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ASCP Corner

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Thyroid Hormone Use in Mood Disorders:
Revisiting the Evidence

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Alterations in thyroid functioning have been of long-standing interest in the research and treatment of depressive disorders. Thyroid hormones may play a role in mood regulation by modulating serotonin and norepinephrine neurotransmission. As such, thyroid hormone therapy (THT) has been investigated as a treatment option for depression and has been used clinically to treat mood disorders in patients with and without hypothyroidism.[1–3] What follows is an overview of the available literature discussing the potential benefits and harms of THT in the management of unipolar and bipolar depression.

Major Depressive Disorder

Several randomized controlled trials (RCTs) and non-randomized studies report positive findings for the use of triiodothyronine (T_3) in the *acceleration* of antidepressant response in major depressive disorder (MDD).[2,4] The data reporting T_3 use as an accelerating agent with a tricyclic antidepressant (TCA) are more favorable in older studies than in newer studies when THT is added to a selective serotonin reuptake inhibitor (SSRI) (and there are no published serotonin norepinephrine reuptake inhibitor acceleration trials), making it hard to know if this is a true drug difference or an artifact of older versus newer study designs or their populations. A meta-analysis of 4 RCTs (n = 444) comparing T_3 and SSRI coinitiation therapy with SSRI monotherapy for MDD showed no added benefits of combining T_3 with an SSRI in either response or remission rates.[5]

Thyroid hormone augmentation is widely used as a treatment option in MDD when first-line treatment approaches have been unsuccessful.[6–8] A meta-analysis of controlled clinical trials suggested a positive effect of T_3 addition to TCA in partial responders.[3] However, the authors concluded a need for replication of these findings in large RCTs. Sequenced Treatment Alternatives to Relieve Depression (STAR*D), a large study that examined several different antidepressant switching and antidepressant augmentation strategies, evaluated the augmentation of antidepressant action by addition of T_3. Subjects with MDD in whom other treatment strategies had already failed were randomly assigned to receive augmentation with either T_3 or lithium. Each study arm showed only modest improvement, and there was no statistical difference in outcomes between the two augmentation strategies.[9] A few studies have used levothyroxine (L-T_4) as an augmentation agent as well, with some encouraging results.[10,11] In a recent network meta-analysis of 65 studies evaluating the efficacy of 19 augmentation agents in patients with failure of at least one antidepressant, thyroid hormones (both T_3 and L-T_4) were effective augmentation agents.[12] Supraphysiologic doses of up to 500 µg/d (with the goal to achieve TSH suppression and to increase free T_4 [fT_4] levels by ≥ 50% compared with the pretreatment level) of L-T_4 have been used in highly treatment-refractory patients and were overall well tolerated.[13]

Thyroid hormone therapy is often used among depressed patients with subclinical hypothyroidism (SCH) and high-normal TSH levels.[7] There is debate about what TSH cutoff level should constitute euthyroid status with respect to predicting depression outcomes and whether high-normal TSH levels signal a role for considering optimization of thyroid function. Some authors note that monoaminergic antidepressants may be less effective when TSH levels are higher than 2.5 mIU/L.[7,14] However, the use of THT for SCH remains controversial, and elements to consider include level of TSH, presence of thyroid antibodies, and comorbid medical conditions.[15] An ancillary study of a large RCT investigated the efficacy of L-T_4 on the development of depressive symptoms at 12 months in older adults (age ≥ 65 years, n = 427) with SCH.[16] This study showed no significant difference in the depression scores (measured using Geriatric Depression Scale at 12 months) between the L-T_4 (n = 211) and placebo (n = 216) groups.[16] This study was limited by the fact that most patients had low depression scores at baseline, and the effect of L-T_4 among severely depressed patients is to be considered still an area of active investigation.

Bipolar Disorder

Adjunctive THT has been studied in RCTs for bipolar depression, but it is a lower-tiered recommendation in most

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practice guidelines, such as the 2018 Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines.[17] Overall, the evidence base for THT use in bipolar depression is sparse and based on small sample size studies with significant heterogeneity.[18]

A prospective study of 30 patients reported a possible intrinsic association with rapid cycling and grade I hypothyroidism (defined as decreased serum T_4 level) and suggested that hypothyroidism is a risk factor for rapid cycling.[19] This finding was not unequivocally replicated.[20,21] A large multicenter study reported high prevalence of thyroid autoimmunity in patients with bipolar disorder, which was associated with thyroid failure but not with rapid cycling or lithium exposure.[22]

A recently published double-blind, placebo (n = 9) controlled RCT compared L-T_4 (n = 13) and T_3 (n = 10) as adjunctive treatments in rapid-cycling bipolar disorder.[23] L-T_4 reduced the time spent in depressed or mixed states and increased the time spent in euthymia.[23] However, T_3 was not superior compared to placebo. A pilot study showed some evidence of supraphysiologic L-T_4 doses (400 µg/d), leading to hyperthyroxinemic states, alleviating mood symptoms (depression and mania) in patients with rapid-cycling bipolar disorder.[24] Nonetheless, some patients relapsed despite being on supraphysiologic doses. One explanation provided by the authors was that "supranormal circulating levels of free thyroxine were necessary to induce clinical response." Another RCT investigating the efficacy of supraphysiologic L-T_4 (300 µg/d) as an adjunctive treatment in patients with bipolar depression did not find an overall effect versus placebo at study end, except in a post hoc analysis that identified female sex as a possible moderator of response.[25] Use of supraphysiologic L-T_4 dose is uncommon in clinical settings but worth investigating further, especially due to limited options for treatment-refractory bipolar disorder.

