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Triiodothyronine (T3) supplementation in major depressive disorder

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Abstract

Introduction: The use of thyroid hormones to enhance the effects of antidepressants is based on evidence supporting a link between thyroid function and Major Depressive Disorder. Thyroid abnormalities have been found in patients with Major Depressive Disorder and have been correlated with depression severity. Symptoms associated with clinical hypothyroidism include mood disturbances, primarily depression. In addition, an increase in antidepressant treatment resistance has been associated with thyroid abnormalities. This article reviews the existing data regarding triiodothyronine (T_3) supplementation of antidepressants in the treatment of major depressive disorder.

Methods: Medline and EMBASE were searched from 1996 to November 2014 using the key terms *triiodothyronine*, *T3*, and *treatment-resistant depression*.

Results: T_3 may increase serotonergic neurotransmission and has been studied as an add-on agent in patients with unipolar depression with and without thyroid dysfunction to accelerate, enhance, and augment the effects of tricyclic antidepressants and selective serotonin reuptake inhibitors.

Discussion: Data support the use of T_3 augmentation (25-50 µg/d) for the treatment of depressive symptoms in some patient populations without thyroid hormone abnormalities who do not respond to an adequate trial of a tricyclic antidepressant or a selective serotonin reuptake inhibitor. Monitoring for adverse effects and conditions that may be exacerbated by T_3 augmentation is recommended.

Keywords: triiodothyronine, T_3, augmentation, treatment-resistant depression

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Introduction and Background

Studies have demonstrated changes in the hypothalamus-pituitary-thyroid axis in patients with psychiatric illnesses, particularly those with depression.[1] Thyroid-stimulating hormone (TSH; also known as thyrotropin) is a pituitary hormone that stimulates the thyroid gland to secrete 2 major hormones, triiodothyronine (T_3) and thyroxine (T_4). TSH is, in turn, stimulated by hypothalamic thyrotropin-releasing hormone and inhibited by serum T_3 and T_4. In the periphery, most T_4 is converted to T_3 (the biologically active thyroid hormone).[1] T_3 is involved in numerous biologic functions and may increase serotonergic activity, particularly in the cerebral cortex, and plasma serotonin concentrations have been found to correlate positively with T_3 concentrations.[1] Neuropsychiatric symptoms occurring in hyperthyroidism or thyrotoxicosis include dysphoria, anxiety, irritability, emotional lability, and difficulty concentrating. Symptoms of depression, cognitive dysfunction, apathy, and psychomotor slowing are common in patients with hypothyroidism.[1] Despite these findings, most patients with major Depressive Disorder (MDD) do not exhibit thyroid hormone abnormalities and are considered to be euthyroid.[1] Depressed patients who present with thyroid dysfunction most often have elevated serum T_4 concentrations, reduced T_3 concentrations, and a blunted TSH response to thyrotropin-releasing hormone.[1]

Methods

A literature search (1996-November 2014) was performed using Medline via OVID and EMBASE. Search terms used

were *triiodothyronine*, *T3*, and *treatment-resistant depression*. Identified articles were included if they were available in English and investigated T3 as an add-on to antidepressant therapy for the treatment of MDD. Clinical trials (randomized, nonrandomized, controlled, and noncontrolled), case-control studies, systematic reviews, and meta-analyses were included. Relevant references in each article were scanned and included, if applicable.

