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Adjunctive Thyroid Hormone Treatment in Rapid Cycling Bipolar Disorder: A Double-Blind Placebo-Controlled Trial of Levothyroxine (L-T_4) and Triiodothyronine (T_3)

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Abstract

Objectives: This report describes the first comparative double-blind, placebo controlled trial of levothyroxine (L-T_4) and triiodothyronine (T_3) as adjunctive treatments in rapid cycling bipolar disorder.

Methods: 32 treatment resistant, rapid cycling patients who had failed a trial of lithium were randomized into three treatment arms: L-T_4, T_3, or placebo, they were followed for ≥ 4 months with weekly clinical and endocrine assessments.

Results: There were no statistically significant differences between the groups in age, gender, duration of illness, or thyroid status. Markov chain analyses were employed to assess treatment effects on cycling patterns among mood states (euthymia, depression, mania, mixed). *Within groups*, post-treatment the L-T_4 group spent significantly less time depressed or in a mixed state

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Data collection for this study ended in 1998 and therefore the study was not registered in a clinical trials database.

and greater time euthymic. T_3 and placebo groups did not differ significantly pre- and post-treatment in any mood state although the pattern of effects was the same for the T_3 group as the L-T_4 group. *Between-groups*, the L-T_4 group had a significantly greater increase in time euthymic and decrease in time in the mixed state than the placebo group. Other group differences were not significant, although they were in the expected direction.

Conclusions: The findings in this first double-blind study directly comparing the effects of L-T_4 and T_3 therapy against placebo provide evidence for the benefit of adjunctive L-T_4 in alleviating resistant depression, reducing time in mixed states and increasing time euthymic. Adjunctive T_3 did not show statistically significant evidence of benefit over placebo in reducing the time spent in disturbed mood states.

Keywords

bipolar disorder; rapid cycling; thyroid; levothyroxine; triiodothyronine

Introduction

Rapid cycling is the most malignant variant of bipolar disorder, affecting some 25–43% of those who suffer bipolar illness[1]. The rapid cycling phenotype has been defined as four or more mood episodes per year[2]. However, many individuals experience more frequent episodes, with approximately two-thirds suffering 4 to 11 per year, and with nearly all of those suffering 12 or more episodes being female[3–4]. Rapid cycling has a refractory clinical course and is commonly associated with greater work impairment, alcohol abuse, more frequent suicide attempts, and lower response to standard pharmacological treatment than bipolar disorder in general[5&6].

Therapeutic intervention is complex. The majority of individuals with rapid cycling bipolar disorder are treatment-resistant and the literature on controlled studies of pharmacologic intervention is sparse. A PubMed search in November 2017 employing the key words “rapid cycling”, “rapid-cycling”, “bipolar”, and “randomized”, yielded only twelve randomized-controlled trials of pharmacologic treatment for rapid cycling, with the majority of other studies being open trials or post-hoc analyses[7].

An association between the thyroid economy and bipolar disorder – and particularly rapid cycling - is evident from clinical and research studies. Patients with bipolar disorder are more likely to have thyroid abnormalities than healthy individuals[8–9]. Thyroid dysfunction is also associated with poor treatment response in bipolar depression[10] and mixed states[11]. In an early study of 30 patients with rapid cycling, 23% were found to have grade I hypothyroidism, while 27% had grade II and 10% grade III[12]. While those individuals suffering rapid cycling bipolar disorder are disproportionately women[13], findings could not be accounted for by the number of women in the study, or simply by the use of lithium carbonate, an anti-thyroid agent. These observations suggest that the development of hypothyroidism, regardless of etiology, may increase the risk of the rapid cycling variant in bipolar individuals. Subsequent studies have confirmed this[14–16].

This association between the hypothyroid state and the rapid cycling bipolar phenotype first prompted the use of thyroid hormone as an adjunct to pharmacologic treatment in those individuals with refractory disease. In an open-label study, the addition of high-dose (supra-physiologic) levothyroxine (L-T_4) to a stable therapeutic regimen of mood stabilizing drugs in rapid cycling bipolar disorder was associated with improvements in depressive symptoms in ten out of eleven patients and a reduction in manic symptoms in five out of seven patients[17]. These findings were replicated in five additional studies. Taken together, these open-label studies reported an improved response rate of approximately 50%, especially in bipolar patients with resistant depression, when L-T_4 was given concomitantly with mood-stabilizers[18–22].

Emerging from these studies was also the observation that some patients responding to high-dose L-T_4 had no evidence of peripheral thyroid dysfunction. This suggested that in such patients, rather than simply "offsetting" a peripheral thyroid hormone deficit, the high doses of adjuvant L-T_4 were playing a "central" therapeutic role, directly impacting the brain-thyroid economy[23]. Subsequently, in an open-label trial of adjuvant high-dose L-T_4 in treatment-resistant, euthyroid bipolar patients, an improvement in depression scores was found that correlated with shifts in cerebral blood flow as measured by positron emission tomography[24]. These studies were confirmed in a double-blind placebo-controlled study of L-T_4 in bipolar depressed patients[25].

The use of triiodothyronine (T_3) as an adjunct in bipolar illness has been less studied. However, in a retrospective chart review of 159 treatment-refractory patients with diagnoses of bipolar II or bipolar disorder not otherwise specified (NOS) who were treated with T_3, 84% had improvement in depression symptoms and 33% had full remission of their illness[26].

