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Clinical Applications of Levothyroxine in Refractory Mood Disorders

M Bauer,[1,2*] M Adli,[1] T Bschor,[3] A Heinz,[1] N Rasgon,[4] M Frye,[2] H Grunze,[5] R Kupka,[6] and PC Whybrow[2]

[1]Department of Psychiatry and Psychotherapy, Humboldt University at Berlin, Charité University Hospital, Schumannstr. 20/21, 10117 Berlin, Germany (**for correspondence*); [2]Neuropsychiatric Institute and Hospital, Department of Psychiatry and Biobehavioral Sciences, University of California at Los Angeles (UCLA), Los Angeles, CA, USA; [3]Technische Universität Dresden, Germany; [4]Department of Psychiatry, Stanford School of Medicine, Palo Alto, CA, USA; [5]Ludwig-Maximilians-Universität Munich, Germany; [6]University Medical Center Utrecht, The Netherlands

E-mail: michael.bauer@charite.de

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A novel approach to refractory bipolar disorder is supplementing standard treatment regimens with levothyroxine (L-T_4). Open-label studies consistently demonstrate that augmentation with thyroid hormone can improve the course of affective illness. Specifically, adjunctive treatment with supraphysiologic doses of L-T_4 may be an effective and well-tolerated strategy for maintenance treatment of patients with rapid cycling and otherwise prophylaxis-resistant bipolar disorders. Evidence has also shown that supraphysiologic doses of L-T_4 may be an effective augmentation agent for acute intervention in unipolar and bipolar patients with a treatment-resistant major depressive episode. This article aims to review the evidence pertaining to treatment of refractory affective disorders with supraphysiologic doses of L-T_4, and provide practice guidelines for its effective and safe use.

Key Words

Bipolar disorder ■ Affective disorder ■ Rapid cycling ■ Prophylaxis-resistance ■ Levothyroxine (L-T_4) ■ Supraphysiologic doses

Introduction

Interest in using thyroid hormones to treat affective disorders arose from observed associations between psychiatric symptoms and thyroid disease states,[1–5] and thyroid hormones have been used as treatment since the early 20th century. In the 1930s and 40s, Norwegian physicians first used hypermetabolic doses of desiccated sheep thyroid gland to successfully treat patients with cyclic disorders they called periodic catatonia.[6,7] This success, coupled with reports of an increased frequency of thyroid axis dysfunction in affective illness, has prompted several groups to administer the synthetic thyroid hormone levothyroxine (L-T_4), to patients with affective disorders.

Review of Treatment Studies with Thyroid Hormone in Affective Disorders

A series of open and controlled clinical trials have been conducted on therapeutic use of thyroid hormones in mood disorders[8,9] since Prange's classic triiodothyronine (T_3) acceleration study in the late 1960s.[10] There is good evidence that T_3 may accelerate the response to tricyclic antidepressants[11] and possibly also augments the response to tricyclic drugs in treatment-refractory patients, although results were inconsistent.[12,13] There are a large number of studies of T_3 augmentation in acute depression, but augmentation with L-T_4 was rarely studied despite several advantages of using L-T_4 instead of T_3. L-T_4 has a longer half-life, better tolerability, is

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easier to measure in blood, and is available in multiple strengths in tablet form.

A few single case reports,[14–19] case series,[20] or open trials of supplementation with L-T_4 were identified in a systematic literature review search of the National Library of Medicine MEDLINE database from February 1966 to February 2003 (summarized in Table 1). Most articles report use of adjunctive L-T_4 in rapid cycling bipolar disorder in adults, but adolescent[18] and geriatric patients[17] have been studied. A single case study describes the repeated prolongation of response to sleep deprivation with concurrent administration of L-T_4 (up to 150 µg/day).[21] Doses of L-T_4 varied broadly from replacement[16] to supraphysiologic doses.[22]