Results

The role of thyroid hormones in the treatment of depression has focused on T3 supplementation; evidence to support the use of T3 monotherapy for the treatment of depression is lacking. A randomized, double-blind trial evaluating the antidepressant-potentiating effects of T3 versus T4 during a 3-week period in tricyclic antidepressant (TCA) nonresponders found that T3 was more effective.[2] A recent study measured the association between thyroid hormone concentrations and depression severity.[3] During the first week of hospitalization, TSH, free T4, and free T3 concentrations were obtained for 44 patients (20 women and 24 men; mean age 51.9 ± 11.5 years, standard deviation) with MDD and treated with a selective serotonin reuptake inhibitor (SSRI). Depression severity and clinical outcomes were evaluated using the 17-item Hamilton Depression Rating Scale (HDRS 17) and the Global Impression Scales for severity (CGI-S) and improvement (CGI-I). Patients with thyroid disease or those already receiving treatment for thyroid disease were excluded. TSH, free T4, and free T3 values were within normal limits in 97.7%, 79.5%, and 68.2% of patients, respectively. Of the patients with normal T3 concentrations, 70% had concentrations in the lower range of normal. Further analysis stratified by sex showed no significant difference in free T4 serum concentrations between men and women ($P = .350$), but significant differences were found in free T3 serum concentrations, with higher concentrations in men ($P = .018$). Free T4 ($P = .034$) and free T3 ($P = .012$) concentrations were positively correlated with clinical improvement as evaluated by the CGI-I. No significant correlation between free T4 ($P = .304$) and T3 ($P = .318$) concentrations and depression severity as assessed with the CGI-S was found. There was a significant correlation between free T4 concentrations and depression severity as assessed by the HDRS 17 ($P = .047$), but there was no such association with free T3 concentrations ($P = .614$). Sex-related differences in free T3 concentrations were believed to be secondary to more efficient T4-to-T3 conversion in men. Based on potential individual differences in thyroid hormone metabolism, the authors concluded that supplementation with T3 instead of T4 would be more beneficial in the acceleration and augmentation of antidepressant therapy.[3]

Studies evaluating the use of T3 in the treatment of MDD have included the following[4]:

1. Acceleration studies: T3 is administered in addition to the antidepressant during the first few weeks to shorten the time to onset of antidepressant effects.
2. Enhancement studies: T3 is administered in addition to the antidepressant throughout the length of therapy to enhance rates of antidepressant response.
3. Augmentation studies: T3 is added to current antidepressant therapy in patients who are unresponsive or partially responsive to an adequate course of antidepressant therapy.

In studies where the goal is accelerating or enhancing response to antidepressant therapy with T3, the potential response to the antidepressant itself is unknown. In augmentation studies, study participants are antidepressant nonresponders, and the objective is to convert these patients to responders with the addition of T3 to the antidepressant regimen. Initially, most of the evidence on the use of T3 for treatment of depression was with TCAs. More recently, several studies have evaluated the addition of T3 to SSRI therapy.

T3 and TCAs

Acceleration

A meta-analysis was conducted to determine whether T3 supplementation accelerated the time to onset of antidepressant effects of TCAs in patients with nonrefractory depression (studies evaluating treatment-resistant patients were excluded).[5] Six randomized, double-blind, placebo-controlled trials (RCTs) where T3 was added to the antidepressant treatment between days 1 and 5 were identified. In 4 studies the dosage of T3 was 25 μg/d, and the other 2 studies evaluated dosages of 20 and 62.5 μg/d. A total of 5 studies used imipramine (150-200 mg/d) and 1 used amitriptyline (100 mg/d) as the antidepressant. All studies assessed depression using the HDRS 17, but not all studies measured participant thyroid hormone concentrations. Most study participants (n = 125) were female (53%-100% per study), and duration of follow-up ranged from 21 to 28 days. In 5 of the 6 studies, T3 significantly increased the onset of antidepressant response compared with placebo (pooled effect size was 0.58 [95% confidence interval, 0.21-0.94]). No significant heterogeneity was detected ($P = .15$). The acceleration effect of T3 was greater in female patients ($P = .04$). One study found no significant difference between the treatments. The authors concluded that the results of the meta-analysis indicated that T3 decreased the time to response to TCA treatment and that this effect appeared to be greatest in females. However, the RCTs included in the meta-analysis had several limitations, including small sample size, no consistent thyroid hormone measurement across studies,

poorly defined diagnostic criteria for depression, the use of suboptimal TCA doses, and short-term follow-up.[5]

