

## The effect of lithium on thyroid function in patients with bipolar disorder

Agnieszka Kraszewska<sup>1</sup>, Maria Abramowicz<sup>1</sup>,  
Maria Chłopocka-Woźniak<sup>1</sup>, Jerzy Sowiński<sup>2</sup>, Janusz Rybakowski<sup>1</sup>

<sup>1</sup>Department of Adult Psychiatry, Poznań University of Medical Sciences

Head: prof. dr hab. J. Rybakowski

<sup>2</sup>Department of Endocrinology, Metabolism and Internal Medicine,

Poznań University of Medical Sciences

Head: prof. dr hab. M. Ruchała

### Summary

Since 1963 lithium treatment has been the best proven long-term pharmacotherapy for bipolar disorder (BD), both in the prevention of depressive and manic episodes, along with the reduction of the suicide risk. Thyroid gland and the hypothalamic-pituitary-thyroid (HPT) axis play a role in the pathophysiology, clinical course and treatment of BD. The influence of lithium on the thyroid gland is one of the key side effects in the long-term therapy with this drug. Lithium is accumulated in the thyroid gland at 3 to 4-fold higher concentrations as compared to its plasma levels. Its administration results in the reduced production with release inhibition of thyroid hormones, altering the immune processes of this gland. The most common thyroid side effects associated with long-term lithium treatment are goiter and hypothyroidism. Hyperthyroidism is a rare complication of lithium therapy. Lithium may also induce an increase in the thyroid autoimmunity, especially if such change had been present before lithium treatment producing structural changes in this gland. This paper reviews the management of complications described above as well as recommendations for monitoring of thyroid function in patients receiving long-term lithium treatment are discussed.

**Key words:** lithium, thyroid, bipolar disorder

### Thyroid gland and the hypothalamic-pituitary-thyroid axis activity in bipolar disorder

In 1963, the British psychiatrist Geoffrey Hartigan was the first to demonstrate that long-term lithium administration can prevent recurrences of affective disorders [1] and this procedure has been the most proven pharmacotherapy for long-term treatment of bipolar disorder (BD), both for the prevention of depressive and manic episodes as well as for reducing the risk of suicide [2]. The influence of lithium on the thyroid gland is one of the most important side effects of long-term therapy with this drug.

In recent meta-analysis of the potential toxicity of long-term use of lithium, it has been shown that lithium causes a five-fold increased risk of hypothyroidism [3].

The activity of the thyroid gland and hypothalamic-pituitary-thyroid (HPT) axis is important for the pathophysiology, clinical course and treatment of BD. The features of thyroid dysfunction in affective disorders have been indicated for many years. The most common abnormalities include features of subclinical or clinical hypothyroidism, with associated lower levels of thyroxine [4], and elevated levels of thyrotropin (thyreotropic stimulating hormone-TSH) [5, 6]. In 25-30% of patients with both unipolar and bipolar affective disorder during acute episode of the illness, a blunted response to intravenous thyreotropin releasing hormone (TRH) administration in the form of decreased pituitary TSH secretion has been observed [7, 8]. Larsen et al [9] found a negative correlation between the intensity of the symptoms of both mania and depression, and blunted TSH response to TRH.

Disturbances of the immune system may be also important for the pathogenesis of BD. This was reflected as an increased incidence of thyroid antibodies (anti-TPO) in patients with bipolar disorder compared with the control population [10]. In 2007, Dutch researchers have suggested that autoimmune thyroiditis (with elevated levels of antibodies as a marker), should be considered as an endophenotype for bipolar disorder and should be associated with a genetic susceptibility to the development of the disease [11]. The same researchers found significantly higher titers of anti-TPO in daughters of parents with BD, compared to control girls of high school age and young adults. Thus, the offspring of patients suffering from bipolar disorder was more susceptible to the development of thyroid autoimmunity, regardless of their susceptibility to the development of mental disorders [12].

Previous studies have shown that higher incidence of thyroid dysfunction occurs in women and in patients with rapid cycling bipolar disorder (RCBD). In the RCBD, all kinds of HPT axis disorders, namely overt hypothyroidism, increased levels of TSH, abnormal TSH response to TRH and increased levels of antibodies have been observed [13, 14]. Hypothyroidism in the course of bipolar disorder is a risk factor for the development of RCBD and a relative thyroid hormone deficiency in BD patients predisposes to rapid cycling course. In some cases, thyroid abnormalities reveal shortly after the start of lithium treatment [15].