Studies using low, 'replacement' doses of L-T_4 in major depression

One larger study of the augmenting effects of L-T_4 in acute unipolar depression[23] directly compared the antidepressant augmenting effects of T_3 versus L-T_4 in patients not responsive to an adequate trial of desipramine or imipramine. In this 3-week, randomized, double-blind study, nine out of 17 patients (response rate, 53%) responded to T_3, which was significantly more than those responding to L-T_4 (four out of 21 patients; 19%). This result suggested that T_3 should be the augmentation thyroid hormone of choice in acute depression. Owing to the long half-life of L-T_4 (1 week, leading to a steady-state approximately 3–4 weeks after the last increase) however, its therapeutic

Table 1: Use of levothyroxine (L-T_4) in affective disorders: review of augmentation and prophylactic studies

Author	Subjects	Study group size (gender F/M)	Design	Thyroid status pre-L-T_4	L-T_4 dose (µg/day)	Co-medication	Duration of L-T_4 treatment	Outcome no. of responders
Augmentation Studies								
Joffe and Singer[23]	UP	38 (24/14)	RA, DB T_3 versus L-T_4	Euthyroid T_3: 37.5	L-T_4: 150	DMI, IMI	3 weeks	L-T_4: 4/21 R T_3: 9/17 R
Bauer *et al.*[26]	Treatment-resistant depression (unipolar/bipolar)	17 (16/1)	Open	Euthyroid	482 (300–600)	Various AD and MS	8 weeks	8 R, 2 PR, 7 NR
Spoov and Lahdelma[27,a]	21 UP, 1 BD	22 (16/6)	RA, DB, Li-X	Thyroid stimulating hormone elevated in 2 subjects	200	Various AD	4 weeks	L-T_4>lithium
Rudas *et al.*[29,a]	Chronic depression UP/dysthymia	9	Open	Euthyroid	150–300	Various AD, lithium, CBZ	8 weeks	Response rate 55%
Prophylactic Studies								
Stancer and Persad[22]	RC-BD, refractory to prophylaxis	10 (8/2)	Open	Euthyroid	240–500	None, except NLP in 1 case	9 months–9 years	5 R (women), 3 PR, 2 NR
Bauer and Whybrow[24,b]	RC-BD, refractory to prophylaxis	11 (10/1)	Open	7 hypothyroid	150–400	Various MS, 8 on lithium	123 days–150 weeks	9 R, 1 PR, 1 NR
Afflelou *et al.*[20]	RC-BD	6 (4/2)	Case series	Euthyroid	50–325	Various central nervous system drugs	5 weeks–3 years	2 R, 2 PR, 2 NR
Bauer *et al.*[25,c]	UP, BD, SA, refractory to prophylaxis	20 (16/4)	Open	Euthyroid	377.5 (200–600)	Various MS and AD	53 months (range 27–104)	Significant reduction of episodes and morbidity indexes; 52% very much improved, 19% much improved (CGI)

[a]Double-blind, cross-over with lithium augmentation.
[b]Placebo substitution in 4 patients.
[c]Preliminary results in Baumgartner *et al.*[46]
AD, antidepressant; BD, bipolar disorder; CBZ, carbamazepine; CGI, Clinical Global Impression Scale; DB, double-blind; DMI, desipramine; IMI, imipramine; Li-X, cross-over study with lithium; MS, mood stabilizer; NLP, neuroleptic; NR, non-response; PR, partial response; R, response; RA, randomization; RC-BD, rapid cycling bipolar disorder; SA, schizoaffective disorder; T_3, triiodothyronine; UP, unipolar major depressive disorder.

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effects may not be evident in a 3-week trial (as suggested by the authors in a later review[12]).

