–4 TRD episodes may represent up to 50% of the annual costs associated with the treatment of depression. Overall, 21% of patients who seek treatment for depression fail to recover in up to two years, and 12% of patients fail to recover after 5 years.5–7 From an epidemiological perspective, nearly 2 million Americans could experience treatment resistant depression at some point in their lives.8

Similar to the action of certain antidepressants, lithium has been shown to increase the efficacy of the serotonin (5-HT) system in the forebrain.9,10 De Montigny and associates in 1981 first noted the efficacy of lithium when used as an augmentation in patients who had failed to respond to tricyclic antidepressants (TCAs).11 To date, lithium augmentation for patients with depression refractory to anywhere from one to several medications has been shown to be an effective strategy in some, but not all studies.12–27 In many of these studies, however, treatment resistance was determined either retrospectively or in an uncontrolled manner. The goal of this study was to evaluate the effect of lithium augmentation of a TCA for patients whose depression failed to respond to several previous antidepressant trials, in addition to a 6-week prospective open trial of nortriptyline (NT).

METHODS

Subjects were recruited at the Depression Clinical and Research Program (DCRP), Massachusetts General Hospital (MGH). A total of 92 outpatients were entered into this study, with inclusion criteria as follows: men and women ages 18 to 70 with Major Depressive Disorder (MDD) as diagnosed using the Structured Clinical Interview for the DSM-III-R (SCID-P);28 a score on the 17-item Hamilton Depression Rating Scale (HAM-D-17)29 equal to or greater than 18; and treatment resistant depression, defined as at least 1, but no more than 5, failed medication trials during the current depressive episode. Failed medication trials were defined using the Harvard Antidepressant Treatment History (HATH) form,30 which gives specific criteria for the adequate dose and adequate length of a trial for it to be considered a failure. An adequate trial is defined as having an adequate dose (which varies from medication to medication and for some medications is determined by blood levels) for a length of time of at least 6 weeks. Exclusion criteria for this trial were defined as: bipolar I or II disorder, a history of organic mental or seizure disorder, serious or unstable medical illness, active...
substance abuse disorders within the past 12 months, a history of substance dependence, acute suicidal risk, pregnancy, lactation, psychotic disorders, history of adverse reaction or allergy to study medications, concomitant use of psychotropic medications, and clinical or laboratory evidence of thyroid abnormalities. In addition, patients who had failed a 6-week adequate trial of lithium augmentation of NT in the past were excluded from the study.

Eligible subjects were started on open-label nortriptyline 25 mg the first day, and increased by 25 mg per day until a dose of 100 mg unless they had to stop the dose increase due to intolerance. Blood levels of nortriptyline were obtained at weeks 2 and 6; dose adjustments were made after the second week if blood levels were < 100 ng/ml. Subjects were then kept on their dose of NT for 6 weeks, and assessed weekly. NT dose and blood level at week 6 were 116.7 mg ± 31.6 and 95.7 ng/ml ± 46.1, respectively. Those responding to nortriptyline were discontinued from the study and followed for up to 3 years at the DCRP.

Nonresponders were randomized to have either lithium or placebo added to their ongoing NT for an additional 6 weeks. Study visits corresponding to the double-blind phase of the study occurred at weeks 6, 8, 10 and 12. The HAM-D-31, Clinician Global Impression-Severity (CGI-S) and Improvement (CGI-I)31 were completed at each study visit by trained psychiatrists and psychologists. Clinical response was defined as greater than or equal to a 50% reduction in total HAM-D-17 score (week 12–week 6). We conducted both completer (CA) and intent to treat (ITT) analyses for the proportion who responded to lithium augmentation group were 12.5% and 11.1%, respectively. Three patients in the lithium group were rated as “much” or “very much” improved on the CGI-I (p=ns compared to the lithium group). Five of 18 (27.8%) patients in the lithium and 4 of 17 (23.5%) patients in the placebo group were rated as “much” or “very much” improved on the CGI-I (p=ns). Mean HAM-D-17 scores for baseline and weeks 0, 2, 4, and 6 during double-blind treatment for the lithium group were: 21.4, 18.8, 15.4, 16.6, and 15.6; and for the placebo group were: 21.7, 19.8, 17.6, 14.9, and 15.1. No significant differences were found between the two groups for any of these data points (p value range 0.08–0.98). Mean CGI-Severity/CGI-Improvement scores for weeks 0, 2, 4, and 6 for the lithium group were: 4.3/3.8, 3.6/2.9, 3.8/3.5, and 3.6/3.3; and for the placebo group were: 4.5/3.8, 3.7/3.2, 3.3/2.6, and 3.6/3.1. No significant differences existed between the two groups for any of these data points. For the change in HAM-D-17 score from the start of open 6-week NT trial to the end of the double-blind 6-week randomized phase (a total of 12 weeks), mean change was −6.3/−5.5 (CA/ITT) for the lithium and −6.5/−5.8 (CA/ITT) for the placebo group.

