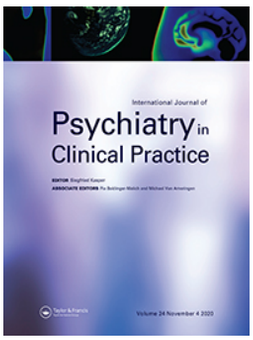

International Journal of Psychiatry in Clinical Practice

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ijpc20

Lithium – past, present, future

Janusz K. Rybakowski

To cite this article: Janusz K. Rybakowski (2020) Lithium – past, present, future, International Journal of Psychiatry in Clinical Practice, 24:4, 330-340, DOI: 10.1080/13651501.2020.1775855

To link to this article: https://doi.org/10.1080/13651501.2020.1775855

Published online: 17 Jun 2020.

INTERNATIONAL JOURNAL OF PSYCHIATRY IN CLINICAL PRACTICE
2020, VOL. 24, NO. 4, 330–340
https://doi.org/10.1080/13651501.2020.1775855

Taylor & Francis
Taylor & Francis Group

Check for updates

REVIEW ARTICLE

Lithium – past, present, future

Janusz K. Rybakowski[a,b]

[a]Department of Adult Psychiatry, Poznan University of Medical Sciences, Poznan, Poland; [b]Department of Psychiatric Nursing, Poznan University of Medical Sciences, Poznan, Poland

ABSTRACT

Objectives: A narrative review of past, present, and future of lithium use in psychiatry.

Methods: The most important references on the topic were reviewed with special emphasis on the author's works.

Results: The history of medical and psychiatric use of lithium dates back to more than one and a half-century ago. However, modern psychiatric history began with the publication of John Cade, in 1949, showing a therapeutic effect of lithium in mania. Currently, lithium is a drug of choice as a mood-stabilizer for the maintenance treatment of the bipolar disorder. The second most important use of lithium is probably augmentation of antidepressants in treatment-resistant depression. In addition to its mood-stabilizing properties, lithium exerts anti-suicidal, immunomodulatory, and neuroprotective action. The drug may protect against dementia and some promising effects of lithium in neurodegenerative disorders have been observed.

Conclusion: Given the clinical and biological properties of lithium, this drug is presently greatly underutilized in mood disorders. Therefore, the efforts should be undertaken for challenging a skepticism about the use of lithium and optimizing its long-term administration. In such a way, more patients with mood disorders can become the beneficiaries of lithium's therapeutic action.

KEY POINTS

- Lithium is a drug of choice as a mood-stabiliser for the maintenance treatment of bipolar disorder.
- Augmentation of antidepressants by lithium is one of the best strategies in treatment-resistant depression.
- Lithium exerts anti-suicidal, immunomodulatory, and neuroprotective action and may protect against dementia.
- Despite the evidence for the efficacy and added favourable properties, lithium is greatly underutilised in mood disorders.
- Challenging a scepticism about the use of lithium and optimising its long-term administration can make more patients with mood disorders the beneficiaries of lithium's therapeutic action.

ARTICLE HISTORY
Received 9 January 2020
Revised 5 May 2020
Accepted 25 May 2020

KEYWORDS
Lithium; mood-stabiliser; bipolar disorder; suicide; herpes; neuroprotection

Historical introduction

The history of medical application of lithium dates back to 1859 when an English physician, Alfred Baring Garrod (1819–1907), introduced lithium salts for the treatment of gout (Garrod 1859). In 1871, an American neurologist, William Alexander Hammond (1828–1900), used lithium bromide for the treatment of mania (Hammond 1871) while in 1886, a Danish physician and scientist, Carl Lange (1834–1900), based on the 'uric acid diathesis' theory of depression, reported on his experiences with lithium carbonate in the treatment and prophylaxis of periodic depression (Lange 1886).

Modern employment of lithium in psychiatry started in 1949, when an Australian psychiatrist, John Cade (1912–1980) described the efficacy of lithium carbonate in the treatment of mania (Cade 1949). The first publication on lithium prophylactic effect in mood disorders took place in the early 1960s (Hartigan 1963). This effect has subsequently been validated and confirmed in many studies and meta-analyses. Presently, the long-term lithium administration for the prevention of manic and depressive recurrences makes the most important recommendation for the use of this drug. Therapeutic activity of lithium in depressive episodes in mood disorders was also demonstrated in the 1970s, and in the early 1980s, the augmentation of the efficacy of antidepressants by lithium was shown (De Montigny et al. 1981). Nowadays, this latter therapeutic strategy employed in treatment-resistant depression can be regarded as the second therapeutic indication for lithium.

Lithium in the treatment of acute episodes in mood disorders

Lithium remains a valuable drug for the management of acute manic and depressive episodes. Following Cade's publication describing the therapeutic action of lithium in ten manic patients, this effect of lithium was demonstrated by Australian investigators on a larger group of such subjects (Noack and Trautner 1951). Several years later, Mogens Schou from Denmark confirmed the antimanic effect of lithium, using a placebo-controlled design (Schou et al. 1954). In the 21st century, several meta-analyses on

CONTACT Janusz K. Rybakowski janusz.rybakowski@gmail.com Department of Adult Psychiatry, Poznan University of Medical Sciences, Szpitalna 27/33, 60-572 Poznan, Poland

the lithium efficacy in mania were performed. In the review of 12 controlled studies, Poolsup et al. (2000) showed a significantly better efficacy of lithium compared with placebo and similar to anticonvulsant drugs as carbamazepine and valproates. A comparison of the 3-week treatment of lithium and placebo in moderate to severe manic episodes revealed a significantly better effect of lithium with a relative risk of 0.40 (Storosum et al. 2007). However, in a recent meta-analysis comparing many anti-manic medications, lithium was outperformed by both haloperidol and new antipsychotic drugs such as olanzapine and risperidone (Cipriani et al. 2011).

Nowadays, the best candidates for lithium are patients with hypomania, where lithium can be used as monotherapy, with a concentration in the range of 0.6–0.8 mmol/l. In a manic episode, lithium monotherapy is mostly indicated for patients with 'euphoric' mood elevation, without irritability of mixed features, and moderate psychomotor hyperactivity. The concentration of lithium for the treatment of manic episode should be in the range of 0.8–1.2 mmol/l. For patients with severe bipolar illness, frequent hospitalisations, and rapid cycling, lithium in mania is usually combined with other mood-stabilizing drugs.

Antidepressant effects of lithium were reported in the 1970s (Rybakowski et al. 1974; Mendels 1976). It was suggested that such a response to lithium may be better in bipolar than unipolar depression although generally weaker than tricyclic antidepressants. Thereafter, the use of lithium for the treatment of bipolar depression was recommended in several guidelines. However, it seems that more important was a finding of Canadian psychiatrists, demonstrating that in case of insufficient effect, adding lithium to antidepressant drugs brings a substantial, and sometimes very rapid, improvement of mood (De Montigny et al. 1981). This heralded the era of using lithium for augmenting the efficacy of antidepressant drugs. Rybakowski and Matkowski (1992) showed that the addition of lithium to antidepressants results in a more favourable outcome in depression in the course of bipolar disorder than in unipolar disorder. A review on this subject by the German psychiatrists, also comparing the effect of lithium with a placebo, demonstrated that lithium is an effective remedy augmenting the effect of antidepressant drugs in treatment-resistant depression both bipolar and unipolar, and a successful outcome may be expected in at least 50% of patients (Crossley and Bauer 2007).

Given the increasing occurrence of treatment-resistant depression, a strategy of adding lithium to antidepressants can be considered as an important indication for lithium use. Lithium can be safely added to various kinds of antidepressants (tricyclic, SSRI, SNRI), obtaining a concentration of 0.6–0.8 mmol/l. In about ¼ of patients, a rapid response (within several days) is observed. The associations of better outcomes with more severe depressive symptomatology, significant weight loss, psychomotor retardation, a history of more than three major depressive episodes and a family history of major depression have been reported (Bauer et al. 2014). Adli et al. (2007) suggested a predictive role of the −50 T/C single nucleotide polymorphism of the glycogen synthase kinase 3 beta (*GSK3β)* gene in the probability of response to lithium augmentation.