Augmentation

A meta-analysis of T3 augmentation of TCAs identified 8 controlled clinical studies in euthyroid patients (n = 292) with nonpsychotic depression refractory to TCA therapy.[6] Trials were included if accepted criteria for depression, stated definitions of refractory depression, and biochemical evidence of euthyroid status were provided. Studies were excluded if there was concurrent use of medications known to affect thyroid function (eg, lithium), if sufficient outcome data for each treatment arm were not provided, and if multiple studies included the same patient population. Data that compared T3 to a control group were included in studies with multiple treatment arms. A total of 3 of the studies were randomized, double blind, and placebo controlled; 1 study was a randomized, double-blind trial that compared T3 and T4 augmentation; 3 studies used historical or sequential controls, and therapy was unblinded; and 1 study employed a self-controlled design comparing pretreatment and posttreatment outcomes. Seven studies rated depression severity using the HDRS 17 and one used the Bunney-Hamburg Scale (modified version). Antidepressant use prior to augmentation ranged from 10 days to 12 weeks. Imipramine was the TCA in 5 studies; 3 studies did not report the TCA used. Dosages of T3 ranged from 20 to 50 μg/d, and follow-up after augmentation ranged from 7 to 28 days. Overall, 57% of the study participants who received T3 augmentation and 24% of patients in the control group met response criteria. Pooled treatment effects indicated that patients who received adjunctive T3 were two times more likely than controls to respond (relative response rate of 2.09; $P = .002$). The number needed to treat to obtain one responder was 4. The pooled standardized effect size for response as measured by improvement in depression scores was statistically significant (0.62; $P < .001$). However, pooled data analysis of relative response rates from the 4 RCTs were not significant (1.53; $P = .29$). There was significant heterogeneity in response rates among the RCTs, primarily due to one RCT in which response rates were higher in the control group. The 5 studies that assessed adverse effects reported no significant differences between T3 and the control groups. The authors concluded that although T3 augmentation may be effective in increasing response rate in TCA refractory depression, larger randomized, placebo-controlled trials are needed.[6]

T3 and SSRIs

Enhancement and Acceleration

The addition of T3 to enhance the effects of 30 mg of paroxetine daily was evaluated in an 8-week RCT.[7] A total of 113 outpatients with MDD based on the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria were randomized to receive paroxetine in addition to placebo (n = 53), 25 μg/d T3 (n = 30), or 50 μg/d T3 (n = 30). Paroxetine dosages were titrated during a 3-week period (10 mg/d during week 1; 20 mg/d during week 3; and 30 mg/d for the remaining 6 weeks) to minimize potential anxiety and agitation side effects of T3 and paroxetine. Baseline characteristics were similar among the 3 treatment arms, with the exception of chronic major depression, defined as duration greater than 2 years, being higher in the 25-μg T3 group. The primary end point was response defined as a ≥50% reduction in the HDRS 17 score from baseline to week 8. Secondary end points included response (≥50% reduction) measured by the Montgomery Asberg Depression Rating Scale (MADRS), the Hamilton Anxiety Rating Scale, and the Beck Depression Inventory; response (end point score 1 or 2) on the CGI; and remission (end point score ≤12) on the MADRS. Efficacy assessments were performed and adverse events were monitored at weeks 1, 2, 4, 6, and 8; thyroid function tests were measured at baseline and week 8. To provide sufficient power (90%) to detect an increase in response rates from 60% to 85%, the study was originally designed to enroll 150 patients with MDD (75 patients in the placebo arm and a combined 75 patients in the T3 arms). However, a data-monitoring committee advised terminating the study when a review of the data at interim analysis indicated no enhancing effects of T3 addition compared with placebo addition. Outcome analysis was performed on 106 patients because 7 patients withdrew from the study prior to receiving any treatment. All 3 groups showed a significant decrease (≥8.3 ± 6.6 decrease) in HDRS 17 scores from baseline to the last follow-up visit ($P < .001$), with an overall response rate of 46% that did not differ between the 3 groups ($P = .99$). Significant improvements were seen in all secondary efficacy assessments performed for all 3 treatment arms ($P < .001$), although there were no significant differences between the treatment groups for any efficacy assessment. No significant differences in remission, defined as an HDRS 17 score ≤8, were seen in the placebo group compared with the T3 groups combined (36% and 32%, respectively; $P = .92$). A subanalysis of female patients (n = 68) revealed response rates of 47% in the placebo group, 53% in the 25-μg T3 group, and 47% in the 50-μg T3 group ($P = .92$). In addition to a lack of enhancement effects of T3, the time to onset of response did not significantly differ among the 3 groups ($P = .48$). Mean time to response was 5.3 weeks in the placebo group (n = 23), 5.8 weeks in the 25-μg T3 group (n = 13), and 6.3 weeks in the 50-μg T3 group (n = 13). A dose-dependent increase in serum T3 concentrations was observed in the patients receiving T3 augmentation, indicating that compliance was not a problem. Common adverse effects associated with paroxetine included headache, somnolence, insomnia, dry mouth, and sexual