The present study compares L-T_4 and T_3 in bipolar illness, building on these earlier reports. It is the first double-blind placebo-controlled trial of adjuvant thyroid hormone treatment in lithium-refractory rapid cycling bipolar patients. It is also unique in that no study has tested head-to-head the effects of adjunctive L-T_4 against T_3 and placebo. The goal of the study was to determine whether L-T_4 and T_3 are of prophylactic value in reducing episodes of illness in rapid cycling bipolar patients refractory to lithium carbonate and, if so, how they compare to one another. The criteria for improvement focused upon a four-state mood model – specifically whether there was a reduction in the time spent in depressed, mixed, and/or manic states and, correspondingly, an increase in the proportion of time spent euthymic. We were interested both in within-group changes, in the percentage of time spent in each state from pre- to post-treatment, and in whether those changes differed by treatment arm.

Methods

Patients

Patients were enrolled in the Bipolar Clinic within the Department of Psychiatry at the University of Pennsylvania. The study received University of Pennsylvania Institutional Review Board approval prior to enrolling patients. Patients between the ages of 18 and 65 who indicated a willingness to participate had the study procedures explained and completed

written informed consent before being evaluated for possible participation using the Structured Clinical Interview for DSM-III-R[27]. Participants met criteria for bipolar disorder by DSM-III-R and/or Research Diagnostic Criteria, as well as the Dunner-Fieve criterion[2] for rapid cycling (four or more mood episodes per year) for the twelve months prior to study entry. For those patients cycling within hours or days, the symptom duration criteria during episodes were waived. Individuals met severity criteria with a score of ≥ 15 on the Hamilton Depression Rating Scale[28] (HDRS; 17 item) and ≥ 7 on the Young Mania Rating Scale[29] (YMRS), for depressed and (hypo)manic episodes respectively. Patients with current substance abuse were excluded. Inclusion criteria also stipulated that all participants had failed to respond to treatment with lithium for their continued rapid cycling and were euthyroid. Patients remained on lithium throughout the study reported here. Other concomitant medications were stabilized upon entry and were not changed throughout the study follow up period. Thirty-five individuals entered into the study, with 32 participants comprising the final sample for analyses. One participant was lost to follow-up secondary to psychosocial difficulties unrelated to the study, and two were non-compliant with the protocol (see Figure 1; CONSORT diagram).

Procedures and Clinical Measures

Upon study entry, participants underwent an evaluation that lasted at least through one mood cycle (during and into remission of depression, mania, or mixed state), or at least one month for the patients cycling most rapidly. During this prospective evaluation, patients were administered an assessment battery, neuroendocrine assessment at weekly clinic visits, and mood ratings (HDRS, YMRS). Then, participants were randomized into the three treatment arms: levothyroxine (L-T_4), triiodothyronine (T_3), or placebo as an adjunct to their lithium treatment. For the L-T_4 group, dosage of levothyroxine was raised until the free T_4 index was between 4.5 and 7.5 units or until thyroid stimulating hormone (TSH) suppression was reached (<.1 units). For the T_3 group, dosage of triiodothyronine was titrated until serum levels for T_3-resin uptake were between 0.65 and 1.36 units. In the control group, participants received increasing numbers of placebo capsules. The L-T_4 and T_3 groups were also supplemented with placebo capsules until all groups were taking 6–8 capsules per day.

Scheduled weekly clinic visits throughout the trial included the clinical battery and neuroendocrine assessment. Outcome variables for analysis were measured starting one month after the achievement of desired serum iodothyronine levels and patients were then followed for at least 3 additional months. The only medication changes made during this follow up period were adjustments to maintain serum lithium concentration within a therapeutic range (0.8–1.2 mEq/L) and doses of benzodiazepine for agitation as needed. One physician, blind to the clinical state, had access to laboratory data and treatment assignment information to manage the medications. Other physicians completed all clinical assessments, without access to thyroid function indices or treatment assignment. Throughout the study, symptom severity was assessed using the HDRS and YMRS. In this study the coefficient α[30] values for inter-rater reliability on the HDRS and YMRS were 0.94 and 0.82, respectively.

Neuroendocrine Assessment

Upon study entry, patients underwent a physical exam and laboratory assessment of thyroid function in order to document presence or absence of grade I or II hypothyroidism[31]. Patients who had been previously treated for hypothyroidism were not excluded. Seven individuals had a history of hypothyroidism. Five of the seven patients were on thyroid hormone replacement therapy and all were determined to be euthyroid upon study entry. Beginning in the prospective period and throughout the trial, participants received weekly serum thyroid hormone determination, including T_4, T_3-resin uptake, and TSH.

Statistical Assessment and Analysis

The treatment arms were compared on baseline clinical and demographic factors using one-way analyses of variance for continuous variables and chi-squared tests for categorical variables. Because of the complexity of the mood data, encompassing multiple states along with significant inter-subject variability in phase and amplitude in these rapid-cycling patients, a Markov chain technique[32] with bootstrap re-sampling was used to test for longitudinal treatment effects, as explained below.

1) Time Periods—The data were divided into two time periods. The pre-treatment period encompassed measurements obtained prior to randomization. The post-treatment period began four weeks after TSH levels reached <0.1 μIU/mL for the L-T_4 group and when the T_3-resin uptake was in the critical range for the T_3 group. To make the assessment windows comparable in length and spacing, for placebo patients the start of the post-treatment period was set to the median time to stabilization in the L-T_4 group (70 days).

2) Treatment Effect Criteria—The primary outcome measures in this study were the HDRS and YMRS. We used these measures to assign subjects to mood states longitudinally, specifically euthymia, depression, mania, and mixed mania and depression. We then used a Markov Chain approach to compare the week-to-week transition dynamics among these four mood states pre- and post-treatment. Markov chains allow one to assess the probability of moving from a single state to any other state and provide estimates of both the proportion of time spent in each state and the times between transitions, capturing precisely the parameters of the rapid cycling process that are of interest in this comparative study. We assessed the overall dynamics of each treatment group for each study period and tested for changes in the distribution of time spent in each of the mood states from pre- to post-treatment, both within each study arm and differentially between treatment arms.

