Unipolar depression in adults: Augmentation of antidepressants with thyroid hormone

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INTRODUCTION

Thyroid hormone can be used in two different ways to treat unipolar major depression. Most commonly, thyroid hormone is used as augmentation for patients who respond insufficiently to antidepressant monotherapy [1-5]. In addition, thyroid hormone can be started simultaneously with a tricyclic at the beginning of pharmacotherapy to accelerate response compared with tricyclic antidepressant monotherapy [6-8]. However, a faster response to treatment does not increase the number of patients who respond by the end of treatment [9]. Thyroid hormone is generally administered as triiodothyronine (T3).

Interest in treating major depression with thyroid hormone initially arose in part because of overlap in the symptoms of major depression and hypothyroidism, including dysphoria, psychomotor retardation, cognitive impairment, fatigue, and weakness [10,11]. Although diminished thyroid function is present in some cases of major depression, adjunctive T3 may be effective for depressed patients who are euthyroid [12].

The use of thyroid hormone in treating major depression is reviewed here. Treatment resistant depression is discussed separately, as is the initial treatment of depression and treatment of hypothyroidism. (See "Unipolar major depression in adults: Choosing initial treatment" and "Treatment of primary hypothyroidism in adults" and "Unipolar depression in adults: Choosing treatment for resistant depression".)

INDICATIONS

Indications for treating nonpsychotic, unipolar major depression with triiodothyronine (T3) include [6]:

- Augmenting response – T3 is added to ongoing antidepressant monotherapy because the patient has not responded adequately; this is the most common indication.
- Accelerating response – T3 plus a tricyclic antidepressant are started simultaneously at the beginning of treatment to provide a more rapid response compared with tricyclic monotherapy. However, a faster response to treatment does not enhance response, ie, does not increase the number of patients who respond by the end of treatment.

There is no evidence that T3 monotherapy is efficacious for treating major depression in the absence of hypothyroidism [10,13].

Contraindications — T3 is contraindicated in patients with adrenal insufficiency, unstable angina, or recent myocardial infarction or compromised cardiovascular function, because increasing the metabolic rate in these conditions can be unsafe. In addition, T3 should be used cautiously in older adult patients (eg, age ≥65 years) to avoid cardiac complications, and in patients with diabetes mellitus to avoid aggravating diabetic symptoms. (See "Treatment of primary hypothyroidism in adults", section on 'Older patients or those with coronary heart disease'.)

GOAL OF TREATMENT

The goal of treating unipolar major depression is remission, which is defined as resolution of depressive symptoms, or improvement to the point that only one or two symptoms of mild intensity persist. For patients who do not achieve remission, a reasonable goal is response, which is defined as stabilization of the patient's safety and substantial improvement in the number, intensity, and frequency of symptoms. Standardized rating scales such as the self-report Patient Health Questionnaire – Nine Item (table 1) [14] can be used to quantify response, but this is not standard clinical practice. Use of scales in treating depression is discussed separately. (See "Using scales to monitor symptoms and treat depression (measurement based care)".)

AUGMENTING RESPONSE TO ONGOING ANTIDEPRESSANT THERAPY

For patients with nonpsychotic, unipolar major depression, triiodothyronine (T3) can be used to augment response to existing antidepressant monotherapy [1-5]. Add-on therapies are frequently necessary because many patients fail to remit after initial treatment with antidepressant monotherapy, even with an optimal trial [15-17]. It is commonly thought that an adjuvant may be more effective for patients who initially have a partial response to antidepressant monotherapy, compared with patients who do not respond at all, but this is not established [18]. Additional information about treatment resistant depression is described separately. (See "Unipolar treatment-resistant depression in adults: Epidemiology, risk factors, assessment, and prognosis" and "Unipolar depression in adults: Choosing treatment for resistant depression".)

Multiple practice guidelines for treating unipolar major depression, including those from the American Psychiatric Association and the Canadian Network for Mood and Anxiety Treatments, suggest adjunctive thyroid hormone as one of several options for patients who do not respond to antidepressant monotherapy [1-5]. However, the United Kingdom National Institute for Clinical Excellence guideline suggests that clinicians should not routinely augment an antidepressant with thyroid hormone because there is inconsistent evidence of effectiveness [19].