Studies using high, 'supraphysiologic' doses of L-T_4

Prophylaxis studies in refractory unipolar and bipolar disorder

Studies using supraphysiologic doses (defined as ≥200 µg/day) of L-T_4 aim to elevate thyroid hormone levels beyond the normal (reference) range. Administering supraphysiologic doses of L-T_4 (up to 500 µg/day) as prophylactic medication (Table 1), Stancer and Persad[22] reported that rapid cycling ceased in five out of eight women with bipolar disorder, but not in two men. Later, a study using adjunctive supraphysiologic doses of L-T_4 to treat 11 patients (10 women [of whom nine were pre-menopausal] and one man) with refractory rapid cycling bipolar illness was described.[24] L-T_4 treatment was initiated after stable 'therapeutic' blood levels of mood stabilizing medications had been reached, and the physiological criteria for optimum treatment with L-T_4 was elevation of T_4 serum levels to approximately 150% of normal. Adjunctive treatment with L-T_4 reduced the manic and depressive phases in both amplitude and frequency, and led to remittance in some patients. Four patients also underwent single- or double-blind placebo substitution: three patients relapsed, after switching to placebo, into depression or cycling.[24]

In a recently published, 8-year long-term study, adjunctive treatment of prophylaxis-resistant unipolar and bipolar patients (21 women, five men) with supraphysiologic doses of L-T_4 prevented affective episodes in approximately 60% (for details see Table 1). There was a significant reduction in number of affective recurrences and morbidity indexes during treatment, compared with the same time period before L-T_4 administration (mirror-image method). A substantial number of these refractory patients also experienced full remission. The mean length of adjunctive treatment with L-T_4 was 51.4 months, and mean L-T_4 dose at study end was 378.6 µg/day.[25]

L-T_4 augmentation studies of major depressive episodes

Evidence emerging from acute intervention studies suggests that add-on treatment with supraphysiologic doses of L-T_4 is also effective in reducing depression in treatment-refractory patients with a major depressive episode. An open-label study was conducted on 17 severely treatment-resistant, acutely depressed bipolar (n=12) and unipolar (n=5) patients, who had failed to respond to at least two adequate treatment trials with antidepressants. Eight weeks after addition of L-T_4 to the treatment regimen, the patients' mean score on the Hamilton Rating Scale for Depression (HRSD, 21 items) was 11.6, compared with 26.6 before addition of L-T_4. Eight patients were in full remission (defined as a ≥50% reduction in HRSD-21 score and an end score of ≤8) after 8 weeks of treatment and two other patients were in full remission after 12 weeks.[26]

Spoov and Lahdelma[27] compared lithium augmentation, an established strategy for patients not responding to antidepressants, with L-T_4 augmentation (L-T_4 dose, 200 µg/day) in a group of unipolar depressed patients non-responsive to 4-weeks of treatment with an antidepressant. The percentage reduction in depression ratings was significantly greater in patients taking L-T_4.[27]

The effects of open-label, add-on L-T_4 medication (mean dose 320 µg/day) for 7 weeks were investigated in euthyroid, young women with refractory bipolar depression.[28] L-T_4 treatment improved mood as indicated by a reduction of the HRSD-21 score from 23.2 to 6.0, and reduction of the Beck Depression Inventory score from 33.4 to 11.6, at study end (P<0.001 for both). Of the 10 patients enrolled, seven women were full responders to augmentation with L-T_4 (reduction in HRSD-21 score of >50%; end score ≤7), and three women were partial responders (reduction in HRSD-21 score of >50%; endpoint score ≥8). Similarly, Rudas *et al.*[29] reported that augmentation with high-dose L-T_4 (mean dose, 235 µg/day) showed antidepressant effects in six out of seven patients with chronic depression and dysthymia in an 8-week open-label study.

In summary, the diagnostic group within affective disorders, age of study participants, indication for L-T_4 augmentation, and L-T_4 dose used in the case reports and studies varied greatly (Table 1). The results, however, indicate that augmentation with supraphysiologic doses of L-T_4 is a viable treatment strategy for patients with refractory affective disorders. Augmentation with L-T_4 has not yet been studied in a double-blind, placebo-controlled trial in affective illness, but studies to date (Table 1) describe beneficial effects, and in some refractory patients dramatic responses were seen.[22,24–26]

Side Effects and Tolerability of Treatment with Supraphysiologic L-T_4 Doses

General side effects

In studies using supraphysiologic doses of L-T_4, a striking finding was that patients tolerated the high doses of thyroid hormone surprisingly well.[22,24–26,30] The low rate of side effects contrasts

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with that typically seen in patients with primary thyroid disorders, or healthy controls, treated with higher than replacement doses of L-T_4.[31] Despite increased serum thyroid hormone levels ('hyperthyroxinemia'), patients with affective disorders reported only minimal side effects. Increased sweating, tremor, pulse increase, and increase in agitation were most commonly reported. No serious adverse events were observed, even after treatment with supraphysiologic doses of L-T_4 over a period of several years,[24,25,30] but the total patient numbers are small.

