

'Supercharge' antidepressants by adding thyroid hormones

Why hormones help, and new data on SSRI augmentation

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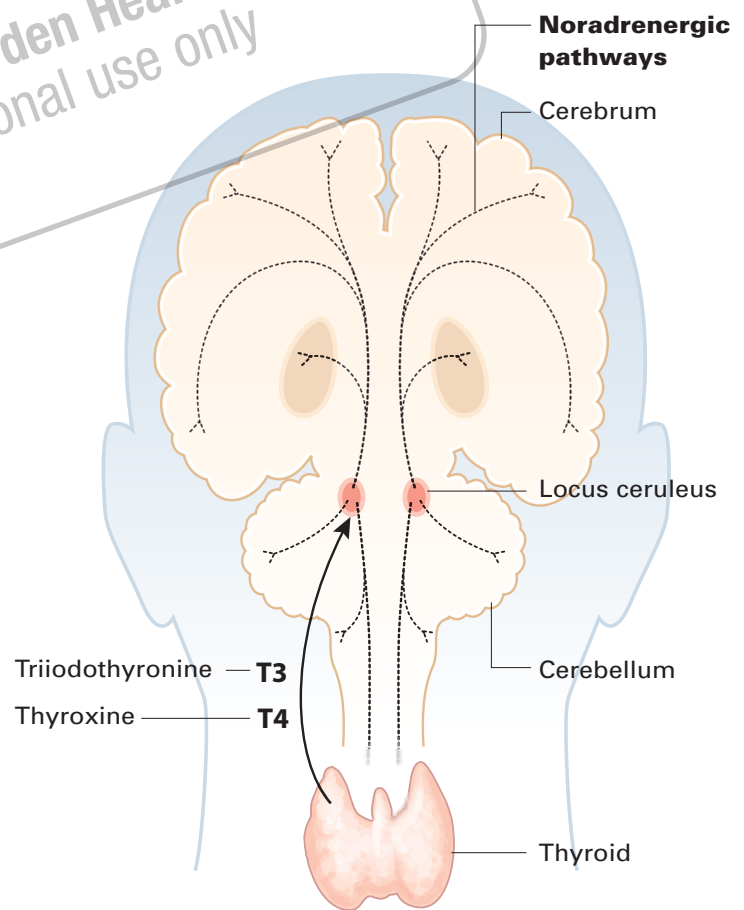
Prescribing thyroid hormones with antidepressants—whether to augment the antidepressant effect or accelerate patient response—is a well-researched strategy for treatment-resistant major depressive disorder (MDD). Thyroid hormones are known to boost response to tricyclics, and preliminary evidence shows they may be useful adjuvants to selective serotonin reuptake inhibitors (SSRIs) as well.

Effective treatments are available for MDD, although 30% to 40% of patients do not respond to one or more antidepressant trials (*Box, page 16*).¹⁻⁴ This article offers:

- new information about why triiodothyronine (T3) and thyroxine (T4) can “super-charge” antidepressant response
- tips on how to use thyroid hormones in patients with MDD, including effective dosages, patient monitoring, and treatment durations.

continued

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Thyroid hormones enter the brain slowly across the blood-brain barrier and choroid plexus. They accumulate in the locus ceruleus and other structures and are distributed widely along noradrenergic pathways.

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Box

Treatment-resistant depression: A common clinical problem

- 30% to 40% of patients with major depressive disorder (MDD) do not respond sufficiently to usual antidepressant treatment¹
- Even under optimal treatment conditions, only one-third of patients achieve remission²
- Among patients who fail to respond to two pharmacologic interventions, remission rates with the next antidepressant are as low as 12%³
- A patient becomes less likely to respond clinically with each additional nonresponse to antidepressant treatment⁴

WHY THYROID HORMONES?

Thyroid hormones enter the brain slowly across the blood-brain barrier and the choroid plexus—cerebrospinal fluid barriers. T₄ is the main source of brain T₃—after attack by 5′ deiodinase—but circulating T₃ also crosses the blood-brain barrier through active transport.

Thyroid hormones accumulate in the locus ceruleus and other central noradrenergic structures and are distributed widely in the brain along noradrenergic pathways.⁵⁻⁷ The mechanism of their therapeutic effect for MDD is not well understood, and various hypotheses have been proposed.