Two patients in the lithium group were responders; completer (CA) and intent-to-treat (ITT) analyses for the proportion who responded to lithium augmentation group were 12.5% and 11.1%, respectively. Three patients in the placebo group (20.0% CA, 17.6% ITT) were responders (p=ns compared to the lithium group). Five of 18 (27.8%) patients in the lithium and 4 of 17 (23.5%) patients in the placebo group were rated as “much” or “very much” improved on the CGI-I (p=ns). Mean HAM-D-17 scores for baseline and weeks 0, 2, 4, and 6 during double-blind treatment for the lithium group were: 21.4, 18.8, 15.4, 16.6, and 15.6; and for the placebo group were: 21.7, 19.8, 17.6, 14.9, and 15.1. No significant differences were found between the two groups for any of these data points (p value range 0.08–0.98). Mean CGI-Severity/CGI-Improvement scores for weeks 0, 2, 4, and 6 for the lithium group were: 4.3/3.8, 3.6/2.9, 3.8/3.5, and 3.6/3.3; and for the placebo group were: 4.5/3.8, 3.7/3.2, 3.3/2.6, and 3.6/3.1. No significant differences existed between the two groups for any of these data points. For the change in HAM-D-17 score from the start of open 6-week NT trial to the end of the double-blind 6-week randomized phase (a total of 12 weeks), mean change was −6.3/−5.5 (CA/ITT) for the lithium and −6.5/−5.8 (CA/ITT) for the placebo group.

**RESULTS**

Ninety-two patients entered the study and were treated openly with NT for 6 weeks. Of these 92 patients, 35 (38.0%) completed the open NT phase and were randomized to either placebo or lithium augmentation. As shown in Table 1, the two groups were similar on all baseline demographic and clinical characteristics. Of the 18 patients in the lithium group, two discontinued prior to finishing the entire six-week double-blind phase of this study. One of these patients received inpatient treatment for diabetes 4 days after beginning the double-blind phase and had to discontinue lithium. The other patient was lost to follow up immediately after being randomized, never received lithium, and was therefore dropped from the analysis. Of the 17 patients in the placebo group two were lost to follow-up during the first week of the double-blind phase and received placebo for less than seven days.

Two patients in the lithium group were responders; completer (CA) and intent-to-treat (ITT) analyses for the proportion who responded to lithium augmentation group were 12.5% and 11.1%, respectively. Three patients in the placebo group (20.0% CA, 17.6% ITT) were responders (p=ns compared to the lithium group). Five of 18 (27.8%) patients in the lithium and 4 of 17 (23.5%) patients in the placebo group were rated as “much” or “very much” improved on the CGI-I (p=ns). Mean HAM-D-17 scores for baseline and weeks 0, 2, 4, and 6 during double-blind treatment for the lithium group were: 21.4, 18.8, 15.4, 16.6, and 15.6; and for the placebo group were: 21.7, 19.8, 17.6, 14.9, and 15.1. No significant differences were found between the two groups for any of these data points (p value range 0.08–0.98). Mean CGI-Severity/CGI-Improvement scores for weeks 0, 2, 4, and 6 for the lithium group were: 4.3/3.8, 3.6/2.9, 3.8/3.5, and 3.6/3.3; and for the placebo group were: 4.5/3.8, 3.7/3.2, 3.3/2.6, and 3.6/3.1. No significant differences existed between the two groups for any of these data points. For the change in HAM-D-17 score from the start of open 6-week NT trial to the end of the double-blind 6-week randomized phase (a total of 12 weeks), mean change was −6.3/−5.5 (CA/ITT) for the lithium and −6.5/−5.8 (CA/ITT) for the placebo group.

**Table 1.** Demographic and clinical features

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Lithium augmentation (n = 18)</th>
<th>Placebo augmentation (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frequency/Mean</td>
<td>Frequency/Mean</td>
</tr>
<tr>
<td>Male</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Female</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Mean Age</td>
<td>37.2 years ± 8.3</td>
<td>39.7 years ± 11.9</td>
</tr>
<tr>
<td>Age of 1st onset</td>
<td>18.5 years ± 9.6</td>
<td>21.3 years ± 13.3</td>
</tr>
<tr>
<td># of prior episodes</td>
<td>0.4 ± 0.7</td>
<td>0.9 ± 1.2</td>
</tr>
<tr>
<td># of failed trials in current episode</td>
<td>1.9 ± 1.2</td>
<td>2.5 ± 1.6</td>
</tr>
<tr>
<td>duration of current episode</td>
<td>97.3 months ± 111.8</td>
<td>84.5 months ± 94.9</td>
</tr>
<tr>
<td># of comorbid Axis I dx’s</td>
<td>2.9 ± 1.4</td>
<td>2.8 ± 1.6</td>
</tr>
<tr>
<td># of comorbid Axis II dx’s</td>
<td>2.6 ± 2.2</td>
<td>1.4 ± 2.0</td>
</tr>
<tr>
<td>GAF current</td>
<td>42.5 ± 9.8</td>
<td>45.6 ± 7.1</td>
</tr>
</tbody>
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(p=0.96, p=0.91). For the change in HAM-D-17 score from the beginning to the end of the double-blind phase, mean change was \(-3.3/\pm 2.9\) (CA/ITT) for the lithium and \(-3.9/\pm 3.6\) (CA/ITT) for the placebo group (p=0.79, p=0.72). The 95% confidence interval for the proportion that responded to lithium augmentation was from 0.07 to 0.44. This study had a power of 99% to show that the proportion who responded to lithium augmentation was not 0.60, which is the most widely reported proportion in the literature (α=0.05, 2 tailed). Lithium levels were performed for all patients in the lithium group at after 2 weeks of treatment. For some patients (n=8) a second Li level was performed after 6 weeks. Mean Li blood level at week 2 was 0.63 (range 0.3–1.4) and at week 6 was 0.61 (range 0.6–0.9).

