Supraphysiologic Doses of Levothyroxine as Adjunctive Therapy in Bipolar Depression: A Randomized, Double-Blind, Placebo-Controlled Study

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ABSTRACT

Objective: Suboptimal availability of circulating thyroid hormones may contribute to the high rate of treatment failures in bipolar disorder. This study tested the efficacy of adjunctive treatment with supraphysiologic doses of levothyroxine in patients with bipolar depression and the hypothesis that women would display a better outcome compared to men.

Method: The aims of this multicenter, 6-week, double-blind, randomized, placebo-controlled fixed-dose (300 µg/d) trial conducted from 2004 to 2009 were to assess efficacy and tolerability of levothyroxine adjunctive to continuing treatment with mood stabilizer and/or antidepressant medication for patients with bipolar I or II disorder, currently depressed (*DSM-IV*), and to investigate gender differences in treatment response. The primary efficacy variable was mean change in Hamilton Depression Rating Scale (HDRS) score.

Results: Of 74 patients enrolled in the study, 62 (35 with bipolar I; mean age = 44.9 years) were randomized. Mean change in HDRS score from randomization to week 6 was larger in the levothyroxine group compared to the placebo group, with a 2.7-point difference (decline of −7.8 [38.3%] vs −5.1 [25.5%]; last-observation-carried-forward analysis). The course of HDRS scores over time from randomization to week 6 was significantly different between groups at week 4 ($P = .046$) but not at the end of the placebo-controlled phase ($P = .198$). The secondary analysis of women (n = 32) revealed a significant difference between groups in mean change in HDRS score (−16.6% placebo vs −42.4% levothyroxine, $P = .018$). A mixed-effects model for repeated-measures analysis showed a significant between-group difference in HDRS score (6.8, $P = .012$) for women. High thyroid-stimulating hormone levels, indicating suboptimal levels of circulating thyroid hormones, were predictive for positive treatment outcome in women treated with levothyroxine in a linear regression model ($F_3 = 3.47$; $P = .05$).

Discussion: This trial demonstrated that patients treated with levothyroxine did numerically better than those treated with placebo; however, the study failed to detect a statistically significant difference between the 2 groups in the primary outcome measure due to a high placebo response rate. Previous findings that women show better improvement in depression scores with levothyroxine compared to men were confirmed.

Trial Registration: ClinicalTrials.gov identifier: NCT01528839

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The burden of depression represents the most debilitating dimension for the majority of patients with bipolar disorder. Depressive episodes as well as subsyndromal depressive symptoms dominate the long-term course and are highly associated with worse functional outcome.[1–4] Unfortunately, the overall evidence from treatment trials in bipolar depression is sparse, and the role of antidepressants in the treatment of bipolar depression remains controversial.[5–7] In a recent meta-analysis[8] of 6 randomized trials in bipolar depression (N = 1,034), antidepressants were not statistically superior to placebo.

A lack of circulating thyroid hormones in hypothyroid conditions causes impaired mood and cognition associated with decreased brain metabolic activity that resolve after the euthyroid status has been restored.[9] Patients with mood disorders may present with overt or subtle thyroid abnormalities,[10] and a substantial proportion of lithium-[11,12] and anticonvulsant-treated patients[13] develop thyroid abnormalities. Women treated with lithium are at especially high risk to develop thyroid disease.[11] There is also some evidence that a major cause for thyroid disease, autoimmune thyroiditis, is more common in bipolar patients[14] and their female offspring.[15] Furthermore, a proportion of bipolar patients with rapid cycling may have a latent dysfunction in the hypothalamic-pituitary-thyroid axis.[16] In patients receiving lithium prophylaxis, depressive relapses are associated with thyroid function that is low but still within the normal range.[17,18] Similarly, a lower free thyroxine index and higher thyroid-stimulating hormone (TSH) levels were significantly associated with a poorer treatment response during the depressed phase of bipolar disorder.[19]

Adding thyroid hormone (triiodothyronine [T_3] or levothyroxine) to standard antidepressant treatment is one approach for patients with difficult-to-treat and treatment-refractory major depression and bipolar disorders.[10] In studies in bipolar disorder, the doses of levothyroxine varied broadly from replacement doses (between 50 and 150 µg/d, commonly administered to balance lithium-induced subclinical hypothyroid conditions) to supraphysiologic doses (300–600 µg/d).

In this study, we chose adjunctive levothyroxine at supraphysiologic doses because only such high doses offered promise in previous open-label studies in rapid cycling,[20] prophylaxis-resistant bipolar disorders,[21] and refractory bipolar depression.[22,23] In a single-blind study[23] of women with bipolar depression, the decline in depression in those treated with supraphysiologic doses of levothyroxine was significantly associated with changes in regional cerebral metabolism in limbic and subcortical circuits, indicating a close relationship between circulating thyroid hormone levels and brain activity in depression. The encouraging results from these latter studies prompted us to test the hypotheses that (1) treatment with add-on supraphysiologic doses of levothyroxine would be effective in bipolar depressed patients when studied using a randomized placebo-controlled design and (2) women would show a more favorable response than men to levothyroxine.[23]

Clinical Points

- Refractory bipolar depression represents the most challenging condition in bipolar disorder to treat.
- Thyroid dysfunction may contribute to the development of treatment-refractory bipolar disorder.
- Add-on treatment with supraphysiologic doses of levothyroxine is a promising strategy to overcome treatment resistance in bipolar depression, especially in women.

