LITHIUM AND THYROID COMPLICATIONS

DOUGLAS EVANS, APRN, PMHNP-BC

Douglas Evans is a board-certified Psychiatric Mental Health Nurse Practitioner. Douglas has more than a decade of experience working with adult and adolescent mental health populations in Texas and Montana, respectively. He completed his Master of Science in Nursing (PMHNP) at Midwestern State University. Prior to his graduate degree, he earned an Associate of Applied Science in Nursing degree and a Bachelor of Science in Nursing, both from Angelo State University. Douglas enjoys cooking, hiking, photography, and spending time with his family.

Topic Overview

Lithium is a psychotropic drug that is established as an effective treatment for mania and the maintenance of bipolar disorder. In spite of lithium's therapeutic effects, it has also been associated with negative effects such as hypothyroidism, hyperthyroidism, goiter, and autoimmune thyroiditis. Although extensively studied, lithium's alteration of normal thyroid physiology is not yet fully understood.

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Learning Objectives: Upon completion of this educational activity, participants should be able to:

1. **Describe** the effects of lithium on the physiology of the thyroid gland
2. **Identify** common thyroid abnormalities associated with lithium use
3. **Compare** monitoring and treatment guidelines for lithium-induced thyroid abnormalities
4. **Identify** recommendations when prescribing lithium to specific population groups (*e.g.*, children and elderly patients)

Disclosures

The following individuals were involved in the development of this activity: Douglas Evans, APRN, PMHNP-BC, and Susan DePasquale, MSN, PMHNP-BC. There are no financial relationships relevant to this activity to report or disclose by any of the individuals involved in the development of this activity.

Introduction

Lithium is a psychotropic drug that is established as an effective treatment for mania and the maintenance of bipolar disorder. While lithium is an effective treatment, it is well known to have adverse effects across many organ systems. Endocrinopathies, including thyroid abnormalities, are among the most common complications found with lithium treatment. This review will cover the effects of lithium on the physiology of the thyroid gland and the more common thyroid abnormalities associated with lithium use. In addition, it will discuss lithium and its use in special population groups, such as children and the elderly, as well as monitoring and treatment guidelines for lithium-induced thyroid abnormalities.

Lithium-induced Thyroid Dysfunctions

In 1949, Australian psychiatrist, John Cade, established lithium as an effective treatment for bipolar disorder. More than 70 years later, it remains the gold standard treatment for mania and the maintenance of bipolar disorder. Not only does lithium possess known antimanic properties, but it also has notable anti-suicide and neuroprotective qualities.[1,2] However, lithium has also been associated with negative effects. These include hypothyroidism, hyperthyroidism, goiter, and autoimmune thyroiditis. Although extensively studied, lithium's alteration of normal thyroid physiology is not yet fully understood.[3-6]

Scientists have proposed multiple mechanisms to explain lithium's effect on normal thyroid functioning.[3,4] At the cellular level, lithium has been found to be highly concentrated in thyroid cells. Dar, *et al.* (2020) stated: "The lithium-ion is concentrated in the thyroid gland three to four times greater than in plasma where it interferes with various steps in the production of thyroid hormones."[6]

In human subjects, the presence of lithium in thyroid cells has been found to either reduce or increase thyroid radioiodine uptake. These alterations in iodine uptake are proposed to be one of the mechanisms of alteration in thyroid physiology.[3,4] Additionally, lithium has been found to reduce hepatic deiodination and clearance of free thyroxine (T4), which decreases the activity of 5'de-iodinase enzyme type I activity. Other proposed alterations include the activation of pro-proliferative tyrosine kinase and Wnt/beta-catenin signaling pathways and increased production of thyroid peroxidase auto-antibodies.[3,4]