Lithium for 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. More than half a century ago, a British psychiatrist, Geoffrey Hartigan, demonstrated that the administration of lithium for three years to seven patients with bipolar disorder and eight with recurrent depression resulted in a disappearing of illness' recurrences in six bipolar and six depressive patients (Hartigan 1963). A year later, similar observations were made by the Danish psychiatrist, Paul Christian Baastrup, (Baastrup 1964). And four years later, the paper of the Danish psychiatrists appeared, summing up the experiences of lithium administration for an average duration of six years to 88 patients with unipolar and bipolar mood disorder. The authors showed that, while the average duration of mood disorders within a year preceding lithium use was 13 weeks, it decreased on lithium to two weeks, arguing that lithium may exert a favourable prophylactic effect on the course of mood disorders (prophylactic or mood-stabilizing effect) (Baastrup and Schou 1967). However, next year, a backlash on the concept of lithium prophylaxis appeared in Lancet where British researchers described prophylactic lithium as 'another therapeutic myth' (Blackwell and Shepherd 1968).

Publication of the results of eight controlled studies, including the use of placebo performed in Europe (in Denmark and the UK) and in the USA, researching the prophylactic effectiveness of lithium, took place in 1970–1973. All patients studied, had, in the period of the preceding 2 years, at least two recurrences of illness. Analysis of all research showed that the percentage of patients in whom recurrences of depression or mania occurred, was on average 30% while receiving lithium, and on average 70% while taking a placebo (Schou and Thompsen 1975). Following these publications, the use of lithium for prophylaxis of mood disorders had been flourishing, reaching its peak on 1980/1990.

Three meta-analyses of the 21st century have amply confirmed the prophylactic effectiveness of lithium in bipolar disorder. The first analysis performed by Geddes et al. (2004) including five randomised controlled trials of total of 770 patients showed that lithium was significantly more effective than a placebo in preventing all affective relapses, being slightly better against manic than against depressive recurrences. In the second study, Nivoli et al. (2010) analysed long-term controlled trials lasting at least half a year, with 1561 patients, of whom 534 were receiving lithium. They noticed that earlier research had suggested the nearly equal effectiveness of lithium against both mania and depression, while in more recent studies, lithium prophylaxis has been perceived as more effective against manic than against depressive relapses. The most recent meta-analysis was performed by Severus et al. (2014). Including seven trials (1580 patients) comparing lithium with placebo, the authors concluded that lithium was significantly superior to placebo in preventing any mood episodes and manic episodes. In some analyses, lithium was also better than a placebo in preventing depressive episodes.

The term 'excellent lithium responders' was introduced by a Canadian psychiatrist, Paul Grof (1999), for patients who on monotherapy with lithium experienced a dramatic change in their life as their mood episodes were completely prevented. To verify this, we followed-up for ten years 60 patients who started lithium prophylaxis in the 1970s, and 49 patients beginning this procedure in the 1980s. Those without mood episodes during this period (ER) made 35% of the first group and 27% of the second one, roughly one-third of bipolar subjects treated longitudinally with lithium (Rybakowski et al. 2001). Grof (2010) suggests that lithium responders can be characterised by distinct mood episodes, with full remissions between them, the absence of other psychiatric morbidity and frequent history of bipolar illness in their families. This may remind the aspects of the illness, defined by Emil Kraepelin (1899) as 'manisch-depressives Irresein'. Grof implies

that the favourable reaction to lithium also occurs in the next generation of lithium responders what was confirmed in a Polish study (Kliwicki et al. 2014). Recent meta-analyses indicated that the most favourable factors for lithium prophylaxis include episode sequence mania-depression-remission, later onset of the illness, non-rapid cycling course, and early implementation of lithium (Hui et al. 2019). In the following years, a prospective cohort study named the Response to Lithium Network (R-LINK) aims to examine the early prediction of lithium response combining clinical syndrome subtyping with examinations of multi-modal biosignatures (Scott et al. 2019).

The quality of prophylactic lithium response made a topic for molecular-genetic studies. A review of genetic influences on the efficacy of lithium prophylaxis was made by the author of this article. Using the 'candidate gene' approach, several genes were found to be associated with prophylactic lithium response. They have been those connected with neurotransmitters (serotonin transporter, dopamine D1 receptor – *DRD1*) genes, second messengers (inositol polyphosphate 1-phosphatase – *INPP1*, cAMP response element-binding protein – *CREB1*) genes, glycogen synthase kinase 3-β (*GSK-3β*) gene, brain-derived neurotrophic factor (*BDNF*) gene, glucocorticoid receptor (*NR3C1*) gene, circadian rhythms (*Rev-Erba-α*) gene, and genes located on chromosome 22q11-13 (breakpoint cluster region – *BCR*, X-box binding protein 1 – *XBP1*, and the calcium channel gamma-2 subunit – *CACNG2*) genes (Rybakowski 2013).

In 2009, an initiative of the National Institutes of Mental Health and the International Group for the Study of Lithium-treated Patients (IGSLI) resulted in the formation of the International Consortium on Lithium Genetics (ConLiGen) (Schulze et al. 2010). In 2013, the first report of the key phenotypic measures of the 'Retrospective Criteria of Long-Term Treatment Response in Research Subjects with Bipolar Disorder' scale, known as the Alda's scale, used by ConLiGen was presented (Manchia et al. 2013). The first genome-wide association study (GWAS) of lithium response, in which 2563 patients were included, coming from 22 participating sites of the ConLiGen, revealed a single locus of four linked single nucleotide polymorphisms (SNPs) on chromosome 21 met genome-wide significance criteria for association with lithium response. This region contains two genes for long, non-coding RNAs (lncRNAs) which are important regulators of gene expression in the central nervous system (Hou et al. 2016).

Nowadays, lithium is regarded as a drug of the first choice for long-term prevention of mood recurrences in bipolar disorders. Most clinicians agree that the lithium concentration for prophylactic purposes should be within the range of 0.6–0.8 mmol/l. Kessing et al. (2018) analysed observational studies comparing monotherapy with lithium and monotherapy with other mood stabilisers. They found that prophylactic lithium monotherapy was more effective, compared to monotherapy with such mood stabilisers as valproate, lamotrigine, olanzapine and quetiapine. Finnish authors studied the comparative effectiveness of pharmacological treatments in a nationwide cohort of patients with bipolar disorder and found that lithium was most effective in the prevention of hospitalisation in such patients (Lähteenvuo et al. 2018).

As a proportion of excellent responders to monotherapy with lithium is about 1/3, a majority of bipolar patients are treated with combination therapy. Many studies have shown that a combination of lithium with quetiapine, olanzapine and aripiprazole is much better prophylactically that either of this drug alone (Marcus et al. 2011; Katagiri et al. 2012; Suppes et al. 2013). In the study of Altamura et al (2008), it was shown that the efficacy of combined lithium and quetiapine doubles that of monotherapy with each drug.

The seminal paper of Hartigan (1963) reported a good prophylactic effect of lithium in recurrent depression. However, this indication for long-term lithium administration has been rather neglected. A meta-analysis performed in 1991 showed a significantly lower number of episodes in patients being on lithium (average 30%) than those on a placebo (average 65%). In addition, no difference as to the prophylactic effect between lithium and antidepressant drugs was demonstrated (Souza and Goodwin 1991). The most recent analysis included five randomised controlled studies comparing lithium and placebo and five such studies differentiating lithium and antidepressants. The prophylaxis with lithium was significantly better than the placebo and insignificantly so than antidepressants (Undurraga et al. 2019). Finnish researchers assessed the risk of rehospitalization in 1996–2012 in a cohort of 123,712 patients with severe recurrent depression. Lithium administration 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). The reduced risk was even higher when lithium was used as monotherapy (Tiihonen et al. 2017).

Adverse effects of long-term lithium treatment and their management

The adverse effects of lithium perceived as posing a significant challenge for its long-term administration include mostly kidney and thyroid effects. Polyuria and polydipsia may occur within several weeks of lithium treatment. The main reason is a decrease in renal concentrating capacity caused by lithium. This side-effect can alleviate after reducing lithium dose and disappears after lithium discontinuation. However, with long-term lithium use, the most serious concern is the possibility of lithium-induced interstitial nephropathy. This complication can develop after 10–20 years of treatment and leads to increased creatinine concentration and a decreased glomerular filtration rate (GFR). In a recent international study (12 participating centers), the data of 312 patients with bipolar disorder, with the mean age of 56 (range 20–89) years receiving lithium carbonate for 8–48 (mean 18) years were analysed. Nearly 1/3 of subjects had the value of GFR $<$60 mL/min/1.73 m^2, more frequently after $\geq$15 years of lithium administration, and after 55 years of age. However, no case of end-stage renal failure was detected (Tondo et al. 2017).

In long-term lithium-treated patients with progressive renal damage, discontinuation of lithium and replacing with other mood-stabiliser can be considered. However, a decision about stopping lithium should be taken with caution, especially in good responders, since other mood stabiliser may not be equally efficacious. This may result in a high risk of relapse of the illness and a further treatment-resistant course. In patients with lithium-induced nephropathy, kidney function should be closely and frequently monitored and some guidelines for managing such patients were recently published (Severus and Bauer 2013).

