Psychiatr. Pol. 2020; 54(6): 1047–1066
PL ISSN 0033-2674 (PRINT), ISSN 2391-5854 (ONLINE)
www.psychiatriapolska.pl
DOI: https://doi.org/10.12740/PP/128340

Lithium treatment – the state of the art for 2020

Janusz Rybakowski

Department of Adult Psychiatry, Poznań University of Medical Sciences

Summary

The paper presents the current state of knowledge on lithium treatment. The history of the therapeutic application of lithium began in 1859 and its introduction to modern psychiatry took place 90 years later. Since the early 1960s, lithium became a precursor of mood-stabilizing drugs and nowadays is the drug of choice for the prevention of manic and depressive recurrences in mood disorders. It remains a valuable drug for the treatment of acute episodes of mania and depression, especially for the augmentation of antidepressant drugs in treatment-resistant depression. The factors of prophylactic efficacy of lithium in the context of the so-called excellent lithium responders and the efficacy in affective episodes were discussed. Among mood-stabilizing drugs, lithium exerts the biggest effect on preventing suicidal behaviors. It also shows antiviral (mainly against herpes viruses) and immunomodulatory activity. The evidence has recently been gathered on neuroprotective and 'antidementia' properties of lithium, which prompted its use in neurodegenerative disorders. The biochemical mechanism of lithium is associated mainly with the inhibition of glycogen synthase kinase-3 and an effect on intracellular signaling. The recommendations for managing lithium-induced adverse effects both in the early and late period of treatment as well as for lithium use in pregnancy and perinatal period were given. The necessity of overcoming negative perceptions of lithium was pointed out to increase the number of possible beneficiaries of lithium treatment. Both introduction of lithium into modern psychiatry and its therapeutic effects have been reflected in literature and art.

Key words: lithium

Historical introduction

The medical application of lithium began in 1859, when an English physician, Alfred Baring Garrod (1819-1907), introduced lithium carbonate for the treatment of gout [1]. In 1871, an American neurologist, William Alexander Hammond (1828-1900), used lithium bromide for the treatment of mania [2], whereas in 1886, a Danish physician and scientist, Carl Lange (1834-1900), relying on the "uric acid diathesis" theory of depression, reported on his positive experiences with lithium carbonate in the treatment and prophylaxis of recurrent depression [3].

The year 1949 is regarded as the date of introducing lithium into modern psychiatry, when an Australian psychiatrist, John Frederick Cade (1912-1980), described the efficacy of lithium carbonate in the treatment of mania [4]. In the early 1960s, publications appeared pointing to the possibility of lithium preventing recurrences of mood disorders. Their authors were a British psychiatrist, Geoffrey Hartigan (1917-1968) [5], and a Danish psychiatrist, Poul Christian Baastrup (1918-2002) [6]. In the 1970s, the therapeutic activity of lithium in depressive episodes was demonstrated [7], while in the early 1980s, the augmentation of the efficacy of antidepressants by lithium was shown [8].

In this paper, the current status of knowledge on lithium treatment is presented, following 161 years after introducing lithium to medical therapy and 71 years of its use in modern psychiatry. A detailed account of this topic was also recently discussed in the book "Lithium – the amazing drug in psychiatry" [9].

The prevention of recurrences in mood disorders

The main indication of using lithium nowadays is the prevention of manic and depressive recurrences in mood disorders. The preventive effect of lithium on affective recurrences is termed as mood-stabilizing. Lithium is a precursor of mood-stabilizing drugs and belongs to the first generation of these drugs (together with valproate and carbamazepine), introduced in the 1960s/70s. The second generation was initiated in 1995, after demonstrating mood-stabilizing properties of clozapine [10], followed by olanzapine, quetiapine, lamotrigine, aripiprazole, and risperidone [11, 12].

My experiences with assessing lithium prophylactic efficacy date back to 1980, when the evaluation of 61 patients with bipolar disorder (BD) receiving lithium for an average five years was published in "Psychiatria Polska". It was shown that during lithium administration compared with the identical period before lithium initiation, the number of recurrences was reduced by 71%, and that of hospitalizations – by 72%. In 44% of patients, no recurrences were observed during lithium treatment [13]. In the 21st century, the prophylactic effectiveness of lithium was amply demonstrated in three meta-analyses. They showed that lithium was significantly better than placebo for the prevention of all kinds of recurrences and manic episode recurrences, and in the majority of studies also for the prevention of depressive episodes [14-16].

The main projects comparing lithium with the 1st generation mood-stabilizing drugs are the MAP (***M****ulticenter study of long-term treatment of* ***A****ffective or schizoaffective* ***P****sychoses*), and the BALANCE (***B****ipolar Affective disorder* ***L****ithium/* ***AN****ti****C****onvulsant* ***E****valuation*). In the former, the prophylactic efficacy of lithium and carbamazepine was assessed for a period of 2.5 years. It was shown that lithium was more efficacious in the classic forms of BD, while carbamazepine performed better in the atypical forms (among others, with psychiatric comorbidity and mood-incongruent delusions) [17]. In the BALANCE study, the prophylactic efficacy of valproate monotherapy, lithium monotherapy, and a combination of the two drugs was evaluated for a period of two years. It was found that lithium monotherapy resulted in a better prophylactic effect than valproate monotherapy, and the best prophylactic efficacy was achieved with the combination treatment [18].

A comparison of lithium with the 2nd generation mood-stabilizers was performed for lamotrigine and quetiapine. In the first study, comparing lithium and lamotrigine for 1.5 years, it was shown that the prophylactic potential of either drug was significantly greater than the placebo, and that lithium was significantly better than lamotrigine in the prevention of mania while lamotrigine outperformed lithium in the prevention of depression [19]. In the CHOICE project (*The **C**linical and **H**ealth **O**utcomes **I**nitiative in **C**omparative **E**ffectiveness for Bipolar Disorder*) assessing lithium and quetiapine for a period of six months, no differences between drugs were found for the therapeutic and prophylactic efficacy [20]. However, in a four-year study, Altamura et al. [21] showed that the percentage of patients without recurrences was greater in those treated with lithium (46%) than in patients receiving quetiapine (29%).

A recent comparison by Kessing et al. [22] proved that lithium monotherapy is significantly more effective prophylactically than monotherapy with other mood-stabilizing drugs, such as valproate, lamotrigine, olanzapine, and quetiapine. Finnish researchers showed that lithium was the most effective in preventing hospitalizations in BD patients [23].

On the 50th anniversary of introducing lithium into modern psychiatry, a Canadian psychiatrist of Czech origin, Paul Grof, presented the concept of "*excellent lithium responders*" for patients with BD for whom lithium monotherapy leads to a complete recovery of the illness [24]. In a medical center in Poznań, an assessment of the percentage of excellent lithium responders was made, showing that in about 1/3 patients with BD who completed the ten-year observation, there were no recurrences [25]. Grof [26] in his subsequent paper suggests that excellent lithium responders can be characterized by a moderate number of affective episodes with full remissions between them and the absence of psychiatric comorbidity. This may correspond to the classic description of *"manisch-depressives Irresein"* made by Kraepelin [27]. A favorable effect of lithium is also observed in the morbid offspring of such patients [26].

A study of clinical factors related to the prophylactic efficacy of lithium use was also conducted in Poznań in a group of 111 patients treated with lithium for 5-39 years (average 18 years). It was found that a better lithium prophylaxis efficacy was achieved in patients with later onset of the disease, without a family history of affective disorders, with other family members taking lithium for prophylaxis, in women with coexisting anxiety disorders, and in men who do not abuse alcohol [28].

