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Review

Antiviral, immunomodulatory, and neuroprotective effect of lithium

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Abstract

Currently, in psychiatry, lithium is a drug of choice as a mood stabilizer in the maintenance treatment of bipolar disorder for the prevention of manic and depressive recurrences. The second most important psychiatric use of lithium is probably increasing the efficacy of antidepressants in treatment-resistant depression. In addition to its mood-stabilizing properties, lithium exerts antisuicidal, antiviral, immunomodulatory, and neuroprotective effects. The goal of the review is to describe the experimental and clinical studies on the last three properties of lithium. Antiviral effects of lithium pertain mostly to DNA viruses, especially herpes viruses. The therapeutic effects of lithium in systemic and topical administration on labial and genital herpes were demonstrated in clinical studies. There is also some evidence, mostly in experimental studies, that lithium possesses antiviral activity against RNA viruses, including coronaviruses. The immunomodulatory effect of lithium can mitigate "low-grade inflammatory" conditions in bipolar illness. The neuroprotective properties of lithium make this ion a plausible candidate for the prevention and treatment of neurodegenerative disorders. A favorable effect of lithium was shown in experimental models of neurodegenerative disorders. On the clinical level, some preventive action against dementia and moderately therapeutic activity in Alzheimer's disease, and mild cognitive impairment were observed. Despite promising results of lithium obtained in animal models of Huntington's disease and amyotrophic lateral sclerosis, they have not been confirmed in clinical studies. A suggestion for common mechanisms of antiviral, immunomodulatory, and neuroprotective effects of lithium is advanced.

Keywords: Lithium; Mood-stabilizer; Bipolar disorder; Herpes virus; Immunomodulation; Neuroprotection

1. Introduction

Medical use of lithium started in 1859 when an English physician, Alfred Baring Garrod (1819–1907), applied lithium carbonate in the treatment of gout [1]. Exactly one and half-century ago (in 1871), an American neurologist, William Alexander Hammond (1828–1900), used lithium bromide in the treatment of mania [2]. Fifteen years later, a Danish physician and scientist, Carl Lange (1834–1900), based on the "uric acid diathesis" theory of depression, reported on lithium carbonate in the treatment and prophylaxis of periodic depression [3]. The introduction of lithium in contemporary psychiatry is credited to an Australian psychiatrist, John Cade (1912–1980), who described the efficacy of lithium carbonate in mania in 1949 [4]. Samuel Gershon, who is now the only living witness of Cade's activity in Australia, after he came to the USA, greatly contributed to the development of lithium therapy in this country [5]. The first publications on lithium prophylactic effect in mood disorders took place in the early 1960s [6,7]. Thirty years ago, lithium was shown to augment the efficacy of antidepressants [8].

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. Three meta-analyses of the 21st century have fully confirmed the prophylactic effectiveness of lithium in bipolar disorder, slightly better against manic than against depressive recurrences [9–11]. The studies also supported lithium prophylactic efficacy in recurrent depression [12]. Lithium augmentation of antidepressants in treatment-resistant depression can be regarded as the second therapeutic indication for lithium. A review on this subject demonstrated that lithium is effective in both bipolar and unipolar depressed patients, and a successful outcome may be expected in at least 50% of them [13].

In addition to mood-stabilizing properties, lithium exerts antisuicidal, antiviral, immunomodulatory, and neuroprotective action. The evidence for the antisuicidal effect of lithium in bipolar disorder and recurrent depression has been accumulating since the early 1990s [14] and it has been confirmed by meta-analyses performed in the 21st century [15,16]. While being on lithium prevents suicide, its discontinuation significantly increases this risk. The antisuicidal effect is not correlated with mood stabilization, which may seem counter-intuitive, however, it points to a specific and very important aspect of lithium activity [17]. In the recent decade, in many countries, a negative correlation between suicides and lithium concentration in drinking water has also been demonstrated [18].

The main biochemical mechanisms of lithium action are connected with the inhibition of the glycogen synthase kinase-3beta (GSK-3β) and the effects on intracellular signaling, especially, the phosphatidylinositol (PI) system [19]. The GSK-3β regulates gene transcription, synaptic plasticity, apoptosis, cellular structure and resilience, the