Thyroid hormonal status may play a role in the treatment of affective disorders. In depression, higher baseline concentration of thyroxine is associated with better effect of antidepressant drugs [16]. For many years, thyroid hormones have been also used for augmentation of antidepressants in treatment-resistant depression both in the course of unipolar and bipolar illness. Results of studies in which triiodothyronine (T3) was added in a dose of 25-50 µg/d have showed a significant efficacy of such procedure [17, 18]. A study conducted in the Department of Adult Psychiatry, Poznań University of Medical Sciences demonstrated the beneficial effects of levothyroxine (100 µg daily) as a method of augmenting serotonin antidepressants in women, also in those where baseline HPT axis function was within normal limits [19]. Noteworthy is also the effective use of mega-doses of thyroxine (up to 400 µg/d) in refractory depression and in rapid cycling bipolar illness [20, 21].

### **Effects of lithium on the thyroid gland and the hypothalamic-pituitary-thyroid (HPT).**

Lithium is accumulated in the thyroid gland in a concentration of 3 to 4-fold greater than in plasma [22]. This process is due to the active Na/I transport against the concentration gradient [23]. Lithium reduces thyroid iodine uptake and impairs the synthesis of iodotyrosine by decreasing iodination of tyrosine, changing the structure of thyroglobulin and inhibiting the formation of colloid in the apical part of the thyroid cells. Lithium administration lowers deiodination in the liver and decreases the clearance of free serum thyroxine (FT<sub>4</sub>), which results in reduced activity of type I 5' deiodinase. It has been also shown that lithium decreases the activity of type II deiodinase and alters the structure of thyroglobulin, thus affecting its function that contributes to defects in iodotyrosine coupling [24].

Lithium administration leads to a decrease of production and release of thyroid hormones, which results in increased levels of TSH – thyroid stimulating factor, and excessive TSH response to stimulation with TRH. Lithium also affects the cellular and humoral immune reaction which could result in disturbances in the production of thyroid antibodies [25].

In a study conducted on rats, it was found that lithium accumulates in both the pituitary gland and in the hypothalamus. It was also shown that lithium affects the activity of binding thyroid hormones to receptors in the brain and regulates expression of genes for the thyroid hormone receptors [26].

Multiple mechanisms of lithium action in the thyroid gland and HPT axis may be associated with clinical effects that occur during long-term lithium treatment in patients with BD, such as goiter, hypothyroidism, hyperthyroidism, immune disorders and structural changes of the gland.

The status of PPT axis may be related to the effectiveness of lithium in patients with bipolar disorder. Higher concentrations of T<sub>3</sub> predisposed to a greater likelihood of recurrence of depression during initial few years of treatment [27]. On the other hand, lower levels of free T<sub>4</sub> were associated with a greater number of affective episodes and higher severity of depression during the first year of treatment with lithium [28]. Recently Frye et al [29] have showed that patients treated with lithium who required intervention during an episode of depression had significantly higher level of TSH, compared to patients treated with lithium, who did not require intervention during depressive episode.

### **Goiter associated with the use of lithium.**

Goiter is the most common thyroid clinical complication associated with long-term use of lithium. In 1968, Schou et al [30] were the first to report goiter in 12 of 330 patients treated with lithium for five months to two years. The estimated incidence of goiter during lithium therapy was 3.6%, and the annual incidence was 4%, compared to 1% among the general population of Copenhagen. Since then, the phenomenon has been described in a number of studies on the long-term use of lithium. However,

different values of the frequency of the occurrence of goiter have been reported, which can be explained by the differences in the availability of iodine in the environment, duration of lithium treatment and the diagnostic techniques used. Goiter, as assessed by palpation examination may develop within a few weeks, but it can also occur after many years.

In an article published in 1980, Männistö [31] showed the 5,6% incidence of goiter in a group of 1257 patients. In 1990, the assessment made by the Danish research group of 100 patients with BD showed that goiter occurs in 44% of patients treated for 1-5 years and in 50% of those treated for more than 10 years, compared to 16% in the control group. In 4% of patients treated for 1-5 years and in 21% of patients treated for over 10 years, the features of subclinical or clinical hypothyroidism have been shown [32]. In 1991, thyroid function was assessed by Italian researchers in a group of 150 outpatients treated with lithium for varying lengths of time. Visible or palpable goiter was detected in 51% of patients, and no significant correlation with treatment duration was found [33]. Following further 10 years of observation of this group of patients, it was found that the average annual increment of goiter was 2,1% of patients [34]. In studies conducted at the beginning of XXI century, the prevalence of goiter in patients receiving lithium ranged between 30-59% [35-37].