The analyses performed so far on this topic are consistent with the notion that favorable factors of prophylactic lithium treatment include an episode sequence of mania-depression-remission, later onset of the illness, a non-rapid-cycling course, and early implementation of lithium [29, 30]. The reduced effect of lithium in alcohol abusers, shown in our study, has also been confirmed by American researchers [31], whereas a good response to lithium in family members is in line with Grof's opinion that the beneficial effects of lithium can be demonstrated by relatives in the next generation [26].

We also studied the correlation between lithium prophylactic efficacy and personality traits categorized on the TEMPS-A scale (*Temperament Scale of Memphis, Pisa, Paris, and San Diego Autoquestionnaire),* such as hyperthymic, cyclothymic,

depressive, anxious and irritable temperaments. A positive correlation with lithium efficacy was shown by the hyperthymic temperament, while a negative correlation was shown by the anxious, cyclothymic, and irritable temperaments [32]. Another study evaluated the efficacy of prophylactic use of lithium depending on schizotypal characteristics measured on the O-LIFE scale *(Oxford-Liverpool Inventory of Feelings and Experiences)*. This scale distinguishes four schizotypal dimensions, such as unusual experiences, cognitive disorganization, introvertive anhedonia, as well as impulsive nonconformity. A significant negative correlation between the efficacy of lithium and the dimension of cognitive disorganization was shown, and this dimension is most strongly related to a predisposition to psychotic symptoms [33].

An essential element connected with lithium prophylactic efficacy is genetic prediposition. In the article published in the journal "CNS Drugs" in 2013, the updated knowledge on the role of so-called "candidate genes" in this respect was presented [34]. The Poznań center was the first to show an association between the Val66Met polymorphism of the *BDNF* (*brain-derived neurotrophic factor)* gene and lithium prophylactic efficacy [35]. We also found a connection between lithium prophylactic efficacy and the – 48A/G polymorphism of the *DRD1* (*dopamine receptor D1*) gene [36] and the polymorphisms of so-called "clock" genes related to biological rhythms, such as *ARNTL* (*aryl hydrocarbon receptor nuclear translocator-like*) gene and *TIM (timeless*) gene [37].

The 2005 meta-analysis showed that poor social status, stress factors and life events can be linked to a worse prophylactic effect of lithium [38]. Recently, French authors found that lower lithium efficacy is also connected to early childhood stress events [39]. The molecular-genetic studies carried out in Poznań indicate a relationship between lithium prophylactic efficacy and stress-system genes. An association was found between lithium efficacy and the polymorphism of the glucocorticoid receptor *NR3C1* (*Nuclear receptor subfamily 3 group C member* 1) gene [40] and three polymorphisms of the *FKBP5* (*FK 506 binding protein 5*) gene [41]. The *FKBP5* gene is one of the most important genes mediating psychopathological consequences of early childhood trauma, mainly in the form of a more severe course of mood disorders [42].

The first genome-wide association study (*GWAS*) concerning the prophylactic effects of lithium, conducted as part of the International Consortium on Lithium Genetics (*ConLiGen*) project, showed a significant association of lithium efficacy with the locus on chromosome 21, which contains two genes of long non-coding RNA (*lncRNAs*), a regulator of gene expression in the central nervous system [43]. Using this method, a connection between a worse lithium effect and the presence of psychotic symptoms was found [44], which corresponds with the schizotypal dimension predisposing to such symptoms [33].

The latest guidelines of the Task Force of ISBD (*International Society of Bipolar Disorder*) and IGSLI (*International Group for the Study of Lithium-treated Patients*) recommend maintaining lithium concentrations for prophylactic purposes at 0.6-0.8 mmol/l. In the case of good response but poor tolerance, the level of 0.4-0.6 mmol/l is acceptable, whereas in the case of insufficient response and good tolerance, the con-

centration may be increased up to 0.8-1.0 mmol/l [45]. As the proportion of excellent responders to monotherapy with lithium is about 1/3, the majority of BD patients are treated with combination therapy, also including lithium with other mood-stabilizing drugs. A combination of lithium with valproate, quetiapine, olanzapine, or aripiprazole is much better prophylactically than either of these drugs alone [18, 46-48]. The prophylactic efficacy of combined lithium and quetiapine is doubled compared to monotherapy with either drug alone [21].

Lithium also prevents depressive recurrences in unipolar depression, which was already noticed in the first article on lithium prophylactic efficacy [5]. The 2019 review included five randomized controlled studies comparing lithium monotherapy and placebo, and five such studies comparing lithium and antidepressants. The prophylaxis with lithium was significantly better than with the placebo and insignificantly so than with antidepressants [49]. Finnish researchers assessed the risk of rehospitalization in patients with severe recurrent depression. Lithium administration, especially as monotherapy, was associated with a significantly reduced risk of rehospitalization, while such an effect was not found for antidepressant drugs (except for amitriptyline) and antipsychotic drugs (except for clozapine) [50]. Therefore, the prophylactic use of lithium to prevent recurrence of periodic depression is worth considering, e.g., not only after the successful introduction of lithium for potentiation of antidepressants in drug-resistant depression, but also in the case of frequent recurrences occurring during the use of antidepressants.

The treatment of mania

Lithium still retains its value as an anti-manic drug, although lithium monotherapy is recommended rather in less intense manic states. Severe manic episodes, with psychotic symptoms and significant psychomotor agitation, usually require intramuscular administration of drugs, and after switching to oral treatment, lithium is usually used in such cases in combination with another mood-stabilizing drug. The meta-analysis carried out in 2000 showed a significantly higher antimanic efficacy of lithium than placebo. Compared to antipsychotics, lithium showed effects similar to haloperidol and risperidone, better than chlorpromazine, and comparable to antiepileptic drugs, such as carbamazepine and valproate [51]. However, in a recent review from 2011, both haloperidol and atypical antipsychotics, such as risperidone and olanzapine, were found to be more effective than lithium in the treatment of mania [52].

In a manic state, lithium carbonate can be initiated at a dose of 750-1000 mg per day to achieve a concentration of more than 0.8 mmol/l. Some researchers believe that this concentration may be as high as 1.2 mmol/l in the manic state because such patients tolerate it well. The first lithium test should be carried out 3 days after initiating treatment and the "anti-manic" concentration of lithium is usually obtained at a dose of 1000-2000 mg of lithium carbonate per day. This also applies to situations where lithium is used together with other antimanic drugs. Side effects of lithium in manic episodes are rare and are the same as in the initial period of its introduction, i.e., nausea, hand tremor, drowsiness, and fatigue. Usually, they subside with dose reduction.

The best candidates for lithium administration during a manic episode are patients who have a "euphoric" elevation of mood (with no clear signs of irritability or mixed state) and not very severe psychomotor agitation. If a subsequent episode occurs, it is important to note whether a beneficial effect of lithium was reported in the previous episode. Lithium monotherapy should not be considered in the case of a severe course of the disease, frequent hospitalizations, and rapid cycling BD.

Lithium is a good choice for patients with hypomanic episodes occurring in type II BD, where depressive episodes usually predominate. The use of lithium in these patients can prevent depression, which can be of severe intensity and is often accompanied by suicidal tendencies. In the treatment of hypomania, a lithium concentration of 0.6-0.8 mmol/l is sufficient and treatment can be started from a dose of 750 mg/day.

