Neuropsychiatric Manifestations of Thyroid Disease

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KEY POINTS

- The symptoms of hypothyroidism often mimic those of depression, whereas those of hyperthyroidism include anxiety, dysphoria, emotional lability, intellectual dysfunction, mania, or depression.
- Most patients with depression have normal thyroid function, but 1% to 4% of patients with affective disorders are overtly hypothyroid while 4% to 40% may have subclinical hypothyroidism.
- Up to 52% of patients with refractory depression may have evidence of subclinical hypothyroidism, compared with 8% to 17% in an unselected population of depressed patients.
- Thyrotoxicosis may commonly present with anxiety, dysphoria, emotional lability, intellectual dysfunction, and mania, so a diagnosis of thyrotoxicosis should be considered in any patient with new onset of anxiety or mania.
- The indications for treatment of subclinical hyperthyroidism are controversial, and current guidelines do not address treatment based on neuropsychiatric symptoms, but rather for other potential morbidities.
- Iatrogenic thyrotoxicosis may be symptomatic, occurring after exposure to medications or other physician-directed disruptions of normal function of the thyroid gland.

INTRODUCTION

For more than 125 years[1] it has been recognized that thyroid disease may give rise to psychiatric disorders that can be corrected by reestablishment of normal thyroid function. More than 60 years ago we learned that patients with profound hypothyroidism may present with depressive psychosis.[2] The symptoms of hypothyroidism mimic

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those of depression, whereas those of hyperthyroidism include anxiety, dysphoria, emotional lability, and mania.

Assuming a thyroid link to depression, ingestion of thyroid hormone was projected to benefit depressed patients. But controlled studies have not documented success with this approach,[3,4] leaving the role of thyroid hormones in the treatment of euthyroid depression in question.[5] Likewise, combinations of LT_3 and antidepressants in euthyroid patients, as well as LT_3 with levothyroxine in fully replaced hypothyroid subjects, have been explored but remain a matter of much debate.[10–12]

The prevalence of hypo- and hyperthyroidism in the US population is outlined below in **Table 1**. Surks and Hollowell[13] demonstrated that up to 14.5% of disease free older individuals have a thyrotropin (TSH) level higher than 4.5 mIU/mL, therefore the prevalence of subclinical hypothyroidism (SCH) in the elderly may be overestimated.[14] TSH values in seniors with extreme longevity are higher than expected,[15] and they also have TSH values higher than appropriate controls.[16,17] So not every elevation of TSH represents thyroid disease.

1% to 4% of patients with affective disorders are overtly hypothyroid and 4% to 40% may have SCH.[16] Many patients with refractory depression may have SCH, compared with unselected depressed patients.[18]

Thyrotoxicosis commonly presents with anxiety, dysphoria, emotional lability, intellectual dysfunction, and mania.[19] After restoration of biochemical euthyroidism, many hyperthyroid patients have persistent residual neuropsychiatric symptoms.[20,21] Patients with subclinical hyperthyroidism may be nervous, irritable,[22] and anxious in comparison with controls.[23] Some have found dementia in elderly patients with subclinical hyperthyroidism,[24] while others have failed to show this association.[25] The indications for treatment of subclinical hyperthyroidism,[26] do not consider neuropsychiatric symptoms.[27] Iatrogenic thyrotoxicosis may be symptomatic, occurring after exposure to medications[28] or other disruptions of normal thyroid gland function.[29]

RELATIONSHIP OF THYROID HORMONES WITH MOOD AND COGNITION

In most depressed subjects, the basal serum TSH, thyroxine (T_4) and triiodothyronine (T_3) are within the expected range, although in one report a third of such patients were observed to have suppressed TSH levels.[30] Depressed patients admitted to a psychiatry unit, may have an increase in serum total or free T_4 levels, which generally regresses following successful treatment.[30] 25% of patients with depression have a "blunted" TSH response to thyrotropin-releasing hormone (TRH) administration (as defined by a TSH increase of <5 μU/mL). A blunted TSH response has been observed more frequently in unipolar than in bipolar depression, but differentiating these disorders with TRH stimulation has been disappointing.[31] The blunted TSH response has

Table 1						
Prevalence of hypothyroidism and hyperthyroidism in the United States population						
	Hypothyroidism			**Hyperthyroidism**		
Study	**TSH Cutoff**	**Subclinical**	**Overt**	**TSH Cutoff**	**Subclinical**	**Overt**
Colorado Thyroid Disease Prevalence Study[6]	>5.1 mIU/mL	8.5%	0.4%	<0.3 mIU/mL	0.9%	0.1%
National Health and Nutrition Examination Survey III[7]	>4.5 mIU/mL	4.3%	0.3%	<0.1 mIU/mL	0.7%	0.5%

Data from Refs.[6–9]

been considered a "state" marker that normalizes on recovery from the depression. The mechanism for the blunted TSH response in affective disorders is not known; however, glucocorticoids, known to inhibit the hypothalamic-pituitary-thyroid axis, are elevated in depression and could be responsible.[19]

An enhanced TSH response may occur in up to 15% of depressed subjects. The majority of such patients have positive antithyroid antibodies, suggesting that latent hypothyroidism caused by autoimmune thyroiditis. Indeed in one such study, individuals with positive antithyroid peroxide antibodies were found to have symptoms of anxiety and depression more frequently than in controls.[32] Not all studies, however, have found an increased prevalence of antithyroid antibodies or apparent mild hypothyroidism in depressed subjects when compared with matched control groups.[33]

In normal subjects, the TSH level begins to increase in the evening before the onset of sleep, reaching a peak between 11 PM and 4 AM.[34] In depression, the nocturnal surge of TSH is frequently absent, resulting in a reduction in thyroid hormone secretion, supporting the view that functional central hypothyroidism might occur in some depressed subjects.[35] Sleep deprivation, which has an antidepressant effect, returns TSH circadian rhythm to normal.[36] The mechanism responsible for the impaired nocturnal increase in TSH is unknown.