dysfunction (decreased libido and erection/ejaculation problems). Eight patients did not complete the study because of adverse effects. T3-related adverse effects included palpitations, sweating, nervousness, and tremor. The authors concluded that the study results do not support the addition of T3 to enhance SSRI therapy in patients with nonrefractory MDD, and this addition may increase the incidence of adverse effects.[7]

The ability of T3 to enhance antidepressant effects when administered concurrently with sertraline was evaluated in a double-blind, randomized, placebo-controlled trial.[8] A total of 124 patients ages 18 to 70 years with nonresistant MDD without psychotic features (DSM-IV) were randomized to receive sertraline plus placebo or sertraline plus T3 for 8 weeks. Sertraline was dosed 50 mg/d for the first week and then, if tolerated, 100 mg/d for weeks 2 through 8. T3 was dosed 20 to 25 μg/d for the first week, followed by 40 to 50 μg/d for the remainder of the study, if tolerated. Exclusion criteria included significant suicidal risk, past or current thyroid disease, a medical condition that could make T3 use unsafe, and previous treatment with sertraline. Baseline psychiatric evaluations included the HDRS 17 and a 100-mm visual analog scale for self-rating of mood. The primary end point was response to treatment defined as a $\geq$50% decrease in HDRS 17 scores from baseline to study end point. Secondary outcome measures included remission (response plus end point HDRS 17 score $\leq$6) and visual analog scale response ($\geq$50% improvement) or visual analog scale remission (>75% improvement). The study was adequately powered to detect a significant difference in response rate between the sertraline-placebo and sertraline-T3 groups. Intent-to-treat analysis included any patient who completed at least 1 clinic visit after randomization. Baseline patient demographic and clinical characteristics did not differ significantly between the 2 treatment arms. A total of 50 of the 60 patients randomized to the placebo arm and 53 of the 64 patients randomized to the T3 arm completed at least 1 visit, with 37 (74%) in the placebo group and 40 (75%) in the T3 group completing the 8-week trial. Primary reasons for study discontinuation included withdrawal of consent, adverse effects, lack of efficacy, and loss to follow-up. Thyroid hormone concentrations were measured at baseline and after 8 weeks of treatment. After treatment, TSH and T4 concentrations significantly decreased ($P < .001$ for both), and T3 concentrations significantly increased in the sertraline-T3 group ($P = .001$). In the sertraline-placebo group, a small but significant decrease in T3 concentration ($P < .01$) and no significant changes in TSH or T4 concentrations were seen. Rates of response (70% versus 50%; $P = .02$) and remission (58% versus 38%; $P = .02$) based on HDRS 17 favored the sertraline-T3 arm. These findings were supported by higher remission rates based on self-reported visual analog scale scores (30% versus 12%, respectively; $P = .03$) in the sertraline-T3 group compared with the sertraline-placebo group. When compared with sertraline alone, patients receiving concurrent sertraline and T3 were 2.9 times more likely to respond and 2.7 times more likely to achieve remission. In patients randomized to the sertraline-T3 who met criteria for remission, baseline T3 values were significantly lower than for nonremitters ($P = .002$), and remission was associated with a significant decrease in TSH concentrations after treatment ($P < .05$). Baseline T3 values did not differ between remitters and nonremitters in the sertraline-placebo group ($P = .38$). There were no significant differences in the type or frequency of adverse effects reported in each treatment arm. The results of the study support the enhancement of sertraline efficacy with concurrent administration of T3 in patients with MDD, particularly in patients with lower basal T3 at baseline.[8]

