Dialogues in Clinical Neuroscience & Mental Health

DOI 10.26386/obrela.v1i2.46 ISSN 2585-2795

Special article

Is there a connection between lithium induced hypothyroidism and lithium efficacy in bipolar disorder?

Orestis Giotakos

Abstract

Hypothyroidism, more commonly subclinical, appears a common abnormality, while the hypothalamic-pituitary-thyroid (HPT) axis abnormalities are quite common among patients with bipolar disorder. On the other hand, lithium has been used successfully in treating bipolar disorders, but lithium influence on the thyroid gland is one of the key side effects in the long-term therapy. Lithium administration leads to a decrease of production and release of thyroid hormones, which results in increased levels of thyroid stimulating factor (TSH), and excessive TSH response to stimulation with TRH. Inhibition of thyroid hormone release, a process mediated by cyclic adenosine monophosphate, appears to be the critical mechanism in the development of lithium-induced hypothyroidism. Lithium also inhibits thyroidal iodine uptake and iodotyrosine coupling, alters thyroglobulin structure, and interferes with the deiodination of T4 to T3, by inhibiting type-II deiodinase in the brain. Lithium may also demonstrate an immunostimulant effect, either by inducing, or by exacerbating a preexisting autoimmune disease. Additionally, lithium alters cellular responsiveness to thyroxine, and influences thyroid hormone receptor gene expression. Deficits in any one or more of these mechanisms may result in reduced bioavailability of thyroid hormones at cerebral target regions despite normal peripheral serum levels of thyroid hormones. Rethinking lithium mechanisms of action, and especially lithium induced hypothyroidism, may help to enhance our understanding of the thyroid-bipolar disorder connection. In the course of lithium therapy, excessive TSH response to TRH occurs in at least 50% of bipolar patients. This "disordered" thyroid-hypothalamic-pituitary axis seems to be temporary in most patients, which suggests that the axis is adjusting to the new «state» during therapy. Moreover, rapid cycling bipolar disorder is associated with a latent hypofunction of the HPT system, which becomes manifest even with short-term lithium challenge. Lithium-treatment exaggeration of TSH responses to TRH, indicate that lithium push forward these patients in a temporary "more hypo-thyroid" status". It is possible that the lithium induced 'central hypothyroidism' may enhance the HPT axis activation, resulting to the thyroid system re-activation, and to the thyroid hormones' availability and effect re-adaptation. This compensatory process may results to the correction of a possible peripheral resistance to thyroid hormones, as well as to the correction of an isolated CNS hypothyroidism. We may hypothesize that these compensatory mechanisms, which operate to prevent the development of hypothyroidism or goiter, represent a therapeutic process of lithium therapy in bipolar disorder, acting through a thyroid system resetting.

Key words: *thyroid hormones, hypothyroidism, thyroid, lithium, bipolar disorder.*

Corresponding Author: Orestis Giotakos, Psychiatrist (MD, MSc, PhD), Founder of the non-profit organization "obrela", Erifilis 2, 11634 Athens, Greece, Info@obrela.gr, www.obrela.gr

Received: January 2, 2018, Accepted: February 5, 2018

DOI 10.26386/obrela.v1i2.46 ISSN 2585-2795

The thyroid hormones

Thyroid hormones are made from the amino acid tyrosine. T3 is the "active" version of the hormone. About one fifth of the hormone produced by thyroid gland comes out as T3. Cells in the brain, liver and some other organs take T4 from the bloodstream and convert it to T3 by removing one of the iodine atoms. The activity of specific thyroid hormone transporters, like monocarboxylate transporter, and the carrier transthyretin, is involved in determining intracellular concentrations of thyroid hormones via mediating their cellular influx and efflux [1]. Deiodinases control regional effectivity of T3 in concert with other mechanisms [2], that is, the local distribution of the different nuclear thyroid hormone receptors TRα and TRβ. As part of the nuclear superfamily of ligand-modulated transcription factors, thyroid hormones bind to nuclear receptors [3], where they control, and usually increase, gene expression influencing a broad array of metabolic processes [4]. Genes that are regulated by thyroid hormones are known to encode for proteins essential for important brain function such as myelin and neurotrophines. Non-genomic actions after binding to cytoplasmic thyroid hormone receptors include rapid activation of the phosphatidylinositol-3-protein kinase pathway and thereby achievement of vasodilatory and neuroprotective effects [5]. Thyroid hormone in general, regulates nuclear transcription of genes responsible for protein synthesis, increases cellular metabolism and growth rates, facilitates mental processes, increases endocrine gland activity, stimulates carbohydrate and fat metabolism, increases fatty acids, and also increases heart rate, respiration and muscle action. In parallel, thyroid hormones decreases body weight, as well as cholesterol, phospholipids, and triglycerides [4].

Thyroid hormones and affective disorders

Thyroid hormone receptors are widely distributed in the brain with high concentrations in the cerebral cortex, hippocampus and the amygdala, the latter being limbic structures that are implicated in the pathogenesis of mood disorders [6]. The regulation of thyroid hormone homeostasis in the brain underlies a complex interaction of different mechanisms, some of which overlap with mechanisms involved in affect regulation. A lack of thyroid hormones can lower the threshold for depression, while an excess can contribute to a state of tense dysphoria. Thyroid function in some persons also appears to influence the course of affective disorders. Adequate mobilization of thyroid hormones favors recovery from depression; excess mobilization increases the risk of mania in vulnerable individuals [7]. Although other mechanisms may be involved, evidence suggests that the modulation by thyroid hormones of the β-adrenergic receptor response to catecholamines may contribute to these effects. Norepinephrine stimulates such receptors and thyroid hormones increase their ability to receive stimulation. The plausibility of such interactions between catecholamines and thyroid hormones occurring in the CNS is strengthened by their common origin in the amino acid tyrosine and by their synergism in many metabolic processes [8]. Interactions of the thyroid and neurotransmitter systems, primarily norepinephrine and serotonin, which are generally believed to have a major role in the regulation of mood and behavior, contributes also to the mechanism of action in the developing and mature brain. In particular, there is robust evidence from animal research that thyroid hormones have a modulatory effect leading to an increase in serotonergic neurotransmission. Thyroid hormones also interact with other neurotransmitter systems involved in mood regulation, including dopamine postreceptor and signal-transducing processes, as well as gene regulatory mechanisms [9, 10].

Overt psychiatric disorder occurs in no more than 10% of the thyroid disordered patients [11]. The most common psychiatric symptoms related to hypothyroidism are depression and cognitive dysfunction [12], with possible underlying mechanism the dysregulation of CNS catecholamine receptor sensitivity or the disruption of circadian rhythms [13]. On the other hand, hyperthyroidism or thyrotoxicosis is usually associated with symptoms such as anxiety, depression, mood lability, and insomnia. Overt hyperthyroidism prevalence is no greater than 2% in bipolar patients [14], while much of this

DOI 10.26386/obrela.v1i2.46 ISSN 2585-2795

has been attributed to lithium [15], which can induce thyrotoxicosis by autoimmune mechanisms or thyroiditis [16]. In addition, mixed affective states have been associated with reduced thyroid functioning [7] and a higher rate of positive anti-thyroid antibody titres, than other unipolar or bipolar subgroups, apparently unrelated to lithium treatment, although not all studies confirm this association [17].

