T_3 Augmentation in Major Depressive Disorder: Safety Considerations

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Many cases of major depression are difficult to treat, and effective options are an urgent priority. Triiodothyronine (T_3) has been used to augment or accelerate treatment of major depression, and while there is good evidence for its efficacy in the short term, there is a limited evidence base to guide long-term adjunctive use. In a collaborative case from the endocrinology and psychiatry perspectives, we review the evidence for the safety of this intervention. A case presentation from our clinical practice is used to illustrate issues of efficacy, adherence, and use in the setting of medical comorbidity, and suggested guidelines are presented for monitoring the safety of T_3 when used as longer-term augmentation.

Mechanism of Action of T_3 Augmentation

Abnormalities of thyroid regulation have been detected in many patients with depressive syndromes. Patients with major depression appear to have a higher incidence of subclinical thyroid abnormalities (1), and it is clear that diseases of the thyroid can have a profound effect on mood.

Thyroid hormone is important for protein synthesis and metabolism for virtually every organ, including the brain. The release of thyroid-stimulating hormone (TSH) from the anterior pituitary is regulated by thyroid-releasing hormone (TRH) from the hypothalamus. TSH in turn prompts the release of mainly levothyroxine (T_4), and to a lesser extent T_3, from the thyroid gland; T_4 is considered a "prohormone" with very little intrinsic activity and is transformed in the peripheral tissues into T_3, the biologically active form of thyroid hormone. Through negative feedback, pituitary TSH levels are regulated by the serum free T_4 and free T_3, and even subtle changes often lead to substantial changes in TSH levels, making TSH a particularly useful screening test for hypothalamic-pituitary-thyroid (HPT) axis function (2).

T_3 acts in the cell nucleus, stimulating gene expression and energy metabolism in cells in every organ and potentially enhancing neurogenesis in the CNS (2). T_3, both alone and in combination with fluoxetine, modulates gene transcription, with changes in mRNA coding for the 5-HT_{1A} and 5-HT_{1B} receptors (3). In the CNS, T_4 conversion to T_3 occurs intracellularly, which may be why T_3 administration seems to have particular benefit in the treatment of affective disorders (4). The enzymes responsible for the conversion of T_4 to T_3 are also different in the CNS, perhaps explaining individual responses to T_3 supplementation and the variability of symptoms in subclinical hypothyroidism. Cooper-Kazaz et al. (5) have demonstrated that genetic polymorphisms in the type 1 deiodinase (DIO1) gene, which assists in the conversion of T_4 to T_3, might help determine which patients will respond to T_3 augmentation.

It is also possible that T_3 acts directly as a neurotransmitter or that it directly influences neurotransmission through monoamines (3). Actions at noradrenergic, serotonergic, and beta-adrenergic neurons have all been demonstrated, largely through studies of hypo- and hyperthyroid states. Rodent studies have demonstrated serotonergic effects of T_3 and T_4, supporting the idea that serotonergic transmission is enhanced by normal thyroid functioning, potentially through desensitization of the 5-HT_{1A} autoreceptor (6). T_3 was initially thought to be active solely within the noradrenergic projection pathway, and it may serve as a co-transmitter with norepinephrine in the limbic system, but it has also been demonstrated in high concentrations in the serotonergic raphe nuclei and their projections (7).

Evidence Base for Thyroid Augmentation

T_3 in Conjunction With Tricyclic Antidepressants

Augmentation of antidepressants with T_3 is one of the oldest evidence-based treatments for major depressive disorder. In 1969, Prange et al. conducted a pivotal study (8) demonstrating that administration of liothyronine enhanced response to tricyclic antidepressants in patients with treatment-resistant depression. Thyroid function

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A 37-year-old man with chronic severe major depression, poor response to antidepressants, and physical health problems, including morbid obesity, high blood pressure, and diabetes, is treated with T_3 augmentation of an antidepressant.

"Mr. Y" is a 37-year-old man with a history of severe major depressive disorder who was brought to our community mental health clinic by his homeless outreach worker. His chief complaint was that he suffered with an "overwhelming low mood" along with poor sleep, poor energy, anhedonia, poor concentration, hypersomnia, and lack of motivation for basic day-to-day functioning. He had no history of bipolar symptoms. The current episode was chronic in duration, now having lasted at least 3 years, during which time Mr. Y lost his job and became homeless.