Lithium has been shown to inhibit the synthesis and release of thyroid hormones.[5,6] Lithium has an inhibitory effect on thyroid-stimulating hormone (TSH) on cyclic adenosine monophosphate (c-AMP) and alters tubulin polymerization. Furthermore, lithium alters thyroglobulin structure, which affects protein conformation and function, leading to iodotyrosine coupling defects. The impairment of coupling inhibits the formation and release of thyroxine (T4) and triiodothyronine (T3).[3,4]

Lithium-Induced Goiter

The goitrogenic effects of lithium were observed and documented not long after its introduction as an antimanic agent. The prevalence of goiter associated with lithium treatment has been reported to be zero to 60%.[5] More recent reviews have reported rates of 5.6% to 60%.[6] The wide variance of goiter in studies of lithium-treated populations is reportedly due to geographical differences in the iodine content used in testing, and differences in the diagnostic tools used for testing.[6] In spite of the variance in reported rates, goiter is regarded as the most common thyroid abnormality associated with lithium treatment.[7]

The main mechanism behind lithium-induced goiter is the inhibition of thyroid hormone synthesis and release. The decreased levels of circulating thyroid hormone lead to increased TSH release by the pituitary gland, which ultimately ends in thyroid enlargement.[3] Another proposed mechanism for

lithium-induced goiter is through growth factor alterations in the post-receptor tyrosine kinase pathway and/or Wnt/beta-catenin signaling.[3]

Lithium-Induced Hypothyroid

Another prevalent lithium-induced thyroid condition is hypothyroidism, including subclinical hypothyroidism. As early as the 1970s, this condition was identified in relation to lithium treatment. The exact prevalence varies greatly in the literature and may be as high as 52% of lithium-treated subjects.[7] Goiter may or may not be present with hypothyroidism. Lithium-induced hypothyroidism may result in overt clinical symptomatology. However, most subjects have a subclinical presentation meaning that they have a clinically significant elevation in TSH but maintain normal T4 and T3 levels.[3,5,8,9]

Like goiters, the primary mechanism behind lithium-induced hypothyroidism is the inhibition of thyroid hormone production and release. However, lithium-induced production of thyroid peroxidase auto-antibodies may be a factor as well.[3,5]

Lithium-induced hypothyroidism is widely considered to be a reversible condition, which will resolve with the discontinuation of lithium. Risk factors for the development of lithium-induced hypothyroidism include female sex, age >50 years, the first year of lithium treatment, length of lithium treatment >18 months, environmental factors (*i.e.*, iodine deficiency), and a family history of thyroid dysfunction.[3,5]

Lithium-Induced Hyperthyroid

Hyperthyroidism in lithium-treated persons has been noted since the 1970s but is widely considered to be a rare condition.[5,6,8] In fact, researchers have differed on the involvement of lithium in these cases, with some concluding that lithium plays no role.[5] Other reports found a link only in cases of chronic lithium use or based on clinical hypotheses.[6] Regardless, there have been cases of lithium-induced hyperthyroidism documented in the literature.[5]

Most such cases are transient, painless thyroiditis, but instances of granulomatous and lymphocytic thyroiditis have been associated with lithium.[5]

It is proposed that lithium-induced thyroiditis stems from the direct toxic effect of lithium on the thyroid gland, whereas others have suggested that it has to do with auto-antibody production stimulated by lithium.[3,5]

Lieber, *et al.* (2022) reviewed nine (9) episodes of hyperthyroxinemia in persons experiencing lithium intoxication. The authors found that these events are uncommon (1.3 episodes/1000 person-years), and a direct causal link could not be established.[10]

Lithium-Induced Autoimmune Thyroiditis

Controversy exists as to the role of lithium in autoimmune antithyroid antibodies. Some research suggests that lithium may accelerate pre-existing thyroiditis.[3] Furthermore, it is important to note that thyroid autoimmunity has been found to correlate with affective disorders irrespective of lithium exposure strongly.[3,5] After reviewing family and twin studies, Bocchetta, *et al.* (2016) found a genetic vulnerability for thyroid antibodies in families with bipolar disorder. The authors suggested that autoimmune thyroiditis may be an endophenotype for bipolar disorder.[10] Other known risk factors for antithyroid autoimmunity include female sex and middle age.[3,5] Lithium treatment has been shown to increase B cell activity and decrease the ratio between suppressor-to-cytotoxic T cells, which may induce thyroid autoimmunity in susceptible populations.[3]