The hypothesis that interactions between thyroid and neurotransmitter systems may have a causal role in the pathophysiology of mood disorders was originally proposed by Whybrow and Prange (1981) [8]. They suggested that the antidepressant properties of T3 could be explained by its augmentation of postsynaptic beta-adrenergic activity. Hypothyroidism was, thus, believed to cause depression by producing a functional decrease in noradrenergic transmission. The role of several neurotransmitter systems including norepinephrine (NE), serotonin (5-HT), dopamine (DA), and gamma aminobutyric acid (GABA) in the pathogenesis of mood disorders is now well established [18, 19, 20]. Interactions between thyroid hormones and these neurotransmitter systems may not only account for the psychiatric symptoms accompanying thyroid disease, but also for the hypothalamic-pituitary-thyroid (HPT) dysfunction in mood disorders, and the therapeutic actions of thyroid hormones in mood disorders [21]. The interactions between thyroid and neurotransmitter systems are often complex and reciprocal. NE stimulates both TRH and TSH release, while 5-HT, DA, and GABA inhibit their release [22, 23]. Evidence about the effect of thyroid hormones on neurotransmitters is mostly derived from animal studies. Such evidence principally consists of altered responsiveness of NE, 5-HT, DA, and GABA systems in the adult/mature brain, resulting from experimentally induced hypothyroid or hyperthyroid states [24].

The hypothalamic-pituitary-thyroid axis in affective disorders

The features of thyroid dysfunction in affective disorders have been indicated for many years. The activity of the thyroid gland and hypothalamic-pituitary-thyroid (HPT) axis seems to be important for the pathophysiology, clinical course and treatment of bipolar disorder. The most common abnormalities include features of subclinical or clinical hypothyroidism, with associated lower levels of thyroxine [25], and elevated levels of thyrotropin (thyreotropic stimulating hormone-TSH) [26].

The TSH is the most widely used test for detecting HPT dysfunction response to an intravenous dose of TSH. The response is usually exaggerated in hypothyroidism and blunted in hyperthyroidism. A blunted TSH response occurs in 25–30% of patients with unipolar major depression, in the form of decreased pituitary TSH secretion [27], and is far more common among patients with bipolar disorder, including those with mania, bipolar depression, and rapid cycling disorder [28, 29]. Moreover, the severity of mood symptoms and milder fluctuations in these symptoms has been found to correlate with blunted TSH responses to TRH [30]. However, many patients with bipolar disorder show an exaggerated response of TSH to TRH [31], along with elevated basal levels of TSH, especially in patients with rapid cycling, and this finding is consistent with the high prevalence of subclinical hypothyroidism often found in this condition [32]. All categories of HPT axis dysfunctions have been reported in rapid cycling bipolar patients, like overt hypothyroidism [33], elevated TSH levels [34], exaggerated TSH responses to TRH [35], elevated antibody titres [36], and antidepressant-induced rapid cycling [37], although a number of studies have been unable to document this association [38, 39]. Methodological problems such as retrospective designs, lack of controls, predominance of female subjects, and varying definitions of hypothyroidism have all hindered any consistent conclusions from these data [40]. Hypothyroidism in the course of bipolar disorder is a risk factor for the development of rapid cycling bipolar disorder and a relative thyroid hormone deficiency in bipolar disorder patients predisposes to rapid cycling course. Moreover, in many cases, thyroid abnormalities reveal shortly after the start of lithium treatment [41].

DOI 10.26386/obrela.v1i2.46 ISSN 2585-2795

Lithium in affective disorders

Lithium is the lightest alkali metal and a monovalent cation. Lithium shares some properties with sodium, potassium, and calcium. Substitution or competition with other cations may contribute to its effects and many other factors may influence lithium levels. Lithium displaces magnesium ions and inhibits at least 10 cellular targets, all of which are components of intracellular signalling pathways. Lithium reduces 5-HT_2 receptor function in mouse [42] and in humans [43], and this may be linked to lithium's antidepressant action. This action seem to be mediated by the prefrontal cortex [44], which is believed to be the target of lithium in the treatment of bipolar disorder [45]. In general, lithium affects cell function via its inhibitory action on adenosine triphosphatase (ATPase) activity, cyclic adenosine monophosphate (cAMP), and intracellular enzymes. The inhibitory effect of lithium on inositol phospholipid metabolism affects signal transduction and may account for part of the action of the cation in manic depression. Lithium also alters the in vitro response of cultured cells to thyrotropin-releasing hormone (TRH) and can stimulate DNA synthesis. Based in the indications that both mania and bipolar depression are characterized by elevations of intracellular sodium concentrations, Huang et al (2007) [46] suggested that lithium can normalize abnormally elevated intracellular sodium levels and this may be an important mechanism of lithium action. Reduction of sodium influx is a proposed shared mechanism of action of effective mood stabilizers, but direct documentation of this effect for lithium has never been demonstrated [47].

Multiple interactions and overlapping systems are involved in regulating mood and the chronic administration of therapeutic doses of lithium affects the function of second messenger generating systems [48]. The initial studies of molecular targets for lithium action were based on the assumption that this simple cation can interfere with transporting systems for sodium and potassium in the plasma membranes of neurons and alter the propagation of electrical signals, while some studies indicated that the lithium inhibition of the counter-transport mechanism may be significant clinically and relevant to the lithium therapeutic action [49]. Alterations in neurotransmitter systems, such as noradrenaline, dopamine, glutamate, and serotonin have been noted in patient brains, as well as in animal models. These are closely connected with changes in corresponding signalling systems in membranes, the activities of the enzymes involved and the production of second messengers. In fact, lithium has been found to alter the brain cAMP level, cAMP-mediated processes in the CNS, and fluoride stimulated adenylyl cyclase activity [50]. In addition, the allosteric modulation of some proteins including G proteins has been suggested as the mechanism of the long-term prophylactic efficacy of lithium [48].

The theory that lithium ions might exert their therapeutically relevant effect at the site of the inositol-lipid signalling pathway has been widely discussed. The hypothesis has been postulated that the stimulated turnover of phosphatidylinositol-4,5-bisphosphate (PIP_2) reflects the increased receptor activation in pathogenic neurons. Berridge et al (1989) [51], suggested the "inositol depletion hypothesis", based on a presumption that in parts of the brain where receptors are overstimulated and PIP_2 hydrolysis thus occurs, lithium inhibits the dephosphorylation of inositol-1-phosphatase. Lithium has been shown to decrease the level of neuronal inositol through the inhibition of inositol monophosphatase (IMPase), which converts myo-inositol monophosphates to myo-inositol, to reconstitute the membrane phospholipids, PIP_2 pool. Eventually, the latter generates the Ca^{2+}-mobilizing second messenger D-myo-Inositol-1,4,5-trisphosphate ($InsP_3$) and diacylglycerol (DAG). The lithium-induced inositol depletion, and the consequent disturbance of the Ca^{2+} signaling operation, showed to affect the behavior of neurons in culture, impairing neurotransmission and altering growth cone and the cytoskeleton [51, 52].