Deiodinases are selenocysteine enzymes that remove iodine molecules from thyroid hormones. Three types of deiodinases have been identified. Deiodinase 1 (D1) is found mainly in liver and kidney, whereas deiodinase 2 (D2) is found in adipose tissue, brain, and pituitary gland. Both D1 and D2 result in the conversion of T_4 to T_3. Deiodinase 3 (D3) inactivates T_4 by converting it into reverse T_3 and converts T_3 to diiodothyronine (T_2). Brain derives most of its T_3 from the conversion of T_4 to T_3 from D2 enzyme activity.[37,38] Single-nucleotide polymorphisms (SNPs) have been identified in the deiodinase genes. One such polymorphism identified is related to D2 coding and is cited as the Thr92Ala polymorphism. This SNP is seen commonly in various ethnic groups.[39] This polymorphism has been studied for an association of any changes in well-being and neurocognitive functioning, as well as to potentially identify a preference for combined LT_4 and LT_3 therapy for treatment of hypothyroidism, with mixed results. No differences in symptoms were noted, and there was no benefit of adding LT_3 to levothyroxine in the 2005 study by Appelhof and colleagues.[40] Panicker and colleagues,[41] however, reported that patients with the Thr92Ala polymorphism had worse baseline General Health Questionnaire scores while on LT_4 monotherapy for hypothyroidism, but showed greater improvement on LT_4/LT_3 combination therapy for hypothyroidism compared with continued LT_4 alone. Under hypothyroid conditions, it has been proposed that the D2 enzyme with this polymorphism may deiodinate less effectively and therefore lead to diminished levels of local T_3 production and, perhaps, an increased dependence on circulating T_3 to maintain optimal brain T_3 levels.[41]

Serotonin deficiency has been proposed as a central pathologic factor in depression. In one study, brain serotonin levels correlated positively with T_3 levels in rat brain.[42] A state of relative hypothyroidism in brain with coexisting systemic euthyroidism attributable to deficient D2 has therefore been proposed.[43,44] Alternatively, D2 activity may be depressed by the elevated cortisol levels seen in depression and stress, resulting in T_4 being converted to reverse T_3 by D3 activity, leading to decreased brain T_3 and increased reverse T_3 levels.[45] Selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants appear to promote the activity of D2, which results in an increased conversion of T_4 to T_3 within the brain tissues.[46]

Organic anion transporting polypeptides (OATPs) are proteins capable of transporting thyroid hormone into the cell.[47] Genetic coding for OATP1C1 is located on chromosome 12p12, and the protein is a thyroid hormone (T_4 and reverse T_3)

transporter expressed at the blood-brain barrier, considered to play a key role in delivering serum T_4 to the brain. One hundred forty-one patients with primary autoimmune hypothyroidism were studied to determine the presence of this polymorphism in the gene encoding for this protein. The presence of the OATP1C1 SNP was associated with an increased frequency of hypothyroid symptoms, including fatigue and depression.[47]

Altered cerebral perfusion has been demonstrated under hypothyroid conditions. Both global[48–51] and regional[51] hypoperfusion have been demonstrated. Whereas some researchers have demonstrated partial normalization following LT$_4$ treatment,[49,50,52] others have found no improvement in perfusion[51] following correction of the hypothyroid state.

NEUROPSYCHIATRIC MANIFESTATIONS OF OVERT HYPOTHYROIDISM

There is a considerable overlap between the clinical manifestations of mood disorders and those of hypothyroidism, as shown in **Table 2**. In fact, many of the symptoms attributed to both hypothyroidism and depression such as poorer memory, slower thinking, and being more tired are seen in almost equal frequency when comparing those with documented hypothyroidism and non-depressed euthyroid controls.[6] An evaluation of overtly hypothyroid and euthyroid controls for the presence of classic hypothyroid symptoms, including several considered neuropsychiatric in nature, revealed no significant differences in the percentage complaining of tiredness, feeling depressed, thinking slowly, having poor memory, or having difficulty in performing math operations.[53] Individuals report fatigue as a response to the question "Do you feel tired?" with nearly equal frequency if hypothyroid or euthyroid controls.[54] Moreover, the subscale on vitality of the RAND 36-item Health Survey and the Shortened

Table 2 Common clinical features in hypothyroidism and mood disorders		
	Hypothyroidism	**Mood Disorders**
Depression	Yes	Yes
Diminished interest	Yes	Yes
Diminished pleasure	Yes	Yes
Decreased libido	Yes	Yes
Weight loss	No	Yes
Weight gain	Yes	Sometimes
Appetite loss	Yes	Yes
Increased appetite	No	Yes
Insomnia	No	Yes
Hypersomnia	Yes	Yes
Agitation/anxiety	Occasionally	Yes
Fatigue	Yes	Yes
Poor memory	Yes	Yes
Cognitive dysfunction	Yes	Yes
Impaired concentration	Yes	Yes
Constipation	Yes	Sometimes

Data from Hennessey JV, Jackson IM. The interface between thyroid hormones and psychiatry. Endocrinologist 1996;6:214–23.