circadian cycle, and cytokine secretion, 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 [20]. GSK-3β is also a key enzyme in the metabolism of the amyloid precursor protein and the phosphorylation of the tau protein, and its inhibition may be connected with a possible favorable effect of lithium in neurodegenerative disorders [21]. Lithium inhibits inositol monophosphatase-1 as well as protein kinase C (PKC), and also influences the adenylyl cyclases, which convert ATP into cyclic adenosine monophosphate (cAMP). The element of this system is the cAMP response element-binding protein (CREB), the regulator of gene expression. Lithium also influences the brain-derived neurotrophic factor (BDNF), the most important member of the neurotrophin family, necessary for the survival and function of neurons. In clinical studies, lithium treatment increases the blood level of BDNF. The Val66Met polymorphism of the *BDNF* gene has been associated with a predisposition to bipolar disorder [22], the cognitive functions in this illness [23], and the prophylactic lithium response [24]. The enhancement by lithium of the BDNF system plays a role in its mood-stabilizing, and probably also has neuroprotective activity. It was found that the long-term lithium treatment increases intracellular and extracellular BDNF in cortical and hippocampal neurons [25]. The upregulation of BDNF is possibly a downstream consequence of lithium's direct inhibition of the GSK3β activity [26].

In the present review, the experimental and clinical studies pertaining to antiviral, immunomodulatory, and neuroprotective properties of lithium are described. The mechanisms and clinical implications of these effects are discussed. Furthermore, a suggestion for a common mechanism for the antiviral, immunomodulatory, and neuroprotective effects of lithium is advanced.

2. Antiviral effect of lithium

2.1 Lithium effect on herpes and other DNA viruses

Experimental evidence for the antiviral effect of lithium was initially provided in 1980 when the researchers from the University of Birmingham showed that lithium in a concentration of 5–30 mmol/L inhibits replication of the herpes simplex virus (HSV) in hamster kidney cells [27]. Several years later, the *in vitro* antiviral activity of lithium on HSV in rabbit cells was observed [28]. In 1988, Romanian virologists demonstrated a reduction in virus yield in human embryo fibroblasts cultures infected with HSV when pre-treated with lithium chloride at concentrations of 1–10 mmol/L [29]. Birmingham's researchers suggested that lithium may directly inhibit HSV replication as well as impair the viral DNA synthesis by the displacement of potassium and magnesium ions in biochemical reactions [30].

Labial herpes is caused by an infection of herpes simplex virus type 1 (HSV-1), occurring in approximately 1/3 of the population. Its course is characterized by frequent recurrences. At the time of Skinner and collaborators' [27] findings, the case reports of labial herpes remissions while using lithium appeared [31,32]. A further case report on suppression by lithium of recurrent herpes labialis came out in 1999 [33].

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. The studied Polish population consisted of 69 patients (24 male, 45 female) receiving lithium for 8 years. Among them, 28 persons had 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 in 2 it increased. The general decrease in recurrence frequency was 64%. The best effect was observed in patients in whom lithium concentration in the serum was higher than 0.65 mmol/L, and intracellular (erythrocyte) lithium concentration exceeded 0.35 mmol/L. The American population consisted of two groups of 52 people, matched by gender (21 males and 31 females in each group), age (on average 45 years), and length of systematic drug treatment (on average 5 years). In the first group, including patients with bipolar disorder treated with lithium, the frequency of labial herpes recurrences in comparison with the 5-year period preceding the treatment decreased by 73%. In the second group, including patients with recurrent depression receiving antidepressant drugs, no significant difference was observed [34].

The therapeutic efficacy of lithium succinate ointment in the treatment of focal herpes lesions has also been demonstrated. A preparation called Efalith, produced by Nova Scotia, containing 8% of lithium succinate and 0.05% of zinc sulfate was used. The study included 42 patients (4 male, 38 female) with recurrent herpes. In most of them, recurrences were very frequent (every 1–6 months). Application of the ointment commenced 1–3 days after the appearance of lesions and continued 3–7 times a day for the first 3 days and then 1–2 times a day. All patients were completely cured after 2–7 (on average 4) days of treatment. In 6 patients, herpes lesions showed signs of bacterial infection—the lesions subsided when lithium succinate was used, without the need for antibacterial treatment. In a period of one-year follow-up, herpes lesions reappeared in 6 patients, but never in the area where the ointment was previously applied [35]. Thus, the antiviral effect of lithium on HSV-1 infection was confirmed with both systemic and topical treatment. However, in the case of the latter, a possible therapeutic contribution of zinc cannot be excluded.

Genital herpes, which may also be a recurring affliction, is caused by an infection of herpes simplex virus type 2 (HSV-2). In this condition, the first use of lithium was

that of topical application of 8% lithium succinate ointment in a controlled study by Skinner [36], including 73 patients with recurring genital (HSV2) herpes. The ointment was applied 4 times a day for 7 days, and a quantitative measure of HSV2 was performed. The median duration of pain/discomfort was reduced in lithium-treated patients compared with the placebo group from 7 to 4 days. HSV2 excretion at day 4 or 5 was present in 11/20 (55%) placebo-treated compared with 5/37 (14%) lithium-treated patients. Virus concentration in the lithium group was reduced by 30-fold as compared to patients receiving a placebo.