Subclinical hypothyroidism. Early studies such as by Howland⁸ of treatment-refractory MDD suggested that thyroid hormone augmentation might correct a hypothyroid state. However, blood thyroid hormone levels are not associated with resistance to antidepressant treatment, according to

Increased 5-HT does not fully explain the rapid antidepressant effect of thyroid hormone therapy

studies of MDD populations.⁹⁻¹⁰ Also, thyroid hormones' therapeutic action in MDD appears unlikely to be related to treating subclinical hypothyroidism because patients' euthyroid status was verified in all adjuvant studies since 1980.

Joffe et al¹¹ proposed that MDD is characterized by a relative excess of T₄ versus T₃—probably related to a deficit in converting T₄ to T₃ in the periphery—and administering T₃ would therefore correct this imbalance. They offered no strong evidence for an increased T₄ level, however, and later studies failed to detect the postulated blood T₃ abnormalities in MDD.⁹⁻¹⁰ Also—as suggested by studies with high-dose T₄ augmentation^{12,13}—the adjuvant antidepressant effect of thyroid hormones is not restricted to T₃, although T₃ may be more efficacious than T₄.¹⁴

Neurotransmitter effects. Thyroid hormones' role in increasing serotonin (5-HT) release could partially explain the benefit of adjuvant thyroid hormone therapy in MDD. Researchers found:

- T₃ increased cortical 5-HT levels, probably by reducing the autoinhibitory effect of the presynaptic 5-HT_{1A} receptor¹⁵
- adding T₃ to clomipramine therapy increased 5-HT levels to a greater extent than T₃ or clomipramine used alone¹⁶
- Low 5-HT activity, shown in hypothyroid patients, increased after T₄ replacement.¹⁷

This 5-HT release theory cannot explain why thyroid hormones have a rapid clinical effect in MDD. Most studies report the hormones have clinical efficacy in MDD within 4 weeks.¹⁸ Similarly, selective serotonin reuptake inhibitors (SSRIs) increase 5-HT levels within hours of treatment onset, but the clinical effect occurs 4 to 6 weeks later.¹⁹ Therefore, increased 5-HT levels cannot fully explain thyroid hormones' early effect.

Table

Treatment-resistant MDD: Controlled studies of thyroid hormone augmentation

| Study authors/design | Initial therapy | Augmentation | Results |
|---|---|---|---|
| Steiner et al, 1978 Randomized double-blind; 8 patients* | Several TCAs (6 weeks) | T3, 25 mcg/d, or placebo (35 days) | T3: 75% responders (3/4) Placebo: 75% (3/4) |
| Goodwin et al, 1982 Double-blind, mirror design; 12 patients* | Desipramine or imipramine (4 weeks) | T3, 25 to 50 mcg/d, or placebo (21 days) | T3: 33% responders (4/12) Placebo: 0% (0/6) |
| Gitlin et al, 1987 Double-blind with crossover; 16 patients | Imipramine (4 weeks) | T3, 25 mcg/d, or placebo (2 weeks); crossover (2 weeks) | No difference between T3 and placebo |
| Joffe and Singer, 1990 Randomized double-blind; 38 patients | Desipramine or imipramine (4 weeks) | T3, 37.5 mcg/d, or T4, 150 mcg/d (21 days) | T3: 53% responders (9/17) T4: 19% (4/21) |
| Joffe et al, 1993 Randomized double-blind; 33 patients | Desipramine or imipramine (5 weeks) | T3, 37.5 mcg/d, or placebo (14 days) | T3: 59% responders (10/17) Placebo: 19% (3/16) |
| Sopov and Lahdelma, 1998 Randomized double-blind with crossover; 22 patients* | TCA, MAOI antidepressants | T4, 200 mcg/d, or lithium, 500 mg/d, (4 weeks); then crossover (4 weeks) | T4: 64% responders (7/11) Lithium: 18% responders (2/11) |

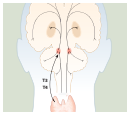
* Included patients with unipolar or bipolar depression
MAOI: monoamine oxidase inhibitor; SSRI: selective serotonin reuptake inhibitor; T3: triiodothyronine; T4: thyroxine;
TCA: tricyclic antidepressant.