The treatment of depression and the augmentation of antidepressant drugs

Lithium monotherapy is not recommended as the first-line treatment of a depressive episode, especially in the course of recurrent depression. In bipolar depression, lithium is rarely used as monotherapy, and is more frequently combined with lamotrigine or quetiapine. However, an important application of lithium is for the augmentation of antidepressant drugs in treatment-resistant depression, in the course of both BD and recurrent depression. The augmentation of antidepressants by lithium can constitute the second indication for lithium use, after the first indication of the prevention of mood episodes. In our research, we demonstrated that a significant clinical amelioration, assessed after 28 days of lithium administration, takes place in at least a half of the patients and is greater in depression in the course of BD than in unipolar disorder and in patients with rapid improvement (within several days after lithium introduction) [53, 54].

When introducing lithium to potentiate the effect of antidepressants in treatment-resistant depression, the desired drug concentration is 0.6-0.8 mmol/l and the drug should be continued for four weeks. After that time, a clear improvement can be expected in at least 50% of patients. In about 1/4 of patients, the effect of lithium can be observed very quickly, within a few days after initiating the administration of the drug. If no significant improvement is observed within four weeks, lithium can be stopped. However, if a good therapeutic effect is achieved, in order to prevent the recurrence of depression, the drug should be continued for at least one year. [55]. Side effects are rare; the most commonly encountered side effect is hand tremor. If lithium is added to the SSRI drugs, the risk of serotonin syndrome is low. Lithium augmentation can be successfully used in the elderly, where its efficacy can be even better in people over 65 years of age [56].

Lithium as an antisuicidal drug

One of the most valuable outcomes concerning the long-term use of lithium in mood disorders is the prevention of suicidal behavior. The evidence has been accum-

mulated that among mood-stabilizing drugs, the use of lithium results in the biggest reduction of suicides and suicide attempts. As suicides are the most common cause of death in people with mood disorders, this property of lithium significantly translates into its beneficial clinical effect.

The antisuicidal effect of lithium was confirmed by the meta-analyses performed in the 21st century. Baldessarini et al. [57] showed that the risk of committing suicide was five times lower among patients taking lithium than those subjected to other forms of treatment. Cipriani et al. [58] concluded that lithium was significantly better than placebo in reducing the number of suicides and general mortality both in BD and in unipolar depression, and was superior in this aspect to other mood-stabilizers and antidepressants. The discontinuation of lithium significantly increases suicide risk. According to German researchers, the anti-suicidal effect of lithium is not correlated with the prophylaxis of mood recurrences, which points to the specificity of such an effect in reference to lithium [59].

In the recent decade, reports appeared indicating an anti-suicidal effect of trace levels of lithium contained in drinking water. A negative correlation between suicide frequency and lithium concentration in drinking water was demonstrated in research performed in Japan [60], Austria [61], the USA [62], and Greece [63]. In consequence, it was proposed to treat lithium as an essential microelement and suggested to supplement drinking water with lithium in areas with low levels.

It seems important to recommend considering using lithium in every patient with an affective mood disorder where the risk of suicide is present. An assessment of such risk factors should include, among others, family history of suicidal behavior, the occurrence of suicidal behavior during the current course of the illness, and the patient's present life situation and clinical condition. In the case of patients whose clinical course corresponds with the profile of excellent lithium responders, the use of lithium in monotherapy is sufficient to prevent suicidal behavior. In other patients with a high risk of suicidal behavior, lithium should be used as an essential component of combined mood-stabilizing treatment.

The antiviral and immunomodulatory effects

The antiviral effect of lithium, especially against herpes viruses, has been known for the past 40 years when British researchers showed that lithium inhibits the replication of the herpes virus (*herpes simplex virus* – HSV) in an experimental model [64], and the observations of remission of labial herpes during lithium treatment were published [65].

In 1991, the "Lithium" journal presented the results of a Polish-American retrospective study of the occurrence of oral herpes in patients receiving lithium for prophylactic purposes. The Polish population consisted of 69 patients receiving lithium for an average of 8 years, wherein 28 patients had recurrent labial herpes. In the course of lithium treatment, 13 patients (46%) experienced complete elimination of herpes recurrences, and in seven cases, the frequency of herpes recurrences decreased. A better "anti-herpes" effect was observed in patients with serum lithium

concentration over 0.65 mmol/l, and erythrocyte lithium concentration over 0.35 mmol/l. The American population consisted of two groups of 52 people, matched by gender, age, and length of systematic drug treatment (on average 5 years). In the first group of patients, with BD, lithium was administered, while the second group, with recurrent depression, was given antidepressants. The frequency of recurrences of oral herpes, compared to a 5-year period before the treatment, decreased in the group receiving lithium by 73%, while there was no significant difference in the group receiving antidepressants [66]. In the same year, in a study carried out jointly with the Department of Dermatology, Medical Academy in Bydgoszcz, excellent results of lithium succinate ointment were obtained in the topical treatment of herpes, mainly labial [67].

Lithium also influences the hematological and immunological systems. The increase in leukocytes in the course of lithium treatment was observed as early as 70 years ago [68]. This effect has been well known and clinically utilized. Lithium can mitigate the immune-endocrine component of the pathogenesis of BD, such as acute-phase reaction, production of pro-inflammatory cytokines, and excessive activation of the hypothalamic-pituitary-adrenal axis [69]. Together with the Szczecin center, we examined the impact of long-term lithium administration on very small embryonic-like stem cells (VSELs) and the mRNA expression of neuronal and glial markers, in peripheral blood of BD patients with long duration of the illness. The obtained results demonstrate that long-term lithium therapy can alleviate excessive regenerative and inflammatory processes in BD [70].

The neuroprotective and "antidementia" effects

In the second decade of the 21st century, attention was turned to the neuroprotective and "antidementia" effects of lithium, which have been validated in experimental, epidemiological, and clinical studies [71]. It was shown that lithium administration causes an increase in cerebral grey matter volume, especially that of the prefrontal cortex, anterior cingulate, and hippocampus. Such an effect was not demonstrated by any other mood-stabilizing drug. In the IGSLI study, it was found that BD patients receiving lithium had larger hippocampal volumes compared to non-lithium patients, and similar hippocampal volumes to healthy controls [72].

Based on the assumption of the neuroprotective effects of lithium, suggestions were put forward that lithium could protect against dementia. In population studies, a relationship was observed between lithium treatment and dementia risk reduction [73]. The analysis of the Danish National Prescription Registry showed that in BD patients taking lithium for a long time, the rate of dementia was similar or lower than in the general population, while this rate of dementia was significantly higher in patients treated with anticonvulsant, antidepressive, and antipsychotic drugs [74]. In two studies, a negative correlation was demonstrated between lithium concentration in drinking water and the frequency and severity of dementia [75, 76]. However, a meta-analysis of trials on the therapeutic application of lithium in dementia suggested moderately promising results of such a procedure [77].

Biological mechanism of lithium action

The most important biochemical mechanisms of lithium action include the inhibition of the glucogen synthase kinase-3beta (GSK-3β) enzyme and its effect on the intracellular signaling processes, especially on the phosphatidylinositol (PI) system [78].

GSK-3β regulates gene transcription, synaptic plasticity, apoptosis, cellular structure, stress resilience and biological rhythms. The GSK-3β inhibition by lithium plays a role in the mechanism of therapeutic action in mood disorders as well as in neurodegenerative disorders since GSK-3β is also a key enzyme in the metabolism of the amyloid precursor protein and the phosphorylation of the tau protein. The effect of lithium on GSK-3β may also play a certain role in the formation of side effects, in the kidney and thyroid among others, and be connected with the antisuicidal effect of lithium [9].