3) Determining Mood State Sequences—We considered two important elements in making mood state assignments. The first consideration was in setting the appropriate thresholds corresponding to the different mood categories. We considered using absolute clinical cutoffs. However, the patients in our sample were not only treatment refractory, spending little time below the full clinical thresholds, but also with many experiencing considerable individual variation in symptom levels. Therefore, in order to be able to capture effectively treatment-related improvements that were potentially relevant for an individual patient, even when they did not meet clinical remission standards, we instead used the median scores of each patient's pre-treatment HDRS and YMRS assessments as their

personal reference thresholds. By indexing to baseline we were effectively able to capture changes in the patterns of mood over time. We retained the state labels of euthymic, depressed, manic and mixed for interpretive convenience.

Secondly the Markov chain approach requires state assignments at a common set of regularly spaced time-intervals. We opted for a one-week *chain time* since this was the schedule of the clinical visits. However, in practice, mood symptom measurements were somewhat unevenly spaced with an average separation of about two weeks. The original observations were therefore first linearly interpolated and then the mood states were assigned at weekly intervals using the interpolated values to create complete mood state sequences for each patient (Figure 2).

4) Calculating the Transition Matrices and the Long-run Stationary Distributions—In a stationary Markov chain, subjects are assumed to move among a fixed set of states over time and that process is defined by a *transition matrix*, which gives the probability of staying in the current state or moving from it into any of the other states. The transition probabilities are assumed to be fixed and to depend only on a subject's current state (the *Markov property)*. The diagonal elements of the transition matrix (which give the probability of remaining in the current state) can be used to calculate the expected duration of a mood state (higher probabilities mean longer durations). The transition matrix, as a whole, then can be used to calculate the *stationary distribution* of the chain, which gives the long-run (or steady-state) proportion of the time that subjects will spend in each of the mood states. For each treatment arm (placebo, T_3, L-T_4), and treatment period (pre-randomization, post-stabilization) we estimated the transition matrix by pooling the corresponding patient mood state sequences and calculating the fraction of times those patients in a given state had moved to other states at the next week's evaluation. We then used those transition matrices to calculate the corresponding stationary distributions (see Figure 3).

5) Assessing Treatment Effects—Changes in the long-run distributions from the pre-treatment to post-treatment period were used to assess treatment effects within each study group. Subsequently the within-group changes were compared to test for differential treatment effects across the study groups. These analyses were performed for each mood state individually. Since the long-run proportion of time spent in each mood state does not have a standard distribution, to assess statistical significance of treatment effects we used a non-parametric technique called the *bootstrap*[33] whereby one repeatedly resamples observations from the original data set and recalculates the parameter or test statistic of interest to simulate its distribution and corresponding standard errors or confidence intervals. Here we resampled subjects to appropriately preserve the transition structure, generating 10,000 bootstrap data sets, and calculated the appropriate *within* and *between* group differences for each one (see Figures 4 and 5).

Results

Demographic and Clinical Data

No statistically significant differences between groups were observed for age, gender, bipolar disorder type, duration of illness, or other clinical variables (Table 1). The durations

of pre-treatment, stabilization, and post-treatment maintenance periods for each group are described in Table 2. Patients remained in the post-treatment phase of the study for a minimum of 3 months, although the most were followed for longer (4–11 months). One patient was removed from the study at 8 weeks post-treatment (T_3 group) for an episode of tachycardia, but the data were included in the analysis. Side effects in general were minimal (Table 2) and, with the exception of the patient noted above, did not cause individuals to withdraw from the study.

Mood State Analyses – Markov Chain

The transition matrices and long-run stationary distributions are shown in Table 3. Sample estimates and bootstrap distributions were computed for both within group change and between group differences in treatment effects on the long-run fraction of time spent in each of the four mood states and are shown in Figures 4 and 5 respectively:

Within group results indicated that in the post-treatment period the L-T_4 group spent significantly less time depressed (−18.1%, p=.022) or in a mixed state (−13.3%, p=.031) as compared to pre-treatment (see Fig 3) and correspondingly showed a significant increase in the percentage of time euthymic (+33.1%, p=.022). The estimated time spent in the manic state also decreased post-treatment but this change was not significant. The T_3 and placebo groups did not show significant changes from pre- to post-treatment in percentage of time spent in any of the mood states. However, it is worth noting that the estimated changes in the T_3 group followed the same pattern of effects as the L-T_4 group, although the improvements were not as big. The placebo group appeared to spend a greater percentage of time in a mixed state during post-treatment although again this was not statistically significant (Figure 4).

Between-group results showed that those participants receiving L-T_4 had significantly greater gains in time spent euthymic than those in the placebo group (+33.1% vs −6.5%, p=.033). They also showed greater improvement in terms of time spent in a mixed state than the placebo group (−13.3% vs +9.3%, p=.045) and a trend towards having a greater reduction in time spent depressed than did the T_3 group (−7.2% vs −2.7%, p=.121), although this latter effect did not reach significance. Participants in the T_3 group demonstrated a similar pattern of effect over placebo as the L-T_4 group for mixed state, although again this was not significant. The T_3 group, however, did not show the improvement in time spent euthymic that the L-T_4 group did, being similar to the placebo group in this regard. No between group differences were observed in mania (see Figures 5).