Lithium-induced Hypercalcemia

Similar to its direct actions on the thyroid gland, lithium can interfere with proper parathyroid gland function. By antagonizing the calcium-sensing receptor on the parathyroid gland, lithium can induce elevations in both parathyroid hormone and calcium levels. Furthermore, lithium may increase

the reabsorption of calcium in the intestines and kidneys, which adds to the serum level elevations.[3]

Special Populations

Children and Adolescents

The prescribing of lithium to children and adolescents with affective disorders has become an established treatment option. With this comes the responsibility to weigh the risks and benefits, including the effects of lithium on developing endocrine systems.

Sethy and Sinha (2016) performed ultrasonography and thyroid function tests (TSH, T3, and T4) on 30 adolescents on long-term lithium (one year or more) and compared them to controls receiving other mood stabilizing medications.[11] The authors found both increased TSH and thyroid volume in the lithium-treated participants. A significant elevation in TSH was found in the lithium-treated group, but T3 and T4 levels were not significantly elevated in either group. Thyroid volume was increased in 50% of the lithium therapy participants, but only in 17% of controls. The thyroid gland was palpable in 15% of the lithium group and none of the controls.[11] Masi, *et al.* (2018) conducted a naturalistic, retrospective study of 30 adolescents receiving lithium over the course of 8 months.[12] The authors found a significant increase in TSH across the study. For most participants, TSH levels remained within the normal range, as did the T3 and T4 levels. Only two participants required thyroid hormone supplementation.[12] Amitai, *et al.* (2014) had similar results in a retrospective, naturalistic study of 61 adolescents.[13] The authors found a significant increase in TSH levels, with 25% of participants having TSH levels >4.0mU/L. Only one participant had TSH >10.0mU/L, which necessitated thyroid hormone supplementation.[13]

Gracious, *et al.* (2004) conducted an open-label study of 82 bipolar patients, ages 5 to 17 years old, treated with lithium and divalproex for up to 20 weeks.[14] The authors found lithium was associated with a significant rise in

thyrotropin (TSH). Of the 20 participants that developed TSH levels of 10mU/L or greater, only one developed overt clinical symptoms.[14] Although generally well tolerated in child and adolescent populations, lithium does pose the potential for thyroid dysfunction, and, therefore, this should be a consideration when prescribing.

Elderly

Thyroid conditions are more commonly seen in elderly populations, in particular, hypothyroidism. During the aging process, there is a natural downward trend in thyroid function. Not surprisingly, hypothyroidism is frequently seen in elderly patients taking lithium.[15]

Bochetta, *et al.* (2017) observed the effects of lithium on 110 lithium-treated elderly patients over a 6-year period.[16] The authors noted that one-third of the cohort was taking prescribed thyroid hormone replacement therapy, but only two started the supplementation during the course of the study. Hyperthyroidism was found in 4% of the cohort, with two of the cases developing during the 6-year follow-up.[16]

A study published in 2010 looked at the effects of lithium on the thyroid function of elderly (65 and older) persons with affective disorders.[17] The study compared 79 lithium-treated persons with 85 persons who were not treated with lithium. In the lithium group, 35.4% had hypothyroidism - both clinical and subclinical - whereas the control group had a prevalence of 7.1%. Of note, female gender was the strongest determinant, with 41.3% of lithium-treated females having hypothyroidism.[17]

Elderly persons are among the highest risk for lithium-induced thyroid dysfunction. Nevertheless, lithium remains a treatment option for elderly persons with affective disorders.