The mechanism of goiter formation has been explained by the inhibition by lithium of the synthesis and release of thyroid hormones, resulting in an increase of TSH level, leading to enlargement of the gland. Another proposed mechanism of the proliferation of thyrocytes in patients treated with lithium is an activation of tyrosine kinase by lithium ion and lithium effects on intracellular signaling connected with adenylate cyclase and that of Wnt/ beta-catenin [24].

Patients with lithium-induced goiter should be treated in a similar manner to other patients who developed goiter. Because levothyroxine may protect against the development of the goiter, and as previously mentioned, it may improve the effectiveness of treatment, it is reasonable to give it to patients with significant enlargement of the thyroid gland, especially if it is associated with symptoms of neck constriction. Bauer et al [38] argue that levothyroxine should be considered, if thyroid size exceeds the norm. Other authors recommend goiter treatment in order to prevent the development of nodules and autonomous regions [39], while some other authors suggest levothyroxine prophylaxis in all patients treated with lithium, if they come from iodine-deficient areas [40].

During levothyroxine replacement therapy, the dose should be adjusted allowing not to suppress totally the secretion of TSH, and fT3 and fT4 levels (especially fT3) should be maintained within normal limits. Levothyroxine therapy is not effective in patients with goiter of long duration, where fibrotic changes have developed. If such treatment does not reduce the size of goiter, or symptoms of constriction are overwhelming, a surgery should be performed.

### **Hypothyroidism associated with the use of lithium.**

The occurrence of goiter in the course of lithium therapy show an association with hypothyroidism. In the pathogenesis of hypothyroidism, autoimmunity and production of antibodies may also play the role. In some patients with bipolar disorder treatment with lithium may exacerbate already existing subclinical hypothyroidism [41]. The clinical picture of hypothyroidism in patients treated with lithium is not different from that of the other cases of hypothyroidism. The average time from the start of therapy with lithium for producing an underactive thyroid gland is 1,5 years, although it may occur in the first few months or not occur at all.

The incidence of hypothyroidism and coexisting goiter differs in various studies, which may be caused by differences in the criteria used for diagnosis (e.g. overt or subclinical hypothyroidism) and the population studied (gender, geographical origin, the uptake of iodine, the proportion of patients with autoimmune disturbances). In a review of sixteen studies including 4681 patients, completed by the 1986, the rate of hypothyroidism was 3.4% (range 0-23.3%) [42]. Studies performed from 1986 to 2005 indicate the frequency in the range of 6 – 52% [24]. The ratio of women to men having this complication is 5:1.

Bocchetta et al [33] in a study of 150 Sardinian outpatients undergoing therapy with lithium, reported subclinical hypothyroidism in 19% of patients. There was a higher incidence of hypothyroidism in patients with antithyroid antibodies. In a study conducted 15 years later these researchers estimated the annual increment of hypothyroidism in patients on long-term treatment with lithium at 1,5% [43].

Johnson and Eagles [44] in a retrospective review of 718 patients receiving lithium therapy, reported hypothyroidism in 10.4% of patients (14% of women and 4.5% of men). Women were most at risk of developing hypothyroidism during the first two years of treatment, and the highest incidence of hypothyroidism was observed in women who start treatment at the age of 40-59 years (> 20%).

Kirov et al [45] evaluated 115 men and 159 women with bipolar disorder on long-term lithium therapy and noted the 10.3% incidence of hypothyroidism (17% of women and 3.5% of men). During long-term observation of 57 patients, it was found that the risk of developing hypothyroidism increased especially in women over the age of 50 years. The incidence of hypothyroidism in women was 27.4 cases per 1000 years of treatment and was 8x higher than obtained in a study conducted on a general population of women from this region (3.5 cases per 1000 years of observation).

Risk factors for developing hypothyroidism in patients taking lithium are similar to those of the general population, with higher incidence in women and those with positive thyroid antibodies. Lithium may therefore be considered as a factor predisposing to the development of hypothyroidism in women and/or in those with the presence of antibodies.

