Lithium-Induced Subclinical Hypothyroidism: Review of the Literature and Guidelines for Treatment

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Background: This review addresses the definition, prevalence, etiology, and clinical significance of lithium-associated subclinical hypothyroidism and offers guidelines for evaluation and treatment of this condition.

Data Sources: MEDLINE was used to search all articles written in English from 1964–present that included the words *lithium* and *thyroid*; *lithium* and *subclinical hypothyroidism*; *mood* and *thyroid function*; and *bipolar illness* and *thyroid function*.

Study Findings: Lithium interferes with thyroid metabolism and increases the incidence of overt and subclinical hypothyroidism. Subclinical hypothyroidism may be associated with the presence of somatic and neuropsychiatric symptoms and interfere with treatment responsiveness.

Conclusion: A careful assessment of thyroid function is recommended prior to initiating lithium treatment and during maintenance treatment. Recommendations regarding the threshold for initiation of thyroxine supplementation in patients with lithium-associated subclinical hypothyroidism are discussed in relationship to the degree of detrimental effects potentially associated with thyroid dysfunction.

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Lithium, a mainstay in the treatment of bipolar disorder, has been reported to suppress thyroid function in up to 42% of patients.[1–6] While overt, or "clinical," hypothyroidism may produce significant somatic and neuropsychiatric symptoms, the effects of milder forms of thyroid dysfunction, termed "subclinical" hypothyroidism, have been less well studied. This paper will review the literature on (1) the prevalence of lithium-associated subclinical hypothyroidism, (2) the probable mechanisms by which lithium alters thyroid function, and (3) the psychiatric and neurocognitive symptoms of subclinical hypothyroidism. As some investigators have suggested that subtle thyroid dysfunction may be associated with impaired cognition, mood, and response to psychotropic medication,[1,4,5,7–25] guidelines for an approach to the bipolar patient with lithium-associated subclinical hypothyroidism will be proposed.

DATA SOURCES

MEDLINE was used to search all articles written in English from 1964–present that included the words *lithium* and *thyroid*; *lithium* and *subclinical hypothyroidism*; *mood* and *thyroid function*; and *bipolar illness* and *thyroid function*. Abstracts for all such articles were printed and the papers then were reviewed.

DEFINITION OF CLINICAL AND SUBCLINICAL HYPOTHYROIDISM

Hypothyroidism is a graded phenomenon with varying degrees of clinical severity and biochemical abnormalities.[26] Overt hypothyroidism is marked by abnormally low free thyroxine and elevated thyroid stimulating hormone (TSH). Furthermore, overt hypothyroidism is usually, but not always, associated with symptoms. In subclinical hypothyroidism, the basal serum TSH level is elevated (> 5 μU/L) but free thyroxine is normal (FT_4 index, 5–11). The term "subclinical" implies that clinical symptoms are absent; however, some studies report the presence of somatic and neuropsychiatric symptoms in subjects with elevated TSH and normal FT_4 level (Table 1).[8,11,13,15–18,23,27–31] It should be noted that many of these symptoms can be caused by lithium alone and/or by depression, thus at times making it difficult to discern whether subclinical hypothyroidism is causing or contributing to the presence of these symptoms.

PREVALENCE OF SUBCLINICAL HYPOTHYROIDISM

Rates of thyroid dysfunction vary greatly by region and are affected by the diagnostic criteria applied. Sub-

Table 1. Symptoms of Hypothyroidism and Subclinical Hypothyroidism

Fatigue, weakness
Lethargy
Constipation
Weight gain
Dry skin
Cold intolerance
Decreased memory
Diminished concentration, slowed mentation
Depressed mood
Changes in menstruation

clinical hypothyroidism is reported to occur in 2.5% to 10.4% of the general population.[7,29,32] As with overt hypothyroidism, women have higher rates of subclinical hypothyroidism than men,[32–34] and the prevalence increases with age and with iodine excess or deficiency.[28,34–37] Iodine deficiency is the greatest source of thyroid dysfunction in the world at large,[37] but in industrialized nations, autoimmune diseases, including Hashimoto's thyroiditis and atrophic thyroiditis, are the leading causes of subclinical and overt hypothyroidism.[28,37] Additional etiologies of thyroid dysfunction include damage to the thyroid from treatment for thyroid cancer, surgical or radioiodine treatment of Grave's disease,[28,29,37,38] suppression of thyroid hormone release by medications such as lithium,[3-7,36,39–54] postpartum autoimmune thyroiditis,[11,52] and rarely, dyshormonogenesis.[37]