The influence of lithium on the thyroid gland is also regarded as important in long-term therapy with this drug. Lithium is accumulated in the thyroid gland at 3 to 4-fold higher concentrations as compared to its plasma levels. Its administration results in reduced production with release inhibition of thyroid hormones, altering the immune processes of this gland. The most common thyroid side effects associated with long-term lithium treatment are goitre and hypothyroidism. However, in bipolar disorder, the thyroid function should be examined in the context of the role of

the thyroid gland, the hypothalamic–pituitary–thyroid axis, and the thyroid autoimmunity in the pathophysiology of this illness. In our recent study, the concentration of the thyroid-stimulating hormone (TSH) and the volume of the thyroid gland were significantly higher in bipolar patients receiving lithium compared with such patients lithium-naïve. However, the frequency of hypothyroidism in the course of the illness was similar in both groups, higher in women than in men. In lithium-treated subjects, hypothyroidism developed usually in the first years of lithium therapy, and all hypothyroid subjects were successfully treated with levothyroxine (Kraszewska et al. 2019a). In another study, no difference in thyroid autoantibodies was found between the two groups (Kraszewska et al. 2019b).

A moderate cognitive impairment has also been perceived by clinicians as connected with lithium treatment. However, since patients with bipolar disorder present cognitive problems of mild intensity across mood states, this should be taken into account when assessing the lithium effect. A review of the effect of lithium on cognitive functions was recently published (Rybakowski 2016). It seems that lithium treatment may not negatively affect previously impaired cognitive functions in bipolar patients (López-Jaramillo et al. 2010). We correlated cognitive functions in lithium-treated patients with a quality of lithium prophylactic effect. Non-responders to lithium had significantly worse performance on many domains of the Wisconsin Card Sorting Test, compared to excellent and partial responders (Rybakowski et al. 2009). In another study, using neuropsychological tests from a CANTAB battery which measured spatial working memory and sustained attention, we demonstrated that bipolar patients who are excellent lithium responders have cognitive functions comparable to those of matched control subjects, thereby probably constituting a specific subgroup of bipolar patients in which long-term lithium administration can produce complete normality in this respect (Rybakowski and Suwalska 2010).

In women with bipolar disorder, there is an increased risk for a recurrence of illness during pregnancy. Therefore, women with the previous favourable effect of lithium should continue using lithium during pregnancy. A recent meta-analysis included data from pregnant women and their children from six international cohorts based on the community (Denmark, Sweden and Canada) and clinics (the Netherlands, UK and the USA), identifying 727 lithium-exposed out of 22,124 eligible pregnancies. Lithium exposure was not associated with any of the predefined pregnancy complications or delivery outcomes. Such an exposure during the first trimester was associated with a 1.7-fold increased risk of major malformations but for major cardiac malformations, the difference was not significant. A 1.6-fold increased risk for neonatal readmission within 28 days of birth was also seen in the lithium-exposed group (Munk-Olsen et al. 2018). It is recommended that in the first trimester, the daily dose of lithium carbonate should not exceed 500 mg. Starting with the second trimester, there is a necessity to increase the lithium dose. The dose of lithium should be reduced or lithium temporarily stopped for one or two days before expected delivery. Lithium is excreted in breast milk and then in infants, the plasma levels may reach 30–50% of the mother. Therefore, the mother should rather avoid breastfeeding or reduce lithium dose and monitor closely the infant for any signs of toxicity (Rybakowski et al. 2019).

Recently, we described five patients (two men and three women, aged 64–79 years) with a good response to the ultra-long-term lithium treatment (40–45 years). Serum lithium in them was in the range of 0.60–0.65 mmol/l, except for one male, having 0.7–0.8 mmol/l. Both males had impaired renal function with no progression in the last five years. One female suffered from Hashimoto's disease and was treated with levothyroxine. In all patients, the cognition and professional activity were at the level of healthy subjects with comparable age and education's years. Their functioning in family and social roles was good. The beginning of lithium prophylaxis usually has been made within the first three years of the illness. Thus, in patients with favourable response to lithium, such a longitudinal administration of the drug can produce a satisfactory performance in vocational and psychosocial areas, and the management of potential adverse effects can be adequate (Permoda-Osip et al. 2016).

Lithium as an antisuicidal drug

The antisuicidal effect of lithium can be a valuable asset of the long-term treatment with this drug. The evidence that such treatment can decrease mortality, primarily by preventing suicide, has been accumulated since the early 1990s (Coppen et al. 1991). The decade of the 1990s made the period of intensive studies on the antisuicidal effect of lithium made by the researchers assembled in the International Group for the Study of Lithium-treated Patients (IGSLI). While analysing 827 patients with bipolar and schizoaffective disorder given lithium treatment for more than six months they observed that the mortality of these patients did not differ significantly from that of the general population (Müller-Oerlinghausen et al. 1992). In 471 patients, mortality and suicidal behaviour were compared during the initial and later period of lithium treatment. In the initial period, the mortality was twice that of the general population, and suicides were 16-fold more frequent. In the later period, both mortality and suicides were similar to the general population. The authors concluded that the full antisuicidal effect of lithium comes after two years of lithium treatment (Müller-Oerlinghausen et al. 1994)

The antisuicidal effect of lithium was confirmed by the meta-analyses performed in the 21st century. Harvard University group included 45 papers containing data on suicides committed while taking lithium (on average for 1.5 years) and 34 papers registered suicides of persons not receiving lithium, showed that the risk of committing suicide was five times lower among patients taking lithium than those subjected to other forms of treatment (Baldessarini et al. 2006). A recent meta-analysis performed by Cipriani et al. (2013) with 6674 patients concluded that lithium was significantly better than a placebo in reducing the number of suicides and deaths from any cause both in bipolar disorder and recurrent depression and superior to other mood-stabilisers or antidepressants.

Currently, the anti-suicidal effect of lithium in mood disorders is well documented and it has been shown that it is significantly greater than other mood-stabilizing drugs. While being on lithium prevents suicide, its discontinuation significantly increases this risk. The anti-suicidal effect is not correlated with the quality of prevention of mood recurrences by lithium, which points to the specificity of such an effect in reference to lithium (Lewitzka et al. 2015).

Given the evidence of the antisuicidal effect of lithium, it seems reasonable to consider long-term lithium administration in each patient with a mood disorder with a high suicidal risk. Such a risk can be assessed according to appropriate guidelines (Costa et al. 2015). In excellent lithium responders, lithium can be administered as monotherapy. In the remaining patients with a high suicidal risk, lithium should be a component of combined mood-stabilizing therapy.

Interestingly, in the recent decade, the antisuicidal effect of lithium has also been demonstrated with trace levels of this drug.

In studies performed in Japan, Austria, Greece and the USA, a negative correlation between suicides and lithium concentrations in drinking water was found (Ohgami et al. 2009; Kapusta et al. 2011; Blüml et al. 2013; Giotakos et al. 2013). These findings prompted an idea of recognising lithium as being an essential trace element for mental health. There have been also proposals for lithium supplementation of drinking water in lithium-deficient areas.

Antiviral and immunomodulatory properties of lithium

The antiviral and immunomodulatory properties of lithium have been matters of increasing interest. Four decades ago, researchers from the University of Birmingham showed that lithium in 5–30 mmol/l concentration inhibits replication of the herpes simplex virus (Skinner et al. 1980). At that time, the descriptions of labial herpes remissions while using lithium appeared (Lieb 1979; Gitlin 2016). Labial herpes is caused by an infection of herpes simplex virus type 1 (HSV-1) and occurs in approximately 1/3 of the population, and its course is characterised by frequent recurrences.

Retrospective research of labial herpes in patients receiving lithium for prophylactic purposes was carried out within a collaborative study of the Department of Adult Psychiatry, Poznan University of Medical Sciences, and the Department of Psychiatry of the University of Pennsylvania. In the Polish population of 28 persons with recurrent labial herpes, during lithium therapy, the full cessation of recurrence of herpes occurred in 13 patients, among 7 the frequency of recurrences decreased, among 6 it remained at the same level and among 2 it increased. The general decrease in recurrence frequency was 64%. The better effect was observed in patients in whom lithium concentration in the serum was higher than 0.65 mmol/l, and erythrocyte lithium concentration exceeded 0.35 mmol/l. The American population comprised of two groups, 52 persons in each, matched with regard to sex, age and the duration of systematic pharmacological treatment. In the first group, including mostly patients with bipolar disorder treated with lithium, the frequency of labial herpes recurrences in comparison with the 5-year period before the treatment decreased by 73%. In the second group, including patients with recurrent depression receiving antidepressant drugs, no significant difference was observed (Rybakowski and Amsterdam 1991).