Mood stabilizers lithium and valproic acid, used for treating bipolar disorder, cause cellular inositol depletion, which has been proposed as a therapeutic mechanism of action of both

DOI 10.26386/obrela.v1i2.46 ISSN 2585-2795

drugs. As glycogen synthase kinase-3α (GSK-3α) inhibition has been proposed as a likely therapeutic mechanism of action, the finding that inhibition of inositol synthesis results in the inactivation of GSK-3α suggests a unifying hypothesis for mechanism of mood-stabilizing drugs. Inositol is an essential metabolite that serves as a precursor for inositol lipids and inositol phosphates. Ye & Greenberg (2015) [53] reported that inhibition of the rate-limiting enzyme of inositol synthesis leads to the inactivation of GSK-3α by increasing inhibitory phosphorylation of this kinase. These findings have implications for the therapeutic mechanisms of mood stabilizers and suggest that inositol synthesis and GSK 3α activity are intrinsically related. Lithium also affects some enzymes involved in energy metabolism, such as hexokinase, pyruvate kinase, cholinesterase, tryptophan hydroxylase, and glycogen synthetase [54]. Plenge (1985) [55] proposed the theory that lithium inhibits enzymes which have essential cofactor cations, such as Na+, K+, Ca2+, Mg2+, and Zn2+ by displacement of these cations from the enzyme. Lithium moves into the site vacated by the Mg2+ and the resulting enzyme-phosphate-lithium complex is very stable and in this conformation it cannot hydrolyse a further substrate molecule. Lithium competes for a magnesium binding site in inositol polyphosphate 1-phosphatase, glycogen synthase kinase-3, fructose 1,6-bisphosphatase, bisphosphate nucleotidase, and phosphoglucomutase [56].

Lithium and thyroid axis

Lithium treatment seems to contribute to the development of hypothyroidism among patients with rapid cycling [4]. Low or normal T4 levels and elevated TSH levels are reported among 5 to 35% (average of about 25%) patients on lithium [57]. The investigators hypothesized that rapid cycling bipolar disorder is associated with a latent hypofunction of the HPT system, which becomes manifest even with short-term lithium challenge. A latent hypofunction of the thyroid axis in rapid cycling bipolar disorder may also explain why high doses of T4 added to the established treatment with lithium and other psychotropic drugs can reverse the rapid cycling pattern [11]. Gyulai et al. (2003) [4] found that patients with rapid cycling did not differ from controls on any of thyroid function tests prior to treatment with lithium, but after 4 weeks of lithium-treatment, exaggerated TSH responses to TRH were significantly more common among such patients. The authors proposed that rapid cycling is associated with a latent hypofunction of the HPT system, which becomes manifest with lithium treatment. Given lithium's antithyroid actions, it is not surprising that an exaggerated TSH response to TRH stimulation is extremely common and has been reported in 50–100% of lithium-treated patients [58]. In addition, evidence of overt or subclinical hypothyroidism, including raised antibody titres, has often been found among patients with bipolar disorder, prior to treatment with lithium [59]. In summary, it appears that at least in a subgroup of patients with bipolar disorder, treatment with lithium, rather than inducing hypothyroidism, actually exacerbates a preexisting (overt) HPT dysfunction [15].

Lithium and thyroid antibodies

Disturbances of the immune system may be important for the pathogenesis of bipolar disorder. This was reflected as an increased incidence of thyroid antibodies (anti-TPO) in patients with bipolar disorder, compared with the control population [59]. Studies are similarly inconsistent as to whether thyroid antibodies are elevated in bipolar disorder, unrelated to lithium-treatment; reported rates range from 0 to 43% among patients with bipolar disorder not on lithium. Some controlled comparisons have reported a higher prevalence of thyroid antibodies in bipolar disorder, especially in depressed and mixed states [60], and rapid cycling bipolar patients [36]. Kupka et al (2002) [59] found thyroperoxidase antibodies in 64 of 226 (28%) outpatients with bipolar disorder, a rate higher than general population subjects and patients with other psychiatric disorders, while the presence of anti-thyroid antibodies among patients with bipolar disorder was associated with thyroid failure, but not with age, gender, mood state, rapid cycling, or lithium exposure.

DOI 10.26386/obrela.v1i2.46 ISSN 2585-2795

However, other controlled studies have not been able to find a higher prevalence of raised antibody tires in bipolar disorder, unrelated to lithium treatment, and the authors 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 [60, 61, 62]. Significantly higher titers of anti-TPO has been found in daughters of parents with bipolar disorder, 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 [47, 63]. Finally, several studies of patients on lithium have found an elevated rate of anti-thyroid antibodies, ranging from about 8 to 49% in such patients; these rates were significantly higher than those among control patients or the general population [64]. However, an almost equal number of studies have failed to find an association between elevated antibody titres and exposure to lithium [65].

Despite some evidence suggesting that the increase in titers of thyroid antibodies could be stimulated by 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 [47].

The lithium anti-thyroid effect

The influence of lithium on the thyroid gland is one of the most important side-effect of long-term therapy with this drug. The anti-thyroid effects of lithium carbonate are well documented [58, 66] and include goitre, hypothyroidism, hyperthyroidism and autoimmune thyroiditis. In a meta-analysis of the potential toxicity of long-term use of lithium, it has been found that lithium causes a five-fold increased risk of hypothyroidism [67]. Goiter, due to increased thyrotropin (TSH) after inhibition of thyroid hormone release, occurs at various reported incidence rates and is smooth and nontender. Cross-sectional studies of lithium-induced goitre reveal a prevalence of 0 to 60% [58]. Prevalence estimates are much higher (30–59%) when more sensitive ultrasonographic scans are used to detect increases in thyroid volumes [15]. As already mentioned, lithium therapy is associated with exaggerated response of both TSH and prolactin to TRH in 50%-100% of patients, although basal levels are not usually high. It is probable that the hypothalamic pituitary axis adjusts to a new setting in patients receiving lithium [58]. Subclinical and clinical hypothyroidism due to lithium is associated with circulating anti-thyroid peroxidase (TPO) antibodies but may occur in their absence. Iodine exposure, dietary goitrogens, and immunogenetic background may all contribute to the occurrence of goiter and hypothyroidism during long-term lithium therapy [64].

Rates of *overt hypothyroidism* vary from 0 to 47% (average of about 10%) among patients on long-term treatment with lithium [15, 68]. Differences in study design, definitions of hypothyroidism, age, gender, and geographical origin of patients, are often responsible for such wide variations in rates. Nevertheless, both the incidence and prevalence of overt hypothyroidism is significantly higher among patients on lithium, compared to general population figures [15]. The average duration of lithium therapy before the diagnosis of hypothyroidism is around 18 months, though there are a few reports of hypothyroidism occurring within the first few months of lithium-treatment [68, 69]. Female gender, middle age (>50 years), preexisting autoimmunity, and family history of thyroid diseases are established risk factors for lithium-induced hypothyroidism [70]. An even larger number of patients appear to develop *subclinical hypothyroidism*. Low or normal T4 levels and elevated TSH levels are reported among 5 to 35% (average of about 25%) patients on lithium [57], while exaggerated TSH responses are found among 50%, or more, of such patients. *Hyperthyroidism* in the course of lithium therapy is rare, but occurs more often than in the general popu-

DOI 10.26386/obrela.v1i2.46 ISSN 2585-2795

lation. 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 [71].