Close interaction between thyroid hormones and the noradrenergic system also has been examined. Brain T3 is primarily localized in the central noradrenergic systems, with axonal anterograde transport of T3 from the locus ceruleus. T3 is processed and accumulated in the noradrenergic system, carried via axonal transport, then delivered from nerve cell bodies to its neuronal targets.^{5,7} T3 thus functions as a coneurotransmitter with norepinephrine.

Cellular energy metabolism. We recently reported that thyroid hormones' antidepressant effect may

be related to brain cellular energy metabolism. Thyroid hormones increase cellular levels of adenosine triphosphate (ATP) and phosphocreatine (PCr) in the hypothyroid brain.²⁰ Brain imaging—phosphorus-31 nuclear magnetic resonance spectroscopy (31P-MRS)—of subjects with MDD shows decreased brain levels of ATP and increased PCr.²¹

Our group showed that the antidepressant effect of T3 augmentation of SSRIs is correlated with significant increases in ATP levels and decreases in PCr. This effect—which appears to



Thyroid hormones

represent re-normalization of brain bioenergetics in treatment responders—did not occur in non-responders (Iosifescu et al, presented at APA, 2004).

The effect of thyroid hormones on bioenergetic metabolism is compatible with the hypothesized effects on noradrenergic and serotonergic systems.^{5,7} These mechanisms may represent different links in the same chain of events.

ANTIDEPRESSANT BOOSTERS

Thyroid hormones have been used extensively to treat MDD since the 1950s, when researchers reported that T3 monotherapy was efficacious for treating depression. These early studies had important methodologic limitations, including open designs and poorly defined diagnostic criteria and response.

For MDD, the most extensively researched uses of thyroid hormones are to augment therapy for antidepressant nonresponders and to accelerate partial response to antidepressants.

Tricyclics. Open studies primarily among outpatients in the 1970s and '80s suggested that thyroid hormones are a valid augmentation strategy for nonresponders to tricyclic antidepressants. Most—but not all—reported response rates >50% with T3 dosages of 20 to 50 mcg/d.^{22,23}

Compared with outpatient studies, however, an open trial of T3 augmentation by Birkenhager et al²⁴ found no evidence of efficacy in 14 severely depressed inpatients who had not responded to 6 weeks of tricyclics. These patients—mainly with melancholic and/or psychotic depression—showed greater response to a monoamine oxidase inhibitor (MAOI) or electroconvulsive therapy than to thyroid hormone.

Three of five double-blind controlled studies of thyroid hormone augmentation of tricyclics reported response rates of 50 to 65% (Table, page

17).^{14,18,25} Earlier controlled studies, including two negative studies^{26,27} had important methodologic limitations: all included few subjects (≤ 16), and two studies included both unipolar and bipolar patients. Joffe et al partially addressed these problems with two randomized, double-blind studies that were controlled with placebo or T4:

- In a 3-week trial, T3 was more effective than T4 when added to imipramine or desipramine.¹⁴
- In a 2-week trial, T3 was significantly more effective than placebo when added to imipramine or desipramine.²⁵

In the latter study, T3 and lithium augmentation appeared equally effective. Conversely, T4 was more effective than lithium as the first augmentation strategy in a double-blind, crossover study by Spooov and Lahdelma.²⁸

In conclusion, depressed patients given T3 with tricyclic antidepressants may be twice as likely as controls to respond to treatment, according to a meta-analysis of eight studies totalling 292 patients. This analysis by Aronson et al²⁹ supports T3 augmentation while addressing the surveyed studies' limitations.

MAOI inhibitors. One small report has addressed the efficacy of thyroid hormones as adjuvants to MAOIs.³⁰ In two patients, adding T3 to phenelzine enhanced the antidepressant response.

High-dose T4. Two open studies of patients with treatment-resistant bipolar or unipolar depression^{12,13} have examined the efficacy of high-dose T4 augmentation. These patients were taking a variety of antidepressants, including TCAs and SSRIs.