The patient's anergic symptoms were compounded by morbid obesity and gout, making it difficult and painful for him to move around. He also had type 2 diabetes, poorly controlled hypertension, recurrent nephrolithiasis, and chronic sinusitis. Mr. Y met diagnostic criteria for major depressive disorder, and he reported no improvement in depressive symptoms on his intake regimen of 40 mg of escitalopram and 100 mg of trazodone. On physical examination, his blood pressure was 180/110 mm Hg; heart rate, 83 bpm; height, 6 feet 2 inches; and weight, more than 350 lbs, the maximum of the clinic scale, representing a body mass index of at least 45. His blood pressure results were communicated to his internist at a community free clinic, who reported that Mr. Y consistently had similar blood pressure levels at clinic visits and that the patient's adherence to prescribed treatments was uncertain.

Psychiatric and Family History

Mr. Y reported a childhood onset of depressive symptoms, but his first disabling episode was in his freshman year of college. "I remember staying in my room for a year, and I did almost nothing." A year before he presented at our clinic, Mr. Y's shelter petitioned for an involuntary commitment for suicidal ideation, and he was admitted for a brief acute hospitalization. At that time, escitalopram and trazodone were started, and they were continued by his primary care doctor after his discharge.

Mr. Y's family history was strongly positive for depression, including in his mother, maternal grandmother, maternal uncle, and sister.

Treatment Course

After initial assessment, Mr. Y declined therapy, but frequent meetings with the psychiatrist and outreach worker were scheduled to encourage behavioral activation. Trazodone was discontinued, as the patient reported sleeping most of the day. No benefit was obtained after bupropion was added to the escitalopram at up to 375 mg/day, so both antidepressants were cross-titrated to venlafaxine monotherapy. Venlafaxine was titrated in increments of 75 mg/day over 12 weeks to a dosage of 300 mg/day, which produced partial benefit for the patient's anergic symptoms. After 4 weeks at 300 mg/day with response but not remission, venlafaxine was further titrated to 450 mg, and the patient's blood pressure was monitored every 90 days. His blood pressure remained elevated as at baseline without significant change.

In the setting of residual symptoms of anhedonia and anergia, T_3 supplementation (using liothyronine sodium, which is L-triiodothyronine, a synthetic T_3) at 25 μg/day was chosen as an augmentation strategy with the goal of remission. Thyroid-stimulating hormone (TSH) at baseline was within normal limits. T_3 supplementation was increased to 50 μg/day after 4 weeks with a very good clinical response. Mr. Y reported engaging in more activity, feeling more able to get out of bed, spending time with his family, and attempting daily activities. Given Mr. Y's improving response, including improvements in energy, anhedonia, and mood, T_3 was continued at 50 μg/day.

After 18 months of treatment, Mr. Y's blood pressure was measured during routine 90-day monitoring at 200/120 mm Hg, his heart rate at 120 bpm, and his (nonfasting) blood glucose level at 196 mg/dl. He reported having missed his medications that morning, which included a beta-blocker, an angiotensin-converting enzyme inhibitor, and metformin, along with venlafaxine and T_3. On assessment in the emergency department, an ECG was normal except for sinus tachycardia (108 bpm). After Mr. Y's usual doses of his missed medications were administered, his blood pressure decreased to 193/94 mm Hg and his heart rate to 92 bpm, and his blood glucose level was 147 mg/dl. Thyroid function testing showed low levels of TSH (0.13 μIU/ml; range=0.35–5.50) and free T_4 (0.7 ng/dl; range=0.9–1.8) and a normal total T_3 level (1.32 ng/ml; range=0.60–1.81).

After Mr. Y acknowledged intermittent nonadherence to his medication regimen, daily observed administration logs were requested from his shelter residence. The risks and benefits of continued treatment were discussed with the patient, and expectations for adherence to treatment were outlined. Switching his augmentation agent and antidepressant was considered, but his diabetes and severe obesity made use of any second-generation antipsychotic an unattractive option, and the potential for intermittent adherence made use of lithium seem comparatively dangerous. Mr. Y's response to T_3, even without full adherence, made continuation seem likely to be of benefit. In general, nonadherence is not atypical for many patients in this clinic, and our first-line approach is to maintain a patient's existing treatment while addressing factors related to adherence.