The research on oral lithium carbonate as a prophylactic treatment of genital herpes recurrences was performed in two placebo-controlled studies by Amsterdam and collaborators [37,38]. In the first one, 10 women with recurrent genital HSV-2 infection were given oral lithium for 12 months and followed for 18 months. During the active treatment phase, average daily lithium doses were 587 $\pm$ 49 mg and mean plasma levels 0.51 mmol/L. Patients in the active arm of the study showed a trend towards an average monthly reduction in the number and duration of herpetic lesions, maximum symptom severity, and clinical severity. In the second study, 2 male and 9 female patients aged 28–65 (mean 38) years, with a personal history of HSV-2 infection with four or more recurrences were randomly assigned to lithium (n = 6) or placebo (n = 5) for at least five months. The mean lithium daily dosage was 437 $\pm$ 185 mg, and the average serum concentration 0.56 mmol/L. Lithium treatment resulted in a reduction in the mean number of episodes per month, the average duration of each episode, the total number of infection days/month, and the maximum symptom severity. On the other hand, treatment with placebo resulted in an increase in three out of the four severity measures.

The antiviral effect of lithium on the DNA viruses has also been demonstrated for the Parvoviridae family. Chen and collaborators [39] observed the inhibition of porcine parvovirus (PPV) replication in swine testis cells by lithium chloride at a lithium concentration of 5 mmol/L, and, as in other DNA viruses, the effect occurred in the early phase of PPV replication. It was also shown that lithium suppressed the synthesis of viral DNA and proteins of canine parvovirus and inhibited viral entry into feline kidney cell cultures [40]. Parvoviruses are the pathogens in a few diseases in humans (e.g., *erythema infectiosum* caused by parvovirus B19). However, no trials of lithium in these conditions have been conducted so far.

2.2 Lithium effects on RNA viruses

Experimental studies performed in the last three decades demonstrated the antiviral effect of lithium on some RNA viruses. In the murine acquired immune deficiency syndrome induced by the murine leukemia retrovirus, the animals receiving lithium, 1 mmol/L, demonstrated a marked reduction in the development of lymphadenopathy and splenomegaly [41]. Lithium chloride also inhibited the replication of the foot-and-mouth disease virus [42], feline calicivirus [43], and mammalian orthoreovirus [44].

On the clinical side, the studies of lithium effect on the RNA viruses pertained mostly to those responsible for respiratory infections. Amsterdam and collaborators [45], in a retrospective study including 236 patients with mood disorders, among those 177 taking lithium carbonate and 59 receiving antidepressants on a chronic basis, showed a statistically significant reduction in mean yearly rates of flu-like infections in lithium- but not antidepressant-treated patients. Recently, Landen and collaborators [46] demonstrated a 28% decrease in respiratory infections, part of which most likely due to the RNA viruses, during chronic lithium administration. To rule out the possibility that this could be due to lithium's effect on psychiatric symptoms, the effect of another mood-stabilizer valproate was studied, which turned out to increase such infections by 35%. However, the comparison of the efficacy in preventing mood recurrences between these two mood stabilizers was not performed.

Given the Covid-19 (Coronavirus Disease 2019) pandemics, experimental studies on lithium effect on the representatives of Coronaviridae family performed in the last two decades are of interest. The study of lithium chloride effect on the replication of avian coronavirus infectious bronchitis virus (IBV) in Vero cells (an African Green monkey kidney-derived epithelial cell line), and DF-1 cells, (an immortalized chicken embryo fibroblast cell line) showed that with lithium chloride concentrations, 5–50 mmol/L, the RNA and protein levels of IBV, as well as viral progeny production were reduced dose-dependently in both cell types [47]. Also, lithium chloride limited *in vitro* both early and late stages of infection and inhibited apoptosis in porcine coronavirus causing transmissible gastroenteritis [48]. In type II porcine reproductive and respiratory syndrome virus, lithium chloride reduced RNA production and protein transduction [49]. In Vero cells, lithium chloride showed effectiveness in suppressing infection of the porcine epidemic diarrhea virus by inhibiting the virus entry, replication, and apoptosis [50]. Furthermore, lithium chloride at concentrations of 10–60 mmol/L inhibited viral replication of porcine delta coronavirus (PDCoV) in porcine kidney cells (LLC-PK1). These effects occurred at the early stage of PDCoV replication and were associated with the inhibition of the PDCoV induced apoptosis [51].

It should be noted that in most experimental papers, lithium concentration exceeds several times the concentration needed for clinical lithium use (i.e., 0.5–1.0 mmol/L). Therefore, the extrapolation from experimental studies to the clinic should be done with caution.