METHOD

Study Design

This 6-week, randomized, double-blind, parallel-group, placebo-controlled multicenter study tested the efficacy and tolerability of add-on levothyroxine (300 µg/d) versus add-on placebo in the treatment of patients with bipolar disorder, currently in a depressive episode unresponsive to at least 6 weeks of mood-stabilizing and/or antidepressant treatment, and was conducted at 5 academic centers (4 in Germany, 1 in the United States) in 2004–2009. The study was approved by institutional review boards for each site and performed in accordance with the current amendment of the Declaration of Helsinki and the International Conference on Harmonization/Good Clinical Practice guidelines. Written informed consent was obtained from all subjects. The study was registered with ClinicalTrials.gov (identifier: NCT01528839).

Patient Population

Male or female inpatients and outpatients, aged 18 to 65 years, with a *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*) diagnosis of bipolar I or II disorder, currently depressed, were eligible for inclusion in the study. Patients were required to have a 17-item Hamilton Depression Rating Scale (HDRS)[24] score ≥ 14, an HDRS item 1 (depressed mood) score ≥ 2, and a Young Mania Rating Scale (YMRS)[25] score ≤ 12 at the screening and randomization visits.

Patients had to be unresponsive to a mood stabilizer and/or an antidepressant at standard doses[26] for at least 6 weeks, and serum levels of mood stabilizer were required to be within therapeutic ranges. Patients were excluded from the study if they were diagnosed with another Axis I disorder, a recent rapid-cycling course, or substance dependence (*DSM-IV*) or substance use (except for nicotine) within 12 months before inclusion. Other exclusionary criteria were psychotic features, organic brain disorder, serious suicidal risk, endocrine disorders, and severe cardiovascular diseases. Thyroid-stimulating hormone levels had to be in normal range (serum TSH, 0.3–4.7 mIU/L), and no history of thyroid disease or thyroid hormone treatment was allowed. Random assignment was achieved using blocked randomization (block size = 6), which was stratified by center.

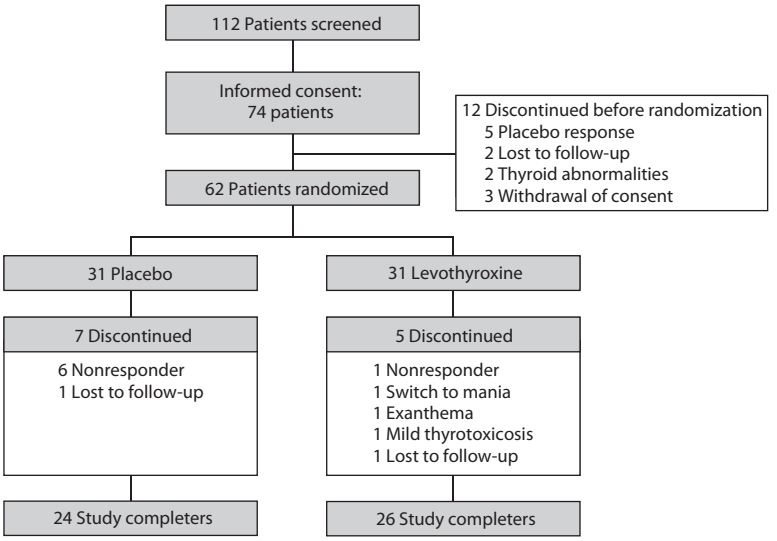
Study Procedures

After written informed consent was obtained, diagnosis of bipolar disorder was confirmed by the Structured Clinical Interview for *DSM-IV* Axis I Disorders[27] and a medical examination, laboratory evaluation, vital signs, and electrocardiogram (ECG) were performed. Affective symptoms were assessed with the $HDRS_{17}$ and the Montgomery-Asberg Depression Rating Scale (MADRS).[28]

Zolpidem tartrate (5–10 mg/d for insomnia) and lorazepam (1–3 mg/d for agitation) were permitted only during the first 3 weeks of treatment. The use of all other psychotropic drugs was prohibited during the entire study. After the screening procedures, patients were treated in a single-blind placebo run-in phase for 1 week to exclude fast placebo responders (study phase 1). When still fulfilling inclusion criteria after this run-in phase, patients were randomly assigned to receive adjunctive levothyroxine or placebo for a 6-week double-blind period (study phase 2). No adjustments of the concomitant medication were allowed after randomization. Levothyroxine and placebo were administered orally, in a single dose, once daily before breakfast. Levothyroxine was initiated at a dose of 100 µg/d for the first week, 200 µg/d for the second week, and 300 µg/d for weeks 3–6. All packaging of treatments was identical, with placebo and active tablets identical in appearance and number.