Discussion

This study of the rapid cycling phenotype in bipolar disorder is the first to compare the effects of L-T_4 and T_3 adjunctive therapy against placebo in a double-blind design. The findings provide evidence for the beneficial effects of over placebo. In within-group analyses, adjunctive L-T_4 reduced the time spent in the depressed or mixed states and increased the time spent in euthymia. Moreover, the improvements in euthymia and mixed depression/mania were significantly greater in the L-T_4 than in the placebo group. Results from the present study did not provide significant evidence that T_3 adds benefit over placebo

in reducing the time spent in disturbed mood states for these bipolar patients. Most of the effects observed, however, were in that direction suggesting that an adjunctive benefit may exist, albeit smaller than L-T_4. This needs to be further assessed in a larger study.

The L-T_4 findings are consistent with prior open-label research in high-dose adjunctive L-T_4 for bipolar patients[17]. They also complement the recent findings of a randomized placebo-controlled trial of adjunctive L-T_4 where reduction in depressive symptoms was associated with decreases in limbic network glucose metabolism as measured by positron emission tomography[34]. However, most of these previous studies have focused principally on the improvement of depressive symptoms rather than mitigating the course of rapid cycling. Thus, the finding in this double-blind placebo-controlled study that L-T_4 may also reduce the time spent in mixed states is an important one[1].

The study reported here has several limitations. First due to the inherent challenges in studying this refractory population the study is limited in its sample size. The original study was powered for N=60 (20 participants per group). Thus the smaller sample limited our statistical analyses and potential questions we could answer using the original statistical methods proposed (repeated measures ANOVA), which are precarious with respect to power. We therefore used a customized sophisticated suite of non-parametric statistical methods to obtain a more powerful assessment of treatment effects. While this was effective at the group level, the small sample size still prevents us from examining treatment effects at the individual level or looking at differences in individuals who entered the study with a history of hypothyroidism versus those who were euthyroid at entry. Also we were not able to examine the comparative effects of L-T_4 and T_3 in men and women. Life-long sex differences in thyroid axis function, with women disadvantaged, are well documented and known to modify response to pharmacologic treatments. As noted in the introduction other placebo-controlled studies do support that high-dose L-T_4 has particular benefit in women suffering treatment resistant bipolar depression [25].

The value of T_3 in bipolar illness is less clear, both from this study and in the literature. The advantages of adjunctive T_3 for women suffering *unipolar* depression, however, have been demonstrated[25]. A meta-analysis of six double-blind, placebo-controlled studies in unipolar depression revealed that administration of adjunctive T_3 *accelerated* the effects of tricyclic antidepressants, particularly for women[35]. T_3 has also been studied as an *augmentation* agent for patients with treatment resistant unipolar depression. Evidence from a meta-analysis of eight studies suggested that T_3 *may* augment the response to tricyclic antidepressants in some patients, although results were inconsistent[36]. As yet, no one has prospectively examined the augmenting effects of T_3 in treatment resistant bipolar depressed women, potentially an important next step for randomized investigation.

Taken together with previous reports, the results of this study underscore the intimate association between thyroid metabolism and the regulation of mood in bipolar illness, and emphasize the potential value of levothyroxine as an adjuvant agent in the treatment of rapid-cycling bipolar disorder. This growing body of knowledge also confirms, in those with lithium-resistant bipolar illness, that evidence of peripheral hypothyroidism is not a necessary pre-condition to therapeutic response to supraphysiological doses of L-T_4. In this

study, while eight of the rapid cycling individuals had a history of hypothyroidism (L-T_4 group=4; T_3 group=1; Placebo group=3) and 7 were on thyroid hormone replacement therapy (L-T_4 group=4; T_3 group=1; Placebo group=2), all were “euthyroid” in their peripheral thyroid economy upon entry into the protocol and all were treatment resistant. At the other end of the thyroid metabolic spectrum, others with no baseline hypothyroidism, or history of it, also improved with the administration of high-dose L-T_4.

How may this conundrum potentially be explained? Our working hypothesis builds on evidence that the *central* brain-thyroid economy is independently and more precisely regulated than is the peripheral thyroid metabolism[37]. Does the patient with rapid cycling or resistant bipolar depression who responds to high-dose L-T_4, but who has normal peripheral thyroid indices at baseline testing, have a vulnerable and easily disrupted *central* thyroid economy? Further, does lithium, which is known to be an anti-thyroid agent and an inhibitor of the de-iodinase enzymes in the brain and pituitary, further burden central thyroid metabolism[38]? An earlier study from our group, of lithium challenge in 20 medication free patients who presented to the clinic with the rapid cycling phenotype but with normal peripheral thyroid indices, lends some support to this hypothesis. When compared to an age and sex matched normal control group, similarly exposed to a 4-week course of lithium at therapeutic doses, a TRH challenge test at the end of the study period revealed latent hypothyroidism in the rapid-cycling group of patients[23].

In such patients, do changes in central brain-thyroid homeostasis modify the phenotypic expression of bipolar disorder, resulting in a continuous cycling pattern? Both thyroid disease and bipolar disorder are familial illnesses, with strong genetic loading. Rapid cycling is also a robust behavioral phenotype. Rapidly advancing genetic and genomic technologies and a dramatic reduction in the cost of genome-wide association studies now offer a promising opportunity to further pursue this question[39].

Finally, in regards to methodology, we would note that this type of longitudinal study with multiple assessments is difficult to do, and particularly so in rapid cycling bipolar disorder. We also found that the study offered unique statistical challenges and novel techniques have been used in the analysis of these data. Despite these complexities, we believe the study, the first of its kind, is of importance in further establishing the value of the thyroid hormones in modifying the clinical course of refractory bipolar disorder.