Shortly after the outbreak of the Covid-19 pandemics, Nowak and Walkowiak [52] presented the above experimental data on the possible effect of lithium on coro-

naviruses in experimental studies. They postulate that lithium could be clinically useful in this condition given that it inhibits GSK-3β, which is indispensable for the production of coronaviral genomic RNA, as evidenced in the study of Wu and collaborators [53]. Also, Murru and collaborators [54] describing the antiviral effect of lithium suggested its possible usefulness in patients with the Covid-19 disease. However, clinical observations on lithium and Covid-19 are controversial. Gattner and Rybakowski [55] described a severe course of the Covid-19 in an inhabitant of Lombardy receiving lithium treatment for several years. On the other hand, Spuch and collaborators [56] treated six Covid-19 patients with lithium carbonate and observed an improvement in both inflammatory activity and the immune response in them. It seems that the role of lithium treatment in the occurrence and course of Covid-19 should be analyzed on a large group of lithium-treated patients.

3. Immunomodulatory effect of lithium

3.1 Effect on hematological system

The first mention of the immunomodulatory effect of lithium can be traced back to 1950 when Radomski and collaborators [57] reported an increase of leukocytes during lithium treatment. This effect was subsequently confirmed in many clinical reports [58,59] and its mechanisms have been extensively studied. It has been found that lithium induces marrow granulopoiesis, influencing hematopoietic stem cells (HSC). Lithium influences SC directly, by stimulating pluripotent stem cell (PSC) proliferation, and indirectly, by increasing the production of granulocyte colony-stimulating factor (G-CSF) and other growth factors. Hammond and Dale [60] demonstrated that administration of lithium to dogs with cyclic neutropenia eliminated abnormalities in neutrophils, as well as in platelets, reticulocytes, and monocytes, indicating the effect of lithium on the HSC level. Levitt and Quesenberry [61] found that lithium primarily stimulates pluripotential SC and the progenitor cells for granulocytes and monocytes (GMP). Lithium also stimulates the production of hematopoietic growth factors. In healthy persons, lithium administration results in an increased release of G-CSF and increased bone marrow neutrophil production *in vitro* [62]. Elevated G-CSF levels in the urine and enhanced production of G-CSF by peripheral blood mononuclear cells (PBMCs) were observed [63,64].

The use of the aforementioned effect in psychiatry is for the prevention and treatment of neutropenia that may occur during clozapine treatment [65]. This applies primarily to schizophrenic patients, but also to bipolar affective disorder, for which clozapine has been increasingly employed. Lithium should be introduced at leukocyte values of 3.5×10^9/L, and good results are achieved at a lithium carbonate dose of 500 mg/day. In the case of clozapine administered in bipolar affective disorder, the addition of lithium also potentiates the therapeutic effect. Similarly, the addition of lithium prevents neutropenia induced by carbamazepine, at the same time reinforcing its mood-stabilizing effect [66]. Focosi and collaborators [67], in a review article on the possibility of using lithium in hematological diseases, reported on their experiences with the administration of lithium carbonate in idiopathic neutropenia (in both adults and children), and with infection-related neutropenia. They also discuss the use of lithium in neutropenia connected with the anticancer drugs or complications of chemo- and radiotherapy.

3.2 Effect on inflammatory processes

Immuno-inflammatory processes are thought to play an important role in the pathogenesis of mood disorders. For many years, bipolar illness has been perceived as a condition characterized by a "low-grade inflammation". Furthermore, in these inflammatory processes occurring in the central nervous system (neuroinflammation), the most important cells are microglia [68,69]. Probably, the main immunomodulatory effect of lithium is a mitigation of the immune-endocrine component of bipolar disorder. In a review paper in 2000 by the author of this article, it was mentioned that lithium attenuates the acute-phase reaction, production of pro-inflammatory cytokines, and excessive activation of the hypothalamic-pituitary-adrenal axis [70]. A subsequent review of the anti-inflammatory effect of lithium was published in 2014 [71].

For lithium's immunomodulatory activity, its inhibition of the GSK-3β is most important. The GSK-3β inhibition reduces the production of pro-inflammatory mediators such as interleukin (IL)-1β, interferon (IFN)-γ, IL-6, and increases the production of anti-inflammatory cytokines such as IL-10 [72]. It was shown that the pretreatment of the rat primary glial cells with lithium suppressed lipopolysaccharide (LPC)-induced inflammation, and reduced levels of markers such as tumor necrosis factor (TNF)-α and IL-1β. However, these results were obtained by using lithium concentrations higher than in the clinical conditions [73]. In another study, the influence of lithium on microglia activation and migration was analyzed. The drug decreased microglial migration in mouse BV-2 cells and attenuated the injury-induced migration of microglia in situ in hippocampal mouse slices. Lithium also decreased inflammatory markers in microglial cells stimulated with LPC [74]. It was also demonstrated that the pretreatment of primary microglial cells with lithium followed by LPS stimulation inhibited LPS-induced microglial activation and pro-inflammatory cytokine production. This suppression resulted from LPS-induced toll-like receptor 4 (TLR4) downregulation and proceeded via inhibition of the PI3K/Akt/FoxO1 signaling pathway [75]. The anti-inflammatory effect of lithium was also confirmed in the recent study in rats, where 12-week lithium treatment decreased pro-inflammatory cytokines' levels (IL-1β, IL-6) in plasma and the orbitofrontal cortex, leading to reduced motor impulsivity. The authors suggested that the reduced pro-