**In the course of** lithium therapy, excessive TSH response to TRH occurs in at least 50% of patients. Approximately 10% of patients, with no evidence of thyroid dysfunction before lithium therapy, had elevated TSH basic values [35]. Caykoylu et al [36] reported a significant increase in the basic TSH in 82% of patients and TSH

increase after TRH stimulation in 11 of 12 patients after one year of therapy. An excessive response to TRH stimulation has been shown in patients with rapid cycling bipolar disorder (significantly higher delta (max) of TSH than in the control group) after a 4-week lithium treatment, which may indicate HPT axis dysfunction in these patients, even after a short use of this drug [37]. The disorder of the hypothalamic-pituitary axis was temporary in most patients, which suggests that the axis is adjusting to the new „state” during therapy.

The indications for supplementation of levothyroxine include: overt hypothyroidism, a significant enlargement of the gland, clear evidence suggesting subclinical hypothyroidism, rapid cycling bipolar disorder and poor efficacy of lithium [35]. It is recommended to start supplementation with low doses of levothyroxine (25-75 mg/d) if TSH>10mu/l, but it can be also performed with lower TSH values. During administration of levothyroxine, lithium therapy should not be interrupted and the dose of lithium changed unless serum concentration of lithium is beyond the therapeutic range [46].

### **Hyperthyroidism associated with the use of lithium**

Although lithium generally inhibits thyroid function, a number of cases of the hyperthyroidism have been documented in lithium-treated patients. The first such case was reported in 1974 in New Zealand [47], and until 1986, 40-50 cases were described [42].

In the etiology of hyperthyroidism occurring in lithium-treated patients, an important role is played by autoimmune factors inducing Graves-Basedow disease and silent thyroiditis as well as toxic nodular goiter. Lithium may directly destroy the thyroid cells, with consequent release of thyroglobulin and thyroid hormones into circulation. Lithium-induced hyperthyroidism is characterized mainly by the transient, painless thyroiditis. Some publications indicate a relationship between the use of lithium and lymphocytic or non-specific inflammation of the thyroid gland. Miller and Daniels [48] in 400 patients (300 with Graves' disease and 100 with silent thyroiditis) who underwent scintigraphic study, observed that thyrotoxicosis associated with lithium occurred twice as often as thyroiditis in patients undergoing lithium therapy, suggesting that it can be also caused by silent thyroiditis.

In a retrospective study performed by Kirov et al [49] hyperthyroidism has been found in only 2 of 209 patients with bipolar disorder on long-term treatment with lithium including women of younger age at the beginning of treatment. In a study published seven years later, the same researchers found thyrotoxicosis in 1,8% of 109 men and in 3,9% of 152 women during lithium therapy lasting on average of 80 and 73,3 months, respectively. In a prospective study of 33 women during observation period of 53,1 months, only one developed thyrotoxicosis [45]. Bocchetta et al [34] during the 10-year follow-up did not find any case of thyrotoxicosis, and after 16 years reported only one case among 150 patients on long-term lithium therapy [43].

There is also data indicating a higher incidence of lithium-induced thyrotoxicosis. In a study from New Zealand, 14 cases were observed during the 18-year follow-up, that is 3-fold more than incidence of thyrotoxicosis in the general population [50]. The same researchers in subsequent 12-year period (1995-2006) observed 23 such

cases (20 women and 3 men), and in 9 of them found the painless thyroiditis [51]. There are also reports of the exophthalmos in connection with lithium therapy in 25% of 73 patients [35] and the disappearance of such complication after discontinuation of lithium treatment [52].

In general, it can be said that hyperthyroidism in the course of lithium therapy is relatively rare, but occurs more often than in the general population. Treatment of patients with hyperthyroidism associated with lithium is dependent on the mechanism of its development. Usually, treatment with antithyroid drugs such as carbimazol alone or in combination with corticosteroids brings the best results. Toxic nodular goiter may require surgical intervention, particularly if there are symptoms of constriction in the neck [53].

### **Thyroid immunological disturbances associated with the use of lithium**

Lithium affects many aspects of cellular and humoral immunity both *in vitro* and *in vivo*. There is evidence that treatment with lithium is associated with an increase in antibody titers, especially, when these antibodies had been present at the start of treatment. Lithium effect on the concentration of antithyroid antibodies leads to a faster autoimmunization of thyroid that can cause goiter and hypothyroidism, however, hyperthyroidism is also possible. Thyroid biopsy in some patients indicates autoimmune thyroiditis. In many studies carried out on lithium-treated patients, elevated levels of antithyroid antibodies were observed (range 8-49%), which is much higher than the values obtained in the control group or in the general population. Thyroid autoimmunity is more common among women than men. However, in some studies no association between elevated antithyroid antibodies and exposure to lithium was found.