Concomitant Use of Anticonvulsants

In the treatment of bipolar disorder, the concomitant use of lithium, along with anticonvulsant medications, especially divalproex or valproate, is relatively common. Some controversy exists as to whether anticonvulsants have their own suppressive or detrimental effect on thyroid function, thereby potentially exacerbating lithium-induced thyroid dysfunction when used in combination.

Mutlu (2019) studied the thyroid functions of 82 epileptic patients, ages 18 to 45, while on anticonvulsant medications - namely carbamazepine, valproic acid, lamotrigine, and levetiracetam.[18] Of the participants, 44 received monotherapy, while 38 received anticonvulsant polypharmacy. In conclusion, the author did not find significant changes in thyroid function with the various medications, except for significantly decreased fT4 as serum carbamazepine levels increased.[18] In contrast, Yilmaz, *et al.* (2014) found significant thyroid impairment in youth treated with various anticonvulsants, namely valproate, oxcarbazepine, levetiracetam, phenobarbital, and carbamazepine.[19] At the end of 12 months, the authors found subclinical hypothyroidism in 28% treated with valproate, 21.4% treated with oxcarbazepine, 18.2% treated with phenobarbital, and 13.9% treated with carbamazepine. Levetiracetam did not affect thyroid function in the study.[19]

Gracious, *et al.*, considered the use of lithium and divalproex in combination for youth with bipolar disorder. The authors concluded that only lithium was predictive of TSH elevation when both medications were considered.[14]

Hayes, *et al.* (2016) looked at adverse events associated with lithium, divalproex, and certain antipsychotics within the United Kingdom's electronic health records from 1995 to 2013.[20] Hayes, *et al.*, found that rates of thyroid dysfunction were consistently higher in lithium-treated individuals compared to those receiving divalproex or certain antipsychotics.[20] The literature remains unclear regarding the effect of anticonvulsant medications on thyroid function.

However, it is important to note that the concomitant use of lithium and anticonvulsants has not been conclusively shown to affect thyroid function adversely.

Monitoring Guidelines for Lithium-Induced Thyroid Dysfunctions

A review of well-established treatment guidelines indicated relative harmony on the topic of thyroid monitoring while on lithium.[21] The American Psychiatric Association's Practice Guideline for Treatment of Patients With Bipolar Disorder, 2nd edition (2002) recommends a baseline thyroid function evaluation prior to initiating lithium, and then follow-up thyroid function testing once or twice in the first 6 months of lithium treatment.[21] After the initial 6 months, thyroid function may be checked every 6 months to 1 year or whenever clinically indicated. Clinical indications for thyroid testing include breakthrough affective symptoms, changes in side effects, and new medical or psychiatric signs/symptoms.[21]

The 2018 guidelines from the Canadian Network for Mood and Anxiety Treatments (CANMAT) and the International Society for Bipolar Disorders (ISBD) offer similar guidance for thyroid function monitoring.[22] For children and adolescents, the Psychotropic Medication Utilization Parameters for Children and Youth in Texas Public Behavioral Health (2019) recommends baseline thyroid studies and then TSH monitoring every 6 months thereafter.[23]

Goiters may be detected by clinical palpation, serum thyroid hormone tests, or by ultrasonography. Ultrasound has been shown to detect more goiters than palpation alone.[3] These tests are not always dispositive. Tunçel, *et al.* (2017) found that 90% of goiters were in euthyroid subjects and concluded that serum thyroid hormone monitoring alone is insufficient to detect lithium-induced goiters.[8]