inflammatory signaling for neuronal activity may improve impulse control deficits in patients treated with lithium [76].

In a clinical study, decreased levels of inflammatory markers in serum in rapid cycling bipolar patients after 30 days of lithium treatment were observed [77]. Boufidou and collaborators [78] presented a study comparing the cytokine levels (IL-2, IL-6, IL-10, and IFN-γ) in the peripheral blood of healthy volunteers and lithium-naïve patients with bipolar disorder (BD) before and after lithium treatment. Lithium-naive BD patients were not different in cytokine production than healthy control subjects. After three months on lithium, the patients presented a significant decrease in all analyzed cytokines compared to controls. A study analyzing *ex vivo* interleukin IL-1β and IL-6 secretion in BD patient-derived monocytes stimulated with LPS showed that lithium treatment decreased the production of IL-6 compared to the non-treated control [79]. A research carried out in Poznań has shown that, in BD patients in sustained remission (6 months or more) during long-term lithium treatment, cytokine concentrations did not differ from those observed in healthy subjects [80]. Recently, Wu and collaborators [81] analyzed immunophenotypes of BD patients and found that they had significantly higher percentages of total T cells, CD4+ T cells, activated B cells, and monocytes than healthy controls, whereas the treatment of patient-derived PBMCs with lithium *in vitro* increased the percentage of CD14+ monocytes and dendritic cells. The authors suggested that lithium plays an immunomodulatory role in CD14+ monocytes and dendritic cells. Queissner and collaborators [82] in 267 bipolar patients treated with lithium examined symptom progression in relation to the levels of high sensitivity C-reactive protein (hsCRP). They showed that an altered inflammatory state was associated with a more severe illness course. On the other hand, a longer duration of lithium treatment was connected with lower symptom progression and lower levels of hsCRP.

3.3 A study of very small embryonic-like stem cells and expression of mRNAs of neuronal and glial markers

We conducted a study assessing the influence of long-term lithium treatment on VSELs (very small embryonic-like stem cells) and expression of mRNAs of neuronal and glial markers in peripheral blood of bipolar disorder patients with a long lasting disease. Patients not treated with lithium were characterized by a significantly higher number of VSEL cells, proportional to the duration of the disease, and higher expression of markers in comparison to healthy individuals matched in terms of sex and age. This may indicate that the excessive mobilization of VSELs and higher expression of mRNA of neuronal and glial markers cause an exaggeration of regenerative and inflammatory processes during the course of the bipolar disorder. On the other hand, in patients treated with lithium, the number of VSEL cells did not differ from the values found in healthy individuals and showed a negative correlation with the duration of treatment with lithium and serum concentrations of lithium. Also, the expression of neuronal and glial markers was, in many cases, similar to that of healthy individuals. The results indicate that long-term treatment with lithium of bipolar affective disorder may inhibit excessive regenerative and inflammatory processes in this disease [83]. This may be in contrast with the stimulating effect of lithium on hematopoietic stem cells [61], which is also clinically beneficial.

4. Neuroprotective effect of lithium

4.1 Lithium-induced increase in cerebral grey matter

The neuroprotective effect of lithium may be reflected by the lithium-induced increase in cerebral grey matter volume both in healthy subjects and in patients with bipolar disorders. This was first suggested in 2000 [84] and confirmed in several reports reviewed by Hajek and Weiner [85]. The brain structures influenced by either short-term or long-term lithium administration included the prefrontal cortex, anterior cingulate, and hippocampus. The most frequent reports demonstrated larger grey matter volumes in patients treated with lithium compared to those not receiving lithium. The association between lithium treatment and larger grey matter volume was not dependent on mood state and diagnostic subtype. In our own study, bipolar patients receiving lithium had larger hippocampal volumes than those not receiving lithium, and the volumes of lithium-treated subjects were similar to those of healthy controls [86]. In two studies, the effects of lithium were compared with anticonvulsants and antipsychotics, possessing mood-stabilizing properties. The use of lithium increased grey matter volume of the subgenual anterior cingulate, the hippocampus-amygdala complex and the insula, which was associated with better clinical effect. Such an outcome was not found by using any other mood stabilizer [87,88]. In experimental studies, it was found that lithium accumulates in neurogenic regions that may be relevant to the effects described above [89].