Lithium inhibits inositol monophosphatase 1, a key enzyme of the PI system. A British physiologist, Michael Berridge, advanced the inositol depletion hypothesis as a mechanism of therapeutic action of lithium in BD [79]. Apart from the above-mentioned monophosphatase, in the mechanism of lithium action, the inhibition of protein kinase C (PKC) plays a role, as well as the inhibition of adenyl cyclase, which converts adenosine triphosphate (ATP) into cyclic adenosine monophosphate (cAMP). An important element of this system is the cAMP response element-binding protein (CREB), the regulator of gene expression, which is activated by lithium.

In the mechanism of lithium action, its stimulatory action on the brain-derived neurotrophic factor (BDNF) is also important. BDNF is necessary for the survival and function of neurons and modulates the activity of such neurotransmitters like glutamate, gamma-aminobutyric acid, dopamine, and serotonin. The disturbances of the BDNF system are essential in the pathogenesis and treatment of mood disorders. Low serum BDNF is regarded as a marker of late stage BD. In experimental studies, it was found that lithium increases the expression of the *BDNF* gene in the rat's brain, and one of the mechanisms here is the activation of CREB. In clinical studies, it was demonstrated that serum BDNF concentration is decreased during a manic or depressive episode and increases with lithium treatment. The *BDNF* gene polymorphism is connected with lithium prophylactic efficacy [80].

Adverse effects of lithium and their management

Gastrointestinal side effects, such as nausea and diarrhea, occur in 10-20% of patients during the initial period of lithium use and usually disappear with further treatment. Sometimes, the side effects may depend on the type of lithium preparation used (standard or extended release). Weight gain is relatively frequent in the course of treatment with lithium and affects about 25% of patients. In some women, this undesired weight gain may be a reason to stop taking the medication. Therapy options include diet, physical activity, and/or coadministration of topiramate. In extreme cases, it may be necessary to switch from lithium to another mood-stabilizing drug.

Tremor occurs in about 20% of patients treated with lithium and usually appears in the initial period of its administration. It is a fine tremor of the upper limbs, occurring in the form of an idiopathic or action tremor, for example, when pouring liquids. The tremor caused by lithium is usuallly mild and often disappears when the dose of the drug is reduced. However, if the reduction of the dose is not possible and this symptom interferes with the daily activities of the patient, beta-adrenolytic drugs, such as propranolol at a dose of 20-80 mg/day, can be used with good results.

Among the dermatological side effects of lithium, we can mention exacerbated acne and psoriasis, as well as *de novo* occurrence of such disorders. Psoriasis of moderate to severe intensity may be a contraindication to initiating lithium treatment. Dermatological symptoms may be related to the concentration of lithium and therefore, an attempt at dose reduction may be made. If the effects of lithium are good, drugs recommended for these dermatological diseases can be used. Only in very severe cases, it may be necessary to replace lithium with another mood-stabilizing drug.

The most common adverse effect of lithium with regard to the cardiovascular system is non-specific changes in the repolarization period in ECG, without significant clinical symptoms. However, cases of arrhythmia have been observed, of which sinus bradyarrhythmia is the most common. In severe cases of arrhythmia, if lithium therapy is necessary, cardiological treatment should be introduced [9].

Increased urination (polyuria), accompanied by increased thirst (polydipsia), may occur in the first weeks of lithium administration. The reason for this is reduced renal concentrating ability caused by lithium. In extreme cases, polyuria may reach the severity of nephrogenic diabetes insipidus. This symptom is alleviated when the dose is reduced or when amiloride is administered. Polyuria usually disappears after lithium is discontinued and such a decision is usually made in the case of diabetes insipidus. Various degrees of reduced renal concentrating ability may persist for many years during the long-term use of lithium. A genetic-molecular study conducted in Poznań showed an association between this disorder and the *GSK-3β* gene polymorphism [81].

The most serious concern connected with kidneys is lithium-induced interstitial nephropathy that can develop after 10-20 years of treatment, and leads to an increased creatinine concentration and a decreased glomerular filtration rate (GFR). In a study consisting of 80 patients with BD receiving lithium for 5-39 (on average 16) years, we found values of GFR <60 ml/min/1,73^2 in 38% of males and 16% of females, and urinary specific gravity of ≤1.005 in 21% of males and 14% of females [82]. The data of 312 patients from 12 IGSLI centers, treated with lithium for 8-48 (on average 18) years, were also analyzed. An average decrease of 0.9% in the GFR value was found with each year of lithium administration. Risk factors for lowered GFR included a longer duration of lithium treatment, a higher serum concentration of lithium, older age, presence of comorbidities, and initiation of lithium treatment after the age of 40. No person was found to have end-stage renal failure [83].

The ascertainment of kidney injury may result in a decision to discontinue lithium and replace it with another mood-stabilizing drug. However, other mood-stabilizing drugs, especially in excellent lithium responders, may not be effective, and the fur-

ther course of the illness may be drug-resistant. In patients with lithium nephropathy, the kidney function should be frequently monitored and, if progressive changes are observed, the lithium dose should be reduced.

The most frequent thyroid adverse effects connected with lithium are goiter and hypothyroidism. Lithium administration results in reduced production with release inhibition of thyroid hormones. The symptoms of hypothyroidism usually appear at the early stage of lithium treatment, and are more frequent in women and persons with a family history of thyroid dysfunction. In our study of 98 BD patients receiving lithium for at least three years (on average 19±10 years), TSH concentration and thyroid volume were significantly higher compared with 39 BD patients never treated with lithium. However, the frequency of hypothyroidism was similar in both groups (24% vs 18%) and 3-4-fold higher in women than in men, which may suggest that BD itself may predispose to this disorder. All hypothyroid subjects were successfully treated with thyroxine. The frequency of goiter in lithium-treated patients was similar in men and women and no correlation was found between goiter and thyroid hormones [84]. A comparison of thyroid autoantibodies between lithium-treated and lithium-naive patients revealed no significant differences [85].

Lithium can increase calcium reabsorption in the kidneys, stimulate parathormone secretion, and cause a calcium-phosphate imbalance in the form of primary lithium-induced hyperparathyroidism. In our study of 90 patients receiving lithium for 16±10 years, hypercalcemia was found in 10% and hyperparathyroidism in three of the patients [86]. This indicates the advisability to monitor serum calcium levels in such patients. In the case of lithium-induced hyperparathyroidism with significant clinical symptoms, treatment is similar to that of primary hyperparathyroidism.

According to the opinion of some clinicians, lithium may exert an unfavourable effect on cognitive function. Conversely, experimental studies have pointed to a favorable effect of lithium on these processes. Patients with BD may have cognitive dysfunction of primary nature, intensified during the episodes of the illness, and treatment with lithium does not cause significant changes here [87]. In our own studies, it has been shown that the effect of lithium on cognitive functions is connected with the quality of prophylactic efficacy. Non-responders to lithium had significantly worse performances on the neuropsychological tests compared with good responders and the healthy controls [88]. The results obtained by the excellent lithium responders were significantly better that in the remaining lithium-treated patients and similar to healthy subjects. Also, serum BDNF concentration in excellent responders was comparable to healthy controls [89]. The favorable effect of lithium on cognitive functions can be associated with its neuroprotective and antiherpes activity. In order to minimize possible negative effects of lithium in susceptible persons, it is recommended to maintain serum lithium concentration at the lowest effective level, i.e., 0.4-0.6 mmol/l [87].