In conclusion based on the findings reported here we believe that levothyroxine remains a viable adjunctive treatment in rapid cycling bipolar disorder. Further research into the molecular mechanisms underpinning its therapeutic action is warranted.

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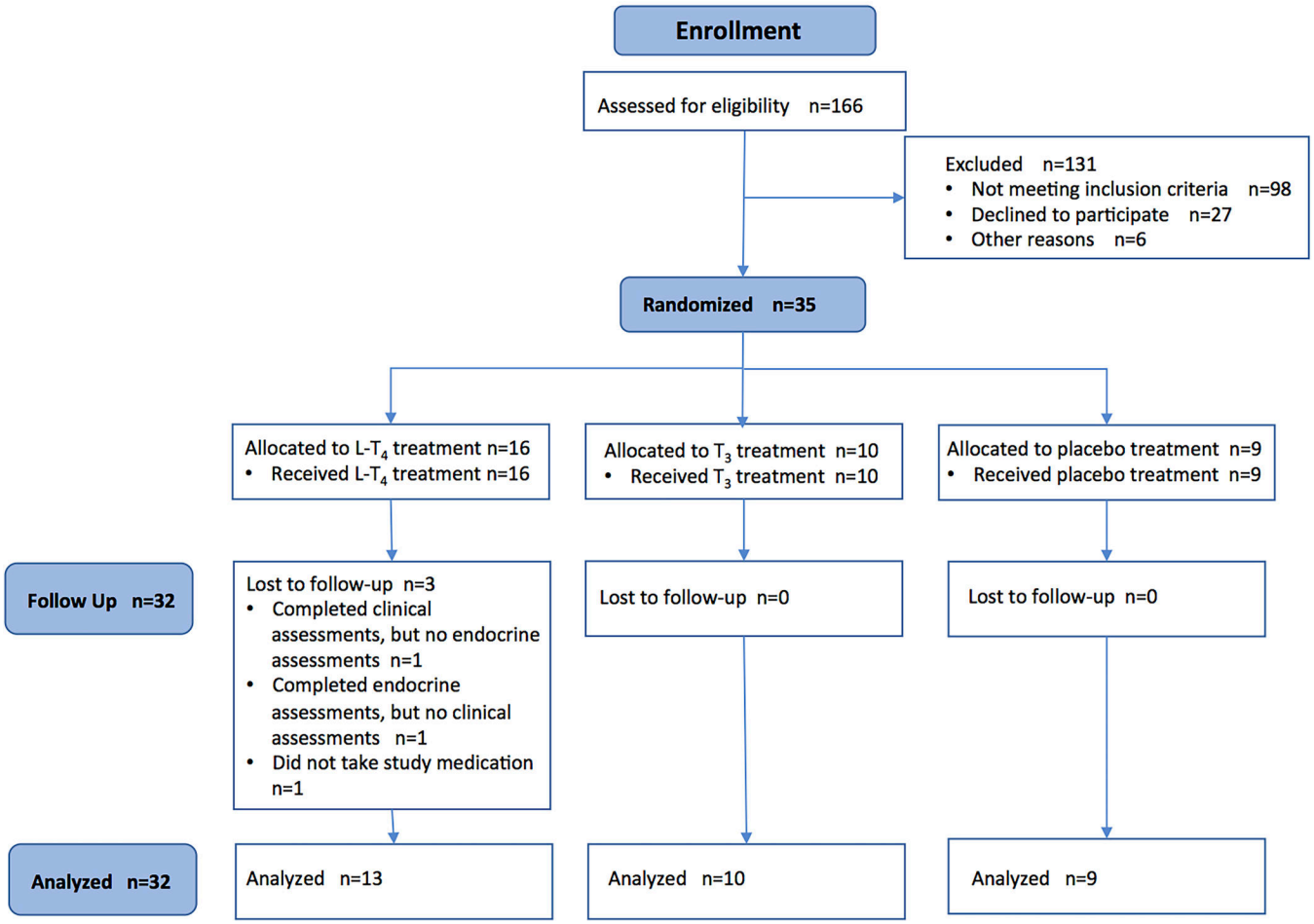

Figure1:
Consolidated Standards of Reporting Trials (CONSORT) diagram.