Mr. Y's T_3 dosage was lowered to 25 μg/day, and his medication adherence improved, with improved blood pressure control despite his high dosage of venlafaxine. Follow-up thyroid function testing after 90 days showed normal results (TSH level, 0.72 μIU/ml; total T_3 level, 1.16 ng/ml; free T_4 level, 1.0 ng/dl), and his clinical response was excellent.

was monitored, but methods available at that time were not sensitive or specific. Based on ankle jerk reflexes and protein-bound iodine assays, patients in the study appeared to have elevated thyroid function after treatment. Many subsequent studies have confirmed the Prange et al. study's finding of efficacy, but few have formally assessed the HPT axis during treatment.

The majority of the evidence base for use of T_3 is for its coadministration with tricyclics. Two meta-analyses of T_3 coadministration with tricyclics have been published, one reviewing acceleration trials (9) and the other augmentation trials (10). Acceleration is defined as the use of T_3 at commencement of antidepressant treatment to enhance and hasten response. Augmentation is the administration of T_3 in patients who are unresponsive or partially responsive to an adequate course of antidepressant treatment initiated previously.

Acceleration of antidepressant response with T_3. A meta-analysis by Altshuler et al. (9) of six double-blind, placebo-controlled studies (125 patients total) of T_3 acceleration of tricyclics was positive. By definition, these were short-term studies of 2 to 3 weeks, and none discussed the option of continuing T_3 once antidepressant response was achieved. In addition, many were conducted before the advent of more sensitive assays of thyroid functioning in the late 1980s. Three of these acceleration studies (11–13) obtained initial lab values of protein-bound iodine and looked at ankle jerk reflexes and serum T_4 binding, but none performed follow-up testing. No differences in baseline thyroid tests were found between patients who responded to T_3 and those who did not, but some authors speculated that there may have been subtle thyroid dysfunction in the responders that was undetectable by the assays. In addition, a significant gender effect was observed, with women responding more robustly than men. While women generally have been found to have higher rates of both comorbid depressive syndromes and thyroid disease, a consistent association has not been replicated.

"There is good evidence to suggest that T_3 administration is helpful in the treatment of depressive states, but only limited data are available on long-term safety."

Augmentation of antidepressant response with T_3. Aronson et al. (10) conducted a positive meta-analysis of T_3 augmentation of tricyclics, finding eight controlled clinical studies with 292 patients. The studies were up to 12 weeks long, and several performed baseline and follow-up modern thyroid assays (4, 14–16). One positive study in 1977 conducted initial thyroid screening and additionally tested the CSF monoamine metabolites 5-hydroxyindoleacetic acid and homovanillic acid, hypothesizing that the mechanism of treatment with T_3 was an increase of available monoamines (17). However, the study found no differences in CSF monoamine metabolites between the placebo and active T_3 groups or between responders and nonresponders to T_3.

Thase et al. (14) found no association between results of thyroid function tests or TRH stimulation testing at baseline and outcome in a subset of patients treated with T_3. Joffe and Singer (4) evaluated T_3 versus T_4 in a randomized trial and found significant changes after 3 weeks in T_3, T_4, free T_4, TSH, and T_3 resin uptake in both groups, but these changes were not positive predictors of response; the main finding was that T_3 was more effective than T_4 as an augmenter. A 2-week augmentation study of lithium and T_3 (15) found in 1993 that the two were equally effective and outperformed placebo, with baseline TSH documented as being within normal range.

T_3 in Conjunction With SSRIs

Recently a number of studies have examined the augmentation of selective serotonin reuptake inhibitors (SSRIs) with thyroid hormone, but the data are more limited than with tricyclics. A review by Cooper-Kazaz and Lerer (18) found that not enough data were available yet for a meta-analysis but that a positive trend was revealed when the available double- and single-blind studies were analyzed. Papakostas et al. (19) reported a negative meta-analysis using strict inclusion criteria and finding only three adequate double-blind, randomized, placebo-controlled studies. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study (20) evaluated SSRI augmentation using either lithium or T_3 and found no statistical difference in efficacy between the treatments, but T_3 had superior tolerability and adherence. All of these studies were short term, with the longest (STAR*D) lasting 12 weeks.