Evidence of efficacy — For patients with major depression who have not responded adequately to antidepressant monotherapy, the benefit of adjunctive thyroid hormone is not clear, due to mixed results across studies [6]:

- A meta-analysis of four randomized trials (95 depressed patients unresponsive to a tricyclic) compared adjunctive T3 to either adjunctive placebo or thyroxine (T4) [20]. Response (reduction of baseline symptoms ≥50 percent) was comparable in patients who received T3 or the control condition (relative response 1.5, 95% CI 0.7-3.4).

- A meta-analysis of three randomized trials, in 134 patients unresponsive to paroxetine or a tricyclic, found that response with add-on thyroid hormone (either T3 or T4) or add-on placebo was comparable (odds ratio 1.6, 95% CI 0.3-8.1) [21].

- A network meta-analysis of 48 randomized trials (n >6000 depressed patients) evaluated the efficacy of 11 augmentation agents by using results from direct comparisons between the drugs, as well as indirectly comparing drugs through their relative effect with a common comparator (typically placebo) [22]. Remission occurred more often with thyroid hormone (either T3 or T4) than placebo (odds ratio 3, 95% credible interval 2-7). In addition, discontinuation of treatment due to side effects was comparable with thyroid hormone and placebo, and was less with thyroid hormone than quetiapine.

Compared with other adjunctive treatments — For patients with unipolar major depression, add-on T3 has been compared with add-on lithium. A meta-analysis of two randomized trials in 176 patients with treatment resistant depression found that the two drugs were comparable in efficacy (odds ratio 1.5, 95% CI 0.7-3.1) [21]. Additional information about these two trials is discussed separately. (See "Unipolar depression in adults: Treatment with lithium", section on 'Triiodothyronine (T3)'.)

Adjunctive medications other than T3 are available for patients who do not respond to antidepressant monotherapy. The options include augmentation with lithium, a second-generation antipsychotic, and a second antidepressant; these are discussed separately. (See "Unipolar depression in adults: Treatment with lithium", section on 'Add-on lithium for treatment-resistant depression' and "Unipolar depression in adults: Treatment with second-generation antipsychotics", section on 'Adjunctive treatment for nonpsychotic depression'.)

Pretreatment evaluation — The initial assessment of patients with unipolar major depression includes a psychiatric and general medical history, mental status and physical examination, and focused laboratory tests. Prior to prescribing T3, clinicians should screen for thyroid disease by obtaining a baseline serum thyrotropin (TSH) concentration if not previously done:

- If the TSH is normal, thyroid disease is unlikely
- If the TSH is elevated, a serum free thyroxine (T4) concentration should be obtained to determine the degree of hypothyroidism
- If the TSH concentration is low, a serum free T4 and a total T3 concentration should be obtained to determine the degree of hyperthyroidism, and T3 should not be prescribed

A baseline electrocardiogram is not routinely required. However, a pre-existing cardiac condition warrants a consult from the patient's internist or cardiologist.

Additional information about diagnosing hypothyroidism and hyperthyroidism is discussed separately. (See "Diagnosis of and screening for hypothyroidism in nonpregnant adults" and "Diagnosis of hyperthyroidism".)

Choice of thyroid hormone — T3 is generally preferred over T4 for augmenting an antidepressant in unipolar major depression. Although both thyroid hormones are biologically active, T3 appears to be superior to T4 [23], and T3 has been more widely studied [24].

A randomized trial compared T3 (37.5 mcg per day) with T4 (150 mcg per day) as adjunctive treatment in 38 patients with unipolar major depression who did not respond to desipramine or imipramine [23]. After three weeks of treatment, response (improvement from baseline on the

depression rating scale ≥50 percent) occurred in significantly more patients who received adjunctive T3 compared with adjunctive T4 (53 versus 19 percent).

Additional information about T3 and T4 is discussed separately. (See "Thyroid hormone synthesis and physiology".)

Dose and administration — We generally start T3 at 25 mcg per day for one to two weeks, and if there is little or no improvement, increase the dose to 50 mcg per day; this is consistent with practice guidelines from the American Psychiatric Association and Canadian Network for Mood and Anxiety Treatments [1,2]. For frail, older adult patients (eg, age ≥65 years), the initial dose is 12.5 mcg per day; if there is little or no improvement after one to two weeks, the dose is increased each week by 12.5 mcg per day, to no more than 50 mcg per day.