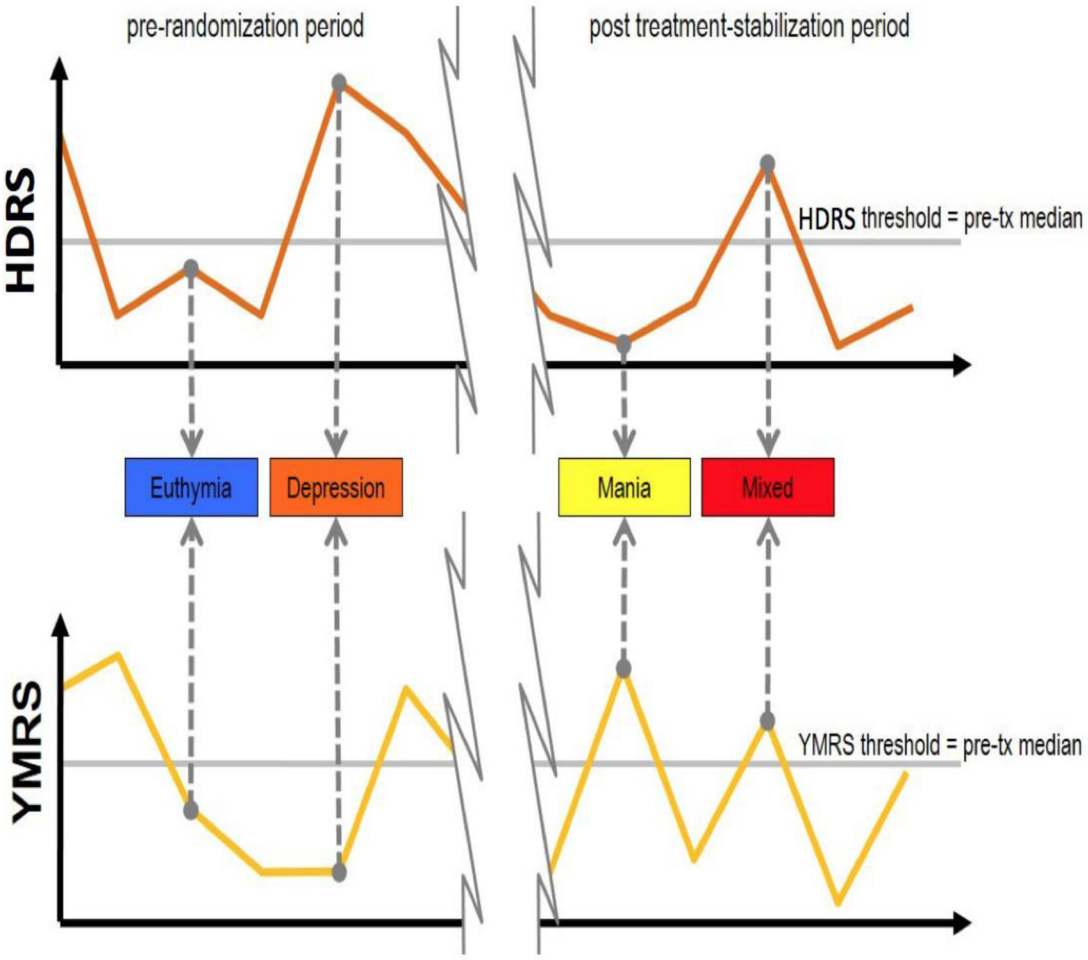

Figure 2.

Mood states were assigned at weekly intervals based on each individual's interpolated scores on HDRS and YMRS relative to their own pre-treatment median (as indicated by the grey lines).

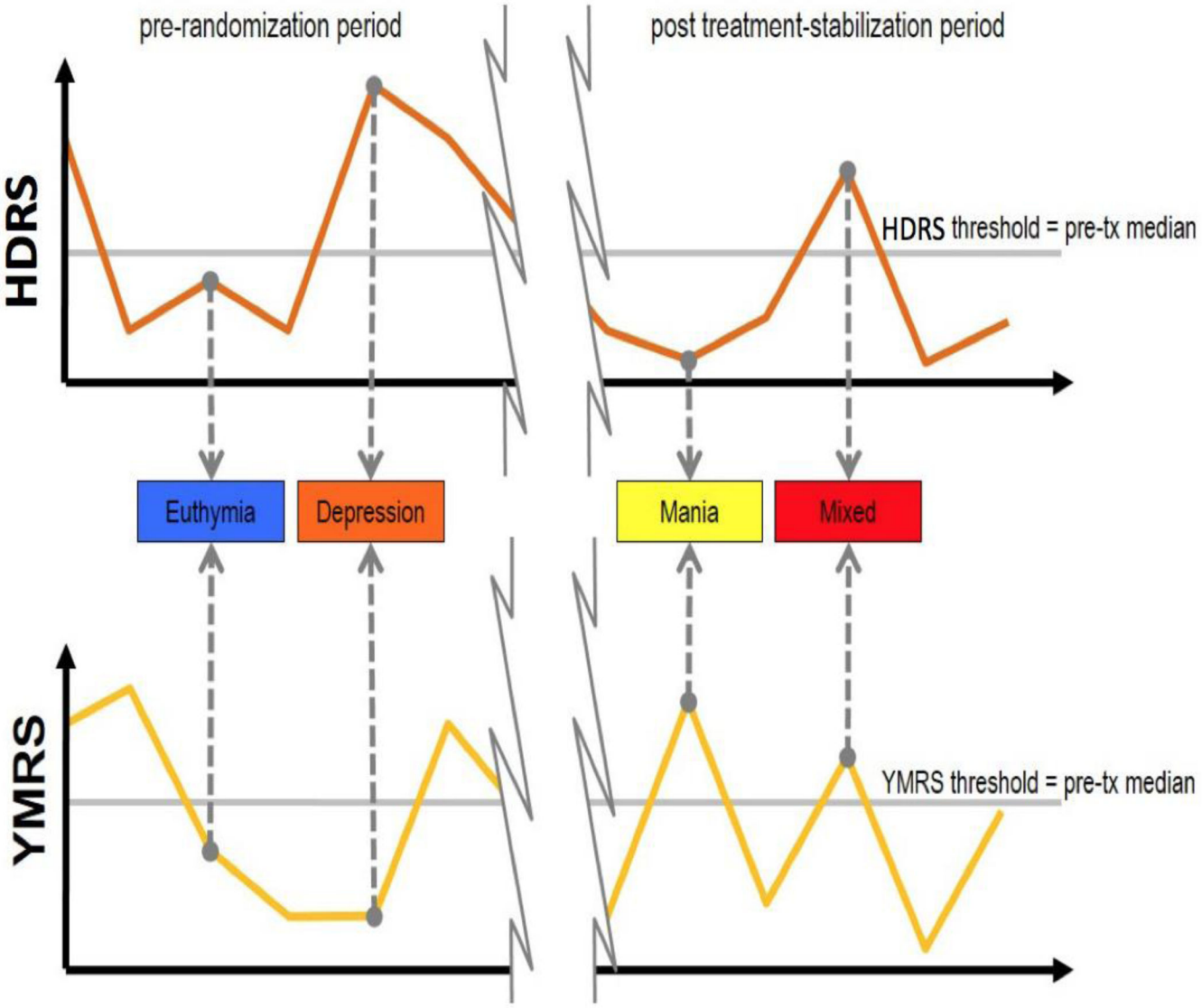

Figure 3.