Elevated TSH levels may reflect a transient abnormality in thyroid function,[53] a stable adaptation to moderate thyroid gland dysfunction,[38] or the onset of progressive thyroid dysfunction.[7,38] Progression to overt hypothyroidism occurs in 5% to 10% of subjects with subclinical hypothyroidism per year.[32,33,35,54–56] It is more likely to occur in subjects with a chronic progressive disorder, such as Hashimoto's thyroiditis (suggested by the presence of significantly elevated antithyroid antibodies), and in individuals with a TSH level of 10 μU/L or higher.[29,31,33,35,37,38,53,55,56]

PREVALENCE OF LITHIUM-ASSOCIATED HYPOTHYROIDISM

It is well known that lithium exposure increases the incidence of thyroid dysfunction. The prevalence of overt hypothyroidism has been reported to be between 8% to 19% in patients taking lithium,[39–42,44–50,57–59] compared to a prevalence of 0.5% to 1.8% reported in the general population.[29,32] Furthermore, subclinical hypothyroidism has been reported in up to 23% of patients on lithium therapy,[2,36,41,42,44–46,48–50,58,60] compared to rates of up to 10.4% in the general population.[32] Thus, lithium therapy increases the incidence of subclinical hypothyroidism.

Initial perturbations in thyroid function with lithium therapy may be transient. Several prospective studies have shown that many patients who have 1 abnormal set of thyroid function tests following initiation of lithium therapy revert to euthyroid status within 1 to 2 years.[2,41–44,58] Thus, rates of lithium-induced subclinical hypothyroidism have been reported to be lower in some studies when they are based on more than 1 abnormal TSH value[2,42,44,46,58] and/or when subjects have been on lithium therapy for more than 1 year.[36,41,42,44,46,48,49,58] However, some of these studies have such strict criteria for "abnormal" (patients considered to have abnormal thyroid function only when symptomatic or if TSH > 10 μU/L),[39,44] that they may underrepresent the percentage of patients who develop persistent lithium-associated thyroid dysfunction. Studies examining rates of lithium-associated subclinical hypothyroidism in long-term treatment indicate an increasing incidence with multiple years of treatment.[50,60,61] There appears to be a cumulative risk of developing subclinical hypothyroidism with continued lithium treatment.

MECHANISMS OF LITHIUM-ASSOCIATED HYPOTHYROIDISM

Lithium has been reported to interfere with the synthesis and release of thyroid hormones through several mechanisms.[2,59,62–69] Inhibition of the thyroid gland's ability to concentrate iodine[45,63] and to synthesize adequately iodinated thyroglobulin[64] has been described. Lithium interferes with thyroid hormone release, perhaps via a stabilizing effect on thyroid microtubules,[69] or possibly by decreasing adenylate cyclase responsiveness to TSH and suppressing cyclic adenosine monophosphate (cAMP) production.[65,66] Some studies suggest the interference occurs in cAMP signal transduction at a step following cAMP production.[63] Furthermore, lithium inhibits the conversion of T_4 to T_3 (the active form of thyroid hormone) in the periphery[67] and within neurons.[68] Patients may respond to these thyroid suppressive effects with a compensatory rise in TSH, which is usually temporary.[39,42,43,48,59] However, some patients maintain elevated TSH levels and progress to develop signs of clinical hypothyroidism. Even when thyroid function tests remain within normal limits, lithium can promote goiter formation of varying clinical severity.[36,43,47]