At the randomization visit, 21 (34%) of the patients received monotherapy with a mood-stabilizing agent, and 41 patients (66%) took a combination of 1 or 2 mood-stabilizing drugs and 1 or 2 antidepressants. These medications were as follows: lithium carbonate n = 22 (300–1,800 mg/d); lamotrigine n = 21 (100–400 mg/d); valproate n = 8 (500–2,000 mg/d); carbamazepine n = 2 (200–600 mg/d); antidepressants: selective serotonin reuptake inhibitors (citalopram n = 10 [20–60 mg/d], paroxetine n = 4 [20 mg/d], sertraline n = 2 [100–150 mg/d], and fluoxetine n = 1 [20 mg/d]), venlafaxine n = 9 (75–375 mg/d), mirtazapine n = 7 (30–45 mg/d), reboxetine n = 5 (8–10 mg/d), tranylcypromine n = 4 (20–80 mg/d), amitriptyline n = 2 (75–125 mg/d), bupropion n = 2 (300 mg/d), duloxetine n = 1 (120 mg/d), nortriptyline n = 1 (100 mg/d), and maprotiline n = 1 (150 mg/d); antipsychotics: olanzapine n = 6 (10–15 mg/d), quetiapine n = 4 (300–700 mg/d), risperidone n = 3 (2–4 mg/d), and

Figure 1. Disposition of Patients at Each Stage of the Study and Reasons for Discontinuation



ziprasidone n = 2 (80 mg/d); others: methylphenidate n = 1 (35 mg/d), pregabalin n = 1 (300 mg/d), and sulpiride n = 1 (100 mg/d).

Efficacy Evaluations

Clinical assessments were conducted at screening, at baseline, and weekly from visits 1 to 6. The primary efficacy variable was the mean change in the HDRS score. Additional efficacy evaluations included change from baseline to each assessment in MADRS and YMRS scores and the proportions of patients who achieved protocol-defined response (50% reduction from baseline in HDRS score) and remission (HDRS score ≤ 7). Participating investigators received standardized video training sessions.

Safety and Tolerability Evaluations

Safety and tolerability were evaluated by assessing adverse events, as well as withdrawals due to adverse events. In addition, the Thyroid Symptom List (TSL),[29] a specific assessment of thyroid-related side effects, was administered. Measurements of vital signs, including weight, blood pressure, and heart rate, were obtained at each study visit. Electrocardiogram, clinical chemistry, hematology, and thyroid axis status (basal TSH, free triiodothyronine [FT_3], free thyroxine [FT_4]) assessments were performed at the screening visit and at visit weeks 4, 6, and 8. The assessment of the ECG, vital signs, and thyroid hormone status was performed by an independent study nurse, and the study investigator was blinded to these results. ECG and vital parameter analyses were performed by an independent cardiologist, and results were passed on to the investigator only if there were relevant pathologic findings that would require further investigation or intervention. The incidence of treatment-emergent mania was evaluated by comparing the percentage of patients in each group who had an adverse event of mania or hypomania.

Data Analyses

Statistical analysis was carried out using IBM SPSS Statistics for Windows, Version 16.0 (IBM Corp; Armonk, New York). On the basis of data from 2 pilot studies,[22,23] a sample size calculation was performed. The power calculation was based on an expected difference in mean change from baseline of the HDRS score between the placebo and the levothyroxine group of at least 4 points at week 6. Given a standard deviation of the HDRS score of 6.7 points at week 6 (effect size = 0.6), this difference is detectable with 35 patients per group (power 80%, α = 5%, 2-sided test). Efficacy analyses were conducted in the intent-to-treat population (patients who received at least 1 dose of study medication and had at least 1 postbaseline efficacy assessment) using last-observation-carried-forward methodology. Analysis of variance models were used to assess the difference between the groups in outcome measures at the end of double-blind treatment with age as covariate (age was chosen because of the known relationship between thyroid function and age). General linear models were used for repeated measurements. In addition, a mixed-effects model for repeated measures (MMRM) analysis was performed for the efficacy analysis post hoc. The model included treatment, visit, and treatment-by-visit interaction as fixed effects and visit as the repeated measure. The model included an unstructured covariance matrix. Differences between groups in response and remission were analyzed using the Mann-Whitney test.

RESULTS

Patients and Disposition

Of a total of 112 patients who were screened for the study, 74 patients were enrolled and signed the consent form (Figure 1). Before randomization, 12 patients were excluded due to the following reasons: screening failure (overt thyroid disease, n = 2), withdrawal of consent (n = 3), early placebo response during single-blind run-in phase (n = 5), and loss

to follow-up (n = 2). The remaining 62 patients (bipolar I: n = 35) were randomly assigned to adjunctive therapy with levothyroxine (n = 31) or placebo (n = 31). Twelve subjects dropped out of the study before the end of the double-blind phase because of lack of response (n = 7; 6 in the placebo group, 1 in the levothyroxine group), adverse events (n = 3), and loss to follow-up (n = 2) (Figure 1).