Hypothyroidism and clinically and/or ultrasonographically detected goiter are the most prevalent thyroid abnormalities among patients on long term lithium therapy, while lithium induced hyperthyroidism is very infrequent. Lithium affects normal thyroid functioning through multiple mechanisms. Lithium is concentrated by the thyroid and inhibits thyroidal iodine uptake, inhibits iodotyrosine coupling, alters thyroglobulin structure, and inhibits thyroid hormone secretion. 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. At the cellular level, it decreases thyroid hormone synthesis and release. It also decreases peripheral deiodination of tetraiodothyronine (T4) or thyroxine by decreasing the activity of type I 5′ de-iodinase enzyme. Other proposed mechanisms 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 Wnt/ beta-catenin [72]. In addition, lithium increases the propensity to thyroid autoimmunity in susceptible individuals due to its effect of augmenting the activity of B lymphocytes and reducing the ratio of circulating suppressor to cytotoxic T cells [73]. Lithium affects cell function via its inhibitory action on adenosine triphosphatase (ATPase) activity, cyclic adenosine monophosphate (cAMP), and intracellular enzymes. The inhibitory effect of lithium on inositol phospholipid metabolism affects signal transduction and may account for part of the action of the cation in manic depression. Lithium also alters the in vitro response of cultured cells to thyrotropin-releasing hormone (TRH) and can stimulate DNA synthesis [72].

Thyroid hormone replacement therapy

For many years, thyroid hormones have been used for augmentation of antidepressants in treatment-resistant depression both in the course of unipolar and bipolar illness. Debate continues as to whether to use T3, T4, or T3/T4 combination for mood purposes. Results of studies in which triiodothyronine (T3) was added in a dose of 25-50μg/d have showed a significant efficacy of such procedure. Noteworthy is also the effective use of mega-doses of thyroxine (T4), up to 400 μg/d, in refractory depression and in rapid cycling bipolar illness [74]. Among patients with bipolar disorder, supraphysiological doses of T4 have been used to supplement prophylactic efficacy of mood stabilizing treatments and to augment antidepressant treatment in patients with treatment-refractory bipolar depression [75]. The mechanisms underlying successful treatment with adjunctive T4 are as yet unclear. Earlier, it was suggested that adjunctive T4 counteracts the effects of subclinical hypothyroidism on neuronal adaptation [74].

However, contrary to this notion, most patients who responded had normal thyroid functions. This has led to several alternative hypotheses, such as correction of peripheral resistance to thyroid hormones, correction of isolated CNS hypothyroidism, and positive modulation of cathecholaminergic systems by T4, being responsible for this beneficial effect (Bauer et al, 1998, 2005). Bauer et al (2005) [76] found that treatment with supraphysiologic doses of L-T4 decreased relative activity in the subgenual cingulate cortex, thalamus, amygdala, hippocampus, dorsal and ventral striatum, and the cerebellar vermis. The decrease in relative activity in the latter brain regions was significantly correlated with reduction in depression scores. In a recent research, Bauer et al (2016) [77] assessed with PET cerebral glucose metabolism in depressive patients with bipolar disorder, before and after 6 weeks of treatment with levothyroxine (L-T4), and they found activation in the bilateral thalamus, amygdala, hippocampus, dorsal striatum and ventral striatum, and midline cerebellar vermis and subgenual cingulate cortex. The findings provided evidence that administration of supraphysiologic thyroid hormone improves depressive symptoms in

DOI 10.26386/obrela.v1i2.46 ISSN 2585-2795

patients with bipolar disorder by modulating function in components of the anterior limbic network.

In depression, higher baseline concentration of thyroxine (T4) is associated with better effect of antidepressant drugs, and higher concentrations of T3 predisposed to a greater likelihood of recurrence of depression during initial few years of lithium treatment [47]. On the other hand, lower levels of free T4 were associated with a greater number of affective episodes and higher severity of depression during the first year of treatment with lithium. 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 [47, 69, 78]. Current practice guidelines do not specify criteria for managing thyroid replacement therapy in patients with lithium-induced hypothyroidism. Usually the form that is used as a mood stabilizer is T4. By contrast, T3 is usually used as an "add-on" to antidepressants, because some research has shown it can boost the antidepressant's effects. In the presence of elevated TSH levels without clinical signs of hypothyroidism, some authorities advise monitoring serum TSH levels every 3 months without intervening with adjunctive thyroxine, unless TSH levels rise above 10 mU/L. Others advocate thyroid supplementation whenever TSH levels rise above normal, particularly in the presence of affective symptoms. T4 is generally preferred to T3 because the former tends to produce steadier hormone levels. Typically, thyroxine (T4) is begun at .025 mg, and increased by .025 mg every 3 to 6 weeks until TSH levels have normalized. In the presence of rapid cycling or persistent affective symptoms, thyroxine is increased until the serum T4 level is in the upper quartile of the normal reference range. Lithium-induced thyroid dysfunction has occasionally been shown to remain normalized after stopping T4 following 1-2 years of thyroid supplementation. Long-term or indefinite adjunctive treatment with thyroxine carries arrhythmogenic potential, as well as an increased risk for bone demineralization , requiring medical monitoring of patients at risk [79].

Summarizing, 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 (2007) [79] 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, while some other authors suggest levothyroxine prophylaxis in all patients treated with lithium, if they come from iodine-deficient areas [80, 81]. 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 [70]. 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 [57]. 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 [47].

Can we hypothesize that the lithium induced hypothyroidism represents a therapeutic process of lithium therapy in bipolar disorder?

Approximately 10% of bipolar patients, with no evidence of thyroid dysfunction before lithium therapy, had elevated TSH basic values, while in the course of lithium therapy, excessive TSH response to TRH occurs in at least 50% of bipolar patients.

DOI 10.26386/obrela.v1i2.46 ISSN 2585-2795

The disordered thyroid-hypothalamic-pituitary axis seems to be temporary in most patients, which suggests that the axis is adjusting to the new «state» during therapy [47]. In addition, lithium effect on the concentration of antithyroid antibodies leads to a faster autoimmunization of thyroid that can cause goiter and hypothyroidism, but hyperthyroidism is also possible. Baseline thyroid function tests should be measured prior to starting lithium therapy to ensure that undetected hypothyroidism is not contributing to mood symptoms. Pertinent thyroid function tests include TSH and free T4 levels, as well as antiperoxidase and antithyroglobulin in the presence of an elevated TSH. Subsequent monitoring of thyroid function tests is usually conducted 3 months after starting lithium and every 6-12 months thereafter. Lithium-induced hypothyroidism is usually reversible upon cessation of lithium, and the development of hypothyroidism is not a contraindication to continuing lithium, although, some experts advocate thyroid augmentation therapy [47].