Individual mood state sequences were combined to estimate the transition matrices (i.e.probabilities of moving from any one state to any other state). The transition matrices were then used to calculate the long-run fraction of time participants would be expected to spend in each of the mood states under the specified treatment regimen. The pre-post differences in the stationary distributions were used to assess the treatment effects on euthymia, depression, mania, and mixed mood states.

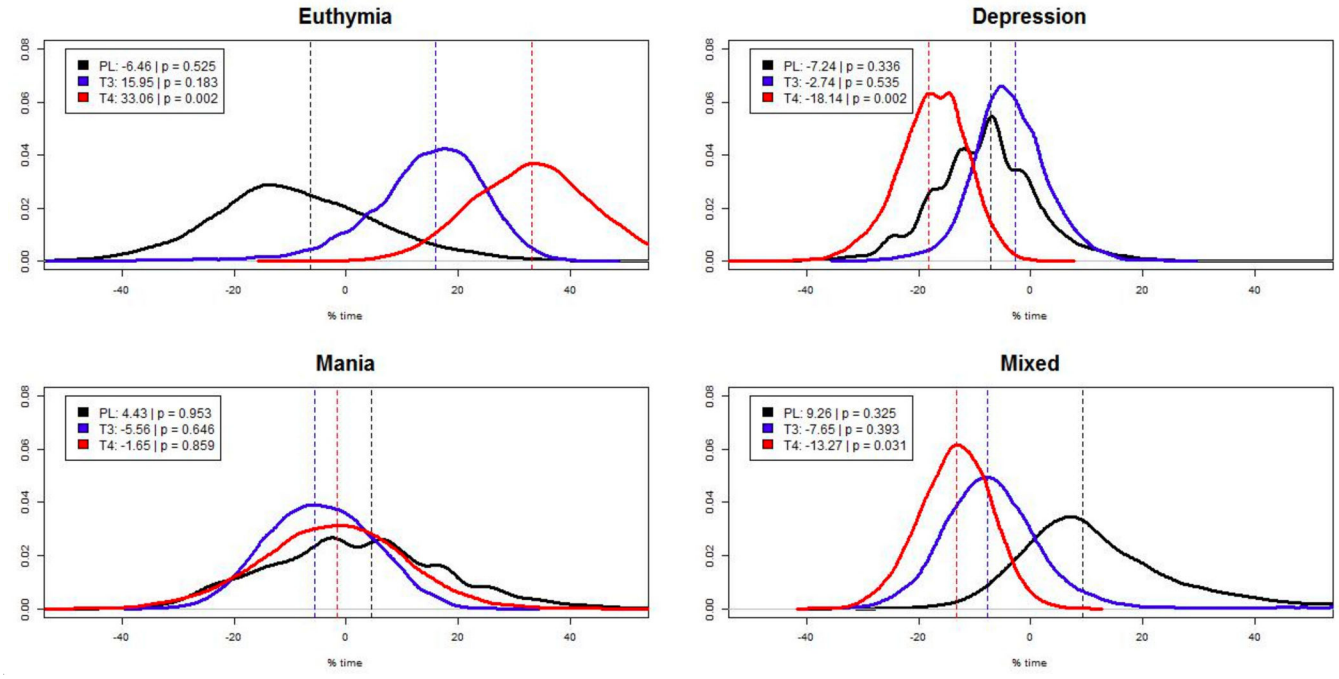

Figure 4.

Figure presents the observed values and smoothed histograms of the bootstrap distributions of the change in percentage time spent in each mood state from baseline to post-treatment within each study arm. The various colors correspond to the treatment arms (black = placebo, blue = T3, red = L-T4). The 0 point on the x-axis indicates where there was no pre-post change in time spent in a particular state. Distributions to the right of 0 indicate an increase in time spent in that state from pre- to post-treatment, while distributions to the left of 0 indicate a decrease in time spent in that state. The dashed lines are observed data estimates for each group. P-values were computed as % of extreme tail to 0, doubled for two-sided test.