Ultrasonography is a simple, affordable, and effective means to diagnose and monitor goiter and other thyroid abnormalities in the lithium-treated population; however, it is not typically mentioned as part of a lithium patient's

workup or routine.[6,8] Importantly, unlike other imaging procedures, ultrasonography does not involve radiation exposure. However, the authors acknowledge that established lithium treatment guidelines make limited mention of ultrasonography.[6] Bochetta and Loviselli (2006) recommend an ultrasonogram before lithium initiation, again after the first year, and then repeated every 2-to-3 years thereafter.[5] Dar, *et al.* (2020) propose that it is better to include an ultrasonographic examination of a patient's thyroid gland as part of the routine workup before initiating lithium treatment.[6] Tunçel, *et al.*, also suggest that incorporating an ultrasonographic examination for lithium-treated patients should be considered.[8]

When abnormal thyroid function levels are detected, measurement of thyroid antibodies, including antibodies against thyroid peroxidase (AbTPO) and thyroglobulin (AbTG), may be clinically warranted. The presence of these antibodies will give clinicians an important understanding of the etiology behind the aberration in thyroid function.[3,5,10]

Based on the guidelines reviewed, establishing baseline thyroid functioning prior to initiation of lithium and then periodic (at least every 6 months) rechecking of TSH levels should be considered the minimum level of monitoring appropriate for lithium prescribing. Ultrasonography and thyroid auto-antibody monitoring should likewise be considered tools.

In individuals with lithium-induced hypercalcemia, Lerena et al. (2022) recommend that serum calcium levels, renal function, and bone mineral density be monitored every 6 to 12 months.[3]

Treatment Options for Lithium-Induced Thyroid Dysfunctions

Lithium-induced Goiter

The treatment of lithium-induced goiter is the same as for goiters of other etiologies. Ultrasonography and fine-needle aspiration may be indicated. Treatment with levothyroxine (T4) may be effective in stabilizing or even

reducing the size of goiters. In rare instances, surgery may be necessary for obstructive goiters.[3,24]

Lithium-induced Hypothyroid

It is important to note that lithium-induced hypothyroidism is widely considered to be reversible and should never warrant discontinuation of the otherwise therapeutic use of lithium. Thyroid hormone replacement therapy utilizing levothyroxine (T4) is the primary method of treatment for lithium-induced hypothyroidism.[3,24] Lieber, *et al.* (2021) caution that thyroid hormone replacement therapy is seldom reversed once initiated therefore, clinicians should carefully weigh the benefits and risks when prescribing levothyroxine for subclinical hypothyroidism.[10]

As previously stated, cessation of lithium due to hypothyroidism alone is generally not advised. Should lithium be discontinued in a person with lithium-induced hypothyroidism, it is advisable to reassess the need for continued thyroid hormone supplementation. Some experts recommend rechecking TSH level two months after lithium discontinuation. If the TSH level is above normal or in the upper half of the normal range, levothyroxine should be continued. If the TSH level is below normal or in the lower half of the normal range, levothyroxine may be discontinued, and the thyroid levels (TSH and free T4) reassessed in six weeks. If, upon reassessment, the TSH level has risen above normal, resuming levothyroxine may be indicated. Clinical assessment and free T4 levels should be considered in the decision to resume levothyroxine.[3,10]

Lithium-induced Hyperthyroid

Lithium-induced hyperthyroidism may be treated with antithyroid drugs, such as carbimazole and steroids. Thyroidectomies and ablative radioiodine are seldom, if ever, clinically necessary.[3,24]

Lithium-induced Autoimmune Thyroiditis

Thyroid antibodies themselves do not require treatment. The focus of treatment should be on establishing euthyroid status and maintaining it by appropriate treatment means. Levothyroxine (T4) supplementation is typically used for autoimmune hypothyroidism, and antithyroid drugs for autoimmune hyperthyroid.[3,5,10,24]

Lithium-induced Hypercalcemia

Lithium-induced hypercalcemia is typically asymptomatic and does not require intervention beyond monitoring.[3] Lerena, *et al.* (2022) offer three options: 1) cessation of lithium, 2) monitoring of calcium levels while continuing lithium, 3) parathyroid exploration and possible surgical intervention.[3] Interestingly, Soh, *et al.* (2022) found that atorvastatin lowers serum calcium levels in lithium users; however, they caution that more research is needed.[25]