The use of lithium in pregnancy and the perinatal period

In women with BD, there is an increased risk for a recurrence of illness during pregnancy and for postnatal disturbances. Among the recommendations of the Polish

Psychiatric Association regarding BD in women, a significant part relates to lithium. In the period of pregnancy planning, it is advisable to obtain a several-month stabilization of the psychiatric state and to establish treatment with one mood-stabilizing drug (except for valproate and carbamazepine). Lithium can be a drug of first choice here. Women taking lithium should continue the drug during pregnancy. In the first trimester, the dose of lithium carbonate should be reduced to 500 mg/day. In the 2nd and 3rd trimester, lithium should be given in divided doses to obtain a concentration of about 0.6 mmol/l. The dose of lithium can be reduced for two weeks before delivery. Lithium given after delivery should reach a concentration of at least 0.6 mmol/l. Due to a high infant/ maternal ratio of serum drug concentration, breastfeeding is not recommended. In exceptional cases, lithium should be given in divided doses, after the breastfeeding session.

Lithium administration in pregnancy creates an efficient strategy to prevent postpartum mood disorders. Therefore, in women with a history of such disturbances who are not taking lithium during pregnancy, it is recommended to introduce lithium immediately after the delivery. It is also possible to safely introduce lithium in the final stage of pregnancy to prevent recurrences in the postnatal period. This measure requires frequent monitoring of lithium concentration to protect the fetus from toxic lithium levels [90].

Ultra – long-term lithium treatment – own experiences

The experiences with long-term lithium treatment exceed multiple times the practices with any other mood-stabilizing drug. In 2016 we presented two men and three women, aged 64-79 years, with a good response to the ultra-long-term lithium treatment for more than 40 years. In 4 of the subjects, the serum lithium concentration was maintained in the range of 0.60-0.65mmol/l, and in the remaining subject, the range was 0.7-0.8 mmol/l. Both males had impaired renal function but with no progression in the last five years. One female suffered from Hashimoto's disease and was treated with levothyroxine. Serum calcium concentrations in all of the subjects were normal. In the entire group, the cognitive functions were at the level of healthy subjects with comparable age and education level. All patients were professionally active until 55-65 years of age and their functioning in family and social roles was proper. The initiation of lithium therapy usually occurred within the first three years of the illness [91].

In the year 2020, a 79-year-old female patient was described who has been taking lithium for 50 years. It was a period of her optimal functioning in terms of mental, general and social health [92].

Underutilization of lithium

One of the reasons for the underutilization of lithium in mood disorders is the introduction and active promotion of other mood-stabilizing drugs, both the 1st and 2nd generation. In this respect, lithium is an "orphan drug" that, due to the low cost

of production, is not promoted by any pharmaceutical company. Another motive may be the perception of lithium as a "toxic" drug due to its adverse effects, mainly on thyroid, renal, and cognitive functions. This notion is common not only among doctors of different specialties but also among some psychiatrists.

Insufficient usage of lithium can be reflected by the trends in the prescription of mood-stabilizers in recent decades. They indicate a significant increase in the administration of new mood-stabilizing drugs, while lithium usage has been on a similar level or slightly decreased. A study performed in Poland showed that during 2004-2010, the prescription of lithium in Poland rose insignificantly by 4%, whereas in 2011-2017 this increase amounted to 16%. However, in the second half of 2017, the prescriptions of lithium were surpassed nearly 3-fold by valproate and about 2-fold by quetiapine, olanzapine, and lamotrigine [93].

In 2018, the eminent specialist in the field of BD, Robert Post, deplored that lithium is greatly underutilized in the USA, even more than in Europe. He pointed to the multiple assets of lithium and argued that the fear of lithium adverse effects is exaggerated [94]. In the same year, the author of this review published a paper titled "Challenging the negative perception of lithium and optimizing its long-term administration", where he demonstrated the advantage of lithium over other mood-stabilizing drugs, and described the benefits of long-term lithium therapy and the possibilities of effective management of side effects [95]. In one of the latest editorials of the journal "Bipolar Disorders", titled "Make lithium great again!", the psychiatrists led by the Chief Editor of the journal, Gin Malhi, call upon a better utilization of lithium's therapeutic potential and for more frequent use of the drug [96].

Lithium treatment in literature and art

Both the introduction of lithium into psychiatric treatment and its therapeutic activity have been reflected in the works of literature and art. The prime initiator of utilizing lithium in modern psychiatry, John Cade, attained in the 21st century a play, a film, and two biographies. In 2003, a play entitled "Dr Cade" was staged in Sydney. The script for the play was written by Neil Cole, former Minister of Justice in the state of Victoria, Australia, who used lithium for therapeutic purposes in his own disorders. In 2004, a documentary film was made, entitled "Troubled minds: The lithium revolution" based on interviews with John Cade's sons, patients, and other persons that knew him. The film won the main prize at the International Vega Awards for popular science content. A biography of Cade, titled "Finding sanity: John Cade, lithium and the taming of bipolar disorder", was written in 2017 by a psychiatrist from Sydney, Greg De Moore, and a health sociologist from Melbourne, Ann Westmore. The second biography of Cade, titled "Lithium: a doctor, a drug, and a breakthrough", by an American psychiatrist, Walter Brown, was published in 2019.

In the 1980s, lithium treatment was described by the Nobel Prize laureate in medicine, Salvador Luria (1912-1991), in his book "A slot machine, a broken test tube: An autobiography", and by an outstanding actress, the youngest Oscar winner in history, Patty Duke (1946-2016), in her autobiography „Call me Anna". Eminent

writers, including Jerzy Broszkiewicz (1922-1993), Ota Pawel (1930-1973), Robert Lowell (1917-1977), and Jamie Lowe, the author of the book "Mental: Lithium, love and losing my mind", published in 2017, all received lithium treatment.

An exceptional personage in popularizing psychiatric knowledge in this respect is Kay Redfield Jamison, currently a professor of psychology at the Johns Hopkins University in Baltimore. She is the author of many books concerning BD. Together with Frederick Goodwin, former head of the American National Institute of Mental Health, she wrote a fundamental work entitled "Manic-depressive illness". The first edition of the book was published in 1990 and was unanimously recognized as the bipolar affective disorder bible. The second edition was published in 2007 and was titled „Manic-depressive illness. Bipolar disorders and recurrent depression". In 1996, in her book „An unquiet mind", Kay Jamison described her own bipolar illness and lithium treatment from the point of view of a distinguished professionalist, for the first time ever in the history of psychiatry. The Polish translation of this book, titled "Niespokojny umysł", has already accomplished two editions: in 2000 and 2018.

Concluding this topic, it should be stated that lithium treatment also became an element of pop culture, as the word "lithium" was an inspiration for the titles of the pieces of music of Kurt Cobain (1967-1994), the rock band "Evanescence", and Sting [97].