Fatigue Questionnaire, which quantify the intensity of fatigue, are similar in hypothyroid patients and non-depressed euthyroid controls.[54] Thus it is evident that the symptoms of hypothyroidism are indeed somewhat nonspecific and require further classification when present. It is therefore recommended that all patients diagnosed with psychiatric disorders be tested for thyroid hormone abnormalities[19,55] because the presence of even SCH may provide an opportunity to treat apparent depression with thyroid hormones.[56]

Severe hypothyroidism may present with melancholic depression.[57,58] Frank psychosis with hallucinations and delusions has been described, but is thankfully rare.[58] Asher described psychosis in 14 hypothyroid patients and coined the term "myxedema madness."[2] There is no clear consensus regarding diagnostic criteria for establishing the diagnosis of myxedema madness, but is has been reported that 5% to 15% of all hypothyroid patients may have some form of psychosis.[59,60] The manifestations of thought disorders vary considerably and include delusions of the paranoid, schizophrenic, or affective type.[58] Capgras syndrome (believing that one's spouse or close family member has been replaced by an identical-looking imposter),[61] visual and auditory hallucinations, perseveration, loose associations, and paranoia[60] have all been reported. These psychotic symptoms are said to be preceded by physical symptoms of hypothyroidism by months to years before manifestation.[62]

EFFECTS OF LT$_4$ TREATMENT OF HYPOTHYROIDISM

Treatment with levothyroxine improves the neuropsychiatric symptoms, although the pattern is inconsistent and complete resolution of all symptoms is variable.[63,64] Usually, normalization of TSH and circulating levels of T$_3$ can be achieved by the oral administration of LT$_4$.[65] Achievement of a TSH level in the expected range seems to be adequate to assure restoration of physical and neuropsychiatric function, as attempts to demonstrate any further superiority of maintaining the TSH in a low normal versus a higher normal range have failed to document any advantage of a certain narrower range.[66,67] Despite achieving euthyroidism as indicated by the serum TSH, some patients may continue to complain of various hypothyroid symptoms, including a picture consistent with that of depression.[68] This particular study's finding of excessive symptoms, however, has been difficult to interpret because at baseline, those treated with T$_4$ were more likely to have additional chronic medical conditions and to be receiving more chronic medications than the comparison group.[68] The results may further be unique to this study because a portion of the TSH levels achieved with treatment would be considered to be in the mildly hypothyroid range as defined in many studies of SCH, so it is unclear whether all subjects were actually euthyroid. For this reason, a clinician following patients with TSH values in the upper end of the range that was considered euthyroid by Saravanan and colleagues[68] would likely increase the replacement dose in a patient with such complaints to return the TSH to the expected range. In addition, Saravanan's findings have been criticized because of issues of potential ascertainment bias, which might provide an alternative explanation for the results.[69] Further studies have also claimed that euthyroid patients on T$_4$ may have worse cognitive function test results compared with a reference population,[70] and others have noted higher anxiety and depression symptoms on the Hospital Anxiety and Depression Scale.[10] As it is not possible to differentiate euthyroid from hypothyroid subjects based on neuropsychiatric symptoms,[6,53,54] it is extremely problematic to then expect that all hypothyroid individuals will experience complete resolution of all subjective symptoms once rendered euthyroid. Despite this obvious

caveat, the persistence of these findings has been cited to justify further research on combination of LT_3 with LT_4 to improve symptomatology.

EFFECTS OF COMBINATION T_4/T_3 THERAPY ON THE NEUROPSYCHIATRIC MANIFESTATIONS OF TREATED HYPOTHYROIDISM

Murray introduced thyroid hormone therapy to the clinical world in 1891. This therapy was from its beginning a treatment based on a combination of LT_4 and LT_3 derived from animal thyroid extracts.[71] Variability of the LT_4 and LT_3 content and ratios of animal extracts from batch to batch and brand to brand[72] led to the replacement of this "natural" combination therapy of extracts with pharmaceutically more precise synthetic T_4 and T_3.[72–74] Eventually the simplicity of T_4 monotherapy was adopted as usual therapy, and seems to provide satisfactory replacement.[75] T_4, like thyroid hormone extract dosage, was initially titrated based on clinical symptoms during the era before serum TSH assays became available. During the 1980s more sensitive TSH assays allowed titration of thyroid hormone therapy to "normal," which resulted in significant dose reductions of LT_4 dosage to as little as 100 µg per day,[76] likely indicating the excessive amounts of both LT_4 and thyroid extracts previously used. When actually euthyroid according to current biochemical parameters, some patients still complained of symptoms consistent with components of the nonspecific symptoms associated with hypothyroidism.[68,77] As patients were no longer routinely overdosed with their thyroid hormone therapy, it was proposed that the difference in outcomes (compared with historical experience with thyroid hormone extracts) might be due to the absence of significant amounts of LT_3 in the LT_4 preparations. Subsequently, multiple reports have appeared evaluating the effectiveness of combining LT_3 with T_4 to improve neuropsychological outcomes. The report of Bunevicius and colleagues,[78] for example, seemed to indicate that substituting 12.5 µg of T_3 for 50 µg of the individual's usual T_4 dose resulted in improvement in mood and neuropsychological function. These results, however, may not be widely applicable, as was evident in an analysis of the subset of this population who were being treated with T_4 for primary hypothyroidism[79] and who demonstrated no significant improvement in clinical outcome with the combination.[79] Several double-blind, randomized controlled trials designed to correct flaws observed in the initial trials have subsequently failed to reproduce the positive effects reported by Bunevicius, and do not demonstrate objective improvement in self-rated mood, well-being, or depression scales with the addition of LT_3 to LT_4 therapy.[5] Furthermore, most of these studies fail to demonstrate differences in cognitive function, quality of life, or subjective satisfaction with treatment, but some do report that anxiety scores were significantly worse in those treated with the LT_4/LT_3 combination.[80] However, more recent investigations have proposed that there may be a subset of T_4-treated patients who may benefit from LT_3 supplementation in those who experience higher depression and anxiety scores than euthyroid counterparts.[10] Preliminary evidence suggests that those patients with the D2 gene polymorphism (Thr92Ala) may have a positive response to T_3 potentiation,[41] but other research has not confirmed this observation,[40] and prospective trials in this situation have not yet been conducted.

