Hypothalamic-pituitary-thyroid system activity during lithium augmentation therapy in patients with unipolar major depression

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Objective: Lithium augmentation is an established strategy in the treatment of refractory depression, but little is known about predictors of response and its mode of action. There is increasing evidence that low thyroid function indices within the normal range are associated with a poorer treatment response to antidepressants, but previous studies on the hypothalamic-pituitary-thyroid (HPT) system during lithium augmentation provide inconclusive results and have methodological limitations. This study aimed at exploring the role of thyroid function in lithium augmentation and used a prospective design that included a homogeneous sample of inpatients with unipolar major depressive disorder. Methods: In 24 euthyroid patients with a major depressive episode who had not responded to antidepressant monotherapy of at least 4 weeks, we measured serum thyroid-stimulating hormone (TSH), total triiodothyronine (T3) and total thyroxine (T4) before (baseline) and during lithium augmentation therapy (follow-up). The time point of the endocrinological follow-up depended on the status of response, which was assessed weekly with the Hamilton Depression Rating Scale, 17-item version (HDRS17). Responders were reassessed immediately after response was determined, and non-responders after 4 weeks of lithium augmentation. Results: There was a statistically significant change in thyroid system activity during lithium augmentation, with an increase of TSH levels and a decrease of peripheral T3 and T4 levels. However, there were no differences in any of the HPT hormones between responders and non-responders at baseline or at follow-up. Conclusions: The decrease of thyroid system activity during lithium treatment reflects the well-established “antithyroid” properties of lithium. However, it appears that thyroid status does not predict response to lithium augmentation in euthyroid patients before treatment.

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Medical subject headings: antidepressive agents; depressive disorder; drug therapy, combination; lithium carbonate; thyrotropin; thyroxine; treatment outcome; triiodothyronine.


Submitted Apr. 17, 2002
Revised Oct. 16, 2002
Accepted Oct. 28, 2002

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Rev Psychiatr Neurosci 2003;28(3)
Introduction

Lithium augmentation was first described in 1981 by de Montigny et al.\(^1\) and since then has been recommended as a first-line strategy among the various treatment options for non-responding depressed patients.\(^2\) In placebo-controlled acute\(^3\)–\(^5\) and continuation\(^6\)–\(^7\) treatment trials using different classes of antidepressants,\(^8\) the efficacy of this treatment intervention has been well documented. In a recent meta-analysis, the evidence that lithium augmentation is superior to placebo augmentation for the treatment of major depressive disorder (MDD) could be confirmed with a median response rate of 50% across placebo-controlled studies.\(^9\) However, approximately 50% of depressed patients do not get significantly better with lithium augmentation. Thus, knowledge of factors that are related to a favourable outcome with lithium augmentation would be helpful for the clinician.

Considerable interest has been generated by the role of modifiable risk factors play in the pathogenesis and treatment of MDD. There is particular debate about whether patients with MDD are predisposed to hypothalamic-pituitary-thyroid (HPT) system abnormalities and whether such dysfunction may contribute to the pathophysiology of the illness.\(^10\)–\(^13\) A recent study by Cole et al.\(^14\) provided evidence that affectively ill patients are particularly sensitive to variations in thyroid function within the normal range. Lower free thyroxine index values and higher thyroid stimulating hormone (TSH) values within the normal range were significantly associated with a poorer treatment response during the acute depression phase.\(^10\)

Previous studies have investigated the HPT hormones in depressed patients on a lithium-augmentation regimen.\(^15\)–\(^18\) However, these studies included non-homogeneous samples of depressed patients (mixed unipolar and bipolar),\(^16\)\(^,\)\(^17\) had a retrospective design,\(^18\) or included relatively small samples with assessment at baseline but no follow-up thyroid assessment.\(^15\) Such limitations and lack of conclusive results prompted us to prospectively investigate the HPT system hormones in a well-defined sample of inpatients with acute MDD before and during lithium augmentation therapy.

Method

This study was conducted at the Department of Psychiatry, Freie Universität Berlin, a tertiary care academic medical centre. It was part of a larger project investigating endocrinological changes during lithium augmentation.\(^19\) Only inpatients from the clinical programs were included. Written informed consent was obtained after a complete description of the study was provided to the subjects. The study protocol was approved by the ethics committee of the University Hospital, Freie Universität Berlin.