References

1. Garrod AB. *Gout and rheumatic gout.* London: Walton and Maberly; 1859.
2. Hammond WA. *Treatise on diseases of the nervous system.* New York: Appleton; 1871.
3. Lange C. *Om periodiske depressionstilstande og deres patogenese.* Copenhagen: Lund; 1886.
4. Cade JFJ. *Lithium salts in the treatment of psychotic excitement*. Med. J. Aust. 1949; 2(10): 349–352.
5. Hartigan GP. *The use of lithium salts in affective disorders*. Br. J. Psychiatry 1963; 109: 810-814.
6. Baastrup PC. *The use of lithium in manic-depressive psychoses*. Compr. Psychiatry 1964; 5(6): 396–408.
7. Rybakowski J, Chłopocka M, Lisowska J, Czerwiński A. *Badania nad skutecznością leczniczą węglanu litu w endogennych zespołach depresyjnych*. Psychiatr. Pol. 1974; 8: 129–135.
8. Dé Montigny C, Grunberg F, Mayer A, Deschenes JP. *Lithium induces rapid relief of depression in tricyclic antidepressant nonresponders.* Br. J. Psychiatry 1981; 138: 252–256.
9. Rybakowski J. *Lit – niezwykły lek w psychiatrii.* Poznań: Wydawnictwo Termedia; 2019. https://www.termedia.pl/Ksiazka/-279.
10. Zarate CA, Tohen M, Banov MD, Weiss MK, Cole JO. *Is clozapine a mood stabilizer?* J. Clin. Psychiatry 1995; 56(3): 108–112.ol
11. Rybakowski JK. *Two generations of mood stabilizers.* Int. J. Neuropsychopharmacol. 2007; 10(5): 709–711.

12. Rybakowski JK. *Meaningful aspects of the term 'mood stabilizer'.* Bipolar. Disord. 2018; 20(4): 391–392.
13. Rybakowski J, Chłopocka-Woźniak M, Kapelski Z. *Ocena kliniczna skuteczności profilaktycznej długotrwałego stosowania węglanu litu u chorych z endogennymi zespołami depresyjnymi.* Psychiatr. Pol. 1980; 14: 357–361.
14. Geddes JR, Burgess S, Kawton K, Jamison K, Goodwin GM. *Long-term lithium therapy for bipolar disorder: Systematic review and meta-analysis of randomized controlled trials.* Am. J. Psychiatry 2004; 161(2): 217–222.
15. Nivoli AMA, Murru A, Vieta E. *Lithium: Still a cornerstone in the long-term treatment in bipolar disorder?* Neuropsychobiology 2010; 62(1): 27–35.
16. Severus E, Taylor MJ, Sauer C, Pfennig A, Ritter P, Bauer M et al. *Lithium for prevention of mood episodes in bipolar disorders: Systematic review and meta-analysis.* Int. J. Bipolar Disord. 2014; 2: 15.
17. Kleindienst N, Greil W. *Differential efficacy of lithium and carbamazepine in the prophylaxis of bipolar disorder: Results of the MAP study*. Neuropsychobiology 2000; 42(Suppl 1): 2–10.
18. BALANCE investigators and collaborators; Geddes JR, Goodwin GM, Rendell J, Azorin J-M, Cipriani A, Ostacher MJ et al. *Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): A randomized open-label trial*. Lancet 2010; 375(9712): 385–395**.**
19. Goodwin GM, Bowden CL, Calabrese JR, Grunze H, Kasper S, White R. *A pooled analysis of 2 placebo-controlled 18-month trials of lamotrigine and lithium maintenance in bipolar I disorder.* J. Clin. Psychiatry 2004; 65(3): 432–441.
20. Nierenberg AA, McElroy SL, Friedman ES, Ketter TA, Shelton RC, Deckersbach T. *Bipolar CHOICE (Clinical Health Outcomes Initiative in Comparative Effectiveness): A pragmatic 6-month trial of lithium versus quetiapine for bipolar disorder.* J. Clin. Psychiatry 2016; 77: 90-99.
21. Altamura AC, Mundo E, Dell'Osso B, Tacchini G, Buoli M, Calabrese JR. *Quetiapine and classical mood stabilizers in the long-term treatment of bipolar disorder: A 4-year follow-up naturalistic study.* J. Affect. Disord. 2008; 110(1–2): 135–141.
22. Kessing LV, Bauer M, Nolen WA, Severus E, Goodwin GM, Geddes J. *Effectiveness of maintenance therapy of lithium vs other mood stabilizers in monotherapy and in combinations: A systematic review of evidence from observational studies.* Bipolar Disord. 2018; Feb 14. Doi: 10.1111/bdi.12623. [Epub ahead of print].
23. Lähteenvuo M, Tanskanen A, Taipale H, Hoti F, Vattulainen P, Vieta E et al. *Real-world effectiveness of pharmacologic treatments for the prevention of rehospitalization in a Finnish nationwide cohort of patients with bipolar disorder.* JAMA Psychiatry 2018; 75(4): 347–355.
24. Grof P. *Excellent lithium responders: People whose lives have been changed by lithium prophylaxis.* In: Birch NJ, Gallicchio VS, Becker RW. ed. Lithium: *50 years of psychopharmacology, new perspectives in biomedical and clinical research.* Cheshire, Connecticut: Weidner Publishing Group; 1999. P. 36–51.
25. Rybakowski JK, Chłopocka-Woźniak M, Suwalska A. *The prophylactic effect of long-term lithium administration in bipolar patients entering treatment in the 1970s and 1980s.* Bipolar Disord. 2001; 3(2): 63–67.
26. Grof P. *Sixty years of lithium responders.* Neuropsychobiology 2010; 62(1): 27-35.

27. Kraepelin E. Psychiatrie. *Ein Lehrbuch für Studierende und Ärzte.* 6 Auflage. Leipzig: Barth; 1899.
28. Kliwicki S, Chłopocka-Woźniak M, Rudnicka E, Rybakowski J. *Skuteczność długoterminowego stosowania litu w chorobie afektywnej dwubiegunowej.* Farmakoter. Psychiatr. Neurol. 2014; 30(1): 5–13.
29. Kleindienst N, Engel R, Greil W. *Which clinical factors predict response to prophylactic lithium? A systematic review for bipolar disorders.* Bipolar Disord. 2005; 7(5): 404–417.
30. Hui TP, Kandola A, Shen L, Lewis G, Osborn DPJ, Geddes JR et al. *A systematic review and meta-analysis of clinical predictors of lithium response in bipolar disorder.* Acta Psychiatr. Scand. 2019; 140(2): 94–115.
31. O'Connell RA, Mayo JA, Flatow L, Cuthbertson B, O'Brien BE. *Outcome of bipolar disorder on long-term treatment with lithium.* Br. J. Psychiatry 1991; 159: 123–129.
32. Rybakowski JK, Dembinska D, Kliwicki S, Akiskal KK, Akiskal HH. *TEMPS-A and long-term lithium response: Positive correlation with hyperthymic temperament.* J. Affect. Disord. 2013; 145(2): 187–189.
33. Dembińska-Krajewska D, Kliwicki S, Chłopocka-Woźniak M, Rybakowski J. *Skuteczność profilaktycznego stosowania litu w chorobie afektywnej dwubiegunowej a cechy schizotypii.* Farmakoter. Psychiatr. Neurol. 2012; 28(3–4): 153–158.
34. Rybakowski JK. *Genetic influences on response to mood stabilizers in bipolar disorder: Current status of knowledge.* CNS Drugs 2013; 27(3): 165–173.
35. Rybakowski JK, Suwalska A, Skibińska M, Szczepankiewicz A, Leszczyńska-Rodziewicz A, Permoda A et al. *Prophylactic lithium response and polymorphism of the brain-derived neurotrophic factor gene.* Pharmacopsychiatry 2005; 38(4): 166–170.
36. Rybakowski JK, Dmitrzak-Weglarz M, Suwalska A, Leszczynska-Rodziewicz A, Hauser J. *Dopamine D1 receptor gene polymorphism is associated with prophylactic lithium response in bipolar disorder.* Pharmacopsychiatry 2009; 42(1): 20–22.
37. Rybakowski JK, Dmitrzak-Weglarz M, Kliwicki S, Hauser J. *Polymorphism of circadian clock genes and prophylactic lithium response.* Bipolar Disord. 2014; 16(2): 151–158.
38. Kleindienst N, Engel RR, Greil W. *Psychosocial and demographic factors associated with response to prophylactic lithium: A systematic review for bipolar disorders.* Psychol. Med. 2005; 35(12): 1685–1694.
39. Etain B, Lajnef M, Brichant-Petitjean C, Geoffroy PA, Henry C, Gard S et al. *Childhood trauma and mixed episodes are associated with poor response to lithium in bipolar disorders.* Acta Psychiatr. Scand. 2017; 135(4): 319–327.
40. Szczepankiewicz A, Rybakowski JK, Suwalska A, Hauser J. *Glucocorticoid receptor polymorphism is associated with lithium response in bipolar patients.* Neuro. Endocrinol. Lett. 2011; 32(4): 545–551.
41. Szczepankiewicz A, Narozna B, Rybakowski JK, Kliwicki S, Czerski P, Dmitrzak-Węglarz M et al. *Genes involved in stress response influence lithium efficacy in bipolar patients*. Bipolar Disord. 2018; 20(8): 753–760.
42. Jaworska-Andryszewska P, Rybakowski JK. *Childhood trauma in mood disorders: Neurobiological mechanisms and implications for treatment.* Pharmacol. Rep. 2019; 71(1): 112–120.
43. Hou L, Heilbronner U, Degenhardt F, Adli M, Akiyama K, Akula N et al. *Genetic variants associated with response to lithium treatment in bipolar disorder: A genome-wide association study.* Lancet 2016; 387(10023): 1085–1093.