In the study conducted by Wilson et al [54] in 1991, it was found that a much larger group of patients treated with lithium had antithyroid autoantibodies compared to non-treated ones (20% vs 7,5%). This study showed that treatment with lithium contributes to increased B-cell activity and to decreased ratio of suppressor/cytotoxic T cells. Bocchetta et al [43] in his article summarizing the 15-year follow-up of patients on long-term lithium treatment found that the proportion of new cases with antithyroid antibodies is 1,7% per year, and that their presence is an important risk factor for the development of hypothyroidism.

Dutch researchers in their 2002-year publication found anti-TPO antibodies in 64 of 226 (28%) of patients with rapid cycling bipolar disorder. Autoimmunity was associated with a dysfunction of the thyroid, but correlation was not detected with lithium treatment, age, sex mood or rapid cycling bipolar disorder. The antibodies were present in 34,3% of those who had never received lithium [10]. In 2005 Baethge et al [55] compared 100 patients with rapid cycling bipolar disorder treated with lithium therapy with a group of 100 people without mental disorders matched for age and sex. No significant difference was shown in the incidence of autoantibodies anti-TPO and anti-TG between the two groups.

Thus, despite some evidence suggesting that the increase in titers of thyroid antibodies could be stimulated by a lithium, and that there may be a risk factor for

the development of hypothyroidism during treatment with lithium, there is no particular reason for monitoring these antibodies during therapy with lithium. Many patients with positive anti-TPO antibodies remain in euthyroid state, on the other hand, the absence of these antibodies does not preclude the development of hypothyroidism or hyperthyroidism during treatment with lithium.

### **The structural changes of the thyroid gland associated with the use of lithium**

Ultrasonographic abnormalities may be also related to inhibition of the release of thyroid hormones in the course of treatment with lithium. Abnormal ultrasonographic findings were observed in many patients receiving long-term treatment with lithium (more frequently in women). Bocchetta et al [56] among patients treated with lithium subjected to a six-year follow-up in 97% of women and 69% of men without thyroid antibodies, showed minor abnormalities on ultrasound examination (decreased echogenicity, inhomogeneous image) and presence of focal lesions in 47% of women and 24% men. Loviselli et al [57] found that ultrasonographic echogenicity in lithium-treated bipolar patients decreases during lithium treatment and has dispersed nature. However, German researchers have shown that there is no significant difference in thyroid echogenicity comparing a small group of 20 patients treated with lithium for at least 6 months, with the 20-person control group matched for sex and age [58].

### **Monitoring of thyroid function in lithium-treated patients**

In contrary to what has been frequently practiced, the presence of abnormalities in thyroid function should not be a contraindication to continuation of therapy with lithium (if clinical effect is positive) but it may be only an indication for a supplementation with levothyroxine, as mentioned earlier. Similarly, lithium therapy should not be discontinued if minor morphologic abnormalities of the thyroid gland occur. It is important that lithium-treated patients were adequately controlled – it will make possible to early detect any adverse effects and for introduce appropriate treatment.

Basic diagnostic tests for thyroid function (TSH, fT3, fT4), evaluation of antibody titer (anti-thyroglobulin antibodies -anti-TG, anti-thyroid peroxidase antibodies anti-TPO, thyrotropin receptor antibodies – anti-TR) and ultrasonographic assessment of thyroid size should be considered as necessary examinations for all patients treated with lithium. These tests should be performed at the beginning of therapy, and then repeated every year. Determination of antibodies and ultrasonographic examination, according to some authors, may be repeated every 2-3 years [59].

Patients with risk factors such as female sex, middle age, autoimmune disease or the history of thyroid disease in the family should be monitored more closely. Also, in older women who have positive antithyroid antibodies, thyroid tests should be performed more frequently, e.g. every 3-4 months and include at least TSH and/or free T4 [45].