Studies have generally utilized daily doses of 20 to 50 mcg per day. In some studies, a lower daily dose (20 to 25 mcg) was increased after one to two weeks to the higher dose (40 to 50 mcg), whereas other studies started T3 at the higher dose [20]. However, there is no evidence that 50 mcg per day is more effective than 25 mcg. One eight week, randomized trial compared adjunctive T3 25 mcg per day with 50 mcg per day in 56 patients with major depression and found no significant difference in response [25].

T3 is generally taken in the morning and can be taken without regard to meals because food does not alter absorption.

Length of an adequate trial — We suggest that clinicians prescribe adjunctive T3 for at least four to six weeks before deciding whether it is helpful. Although remission may occur within one week, it may require months of treatment. In an open-label randomized trial, 73 patients with unipolar major depression were treated with adjunctive T3 for up to 14 weeks [26]. Among the 18 patients who remitted:

- Five remitted after 2 weeks of treatment
- Three after 3 to 4 weeks
- Four after 5 to 6 weeks
- One after 7 to 9 weeks
- None after 10 to 12 weeks
- Five after 13 to 14 weeks

Other controlled studies of T3 have lasted between one to five weeks [20].

Predictors of response — Although individual studies have found predictors of response to adjunctive T3, no single consistent predictor has been identified. Biological predictors have

typically included baseline thyroid indices, including lower serum T3 or higher TSH concentrations [27]. However, many studies required normal baseline thyroid indices as an inclusion criterion, and it is thus unclear whether patients with subclinical hypothyroidism, defined as a normal serum free T4 concentration in the presence of an elevated serum TSH concentration, might preferentially respond to adjunctive T3. Treatment resistance to multiple antidepressant trials or depressive chronicity may predict a poorer response [6].

Safety issues — T3 is contraindicated in certain medical conditions; this is discussed elsewhere in the topic. (See 'Contraindications' above.)

Side effects — Adjunctive T3 at 25 to 50 mcg per day for one to two months is usually well tolerated and has a benign side effect profile compared with other adjunctive medications used in refractory depression (eg, lithium, second-generation antipsychotic, or a second antidepressant) [28]. In nearly all randomized trials, there were no significant differences in adverse effects between T3 and placebo as augmentation with a tricyclic, SSRI, or other type of antidepressant [6,20]. In addition, none of the studies reported a major health complication. Nevertheless, adverse effects consistent with hyperthyroidism may occur, including tremor, palpitations, heat intolerance, sweating, anxiety, increased frequency of bowel movements, shortness of breath, and exacerbation of cardiac arrhythmia [6,28]. In addition, hyperthyroidism that emerges during long-term treatment may lead to bone demineralization, osteoporosis, and an increased risk of fracture [28]. (See "Exogenous hyperthyroidism" and 'Long-term treatment' below.)

Laboratory monitoring — Following a normal baseline TSH concentration, no other laboratory monitoring during a four to six week trial of adjunctive T3 is necessary. However, if T3 is continued longer, a serum TSH concentration should be checked after the first one to three months of treatment and then every six months.

Drug-drug interactions — Specific interactions between T3 and other medications may be determined using the Lexicomp drug interactions tool (Lexi-Interact Online) included in UpToDate.

Long-term treatment — Maintenance treatment has not been studied in depressed patients who respond to augmentation of an antidepressant with T3. Based upon maintenance trials with antidepressant monotherapy, we suggest that patients who respond to adjunctive T3 continue to receive the T3-antidepressant combination for at least one year [1]. Long-term side effects with adjunctive T3 are unlikely, given the low doses prescribed (25 to 50 mcg per day). However, mild hyperthyroidism may occur and is more likely in patients treated with 50 mcg per day; the potential risks of long-term hyperthyroidism include bone demineralization,

osteoporosis, and an increased risk of fracture [28]. Clinicians should monitor serum TSH concentrations every six months and decrease the T3 dose if the TSH concentration falls below the lower range of normal. Hyperthyroidism is discussed separately. (See "Exogenous hyperthyroidism" and "Overview of the clinical manifestations of hyperthyroidism in adults".)

ACCELERATING RESPONSE TO AN ANTIDEPRESSANT

Thyroid hormone started simultaneously with a tricyclic antidepressant (on the same day that the antidepressant is started or within three to five days) may provide a more rapid response compared with tricyclic monotherapy [6]. However, a faster response to treatment does not increase the number of patients who respond by the end of treatment. Thyroid hormone is generally administered as triiodothyronine (T3); the choice of thyroid hormone is discussed separately. (See 'Choice of thyroid hormone' above.)