On the other hand, there is also evidence that a further subset of patients may be predicted to not respond to LT_3 potentiation. Polymorphism in the coding for the organic anion-transporting polypeptide (OATP1C1) appears to be linked to increased depressive symptoms among those with hypothyroidism. When compared with controls, these patients do not appear to have any decrease in depressive scores when LT_3 supplementation is added to LT_4.[47] The clinical significance of this finding is yet

to be determined, but may have a meaningful impact on the future of depression treatment.

At present, meta-analysis has concluded that it would not seem justified to use combined T_4 and LT_3 treatment as a general rule in hypothyroid patients who complain of depressive symptoms after biochemical euthyroidism is restored.[81] In patients with ongoing symptoms despite being euthyroid, a thorough history and physical examination along with a laboratory evaluation including a complete blood count, comprehensive metabolic panel, celiac disease testing, and obstructive sleep apnea screening, along with an endocrine workup including vitamin D levels, thyroid peroxidase antibodies, cortisol levels and, if indicated, cosyntropin stimulation testing, is recommended to rule out other causes.[82] Given the conflicting data in regard of D2 gene polymorphisms, when lifestyle changes (dietary changes, exercise, sleep hygiene) and optimal medical treatment with LT_4 including changes in brand of T_4 have failed, some investigators have recommended that a trial of combination therapy be considered,[82] but others await further evidence of predictable efficacy before making this recommendation.

NEUROPSYCHIATRIC MANIFESTATION OF SUBCLINICAL HYPOTHYROIDISM

SCH is diagnostically defined as the finding of an elevated serum TSH concentration and normal circulating free T_4 and T_3 concentrations. SCH, by definition, cannot be diagnosed by clinical findings. It has been conceptualized as a stage in the continuum of normal thyroid function to overt clinical hypothyroidism.[83] The prevalence of SCH varies with the population studied and the upper limit set for TSH measurement.[26] Various studies investigating this question have determined the presence of hypothyroidism by using a TSH upper normal cutoff ranging between 3 and 4.5 mIU/mL.[55] These differences are the result of assessing populations differing in iodine intake and the use of assays with different performance characteristics. As a result of these issues, there is considerable debate about the upper limit of TSH.[55] Elegant studies have confirmed that TSH levels increase with advancing age among those free of thyroid disease and that, therefore, the use of age-specific TSH levels would predictably reduce the apparent prevalence of SCH in the elderly population.[13] In fact, a study assessing longitudinal change in thyroid function in very elderly subjects free of thyroid disease demonstrated a 12% increase in TSH along with a 1.7% increase in free T_4 and a 13% decline in serum T_3 over a 13-year follow-up period.[14] The upper limit of the expected TSH range was observed to increase from 6.2 mIU/mL in those 80 to 84 years old to 7.96 mIU/mL in those older than 90 years, clearly demonstrating a need for age-adjusted expectations in interpreting TSH.[14]

Experts typically further classify SCH into those with a mildly elevated TSH (4.5–10 mIU/mL) and others with markedly elevated TSH (>10 mIU/mL).[27] The natural history of SCH depends on the underlying cause and the population studied.[26] The estimated annual rate of conversion from SCH to overt disease in the Whickham survey was 2.6% if thyroid autoantibodies were negative and 4.3% if antibodies to thyroid peroxidase were present.[84] In the study reported by Parle and colleagues,[85] 5.5% of the 73 patients older than 60 years presenting with an elevated TSH and normal free T_4 were found to have a normal TSH after 1 year of follow-up while 17.8% progressed to overt hypothyroidism. Somwaru and colleagues[86] showed that nearly half of patients with SCH spontaneously reverted to normal during follow-up in a 4-year study of people older than 65 years at entry. This trend was especially observed in those in whom the initial TSH elevation was minimal and titers of thyroid peroxidase (TPO) antibody were negative.[86] The risk of conversion to overt hypothyroidism during

follow-up increases with the degree of TSH elevation and the positivity of thyroid autoantibodies to thyroid peroxidase, indicating low thyroid reserve.[87]

While it is well accepted that depressive symptoms and anxiety states are common in overt hypothyroidism,[19,88] studies of symptoms in SCH have found mixed results. Higher scores (indicating worse performance) on scales measuring memory, anxiety, somatic complaints, and depression have been reported in many,[64,77,89–92] but not all[93–95] studies. In a recent observational study, 63.5% of patients with SCH had depressive symptoms.[96] Larger cross-sectional studies have mostly failed to show a clear link between SCH and impaired cognition and depression.[93–95,97–99] The symptoms of depression are more frequent and severe in young or middle-aged adults with SCH.[90,100,101] In the elderly, depressive symptoms are less likely to be linked to the presence of SCH, perhaps because of the frequency of depressive symptoms in this population.[97,98]

Mild cognitive impairment with difficulties in new learning and selective attention associated with SCH has been observed in younger individuals.[99] In an elderly subgroup, cognitive impairment has been described in one small study, but these results did not reach statistical significance.[102] Larger population studies using limited neuropsychological assessment have not shown significant cognitive impairment in SCH subjects.[103]