- In the study by Baurer et al,¹² clinical remission (Hamilton Depression Scale [HAM-D] score ≤ 10) occurred in 4 of 5 patients with severe treatment-resistant unipolar depression who received adjunctive T4, mean 482 ± 72

Giving T3 to patients taking tricyclics may double their likelihood to respond to treatment

mcg/d, with antidepressants.

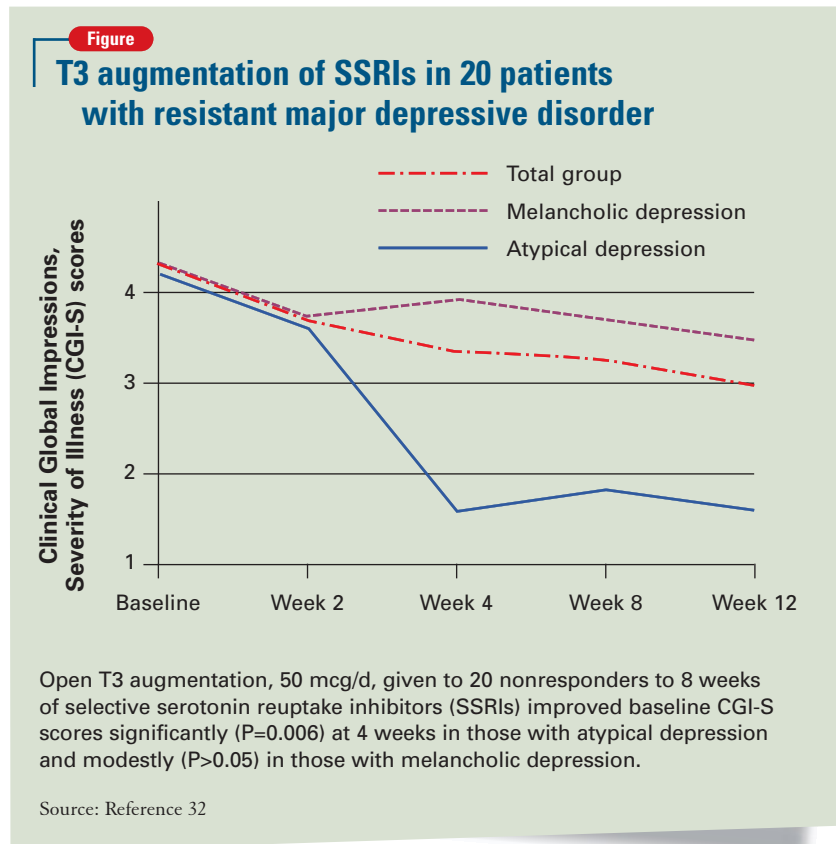
• In the study by Rudas et al,¹³ clinical remission (HAM-D ≤ 9) occurred in 7 of 9 patients with treatment-resistant MDD after T4, 150 to 300 mcg/d, was added to their antidepressant therapy. Side effects may limit this high-dose strategy, however, because 2 of the patients dropped out with thyrotoxicosis symptoms.

SSRIs. Three open trials to date have investigated using thyroid hormones to augment SSRIs in treatment-resistant MDD. In a prospective study by Agid and Lerer,³¹ 10 of 25 (40%) patients who did not respond to SSRI treatment did so after T3 was added. No men improved, however, which led the authors to suggest that men and women might respond differently to T3 augmentation of SSRIs.

In our study, 7 of 20 patients (35%) with MDD who did not respond to 8 weeks of SSRI therapy did so when we added T3, 50 mcg/d, for 4 weeks (*Figure*). Response rates were high (5/5, 100%) in patients with atypical features by DSM-IV criteria and low (1/8, 12.5%) in those with melancholic features.³²

Abraham et al³³ added T3, 50 mcg/d, to the regimens of 12 patients with MDD who did not respond to SSRIs alone. One patient dropped out with side effects. After 4 weeks of T3 augmentation, 5 patients (42%) showed 50% or greater improvement in HAM-D scores from baseline.

Antidepressant accelerators. Five of seven early double-blind, controlled studies indicated that



adding small doses of thyroid hormones at the beginning of antidepressant treatment accelerated treatment response. All were limited by small sample sizes and other methodologic problems. A more-recent meta-analysis of six studies totalling 125 patients by Altshuler et al³⁴ found:

- T3 was significantly more effective than placebo in accelerating clinical response to tricyclics
- the acceleration effect was more pronounced for women than for men.