4.2 Experimental studies on the neuroprotective effect of lithium

Many experimental studies have shown protective effects of lithium either after ischaemic insults or ionizing radiation, both protection from acute injury [90,91] as well as regenerative effects even long after the injury [92,93] were evidenced. In a mouse model, lithium may alleviate the spatial cognitive impairment induced by repeated cerebral ischemia-reperfusion by the inhibition of excessive autophagy through mTOR signaling activation [94]. Also, the neuroprotective effect of lithium makes this ion a plausible candidate for the prevention and treatment of neurodegenerative disorders.

An inhibition by lithium of GSK-3β which is a key enzyme in the metabolism of amyloid precursor protein

and the phosphorylation of the tau protein, the main pathogenetic players in Alzheimer's Disease (AD) was shown in animal models. Lithium treatment causes a reduction of GSK-3β mRNA in cultures of rat cortical and hippocampal neurons [95] and may arrest the development of neurofibrillary tangles in mutant tau transgenic mice with advanced neurofibrillary pathology [96]. In irradiated mice, the neuroprotective effect of lithium was associated with inhibition of GSK-3β [97], and in another mouse model, the inhibition of the GSK-3β was related to the anti-apoptotic effect of lithium [98]. In a triple-transgenic mouse model of Alzheimer's disease, lithium treatment influenced the aspects of neuronal-glial interactions connected with neuroprotection in hippocampus [99] and increased telomere length in the parietal cortex and hippocampus [100].

In the fly *Drosophila* adult-onset model of AD, lithium may ameliorate amyloid-beta pathology through inhibition of GSK-3β [101]. In this insect, experimental studies of presenilin, a gene that may be one of the determining factors in the familial form of AD, were also performed. Reducing presenilin activity in *Drosophila* may contribute to cognitive impairment during aging. In the paper of Mc Bride and collaborators [102], it was found that treatment with lithium during the aging process prevented the onset of these deficits, and treatment of aged flies reversed the age-dependent deficits.

4.3 Epidemiological studies of lithium and dementia

It has also been proposed that lithium protects against dementia. Population studies have shown an association between lithium treatment and a reduction of dementia risk [103]. Employing 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 [104]. 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 [105]. A possible effect of trace doses of lithium has been recently proposed in a Danish study of Kessing and collaborators [106] showing a negative association between the incidence of dementia and lithium concentration in drinking water. Concurring with this, an American study demonstrated that changes in AD mortality were negatively correlated with trace lithium in drinking water [107].

4.4 Clinical studies of lithium in Alzheimer's disease and mild cognitive impairment

The first single-blind, randomized, placebo-controlled multicenter trial investigating the effects of lithium treatment on CSF dementia biomarkers and cognitive performance included 71 patients with early AD treated with a lithium level of 0.5–0.8 mmol/L over 10 weeks. No significant changes in CSF biomarkers or cognitive parameters were found [108]. However, secondary data analysis showed associations of lithium treatment with increased concentration of BDNF and a further subgroup analysis demonstrated that patients showing higher BDNF concentrations also had cognitive improvement [109]. Two years later, Forlenza *et al*. [110] investigated the effects of a low dose lithium treatment (0.25–0.5 mmol/L) on cognitive parameters and CSF biomarkers of dementia in 45 patients with amnestic mild cognitive impairment (aMCI). After 12 months, lithium-treated patients who did not convert to AD showed a significantly reduced concentration of hyperphosphorylated tau protein. In the lithium group, the conversion rate to AD was similar to that of non-lithium-treated patients, although converters showed less cognitive decline. Nunes *et al*. [111] studied the effects of a lithium microdose of 300 μg per day in a randomized, placebo-controlled trial lasting 15 months in 113 patients with AD. The treated group showed no decrease in performance in the mini-mental state examination test, which contrasted with the lower scores observed for the control group during this time [93]. Recently, the results of a randomized, double-blind, placebo-controlled four-year trial were published [112]. The therapeutic effects of low dose lithium (0.25–0.5 mmol/L) in 61 patients with amnestic MCI were examined. Within the lithium group, patients showed stable cognitive and functional scores after 24 months whereas patients in the placebo group demonstrated slightly, but significantly worsened scores. There were no significant differences in the concentration of hyperphosphorylated tau and total tau protein. In the lithium group, there was a trend towards a diminished conversion into AD.