The mechanisms by which lithium can cause hypothyroidism are complex. As already analyzed, inhibition of thyroid hormone release, a process mediated by cyclic adenosine monophosphate, appears to be the critical mechanism in the development of lithium-induced hypothyroidism. Also, lithium is concentrated by the thyroid gland and inhibits thyroidal iodine uptake. It also inhibits iodotyrosine coupling, alters thyroglobulin structure, and interferes with the deiodination of T4 to T3 by inhibiting type-II deiodinase in the brain [58]. Lithium may also demonstrate an immunostimulant effect, either by inducing, or by exacerbating a preexisting autoimmune disease. Additionally, lithium alters cellular responsiveness to thyroxine, and influences thyroid hormone receptor gene expression [82]. Deficits in any one, or several, of these mechanisms may result in reduced bioavailability of thyroid hormones at cerebral target regions despite normal peripheral serum levels of thyroid hormones. This condition has been conceptualized as 'central hypothyroidism' [47]. Compensation for this putative 'central hypothyroidism' might be one reason why a proportion of euthyroid depressed patients benefit from administration of supraphysiologic doses of L-T4. Mice suffering from central hypothyroidism caused by a mutation of the *TRα1* gene [83], showed reduced neuronal density, resulting in reduced cortical thickness in the hippocampal CA1 region [84]. Behaviorally, these mice show increases in surrogate animal markers for depression and anxiety, as well as an increased startle response. Both the behavioral and neural density measures normalized with thyroid hormone administration [85]. Compensatory mechanisms may operate to prevent the development of hypothyroidism or goitre in the majority of patients with lithium-induced impairments in thyroxine secretion. However, when additional risk factors such as iodine deficiency, preexisting autoimmunity, or genetic vulnerability are present, such compensatory mechanisms fail and hypothyroidism eventually ensues [15].

At the moment, the fine details of the pharmacological and toxicological mechanisms of the effects of lithium remain poorly understood [50, 86, 87]. Various studies suggest that some harmful effects of lithium could be related to oxidative stress [47, 88], whereas at therapeutic concentration lithium was found to confer protection against toxic stimuli inducing oxidative stress and apoptosis [89, 90, 90, 91]. Even in trace amounts, as occurs in drinking water, lithium has been inversely related to suicidal mortality, aggression and homicidal violence [92, 93, 94]. It has been found also that chronic administration of lithium significantly changes the expression of a number of genes in rat brains [95, 96]. Lithium responders seem to have some genes different from healthy controls and patients with bipolar disorder who respond well to lithium prophylaxis may constitute a biologically distinct subgroup [97, 98, 99].

Rethinking lithium mechanisms of action, and especially lithium positive and side-effects in thyroid gland, may help to enhance our understanding of the thyroid-bipolar disorder connection and to identify those patients with bipolar disorders who are most likely to benefit from therapeutic manipulations of the HPT axis. As mentioned above, the disordered thyroid-hypothalamic-pituitary axis seems to be temporary in most patients, which suggests that the axis is adjusting to

DOI 10.26386/obrela.v1i2.46 ISSN 2585-2795

the new «state» during therapy [47]. Also, the TSH response is usually exaggerated in hypothyroidism and blunted in hyperthyroidism. A blunted TSH response occurs in 25–30% of patients with unipolar major depression, [27], but many patients with bipolar disorder show an exaggerated response of TSH to TRH, along with elevated basal levels of TSH, especially in patients with rapid cycling, a finding consistent with the high prevalence of subclinical hypothyroidism often found in this condition [32]. Hypothyroidism in the course of bipolar disorder is a risk factor for the development of rapid cycling bipolar disorder and a relative thyroid hormone deficiency in bipolar disorder patients predisposes to rapid cycling course, while in many cases, thyroid abnormalities reveal shortly after the start of lithium treatment [41]. Rapid cycling bipolar disorder is associated with a latent hypofunction of the HPT system, which becomes manifest even with short-term lithium challenge. Lithium-treatment exaggerates TSH responses to TRH, which indicate that lithium seems like to push forward these patients in a temporary "more hypo-thyroid" status". It is possible that this lithium induced 'central hypothyroidism', by the reduced bioavailability of thyroid hormones at cerebral target regions, may provoke a secondary activation of the HPT axis, in order the thyroid system to be re-activated and re-arranged.

Finally, T4 added to the established treatment with lithium and other psychotropic drugs can reverse the rapid cycling pattern [11]. Possibly T4 counteracts the effects of subclinical hypothyroidism on neuronal adaptation [74], through the correction of peripheral resistance to thyroid hormones and the correction of isolated CNS hypothyroidism [76]. The dose of T4 should be adjusted allowing not to suppress totally the secretion of TSH, and fT3 and fT4 levels, while lithium-induced thyroid dysfunction has been shown to remain normalized after stopping T4 following 1-2 years of thyroid supplementation. It may occur a hypothalamic pituitary axis "adjustment to a new setting" in patients receiving lithium [58, 100]. It is possible also that lithium effect is synergistic with that of T4, which has been also used as a mood stabilizer. In this frame, lithium induced "hypothyroidism" may help to rearrange and normalize thyroid hormone secretion. It is possible that the lithium induced 'central hypothyroidism' may enhance the HPT axis activation, resulting to the thyroid system re-activation, and to the thyroid hormones' availability and effect re-adaptation. This compensatory process may results to the correction of a possible peripheral resistance to thyroid hormones, as well as to the correction of an isolated CNS hypothyroidism. We can hypothesize that these compensatory mechanisms, which operate to prevent the development of hypothyroidism or goiter, represents a therapeutic process of lithium therapy in bipolar disorder, acting through an adaptive thyroid system resetting.

References

1 Friesema EC, Grueters A, Biebermann H, Krude H, von Moers A, Reeser M et al. Association between mutations in a thyroid hormone transporter and severe X-linked psychomotor retardation. *Lancet* 2004, 364: 1435–1437, , PMID: 15488219, DOI: 10.1016/S0140-6736(04)17226-7

2 Visser TJ. Thyroid hormone transporters. *Horm Res* 2007, 68: 28–30, PMID: 18174701, DOI: 10.1159/000110469

3 Lechan RM, Toni R. Thyroid hormones in neural tissue. In: Pfaff DW, Arnold AP, Etgen AM, Fahrbach SE, Rubin RT. *Hormones, Brain and Behavior*. Academic Press: San Diego, 2002, pp 157–238.

4 Gyulai L, Bauer M, Bauer MS, García-España F, Cnaan A, Whybrow PC. Thyroid hypofunction in patients with rapid-cycling bipolar disorder after lithium challenge. *Biological Psychiatry* 2003, 53(10):899–905, PMID: 12742677

5 Hiroi Y, Kim HH, Ying H, Furuya F, Huang Z, Simoncini T et al. Rapid nongenomic actions of thyroid hormone. *Proc Natl Acad Sci USA* 2006, 103: 14104–14109, PMID: 16966610 PMCID: PMC1599919, DOI: 10.1073/pnas.0601600103

6 Williams GR. Neurodevelopmental and neurophysiological actions of thyroid hormone. J Neuroendocrinol 2008; 20: 784–794, PMID: 18601701 , DOI: 10.1111/j.1365-2826.2008.01733.x

7 Chang KD, Keck PE, Stanton SP, McElroy SL, Strakowski SM, Geracioti TD. Differences in thyroid function between bipolar manic and mixed states. *Biological Psychiatry* 1998, 43(10):730–733, PMID: 9606526

8 Whybrow Peter C., Prange Jr Arthur J., A Hypothesis of Thyroid-Catecholamine-Receptor InteractionIts Relevance to Affective Illness. *Arch Gen Psychiatry* 1981, 38(1):106-113, PMID: 6257196

9 Yen PM, Brent GA. Genomic and nongenomic actions of thyroid hormones. In: Braverman LE, Cooper DS (eds) Werner & Ingbar's *The Thyroid. A Fundamental and Clinical Text*, Williams & Wilkins: Philadelphia, 2013 p 127–138.