44. International Consortium on Lithium Genetics (ConLi+Gen); Amare AT, Schubert KO, Hou L, Clark SR, Papiol S, Heilbronner U et al. *Association of polygenic score for schizophrenia and HLA antigen and inflammation genes with response to lithium in bipolar affective disorder: A genome-wide association study.* JAMA Psychiatry 2018; 75(1): 65–74.

45. Nolen WA, Licht RW, Young AH, Malhi GS, Tohen M, Vieta E et al. *What is the optimal serum level for lithium in the maintenance treatment of bipolar disorder? A systematic review and recommendations from the ISBD/IGSLI Task Force on treatment with lithium.* Bipolar Disord. 2019; 21(5): 394–409.

46. Katagiri H, Takita Y, Tohen M, Higuchi T, Kanba S, Takahashi M. *Safety and efficacy of olanzapine monotherapy and olanzapine with a mood stabilizer in 18-week treatment of manic/mixed episodes for Japanese patients with bipolar I disorder.* Curr. Med. Res. Opin. 2012; 28(5): 701–713.

47. Marcus R, Khan A, Rollin L, Morris B, Timko K, Carson W et al. *Efficacy of aripiprazole adjunctive to lithium or valproate in the long-term treatment of patients with bipolar I disorder with an inadequate response to lithium or valproate monotherapy: A multicenter, double-blind, randomized study.* Bipolar Disord. 2011; 13(2): 133–144.

48. Suppes T, Vieta E, Gustafsson U, Ekholm B. *Maintenance treatment with quetiapine when combined with either lithium or divalproex in bipolar I disorder: Analysis of two large randomized, placebo-controlled trials.* Depress. Anxiety 2013; 30(11): 1089–1098.

49. Undurraga J, Sim K, Tondo L, Gorodischer A, Azua E, Tay KH et al. *Lithium treatment for unipolar major depressive disorder: Systematic review.* J. Psychopharmacol. 2019; 33(2): 167–176.

50. Tiihonen J, Tanskanen A, Hoti F, Vattulainen P, Taipale H, Mehtälä J et al. *Pharmacological treatments and risk of readmission to hospital for unipolar depression in Finland: A nationwide cohort study.* Lancet Psychiatry 2017; 4(7): 547–553.

51. Poolsup N, Li Wan Po A, Oliveira de IR. *Systematic overview of lithium treatment in acute mania*. J. Clin. Pharm. Ther. 2000; 25(2): 139–156.

52. Cipriani A, Barbui C, Salanti G, Rendell J, Brown R, Stockton S et al. *Comparative efficacy and acceptability of antimanic drugs in acute mania: A multiple-treatments meta-analysis.* Lancet 2011; 378(9799): 1306–1315.

53. Rybakowski J, Matkowski K. *Synergistyczne działanie litu i tymoleptyków w depresji endogennej.* Psychiatr. Pol. 1987; 21: 115–120.

54. Rybakowski J, Matkowski K. *Adding lithium to antidepressant therapy: Factors related to therapeutic potentiation.* Eur. Neuropsychopharmacol. 1992; 2(2): 161–165.

55. Bauer M, Adli M, Ricken R, Severus E, Pilhatsch M. *Role of lithium augmentation in the management of major depressive disorder.* CNS Drugs 2014; 28(4): 331–342.

56. Buspavanich P, Behr J, Stamm T, Schlattmann P, Bschor T, Richter C et al. *Treatment response of lithium augmentation in geriatric compared to non-geriatric patients with treatment-resistant depression.* J. Affect. Disord. 2010; 251: 136–140.

57. Baldessarini RJ, Tondo L, Davis P, Pompili M, Goodwin FK, Hennen J. *Decreased risk of suicides and attempts during long-term lithium treatment: A meta-analytic review.* Bipolar Disord. 2006; 8(5 Pt 2): 625–639.

58. Cipriani A, Hawton K, Stockton S, Geddes JR. *Lithium in the prevention of suicide in mood disorders: Updated systematic review and meta-analysis.* Br. Med. J. 2013; 346: f3646.