Male and female inpatients (age 18 years or older) with a major depressive episode (single episode or recurrent), according to DSM-IV criteria, were included
in the study. Diagnoses were confirmed by the Structured Clinical Interview for the DSM-IV (SCID I; German version).20

All participants had to have met criteria for a major depressive episode with a score of at least 15 on the Hamilton Depression Rating Scale, 17-item version (HDRS17),23 on the day they were assessed for study inclusion. The exclusion criteria were: history of a manic or hypomanic episode, any other DSM-IV Axis I diagnosis, severe somatic conditions, medical conditions incompatible with lithium therapy, pregnancy or lactation, organic brain diseases and medication with thyroid hormones.

All patients received lithium augmentation for a depressive episode according to a standardized stepwise drug treatment regimen (SSTR) that was established at the Department of Psychiatry of the Freie Universität Berlin.21,22 SSTR algorithms base stepwise medication changes on the results of clinical evaluation with established depression rating scales. According to an algorithm, if there is non-response after completion of the current step, the patient enters the next step. If there is partial response, the patient remains in the current step for an extra 2 weeks before switching to the next step. If at any point there is a response to treatment, the patient remains at the current step.

According to the SSTR used here, the first step was a washout period for psychotropic drugs (1 week). Subsequently, all patients received monotherapy with an antidepressant for 4 weeks. The dosages for the different antidepressants were as follows: fluoxetine, paroxetine and citalopram, 20 mg/d; sertraline, 100 mg/d; tricyclic antidepressants, 150 mg/d; venlafaxine, 225 mg/d; mirtazapine, 30 mg/d; and reboxetine, 8 mg/d.

In the case of a partial response, the current step was prolonged to 6 weeks. Patients who had not achieved remission were switched to the next step of lithium augmentation. The steps that followed lithium augmentation are not relevant for this study and therefore will not be described here.

HPT hormone analyses

All probes were centrifuged, and the serum was stored at –20°C immediately after collection. They were analyzed together in 1 assay at the end of the entire study. Laboratory analyses were done at the Department of Nuclear Medicine (Radiochemistry), Freie Universität Berlin. Commercially available radioimmunoassay (RIA) kits were used for the determination of total T3 and T4, and a commercially available immunoradiometric assay kit was used for TSH determination (all kits: BRAHMS Diagnostica, Berlin, Germany). The detection limit and the intra- and interassay coefficients of variation have been published previously.24 The reference ranges were as follows: T3: 1.23–3.08 nmol/L; T4: 58–154 nmol/L; and TSH: 0.3–4.0 mU/L.

Response to lithium augmentation was assessed using weekly HDRS17 scores (administered between noon and 3 pm on days 7, 14, 21 and 28). Response was defined as a reduction of the HDRS17 score of 50% or more as compared with the patient’s score at study entry and a total HDRS17 score of 9 or less. Response was confirmed if the patient met both criteria when tested again 1 week later. If a patient did not fulfill these criteria within 4 weeks of lithium augmentation, he or she was classified as a non-responder. The measurement of HPT system hormones was repeated the same way as at baseline once response was confirmed or, in case of non-response, after 4 weeks of lithium augmentation therapy. This design was chosen to investigate the HPT system of responders as close as possible to the change in depressive psychopathology.

Statistical analyses

Because the number of responders and non-responders was different and the sample was rather small, non-parametric tests were used for a robust analysis. Changes between the initial thyroid variables at baseline and at follow-up were evaluated using Wilcoxon’s
matched pairs test. Differences between responders and non-responders to lithium augmentation were assessed using Fisher’s exact test or the Mann–Whitney U test, where appropriate. For assessment of correlations between hormones and outcome (HDRS, score changes), Spearman rank correlation coefficients were calculated. Differences were regarded as statistically significant when \( p < 0.05 \). All tests were 2-tailed. For each patient, changes (delta values) of TSH, T3, and T4 were calculated as baseline minus follow-up values.