DOI 10.26386/obrela.v1i2.46 ISSN 2585-2795

10 Chakrabarti S. Thyroid Functions and Bipolar Affective Disorder, *J Thyroid Res* 2011, 2011**:** 306-367, PMID: 21808723 PMCID: PMC3144691 , DOI: 10.4061/2011/306367

11 Bauer M, Goetz T, Glenn T, Whybrow PC. The thyroid-brain interaction in thyroid disorders and mood disorders. *Journal of Neuroendocrinology* 2008, 20(10):1101–1114, PMID: 18673409 , DOI: 10.1111/j.1365-2826.2008.01774.x

12 Bunevičius R, Prange AJ. Thyroid disease and mental disorders: cause and effect or only comorbidity? *Current Opinion in Psychiatry* 2010, 23(4):363–368, doi: 10.1097/YCO.0b013e3283387b50

13 Stowell CP, Barnhill JW. Acute mania in the setting of severe hypothyroidism. *Psychosomatics* 2005, 46(3):259–261. PMID: 15883148, DOI: 10.1176/appi.psy.46.3.259

14 Ezzaher A, Neffati F, Mechri A, Douki W, Gaha L, Najjar MF. Evaluation of thyroid function in bipolar patients. *Clinical Chemistry and Laboratory Medicine* 2009, 47(S1, article S371)

15 Bocchetta A, Loviselli A. Lithium treatment and thyroid abnormalities. *Clinical Practice and Epidemiology in Mental Health* 2006, 2, article 23, PMID: 16968542 , PMCID: PMC1584230 , DOI: 10.1186/1745-0179-2-23

16 Carmaciu CD, Anderson CS, Lawton CA. Thyrotoxicosis after complete or partial lithium withdrawal in two patients with bipolar affective disorder. *Bipolar Disorders* 2003, 5(5):381–384. PMID: 14525561

17 Cassidy F, Ahearn EP, Carroll BJ. Thyroid function in mixed and pure manic episodes. *Bipolar Disorders,* 2002;4(6):393–397, PMID: 12519099

18 Rot MAH, Mathew SJ, Charney DS. Neurobiological mechanisms in major depressive disorder. *CMAJ* 2009, 180(3):305–313. PMID: 19188629, PMCID: PMC2630359, DOI: 10.1503/cmaj.080697

19 Diehl DJ, Gershon S. The role of dopamine in mood disorders. *Comprehensive Psychiatry* 1992, 33(2):115–120.

20 Brambilla P, Perez J, Barale F, Schettini G, Soares JC. GABAergic dysfunction in mood disorders. *Molecular Psychiatry* 2003, 8(8):721–737, PMID: 12888801 , DOI: 10.1038/sj.mp.4001362

21 Bauer M, Heinz A, Whybrow PC. Thyroid hormones, serotonin and mood: of synergy and significance in the adult brain. *Molecular Psychiatry* 2002, 7(2):140–156. PMID: 11840307, DOI: 10.1038/sj.mp.4000963.

22 Abrahamson MJ, Millar RP. Regulation of thyrotrophin secretion. *South African Medical Journal* 1986, 70(8):476–478.

23 Mason GA, Garbutt JC, Prange AJ., Jr. Thyrotropin-releasing hormone. Focus on basic neurobiology. In: Bloom FE, Kupfer DJ, (ed). *Psychopharmacology: The Fourth Generation of Progress*. New York, NY, USA: Raven Press; 1995. pp. 493–503.

24 Strawn JR, Ekhator NN, D'Souza BB, Geracioti TD. Pituitary-thyroid state correlates with central dopaminergic and serotonergic activity in healthy humans. *Neuropsychobiology* 2004, 49(2):84–87. doi.org/10.1159/000076415

25 Rybakowski J, Sowiński J. Free-thyroxine index and absolute free-thyroxine in affective disorders. *Lancet* 1973, 7808: 889, PMID: 4123441

26 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, PMID: 23051081 DOI: 10.1016/j.ajp.2011.02.002

27 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.

28 Rush AJ, Giles DE, Schlesser MA, et al. Dexamethasone response, thyrotropin-releasing hormone stimulation, rapid eye movement latency, and subtypes of depression. *Biological Psychiatry* 1997, 41(9):915–928.

29 Sack DA, James SP, Rosenthal NE, Wehr TA. Deficient nocturnal surge of TSH secretion during sleep and sleep deprivation in rapid-cycling bipolar illness. *Psychiatry Research* 1988, 23(2):179–191.

30 Larsen JK, Faber J, Christensen EM, Bendsen BB, Solstad K, Gjerris A. Relationship between mood and TSH response to TRH stimulation in bipolar affective disorder. *Psychoneuroendocrinology* 2004, 29: 917–924. PMID: 15177707, DOI: 10.1016/j.psyneuen.2003.08.004

31 Kirkegaard C, Faber J. The role of thyroid hormones in depression. *European Journal of Endocrinology* 1998, 138(1):1–9.

32 Hendrick V, Altshuler L, Whybrow P. Psychoneuroendocrinology of mood disorders: the hypothalamic-pituitary- thyroid axis. *Psychiatric Clinics of North America* 1998, 21(2):277–292.

33 Khouzam HR, Bhat VG, Boyer J, Hardy W. Rapid cycling in a patient with bipolar mood disorder secondary to Graves' disease. *American Journal of Psychiatry* 1991, 148(9):1272–1273.

34 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.

35 Kusalic M. Grade II and grade III hypothyroidism in Rapid-Cycling bipolar patients. *Neuropsychobiology* 1992, 25(4):177–181.

36 Oomen HAPC, Schipperijn AJM, Drexhage HA. The prevalence of affective disorder and in particular of a rapid cycling of bipolar disorder in patients with abnormal thyroid function tests. *Clinical Endocrinology* 1996, 45(2):215–223.

37 Kiriike N, Izumiya Y, Nishiwaki S, Maeda Y, Nagata T, Kawakita Y. TRH test and DST in schizoaffective mania, mania, and schizophrenia. *Biological Psychiatry* 1988, 24(4):415–422.

38 Maj M, Magliano L, Pirozzi R, Marasco C, Guarneri M. Validity of rapid cy-

DOI 10.26386/obrela.v1i2.46 ISSN 2585-2795

cling as a course specifier for bipolar disorder. *American Journal of Psychiatry* 1994,151(7):1015–1019.

39 Post RM, Kramlinger KG, Joffe RT, et al. Rapid cycling bipolar affective disorder: lack of relation to hypothyroidism. *Psychiatry Research* 1997,72(1):1–7.