Case Study: Lithium-induced Hyperthyroidism

The authors of this case study reported on a 17-year-old female who was being treated with lithium for bipolar disorder and developed a hyperthyroid condition.[24] She had developed symptoms of dizziness, tremors and palpitations, heat intolerance, and excessive sweating.[24]

The patient's psychiatric history revealed that she had been previously prescribed Concerta, Abilify, and Lamictal with partial benefit. She eventually started on lithium monotherapy with a good outcome over a two-year period. A month before being evaluated for side-effect symptoms, the patient stopped taking lithium. There was no family history of thyroid disease.[24]

Laboratory tests showed a low TSH (<0.02 mcIU/mL, normal range: 0.35–5.50) and elevation of the free T4 (3.5 ng/dL, normal range: 0.8–1.9), indicative of a hyperthyroid condition. A lithium level of <0.3 (normal range:

0.6–1.2 mmol/L) suggested the patient had not been taking lithium as prescribed.[22] Upon physical evaluation, the patient's heart rate was 140 bpm, and blood pressure 132/84 mmHg; she did not have a fever. There was a nontender goiter found on palpation, but no nodules were detected. Follow-up laboratory testing reaffirmed biochemical hyperthyroidism (TSH: <0.02 mcIU/mL, total T3: 351 ng/dl, normal range: 55 to 209) and an elevated free T4 (3.7 ng/dL).[22] The ESR, CRP, CBC, and BMP were normal, and the patient's thyroid autoantibodies (antithyroid peroxidase antibody, antithyroglobulin antibody, and thyroid stimulating immunoglobulin) were all negative. An electrocardiogram showed a prolonged QT interval.[24]

Methimazole, 10 mg PO 3 times a day (0.46 mg/kg/day) was started to suppress the thyroid, and propranolol (60 mg/day~0.92 mg/kg/day) for symptoms of tachycardia and tremors. Lithium was held until her psychiatrist could re-evaluate her. Four weeks after stopping lithium, the hyperthyroid symptoms improved, although the patient's heart rate and blood pressure remained elevated (101 bpm and 133/74 mmHg, respectively), and palpitations and heat intolerance continued.[24]

A lower free T4 level (2.0 ng/dl) was seen as compared with the two prior tests, but the TSH remained suppressed. A few weeks later, the patient had an improved free T4 (1.5 ng/dl). Propranolol was stopped at this point, but the methimazole treatment was continued. The authors described lithium-induced hyperthyroidism as a rare event. In this case, 3 months after the patient was initially diagnosed and started on methimazole treatment, the dose was reduced (10 mg twice daily), and the TSH appeared borderline-low (0.8 ng/dl, normal range of 0.8 to 1.9 ng/dL). Eventually, methimazole was stopped, and several weeks later, the patient reached a euthyroid state.[24]

Discussion

The authors of this case study described how rare lithium-induced hyperthyroidism was in adults, and that prior to this case study, there had not been a reported case of lithium-induced hyperthyroidism in children.[24] This

condition is often missed by clinicians because of the wide range of onset: "The duration of lithium therapy in patients who develop hyperthyroidism and lithium-associated silent thyroiditis range between 6 days and 15 years."[24] Thyrotoxicosis has occurred in patients from 4 days to 5 months after lithium therapy is withdrawn. In this case, the patient had been on lithium therapy for about 2 years.[24]

The authors concluded that although lithium-induced hyperthyroidism had not been seen in children prior to this patient, clinicians must be aware of this potential adverse reaction. Clinicians should not be lulled into a false sense that because a patient has tolerated lithium therapy well during prolonged therapy, the patient does not need to be monitored for hyperthyroidism: "Since lithium-induced hyperthyroidism may occur years of lithium therapy, it is advisable to regularly monitor the thyroid function in children during the whole duration of lithium treatment."[24]

Summary

Lithium is an effective treatment for patients with certain mental disorders, but it has also been associated with thyroid abnormalities. These include hypothyroidism, hyperthyroidism, goiter, and autoimmune thyroiditis. Although extensively studied, lithium's alteration of normal thyroid physiology is not yet fully understood, but lithium becomes highly concentrated in the thyroid cells of patients who take the drug, and this could inhibit the production and release of thyroid hormones.