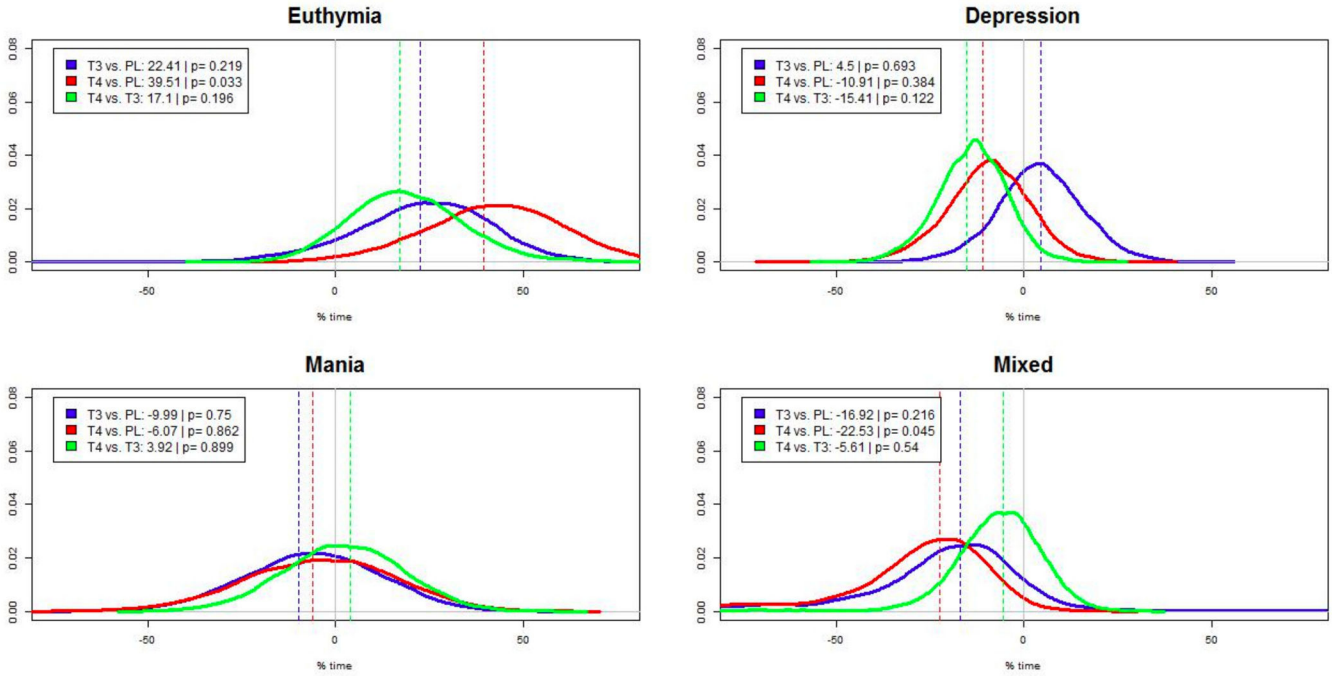

Figure 5.

The figure presents the observed values and smoothed histograms of the bootstrap distributions of the differential treatment effects on the percentage time spent in each mood state for each pair of study arms. The various colors correspond to the pairs (blue = T3 vs placebo, red = L-T4 vs placebo, green = LT4 vs T3). The 0 point on the x-axis corresponds to no difference between the groups in pre-post change in time spent in a particular state. Values to the right of 0 indicate a greater increase (or smaller decrease) in time spent in that state in the first treatment group vs the second, while distributions to the left of 0 indicate a greater decrease (or smaller increase). The dashed lines are observed data estimates for each group comparison. P-values were computed as the % of the extreme tail to 0, doubled for a two-sided test.

Table 1.

Demographics and baseline clinical characteristics

	L-T_4 (*n*=13)	**T_3 (*n*=10)**	**Placebo (*n*=9)**
Age in years, mean (SD)	35.62 (9.88)	37.4 (7.07)	35.44 (9.08)
Duration of illness (years), mean (SD)	12.09 (11.67)	13.89 (7.96)	14.63 (10.8)
Gender (%female)	M=5, F=8 (61.5%)	M=4, F=6 (60%)	M=1, F=8 (88.9%)
Bipolar I/Bipolar II	5/8	6/4	6/3
Co-morbid Axis I:			
Anxiety	3	3	3
History of drug/alcohol	6	5	2
Co-morbid Axis II	2	0	3
Co-medication (in addition to lithium):			
SSRI[1]	1	2	0
Tri-cyclic	1	0	1
Bupropion	0	0	1
Benzodiazepine	6	3	3
Valproate	1	0	1
Levothyroxine	4	1	2
History of Hypothyroidism	4	1	2

[1]SSRI=Selective serotonin reuptake inhibitor

Table 2.

Study characteristics

	L-T_4 (*n*=13)	**T_3 (*n*=10)**	**Placebo (*n*=9)**
Median study period duration (in weeks)			
Pre-treatment	11.7	12.2	14.0
Stabilization	10.7	6.8	10.7
Post-treatment maintenance	16.0	16.6	15.6
Side Effects; *n*			
Diarrhea	5	3	5
Mild tremor	6	4	1
Polyuria	2	2	1
Polydipsia	1	2	2
Dry mouth	1	1	1
Hot flashes/sweating	4	1	0
Dizziness	3	0	0
Fatigue	3	1	2
Tachycardia	0	2	0
Mild palpitations	2	0	0

Table 3:

Transition matrices and stationary distributions pre-randomization and post-treatment stabilization

Transition Matrices									
		pre-randomization				**post-tx-stabilization**			
		Euth	**Dep**	**Manic**	**Mixed**	**Euth**	**Dep**	**Manic**	**Mixed**
Placebo	Euth	.677	.161	.161	.000	.688	.094	.188	.031
	Dep	.217	.522	.043	.217	.188	.625	.063	.125
	Manic	.129	.065	.677	.129	.087	.022	.826	.065
	Mixed	.042	.167	.083	.708	.040	.080	.000	.880
T_3	Euth	.649	.108	.162	.081	.765	.103	.132	.000
	Dep	.172	.586	.034	.207	.308	.577	.000	.115
	Manic	.189	.027	.649	.135	.206	.000	.647	.147
	Mixed	.074	.185	.222	.519	.056	.167	.167	.611
$L\text{-}T_4$	Euth	.448	.276	.241	.034	.846	.057	.081	.016
	Dep	.196	.652	.065	.087	.188	.656	.031	.125
	Manic	.049	.073	.707	.171	.123	.014	.822	.041
	Mixed	.033	.167	.233	.567	.154	.077	.231	.538
Stationary Distributions									
Placebo		.277	.219	.237	.268	.212	.146	.281	.360
T_3		.298	.193	.293	.216	.458	.166	.237	.139
$L\text{-}T_4$		.147	.291	.353	.209	.478	.110	.336	.076