## References

1. Hartigan G. *The use of lithium salts in affective disorders*. Br. J. Psychiatry 1963; 109: 810–814.
2. Rybakowski J. *Leki normotymiczne*. W: Wciórka J, Pużyński S, Rybakowski J. red. *Psychiatria*. Tom III. Wrocław: Elsevier Urban & Partner; 2012. s. 110–124.
3. McKnight RF, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR. *Lithium toxicity profile: a systematic review and meta-analysis*. Lancet 2012; 379: 721–728.
4. Rybakowski J, Sowiński J. *Free-thyroxine index and absolute free-thyroxine in affective disorders*. Lancet 1973; 7808: 889.
5. Valle J, Ayuso-Gutierrez JL, Abril A, Ayuso-Mateos JL. *Evaluation of thyroid function in lithium-naïve bipolar patients*. Eur. Psychiatry 1999; 14: 341–345.
6. Ezzaher A, Haj Mouhamed D, Mechri A, Neffati F, Douki W, Gaha L. i wsp. *Thyroid function and lipid profile in bipolar I patients*. Asian J. Psychiatr. 2011; 4: 139–143.
7. Loosen PT. *The TRH-induced TSH response in psychiatric patients: a possible neuroendocrine marker*. Psychoneuroendocrinology 1985; 10: 237–260.
8. Linkowski P, Brauman H, Mendlewicz J. *Thyrotrophin response to thyrotrophin-releasing hormone in unipolar and bipolar affective illness*. J. Affect. Disord 1981; 3: 9–16.
9. Larsen JK, Faber J, Christensen EM, Bendsen BB, Solstad K, Gjerris A. i wsp. *Relationship between mood and TSH response to TRH stimulation in bipolar affective disorder*. Psychoneuroendocrinology 2004; 29: 917–924.
10. Kupka RW, Nolen WA, Post RM, McElroy SL, Altshuler LL, Denicoff KD. *High rate of autoimmune thyroiditis in bipolar disorder: lack of association with lithium exposure*. Biol. Psychiatry 2002; 51: 305–311.
11. Vonk R, van der Schot AC, Kahn RS, Nolen WA, Drexhage HA. *Is autoimmune thyroiditis part of the genetic vulnerability (or an endophenotype) for bipolar disorder?* Biol. Psychiatry 2007; 62(2): 135–140.
12. Hillegers MH, Reichart CG, Wals M, Verhulst FC, Ormel J, Nolen WA. i wsp. *Signs of a higher prevalence of autoimmune thyroiditis in female offspring of bipolar parents*. Eur. Neuropsychopharmacol. 2007; 17: 394–399.
13. Cowdry RW, Wehr TA, Zis AP, Goodwin FK. *Thyroid abnormalities associated with rapid-cycling bipolar illness*. Arch. Gen. Psychiatry 1983; 40: 414–420.
14. Oomen HA, Schipperijn AJ, Drexhage HA. *The prevalence of affective disorder and in particular of a rapid cycling of bipolar disorder in patients with abnormal thyroid function tests*. Clin. Endocrinol. (Oxf). 1996; 45: 215–223.
15. Cole DP, Thase ME, Mallinger AG, Soares JC, Luther JF, Kupfer DJ. i wsp. *Slower treatment response in bipolar depression predicted by lower pretreatment thyroid function*. Am. J. Psychiatry 2002; 159: 116–121.
16. Aronson R, Offman HJ, Joffe RT, Naylor CD. *Triiodothyronine augmentation in the treatment of refractory depression. A meta-analysis*. Arch. Gen. Psychiatry 1996; 53: 842–848.
17. Altshuler LL, Bauer M, Frye MA, Gitlin MJ, Mintz J, Szuba MP. i wsp. *Does thyroid supplementation accelerate tricyclic antidepressant response? A review and meta-analysis of the literature*. Am. J. Psychiatry 2001; 158: 1617–1622.
18. Łojko D, Rybakowski JK. *L-thyroxine augmentation of serotonergic antidepressants in female patients with refractory depression*. J. Affect. Disord. 2007; 103: 253–256.