The 2 groups were well matched in terms of demographic and clinical characteristics at randomization, with no statistically significant differences between groups (Table 1); a trend for higher mean age and illness duration was seen in the placebo group. The mean (SD) HDRS score at the time of randomization was 20.9 (3.0) in the levothyroxine group and 21.4 (4.3) in the placebo group.

Efficacy

The mean change in HDRS score from randomization to week 6 was larger in the levothyroxine group compared to the placebo group (−7.8 [38.3%] vs −5.1 [25.5%]). However, the difference between groups adjusted for age did not reach statistical significance ($P = .157$). The course of HDRS scores over time from randomization to week 6 (end of double-blind treatment) adjusted for age was significantly different between groups at week 4 ($P = .046$), but not at the end of the placebo-controlled phase ($P = .198$) (Figure 2A). Other possible confounders such as TSH level, gender, HDRS score at the beginning, and concomitant medication as covariates did not change the outcome and were therefore not included in the final model. Similarly, there was no statistically significant difference between groups in MADRS scores at the end of double-blind treatment after adjusting for age and MADRS score at randomization (mean [SD] scores at week 6: levothyroxine, 18.6 [10.7] vs placebo, 21.5 [12.0]; $P = .652$ [analysis of covariance]).

A secondary analysis of women (levothyroxine, n = 17; placebo, n = 15) revealed a significant difference between groups in mean change in HDRS score (levothyroxine, −42.4% vs placebo, −16.6%; $P = .018$) (Figure 2B), but not in men (Figure 2C). When adjusted for age, the latter effect was not significant but showed a statistical trend ($P = .081$).

An MMRM analysis estimated the drug effect on the basis of observed data. The between-group difference (3.6) was not statistically significant ($P = .084$). A secondary analysis of women showed a significant between-group difference in HDRS score (6.8, $P = .012$). There was no statistically significant result for the secondary analysis of men (between-group difference = 0.8, $P = .827$).

The proportion of responders (≥ 50% reduction in HDRS score) at week 6 was 36% (n = 11) for levothyroxine versus 26% (n = 8) for placebo; the difference between groups was statistically nonsignificant ($P = .409$). Remission rates at week 6 were 23% (n = 7) for levothyroxine and 16% (n = 5) for placebo ($P = .520$). No differences between groups were detected regarding the use of sedatives/hypnotics (7 patients received lorazepam in the experimental group vs 8 patients in the placebo group). The mean (SD) cumulative dosage of lorazepam over 6 weeks was 29.1 (18.5) mg for the levothyroxine group versus 27.9 (24.7) mg for the placebo group.

Table 1. Demographic and Baseline Clinical Characteristics (intent-to-treat population)

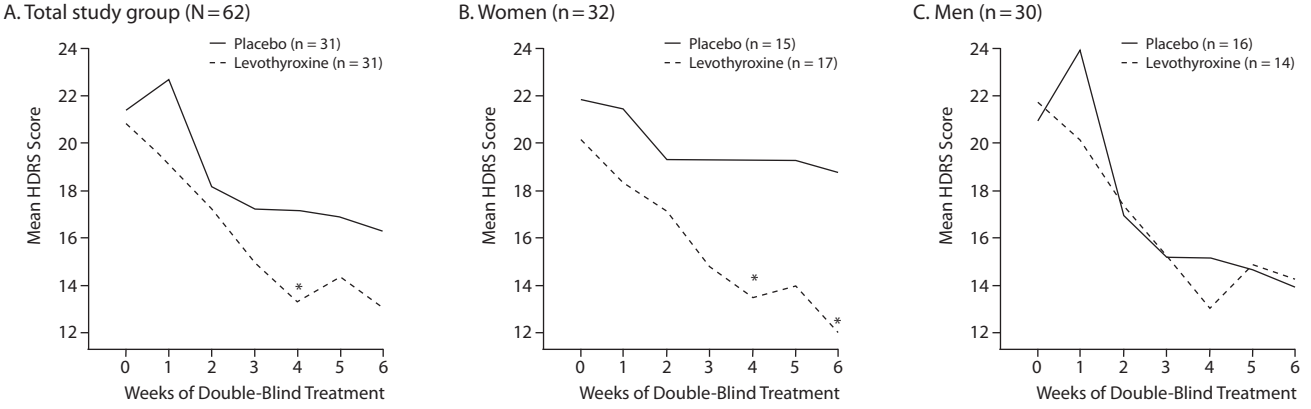
Characteristic	Levothyroxine (n = 31)	Placebo (n = 31)
Bipolar I/II, n	16/15	19/12
Sex, male/female, n	14/17	16/15
Age, mean (SD), y	41.8 (12.9)	48.0 (14.2)
Total no. of mood episodes, mean (SD)	8.0 (7.8)	9.5 (9.2)
Duration of illness, mean (SD), y	12.3 (9.7)	18.1 (15.1)
Duration of current episode, mean (SD), d	134.2 (141.1)	124.2 (156.8)
HDRS baseline score, mean (SD)	20.9 (3.0)	21.4 (4.3)
MADRS baseline score, mean (SD)	28.8 (5.6)	30.3 (6.0)
Comedication, n		
Mood stabilizer monotherapy	11	10
Combination of mood stabilizer and antidepressant(s)	20	21