Patients' subjective response and attitude to supraphysiologic L-T_4 treatment was favorable. In a study of 16 patients, none expressed a negative response, and the majority felt this was the right medication for them.[30]

The mechanism behind tolerability of supraphysiologic doses of L-T_4 in patients with affective disorders remains speculative. Treating mood disorders with high dose L-T_4, however, does not result in excessive peripheral levels of T_3 (the hormone with the highest biologic activity),[24–26,31] in contrast with endogenous production of thyroid hormone secondary to hyperthyroidism. It has been speculated that a low thyroid reserve may contribute also to the excellent tolerability to L-T_4 supplementation of patients with bipolar disorder.[9]

Bone density studies

A concern over long-term prophylactic treatment with thyroid hormone is the increased risk of bone density loss and consequent osteoporosis. Thyrotoxicosis – the clinical syndrome of hypermetabolism, when serum concentrations of free thyroxine (fT_4), free T_3 (fT_3), or both are increased – causes a decrease in bone mass. A history of thyrotoxicosis is a known risk factor for osteoporosis. In two cross-sectional studies, 26 pre-menopausal and postmenopausal women and men with mood disorders received supraphysiologic L-T_4 treatment for 12 months or longer. No significant loss of bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry.[32,33] In a prospective, longitudinal study of 21 patients (16 women, five men), BMD measurement was performed after patients had received thyroid stimulating hormone (TSH)-suppressive therapy with L-T_4 (mean dose 411 µg/day) for an average of 16.4 months, and again after 33.6 months (mean dose 416 µg/day). Comparison of BMD after treatment with an age-matched reference population found no significant bone loss (Bauer M, personal communication, 2003). Regular assessment of BMD during long-term supraphysiologic thyroid hormone treatment is recommended, however, particularly for postmenopausal women and those with a history of thyroid disease.

Cardiovascular system

Thyrotoxicosis is associated also with an increased risk of cardiovascular changes, including atrial fibrillation. Cardiovascular assessment, including 12-lead electrocardiograms and monitoring blood pressure and body weight in patients receiving supraphysiologic doses of L-T_4 detected no significant changes or adverse effects during long-term treatment.[25,26,34] In some patients, there was an increase in pulse rate (typical increase, 10–20 beats/minute; rarely beyond 100 beats/minute) that usually subsided after a decrease in L-T_4 dose. The long-term effects of treatment with supraphysiologic doses of L-T_4 on other cardiovascular functions, e.g. ventricular function, cardiac output, and systemic vascular resistance, have not been objectively studied.

Practice Guidelines for Use of L-T_4 in Refractory Affective Disorders

Indications

Treatment with supraphysiologic doses of L-T_4 should be reserved for patients with refractory mood disorders because of limited evidence from controlled data and potential hazards. Overall, there is more evidence on L-T_4 efficacy in bipolar disorder, but some evidence that it works in unipolar depressive disorders. Specifically, augmentation with L-T_4 is indicated in patients with:

- Rapid cycling bipolar affective disorder
- Prophylaxis-resistant bipolar and unipolar affective disorders
- Treatment-resistant major depressive episodes (with or without a history of mania or hypomania).

Prophylaxis- and treatment-resistance is usually defined as failure to respond to two medication trials given at adequate doses for an appropriate duration.[25,26] Initiation of L-T_4 treatment is not recommended during a manic or hypomanic episode due to the lack of experience and risk of worsening the manic state.[3] In rare cases, however, manic states may be associated with hypothyroid conditions;[3] in such cases, supplementation with thyroid hormone is indicated in addition to standard antimanic drug treatment.