19. Bauer M, Hellweg R, Gräf KJ, Baumgartner A. *Treatment of refractory depression with highdose thyroxine*. *Neuropsychopharmacology* 1998; 18: 444–455.
20. Bauer MS, Whybrow PC. *Rapid cycling bipolar affective disorder. II. Treatment of refractory rapid cycling with high-dose levothyroxine: a preliminary study*. *Arch. Gen. Psychiatry* 1990; 47: 435–440.
21. Spaulding SW, Burrow GN, Bermudez F, Himmelhoch JM. *The inhibitory effect of lithium on thyroid hormone release in both euthyroid and thyrotoxic patients*. *J. Clin. Endocrinol. Metab.* 1972; 35: 905–911.
22. Berens SC, Wolff J, Murphy DL. *Lithium concentration by the thyroid*. *Endocrinology* 1970; 87: 1085–1087.
23. Eskandari S, Loo DD, Dai G, Levy O, Wright EM, Carrasco NJ. *Thyroid Na<sup>+</sup>/I<sup>-</sup> symporter. Mechanism, stoichiometry, and specificity*. *J. Biol. Chem.* 1997; 272: 27230–27238.
24. Lazarus JH, Kirov G, Harris B. *Effect of lithium on thyroid and endocrine glands*. W: Bauer M, Grof P, Müller-Oerlinghausen B. red. *Lithium in neuropsychiatry*. Oxfordshire: Informa Healthcare; 2006. s. 259–270.
25. Livingstone C, Rampes H. *Lithium: a review of its metabolic adverse effects*. *J. Psychopharmacol.* 2006; 20: 347–355.
26. Hahn CG, Pawlyk AC, Whybrow PC, Gyulai L, Tejani-Butt SM. *Lithium administration affects gene expression of thyroid hormone receptors in rat brain*. *Life Sci.* 1999; 64: 1793–1802.
27. Baumgartner A, von Stuckrad M, Müller-Oerlinghausen B, Gräf KJ, Kürten I. *The hypothalamic-pituitary- thyroid axis in patients maintained on lithium prophylaxis for years: higher triiodothyronine serum concentrations are correlated to the prophylactic efficacy*. *J. Affect. Disord.* 1995; 34: 211–218.
28. Frye MA, Denicoff KD, Bryan AL, Smith-Jackson EE, Ali SO, Luckenbaugh D. i wsp. *Association between lower serum free T4 and greater mood instability and depression in lithium-maintained bipolar patients*. *Am. J. Psychiatry* 1999; 156: 1909–1914.
29. Frye MA, Yatham L, Ketter TA, Goldberg J, Suppes T, Calabrese JR. i wsp. *Depressive relapse during lithium treatment associated with increased serum thyroid-stimulating hormone: results from two placebo-controlled bipolar i maintenance studies*. *Acta Psychiatr. Scand.* 2009; 120: 10–13.
30. Schou M, Amdisen A, Eskjaer Jensen S, Olsen T. *Occurrence of goitre during lithium treatment*. *Br. Med. J.* 1968; 3: 710–713.
31. Mannisto PT. *Endocrine side-effects of lithium*. W: Johnson FN. red. *Handbook of lithium therapy*. Lancaster: MTP Press; 1980. s. 310–322.
32. Perrild H, Hegedüs L, Baastrup PC, Kayser L, Kastberg S. *Thyroid function and ultrasonically determined thyroid size in patients receiving long-term lithium treatment*. *Am. J. Psychiatry* 1990; 147: 1518–1521.
33. Bocchetta A, Bernardi F, Pedditzi M, Loviselli A, Velluzzi F, Martino E. i wsp. *Thyroid abnormalities during lithium treatment*. *Acta Psychiatr. Scand.* 1991; 83:193–198.
34. Bocchetta A, Mossa P, Velluzzi F, Mariotti S, Del-Zompo M, Loviselli A. *Ten year follow-up of thyroid function in lithium patients*. *J. Clin. Psychopharmacol.* 2001; 21: 594–598.
35. Ozpoyraz N, Tamam L, Kulan E. *Thyroid abnormalities in lithium treated patients*. *Adv. Ther* 2002; 19: 176–184.
36. Caykoylu A, Capoglu I, Unuyvar N, Erdem F, Cetinkaya R. *Thyroid abnormalities in lithium-treated patients with bipolar affective disorder*. *J. Int. Med. Res.* 2002; 30: 80–84.