40 Bernal J. Action of thyroid hormone in brain. *J Endocrinol Invest* 2002, 25: 268–288, PMID: 11936472 , DOI: 10.1007/BF03344003

41 Cole DP, Thase ME, Mallinger AG, Soares JC, Luther JF, Kupfer DJ. Slower treatment response in bipolar depression predicted by lower pretreatment thyroid function. *Am. J. Psychiatry* 2002, 159: 116–121. PMID: 11772699, DOI: 10.1176/appi.ajp.159.1.116

42 Goodwin GM, DeSouza RJ, Wood AJ, Green AR. Lithium decreases 5-HT1A and 5-HT2 receptor and α2-adrenoreceptor mediated function in mice. *Psychopharmacology* 1986, 90:482–487.

43 Friston KJ, Sharpley AL, Solomon RA, Cowen PJ. Lithium increases slow wave sleep: possible mediation by brain 5-HT2 receptors? *Psychopharmacology (Berl.)* 1989, 98:139–140.

44 González-Maeso J, et al. Hallucinogens recruit specific cortical 5-HT(2A) receptor-mediated signaling pathways to affect behavior. *Neuron* 2007, 53:439–452, PMID: 17270739, DOI: 10.1016/j.neuron.2007.01.008

45 Schloesser RJ, Martinowich K, Manji HK. Mood-stabilizing drugs: mechanisms of action. *Trends Neurosci* 2012, 35:36–46, PMID: 22217451 , DOI: 10.1016/j.tins.2011.11.009

46 Huang X, Lei Z, El-Mallakh RS. Lithium normalizes elevated intracellular sodium. *Bipolar Disord* 2007, 9(3):298-300. PMID: 17430305, DOI: 10.1111/j.1399-5618.2007.00429.x

47 Kraszewska A, Abramowicz M, Chłopocka-Woźniak M, Sowiński J, Rybakowski J. The effect of lithium on thyroid function in patients with bipolar disorder. *Psychiatr. Pol* 2014, 48(3): 417–428, PMID: 25204089.

48 Manji H.K., Potter W.Z., Lenox R.H.: Signal transduction pathways. Molecular targets for lithium actions. *Arch. Gen. Psychiatry* 1995, 52: 531-543,

49 Gallicchio V.S.: Transport of the lithium ion. In: Bach R.O. and V.C. Gallicchio (eds.): *Lithium and cell physiology*. Springer Verlag 1990, pp. 47-57.

50 Shaldubina, A., Agam, G. & Belmaker, R. H. *The mechanism of lithium action: state of the art, ten years later. Prog. Neuropsychopharmacol. Biol. Psychiatry* 2001, 25: 855–866, PMID: 11383981

51 Berridge, M. J. *Inositol trisphosphate, calcium, lithium, and cell signalling. J. Am. Med. Asso*, 1989, 262: 1834–1841, PMID: 2674489

52 Williams, R. et al. *A molecular cell biology of lithium. Biochem. Soc. Trans* 2004, 32: 799–802, PMID: 15494019 , DOI: 10.1042/BST0320799

53 Ye C, Greenberg ML. Inositol synthesis regulates the activation of GSK-3α in neuronal cells. *J Neurochem* 2015, 33(2):273-83. doi: 10.1111/jnc.12978.

54 Geisler A. and Mork A.: The interaction of lithium with magnesium-dependent enzymes. In: In: Bach R.O. and Gallicchio V.C. (eds.): *Lithium and Cell Physiology*. Springer Verlag 1990, pp.125-136.

55 Plenge P.: Lithium effects on brain energy metabolism. In: Gabay S., J. Harris, B.T. Ho (eds.): *Metal Ions in Neurology and Psychiatry,* Alan R. Liss, Inc. New York 1985, pp. 153-164.

56 Gould T.D., Zarate C.A., Manji H.K.: Glycogen synthase kinase-3: a target for novel bipolar disorder treatments. *J. Clin. Psychiatry* 2004, 65: 10-21. PMID: 14744163.

57 Kleiner J, Altshuler L, Hendrick V, Hershman JM. Lithium-induced subclinical hypothyroidism: review of the literature and guidelines for treatment. *Journal of Clinical Psychiatry* 1999, 60(4):249–255. PMID: 10221287

58 Lazarus JH. The effects of lithium therapy on thyroid and thyrotropin-releasing hormone. *Thyroid* 1998, 8(10):909-13, PMID: 9827658 , DOI: 10.1089/thy.1998.8.909

59 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. PMID: 11958781

60 Haggerty JJ, Jr., Silva SG, Marquardt M, et al. Prevalence of antithyroid antibodies in mood disorders. *Depression and Anxiety* 1997, 5(2):91–96], PMID: 9262939

61 Hornig M, Amsterdam JD, Kamoun M, Goodman DBP. Autoantibody disturbances in affective disorders: a function of age and gender? *Journal of Affective Disorders* 1999, 55(1):29–37.

62 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. PMID: 17141745, DOI: 10.1016/j.biopsych.2006.08.041

63 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.

64 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. *Human Psychopharmacology* 2010, 25(2):174–178. PMID: 20196184 , DOI: 10.1002/hup.1093

65 Baethge C, Blumentritt H, Berghöfer A, et al. Long-term lithium treatment and thyroid antibodies: a controlled study. *Journal of Psychiatry and Neuroscience* 2005, 30(6):423–427, PMID: 16327876, PMCID: PMC1277025

66 Livingstone C, Rampes H. Lithium: a review of its metabolic adverse effects. J. *Psychopharmacol* 2006, 20: 347–355, PMID: 16174674 , DOI: 10.1177/0269881105057515

DOI 10.26386/obrela.v1i2.46 ISSN 2585-2795

67 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, PMID: 22265699 , DOI: 10.1016/S0140-6736(11)61516-X

68 Johnston AM, Eagles JM. Lithium-associated clinical hypothyroidism. Prevalence and risk factors. *British Journal of Psychiatry* 1999, 175:336–339.] , PMID: 10789300

69 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. PMID: 10588404, DOI: 10.1176/ajp.156.12.1909

70 Ozpoyraz N, Tamam L, Kulan E. Thyroid abnormalities in lithium-treated patients. *Advances in Therapy* 2002, 19(4):176–184, PMID: 12431043

71 Lazarus J, Richards A, Adison G, Owen G. Treatment of thyrotoxicosis with lithium carbonate. *Lancet* 1974, 2: 1160–168, PMID: 4139588

72 Lazarus JH, Kirov G, Harris B. Effect of lithium on thyroid and endocrine glands. In : Bauer M, Grof P, Müller-Oerlinghausen B. *Lithium in neuropsychiatry.* Oxfordshire: Informa Healthcare, 2006. s. 259–270.

73 Kibirige D, Luzinda K, Ssekitoleko R. Spectrum of lithium induced thyroid abnormalities: a current perspective. *Thyroid Res* 2013, 6(1):3., PMID: 23391071, PMCID: PMC3568739 , DOI: 10.1186/1756-6614-6-3

74 Bauer M, Whybrow PC. Thyroid hormone, brain, and behaviour. In: Pfaff DW, Arnold AP, Etgen AM, Fahrbach SE, Rubin RT, editors. *Hormones, Brain and Behavior*. New York, NY, USA: Academic Press; 2002. pp. 238–264.