A second study evaluating the addition of T3 to a regimen of sertraline found no data to support enhanced or accelerated antidepressant response.[9] This 8-week, double-blind, randomized, placebo-controlled trial examined the addition of T3 (25 μg/d during week 1 and 50 μg/d weeks 2 through 8) or placebo to a starting regimen of sertraline (mean final daily dose was 146 $\pm$ 47.8 mg). Response was defined as $\geq$50% decrease from baseline and a total score of <15 on the 21-item HDRS 17; a HDRS 21 score <8 was required for remission. A total of 153 patients ages 18 to 60 years who met DSM-IV criteria for MDD, did not have thyroid disease, and returned for at least 1 postrandomization visit were included in the modified intent-to-treat efficacy analysis. No statistically significant differences were observed in any outcome measures between treatment groups. Response was observed in 65% of the placebo group and 61.8% of the T3 group, and remission was seen in 50.1% and 40.8% of the placebo and T3 groups, respectively. Furthermore, baseline thyroid function measures were not predictive of treatment outcomes.[9]

The addition of T3 to accelerate and enhance antidepressant effect was evaluated in a 6-week randomized, double-blind, placebo-controlled pilot study that enrolled 50 patients with MDD.[10] Patients who were at least 18 years of age and met DSM-IV criteria for MDD were included. Exclusion criteria included patients with unstable cardiac, endocrine, or renal disease, and those with a history of thyroid disease. Patients with a diagnosis of bipolar disorder, psychotic features, psychiatric comorbidity, or a history of treatment resistance were not excluded. Most patients received an SSRI (n = 26), followed by bupropion (n = 8), venlafaxine (n = 7), and mirtazapine (n = 4). Patients were randomized to receive T3 (n = 23) or placebo (n = 27), and all other treatments

(ie, choice and dosage of antidepressant, use of other medications, psychotherapy) were open label and followed usual clinical practice. There were no statistically significant differences in baseline demographic or clinical features (including baseline TSH concentrations) between the 2 treatment groups. Response was defined as a ≥50% decrease in baseline MADRS scores. During each of the first 3 weeks of treatment, response rates in the T3 treatment group were higher compared with the control group (week 1: 45% versus 24%; week 2: 57% versus 33%; and week 3: 43% versus 24%, respectively). However, these differences were nonsignificant. Using last observation carried forward, response and remission rates were nonsignificantly higher for patients receiving T3 than placebo (response: 61% versus 52%; $P = .5$; and remission: 48% versus 37%; $P = .44$) after 6 weeks of treatment. Adverse effects were self-assessed using an 11-item checklist of symptoms consistent with hyperthyroidism. Nervousness was the only statistically significant adverse effect and was more prevalent in the placebo group compared with the T3 group (46% versus 11%; $P = .01$). Despite the non–statistically significant results, the authors concluded that the study provided preliminary evidence that concurrent administration of T3 and an antidepressant can accelerate the onset of antidepressant effects and improve overall response rates compared with administration of an antidepressant alone.[10]

Augmentation

An open-label study investigated the use of T3 to augment SSRI efficacy in treatment-resistant patients.[11] T3 (50 μg/d) was added to the pre-enrollment antidepressant regimen in 20 patients (mean age, 44.31 ± 0.3 years) who met DSM-IV criteria for MDD and had failed to respond to what the authors referred to as a "standard course of antidepressant treatment with an SSRI." A standard course was defined as follows: SSRI taken for ≥8 weeks with ≥4 weeks at a stable dosage of fluoxetine, paroxetine, or citalopram ≥40 mg/d, sertraline ≥100 mg/d, or escitalopram ≥20 mg/d. Exclusion criteria included medical disorders in which T3 was contraindicated, abnormal TSH concentrations, and hypersensitivity to T3. Response was defined as a ≥50% decrease in HDRS 17 scores from baseline, and remission was defined as a final HDRS 17 score of ≤7. A total of 35% of patients met criteria for response and 30% met criteria for remission. A subanalysis indicated comparable baseline depression severity but significantly greater depression severity at the end of the study between melancholic (n = 8) and nonmelancholic patients (HDRS 17 final scores, 18.3 ± 6.6 versus 11.1 ± 6.1; $P = .03$). Thyroid function was evaluated at the start of T3 augmentation and again after 4 weeks of follow-up. Thyroid hormone concentrations of all participants were within normal limits at the start of T3 augmentation. After 4 weeks of treatment, TSH suppression was noted in 90% of patients enrolled, T3 concentrations were abnormally high, and T4 concentrations were low. No significant differences in pretreatment or end-of-study TSH concentrations were seen between responders and nonresponders. No relationship between sex and any treatment outcome measure was found. The addition of T3 was well tolerated, with 2 patients experiencing fatigue and diaphoresis; 1 patient experiencing tremor, dry mouth, headaches, muscle aches, and vivid dreams; and 1 patient discontinuing treatment after 2 weeks because of muscle aches, fatigue, and photophobia. Data from this study support the use of T3 augmentation of SSRIs in patients with treatment-resistant depression. All nonresponders with atypical depression (n = 5) experienced response following the addition of T3; the rate of response was lower in nonresponders with melancholic depression (12.5%).[11] The overall response rate in this study was similar to the response rate of 40% in a previous study prospectively evaluating T3 augmentation (25 to 50 μg/d) of SSRIs (fluoxetine and paroxetine) in nonresponders.[12] Of the 25 patients who received T3 augmentation, 62.5% of women (10 of 16) and no men (0 of 9) responded. The authors of this study concluded that T3 may augment the antidepressant response of SSRIs in nonresponders, and this effect appears to be greater in women than in men.[12]