**DISCUSSION**

**Efficacy**

To our knowledge, this is the first 6-week, double-blind, placebo controlled study of lithium augmentation in patients whose depression failed to respond to several medications, including a prospective six-week trial of NT. For this group of patients with treatment resistance, there was no statistically significant difference in response rates between lithium and placebo added to NT. One strength of this study is that we prospectively defined treatment resistance by failure to respond to an adequate trial of NT. Prospectively identifying treatment resistance is preferable to just a retrospective assessment, since retrospective definitions are prone to errors resulting in misclassification and recall bias.  

**Clinical trials of lithium augmentation in depression**

Although the addition of lithium to an antidepressant is the most studied augmentation strategy, few controlled trials of adequate duration are available for comparison. Several open trials of lithium augmentation report a wide range of response rates. Some placebo-controlled studies have limitations in methodology that make it difficult to interpret their findings in the context of our study. Others are of two weeks duration or less. Pattern analysis reveals that more patients receiving medication experience a 2-week delay in the onset of improvement compared to patients receiving placebo, while patients in the latter group are more likely to demonstrate an onset of improvement within the first 2 weeks. In addition, depressed patients who experience a 2-week delay in the onset of clinical improvement are more likely to show persistence of improvement, and less likely to relapse. Given the relationship between early and placebo response, the likelihood of mis-classifying placebo as true response is greater in trials of short duration. A trial by Capiello et al. exemplifies this point. Depressed patients were randomized to receive desipramine and either lithium or placebo for 4 weeks. Lithium augmentation was found to be superior to placebo at week 1, 2, and 3, but not at week 4. Furthermore, Fontaine and associates found that while 5 of 18 depressed patients who experienced a clinical response when lithium was added to fluoxetine did so within the first week, 6 of the original 18 responders suffered a relapse within 2 months.

One trial of 4-weeks duration reports a modest response rate. Fava and associates report that only 29% of depressed patients who did not respond to an 8-week open trial of 20 mg of fluoxetine demonstrated a clinical response when lithium was added to their treatment regimen compared to 52% of patients who responded to an increase in the dose of fluoxetine alone. Finally, double-blind, placebo-controlled trials of lithium augmentation of fluoxetine or lofepramine, and TCAs reveal promising response rates of 51.7% and 44% respectively for the lithium group. It is important to note that study subjects had only failed a single antidepressant trial. Furthermore, treatment resistance was defined in retrospectively, which carries the risk of mis-classifying patients who have had inadequate therapy as treatment resistant. This may be particularly true of the latter study, which defined a 3-week trial of TCAs as adequate.

**Limitations**

While in our sample there was no statistically significant difference in efficacy between the placebo and lithium group, this may be because our study had limited power to detect a difference. The study did, however, have enough power to determine that the proportion who responded to lithium augmentation was not 60% (α=0.05, 2 tailed, power to differentiate from 0.60, power=0.99). Furthermore, the lithium augmentation trial followed a 6-week open trial of NT. It is possible, at least in some cases, that the response to lithium may have been a delayed response to the tricyclic antidepressant (total treatment time with NT was 12 weeks), although one would expect this factor to have a similar impact for both groups.

**CONCLUSION**

The addition of lithium to antidepressants is a widespread practice in patients with depression, and extensively studied. The current study focused on the use of lithium in patients whose depression had not responded to between one to five well-documented antidepressant trials of adequate duration and dosage. In addition, in order to confirm the diagnosis of refractory depression, screened patients underwent an open trial of NT for 6 weeks. Our results revealed that only 12.5% of patients receiving lithium augmentation and 20.0% of patients receiving...
placebo augmentation responded to treatment, and that this was not a statistically significant difference. While lithium augmentation seems to be useful in depression refractory to a single medication in some studies, our data suggest limited usefulness of this option in treatment refractory patients. More definitive evidence about the role of lithium augmentation of TCAs for TRD will be forthcoming from the NIMH Sequential Treatment Alternatives to Relieve Depression study (STAR*D: www.ecgp.h. pitt.edu/starb)

REFERENCES