Two meta-analyses suggested possible procognitive effects of lithium in patients with MCI and AD. The first, including three clinical trials with a total of 232 patients, demonstrated a significant slowing of cognitive decline associated with lithium treatment [113]. The second included five randomized controlled trials investigating the effects of lithium and tideglusib, an inhibitor of GSK-3, on cognition in patients with MCI and AD. In the subgroup of lithium-treated patients, some beneficial effects on cognitive parameters were observed, which correlated with treatment duration [114].

4.5 Experimental and clinical studies in Huntington's disease and amyotrophic lateral sclerosis

The attempts to use lithium in another neurodegenerative disorder, Huntington's disease (HD) started in the 1970s. The rationale for such use at that time was associated with the therapeutic effects of lithium regarding movement disorders such as tardive dyskinesia. However, the results of three controlled trials of lithium in HD involving small numbers of patients were negative [115–117]. In recent years, a rationale for using lithium in HD was based on

animal studies. In a rat excitotoxic model of HD disease in which quinolinic acid was unilaterally infused into the striatum, lithium suppressed striatal lesions and promoted neuronal survival and proliferation in this brain structure [118]. HD is caused by a polyglutamine expansion mutation in the huntingtin protein, which can be cleared by macroautophagy. A potential therapeutic mechanism of lithium in HD has also been attributed to its property of augmenting macroautophagy by inhibiting inositol monophosphatase and GSK-3β activity [119]. In experimental studies, the HD model was connected with reduced BDNF expression in several brain structures [120], therefore, the stimulation by lithium of the BDNF system can also contribute to a possible therapeutic effect.

The most recent review regarding the possible use of lithium in HD was performed in 2014, in which the authors compared lithium with another mood stabilizer, valproic acid (VPA). In clinical studies, lithium treatment improved mood, and VPA treatment both stabilized mood and moderately reduced chorea. However, the main features of HD were unaffected by treatment with either drug. In experimental studies, both lithium and valproic acid (VPA) have shown multiple beneficial effects, including behavioral and motor improvement, enhanced neuroprotection, and lifespan extension. In transgenic HD mice, combined lithium/VPA treatment was more effective than treatment with either drug alone. The authors postulate a clinical trial using lithium/VPA combination in HD patients [121]. However, in recent years such a trial has not been performed.

Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disorder that usually leads to death with 3–5 years from diagnosis. There is no effective treatment of ALS and all attempts are at an experimental stage. A part of ALS cases is due to mutations of the gene coding for the enzyme copper-zinc superoxide dismutase (SOD1), and a mouse model of ALS (transgenic mice overexpressing the human mutant SOD1) was created. In this model, administering lithium concurrently with an antioxidant, Neu2000, resulted in an improvement of motor neuron survival, motor function, and reduced mortality [122]. Fornari *et al.* [123] using the ALS mouse showed a marked neuroprotective action of lithium, with a delay of disease onset and increase in life span. However, such a beneficial effect of lithium was not confirmed in two subsequent studies that used this model [124,125]. In a clinical study, Italian investigators were the first to suggest that giving lithium in doses leading to plasma levels 0.4–0.8 mmol/L may delay the progression of ALS [123]. However, another Italian group was not able to confirm lithium effects either in therapeutic (0.4–0.8 mmol/L) or sub-therapeutic (0.2–0.4 mmol/L) doses [126]. Also, American researchers found no evidence that lithium in combination with riluzole, the drug used in ALS, slows the progression of the disease more than riluzole alone [127]. More recently, Van Eijk *et al.* [128] performed a meta-analysis to assess whether genetic subgroups in ALS trials differently responded to treatment with lithium. It was found that the effect of lithium was dependent on the *UNC13A* gene and the 12-month survival probability for *UNC13A* carriers treated with lithium improved from 40% to 70%. Therefore, the possibility of using lithium in some patients with ALS remains an open issue.

The summary of the antiviral, immunomodulatory, and neuroprotective effects of lithium is presented in Table 1 (Ref. [27–30,34–43,45–51,53,54,57–67,72–75,77–93,95–98,100–102,104–107,109–114,118–120,122,123,128,129]).

5. Conclusions

The main indication for lithium in psychiatry is for the prevention and treatment of affective episodes, as a mood stabilizer. The antiviral, immunomodulatory, and neuro-protective effects of this ion contribute to its therapeutic effects in mood disorders. However, these properties of lithium can be also useful in other clinical conditions. For example, in subsection 3.1, it has been shown that the lithium property of increasing leukocyte count can be used both in psychiatry and elsewhere.