EFFECTS OF TREATMENT OF SUBCLINICAL HYPOTHYROIDISM WITH LT$_4$

Results of studies evaluating the effects of treatment with levothyroxine on neuropsychiatric manifestation have also been mixed. Some reports suggest that normalization of thyroid function as determined by the serum TSH with L-thyroxine therapy may completely reverse these neuropsychiatric features.[52,64,104–107] On the other hand, most larger randomized trials have not shown significant improvement in psychiatric symptoms. In the report by Jorde and colleagues,[94] the elegantly controlled design was curiously burdened by screening subclinically hypothyroid individuals with symptoms consistent with the presence of hypothyroidism out of the group that was eventually treated with L-thyroxine. Neurocognitive assessment of the selected, asymptomatic, subclinically hypothyroid subjects, when compared with controls who had not been screened for symptoms consistent with hypothyroidism, was found to be no different. After randomization, the normally functioning, asymptomatic patients with SCH did not become less symptomatic nor function better than controls after achieving a euthyroid state.[94] Another recent and fairly large, well-conducted study by Parle and colleagues[95] also concluded that there was no significant improvement in the well-being of the subclinically hypothyroid treatment group. However, in this trial the initial neuropsychological test scores in both placebo and LT$_4$ groups were within the expected range before the therapeutic intervention, again leaving little opportunity to observe improvement after L-thyroxine.[95] Because of these issues, conclusive evidence supporting the appropriate course to be taken with symptomatic subjects with SCH remains elusive.

EFFECTS OF LT$_4$ TREATMENT ON PATIENTS WITH EUTHYROID DEPRESSION

Asher's report on myxedema madness[2] demonstrated that thyroid hormone deficiency resulted in depression that was reversed with administration of thyroid hormone. This finding led to his suggestion of pursuing further studies on the role of thyroid hormone therapy alone in the treatment of depression and other psychiatric diseases.[2] Initially, open studies of high-dose T$_4$ for refractory bipolar and unipolar depression were conducted in patients with psychiatric problems that were difficult

to treat.[108] In the study of Bauer and colleagues,[109] supratherapeutic doses of LT_4 were used (mean 378 μg/d) for an average of 51 months in 21 patients with refractory bipolar disorder, major depressive disorder, and schizoaffective disorder. Overall, more than 80% improved clinically and with regard to recurrences, as measured by the number of episodes of hospitalization, and a score on a psychiatric morbidity index that significantly declined. Of great interest in these studies is the apparent toleration of such high doses of thyroid hormone by those with these severe psychiatric issues in comparison with normal controls, 38% or more of whom will discontinue such treatment within 8 weeks of being exposed to excessive amounts of LT_4.[108] Euthyroid individuals with typical hypothyroid symptoms considered depressed on psychological testing do not improve when treated with T_4. In fact, patients presenting with symptoms of hypothyroidism with normal thyroid function tests respond more positively to placebo.[4] Limited data on cognitive function in otherwise healthy, young, euthyroid individuals indicates no significant differences in cognitive performance after about 45 days of supraphysiologic doses of LT_4 of up to 500 μg/d with subsequent suppression of TSH.[110]

COMBINED THYROID HORMONE AND ANTIDEPRESSANT THERAPY FOR DEPRESSION

Given the fact that 30% to 45% of the patients on antidepressants do not respond to antidepressant monotherapy,[111,112] the effect of adding thyroid hormones to antidepressant regimes has been studied. Adjuvant therapy has been said to be logical when depression fails to resolve after 6 weeks of adequate antidepressant medication.[113] The role of adjuvant thyroid hormone with tricyclic antidepressants (TCAs) has been investigated for more than 35 years in euthyroid patients with depression. Further studies of open LT_4 treatment in antidepressant-resistant patients have appeared, but the lack of controlled comparisons makes outcome interpretation difficult.[114,115] One of these studies indicated that responders to the levothyroxine and antidepressant combination had significantly lower pretreatment serum T_4 and reverse T_3 levels, leading the investigators to speculate that the responders might have been subclinically hypothyroid.[116] Another open-label trial seemed to indicate that effective augmentation of an antidepressant effect could be achieved with 50 μg of L-thyroxine daily.[117] In a third open-label trial of LT_4, 100 μg LT_4/d was given to euthyroid female patients (n = 17) with treatment-resistant depression, in addition to their antidepressants. More than half (64.7%) of these patients reportedly achieved remission.[118]

Most studies using thyroid hormone as adjuvant therapy have used LT_3 rather than LT_4, and in those reports where the advantages of one over the other were assessed, LT_3 was considered superior.[119] In a randomized trial combining LT_4 or LT_3 with antidepressants, only 4 of 21 patients (19%) treated with 150 μg/d of LT_4 for 3 weeks responded, whereas 9 of 17 (53%) responded with 37.5 μg/d of LT_3.[119] Combination therapy of antidepressants with LT_4 rather than LT_3 may be indicated when SCH or rapidly cycling bipolar disease is present. Because T_4 equilibrates in tissues more slowly than T_3, treatment with LT_4 for at least 6 to 8 weeks, and preferably longer, would be necessary to determine its efficacy in this situation.[19]

LT_3 doses of 25 to 50 μg daily increase serum T_3 levels and cause suppression of serum TSH and T_4 values. Two separate therapeutic effects of LT_3 therapy have been studied: first, its ability to accelerate the onset of the antidepressant response; second, its ability to augment antidepressant responses among those considered pharmacologically resistant.[19,120]

Given that the antidepressant effect of TCAs is known to be delayed, the role of LT_3 in accelerating the therapeutic onset of these drugs has been investigated. Several

reports detailing the clinical outcomes of starting LT_3 (5–40 μg daily) along with varying doses of TCAs as well as SSRIs at the outset of therapy have appeared in the literature.[121,122] The study populations were inhomogeneous, consisting of patients with various types of depression. Furthermore, there were important methodologic limitations, including small sample sizes, inadequate medication doses, lack of monitoring of serum medication levels, and variable outcomes measures.[19] As 2 relatively large, prospective, randomized, placebo-controlled studies have come to opposite conclusions, it still has not been clearly established that LT_3 accelerates the antidepressant effect of SSRIs.[123,124] A recent meta-analysis of double-blind clinical trials comparing SSRI-LT_3 treatment with SSRI alone showed no significant difference in rates of remission.[12] However, a smaller pilot study to evaluate the effectiveness of LT_3 in accelerating and potentiating the antidepressant response, using various antidepressants according to the clinician's choice, showed that LT_3 may help accelerate the antidepressant response and possibly improve overall outcomes for depressed patients.[125] Clearly the debate will continue.