Goiter is regarded as the most common thyroid abnormality associated with lithium treatment. Hyperthyroidism is rarely seen in patients taking lithium, and some researchers believe that lithium plays no role in the development of this condition.

The prescribing of lithium to children and adolescents with affective disorders has become an established treatment option. With this comes the responsibility to weigh the risks and benefits, including the effects of lithium

on developing endocrine systems. Thyroid conditions are more commonly seen in elderly populations, hypothyroidism, in particular. During the aging process, there is a natural downward trend in thyroid function. Not surprisingly, hypothyroidism is frequently seen in elderly patients taking lithium.

Thyroid function may be assessed using clinical palpation, serum thyroid hormone tests, or ultrasonography. Baseline thyroid functioning should be assessed prior to initiation of lithium, and then periodic (at least every 6 months) rechecking of TSH levels should be considered the minimum level of monitoring appropriate for lithium prescribing. Ultrasonography and thyroid auto-antibody monitoring should likewise be considered tools.

The treatment of lithium-induced goiter is the same as for goiters of other etiologies. Levothyroxine (T4) is the primary method of treatment for lithium-induced hypothyroidism. Lithium-induced hyperthyroidism may be treated with antithyroid drugs, such as carbimazole and steroids. Levothyroxine (T4) supplementation is typically used for autoimmune hypothyroidism and antithyroid drugs for autoimmune hyperthyroid. In rare instances, surgery may be an option to resolve thyroid abnormalities caused by lithium use.

Course Test

1. **At the cellular level, lithium has been found to be highly _____ in thyroid cells**

    a. diluted
    b. concentrated
    c. saturated
    d. obsolete

2. **Lithium has been shown to inhibit the _____ and release of thyroid hormones.**

    a. division
    b. replication
    c. dissection
    d. synthesis

3. **What is the most common thyroid abnormality associated with lithium treatment?**

    a. hyperthyroidism
    b. autoimmune thyroiditis
    c. goiter
    d. hypothyroidism

4. **Which of the following are risk factors for lithium-induced thyroiditis?**

    a. Female sex
    b. Middle-age
    c. Bipolar disorder
    d. All of the above

5. **Several studies have shown that when lithium is used to treat affective disorder in children and adolescents, it _____ their TSH level.**

    a. increases
    b. decreases
    c. has no effect on
    d. doubles

6. **What age population has the highest risk for lithium-induced thyroid dysfunction?**

    a. Child
    b. Adolescent
    c. Middle-aged adult
    d. Senior Adult

7. **True or False: Lithium-induced hypothyroidism is widely considered to be a reversible condition that resolves with the discontinuation of lithium.**

    a. True
    b. False

8. **When does The American Psychiatric Association's Practice Guideline for Treatment of Patients With Bipolar Disorder, 2nd edition (2002) recommend thyroid function evaluation in regard to lithium treatment?**

    a. Prior to initiating lithium
    b. once or twice in the first 6 months of lithium treatment
    c. After the initial 6 months, every 6 months to 1 year or whenever clinically indicated
    d. All of the above

9. **What is the primary treatment for lithium-induced hypothyroidism?**

    a. Liothyronine
    b. Triiodothyronine
    c. Levothyroxine
    d. Thyroxine

10. **What is the most common treatment for lithium-induced hyperthyroidism?**

    a. Antithyroid medications
    b. Radioactive Iodine
    c. Thyroidectomy
    d. All of the above

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