Investigations prior to and during L-T_4 treatment

The experimental nature of supraphysiologic L-T_4 treatment must be recognized. Careful examination of patients to identify potential hazards and exclude conditions that place a patient at predictable risk is required (Table 2).

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Table 2: Contraindications for use of supraphysiologic doses of levothyroxine in patients with refractory affective disorders

Thyroid conditions
- Current hyperthyroidism
- Previous or current thyroid adenoma

Cardiac
- History of myocardial infarction
- Arrhythmia
- Insufficiency
- Malignant, unstable hypertension

Pregnancy and breast feeding

Postmenopausal women with evidence of osteopenia/osteoporosis, and without concurrent protection for bone loss

Age >70 years

Severe organic brain disorder (dementia)

A series of investigations are recommended for baseline (pre-treatment) medical evaluation of the patient and during treatment, which are summarized in Table 3. If pre-treatment investigations show abnormal findings, or if any medical problems arise during L-T_4 treatment, consultation with an endocrinologist or internist is recommended.

In the past, many endocrinologists and internists hesitated or resisted treating psychiatric patients with L-T_4. Experience has shown that it is wise to provide such consultants, before discussing a patient, with copies of reprints documenting experience with this treatment in psychiatry and the observation that patients with bipolar disorder tolerated this approach unusually well. In discussions with medical consultants, the suicide risk of a patient with refractory mood disorder should be considered and weighted against the risks of L-T_4 treatment (risk–benefit assessment).

Dosing regimen of L-T_4 treatment

Pre-treatment thyroid status determines the dosing regimen (summarized in Table 4). The speed by which the L-T_4 dose can be increased varies with the patient's pre-treatment thyroid status, and tolerability to the agent during the initial treatment phase.

Generally, the dose should be increased more slowly in patients with overt and subclinical hypothyroidism. In hypothyroid patients, the appropriate speed of treatment depends on duration and severity of hypothyroidism, and presence of other associated medical disorders. The initial dose may range from 25–50 µg/day, to a full replacement dose based on age, weight, cardiac status, and severity of hypothyroidism.[35] Once a euthyroid state is established, we recommend a 'wait and see' approach for 4–8 weeks before deciding if additional supraphysiologic L-T_4 treatment would be beneficial.

A faster speed of dose increase is recommended for baseline euthyroid patients (see bottom row in Table 4). If side effects occur (most often sweating or tremor), a reduction in dose or slower speed of dose increase usually helps. The target dose of L-T_4 is a matter of debate, but our experience suggests that 250–400 µg/day is the preferred range, depending on tolerability and response.

Table 3: Recommended investigations prior to and during treatment with supraphysiologic doses of levothyroxine (L-T_4)

Investigation[a]	Pre-L-T_4 treatment	Every 3 months	Every 12 months
Psychiatric history and status	✘	✘	✘
Comprehensive medical history	✘	✘	✘
Physical examination	✘	✘	✘
Consultation with endocrinologist/intern	✘[b]	✘[e]	✘[e]
Vital signs (blood pressure and pulse)	✘	✘	✘
Body weight	✘	✘	✘
Electrocardiogram[c]	✘	✘	✘
Thyroid function tests (thyroid stimulating hormone, thyroid hormones[d])	✘	✘	✘
Routine laboratory evaluations (liver enzymes, white and red blood cell count, electrolytes, creatinine)	✘		✘
Bone mineral density (dual-energy X-ray absorptiometry)	✘[f]		✘

[a]Consider additional radiological investigations in patients with history or suspected thyroid disorder (e.g. sonography or scintigraphy of the thyroid gland).
[b]If pre-treatment shows abnormalities.
[c]Consider 24-h electrocardiography recording if history of arrhythmia.
[d]Total T4, free T4, and total T3 levels; optional free T3 levels and thyroid antibodies (TPO antibodies).
[e]Only in case of tolerability problems or side effects.
[f]Only in patients who receive L-T_4 prophylactically (≥3 months).