Two studies of T_3 in combination with SSRIs included baseline and follow-up thyroid testing. In the first, Cooper-Kazaz et al. (21) compared sertraline (50–100 mg) combined with either T_3 (25–35 μg) or placebo in an 8-week study and found that the sertraline-T_3 combination produced superior response and remission rates. After 8 weeks of T_3 supplementation, the mean TSH level fell significantly from 1.70 μIU/ml at baseline to 0.28 μIU/ml in responders, whereas nonresponders had mean pre- and posttreatment levels of 1.88 μIU/ml and 0.76 μIU/ml, respectively; responsiveness to treatment was significantly correlated ($p=0.01$) with the change in TSH level, suggesting that the therapeutic benefit could have been due to changes in the thyroid axis in this population. In a post hoc analysis, baseline T_3 levels in patients who responded to T_3 augmentation were significantly lower than in those who did not respond (107.60 ng/dl compared with 137.4 ng/dl, $p=0.002$). There was also a small but significant decline in TSH levels in the placebo group.

FIGURE 1. Recommended Safety Guidelines for T_3 Augmentation of Antidepressant Medication

1. Obtain baseline TSH, free T_4, and free T_3 levels prior to augmentation.
2. Recheck thyroid indices at 3 months and then every 6 months, or at minimum annually. The goal is for the TSH level to be at least at the lower limit of the normal range (around 0.4 μIU/ml) or below in the absence of hyperthyroid symptoms. Free T_3 level can be maintained at the upper limit of the normal range based on the severity of depressive symptoms and response to T_3.
3. In the longer term, if the patient has a history of multiple episodes or significant treatment resistance, maintenance on T_3 is reasonable as an open-ended treatment option. If there are no symptoms of hyperthyroidism and no known cardiac disease, consider maintenance T_3 supplementation even if the TSH level is below the normal reference range, depending on clinical efficacy.
4. Document a discussion of the risk-benefit profile of long-term T_3 augmentation, including potential cardiac and bone disease risk.
5. In postmenopausal women, bone density should be monitored with densitometry every 2 years. If bone density is declining, referral for evaluation of osteoporosis should be made. Standard recommendations for all postmenopausal women also include calcium (1200 mg/day) and vitamin D (800–1000 IU / day) supplementation.
6. Periodically reevaluate the risks and benefits of T_3 supplementation, focusing specifically on depressive symptoms or change in status of cardiovascular disease.

A combination study by Appelhof et al. (22) in which 124 patients were randomly assigned to receive paroxetine combined with 25 μg of T_3, 50 μg of T_3, or placebo showed a statistically significant dose-dependent increase of T_3 levels along with lowered T_4 (the final T_4 levels after 8 weeks of treatment were 0.9 pmol/liter in the placebo group, 0.6 pmol/liter in the 25-μg T_3 group, and 0.4 pmol/liter in the 50-μg T_3 group). Significant changes in thyroid function on testing were associated with significant side effects in nine of 28 patients in the 50-μg group, including sweating, tremor, nervousness, and palpitations, but there were no significant differences between the 25-μg T_3 and placebo groups. It is possible that noradrenergic effects of paroxetine due to norepinephrine transporter blockade exacerbated somatic symptoms that were consistent with a hyperthyroid state. Efficacy outcome was negative, with no differences between placebo and the two T_3 groups.

While T_3 compared well with lithium in STAR*D (20), and results with T_3 as an augmentation or combination strategy are encouraging, more controlled trials are needed to fully determine the efficacy of T_3 in combination with SSRIs.

Safety in Longer-Term Studies

In a study of pre- and postmenopausal women on high-dosage T_4 (not T_3) for bipolar disorder or major depressive disorder, Gyulai et al. (23) found no significant differences in bone density after at least 1 year of treatment (with several patients having up to 5 years of treatment), but they noted a nonsignificantly greater decline in bone density in postmenopausal women. Prior to follow-up scanning for bone density, the mean TSH level on high dosages of T_4 (300–500 μg/day) was normal at 0.4 μIU/ml. Similarly, Kelly and Lieberman (24) administered up to 150 μg of T_3 daily to 14 patients for an average duration of 24 months, and no cardiac or skeletal sequelae were detected.