The efficacy of using T3 to accelerate response seems to depend upon the antidepressant class that is used; T3 accelerates response to tricyclics but not selective serotonin reuptake inhibitors (SSRIs):

- A meta-analysis of six randomized trials (125 depressed patients) compared T3 (typically 25 mcg per day) plus a tricyclic antidepressant (typically imipramine 150 mg per day) at the start of treatment with placebo plus a tricyclic [7]. A significantly faster response of approximately 9 to 11 days occurred with concomitant T3 than placebo.

- A meta-analysis of four randomized trials (444 patients with unipolar major depression) compared T3 (25 or 50 mcg per day) plus an SSRI with placebo plus an SSRI, and found no significant difference in how quickly response occurred [9].

Both meta-analyses found that T3 was well tolerated [7,9]. Other safety issues regarding T3 as a treatment for depression are discussed elsewhere in the topic. (See 'Safety issues' above.)

The length of an adequate trial of T3 used as an accelerator is commensurate with the duration of an antidepressant trial, which is generally four to eight weeks. Other aspects of prescribing T3 are discussed elsewhere in the topic. (See 'Pretreatment evaluation' above and 'Dose and administration' above and 'Safety issues' above.)

ENHANCING RESPONSE TO AN ANTIDEPRESSANT

Compared with antidepressant monotherapy, thyroid hormone plus an antidepressant at the beginning of treatment does not increase the probability of response or remission. A meta-analysis of four randomized trials (444 patients with unipolar major depression) compared T3 plus a selective serotonin reuptake inhibitor (SSRI) with placebo plus an SSRI and found no evidence that T3 enhanced the effect of an SSRI [9]. A subsequent eight-week trial compared triiodothyronine (T3; 50 mcg per day) plus sertraline (50 to 200 mg per day) with placebo plus sertraline in 153 patients with major depression; response and remission were comparable for the two groups [29].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Depressive disorders".)

SUMMARY

- The most common indication for treating nonpsychotic, unipolar major depression with triiodothyronine (T3) is augmentation, ie, T3 is added to ongoing antidepressant monotherapy because the patient has not responded adequately. In addition, T3 plus a tricyclic antidepressant can be started simultaneously at the beginning of treatment to accelerate (provide a more rapid) response compared with tricyclic monotherapy. However, a faster response to treatment does not increase the number of patients who respond by the end of treatment. (See 'Indications' above.)

- T3 is contraindicated in patients with adrenal insufficiency, unstable angina, or recent myocardial infarction or compromised cardiovascular function. In addition, T3 should be used cautiously in older adult patients (eg, age ≥65 years) to avoid cardiac complications, and in patients with diabetes mellitus to avoid aggravating diabetic symptoms. (See 'Contraindications' above.)

- The initial assessment of patients with unipolar major depression includes a psychiatric and general medical history, mental status and physical examination, and focused laboratory tests. Prior to prescribing T3, clinicians should screen for thyroid disease by obtaining a baseline serum thyrotropin (TSH) concentration. A baseline electrocardiogram is not routinely required. However, a pre-existing cardiac condition warrants a consult from the patient's internist or cardiologist. (See 'Pretreatment evaluation' above.)

- T3 is generally preferred over T4 either for augmenting an antidepressant in unipolar major depression, or accelerating response. The initial dose of T3 is typically 25 mcg per day for one to two weeks, and if there is little or no improvement, the dose is increased to 50 mcg per day. We suggest that clinicians prescribe adjunctive T3 for at least four to six weeks before deciding whether it is helpful. (See 'Choice of thyroid hormone' above and 'Dose and administration' above and 'Length of an adequate trial' above.)

- Adjunctive T3 at 25 to 50 mcg per day is usually well-tolerated. However, adverse effects consistent with hyperthyroidism may occur, including tremor, palpitations, heat intolerance, sweating, anxiety, increased frequency of bowel movements, shortness of breath, and exacerbation of cardiac arrhythmia. In addition, hyperthyroidism that emerges during long-term treatment may lead to bone demineralization, osteoporosis, and an increased risk of fracture. (See 'Side effects' above and 'Long-term treatment' above and "Exogenous hyperthyroidism".)

- We suggest that patients who respond to adjunctive T3 continue to receive the T3-antidepressant combination for at least one year. Clinicians should monitor serum TSH concentrations every six months and decrease the T3 dose if the TSH concentration falls below the lower range of normal. (See 'Long-term treatment' above and 'Laboratory monitoring' above.)

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