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Table 4: Recommended dosing regimens for the use of supraphysiologic doses of levothyroxine (L-T_4) in patients with refractory affective disorders

	L-T_4 start dose (µg/day)[a]	L-T_4 dose (µg/day) increase[a]	Target L-T_4 dose (µg/day)	Projected thyroid axis status for treatment with supraphysiologic L-T_4 doses
Patients with overt hypothyroidism[b] (thyroid stimulating hormone increased, thyroid hormones decreased)	25–50	Slow[c]	250–400	Thyroid stimulating hormone suppressed
Patients with subclinical hypothyroidism[b] (thyroid stimulating hormone increased)	25–50	Slow[c]	250–400	Increase T4 level to ≥50% of pre-treatment level, thyroid stimulating hormone suppressed
Euthyroid patients (normal thyroid stimulating hormone)	100	100/week	250–400	Increase T4 level to ≥50% of pre-treatment level, thyroid stimulating hormone suppressed

[a]Single morning dose (approximately 30 min before breakfast).
[b]Slower L-T_4 dose increase and closer monitoring recommended.
[c]Appropriate dose increase after 6–8 weeks of treatment to achieve euthyroid status; for details see guidelines of the American Association of Clinical Endocrinologists.[35]

Duration and discontinuation of treatment with L-T_4

Duration of L-T_4 treatment is determined by clinical indication of use. In patients with treatment-resistant depression, augmentation with L-T_4 should be administered for at least 8 weeks, to allow assessment of the patient's response. This time period is necessary because with a half-life of 1 week, a steady-state is not reached until approximately 3–4 weeks after the last dose increase. If the patient responds, L-T_4 should be continued as long as antidepressant medication is required.

The recommended minimum duration of treatment for patients with rapid cycling bipolar disorder is 6 months, and should be 12 months for patients with other prophylactic-resistant bipolar disorder. If the patient responds, prophylactic treatment may need to be continued for long periods (as long as no severe adverse effects develop), but a minimally effective duration is recommended because of cardiac and bone risks.

Discontinuation of treatment is recommended when the patient does not respond to this intervention. Due to the long half-life of L-T_4, discontinuation can be performed over 1–2 weeks, or even immediately (depending on the reason for discontinuation), without adverse effects.

Mechanisms of Action

Thyroid hormone receptors are widely distributed in the brain, and thyroid hormones have multiple effects on the central nervous system (CNS).[36,37] This action includes the limbic system structures that have been implicated in the pathogenesis of mental disorders, and where thyroid hormone receptors are prevalent.[36] The specific neurochemical basis and functional pathways of thyroid hormones that underlie therapeutic effects on mood are unknown.[37] Influence of the thyroid system on neurotransmitters that putatively play a major role in regulating mood and behavior, particularly serotonin and norepinephrine, may contribute to the mechanisms of action.[37–39] However, it is not clear whether these are the seminal disturbances accounting for mood modulation and behavioral change. Furthermore, within the CNS, the regulatory cascade, through which thyroid hormones exert their effects, is not well understood: thyroid hormone transport into the CNS, deiodinase activity in the brain, nuclear binding to genetic loci, and ultimately protein synthesis, may all be involved.[40,41] For instance, reduced levels of transthyretin (TTR), as detected in the cerebrospinal fluid of depressed patients,[42] might disrupt delivery of thyroid hormones to regions inside the blood–brain barrier despite feedback to the

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hypothalamus and pituitary to maintain peripheral thyroid hormone levels. One hypothesis for depression is that lack of TTR accounts for 'brain hypothyroidism', with normal peripheral (serum) thyroid hormone concentration, and thus contributes to the failed response to standard antidepressive treatments.[42]