Lithium can also greatly influence the hematological and immunological system. An increase of leukocytes by lithium treatment was observed 70 years ago (Radomski et al. 1950) and subsequently confirmed in many studies. Such a property of lithium made possible its therapeutic uses also beyond psychiatry (e.g., in hematology) (Focosi et al. 2009).

It was also found that lithium can mitigate the immune-endocrine component of the pathogenesis of bipolar disorder, such as acute-phase reaction, production of pro-inflammatory cytokines and excessive activation of the hypothalamic–pituitary–adrenal axis (Rybakowski 2000). The recent review of the anti-inflammatory effect of lithium was done by Nassar and Azab (2014). We examined the impact of long-term lithium administration on very small embryonic-like stem cells (VSELs) and the mRNA expression of pluripotency and glial markers, in peripheral blood. Our results showed that lithium can alleviate excessive regenerative and inflammatory processes in bipolar disorder (Ferensztajn-Rochowiak et al. 2018).

Neuroprotective effect of lithium – a possibility of its use in neurodegenerative disorders

The issue of a possible neuroprotective effect of lithium, and consequently, its possible prophylactic and therapeutic effect in dementia, made a fascinating area of research in recent years. There is considerable evidence for lithium causing an increase in cerebral grey matter volume both in healthy subjects and in patients with bipolar disorders. This may reflect a neuroprotective effect at a clinical level. Moore et al. (2000) first suggested a lithium-induced increase in human brain grey matter. Following this, the results of several confirmatory studies have been reported and reviewed by Hajek and Weiner (2016). The brain structures influenced by either short-term or long-term, lithium treatment were the prefrontal cortex, anterior cingulate and hippocampus. The most frequently reported pattern was larger grey matter volumes in patients currently treated with lithium compared to those currently not on lithium. The association between lithium treatment and higher grey matter volume was reported regardless of mood state and diagnostic subtype. In the IGSLI study, bipolar patients receiving lithium had larger hippocampal volumes compared to non-lithium patients, similar to healthy controls (Hajek et al. 2014). Two studies comparing the effects of lithium with those of anticonvulsants and antipsychotics, possessing mood-stabilizing properties, found that lithium caused an increase in grey matter volume of subgenual anterior cingulate, the hippocampus–amygdala complex and the insula, what was associated with a positive clinical response. Such an effect was not demonstrated by any other treatment (Germaná et al. 2010; Lyoo et al. 2010).

Corresponding with lithium neuroprotective effects, the suggestions were advanced that lithium could protect against dementia. The population studies have shown an association between lithium treatment and dementia risk reduction or reduced dementia severity (Donix and Bauer 2016). Using the Danish nationwide register of lithium prescriptions, it was found that in patients taking lithium for a long time, the rate of dementia decreased to the same level as the rate for the general population while in persons treated with anticonvulsant drugs, the risk of dementia increased with the duration of treatment (Kessing et al. 2008). Long-term treatment with lithium was also associated with a reduced rate of dementia in patients with bipolar disorder, in contrast to such treatment with anticonvulsants, antidepressants and antipsychotics (Kessing et al. 2010).

Three studies on lithium treatment of Alzheimer's disease (AD) or mild cognitive impairment (MCI) were meta-analysed by Matsunaga et al. (2015). The results of this analysis suggest some benefit from lithium treatment. Of interest, one of these studies (Nunes et al. 2013) evaluated the effect of a microdose of 300 μg lithium, administered to AD patients once daily for 15 months. The treated group showed no decreased performance in the mini-mental state examination test, in opposition to the lower scores observed for the control group during this time. A possible effect of trace doses of lithium has been recently proposed in a Danish study of Kessing et al. (2017) showing a negative association between the incidence of dementia and lithium concentration in drinking water. Concurring with this, a recent American study demonstrated that changes in AD mortality were negatively correlated with trace lithium in drinking water (Fajardo et al. 2017).

There were also attempts to use lithium in other neurodegenerative disorders, based on promising experimental findings on the animal models. However, the results of clinical studies were not significant (Rybakowski et al. 2018).

Mechanisms of lithium action

It has been generally accepted that the most important biochemical mechanisms of lithium action are connected with intracellular signalling, especially, the phosphatidylinositol (PI) system, and with the inhibition by lithium of the glycogen synthase kinase-3beta (GSK-3β) (Brown and Tracy 2013). Lithium inhibits inositol monophosphatase-1 which ameliorates inositol depletion-related mitochondrial dysfunction. Changes in PI signalling measured as a spread of growth cones were postulated to make a common effect of the first generation mood stabilisers (lithium, valproate and carbamazepine) (Williams et al. 2004). Lithium also influences the adenylyl cyclases which convert ATP into cyclic adenosine monophosphate (cAMP), an element of this system being the cAMP response element-binding protein (CREB), the regulator of gene expression. Lithium inhibits another component of intracellular signalling such as protein kinase C (PKC). This mechanism of lithium is shared with another mood-stabilizing drug, valproate, and made a basis to introduce PKC inhibitor, tamoxifen, to the treatment of mania (Palacios et al. 2019).

The evidence has accumulated using various experimental models showing that lithium inhibits GSK-3β activity (Stambolic et al. 1996). GSK-3β is a serine/threonine kinase that regulates gene transcription, synaptic plasticity, apoptosis, cellular structure and resilience and the circadian cycle, all of which are implicated in the pathophysiology of mood disorders. Therefore, the GSK-3β inhibition by lithium can make an important mechanism of therapeutic action in these conditions (Jope 2011). GSK-3β is also a key enzyme in the metabolism of amyloid precursor protein and the phosphorylation of the tau protein, playing the main pathogenetic role in AD and its inhibition may underlie a favourable effect of lithium in this illness (Morris and Berk 2016).

Many experimental and clinical studies demonstrated that lithium can ameliorate and rectify circadian rhythm due to its effect on the GSK-3β and PI system and by modulating the expression of certain clock genes. In our molecular-genetic study, we found an association between the prophylactic effect of lithium and polymorphisms in the biological clock genes (Rybakowski et al. 2014).

Lithium exerts a stimulatory action on the brain-derived neurotrophic factor (BDNF), the most important member of the neurotrophin family, necessary for the survival and function of neurons. BDNF modulates the activity of such neurotransmitters like glutamate, gamma-aminobutyric acid, dopamine and serotonin. In clinical studies, lithium treatment increases the blood level of BDNF (Rybakowski 2014). The Val66Met polymorphism of the BDNF gene was associated with cognitive functions in patients with bipolar disorder (Rybakowski et al. 2006), and with prophylactic lithium response (Rybakowski et al. 2005). Enhancing by lithium the BDNF system plays a significant role in its pro-cognitive and neuroprotective activity.

It has been also hypothesised that the antiviral effect of lithium against herpes infections may be important for its pro-cognitive action in bipolar disorder and both prophylactic and therapeutic activity in dementia. Dickerson et al. (2004) demonstrated that infection with HSV-1 was an independent predictor of decreased cognitive functioning (mostly immediate verbal memory) in bipolar patients. Recently, Itzhaki (2018) reviewed the evidence for a major role for HSV-1 in AD, and a possible anti-HSV-1 mechanism of lithium in its anti-dementia activity was proposed (Rybakowski 2019).

Underutilisation of lithium

Despite the evidence of efficacy and beneficial clinical effects, it looks like the use of lithium in the treatment of mood disorders is inadequate. One of the reasons may be the introduction and active promotion of other mood-stabilizing drugs. These drugs may be divided into first-generation mood stabilisers, introduced between 1960 and 1970 (lithium, valproates and carbamazepine), and second-generation mood stabilisers, introduced since the second half of the 1990s, which include atypical antipsychotics (clozapine, olanzapine, quetiapine, aripiprazole and risperidone) and lamotrigine (Rybakowski 2007, 2018b). Another reason for the limited use of lithium may be the perception of it as a 'toxic' drug due to its side effects, mainly on thyroid, renal and cognitive functions. This perception is common not only among doctors of different specialties but also among some psychiatrists.