The risk of progression of lithium-associated thyroid dysfunction may be increased in patients whose initial thyroid function is mildly compromised and who are therefore less able to override the thyroid suppressive effects of lithium. This may include those with a history of prior thyroid disease or those who have, at baseline, elevated antithyroid antibodies (indicative of autoimmune thyroiditis).[59] Multiple prospective studies have reported that patients whose test results are positive for antithyroid antibodies prior to lithium therapy have higher rates of lithium-associated thyroid abnormalities than their antibody-negative cohorts,[42,46,49,58] and that these abnor-

malities are likely to be more severe[46,58] or persistent[42,46] or both. However, patients whose test results are positive for antithyroid antibodies prior to lithium treatment do not universally develop lithium-associated thyroid dysfunction,[41,51,70] and the development of thyroid abnormalities has been reported initially in a number of antibody-negative patients.[48,49,51,70] Thus, the value of initial antibody levels to predict vulnerability to developing subclinical hypothyroidism remains questionable.

It has also been suggested that lithium functions as an immunostimulant that promotes or exacerbates the development of autoimmune thyroiditis.[38,42,45,46,49,59,71] Lithium has been shown to affect markers of immunomodulation.[62,71,72] However, since these changes have not been linked to an actual increase in antithyroid antibody production, they do not provide direct support for lithium's role as an immunostimulant.[62] Most,[36,42,45,70,71] but not all,[73] cross-sectional studies show higher rates of thyroid antibodies in patients treated with lithium compared with those treated with other agents. Lithium exposure has been associated with a significant rise in antibody titers in those subjects who were antibody positive prior to treatment with lithium in many,[41,42,46,49] but not all,[57,62] prospective studies. Subsequent progression to thyroid dysfunction occurred in 2 of the studies.[42,46] However, prospective studies have not shown significantly greater incidence rates of thyroid antibody formation in subjects exposed to lithium compared with controls or with the general population.[42,52,57,58,62] In addition, some data suggest that the association between lithium and antithyroid antibodies may be an artifact of the increased prevalence of thyroid autoimmune disease in patients with affective disorders.[11,41,57,73] Thus, lithium probably contributes to autoimmune thyroid dysfunction primarily via exacerbating preexisting autoimmune thyroid disease rather than promoting the onset of new disease.[67]

SYMPTOMS OF SUBCLINICAL HYPOTHYROIDISM

Somatic Symptoms

Biochemically defined subclinical hypothyroidism can be accompanied by clinical symptoms (see Table 1) and metabolic effects. Subtle alterations in lipid metabolism,[27,31,37] cardiac contractility,[27,37] menstrual cyclicity,[30] and fertility[31] have been documented in patients with subclinical hypothyroidism. Whether these perturbations are clinically significant enough to require treatment remains controversial.[28,31,37] However, there is evidence of partial normalization of some of these symptoms following treatment with thyroxine.[27,31,37]