Level 3 of the Sequenced Alternatives to Relieve Depression (STAR*D) compared the addition of lithium or T3 as augmentation in patients with nonpsychotic MDD who did not achieve remission after 2 trials of antidepressant therapy.[13] Patients were randomized to receive lithium (up to 900 mg/d; n = 69) or T3 (up to 50 μg/d; n = 73) for up to 14 weeks. Other than a greater number of patients in the lithium group experiencing their first depressive episode before the age of 18 years, and the mean age at onset of the first episode being lower in the lithium group, patient characteristics at the start of level 3 were not statistically significantly different between treatment groups. Antidepressant treatment in the prior treatment level (2 or 2A) included sustained-release bupropion (n = 30), citalopram plus bupropion (n = 34) or buspirone (n = 27), sertraline (n = 21), or extended-release venlafaxine (n = 30). Remission was the primary outcome measure and was defined as an HDRS 17 score of ≤7. After a mean follow-up time of 9.2 ± 5.2 weeks, 15.9% of patients receiving lithium (mean daily dose at exit was 859.8 ± 373.1 mg) and 24.7% of patients receiving T3 (mean daily dose at exit was 45.2 ± 11.4 μg) achieved remission ($P = .43$). In addition, differences in mean time to response and remission were not statistically significant between the 2 groups. The Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR) was used by participants to measure response or remission (secondary outcomes), defined as a reduction of ≥50% in QIDS-SR score from level 3 baseline and a total QIDS-SR score ≤5 at study end point, respectively. No statistically significant differences were observed between the 2 treatment

groups in response or remission as assessed by the QIDS-SR. Compared with the T3 group, significantly more participants in the lithium group withdrew from the study because of side effects (23.2% versus 9.6%; $P = .027$), suggesting that T3 augmentation was better tolerated. STAR*D level 3 data suggest an advantage with T3 augmentation for individuals who do not respond to 2 antidepressant regimens. Limitations to the STAR*D level 3 include a lack of statistical power to detect small differences in remission rates, a lack of thyroid function and lithium concentration assessments for all patients, a lack of a placebo control, the use of low doses of lithium, and that the augmentation therapies were administered in an open-label manner.[13]

T3 was found to be a safe and effective augmentation option in 12 (8 women and 4 men) euthyroid patients with MDD who failed to respond an adequate 6-week SSRI regimen.[14] A total of 5 patients were taking sertraline (mean dosage of 130 mg/d), 4 were taking citalopram (mean dosage of 50 mg/d), 2 were taking fluvoxamine (150 mg/d), and 1 patient was taking paroxetine (40 mg/d). All patients continued the same SSRI they were taking before entering the study, and all were started on 25 µg/d of T3, which was increased to 50 µg/d as tolerated. T3 augmentation was evaluated after 3 weeks. The HDRS 17 was used to measure response (≥50% score reduction) and remission (scores ≤7). No significant differences in baseline HDRS 17 scores, sex, number of previous antidepressant trials, or changes in TSH concentrations were identified between responders and nonresponders. Response was seen in 5 patients (42%), and 3 of these patients achieved remission. One patient withdrew from the study during week 1 because of increased anxiety and agitation.[14]