Insufficient usage of lithium can be reflected by trends in the prescription of mood-stabilisers in recent decades. Baldessarini et al. (2007) evaluated prescriptions for a group of American patients with bipolar disorder during 2002–2003. They found that lithium was prescribed to 7% of such patients while mood-stabilizing anticonvulsants to 17%, and antipsychotics to 11% of them. Hayes et al. (2011) assessed prescribing patterns of antipsychotics and mood stabilisers in primary care in bipolar patients in the United Kingdom in 1995–2009. During this period, the use of lithium increased from 22.5% to 29.3%, that of valproate from zero to 22.7%, carbamazepine from 6.5% to 7.3%, lamotrigine from zero to 6.2% and second-generation antipsychotics from zero to 35% (most frequently used were olanzapine – 18%, and quetiapine – 6%). Stephenson et al. (2013) analysed the trends in the prescription of psychotropic medications in Australia from 2000 to 2011. In 2011, mood stabilisers such as lithium, valproate, carbamazepine and lamotrigine accounted for 5.8% of total psychotropic defined daily doses. From 2000 to 2011, lithium prescription remained stable while valproate and lamotrigine markedly increased.

Among Scandinavian countries, the data for a group of Danish patients with a diagnosis of mania or bipolar disorder during the decade from 2000 to 2011, showed that one-year prescription rate of lithium during this period decreased from 41.1% to 34%, and, in 2011, this drug was exceeded by lamotrigine (increased from 3.4% to 42.1%), and by quetiapine (increased from 0 to 39.5%). In the same period, the prescription of valproate increased from 6.9% to 14.4%, olanzapine from 8.7% to 14.3%, and aripiprazole from 0 to 10.5% (Kessing et al. 2016). In Sweden, among mood stabiliser prescriptions for bipolar disorder during 2007–2013, the lithium use decreased from 51% to 41%, with a concomitant increase of lamotrigine (from 25% to 33%) and quetiapine (from 9% to 25%). The use of valproate decreased (from 18% to 14%) as well as that of olanzapine (from 21% to 17%) (Karanti et al. 2016).

An attempt has also been made to study the prescription of lithium in Poland, the home country of the author of this review. During 2004–2010, the prescription of lithium in Poland rose by 4% while in 2010–2017, this increase amounted to 16%. However, in the second half of 2017, the prescriptions of lithium for bipolar disorder were surpassed 2.9-fold by valproate, 2.1-fold by quetiapine, 1.9-fold by olanzapine and 1.8-fold by lamotrigine (Rybakowski and Checinska 2018).

Challenging the negative perception of lithium and optimising its long-term administration

The eminent specialist on bipolar disorder, Robert Post (2018) deplores that lithium is greatly underutilised in the USA. He points to the multiple assets of lithium beyond its antimanic and prophylactic effect, such as antidepressant action, suicide

prevention, pro-cognitive and anti-dementia effects as well as diminishing the frequency of a few medical conditions. He argues that the fear of lithium side-effects such as progressive renal impairment can be exaggerated and also points at the purposefulness of the early start of the long-term prophylaxis with lithium such as following the first episode of mania.

The title of this subchapter is that of a recent article written by the author of this review (Rybakowski 2018). The main point is that a sceptical perception of lithium as a first-line candidate for the prophylaxis of bipolar disorder, made by many psychiatrists can be challenged, based on the data showing its clinical efficacy and the possibility of managing its main adverse effects. There has also been a postulate to begin prophylaxis with lithium in the initial stage of the illness. More than twenty years ago, Franchini et al. (1999) showed that beginning lithium therapy within the first ten years of illness predicts better outcomes of the prophylaxis. In addition, Kessing et al. (2014) demonstrated that starting lithium treatment following the first manic episode is associated with an increased probability of the good response. There has also been data that such an approach can provide a favourable influence on neuroprogression of the illness. Recently, it was found that, after the first episode of mania, lithium was superior to quetiapine in limiting white matter reduction and regulating neural connection between the ventral striatum and the cerebellum (Berk et al. 2017, Dandash et al. 2018).

Some other beneficial effects of lithium were described such as enhancing bone mineral density (Zamani et al. 2009) reflecting in reduced relative risk of fractures in lithium-treated patients (Vestergaard et al. 2005). In addition, the suggestions have been advanced that lithium treatment can lower cancer risk (Huang et al. 2016).

Recently, recommendations concerning safe clinical use of lithium were presented by the International Group for Studies of Lithium (IGSLI) (Tondo et al. 2019). While lithium is an orphan drug, without active support by any major pharmaceutical company, it only remains the sound scientific evidence that can promote the more extensive and long-term application of lithium in mood disorders, and especially, bipolar disorder. A belief can be expressed that this review may provide a small contribution to this aim, providing more patients with mood disorders to become the beneficiaries of lithium's therapeutic action. It is also hoped that the data on the neuroprotective effect can bring novel possibilities for the therapeutic use of lithium.

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Janusz K. Rybakowski http://orcid.org/0000-0003-0577-0381

References

Adli M, Hollinde DL, Stamm T, Wiethoff K, Tsahuridu M, Kirchheiner J, Heinz A, Bauer M. 2007. Response to lithium augmentation in depression is associated with the glycogen synthase kinase 3-beta -50T/C single nucleotide polymorphism. Biol Psychiatry. 62(11):1295–1302. doi:10.1016/j.biopsych.2007.03.023

Altamura AC, Mundo E, Dell'Osso B, Tacchini G, Buoli M, Calabrese JR. 2008. Quetiapine and classical mood stabilizers in the long-term treatment of bipolar disorder: a 4-year follow-up naturalistic study. J Affect Disord. 110(1–2):135–141. doi:10.1016/j.jad.2008.01.017

Baastrup PC. 1964. The use of lithium in manic-depressive psychoses. Compr Psychiatry. 5(6):396–408. doi:10.1016/S0010-440X(64)80049-3

Baastrup PC, Schou M. 1967. Lithium as a prophylactic agents. Its effect against recurrent depressions and manic-depressive psychosis. Arch Gen Psychiatry. 16(2):162–172. doi:10.1001/archpsyc.1967.01730200030005

Bauer M, Adli M, Ricken R, Severus E, Pilhatsch M. 2014. Role of lithium augmentation in the management of major depressive disorder. CNS Drugs. 28(4):331–342. doi:10.1007/s40263-014-0152-8

Baldessarini RJ, Tondo L, Davis P, Pompili M, Goodwin FK, Hennen J. 2006. Decreased risk of suicides and attempts during long-term lithium treatment: a meta-analytic review. Bipolar Disord. 8(5p2):625–639. doi:10.1111/j.1399-5618.2006.00344.x

Baldessarini RJ, Leahy L, Arcona S, Gause D, Zhang W, Hennen J. 2007. Patterns of psychotropic drug prescription for U.S. patients with diagnoses of bipolar disorders. Psychiatr Serv. 58(1):85–91. doi:10.1176/ps.2007.58.1.85

Berk M, Dandash O, Daglas R, Cotton SM, Allott K, Fornito A, Suo C, Klauser P, Liberg B, Henry L, et al. 2017. Neuroprotection after a first episode of mania: a randomized controlled maintenance trial comparing the effects of lithium and quetiapine on grey and white matter volume. Transl Psychiatry. 7(1):e1011–e1011. doi:10.1038/tp.2016.281

Blackwell B, Shepherd M. 1968. Prophylactic lithium: another therapeutic myth? An examination of the evidence to date. Lancet. 291(7549):968–971. doi:10.1016/S0140-6736(68)90917-3

Blüml V, Regier MD, Hlavin G, Rockett IRH, König F, Vyssoki B, Bschor T, Kapusta ND. 2013. Lithium in the public water supply and suicide mortality in Texas. J Psychiatr Res. 47(3):407–411. doi:10.1016/j.jpsychires.2012.12.002

Brown KM, Tracy DK. 2013. Lithium: the pharmacodynamic actions of the amazing ion. Ther Adv Psychopharmacol. 3(3):163–176. doi:10.1177/2045125312471963

Cade JFK. 1949. Lithium salts in the treatment of psychotic excitement. Med J Aust. 2(10):349–352. doi:10.5694/j.1326-5377.1949.tb36912.x

Cipriani A, Barbui C, Salanti G, Rendell J, Brown R, Stockton S, Purgato M, Spineli LM, Goodwin GM, Geddes JR. 2011. Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. Lancet. 378(9799):1306–1315. doi:10.1016/S0140-6736(11)60873-8

Cipriani A, Hawton K, Stockton S, Geddes JR. 2013. Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. BMJ. 346:f3646. doi:10.1136/bmj.f3646

Coppen A, Standish-Barry H, Bailey J, Houston G, Silcocks P, Hermon C. 1991. Does lithium reduce the mortality of recurrent mood disorders? J Affect Disord. 23(1):1–7. doi:10.1016/0165-0327(91)90030-V

Costa L. d S, Alencar ÁP, Nascimento Neto PJ, dos Santos M. d S V, da Silva CGL, Pinheiro S. d F L, Silveira RT, Bianco BAV, Pinheiro RFF, de Lima MAP, et al. 2015. Risk factors for suicide in bipolar disorder: a systematic review. J Affect Disord. 170:237–254. doi:10.1016/j.jad.2014.09.003

Crossley NA, Bauer M. 2007. Acceleration and augmentation of antidepressants with lithium for depressive disorders: two meta-analyses of randomized, placebo-controlled trials. J Clin Psychiatry 68: 935–940.