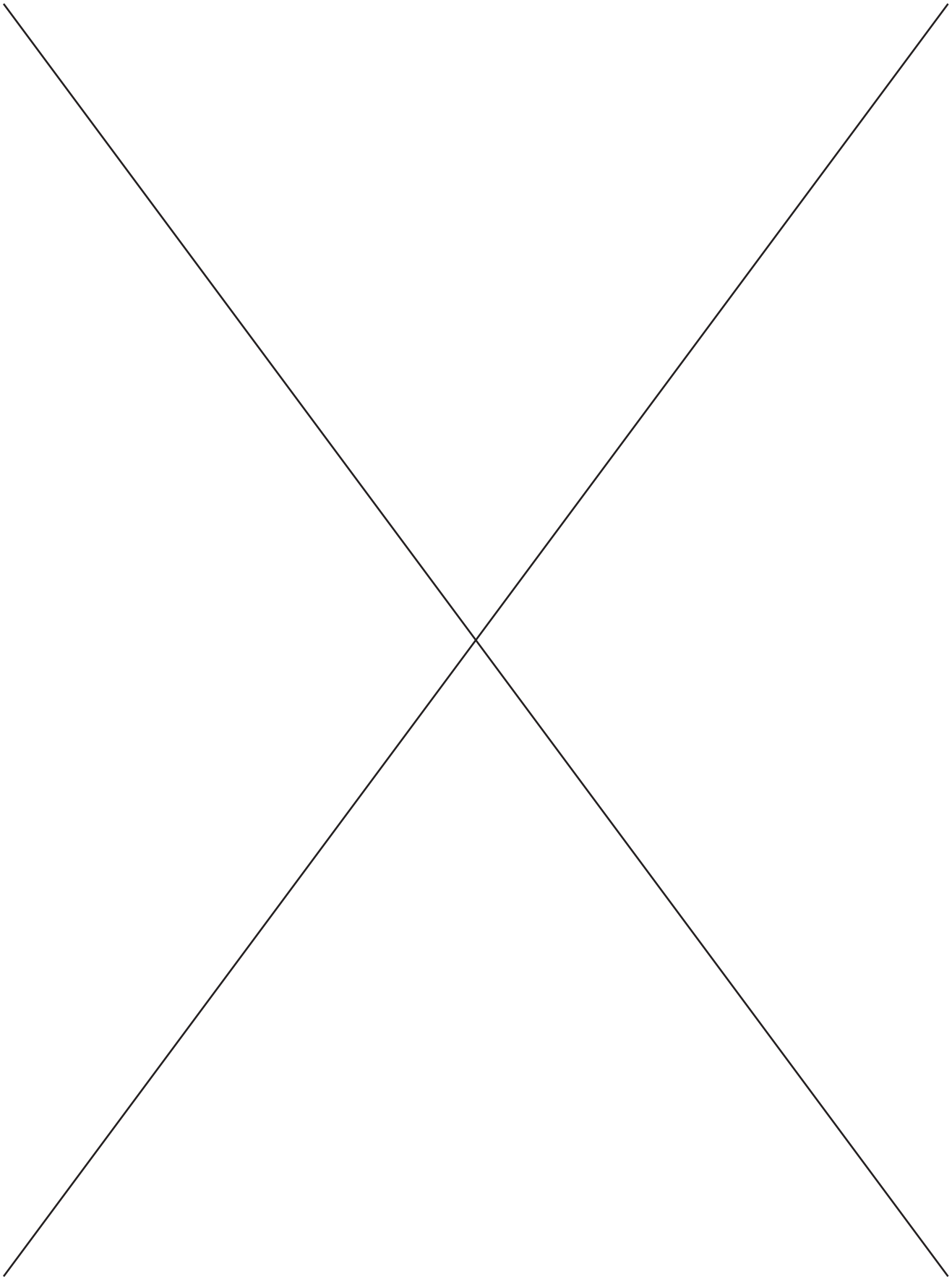
In one study, subjects with subclinical hypothyroidism reported significantly more symptoms than euthyroid controls, scoring between controls and patients with overt hypothyroidism on the Clinical Index of Billewicz (CIB),[31] a diagnostic screening procedure designed to selectively identify hypothyroid individuals based on the presence or absence of statistically weighted signs and symptoms.[74] In another study, in which a questionnaire based on the CIB was given to subjects with subclinical hypothyroidism and euthyroid controls, subjects with subclinical hypothyroidism reported symptoms such as dry skin, cold intolerance, and easy fatigability significantly more often than controls. The group of subjects who subsequently received treatment with thyroxine supplementation for 1 year showed significant improvement (lower symptom scores) than those who received placebo.[27]

Neuropsychiatric Symptoms

The neuropsychiatric manifestations of subclinical hypothyroidism may be clinically problematic for patients. Several,[11,13,16,23] but not all,[75] studies report that patients with subclinical hypothyroidism have symptoms of lethargy, mental slowing, decreased concentration and memory, and/or depression. In one report, 85% of nonpsychiatric subjects with subclinical hypothyroidism functioned abnormally on at least one of the subscales of the Wechsler Memory Scale (WMS), with improvement in scores following thyroid hormone therapy.[11] In another study, 14 subjects with subclinical hypothyroidism had significantly lower scores on the WMS compared with euthyroid age- and sex-matched controls. After these subjects were treated for 6 months with thyroxine, their scores improved significantly, becoming similar to those of the control group.[23]