59. Lewitzka U, Severus E, Bauer R, Ritter P, Müller-Oerlinghausen B, Bauer M. *The suicide prevention effect of lithium: More than 20 years of evidence-a narrative review.* Int. J. Bipolar Disord. 2015; 3(1): 32.
60. Ohgami H, Terao T, Shiotsuki I, Ishii N, Iwata N. *Lithium levels in drinking water and risk of suicide.* Br. J. Psychiatry 2009; 194(5): 464–465.
61. Kapusta ND, Mossaheb N, Etzersdorfer E, Hlavin G, Thau K, Willeit M et al. *Lithium in drinking water and suicide mortality.* Br. J. Psychiatry 2011; 198(5): 346–350.
62. Blüml V, Regier MD, Hlavin G, Rockett IRH, König F, Vyssoki B et al. *Lithium in the public water supply and suicide mortality in Texas.* J. Psychiatr. Res. 2013; 47(3): 407–411.
63. Giotakos O, Nisianakis P, Tsouvelas G, Giakalou VV. *Lithium in the public water supply and suicide mortality in Greece.* Biol. Trace Elem. Res. 2013; 156(1–3): 376–399.
64. Skinner GRB, Hartley C, Buchan A, Harper L, Gallimore P. *The effect of lithium chloride on the replication of herpes simplex virus.* Med. Microbiol. Immunol. 1980; 168(2): 258–265.
65. Lieb J. *Remission of recurrent herpes infection during therapy with lithium.* N. Eng. J. Med. 1979; 301(17): 942.
66. Rybakowski JK, Amsterdam JD. *Lithium prophylaxis and recurrent labial herpes infections.* Lithium 1991; 2: 43–47.
67. Rybakowski J, Gwieździński Z, Urbanowski S. *Lithium succinate ointment in topical treatment of herpes simplex infections.* Lithium 1991; 2: 117–118.
68. Radomski J, Fuyat HN, Nelson AA, Smith PK. *The toxic effects, excretion and distribution of lithium chloride.* J. Pharmacol. Exp. Ther. 1950; 100(4:1): 429–440.
69. Rybakowski JK. *Antiviral and immunomodulatory effect of lithium.* Pharmacopsychiatry 2000; 33(5): 159–164.
70. Ferensztajn-Rochowiak E, Kucharska-Mazur J, Tarnowski M, Samochowiec J, Ratajczak MZ, Rybakowski JK. *Stem cells, pluripotency and glial cell markers in peripheral blood of bipolar patients on long-term lithium treatment.* Prog. Neuropsychopharmacol. Biol. Psychiatry 2018; 80(Pt A): 28–33.
71. Rybakowski JK, Suwalska A, Hajek T. *Clinical perspectives of lithium's neuroprotective effect.* Pharmacopsychiatry 2018; 51(5): 194–199.
72. Hajek T, Bauer M, Simhandl C, Rybakowski J, O'Donovan C, Pfennig A et al. *Neuroprotective effect of lithium on hippocampal volumes in bipolar disorder independent of long-term treatment response.* Psychol. Med. 2014; 44(3): 507–517.
73. Donix M, Bauer M. *Population studies of association between lithium and risk of neurodegenerative disorders.* Curr. Alzheimer Res. 2016; 13(8): 873–878.
74. Kessing LV, Forman JL, Andersen PK. *Does lithium protect against dementia?* Bipolar Disord. 2010; 12(1): 87–94.
75. Kessing LV, Gerds TA, Knudsen NN, Jørgensen LF, Kristiansen SM, Voutchkova D et al. *Association of lithium in drinking water with the incidence of dementia.* JAMA Psychiatry 2017; 74(10): 1005–1010.
76. Fajardo VA, Fajardo VA, LeBlanc PJ, MacPherson REK. *Examining the relationship between trace lithium in drinking water and the rising rates of age-adjusted Alzheimer's disease mortality in Texas.* J. Alzheimers Dis. 2018; 61(1): 425–434.
77. Matsunaga S, Kishi T, Annas P, Basun H, Hampel H, Iwata N. *Lithium as a treatment for Alzheimer's disease: A systematic review and meta-analysis.* J. Alzheimers Dis. 2015; 48(2): 403–410.

78. Brown KM, Tracy DK. *Lithium: The pharmacodynamic actions of the amazing ion.* Ther. Adv. Psychopharmacol. 2013; 3(3): 163–176.

79. Berridge MJ, Downes CP, Hanley MR. *Neural and developmental actions of lithium: A unifying hypothesis.* Cell 1989; 59(3): 411–419.

80. Rybakowski JK. *Response to lithium in bipolar disorder: Clinical and genetic findings.* ACS Chem. Neurosci. 2014; 5(6): 413–421.

81. Rybakowski JK, Abramowicz M, Szczepankiewicz A, Michalak M, Hauser J, Czekalski S. *The association of glycogen synthase kinase-3beta (GSK-3β) gene polymorphism with kidney function in long-term lithium-treated bipolar patients.* Int. J. Bipolar Disord. 2013; 1: 8.

82. Rybakowski JK, Abramowicz M, Drogowska J, Chłopocka-Woźniak M, Michalak M, Czekalski S. *Screening for the markers of kidney damage in men and women on long-term lithium treatment.* Med. Sci. Monit. 2012; 18(11): CR656–660.

83. Tondo L, Abramowicz M, Alda M, Bauer M, Bocchetta A, Bolzani L et al. *Long-term lithium treatment in bipolar disorder: Effects on glomerular filtration rate and other metabolic parameters.* Int. J. Bipolar Disord. 2017; 5(1): 27.

84. Kraszewska A, Ziemnicka K, Jończyk-Potoczna K, Sowiński J, Rybakowski JK. *Thyroid structure and function in long-term lithium-treated and lithium-naïve bipolar patients.* Hum. Psychopharmacol. 2019; 34(4): e2708.

85. Kraszewska A, Ziemnicka K, Sowiński J, Ferensztajn-Rochowiak E, Rybakowski JK. *No connection between long-term lithium treatment and antithyroid antibodies.* Pharmacopsychiatry 2019; 52(5): 232–236.

86. Abramowicz M, Chłopocka-Woźniak M, Kraszewska A, Czekalski S, Rybakowski J. *Hiperkalcemia i nadczynność przytarczyc u pacjentów z chorobą afektywną dwubiegunową długotrwale leczonych litem.* Farmakoter. Psychiatr. Neurol. 2014; 29(1): 21–27.

87. Rybakowski JK. *Effect of lithium on neurocognitive functioning.* Curr. Alzheimer Res. 2016; 13(8): 887–893.

88. Rybakowski JK, Permoda-Osip A, Borkowska A. *Response to prophylactic lithium in bipolar disorder may be associated with a preservation of executive cognitive functions*. Eur. Neuropsychopharmacol. 2009; 19(11): 791–795.

89. Rybakowski JK, Suwalska A. *Excellent lithium responders have normal cognitive functions and plasma BDNF levels.* Int. J. Neuropsychopharmacol. 2010; 13(5): 617–622.

90. Rybakowski J, Cubała WJ, Gałecki P, Rymaszewska J, Samochowiec J, Szulc A, Dudek D. *Rekomendacje Polskiego Towarzystwa Psychiatrycznego dotyczące leczenia zaburzeń afektywnych u kobiet w wieku rozrodczym. Część II: Choroba afektywna dwubiegunowa.* Psychiatr. Pol. 2019; 53(2): 263–276.

91. Permoda-Osip A, Abramowicz M, Kraszewska A, Suwalska A, Chłopocka-Woźniak M, Rybakowski JK. *Kidney, thyroid and other organ functions after 40 years or more of lithium therapy: A case series of five patients.* Ther. Adv. Psychopharmacol. 2016; 6(4): 277–282.

92. Ferensztajn-Rochowiak E, Chłopocka-Woźniak M, Rybakowski JK. *Ultra-long-term lithium administration: All important matters and a case report of successful 50-year lithium treatment.* Braz. J. Psychiatry. [Ahead of print Epub Sep 18, 2020]. http://dx.doi.org/10.1590/1516-4446 – 2020-1111.

93. Rybakowski J, Chęcińska K. *Stosowanie litu w Polsce w latach 2004–2017.* Farmakoter. Psychiatr. Neurol. 2018; 34(2): 85–94.

94. Post RM. *The new news about lithium: An underutilized treatment in the United States.* Neuropsychopharmacology 2018; 43(5): 1174–1179.
95. Rybakowski JK. *Challenging the negative perception of lithium and optimizing its long-term administration.* Front. Mol. Neurosci. 2018; 11: 349.
96. Malhi GS, Bell E, Boyce P, Hazel P, Murray G, Basset D et al. *Make lithium great again!* Bipolar Disord. 2020; 22(4): 325–327.
97. Rybakowski J. *Leczenie litem w literaturze i sztuce*. Farmakot. Psychiatr. Neurolog. 2020; 36 (in press).

Address: Janusz Rybakowski
Poznan University of Medical Sciences
Department of Adult Psychiatry
60-572 Poznań, Szpitalna Street 27/33
e-mail: janusz.rybakowski@gmail.com