**Results**

Twenty-four patients (12 men and 12 women) who met the inclusion criteria participated. Their mean age was 45.0 (standard deviation [SD] 15.5) years, and the mean age at onset of the affective illness was 38.7 (SD 15.7) years. The mean HDRS score at study entry was 19.5 (SD 3.8; range 15–30). Subjects were taking antidepressants from various classes (5 tricyclic antidepressants [TCAs], 12 selective serotonin reuptake inhibitors [SSRIs], 2 mirtazapine, 3 venlafaxine and 2 reboxetine). For demographic and clinical characteristics see Table 1.

Ten (4 men, 6 women, 42%) of the 24 patients responded within 4 weeks of the initiation of lithium augmentation (mean 3.0 [SD 0.8] weeks; final mean HDRS score 5.2, SD 1.7). Fourteen patients were classified as non-responders (final HDRS score 16.2, SD 4.2). There were no significant differences between responders and non-responders in terms of age, sex, age at onset of mood disorder, baseline HDRS, duration of index episode, number of previous depressive episodes or admissions to psychiatric hospitals and duration or type of antidepressive medication (all \( p > 0.25 \), Mann–Whitney U tests or Fisher’s exact tests).

**HPT hormones**

At baseline, except for 2 patients with slightly decreased serum TSH levels (0.27 and 0.29 mU/L) and 2 with slightly decreased total T4 levels (54 and 51 nmol/L), all patients showed serum HPT system hormone levels within the normal range. There were no differences in any of the hormones between subsequent responders and non-responders (all \( p > 0.58 \), Mann–Whitney U test; see Table 2).

At follow-up during lithium augmentation, patients had significantly higher serum TSH levels and significantly lower total T4 and T3 levels (all \( p < 0.005 \), Wilcoxon’s matched pairs test; see Table 2). Five of the 24 patients (21%; 3 responders, 2 non-responders) showed TSH values above the reference range (maximum value, 6.4 mU/L). One of those 5 and an additional 5 patients (25%; 2 responders and 4 non-responders) displayed total T4 hormone levels below the normal range (minimum value, 42 nmol/L), indicating a hypothyroid state. The hormone values of the responders were not statistically different from those of the non-responders (all \( p > 0.4 \), Mann–Whitney U test).

In addition, there were no significant correlations between any of the determined thyroid indices and the percentage change of the HDRS score throughout the study (all Spearman rank correlation coefficients between –0.31 and 0.14, \( p > 0.1 \)).

**Table 1: Demographic and clinical characteristics of 24 patients with major depressive disorder who were treated with lithium augmentation**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Non-responder, ( n = 14 )</th>
<th>Responder, ( n = 10 )</th>
<th>Total, ( n = 24 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>42.4 (15.7)</td>
<td>48.7 (15.2)</td>
<td>45.0 (15.5)</td>
</tr>
<tr>
<td>Age at onset of mood disorder, yr</td>
<td>38.7 (15.8)</td>
<td>38.7 (16.3)</td>
<td>38.7 (15.7)</td>
</tr>
<tr>
<td>HDRS score at initiation of lithium augmentation</td>
<td>18.5 (2.7)</td>
<td>20.9 (4.8)</td>
<td>19.5 (3.8)</td>
</tr>
<tr>
<td>Duration of index episode, wk</td>
<td>44.4 (42.6)</td>
<td>28.0 (13.4)</td>
<td>37.6 (34.1)</td>
</tr>
<tr>
<td>No. of previous depressive episodes</td>
<td>1.5 (1.5)</td>
<td>2.1 (2.5)</td>
<td>1.7 (1.9)</td>
</tr>
<tr>
<td>No. of previous psychiatric hospitalizations</td>
<td>1.1 (1.4)</td>
<td>1.4 (1.3)</td>
<td>1.2 (1.4)</td>
</tr>
<tr>
<td>Male:female ratio</td>
<td>8.6</td>
<td>4.6</td>
<td>12:12</td>
</tr>
</tbody>
</table>

*Note: SD = standard deviation; HDRS = Hamilton Depression Rating Scale, 17-item version.*
Discussion

This study revealed 2 results of interest. First, lithium augmentation therapy was associated with a statistically significant reduction of HPT system activity, and second, there are no differences in thyroid function indices between responders and non-responders to lithium augmentation at baseline. Thus, this study did not find evidence that thyroid status may predict response to this treatment intervention.