A double-blind crossover study of 17 women with subclinical hypothyroidism compared changes in cognitive function after 6 months of treatment with thyroxine versus placebo. These subjects were drawn from a larger population study and did not present with clinical symptoms of hypothyroidism. They were given 3 psychometric tests assessing memory, reaction time, and speed of complex perceptual functions. After receiving thyroxine therapy for 6 months, 20% of the subjects showed improved cognitive function (improvement of at least 2 standard deviations on 2 or 3 tests).[16]

Subclinical hypothyroidism has also been associated with mood symptoms in patients with and without preexisting psychiatric diagnoses.[8,11,14,15] In one study, 14 nonpsychiatric patients with subclinical hypothyroidism scored significantly higher than euthyroid controls on the Crown and Crisp Experiential Index (CCEI), a measure of behavioral reactivity. Subjects with subclinical hypothyroidism scored moderately higher than controls on subscales of depression, anxiety, and somatic complaints. Following 6 months of thyroxine treatment, they demonstrated improvement in the CCEI total score and in the subscales of somatic complaints and obsessionality.[23]



Clinical hypothyroidism and subclinical hypothyroidism have been associated with the exacerbation or recurrence of depression.[8–10,12,14,17,18,22] A study of 31 asymptomatic subjects at risk for thyroid dysfunction found that those with subclinical hypothyroidism had a significantly higher lifetime history of depression (56%) than the euthyroid subjects (20%), although none of the group were actively depressed at the time of evaluation.[12] Patients with comorbid subclinical hypothyroidism and major depression have been found to be less responsive to traditional antidepressant therapies.[8,9,12,17,22] A critical review of 6 studies indicated a higher prevalence of subclinical hypothyroidism in patients with refractory depression (range, 29%–100%) than in unselected populations of patients with depression (range, 8%–17%, which is still higher than the 5% prevalence found in the general population).[9] A study of 139 patients with unipolar depression (not on lithium therapy) found that only 3 (16%) of the 19 patients with subclinical hypothyroidism responded to desipramine treatment versus 65 (54%) of the 120 who were euthyroid.[17] It has been suggested that patients with subclinical hypothyroidism often require thyroid supplementation in addition to antidepressant medication to achieve remission and prevent relapse.[8,9,11,12,18,22,76] This suggestion is supported by a study of patients with refractory depression in which 28% were found to have subclinical hypothyroidism. Subjects in this subgroup were more likely to respond to T_3 augmentation than those who did not have subclinical hypothyroidism.[18]

Similarly, in patients with bipolar disorder, some,[4,5,19–21] but not all,[6,10,77,78] studies have observed that subclinical hypothyroidism is associated with treatment refractoriness and/or the rapid-cycling phenotype. Treatment with supranormal doses of levothyroxine has been shown to result in significant decreases in the frequency and intensity of cycling in patients with rapid-cycling bipolar disorder in most,[21,25,79,80,81] but not all,[82] studies. Thyroxine may exert a mood-stabilizing effect independent of the patient's underlying thyroid status.[25] Alternately, in those with subclinical hypothyroidism, thyroxine may be necessary to normalize catecholamine and indolamine function and responsiveness to mood-stabilizing medications.

The mechanisms of the neuropsychiatric effects of subclinical hypothyroidism remain unclear. One possibility is that the brain may experience thyroid deficiency before other organs because of its preferential use of T_4, which is less available than T_3 in early hypothyroidism.[11,16,83] On the other hand, the brain appears to have the capacity to autoregulate thyroid status via the type 2 5'deiodinase pathway for conversion of T_4 to T_3 and preserve near normal neuronal thyroid function even in the presence of systemic hypothyroidism.[68,84] However, this autoregulatory function may be impeded in people taking lithium since it inhibits the type 2 5'deiodinase,[68] thus possibly making them more vulnerable to the neuropsychiatric manifestations of subclinical hypothyroidism.