37. Schiemann U, Hengst K. *Thyroid echogenicity in manic-depressive patients receiving lithium therapy*. J. Affect. Disord. 2002; 70: 85–90.
38. Bauer M, Blumentritt H, Finke R, Schlattmann P, Adli M, Baethge C. i wsp. *Using ultrasonography to determine thyroid size and prevalence of goiter in lithium-treated patients with affective disorders*. J. Affect. Disord. 2007; 104: 45–51.
39. Hegedüs L, Bonnema SJ, Bennedbaek FN. *Management of simple nodular goiter: current status and future perspectives*. Endocr. Rev. 2003; 24: 102–132.
40. Martino E, Placidi GF, Sardano G, Mariotti S, Fornaro P, Pinchera A. i wsp. *High incidence of goiter in patients treated with lithium carbonate*. Ann. Endocrinol. 1982; 43: 269–276.
41. Ozsoy S, Mavili E, Aydin M, Turan T, Esel E. *Ultrasonically determined thyroid volume and thyroid functions in lithium-naïve and lithium-treated patients with bipolar disorder: a cross-sectional and longitudinal study*. Hum. Psychopharmacol. 2010; 25: 174–178.
42. Lazarus JH. *Lithium and the thyroid gland*. W: Lazarus JH. red. *Endocrine and metabolic effects of lithium*. New York, London: Plenum Medical Book Company; 1986. s. 99–124.
43. Bocchetta A, Cocco F, Velluzzi F, Del Zompo M, Mariotti S, Loviselli A. *Fifteen-year follow-up of thyroid function in lithium patients*. J. Endocrinol. Invest. 2007; 30: 363–366.
44. Johnston AM, Eagles JM. *Lithium-associated clinical hypothyroidism. Prevalence and risk factors*. Br. J. Psychiatry 1999; 175: 336–339.
45. Kirov G, Tredget J, John R, Owen MJ, Lazarus JH. *A cross-sectional and a prospective study of thyroid disorders in lithium-treated patients*. J. Affect. Disord. 2005; 87: 313–317.
46. Kleiner J, Altschuler L, Hendrick V, Hershman JM. *Lithium-induced subclinical hypothyroidism: review of the literature and guidelines for treatment*. J. Clin. Psychiatry 1999; 60: 249–255.
47. Franklin LM. *Thyrotoxicosis developing during lithium treatment: case report*. N. Z. Med. J. 1974; 79: 782.
48. Miller KK, Daniels GH. *Association between lithium use and thyrotoxicosis caused by silent thyroiditis*. Clin. Endocrinol. 2001; 55: 501–508.
49. Kirov G. *Thyroid disorders in lithium-treated patients*. J. Affect. Disord. 1998; 50: 33–40.
50. Barclay ML, Brownlie BE, Turner JG, Wells JE. *Lithium associated thyrotoxicosis: a report of 14 cases, with statistical analysis of incidence*. Clin. Endocrinol. 1994; 40: 759–764.
51. Brownlie B, Turner J. *Lithium associated thyrotoxicosis*. Clin. Endocrinol. 2011; 75: 402–403.
52. Byrne AP, Delaney WJ. *Regression of thyrotoxic ophthalmopathy following lithium withdrawal*. Can. J. Psychiatry 1993; 38: 383–390.
53. Lazarus J, Richards A, Adison G, Owen G. *Treatment of thyrotoxicosis with lithium carbonate*. Lancet 1974, 2: 1160–1168.
54. Wilson R, McKillop JH, Crockett GT, Pearson C, Jenkins C, Burns F. i wsp. *The effect of lithium therapy on parameters thought to be involved in the development of autoimmune thyroid disease*. Clin. Endocrinol. 1991; 34: 357–361.
55. Baethge C, Blumentritt H, Berghöfer A, Bschor T, Glenn T, Adli M. i wsp. *Long-term lithium treatment and thyroid antibodies: a controlled study*. J. Psychiatry Neurosci. 2005; 30: 423–427.
56. Bocchetta A, Cherchi A, Loviselli A, Mossa P, Velluzzi F, Derai R. i wsp. *Six-year follow-up of thyroid function during lithium treatment*. Acta Psychiatr. Scand. 1996; 94: 45–48.
57. Loviselli A, Bocchetta A, Mossa P, Velluzzi F, Bernardi F, del Zompo M. i wsp. *Value of thyroid echography in the long-term follow-up of lithium-treated patients*. Neuropsychobiology 1997; 36: 37–41.

58. Schiemann U, Hengst K. *Thyroid echogenicity in manic-depressive patients receiving lithium therapy*. J. Affect. Disord. 2002; 70: 85–90.
59. Bocchetta A, Loviselli A. *Lithium treatment and thyroid abnormalities*. Clin. Pract. Epidemiol. Ment. Health 2006; 2: 23.