Abbreviations: HDRS = Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale.

Thyroid Hormone Measurements

In the levothyroxine group only, thyroid hormone levels increased significantly and basal TSH levels decreased

Figure 2. Change in Hamilton Depression Rating Scale (HDRS) Total Score From Randomization Over Time (6 weeks)



*$P < .05$.

Table 2. Gender-Specific Efficacy Outcomes and Thyroid Measurements

	Men		Women	
	Levothyroxine	Placebo	Levothyroxine	Placebo
Response rate, % (n)	35.7 (5)	25.0 (4)	35.3 (6)	26.7 (4)
Remission rate, % (n)	21.4 (3)	18.8 (3)	23.5 (4)	13.3 (2)
Study entry				
Thyroid-stimulating hormone level, mIU/L	1.8	1.5	2.3	1.7
Free triiodothyronine level, ng/L	3.2	3.1	3.2	2.9
Free thyroxine level, ng/dL	1.2[a]	1.2	0.9[a]	1.7
Study end				
Thyroid-stimulating hormone level, mIU/L	< 0.01	1.7	< 0.01	1.4
Free triiodothyronine level, ng/L	6.0	3.4	5.2	3.2
Free thyroxine level, ng/dL	2.8	2.4	2.2	2.8

[a] *t* Test (men vs women in levothyroxine groups); $P = .01$.

significantly with levothyroxine treatment. All thyroid measurements were not statistically different between the 2 groups at the beginning of the study but were significantly different at the end of study (levothyroxine vs placebo: TSH, 0.05 vs 1.4 mIU/L, $P < .001$; FT_3, 5.8 vs 3.2 ng/L, $P < .001$; FT_4, 2.6 vs 1.7 ng/dL, $P < .001$). In the experimental group, FT_4 levels at study entry were significantly lower in women than in men (0.9 vs 1.2 ng/dL, $P = .01$; Table 2), and a trend was observed for higher TSH values (2.3 vs 1.8 mIU/L, $P = .17$) in women. There was a significant association of the TSH values at the beginning of the study with the reduction of HDRS score in the female levothyroxine group in a linear regression model ($F_3 = 3.47$; $P = .05$) (for an overview of thyroid measurements, see Table 2).

Tolerability and Safety

No serious adverse event occurred during the study. In the levothyroxine group, the study was discontinued in 3 patients due to adverse events (mild thyrotoxicosis, exanthema, and switch into mania in 1 patient each) (Figure 1). Discontinuation in the active drug group required no special care. No cardiovascular complications occurred as detected with ECG and measurement of blood pressure (systolic: mean [SD] at baseline, 123 [17] mm Hg; at 6 weeks, 125 [15] mm Hg; $P = .591$; diastolic: mean [SD] at baseline, 78 [10] mm Hg; at 6 weeks, 79 [8] mm Hg; $P = .519$). There was also no significant change in body weight (mean [SD] at baseline, 81.85 [15.50] kg; at 6 weeks, 82.36 [16.08] kg; $P = .269$).

The TSL sum score did not differ significantly between the groups at baseline (mean [SD] for levothyroxine, 15.61 [10.91]; for placebo, 18.68 [18.71]; $P = .440$) or at 6 weeks (mean [SD] for levothyroxine, 15.54 [10.00]; for placebo, 11.64 [9.44]; $P = .181$). Furthermore, there was no change in the TSL score in the levothyroxine group during treatment. The inner restlessness item was the only difference on a single-item level of the TSL showing a trend toward higher scores in the levothyroxine group (χ^2 test, $P = .054$).

DISCUSSION

To our knowledge, this study is the first to test the efficacy and tolerability of supraphysiologic doses of levothyroxine in bipolar depression in a placebo-controlled, double-blind design. Patients treated with levothyroxine did numerically better at every visit starting at week 2 of double-blind treatment than those treated with placebo, reaching statistical significance at week 4 (see Figure 2A). However, the study failed to detect a statistically significant difference between the 2 groups at the end of the study (week 6).