An additional hypothesis is that adding small doses of LT_3 to the antidepressant therapy for patients who have little or no initial response will enhance the clinical effectiveness of the antidepressant.[19] Resistance to antidepressants is defined as inadequate remission after 2 successive trials of monotherapy with different antidepressants in adequate doses, each for 4 to 6 weeks, before changing to alternative therapies.[126] However, 8 to 12 weeks of ineffective antidepressant therapy is commonly deemed unacceptable, and strategies designed to augment the response are being sought.[127] Early studies assessing LT_3 effectiveness in augmenting the antidepressant response were neither placebo-controlled nor focused on patient populations that could be directly compared.[128–131] The first placebo-controlled, double-blind, randomized study reported results in 16 unipolar depressed outpatients who had experienced no improvement in their clinical outcomes with TCAs alone.[132] The intervention consisted of adding 25 μg of LT_3 or placebo daily for 2 weeks before the patients were crossed over to the opposite treatment for an additional 2 weeks. No beneficial effect of LT_3 was apparent.[132] The only other placebo-controlled, randomized, double-blind trial investigating this question involved 33 patients with unipolar depression treated with either desipramine or imipramine for 5 weeks before random assignment to placebo or 37.5 μg of LT_3 daily.[133] After 2 weeks of observation on LT_3, during which TCA levels were monitored, significantly more patients treated with LT_3 (10 of 17; 59%) had a positive response in comparison with placebo-treated patients (3 of 16; 19%).[133] A subsequent open clinical trial of imipramine-resistant depression, using a prolonged period of TCA treatment preceding the addition of LT_3, showed no demonstrable effect of LT_3.[134]

The SSRI group of substances (including fluoxetine, paroxetine, and sertraline) is the preferred antidepressant medication in the United States today. A large, double-blind, placebo-controlled study to determine the role of LT_3 as augmentation therapy did not demonstrate an effect of LT_3 in augmenting the response of paroxetine therapy in patients with major depressive disorder,[123] but a similar study using sertraline and LT_3 seemed to a demonstrate a positive response.[124] Responders in the report by Cooper-Karaz and colleagues[124] seemed to have had lower circulating thyroid hormone levels before treatment and to have experienced a greater decrease in TSH levels as a result of the intervention. This finding may indicate that those benefiting from the addition of LT_3 may have been subtly hypothyroid and that the addition of LT_3 compensated for this deficiency.[124] A recent meta-analysis of the available data suggests that coadministration of LT_3 and SSRIs has no significant clinical effect in depressed patients when compared with SSRI alone.[12] Another recent, fairly large double-blind,

placebo-controlled study to determine the role of LT_3 as augmentation therapy also did not demonstrate an effect of LT_3 in augmenting the response of paroxetine therapy in patients with major depressive disorder.[135] Controlled data assessing the clinical effects of LT_3 with selective serotonin norepinephrine reuptake inhibitors (SSNRIs) is sparse to nonexistent. Of interest, LT_3 has been reported to augment the antidepressant effect of electroconvulsive therapy.[136] However, there is little to no evidence to guide the duration of treatment with supplemental LT_3, and few studies regarding side effects of long-term LT_3 administration have been published.[137]

As personalized medicine evolves, therapies will inevitably become more directed. New research directed at D1, which is important for peripheral conversion of T_4 to T_3, suggests that certain polymorphisms of D1 may be associated with a positive response to LT_3 potentiation of SSRIs. These patients with certain alleles have inherently lower D1 activity, and therefore have naturally lower serum T_3 levels. When compared with placebo, these patients have decreased depression scores at 8 weeks with LT_3 supplementation in combination with sertraline.[138] More research is necessary to determine whether those patients with a functional D1 gene polymorphism may be more responsive to LT_3 cotreatment.

Further randomized trials and long-term follow-up are required to validate these findings and determine safety.

THYROTOXICOSIS
Neuropsychiatric Manifestations of Overt Endogenous Thyrotoxicosis and Response to Treatment

Thyrotoxicosis is usually diagnosed when a patient has a low TSH value (<0.1 mIU/L) and an increased serum T_4 concentration, or an increased T_3 concentration, along with some clinical clues for excessive thyroid hormone action.[28]

Thyrotoxicosis presents with a wide array of neuropsychiatric symptoms that range from anxiety to depression.[46] Depressive disorders occur in 31% to 69% of hyperthyroid patients while anxiety disorders occur in about 60%, and these 2 states can often occur concurrently.[139,140] Mania may also be observed in hyperthyroidism, but is less common than depression and anxiety.[139,141,142] As outlined in **Table 3**, the classic neuropsychiatric symptoms of hyperthyroidism include anxiety, dysphoria, emotional lability, intellectual dysfunction, and mania.[19] A subset of hyperthyroid patients, usually the elderly population, may present with depression, lethargy, pseudodementia, and apathy, with what is termed apathetic thyrotoxicosis, and generally is reversible with treatment.[143] Psychotic symptoms including unusual presentations such as delusional parasitosis[144] are rare in hyperthyroid patients,[141,142] but case reports and case series have been conducted.[145,146] Severe hyperthyroidism can result in thyroid storm, a condition that ranges in neuropsychiatric presentation from hyperirritability, anxiety, and confusion to apathy and coma.[147]