There is growing evidence, from clinical research, that thyroid hormone levels below or at the lower end of the normal range (thyroid hypofunction), may be especially relevant to the pathophysiology of bipolar disorder and may result in a suboptimal outcome. Frye *et al.*[43] reported that a low level of fT_4, even if within the 'normal' range, was associated with more affective episodes and greater severity of depression during prophylactic lithium treatment in patients with bipolar disorder. It appears, therefore, that a higher fT_4 level is advantageous for treatment with lithium. Lower free thyroxine index values and higher TSH values (but within the normal range) were also significantly associated with poorer treatment response in bipolar patients during an acute depressed phase.[44] A 4-week challenge study, with therapeutic doses of lithium (a prophylactic agent with established 'antithyroid' properties), found significantly higher delta TSH levels after thyroid releasing hormone stimulation in unmedicated rapid cycling bipolar patients compared with healthy controls.[45] The investigators postulated that if 'central' thyroid hypofunction is induced by lithium treatment, or any other mechanism, increasing the availability of thyroid hormone to the brain may be therapeutic, with consequent modification of the mood state and improved clinical outcome.[45]

Conclusions

Open-label studies have consistently demonstrated that the behavioral expression of bipolar disorder can be modified by a change in thyroid status. In many instances, the course of illness is improved through use of supraphysiologic doses of $L\text{-}T_4$. The therapeutic and prophylactic effects of adjunctive supraphysiologic $L\text{-}T_4$ doses in refractory mood disorders are promising, but remain experimental due to the open study design applied in severely ill patient populations. Further research, using more rigorous scientific designs (e.g. randomized, double-blind, placebo-controlled), to confirm these optimistic results is now planned. Acute treatment and prophylaxis of bipolar patients with $L\text{-}T_4$ appears to be a most promising strategy for severely ill patients with affective disorders.

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Key Points

Clinical Applications of Levothyroxine in Refractory Mood Disorders

- Many individuals with refractory mood disorder do not respond adequately to standard medications
- Adjunctive treatment with supraphysiologic doses of $L\text{-}T_4$ appears to be effective and well tolerated in maintenance treatment of some patients with rapid cycling and otherwise prophylaxis-resistant bipolar disorders
- Supplementation of antidepressant and/or mood stabilizer treatments with supraphysiologic doses of $L\text{-}T_4$ may be effective in patients with bipolar disorder during a phase of refractory depression, and in patients with chronic unipolar depression
- The therapeutic and prophylactic effects of adjunctive supraphysiologic $L\text{-}T_4$ doses in refractory mood disorders are promising, but remain experimental. Further research, using rigorous scientific designs is planned to confirm these optimistic results
- Acute treatment and prophylaxis of bipolar patients with $L\text{-}T_4$ appears to be a most promising strategy for severely ill patients with affective disorders

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Key Paper

Search for a common mechanism of mood stabilizers

Harwood AJ, Agam G

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Manic-depression, or bipolar affective disorder, is a prevalent mental disorder with a global impact. Mood stabilizers have acute and long-term effects and at a minimum are prophylactic for manic or depressive poles without detriment to the other. Lithium has significant effects on mania and depression, but may be augmented or substituted by some antiepileptic drugs. The biochemical basis for mood-stabilizer therapies or the molecular origins of bipolar disorder is unknown. One approach to this problem is to seek a common target of all mood stabilizers. Lithium directly inhibits two evolutionarily conserved signal transduction pathways. It both suppresses inositol signaling through depletion of intracellular inositol and inhibits glycogen synthase kinase-3 (GSK-3), a multifunctional protein kinase. A number of GSK-3 substrates are involved in neuronal function and organization, and therefore present plausible targets for therapy. Valproic acid (VPA) is an antiepileptic drug with mood-stabilizing properties. It may indirectly reduce GSK-3 activity, and can up-regulate gene expression through inhibition of histone deacetylase. These effects, however, are not conserved between different cell types. VPA also inhibits inositol signaling through an inositol-depletion mechanism. There is no evidence for GSK-3 inhibition by carbamazepine, a second antiepileptic mood stabilizer. In contrast, this drug alters neuronal morphology through an inositol-depletion mechanism as seen with lithium and VPA. Studies on the enzyme prolyl oligopeptidase and the sodium myo-inositol transporter support an inositol-depletion mechanism for mood stabilizer action. Despite these intriguing observations, it remains unclear how changes in inositol signaling underlie the origins of bipolar disorder.