Clinical Practice

Effective communication with a patient's primary care physician (PCP) is important for the prevention and timely diagnosis of short- and long-term complications of THT. This is especially important when THT is started in euthyroid patients or if one is considering a high/supraphysiologic dose of L-T_4. All patients diagnosed with mood disorders should undergo a baseline thyroid hormone evaluation measuring serum TSH. If the TSH level is low, patients should be further evaluated by their PCP and/or endocrinologist, as it is contraindicated to initiate THT in hyperthyroid patients. If TSH is high, fT_4 and thyroid peroxidase antibody levels are indicated to evaluate the extent and etiology of hypothyroidism, respectively. While TSH levels above 20 mIU/L indicate hypothyroidism, TSH elevations less than 20 mIU/L may be due to hypothyroidism or recovery from euthyroid sick syndrome (ESS). Since it takes several weeks for the TSH to normalize in ESS, it is best to discuss with the PCP and/or endocrinologist before initiating THT.

Although both T_3 and L-T_4 can be used to augment antidepressant treatment, T_3 (the active hormone) has been favored by clinicians based on the older literature.[10] Short- and long-term adverse effects of L-T_4 are the same as for T_3. Table 1 describes some pragmatic differences between T_3 and L-T_4. The benefit and possible adverse effects of THT should be discussed with patients. Those with known or suspected cardiac conditions should be evaluated and cleared by their PCP prior to initiating THT. Since THT increases the metabolic rate, it is not safe to be used in patients with compromised cardiovascular function (eg, cardiac arrythmias, recent myocardial infarction, unstable angina) and untreated adrenal insufficiency. Caution should be exercised in patients who are 65 years and older because they are more susceptible to adverse cardiac events. While studies evaluating short-term use of T_3 at 25–50 µg/d report good tolerability for most patients, hyperthyroid symptoms may still occur (palpitations, dyspnea, diaphoresis, hand tremors, anxiety, insomnia, unintentional weight loss, and hyperdefecation). Hence, patients should be advised to immediately hold the THT in case they experience any of these symptoms and report this to their prescribing physician. In patients who have been on long-term THT therapy, accelerated bone loss resulting in osteoporosis and fragility fractures is a concern, especially in postmenopausal women. Hence, appropriate communication with the PCP to manage bone health with (*a*) adequate calcium and vitamin D intake, (*b*) regular weight-bearing and balance exercises, (*c*) fall prevention efforts, and (*d*) a monitoring plan using a bone density scan is prudent.

The standard practice is to start T_3 at 12.5–25 µg/d, and, based on tolerability and response over 1–2 weeks, the dose can be titrated to a maximum of 50 µg/d.[26] In patients 65 years and older, T_3 is started at a lower dose. When successful, augmentation with T_3 can lead to remission

Table 1. Pragmatic Differences Between Liothyronine (T_3) and Levothyroxine (L-T_4)

	Liothyronine (T_3)	Levothyroxine (L-T_4)
Brand name	Cytomel, Triostat	Synthroid, Levoxyl, Tirosint, Unithroid, Thyquidity, Euthyrox
Half-life	1 day	5–7 days
Initiation dose	12.5–25 µg/d	50–100 µg/d
Maximum dose	50 µg/d	150–200 µg/d
High dose	62.5 µg/d	500 µg/d
Equivalent dose	25–35 µg	100–125 µg
Time to response	2–14 wk	8–12 wk
Monitoring laboratories	TSH	TSH and free T_4
Timing of ingestion	Morning and afternoon	Morning (second dose at nighttime if dose is divided)
Effect of food	Can be taken with food	To be taken on an empty stomach at least 30 min before food
Effect of calcium, iron, and antacids	To be spaced by 4 hours	To be spaced by 4 hours
Formulations	Tablet	Tablet, soft gel capsule, liquid

Abbreviation: TSH = thyroid-stimulating hormone.

anywhere between 2–14 weeks.[9] The maximum tolerated dose of T_3 should be used for 4–6 weeks before a decision is made regarding its efficacy. While minimal data are available to guide physicians regarding long-term use of T_3, duration of therapy likely varies from patient to patient depending on magnitude of clinical response and adverse effects. Some authors advise tapering off T_3 after 60 days, by 12.5 µg every 3 days; T_3 can be reinitiated if there is a relapse of depression symptoms.[27] Some open-label studies have reported safety data on long-term (≥ 1 year) maintenance treatment with THT.[13,28,29] In such scenarios, TSH can be measured every 3–6 months or as needed to monitor thyroid status. If TSH is below the lower limit of reference range, the dose of T_3 should be reduced and TSH rechecked after 7–10 days, as T_3 has a shorter half-life (1 day) compared to L-T_4 (half-life of 5–7 days), for which TSH should be rechecked after 5–6 weeks.

L-T_4 is often started at 50 µg/d and is optimized to 100–150 µg/d. High L-T_4 doses such as 400–500 µg/d, although reported in the literature,[6,24] are rarely used in clinical settings due to concerns regarding short- and long-term adverse events and limited evidence base.

Conclusion

Thyroid functioning can play a pivotal role in mood disorders, with even minor perturbations leading to unstable mood states. Careful use of T_3 and L-T_4 can be critical mood-stabilizing options, especially for depressive illness that has not responded to first-line therapies, and can provide an alternative to other augmentation strategies such as atypical antipsychotics, lithium, or esketamine/ketamine.

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