There are several possible reasons for this outcome. Because of the modest sample size, we could detect only large effects, which we probably did in women but not in men. In addition, the strong response of a 5.1-point difference on the HDRS in the placebo group (see Figure 2A) did quite likely contribute to this result. A limitation of the study was the relatively low entrance criteria for depression severity; the mean HDRS score was 21.2 at baseline. There is evidence from studies of antidepressants in unipolar depression that a significant difference between drug and placebo treatment can usually be achieved only for patients with moderate to severe depression.[30]

Of clinical importance is our finding that a better improvement in depression scores with levothyroxine versus placebo was detected in women (see Figure 2B) but not in men. Actually, results from our previous open-label, single-blind study[23] in women with resistant bipolar depression showed similar effects on depression severity with 300 μg of levothyroxine. The finding that women benefited more from thyroid hormone treatment (T_3 or levothyroxine) across different indications in mood disorders agrees with the literature. Although only a few of the studies of adjunctive supraphysiologic doses of levothyroxine treatment intentionally excluded males, the vast majority of patients were females.[21,22] Most interestingly, in studies using the other often-administered thyroid hormone, T_3, in clinical practice in difficult-to-treat unipolar major depression, a gender treatment effect has been described: between 1969 and 1974, 6 double-blind, randomized, placebo-controlled trials investigated the use of T_3 to accelerate the response to a tricyclic antidepressant in patients with unipolar and bipolar disorder. A meta-analysis[31] of these studies reported that T_3 was significantly more effective than placebo in accelerating the antidepressant response in 5 of the 6 studies

and that the effects of T_3 acceleration were greater as the percentage of females participating in a study increased. It is remarkable that 2 of the 6 studies in the meta-analysis specifically reported an earlier and more favorable response in females.[23,32] A strong gender difference was also observed in an algorithm-based augmentation study,[33] in which the addition of T_3 to selective serotonin reuptake inhibitor nonresponders was effective in 10 (62.5%) of 16 women, while none of the 9 men responded.

Gender differences in thyroid system function of bipolar patients are intriguing.[34] The prevalence of thyroid disease is much higher in females than males and increases with age. The most commonly detected abnormality is subclinical hypothyroidism, occurring in up to 20% of postmenopausal women. Females also have higher rates of thyroid autoimmunity. Lithium-induced hypothyroidism occurs more frequently in those who are at higher risk for autoimmune thyroid disease, with females about 5 times more likely to develop hypothyroidism.[11] The gender-specific aspect might be connected to the higher prevalence of clinical thyroid disease in women with bipolar disorder[35] that would lead to greater and faster efficiency of thyroid therapy. Furthermore, subclinical thyroid abnormalities are associated with a poorer response to standard treatments for mood disorders.[19] Our data support the latter findings: at baseline, we detected lower FT_4 and a trend toward higher TSH levels in women treated with levothyroxine. Furthermore, a prediction of treatment outcome with high TSH levels at the beginning of the study could be shown for women treated with levothyroxine.

Overall tolerability of levothyroxine was good in this study, with no serious adverse event occurring. However, 3 patients in the levothyroxine group discontinued treatment because of switch into mania, exanthema, and mild thyrotoxicosis (Figure 1). The TSL sum score, blood pressure, and body weight did not differ significantly between the study groups. This is consistent with previous research demonstrating that treatment with supraphysiologic doses of levothyroxine in patients with mood disorders is not associated with serious side effects such as loss of bone mineral density, even during long-term treatment.[36,37]

The action of thyroid hormones in the adult brain in the context of affective disorders is still unclear, although many of the molecular mechanisms are being unraveled. Thyroid hormone economy has profound impact on neurotransmitter systems, particularly those involving serotonin (5-HT) and norepinephrine.[38] Changes with thyroid hormones were associated with changes in the levels of 5-HT and its metabolites and with changes in serotonin autoreceptor availability.[39–44]

While thyroid hormone monotherapy is not an adequate treatment of primary mood disorders, most textbooks, reviews, and treatment guidelines recommend adjunctive treatment with thyroid hormones (T_3 or levothyroxine) for treatment-resistant mood disorders.[45,46] From previous research and the findings of this study, it seems adequate to recommend hormone therapy with levothyroxine for difficult-to-treat bipolar disorders, particularly in women. In case of nonresponse to standard pharmacotherapy in bipolar depression, add-on treatment with supraphysiologic doses of levothyroxine might be a promising strategy to avoid treatment resistance. Such supraphysiologic doses of levothyroxine are needed in order to significantly increase circulating thyroid hormones.[20,23] In a follow-up study further exploring the value of levothyroxine hormone treatment in bipolar depression, we would suggest a more homogeneous definition of antidepressant pretreatment, a higher severity threshold for study entry, and inclusion of procedures that have been identified to reduce the placebo effects in double-blind trials.