Neuropsychiatric complaints are commonly the presenting symptoms of hyperthyroidism, and are often mistaken for primary psychiatric illness. As a result, patients frequently wait months before seeking medical help, and once they do they are often misdiagnosed.[20] In a study of hyperthyroid patients with Graves disease, which is the most common cause of hyperthyroidism,[28] Stern and colleagues[20] found that almost half of the patients waited longer than 1 month to receive an accurate diagnosis after first seeking help. One example of misdiagnosis documented in the literature is a case report by Taylor[143] of a hyperthyroid patient who presented with agitated depression, became worse when apparently appropriate psychotropic medications were administered, but improved when antithyroid drugs were prescribed. Of interest, prior

	Mood Disorders	Hyperthyroidism
Table 3		
Clinical features common to hyperthyroidism and mood disorders		
Depression	Yes	Yes
Diminished interest	Yes	Yes
Diminished pleasure	Yes	No
Decreased libido	Yes	Sometimes
Weight loss	Yes	Yes
Weight gain	Sometimes	Occasionally
Appetite loss	Yes	Sometimes
Increased appetite	Yes	Yes
Insomnia	Yes	Yes
Hypersomnia	Yes	No
Agitation/anxiety	Yes	Yes
Fatigue	Yes	Yes
Poor memory	Yes	Occasionally
Cognitive dysfunction	Yes	Yes
Impaired concentration	Yes	Yes
Constipation	Sometimes	No

Data from Hennessey JV, Jackson IM. The interface between thyroid hormones and psychiatry. Endocrinologist 1996;6:214–23.

personal history of psychiatric disease and family history of psychiatric disorders have not been found to predict anxiety or depression in patients with hyperthyroidism.[139] Conversely, others have found that patients with anxiety disorders have an unusually high rate of reporting a history of hyperthyroidism.[148]

Although Trzepacz and colleagues[140] did not find any correlation between thyroid function indices and depression or anxiety in hyperthyroid patients, Suwalska and colleagues[149] found that plasma levels of free T_4 correlated with the level of anxiety in the hyperthyroid patients reported. Similarly, Kathol and Delahunt[139] found that the level of T_4 excess was correlated with the number of symptoms of anxiety, but not symptoms of depression, that hyperthyroid patients experienced, and that severe anxiety symptoms tended to occur in the younger age group of patients.

The neuropsychiatric symptoms associated with hyperthyroidism do not always resolve after treatment and restoration of euthyroid state. Bunevicius and colleagues[150] found that both euthyroid and hyperthyroid women with a history of treated hyperthyroidism and ophthalmopathy caused by Graves disease had significantly more anxiety disorders, including panic disorder, social anxiety, and generalized anxiety, than a control group with no history of thyroid disease. The average time from diagnosis of Graves disease for these women was 2.9 years, with a range from 3 months to 20 years. Similarly, Bommer and colleagues[21] found that patients with remitted hyperthyroidism had significantly more depression, anxiety, hostility, mania, and sleep disturbances compared with controls. Lu and colleagues[151] found that only 50% of hyperthyroid patients with psychiatric illness recovered completely, whereas the other half of the patients showed a chronic or unremitting psychiatric condition after normalization of thyroid function tests, with 35% recovering partially, and 15% showing no change in mental status after treatment. Stern and colleagues[20] found that subjects treated for hyperthyroidism reported residual cognitive deficits of memory, attention, planning,

and productivity even after they became euthyroid. Thus, somatic complaints and psychiatric symptoms can often persist after treatment of hyperthyroidism.[20,21,152] In addition, the less time patients have been euthyroid, the more likely they are to report residual psychopathological symptoms from their hyperthyroidism.[21,152]

Neuropsychiatric Manifestations of Subclinical Endogenous Hyperthyroidism and Response to Treatment

Subclinical hyperthyroidism is diagnosed when a patient has a low serum TSH concentration (<0.1 mIU/L) without increased serum levels of T_4 or T_3.[28] Its prevalence has been found to be between 2% and 16%[153] in several community or large clinic surveys mostly involving older persons.

Subclinical hyperthyroidism may be associated with nervousness and irritability[22]; even mild thyroid dysfunction has been associated with changes in mood.[154] In their study of patients with subclinical hyperthyroidism, Sait Gonen and colleagues[23] found that patients with subclinical hyperthyroidism had significantly more anxiety compared with euthyroid controls. Biondi and colleagues[155] found that compared with controls, young and middle-aged patients with subclinical hyperthyroidism have a significantly higher prevalence of symptoms of thyroid hormone excess, including nervousness, and impaired quality of life. Bommer and colleagues[21] found that patients with a history of treated overt hyperthyroidism who remained subclinically hyperthyroid had significantly more depression, mania, hostility, anxiety, and disturbed sleep compared with controls. In addition, these symptoms were more pronounced in the subclinical group than in patients who had a history of hyperthyroidism and were now euthyroid. However, a large study by Roberts and colleagues[97] did not find an increased rate of anxiety, depression, or problems with cognition in patients older than 65 years with subclinical hyperthyroidism. As a result, it is still unclear whether subclinical hyperthyroidism is generally expected to be associated with neuropsychiatric symptoms, and it is recommended that significant mood disorders or cognitive deficits in patients with subclinical hyperthyroidism be evaluated and treated as separate disorders.[156]

Whether to treat patients with subclinical hyperthyroidism in general is uncertain,[28] and is especially controversial in younger and middle-aged patients.[157] In older patients, subclinical hyperthyroidism often prompts consideration of treatment because of the increased risk of atrial fibrillation and decreased bone density,[28] as well as, possibly, an increased risk of dementia.[24] There have been no large, long-term controlled studies showing a benefit in treating subclinical hyperthyroidism,[26] but some small studies have shown a benefit of treatment on decreasing cardiac abnormalities and improving bone density.[158,159] At present, guidelines recommend treating subclinical hyperthyroidism in the elderly, patients with osteoporosis, heart disease, or cardiac risks, or those with a persistently undetectable TSH,[27] but there are no clear recommendations for treatment based on reversing neuropsychiatric symptoms that may be associated with subclinical hyperthyroidism.