Safety: The Perspective From Endocrinology

There is no consensus in endocrinology on use of thyroid hormone for the treatment of depression in euthyroid patients. When treating patients with hypothyroidism, endocrinology guidelines generally recommend using T_4 monotherapy (25). Multiple studies, including a meta-analysis, have evaluated the difference between T_4 monotherapy and T_3/T_4 combination therapy for the treatment of hypothyroidism. Overall no meaningful statistical differences have been found between the two regimens (26–31). Nevertheless, some studies have reported patient preference for combination therapy that was not explained by symptom outcomes, neurocognitive changes, or quality-of-life assessments (27). In one study (28), 44% of the patients reporting a preference for combination therapy had a suppressed TSH level, suggesting overreplacement of thyroid hormone. A study from Denmark (32) evaluated T_4 monotherapy compared with combination T_3/T_4 therapy while maintaining equivalent TSH values. Quality-of-life scores and depression and anxiety rating scores were significantly better in seven of 11 categories with combined therapy compared with monotherapy, and 49% of patients preferred combination T_4/T_3 therapy, compared with 15% who preferred T_4 monotherapy.

In euthyroid patients, high T_3 dosages carry a higher risk of induction of hyperthyroidism. In this respect, preexisting hypertension, tachycardia, and hyperglycemia could all potentially be worsened by hyperthyroidism (33). Subclinical hyperthyroidism has also been associated with long-term side effects, including reduced bone mineral density and an increased risk of osteoporosis, especially in postmenopausal women (34, 35), and an increased risk of atrial arrhythmias (36). Thus, when thyroid hormones are used in treating depression, clinicians should closely monitor patients for biochemical or clinical evidence of hyperthyroidism.

Ideally, patients who are started on T_3 augmentation for a psychiatric disorder should be monitored in the same manner as patients with hypothyroidism. TSH, free T_4, and free T_3 levels should be measured regularly, as well as whenever there is a report of increased anxiety, tremor, palpitations, insomnia, or other symptoms suggestive of hyperthyroidism. Patients should also be monitored for other conditions that could be exacerbated by T_3 supplementation, including hypertension, tachycardia, os-

teopenia or osteoporosis, atrial arrhythmias, and hyperglycemia. Finally, it should be borne in mind that some beta-blockers influence thyroid hormone metabolism and plasma levels (37).

Conclusions and Recommendations

Pharmacologic augmentation strategies currently approved by the U.S. Food and Drug Administration for major depressive disorder are limited to the second-generation antipsychotics aripiprazole and quetiapine, both of which are associated with safety concerns in long-term use. Lithium is another guideline-recommended agent, but it does not have a better tolerability profile than T_3. Current textbooks and the 2010 APA guidelines (38) agree that there is good evidence for the use of T_3 in depressive syndromes, but largely do not mention monitoring of thyroid functioning. Schatzberg et al. (39) suggest use of T_3 in postmenopausal women or atypical depression and tapering augmentation after 60 days.

There is good evidence to suggest that T_3 administration is helpful in the treatment of depressive states, but only limited data are available on long-term safety. Few of the randomized controlled studies of T_3 included both initial and follow-up thyroid function testing; those that did such testing showed expected changes in the thyroid axis and were largely reassuring on the issue of significant side effects. Many psychiatrists are nevertheless uncomfortable prescribing thyroid hormones to essentially euthyroid patients, and some of our colleagues in endocrinology may also find this practice controversial.

In clinical decision making, the risk to health and safety from partially or inadequately treated major depression must be weighed against any putative risks of treatment. Findings from the STAR*D effectiveness trials (40) and from a meta-analysis (41) have highlighted shortcomings in the efficacy of antidepressants, which reinforces the need for psychiatrists to be flexible and creative in crafting their pharmacotherapy interventions for many patients suffering with major depression. The clinical case presented here highlights the morbidity from persistent depression in one patient in whom, for metabolic reasons, other augmentation strategies were considered high risk. In the case of T_3 augmentation, based on the literature and our clinical experience, we would recommend the safety guidelines summarized in Figure 1.

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Clinical Guidance: Safety Guideline for Longer-Term T_3 Augmentation Treatment of Major Depressive Disorder

Rosenthal et al. point out that no long-term data on the efficacy of T_3 augmentation for SSRI treatment exist beyond the 12-week STAR*D trial (2006; 163:1519–1530). However, the procedure is frequently used successfully in clinical practice, and therefore safety guidelines are needed. In addition to baseline measurements and informed consent with a risk-benefit analysis, Rosenthal et al. suggest endocrine evaluation at 3 and 6 months and then yearly. The TSH level should generally be at least 0.4 μIU/ml, the lower limit of normal; the T_3 level can be at the upper limit of normal. The patient should be clinically evaluated for hyperthyroidism. Bone density should be monitored every 2 years in postmenopausal women.