Dandash O, Yücel M, Daglas R, Pantelis C, McGorry P, Berk M, Fornito A. 2018. Differential effect of quetiapine and lithium on functional connectivity of the striatum in first episode mania. Transl Psychiatry. 8(1):59. doi:10.1038/s41398-018-0108-8

De Montigny C, Grunberg F, Mayer A, Deschenes JP. 1981. Lithium induces rapid relief of depression in tricyclic antidepressant nonresponders. Br J Psychiatry. 138(3):252–256. doi:10.1192/bjp.138.3.252

Dickerson FB, Boronow JJ, Stallings C, Origoni AE, Cole S, Krivogorsky B, Yolken RH. 2004. Infection with herpes simplex virus type 1 is associated with cognitive deficits in bipolar disorder. Biol Psychiatry. 55(6):588–593. doi:10.1016/j.biopsych.2003.10.008

Donix M, Bauer M. 2016. Population studies of association between lithium and risk of neurodegenerative disorders. Curr Alzheimer Res. 13(8):873–878. doi:10.2174/1567205013666160219112957

Fajardo VA, Fajardo VA, LeBlanc PJ, MacPherson REK. 2017. Examining the relationship between trace lithium in drinking water and the rising rates of age-adjusted Alzheimer's disease mortality in Texas. JAD. 61(1):425–434. doi:10.3233/JAD-170744

Ferensztajn-Rochowiak E, Kucharska-Mazur J, Tarnowski M, Samochowiec J, Ratajczak MZ, Rybakowski JK. 2018. Stem cells, pluripotency and glial cell markers in peripheral blood of bipolar patients on long-term lithium treatment. Prog Neuropsychopharmacol Biol Psychiatry. 80(Pt A):28–33. doi:10.1016/j.pnpbp.2017.06.013

Focosi D, Azzarà A, Kast RE, Carulli G, Petrini M. 2009. Lithium and hematology: established and proposed uses. J Leukoc Biol. 85(1):20–28. doi:10.1189/jlb.0608388

Franchini L, Zanardi R, Smeraldi E, Gasperini M. 1999. Early onset of lithium prophylaxis as a predictor of good long-term outcome. Eur Arch Psychiatry Clin Neurosci. 249(5):227–230. doi:10.1007/s004060050091

Garrod AB. 1859. Gout and rheumatic gout. London: Walton and Maberly.

Geddes JR, Burgess S, Hawton K, Jamison K, Goodwin GM. 2004. Long-term lithium therapy for bipolar disorder: systematic review and meta-analysis of randomized controlled trials. Am J Psychiatry. 161(2):217–222. doi:10.1176/appi.ajp.161.2.217

Germaná C, Kempton MJ, Sarnicola A, Christodoulou T, Haldane M, Hadjulis M, Girardi P, Tatarelli R, Frangou S. 2010. The effects of lithium and anticonvulsants on brain structure in bipolar disorder. Acta Psychiatr Scand. 122(6):481–487. doi:10.1111/j.1600-0447.2010.01582.x

Gillis A. 1983. Lithium in herpes simplex. Lancet. 321:516.

Giotakos O, Nisianakis P, Tsouvelas G, Giakalou VV. 2013. Lithium in the public water supply and suicide mortality in Greece. Biol Trace Elem Res. 156(1-3):376–399. doi:10.1007/s12011-013-9815-4

Grof P. 1999. Excellent lithium responders: people whose lives have been changed by lithium prophylaxis. In: Birch NJ, Gallicchio VS, Becker RW, editors. Lithium: 50 years of psychopharmacology, new perspectives in biomedical and clinical research. Cheshire, Connecticut: Weidner Publishing Group; p. 36–51.

Gitlin M. 2016. Lithium side effects and toxicity: prevalence and management strategies. Int J Bipolar Disord 4: 27.

Grof P. 2010. Sixty years of lithium responders. Neuropsychobiology. 62(1):8–35. doi:10.1159/000314305

Hajek T, Bauer M, Simhandl C, Rybakowski J, O'Donovan C, Pfennig A, König B, Suwalska A, Yucel K, Uher R, et al. 2014. Neuroprotective effect of lithium on hippocampal volumes in bipolar disorder independent of long-term treatment response. Psychol Med. 44(3):507–517. doi:10.1017/S0033291713001165

Hajek T, Weiner MW. 2016. Neuroprotective effects of lithium in human brain? Food for thought. Curr Alzheimer Res. 13(8):862–872. doi:10.2174/1567205013666160219112712

Hammond WA. 1871. Treatise on diseases of the nervous system. New York: Appleton.

Hartigan G. 1963. The use of lithium salts in affective disorders. Br J Psychiatry. 109:810–814. doi:10.1192/bjp.109.463.810

Hayes J, Prah P, Nazareth I, King M, Walters K, Petersen I, Osborn D. 2011. Prescribing trends in bipolar disorder: cohort study in the United Kingdom THIN primary care database 1995–2009. PLoS One. 6(12):e28725doi:10.1371/journal.pone.0028725

Hou L, Heilbronner U, Degenhardt F, Adli M, Akiyama K, Akula N, Ardau R, Arias B, Backlund L, Banzato CEM, et al. 2016. Genetic variants associated with response to lithium treatment in bipolar disorder: a genome-wide association study. Lancet. 387(10023):1085–1093. doi:10.1016/S0140-6736(16)00143-4

Huang RY, Hsieh KP, Huang WW, Yang YH. 2016. Use of lithium and cancer risk in patients with bipolar disorder: population-based cohort study. Br J Psychiatry. 209(5):393–399. doi:10.1192/bjp.bp.116.181362

Hui TP, Kandola A, Shen L, Lewis G, Osborn DPJ, Geddes JR, Hayes JF. 2019. A systematic review and meta-analysis of clinical predictors of lithium response in bipolar disorder. Acta Psychiatr Scand. 140(2):94–115. doi:10.1111/acps.13062

Itzhaki RF. 2018. Corroboration of a major role for herpes simplex virus type 1 in Alzheimer's disease. Front Aging Neurosci. 10:324. doi:10.3389/fnagi.2018.00324

Jope RS. 2011. Glycogen synthase kinase-3 in the etiology and treatment of mood disorders. Front Mol Neurosci. 4:16doi:10.3389/fnmol.2011.00016

Kapusta ND, Mossaheb N, Etzersdorfer E, Hlavin G, Thau K, Willeit M, Praschak-Rieder N, Sonneck G, Leithner-Dziubas K. 2011. Lithium in drinking water and suicide mortality. Br J Psychiatry. 198(5):346–350. doi:10.1192/bjp.bp.110.091041

Karanti A, Kardell M, Lundberg U, Landén M. 2016. Changes in mood stabilizer prescription patterns in bipolar disorder. J Affect Disord. 195:50–56. doi:10.1016/j.jad.2016.01.043

Katagiri H, Takita Y, Tohen M, Higuchi T, Kanba S, Takahashi M. 2012. 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. 28(5):701–713. doi:10.1185/03007995.2012.666961

Kessing LV, Sondergard L, Forman JL, Andersen PK. 2008. Lithium treatment and risk of dementia. Arch Gen Psychiatry. 65(11):1331–1335. doi:10.1001/archpsyc.65.11.1331

Kessing LV, Forman JL, Andersen PK. 2010. Does lithium protect against dementia? Bipolar Disord. 12:97–94.

Kessing LV, Vradi E, Andersen PK. 2014. Starting lithium prophylaxis early v. late in bipolar disorder. Br J Psychiatry. 205(3):214–220. doi:10.1192/bjp.bp.113.142802

Kessing LV, Vradi E, Andersen PK. 2016. Nationwide and population-based prescription patterns in bipolar disorder. Bipolar Disord. 18(2):174–182. doi:10.1111/bdi.12371

Kessing LV, Gerds TA, Knudsen NN, Jørgensen LF, Kristiansen SM, Voutchkova D, Ernstsen V, Schullehner J, Hansen B, Andersen PK, et al. 2017. Association of lithium in drinking water with the incidence of dementia. JAMA Psychiatry. 74(10):1005–1010. doi:10.1001/jamapsychiatry.2017.2362

Kessing LV, Bauer M, Nolen WA, Severus E, Goodwin GM, Geddes J. 2018. 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. 20(5):419–431. doi:10.1111/bdi.12623

Kliwicki S, Chłopocka-Woźniak M, Rudnicka E, Rybakowski J. 2014. Efficacy of long-term lithium treatment in bipolar affective illness (in Polish). Pharmakother Psychiatry Neurol. 30:5–13.