It has not been shown that clinical or subclinical hyperthyroidism is more common in older persons with psychiatric disease than in others.[28] However, Kalmijn and colleagues[24] found that patients older than 55 years with subclinical hyperthyroidism have more than a 3-fold increased risk of dementia and Alzheimer disease. The risk of dementia was especially increased in subjects with low TSH who had positive TPO antibodies. On the other hand, van der Cammen and colleagues[25] did not find an increased risk of Alzheimer disease in geriatric patients with subclinical hyperthyroidism. As a result, it is still unclear whether older patients with subclinical

hyperthyroidism have an increased risk of dementia, and there is no evidence that treating subclinical hyperthyroidism has any impact on this outcome.

Approximately 20% of patients admitted to hospital with acute psychiatric presentations, including schizophrenia and major affective disorders, but rarely dementia or alcoholism, may demonstrate mild elevations in their serum T_4 levels, and less often their T_3 levels.[160] The basal TSH is usually normal but may demonstrate blunted TRH responsiveness in up to 90% of such patients. These findings do not appear to represent thyrotoxicosis, as the abnormalities spontaneously resolve within 2 weeks without specific therapy. Such phenomena may be due to central activation of the hypothalamic-pituitary-thyroid axis, resulting in enhanced TSH secretion with consequent elevation in circulating T_4 levels.[33]

Neuropsychiatric Manifestations of Iatrogenic Thyrotoxicosis and Response to Treatment

There are several medications that can cause iatrogenic hyperthyroidism, including amiodarone, iodine (any form), lithium, and levothyroxine, as well as thyroid hormone extract.[28] Amphetamines induce hyperthyroxinemia through enhanced secretion of TSH, an effect that appears to be centrally mediated.[19]

With levothyroxine excess, which can occur with hypothyroid patients taking too much medication, or intentionally in the course of treatment for thyroid cancer, symptoms of overtreatment are similar to those of endogenous hyperthyroidism. However, they may be harder to recognize because of their milder degree, and the patient's adjustment owing to their longer time interval. In addition, older patients taking β-blockers, which can decrease the amount of anxiety and tremulousness they experience, may not exhibit classic neuropsychological symptoms of iatrogenic thyrotoxicosis.[161]

Several studies have evaluated the quality of life of patients with thyroid cancer who are on suppressive levothyroxine treatment. These patients have intentional chronic iatrogenic mild or subclinical thyrotoxicosis. At least one small study found that these patients had an impaired quality of life in comparison with healthy age-matched controls.[162] Specifically, the patients scored lower on emotional, sleep, energy, and social scales, and were found to have poorer mental health compared with controls. However, another randomized controlled study found that quality of life in patients with thyroid cancer and long-term subclinical hyperthyroidism is preserved, and did not improve with restoration of euthyroidism.[163] A recent systematic review of the data concluded that suppressive levothyroxine treatment results in similar or slightly impaired quality of life in comparison with the general population.[164]

Iodine-induced hyperthyroidism can develop after a patient receives iodine-rich medications such as amiodarone, topical iodine-containing antiseptics, or an iodine load from intravenous contrast,[165] which has been noted to result in the precipitation of thyroid storm with its dramatic neuropsychiatric presentation.[166] Arlt and colleagues[167] reported the case of a patient with bipolar disorder on lithium therapy who experienced thyrotoxicosis with rapid mood swings between mania and psychotic depression after receiving iodine contrast. Iatrogenic thyrotoxicosis may also be caused by the release of preformed thyroid hormones into the circulation; medications such as amiodarone or interferon-α[168,169]; and radiation, trauma, cellular injury, or lymphocytic infiltration of the thyroid gland.[29]

Ectopic thyrotoxicosis can occur in the setting of struma ovarii, large metastatic deposits of functioning differentiated thyroid cancer, or factitious ingestion of thyroid hormone.[170] TSH-mediated hyperthyroidism is triggered by a TSH-producing pituitary adenoma or pituitary resistance to thyroid hormone, and is rare.[170]

SUMMARY

The interface between the action of thyroid hormone and neuropsychiatric function is intricate, and several mechanisms of thyroid hormone uptake into brain tissues, hormone activation, and influences on neurotransmitter generation have been identified. Clinical symptoms attributed to thyroid dysfunction have been described. Symptoms of hypothyroidism are nonspecific, and those attributed to thyrotoxicosis may be more characteristic. Neuropsychiatric manifestations triggered by thyroid dysfunction likely respond well to reestablishment of the euthyroid state, although some patients appear to have persistent complaints. Strategies to address residual symptoms in those with hypothyroidism have included restoration of a truly euthyroid state, but further adjustment to "low normal TSH" has not been demonstrated to improve the response. The addition of LT_3 to ongoing LT_4 replacement, which has resulted in adequate TSH control, has yet to be definitively shown to be advantageous. Likewise, treatment of euthyroid depression with LT_3 in addition to contemporary antidepressant therapy lacks convincing evidence of superior outcomes to justify general application. Finally, the identification of SNPs in genes coding for types 1 and 2 deiodinase as well as the organic anion-transporting polypeptide may be useful in predicting the degree of symptoms associated with thyroid dysfunction, and may be useful in predicting the response to various medications and combinations when appropriately controlled, prospective studies are completed in the future.

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