It is also possible that subclinical hypothyroidism causes neuroanatomical changes that result in altered neuropsychiatric function. A decrease in the number of pyramidal cells in the CA1 region of the hippocampus was identified in rats who were made hypothyroid as pups or adults or both. The number of pyramidal cells did not normalize following a return to a euthyroid state.[85] Since no other animal or human studies have assessed whether subclinical hypothyroidism results in neuroanatomical changes, these findings require further study.

MANAGEMENT OF LITHIUM-ASSOCIATED SUBCLINICAL HYPOTHYROIDISM

The management of subclinical hypothyroidism, whether lithium-induced or idiopathic, remains controversial. The effect of thyroid supplementation in patients with lithium-associated subclinical hypothyroidism has not been systematically studied, and literature regarding treatment of subclinical hypothyroidism in both psychiatric and nonpsychiatric populations is limited. The following guidelines reflect our interpretation of the existing literature and our clinical experience.

Prior to initiating lithium, baseline thyroid function should be assessed. Past medical history and family history of thyroid dysfunction should be obtained because they may identify risk factors for lithium-induced hypothyroidism. A baseline checklist of symptoms associated with hypothyroidism and affective dysregulation should be administered, which the patient can repeat monthly for the first year after starting lithium and thereafter at 2-month intervals[86] (see Table 1). Laboratory tests before initiating lithium therapy should include TSH, FT_4, and antiperoxidase and antithyroglobulin measurements. The antibody tests will help to identify patients who may be at greater risk for lithium-induced subclinical hypothyroidism.

TSH should be measured 3 months after lithium therapy has been initiated, and then every 6 to 12 months. TSH should be measured earlier if the patient is experiencing somatic symptoms of hypothyroidism, exacerbation of depressive symptoms (including mental slowing or decreased memory), increases in cycle frequency, or refractoriness to treatment. If the TSH level is elevated, the measurement should be repeated,[28,44] and a free T_4 level (or FT_4 index) obtained.[87] Other potential sources of abnormal thyroid function tests should be considered before initiating thyroid treatment. These include euthyroid sick syndrome, recovery from nonthyroidal illness, and exposure to medications that can lower FT_4 (e.g., phenytoin, carbamazepine) or elevate TSH (e.g., amiodarone).[7,54]

If the serum TSH level is elevated and FT_4 level is subnormal, the patient has overt hypothyroidism and thyroxine supplementation is clearly indicated. If T_4 level is normal and TSH level is elevated, the patient has subclinical

hypothyroidism and the following treatment guidelines are recommended:

1. If the serum TSH level is greater than 5 but less than 10 mU/L and the patient is not symptomatic (i.e., not experiencing affective or cognitive symptoms that could be attributed to thyroid dysfunction), thyroid replacement is not immediately necessary, but TSH level should be measured again after about a month (after at least 2 weeks,[11] but within 2 months.) If TSH level remains elevated, closer monitoring (e.g., every 3 months) should be considered to observe for progression to overt hypothyroidism or symptom exacerbation that may be due to subclinical hypothyroidism. Alternatively, a trial of thyroxine could be initiated in an attempt to prevent the potential exacerbation of the patient's psychiatric condition or treatment response. There have not been enough systematic data collected to determine which strategy is most beneficial.
2. If the serum TSH level is greater than 5 but less than 10 mU/L and the patient reports symptoms that might be related to subclinical hypothyroidism, thyroxine therapy should be initiated. In those patients reporting cognitive dysfunction, a baseline neurocognitive battery is useful, but not essential, to confirm the patient's subjective impression and to serve as a baseline against which to evaluate the effectiveness of thyroxine treatment for these symptoms. In those bipolar patients with depressive symptoms associated with subclinical hypothyroidism, treatment with thyroxine should occur prior to an antidepressant trial. Thyroxine therapy may lead to improvement in mood and obviate the need for antidepressant medication, which carries the risk of inducing mania[19,88,89] or accelerating cycling.[82,88,89] If clinical symptoms of depression do not significantly improve after 6 to 12 weeks of thyroxine treatment, antidepressant medication should be initiated or mood stabilizers should be adjusted. If the patient has had bipolar disorder with rapid cycling within the past year, supranormal doses of thyroxine may be beneficial[25,68,79–82] if the patient's cycling does not diminish following thyroid supplementation to the point of normalization of the TSH. However, it may take up to 6 months to note clinical improvement.
3. If the serum TSH level is greater than 10 mU/L, thyroxine therapy should be initiated whether or not the patient is symptomatic since these patients are at high risk for progression to overt hypothyroidism.[37,38,55,56] If symptoms do not remit following normalization of thyroid indices, psychotropic medications should be initiated or adjusted as described above.