Kraepelin E. 1899. Psychiatrie. Ein Lehrbuch für Studierende und Ärzte. 6 Auflage. Leipzig: Barth.

Kraszewska A, Ziemnicka K, Jończyk-Potoczna K, Sowiński J, Rybakowski JK. 2019a. Thyroid structure and function in long-term lithium-treated and lithium-naïve bipolar patients. Hum Psychopharmacol. 34(4):e2708doi:10.1002/hup.2708

Kraszewska A, Ziemnicka K, Sowiński J, Ferensztajn-Rochowiak E, Rybakowski JK. 2019b. No connection between long-term lithium treatment and antithyroid antibodies. Pharmacopsychiatry. 52(5):232–236. doi:10.1055/a-0838-6062

Lange C. 1886. Om Periodiske Depressionstilstande og deres Patogenese. Lund, Copenhagen.

Lähteenvuo M, Tanskanen A, Taipale H, Hoti F, Vattulainen P, Vieta E, Tiihonen J. 2018. Real-world effectiveness of pharmacologic treatments for the prevention of rehospitalization in a Finnish nationwide cohort of patients with bipolar disorder. JAMA Psychiatry. 75(4):347–355. doi:10.1001/jamapsychiatry.2017.4711

Lewitzka U, Severus E, Bauer R, Ritter P, Müller-Oerlinghausen B, Bauer M. 2015. The suicide prevention effect of lithium: more than 20 years of evidence-a narrative review. Int J Bipolar Disord. 3(1):32. doi:10.1186/s40345-015-0032-2

Lieb J. 1979. Remission of recurrent herpes infection during therapy with lithium. N Engl J Med. 301:942.

López-Jaramillo C, Lopera-Vásquez J, Ospina-Duque J, García J, Gallo A, Cortez V, Palacio C, Torrent C, Martínez-Arán A, Vieta E, et al. 2010. Lithium treatment effects on the neuropsychological functioning of patients with bipolar I disorder. J Clin Psychiatry. 71(8):1055–1060. doi:10.4088/JCP.08m04673yel

Lyoo IK, Dager SR, Kim JE, Yoon SJ, Friedman SD, Dunner DL, Renshaw PF. 2010. Lithium-induced gray matter volume increase as a neural correlate of treatment response in bipolar disorder: a longitudinal brain imaging study. Neuropsychopharmacology. 35(8):1743–1750. doi:10.1038/npp.2010.41

Manchia M, Adli M, Akula N, Ardau R, Aubry J-M, Backlund L, Banzato CE, Baune BT, Bellivier F, Bengesser S, et al. 2013. Assessment of response to lithium maintenance treatment in bipolar disorder: a Consortium on Lithium Genetics (ConLiGen) report. PLoS One. 8(6):e65636. doi:10.1371/journal.pone.0065636

Marcus R, Khan A, Rollin L, Morris B, Timko K, Carson W, Sanchez R. 2011. 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. 13(2):133–144. doi:10.1111/j.1399-5618.2011.00898.x

Matsunaga S, Kishi T, Annas P, Basun H, Hampel H, Iwata N. 2015. Lithium as a treatment for Alzheimer's disease: a systematic review and meta-analysis. J Alzheimers Dis. 48(2):403–410. doi:10.3233/JAD-150437

Mendels J. 1976. Lithium in the treatment of depression. Am J Psychiatry. 133(4):373–378. doi:10.1176/ajp.133.4.373

Moore GJ, Bebchuk JM, Wilds IB, Chen G, Manji HK, Menji HK. 2000. Lithium-induced increase in human brain grey matter. Lancet. 356(9237):1241–1242. doi:10.1016/S0140-6736(00)02793-8

Morris G, Berk M. 2016. The putative use of lithium in Alzheimer's disease. Curr Alzheimer Res. 13(8):853–861. doi:10.2174/1567205013666160219113112

Munk-Olsen T, Liu X, Viktorin A, Brown HK, Di Florio A, D'Onofrio BM, Gomes T, Howard LM, Khalifeh H, Krohn H, et al. 2018. Maternal and infant outcomes associated with lithium use in pregnancy: an international collaborative meta-analysis of six cohort studies. Lancet Psychiatry. 5(8):644–652. doi:10.1016/S2215-0366(18)30180-9

Müller-Oerlinghausen B, Ahrens B, Grof E, Grof P, Lenz G, Schou M, Simhandl C, Thau K, Volk J, Wolf R. 1992. The effect of long-term lithium treatment on the mortality of patients with manic-depressive and schizoaffective illness. Acta Psychiatr Scand. 86(3):218–222. doi:10.1111/j.1600-0447.1992.tb03255.x

Müller-Oerlinghausen B, Wolf T, Ahrens B, Schou M, Grof E, Grof P, Lenz G, Simhandl C, Thau K, Wolf R, et al. 1994. Mortality during initial and during later lithium treatment. A collaborative study by the International Group for the Study of Lithium-treated patients. Acta Psychiatr Scand. 90(4):295–297. doi:10.1111/j.1600-0447.1994.tb01596.x

Nassar A, Azab AN. 2014. Effects of lithium on inflammation. ACS Chem Neurosci. 5(6):451–458. doi:10.1021/cn500038f

Nivoli AMA, Murru A, Vieta E. 2010. Lithium: still a cornerstone in the long-term treatment in bipolar disorder? Neuropsychobiology. 62(1):27–35. doi:10.1159/000314307

Noack CH, Trautner EM. 1951. The lithium treatment of maniacal psychosis. Med J Aust. 2(7):219–222. doi:10.5694/j.1326-5377.1951.tb68249.x

Nunes MA, Viel TA, Buck HS. 2013. Microdose lithium treatment stabilized cognitive impairment in patients with Alzheimer's disease. Curr Alzheimer Res. 10(1):104–107. doi:10.2174/1567205011310010014

Ohgami H, Terao T, Shiotsuki I, Ishii N, Iwata N. 2009. Lithium levels in drinking water and risk of suicide. Br J Psychiatry. 194(5):464–465. doi:10.1192/bjp.bp.108.055798

Palacios J, Yildiz A, Young AH, Taylor MJ. 2019. Tamoxifen for bipolar disorder: systematic review and meta-analysis. J Psychopharmacol (Oxford). 33(2):177–184. doi:10.1177/0269881118822167

Permoda-Osip A, Abramowicz M, Kraszewska A, Suwalska A, Chlopocka-Wozniak M, Rybakowski JK. 2016. Kidney, thyroid and other organ functions after 40 years or more of lithium therapy: a case series of five patients. Ther Adv Psychopharmacol. 6(4):277–282. doi:10.1177/2045125316643299

Poolsup N, Li Wan Po A, de Oliveira IR. 2000. Systematic overview of lithium treatment in acute mania. J Clin Pharm Ther. 25(2):139–156. doi:10.1046/j.1365-2710.2000.00278.x

Post RM. 2018. The new news about lithium: an underutilized treatment in the United States. Neuropsychopharmacology. 43(5):1174–1179. doi:10.1038/npp.2017.238

Radomski J, Fuyat HN, Nelson AA, Smith PK. 1950. The toxic effects, excretion and distribution of lithium chloride. J Pharmacol Exp Ther. 100(4:1):429–440.

Rybakowski JK, Amsterdam JD. 1991. Lithium prophylaxis and recurrent labial herpes infections. Lithium 2: 43–47.

Rybakowski JK. 2000. Antiviral and immunomodulatory effect of lithium. Pharmacopsychiatry. 33(5):159–164.