Drug names: carbamazepine (Carbatrol, Equetro, and others), citalopram (Celexa and others), duloxetine (Cymbalta), fluoxetine (Prozac and others), lamotrigine (Lamictal and others), levothyroxine (Tirosint and others), lithium (Lithobid and others), lorazepam (Ativan and others), methylphenidate (Focalin, Daytrana, and others), mirtazapine (Remeron and others), nortriptyline (Pamelor, Aventyl, and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), pregabalin (Lyrica and others), quetiapine (Seroquel), risperidone (Risperdal and others), sertraline (Zoloft and others), tranylcypromine (Parnate and others), venlafaxine (Effexor and others), ziprasidone (Geodon), zolpidem (Ambien, Edluar, and others).

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REFERENCES

1. Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry*. 2002; 59(6):530–537.
2. Judd LL, Akiskal HS, Schettler PJ, et al. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. *Arch Gen Psychiatry*. 2003;60(3):261–269.

3. Perlis RH, Miyahara S, Marangell LB, et al; STEP-BD Investigators. Long-term implications of early onset in bipolar disorder: data from the first 1000 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Biol Psychiatry*. 2004;55(9):875–881.
4. Altshuler LL, Post RM, Black DO, et al. Subsyndromal depressive symptoms are associated with functional impairment in patients with bipolar disorder: results of a large, multisite study. *J Clin Psychiatry*. 2006;67(10):1551–1560.
5. Ghaemi SN, Hsu DJ, Soldani F, et al. Antidepressants in bipolar disorder: the case for caution. *Bipolar Disord*. 2003;5(6):421–433.
6. Sachs GS, Nierenberg AA, Calabrese JR, et al. Effectiveness of adjunctive antidepressant treatment for bipolar depression. *N Engl J Med*. 2007;356(17): 1711–1722.
7. Bauer M, Ritter P, Grunze H, et al. Treatment options for acute depression in bipolar disorder. *Bipolar Disord*. 2012;14(suppl 2):37–50.
8. Sidor MM, Macqueen GM. Antidepressants for the acute treatment of bipolar depression: a systematic review and meta-analysis. *J Clin Psychiatry*. 2011 ;72(2):156–167.
9. Bauer M, Silverman DHS, Schlagenhauf F, et al. Brain glucose metabolism in hypothyroidism: a positron emission tomography study before and after thyroid hormone replacement therapy. *J Clin Endocrinol Metab*. 2009; 94(8):2922–2929.
10. Bauer M, Goetz T, Glenn T, et al. The thyroid-brain interaction in thyroid disorders and mood disorders. *J Neuroendocrinol*. 2008;20(10):1101–1114.
11. Kirov G, Tredget J, John R, et al. A cross-sectional and a prospective study of thyroid disorders in lithium-treated patients. *J Affect Disord*. 2005;87(2–3): 313–317.
12. Bauer M, Blumentritt H, Finke R, et al. Using ultrasonography to determine thyroid size and prevalence of goiter in lithium-treated patients with affective disorders. *J Affect Disord*. 2007;104(1–3):45–51.
13. Gau CS, Chang CJ, Tsai FJ, et al. Association between mood stabilizers and hypothyroidism in patients with bipolar disorders: a nested, matched case-control study. *Bipolar Disord*. 2010;12(3):253–263.
14. Kupka RW, Nolen WA, Post RM, et al. High rate of autoimmune thyroiditis in bipolar disorder: lack of association with lithium exposure. *Biol Psychiatry*. 2002;51(4):305–311.
15. Hillegers MH, Reichart CG, Wals M, et al. Signs of a higher prevalence of autoimmune thyroiditis in female offspring of bipolar parents. *Eur Neuropsychopharmacol*. 2007;17(6–7):394–399.
16. Gyulai L, Bauer M, Bauer MS, et al. Thyroid hypofunction in patients with rapid-cycling bipolar disorder after lithium challenge. *Biol Psychiatry*. 2003; 53(10):899–905.
17. Frye MA, Denicoff KD, Bryan AL, et al. Association between lower serum free T_4 and greater mood instability and depression in lithium-maintained bipolar patients. *Am J Psychiatry*. 1999;156(12):1909–1914.
18. Frye MA, Yatham L, Ketter TA, et al. Depressive relapse during lithium treatment associated with increased serum thyroid-stimulating hormone: results from two placebo-controlled bipolar I maintenance studies. *Acta Psychiatr Scand*. 2009;120(1):10–13.
19. Cole DP, Thase ME, Mallinger AG, et al. Slower treatment response in bipolar depression predicted by lower pretreatment thyroid function. *Am J Psychiatry*. 2002;159(1):116–121.
20. Bauer MS, Whybrow PC. Rapid cycling bipolar affective disorder, II: treatment of refractory rapid cycling with high-dose levothyroxine: a preliminary study. *Arch Gen Psychiatry*. 1990;47(5):435–440.
21. Bauer M, Berghöfer A, Bschor T, et al. Supraphysiological doses of L-thyroxine in the maintenance treatment of prophylaxis-resistant affective disorders. *Neuropsychopharmacology*. 2002;27(4):620–628.