CLINICAL RECOMMENDATIONS

Thyroid hormones can be useful to augment and accelerate treatment of MDD. Evidence strongly supports their use with tricyclic antidepressants



Thyroid hormones

and suggests they also can be effective adjuncts for patients who do not respond to SSRIs.

Either T3 (up to 50 mcg/d) or T4 (up to 150 mcg/d) can be used as augmentation. T3's antidepressant properties are considered more effective than those of T4, but the only head-to-head study supporting this conclusion was small (38 patients).¹⁴ Some T4 augmentation studies used very high dosages (300 to 600 mcg/d),¹² which increase the risk of acute overdose.

Start T3 augmentation at 25 mcg/d and increase, if tolerated, to 50 mcg/d after 1 week. Measure baseline serum thyroid-stimulating hormone (TSH), and do not treat patients with TSH <0.5 mIU/L). Baseline TSH, T4, or T3 levels do not predict response to T3 augmentation in euthyroid MDD patients.³²

Common side effects. Adjuvant T3, 25 to 50 mcg/d, was well-tolerated in our study of 20 patients also taking SSRIs:

- 2 (10%) experienced fatigue and diaphoresis
- 1 each (5%) had tremor, dry mouth, headaches, muscle aches, and vivid dreams.³²

We saw no significant changes in blood pressure, but heart rates increased significantly in our 4-week study—from 76 ± 12 bpm (range 60 to 96) to 82 ± 9 bpm (range 66 to 96). Thus, T3 aug-

mentation may not be indicated for patients with coronary artery disease or chronic heart failure. Patients' weight decreased an average 2.5 ± 6.6 lbs (range -20 to +7).

Thyroid hormones may cause hypoglycemia and change insulin requirements in patients with diabetes. High doses of T3 or T4 may be associated with hyperthyroidism, weight loss, nervousness, sweating, tachycardia, insomnia, heat intolerance, menstrual irregularities, palpitations, psychosis, or fever. Discontinue treatment if these symptoms develop.

Onset of antidepressant effect.

Assess patient response in 4 to 6 weeks, whether using augmentation to address antidepressant nonresponse^{14,25} or to accelerate response.³³ If you detect only partial improvement, studies support continuing treatment up to 8 weeks.

Treatment duration. No guidelines exist on how long to continue thyroid hormones after the initial antidepressant response. TSH levels become suppressed (TSH <0.1 mIU/L) after 4 weeks of T3, 50 mcg/d, in patients with normal baseline thyroid function.³² This suggests thyroid hormone's booster effect is self limited, and augmentation may not need to continue after 2 to 3 months—even in responders.

T3 augmentation at 25 mcg/d can be discontinued immediately. For 50 to 75 mcg/d, taper across 1 to 2 weeks. The hypothalamic-pituitary-thyroid axis returns to normal function 6 to 8 weeks after T3 augmentation is stopped.

In this model, thyroid hormone augmentation can be used to boost antidepressant efficacy several months at a time. If effective, the same strategy could be tried again for subsequent MDD episodes.

Thyroid hormone can be used to boost antidepressant efficacy as needed if MDD recurs

Evidence supports adding thyroid hormones to antidepressants—especially tricyclics—for patients with treatment-resistant major depressive disorder. T3 also can be effective as an adjunct to SSRIs. The hormones' 'booster' effect appears self-limited and may not need to be continued after 2 to 3 months, even in treatment responders.

BottomLine

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continued on page 25

continued from page 20

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Related resources

- ▶ DeBattista C. Augmentation and combination strategies for depression. *J Psychopharmacol* 2006;20(3):11-18.
- ▶ Massachusetts General Hospital Psychiatric Academy (including web-casts on treatment-resistant depression. www.mghcme.com

DRUG BRAND NAMES

Desipramine • Norpramin
 Imipramine • Tofranil
 Levothyroxine (T4) • Levoxyl,
 Levothroid, Synthroid, others
 Liothyronine (synthetic T3) • Cytomel

DISCLOSURES

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