Two studies investigated the addition of T3 at dosages as high as 150 µg/d to a serotonergic antidepressant in nonresponders.[15,16] One study evaluated the addition of 100 µg/d T3 in 17 women (ages 30-60 years) with unipolar or bipolar depression resistant to clomipramine (n = 11), paroxetine (n = 5), or fluoxetine (n = 1).[15] All patients received T3 supplementation, and no control group was included in this study. At the end of the 4-week study period, 16 patients (94%) met criteria for response (≥50% reduction in HDRS 17 scores), 11 patients (65%) met criteria for remission (≤7 on the HDRS 17), and 1 patient did not respond. Response or remission to T3 augmentation was not correlated with baseline thyroid function, age, diagnosis, or duration of illness.[15] A second study evaluated the addition of T3 at doses of 25 to 150 µg (average dose, 80 µg) in 17 patients (10 women and 7 men) during an average of 24.2 months.[16] All patients had failed to respond to at least 3 adequate antidepressant trials, and TSH concentrations were within normal limits for all patients at the time of enrollment. T3 dosages were initiated at 25 µg/d and increased by 12.5- to 25-µg increments every 2 to 3 weeks, as tolerated, to a maximum of 150 µg/d until remission was achieved. If symptoms of hyperthyroidism, other than minimal tremor or heat intolerance, occurred, the T3 dosage was decreased. The CGI-I was used to measure treatment response (defined as a score of ≥2 lasting at least 2 months). A total of 14 patients (82.4%) responded, achieving an average CGI-I score of 2.5. For patients in whom a response was lost during the study period, the T3 dosage was increased, as tolerated, until response was recovered. Two patients (both male) discontinued T3 treatment because of adverse effects, one because of a leg tremor and one because of sluggishness, irritability, and worsening of anxiety. One patient (male) did not respond to a dose of 125 µg of T3, and higher dosing resulted in adverse effects. All female patients achieved response, supporting previous findings indicating that women are more likely than men to respond to T3 augmentation. Of note, other medications were used and changed as needed throughout the study period and may account for improvements in mood throughout the study.[16]

Discussion

There is little evidence to support the use of T3 administered with SSRIs to accelerate antidepressant response, and studies evaluating the enhancement of SSRI antidepressant activity with concurrent T3 administration are conflicting. However, studies do support the use of T3 augmentation (25-50 µg/d) for the treatment of depressive symptoms in patients without thyroid hormone abnormalities who do not respond to an adequate trial of a TCA or an SSRI. Although most augmentation studies in antidepressant treatment–resistant patients limited the dosage of T3 to a maximum of 50 µg/d, response or remission was achieved using a dosage of 100 µg/d in one study[15] and increasing T3 dosages up to 150 µg/d, as tolerated, in another study.[16] Data from 2 small studies evaluating whether women may respond better than men to T3 augmentation are conflicting. One study (n = 25)[12] found a better response to T3 augmentation in women, and another study (n = 20)[11] found no relationship between response and sex. Limitations to T3 augmentation studies include no control group, small study populations, administration of T3 in an open-label manner, lack of thyroid hormone monitoring, and lack of follow-up to determine long-term response or remission rates. Although the results of the studies summarized in this review indicate that the effectiveness of antidepressants can be enhanced by T3 augmentation, randomized, double-blind, placebo-controlled trials are needed to better identify optimal T3 doses and patient populations that would benefit from this treatment strategy.

Overall, studies evaluating T_3 supplementation in patients with MDD show that it is well tolerated. Regardless, all patients started on T_3 should have thyroid hormone concentrationss monitored regularly and should be evaluated for symptoms of hyperthyroidism, such as an increase in tremor, anxiety, palpitations, heat intolerance, diaphoresis, or sleep disturbances. In addition, it is important to monitor for such conditions as hypertension, tachycardia, arrhythmias, hyperglycemia, and decrease in bone mineral density, which can be exacerbated by T_3 augmentation.

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