22. Bauer M, Hellweg R, Gräf KJ, et al. Treatment of refractory depression with high-dose thyroxine. *Neuropsychopharmacology*. 1998;18(6):444–455.
23. Bauer M, London ED, Rasgon N, et al. Supraphysiological doses of levothyroxine alter regional cerebral metabolism and improve mood in bipolar depression. *Mol Psychiatry*. 2005;10(5):456–469.
24. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry.* 1960;23(1):56–62.
25. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry.* 1978;133(5):429–435.
26. Bauer M, Bschor T, Pfennig A, et al; WFSBP Task Force on Unipolar Depressive Disorders. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders in primary care. *World J Biol Psychiatry*. 2007;8(2):67–104.
27. First MB, Spitzer RL, Gibbon M, et al. *Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV)*. Washington, DC: American Psychiatric Press, Inc; 1996.
28. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry.* 1979;134(4):382–389.
29. Bauer M, Baur H, Berghöfer A, et al. Effects of supraphysiological thyroxine administration in healthy controls and patients with depressive disorders. *J Affect Disord*. 2002;68(2–3):285–294.
30. Rief W, Nestoriuc Y, Weiss S, et al. Meta-analysis of the placebo response in antidepressant trials. *J Affect Disord*. 2009;118(1–3):1–8.
31. Altshuler LL, Bauer M, Frye MA, et al. Does thyroid supplementation accelerate tricyclic antidepressant response? a review and meta-analysis of the literature. *Am J Psychiatry*. 2001;158(10):1617–1622.
32. Coppen A, Whybrow PC, Noguera R, et al. The comparative antidepressant value of L-tryptophan and imipramine with and without attempted potentiation by liothyronine. *Arch Gen Psychiatry*. 1972;26(3):234–241.
33. Agid O, Lerer B. Algorithm-based treatment of major depression in an outpatient clinic: clinical correlates of response to a specific serotonin reuptake inhibitor and to triiodothyronine augmentation. *Int J Neuropsychopharmacol*. 2003;6(1):41–49.
34. Bauer M, Glenn T, Pilhatsch M, et al. Gender differences in thyroid system function: relevance to bipolar disorder and its treatment. *Bipolar Disord*. In press.
35. Baldassano CF, Marangell LB, Gyulai L, et al. Gender differences in bipolar disorder: retrospective data from the first 500 STEP-BD participants. *Bipolar Disord*. 2005;7(5):465–470.
36. Bauer M, Fairbanks L, Berghöfer A, et al. Bone mineral density during maintenance treatment with supraphysiological doses of levothyroxine in affective disorders: a longitudinal study. *J Affect Disord*. 2004;83(2–3): 183–190.
37. Ricken R, Bermpohl F, Schlattmann P, et al. Long-term treatment with supraphysiological doses of thyroid hormone in affective disorders: effects on bone mineral density. *J Affect Disord*. 2012;136(1–2):e89–e94.
38. Whybrow PC, Prange AJ Jr. A hypothesis of thyroid-catecholamine-receptor interaction: its relevance to affective illness. *Arch Gen Psychiatry*. 1981; 38(1):106–113.
39. Bauer M, Heinz A, Whybrow PC. Thyroid hormones, serotonin and mood: of synergy and significance in the adult brain. *Mol Psychiatry*. 2002;7(2): 140–156.
40. Cleare AJ, McGregor A, O'Keane V. Neuroendocrine e9idence for an association between hypothyroidism, reduced central 5-HT activity and depression. *Clin Endocrinol (Oxf)*. 1995;43(6):713–719.
41. Cleare AJ, McGregor A, Chambers SM, et al. Thyroxine replacement increases central 5-hydroxytryptamine activity and reduces depressive symptoms in hypothyroidism. *Neuroendocrinology*. 1996;64(1):65–69.
42. Gur E, Lifschytz T, Lerer B, et al. Effects of triiodothyronine and imipramine on basal 5-HT levels and 5-HT_1 autoreceptor activity in rat cortex. *Eur J Pharmacol*. 2002;457(1):37–43.
43. Gur E, Lifschytz T, Van De Kar LD, et al. Effects of triiodothyronine on 5-HT_{1A} and 5-HT_{1B} autoreceptor activity, and postsynaptic 5-HT_{1A} receptor activity, in rat hypothalamus: lack of interaction with imipramine. *Psychoneuroendocrinology*. 2004;29(9):1172–1183.
44. Lifschytz T, Segman R, Shalom G, et al. Basic mechanisms of augmentation of antidepressant effects with thyroid hormone. *Curr Drug Targets*. 2006; 7(2):203–210.
45. Goodwin FK, Jamison KR. *Manic-Depressive Illness*. 2nd ed. New York, NY: Oxford University Press; 2007.
46. Grunze H, Vieta E, Goodwin GM, et al; WFSBP Task Force on Treatment Guidelines for Bipolar Disorders. The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: update 2010 on the treatment of acute bipolar depression. *World J Biol Psychiatry*. 2010;11(2):81–109.