Prior to initiating treatment with thyroxine, the patient's baseline cardiac status should be established, because increasing thyroid function can result in aggravation of angina or arrhythmias (most commonly atrial fibrillation) in patients with compromised cardiac function,[37] and more conservative thyroxine dosing will be necessary for these patients. Thyroid hormone supplementation is usually well tolerated, although side effects can include transient or persistent anxiety, insomnia, tachycardia, and sweating.[90] Clinicians should also be aware that thyroxine can precipitate mania in bipolar patients not treated with a mood stabilizer.[90,91] TSH-suppressive doses of thyroid hormones have been reported to induce osteoporosis in postmenopausal women[92–95] and have generally been avoided. However, recent studies have not confirmed these findings and have found that suppressive doses of thyroxine do not cause clinically significant bone loss in premenopausal[68,96] or postmenopausal[96] women. Therefore, treatment with suppressive doses of thyroxine may be indicated in the clinical setting of rapid-cycling bipolar disorder, since the benefit obtained by decreasing the frequency of cycling may outweigh the possible risk of accelerating osteoporosis.

T_4 (levothyroxine) rather than T_3 (levotriiodothyronine) supplementation is recommended, since T_4 produces steadier hormone levels. In otherwise healthy patients with subclinical hypothyroidism, levothyroxine can be started at 25–50 μg/day and increased by 25 μg increments each 6 weeks until the serum TSH level has normalized. Doses in the range of 50–100 μg/day are usually sufficient.[37] Lower initial doses (12.5 or 25 μg/day) and slow escalation of treatment (every 6 weeks) with frequent monitoring of side effects are recommended in elderly patients or those with cardiac dysfunction.[28,37,87]

Once thyroid supplementation has been initiated, the standard clinical procedure is to continue it throughout the course of lithium treatment. We are unaware of any studies, however, that have systematically evaluated how long thyroxine supplementation should be maintained in lithium-associated subclinical hypothyroidism. Patients with elevated antithyroid antibodies (indicative of autoimmune disease) probably require ongoing thyroid supplementation and might continue to need thyroxine treatment even if lithium were to be discontinued. However, it seems possible, based on the studies indicating frequent normalization of thyroid function after 1 to 2 years of lithium therapy,[2,41–44,58] that after an extended period of thyroid supplementation some asymptomatic, antibody-negative patients could be gradually tapered off thyroxine (while closely monitored for symptoms of hypothyroidism or abnormal thyroid function tests). However, without clinical trials examining this question, we can only speculate about whether thyroxine should be tapered off after a period of treatment and stabilization.

The above guidelines have addressed the situation in which lithium therapy has been continued despite the onset of thyroid dysfunction. Whenever thyroid abnormalities develop, however, another option is to consider tapering the patient off lithium treatment while initiating treatment with another mood stabilizer. While this carries with it the risks inherent in any new medication trial (e.g., loss of treatment response and the emergence of other adverse medication effects), it is nonetheless another alternative.

Drug names: amiodarone (Cordarone), carbamazepine (Tegretol and others), desipramine (Norpramin and others), levothyroxine (Synthroid and others), levotriiodothyronine (Cytomel, Triostat), phenytoin (Dilantin and others).

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