The statistically significant decrease of thyroid function during lithium treatment reflects the well-established “antithyroid” properties of lithium that have been demonstrated in patients receiving longer-term lithium treatment and in healthy controls.

The results of this study also reflect the findings of other research teams, who administered lithium augmentation to mixed unipolar and bipolar patient groups and also found a decrease in HPT system activity during lithium augmentation.

In contrast to a previous study using antidepressants, we failed to detect baseline differences in thyroid status between subsequent responders and non-responders to lithium augmentation. However, our results confirm the findings of previous studies on lithium augmentation, although some of these studies included different patient populations than the one studied here. On the other hand, in a recent retrospective study of 71 inpatients (most [n = 68] diagnosed with unipolar MDD), we found that a lower total serum T3 level was associated with response to lithium augmentation. This latter finding was not replicated in this study. There was no overlap between the patient samples of the 2 studies. Considerable methodological differences between the 2 studies might explain this discrepancy. In the present study, the design was prospective, the diagnoses were confirmed by a standard diagnostic interview (SCID I) and the laboratory analyses were performed in a controlled setting (e.g., using 1 assay for all probes). On the other hand, the sample in the present study was smaller than in our previous retrospective study, which is a limitation of this study.

Further limitations of the study must also be taken into account. The initial antidepressant treatment trial was rather short. There is considerable evidence that a proportion of patients do not respond to antidepressants until 4–6 weeks or even longer. Thus, considering the open design of the study, it cannot be excluded that at least some of the responders did not respond to lithium augmentation, but to the initial antidepressant. Furthermore, the follow-up examination was performed at different time points in responders and non-responders. This study design was chosen to investigate the HPT system in responders as close to the time point of response as possible. However, it cannot be ruled out that differences between responders and non-responders might have become apparent if the retest had been performed after the same duration of lithium augmentation for both groups.

In conclusion, this study demonstrated that lithium augmentation therapy leads to a statistically significant decline in thyroid function. The result underscores the necessity of monitoring thyroid function during lithium augmentation. It also shows that the thyroid indices measured at baseline (TSH, total T3 and total T4) do not predict response to lithium augmentation—at least if thyroid indices are in a range that does not indicate overt or subclinical hypothyroidism before

| Table 2: Hypothalamic-pituitary-thyroid (HPT) system hormones in 24 patients with major depressive disorder at baseline and during (follow-up) lithium augmentation therapy |
|---|---|---|---|---|---|---|---|
| | Thyroid status: mean (and SD)* | | | | | |
| | Baseline | Follow-up | | | | |
| Patient group | TSH, mU/L | T3, nmol/L | T4, nmol/L | TSH, mU/L | T3, nmol/L | T4, nmol/L |
| Total, n = 24 | 1.63 (0.97) | 1.83 (0.35) | 84.4 (22.6) | 2.95† (1.64) | 1.65† (0.27) | 70.3‡ (15.7) |
| Responder, n = 10 | 1.62 (0.60) | 1.80 (0.38) | 83.1 (20.2) | 3.01† (1.31) | 1.63‡ (0.28) | 69.3§ (16.0) |
| Non-responder, n = 14 | 1.65 (1.20) | 1.85 (0.34) | 85.4 (24.9) | 2.91‡ (1.89) | 1.66 (0.26) | 71.0‡ (16.0) |
| Responder v. non-responder (Mann–Whitney U, 2-tailed) | 0.79 | 0.58 | 0.98 | 0.48 | 0.45 | 0.98 |

Note: TSH = thyroid-stimulating hormone; T3 = total triiodothyronine; T4 = total thyroxine.

*Normal ranges: TSH = 0.3–4.0 mU/L; T3 = 1.23–3.08 nmol/L; T4 = 58–154 nmol/L.
†p < 0.005 (different from respective baseline value; Wilcoxon’s matched pairs test, 2-tailed).
‡p < 0.05.
§p < 0.01.
treatment. However, our results cannot rule out that, in patients with (sub-)clinical hypothyroidism at baseline, a decrease in thyroid hormone levels may be a critical variable and detrimental to the success of lithium augmentation therapy.

Acknowledgements: Supported in part by the Permanent Commission for Research and Young Scientists of the Freie Universität Berlin, FK 41/06/2000.

Competing interests: None declared.

References