75 Kelly T, Lieberman DZ. The use of triiodothyronine as an augmentation agent in treatment-resistant bipolar II and bipolar disorder NOS. *Journal of Affective Disorders* 2009, 116(3):222–226, PMID: 19215985 , DOI: 10.1016/j.jad.2008.12.010

76 Bauer M, London ED, Rasgon N, et al. Supraphysiological doses of levothyroxine alter regional cerebral metabolism and improve mood in bipolar depression. *Molecular Psychiatry* 2005, 10(5):456–469, PMID: 15724143 , DOI: 10.1038/sj.mp.4001647

77 Bauer M, Berman S, Stamm T, Plotkin M, Adli M, Pilhatsch M, London ED, Hellemann GS, Whybrow PC and Schlagenhauf F. Levothyroxine effects on depressive symptoms and limbic glucose metabolism in bipolar disorder: a randomized, placebo-controlled positron emission tomography study. *Molecular Psychiatry* 2016, 21: 229–236;. PMID: 25600111, PMCID: PMC4790155 , DOI: 10.1038/mp.2014.186

78 Frye MA, Yatham L, Ketter TA, Goldberg J, Suppes T, Calabrese JR. Depressive relapse during lithium treatment associated with increased serum thyroid-stimulating hormone: results from two placebo-controlled bipolar maintenance studies. *Acta Psychiatr. Scand.* 2009, 120: 10–13. PMID: 19183414, DOI: 10.1111/j.1600-0447.2008.01343.x

79 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. DOI: 10.1016/j.jad.2007.01.033

80 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, PMID: 6818894

81 Hegedüs L, Bonnema SJ, Bennedbaek FN. Management of simple nodular goiter: current status and future perspectives. *Endocr. Rev*. 2003, 24: 102–132, PMID: 12588812, DOI: 10.1210/er.2002-0016

82 Hahn CG, Pawlyk AC, Whybrow PC, Tejani-Butt SM. Differential expression of thyroid hormone receptor isoforms by thyroid hormone and lithium in rat GH3 and B103 cells. *Biological Psychiatry* 1999, 45(8):1004–1012, PMID: 10386183

83 Venero C, Guadano-Ferraz A, Herrero AI, Nordstrom K, Manzano J, de Escobar GM et al. Anxiety, memory impairment, and locomotor dysfunction caused by a mutant thyroid hormone receptor alpha1 can be ameliorated by T3 treatment. *Genes Dev* 2005, 19: 2152–2163.

84 Alva-Sanchez C, Ortiz-Butron R, Pacheco-Rosado J. Kainic acid does not affect CA3 hippocampal region pyramidal cells in hypothyroid rats. *Brain Res Bull* 2004, 63: 167–171. DOI: 10.1016/j.brainresbull.2004.02.002

85 Pilhatsch M, Winter C, Nordstrom K, Vennstrom B, Bauer M, Juckel G. Increased depressive behaviour in mice harboring the mutant thyroid hormone receptor alpha 1. *Behav Brain Res* 2010; 214: 187–192, PMID: 20580649 , DOI: 10.1016/j.bbr.2010.05.016

86 Hill, E. J. et al. *Effects of lithium and valproic acid on gene expression and phenotypic markers in an NT2 neurosphere model of neural development*. *PLoS One* 2013, 8, e58822 , doi: 10.1371/journal.pone.0058822.

87 Ruocco N, Costantini M, Santella L New insights into negative effects of lithium on sea urchin *Paracentrotus lividus* embryos, *Scientific Reports* 2016, 6: 32157, PMID: 27562248 , PMCID: PMC4999890 , DOI: 10.1038/srep32157

88 Efrati, S. et al. *N-Acetylcysteine ameliorates lithium-induced renal failure in rats. Nephrol. Dial. Transplant*. 2005, 20: 65–70, PMID: 15546888, DOI: 10.1093/ndt/gfh573

89 Chalecka-Franaszek, E. & Chuang, D. M. *Lithium activates the serine/threonine kinase Akt-1 and suppresses glutamate-induced inhibition of Akt-1 activity in neurons*. *Proc. Natl. Acad. Sci. USA* 1999, 96: 8745–8750. PMID: 10411946 PMCID: PMC17587

90 Lai, J. S., Zhao, C., Warsh, J. J. & Li, P. P. *Cytoprotection by lithium and valproate varies between cell types and cellular stresses*. *Eur. J. Pharmacol*. 2006, 539: 18–26. PMID: 16678157 , DOI: 10.1016/j.ejphar.2006.03.076

91 Shao, L., Young, L. T. & Wang, J. F. *Chronic treatment with mood stabilizers lithium and valproate prevents excitotoxicity by inhibiting oxidative stress in rat cerebral cortical cells*. *Biol. Psychiatry* 2005, 58: 879–884. PMID: 16005436, DOI: 10.1016/j.biopsych.2005.04.052

92 Giotakos O, Nisianakis P, Tsouvelas G, Giakalou VV. Lithium in the public

DOI 10.26386/obrela.v1i2.46 ISSN 2585-2795

water supply and suicide mortality in Greece. *Biol Trace Elem Res* 2013, 56(1-3):376-9. doi: 10.1007/s12011-013-9815-4. PMID: 24072668 DOI: 10.1007/s12011-013-9815-4

93 Giotakos O, Tsouvelas G, Nisianakis P, Giakalou V, Lavdas A, Tsiamitas C, Panagiotis K, Kontaxakis V. A negative association between lithium in drinking water and the incidences of homicides, in Greece. *Biol Trace Elem Res* 2015, 164(2):165-8. doi: 10.1007/s12011-014-0210-6. PMID: 25556933, DOI: 10.1007/s12011-014-0210-6

94 Giotakos O. Lithium: Implications for Neuropsychiatry and Wellness. *Int J Ment Health Psychiatry* 2016, 2: 6, 1-10. *doi: 10.4172/2471-4372.1000136*

95 Manji H.K. and Lenox R.H.: Long-term action of lithium: a role for transcriptional and posttranscriptional factors regulated by protein kinase C. *Synapse* 1994, 16: 11-28. PMID: 8134897 , DOI: 10.1002/syn.890160103

96 Lenox R. and Wang H.L.E.: molecular basis of lithium action: Integration of lithium- responsive signaling and gene expression networks. *Molec. Psychiatry* 2003, 8: 135-144. PMID: 12610644, DOI: 10.1038/sj.mp.4001306

97 Grof P., Alda M., Grof E., Zvolsky P., Walsh M.: Lithium response and genetics od affective disorders. *J. Affect. Disord*. 1994, 32: 85-95. PMID: 7829768

98 Alda M., Grof P., Grof E. et al.: Mode of inheritance in families of patients with lithiumresponsive affective disorders. Acta Psychiatr. Scand. 1994, 90: 304-310,. PMID: 7832003

99 Passmore M.J., Garnham J., Duffy A. et al.: Phenotypic spectra of bipolar disorder in responders to lithium versus lamotrigine. *Bipolar Disord* 2003, 5: 110-114. PMID: 12680900

100 Lazarus JH. Lithium and thyroid. *Best Practice and Research: Clinical Endocrinology and Metabolism* 2009, 23(6):723–733. PMID: 19942149 , DOI: 10.1016/j.beem.2009.06.002