Rybakowski JK. 2007. Two generations of mood stabilizers. Int J Neuropsychopharmacol. 10(5):709–711. doi:10.1017/s146114570700795x

Rybakowski JK. 2014. Response to lithium in bipolar disorder: clinical and genetic findings. ACS Chem Neurosci. 5(6):413–421. doi:10.1021/cn5000277

Rybakowski JK. 2016. Effect of lithium on neurocognitive functioning. Curr Alzheimer Res. 13(8):887–893. doi:10.2174/1567205013666160415154701

Rybakowski JK. 2018a. Challenging the negative perception of lithium and optimizing its long-term administration. Front Mol Neurosci. 11:349. doi:10.3389/fnmol.2018.00349

Rybakowski JK. 2018b. Meaningful aspects of the term 'mood stabilizer'. Bipolar Disord. 20(4):391–392. doi:10.1111/bdi.12608

Rybakowski JK. 2019. Commentary: Corroboration of a major role for herpes simplex virus type 1 in Alzheimer's disease. Front Aging Neurosci. 10:433. doi:10.3389/fnagi.2018.00433

Rybakowski JK, Borkowska A, Skibinska M, Hauser J. 2006. Illness-specific association of Val66met BDNF polymorphism with performance on Wisconsin Card Sorting Test in bipolar mood disorder. Mol Psychiatry. 11(2):122–124. doi:10.1038/sj.mp.4001765

Rybakowski JK, Checinska K. 2018. The use of lithium in Poland in 2004-2017. Pharmacother Psychiatry Neurol. 34:85–94.

Rybakowski J, Chłopocka M, Lisowska J, Czerwiński A. 1974. The study on the efficacy of lithium in endogenous depressive syndromes (in Polish). Psychiatr Pol. 8:129–135.

Rybakowski JK, Chlopocka-Wozniak M, Suwalska A. 2001. The prophylactic effect of long-term lithium administration in bipolar patients entering treatment in the 1970s and 1980s. Bipolar Disord. 3(2):63–67. doi:10.1034/j.1399-5618.2001.030203.x

Rybakowski JK, Dmitrzak-Weglar M, Kliwicki S, Hauser J. 2014. Polymorphism of circadian clock genes and prophylactic lithium response. Bipolar Disord. 16(2):151–158. doi:10.1111/bdi.12136

Rybakowski J, Matkowski K. 1992. Adding lithium to antidepressant therapy: factors related to therapeutic potentiation. Eur Neuropsychopharmacol. 2(2):161–165. doi:10.1016/0924-977X(92)90027-6

Rybakowski JK, Permoda-Osip A, Borkowska A. 2009. Response to prophylactic lithium in bipolar disorder may be associated with a preservation of executive cognitive functions. Eur Neuropsychopharmacol. 19(11):791–795. doi:10.1016/j.euroneuro.2009.06.002

Rybakowski JK, Suwalska A. 2010. Excellent lithium responders have normal cognitive functions and plasma BDNF levels. Int J Neuropsychopharmacol. 13(5):617–622. doi:10.1017/S1461145710000404

Rybakowski JK. 2013. Genetic influences on response to mood stabilizers in bipolar disorder: current status of knowledge. CNS Drugs 27: 165–173.

Rybakowski JK, Suwalska A, Hajek T. 2018. Clinical perspectives of lithium's neuroprotective effect. Pharmacopsychiatry. 51(5): 194–199. doi:10.1055/s-0043-124436

Rybakowski JK, Suwalska A, Skibinska M, Szczepankiewicz A, Leszczynska-Rodziewicz A, Permoda A, Czerski PM, Hauser J. 2005. Prophylactic lithium response and polymorphism of the brain-derived neurotrophic factor gene. Pharmacopsychiatry. 38(4):166–170. doi:10.1055/s-2005-871239

Rybakowski J, Cubała WJ, Gałecki P, Rymaszewska J, Samochowiec J, Szulc A, Dudek D. 2019. Recommendations of the Polish Psychiatric Association regarding the treatment of affective disorders in women of childbearing age. Part II: Bipolar disorder. Psychiatr Pol. 53(2):263–276. doi:10.12740/PP/103555

Schou M, Juel-Nielsen N, Stromgren E, Voldby H. 1954. The treatment of manic psychoses by the administration of lithium salts. J Neurol Neurosurg Psychiatry. 17(4):250–260. doi:10.1136/jnnp.17.4.250

Schou M, Thompsen K. 1975. Lithium prophylaxis of recurrent endogenous affective disorders. In: Johnson FN, editor. Lithium research and therapy. London: Academic Press; p. 63–84.

Schulze TG, Alda M, Adli M, Akula N, Ardau R, Bui ET, Chillotti C, Cichon S, Czerski P, Del Zompo M, et al. 2010. The International Consortium on Lithium Genetics (ConLiGen): an initiative by the NIMH and IGSLI to study the genetic basis of response to lithium treatment. Neuropsychobiology. 62(1):72–78. doi:10.1159/000314708

Scott J, Hidalgo-Mazzei D, Strawbridge R, Young A, Resche-Rigon M, Etain B, Andreassen OA, Bauer M, Bennabi D, Blamire AM, et al. 2019. Prospective cohort study of early biosignatures of response to lithium in bipolar-I-disorders: overview of the H2020-funded R-LiNK initiative. Int J Bipolar Disord. 7(1):20. doi:10.1186/s40345-019-0156-x

Severus E, Bauer M. 2013. Managing the risk of lithium-induced nephropathy in the long-term treatment of patients with recurrent affective disorders. BMC Med. 11:34. doi:10.1186/1741-7015-11-34

Severus E, Taylor MJ, Sauer C, Pfennig A, Ritter P, Bauer M, Geddes JR. 2014. Lithium for prevention of mood episodes in bipolar disorders: systematic review and meta-analysis. Int J Bipolar Disord. 2:15. doi:10.1186/s40345-014-0015-8

Skinner GRB, Hartley C, Buchan A, Harper L, Gallimore P. 1980. The effect of lithium chloride on the replication of herpes simplex virus. Med Microbiol Immunol. 168(2):139–265. doi:10.1007/BF02121762

Souza FG, Goodwin GM. 1991. Lithium treatment and prophylaxis in unipolar depression: a meta-analysis. Br J Psychiatry. 158: 666–675. doi:10.1192/bjp.158.5.666

Stambolic V, Ruel L, Woodgett JR. 1996. Lithium inhibits glycogen synthase kinase-3 activity and mimics wingless signalling in intact cells. Curr Biol. 6(12):1664–1668. doi:10.1016/S0960-9822(02)70790-2

Stephenson CP, Karanges E, McGregor IS. 2013. Trends in the utilisation of psychotropic medications in Australia from 2000 to 2011. Aust N Z J Psychiatry. 47(1):74–87. doi:10.1177/0004867412466595

Storosum JG, Wohlfarth T, Schene A, Elferink A, van Zwieten BJ, van den Brink W. 2007. Magnitude of effect of lithium in short-term efficacy studies of moderate to severe manic episode. Bipolar Disord. 9(8):793–798. doi:10.1111/j.1399-5618.2007.00445.x

Suppes T, Vieta E, Gustafsson U, Ekholm B. 2013. 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. 30(11): 1089–1098. doi:10.1002/da.22136

Tiihonen J, Tanskanen A, Hoti F, Vattulainen P, Taipale H, Mehtälä J, Lähteenvuo M. 2017. Pharmacological treatments and risk of readmission to hospital for unipolar depression in Finland: a nationwide cohort study. Lancet Psychiatry. 4(7):547–553. doi:10.1016/S2215-0366(17)30134-7

Tondo L, Abramowicz M, Alda M, Bauer M, Bocchetta A, Bolzani L, Calkin CV, Chillotti C, Hidalgo-Mazzei D, Manchia M, et al. 2017. Long-term lithium treatment in bipolar disorder: effects on glomerular filtration rate and other metabolic parameters. Int J Bipolar Disord. 5(1):27. doi:10.1186/s40345-017-0096-2

Tondo L, Alda M, Bauer M, Bergink V, Grof P, Hajek T, Lewitka U, Licht RW, Manchia M, Müller-Oerlinghausen B, et al. 2019. Clinical use of lithium salts: guide for users and prescribers. Int J Bipolar Disord. 7(1):16. doi:10.1186/s40345-019-0151-2

Undurraga J, Sim K, Tondo L, Gorodischer A, Azua E, Tay KH, Tan D, Baldessarini RJ. 2019. Lithium treatment for unipolar major depressive disorder: systematic review. J Psychopharmacol. 33(2):167–176. doi:10.1177/0269881118822161

Vestergaard P, Rejnmark L, Mosekilde L. 2005. Reduced relative risk of fractures among users of lithium. Calcif Tissue Int. 77(1): 1–8. doi:10.1007/s00223-004-0258-y

Williams R, Ryves WJ, Dalton EC, Eickholt B, Shaltiel G, Agam G, Harwood AJ. 2004. A molecular cell biology of lithium. Biochem Soc Trans. 32 (Pt 5):799–802. doi:10.1042/BST0320799

Zamani A, Omrani GR, Nasab MM. 2009. Lithium's effect on bone mineral density. Bone. 44(2):331–334. doi:10.1016/j.bone.2008.10.001