The antiviral effect of lithium against herpes infections can be applied clinically for the suppression of recurrences of labial and genital infections both in patients with a mood disorder and in other populations. In patients with bipolar disorder, it may also be important for lithium's pro-cognitive action. American researchers found that infection with HSV-1 was an independent predictor of decreased cognitive functioning (mostly immediate verbal memory) in bipolar patients [130]. In our study, we demonstrated that in a cohort of bipolar patients receiving lithium for an average of 13 years, excellent lithium responders presented cognitive functions at the level of healthy subjects without bipolar disorder. We may hypothesize that it could be partly due to the effect of lithium on herpes viruses. Furthermore, in such patients, serum BDNF concentrations were also similar to those of healthy subjects, which may point to lithium's neuroprotective effect [131]. It may also suggest that mood stabilization by itself can be naturally beneficial for cognitive function regardless of anti-HSV effect and BDNF levels. The effect against herpes infection can be also connected with lithium's activity, both prophylactic and therapeutic, in dementia. Recently, Izhaki [132] presented convincing 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 [133].

The immunomodulatory effect of lithium in bipolar disorder plays an important role in mitigating the condition of the "low-grade inflammation" in this illness. In bipolar disorder, this process is present both in the central nervous system and in the peripheral blood including excessive production of proinflammatory cytokines by microglia and in

Table 1. Summary of the antiviral, immunomodulatory, and neuroprotective effects of lithium.

Effect	Experimental studies	Clinical studies	Mechanisms
Antiviral	Inhibiting HSV replication [27–29]	Suppression of labial herpes (HSV-1) and genital herpes (HSV-2) recurrences by systematic and topical administration [34–38]	Impairing the viral DNA synthesis by the displacement of potassium and magnesium [30]
	Inhibiting replication of parvoviruses [39,40]	Beneficial effect on respiratory infections [45,46]	Inhibition of GSK-3β, indispensable for the production of genomic RNA [53,54]
	Inhibiting replication of RNA viruses, including coronaviruses [41–43,47–51]		
Immuno-modulatory	Increase of leukocytes [60,61]	Increase of leukocytes [57–59]	Increased G-CSF production [62–64]
	Decrease of microglial activation [73–75]	Therapeutic effect in drug-induced neutropenia [65–67]	Inhibition of GSK-3β Stimulation of pro- and inhibition of antiinflammatory cytokines [72]
		Mitigating the "low-grade inflammation" in bipolar disorder [77–85]	Decrease of VSELs
		Inhibiting excessive regenerative processes	Reduction of mRNA of neural and glial markers [83]
Neuroprotective	Protective effect after ischemic insults and irradiation [90–93]	Increase in cerebral grey matter [84–89]	Inhibition of GSK-3β [95]
	Amelioration amyloid-β and tau pathology in mice and *Drosophila* [96–98,101,102]	Reduction of dementia risk [104–107]	Stimulation of BDNF [109,120,129]
	Beneficial effects in experimental models of HD and ALS [118,119,122,123]	Beneficial effects in AD, MCI [109–114] and *UNC13A* carriers of ALS [128]	Effect on autophagy through mTOR signaling [100]

HSV, herpes simplex virus; GSK-3β, glycogen synthase kinase 3-beta; G-CSF, granulocyte- colony stimulating factor; VSEL, very small embryonic-like stem cells; HD, Huntington's disease; ALS, amyotrophic lateral sclerosis; AD, Alzheimer's disease; MCI, mild cognitive impairment; BDNF, brain-derived neurotrophic factor.

the periphery as well as an excess of regenerative processes involving some stem cells (VSEL) [83]. De-Paula and collaborators [134] demonstrated that lithium, both in therapeutic and subtherapeutic concentrations inhibited the secretion of proinflammatory and enhanced that of antiinflammatory cytokines in co-cultures of neurons and glial cells. Because the role of proinflammatory cytokines released from microglia was also evidenced in Alzheimer's disease [135], this effect of lithium can also contribute to its therapeutic activity in some neurodegenerative disorders.

The neuroprotective effect of lithium in bipolar disorder may be important for improving neuroplasticity, which is deficient in this illness [136]. This discovery gave rise to attempts of repurposing lithium for neurodegenerative disorders. However, in these disorders, there has been a conspicuous discrepancy between the results of experimental and clinical studies. Despite promising findings with lithium treatment obtained in animal models, an immediate reflection of these in clinical studies of HD and ALS has been weak. The only positive results would be a possibility of decreasing the risk of AD with long-term lithium use as well as some therapeutic effects obtained in AD and MCI, as described in subsection 4.3. Therefore, it seems that the issue of clinical application of lithium in neurological disorders should be a subject of further well-designed clinical studies in the future.

Although the antiviral, immunomodulatory, and neuroprotective effects of lithium can be perceived as distinct, there may be overlapping biological mechanisms. The most important is probably the inhibition by lithium of the GSK-3β, responsible, for example, for inhibiting the production of viral RNA, inhibiting the secretion of pro-inflammatory cytokines, and influencing the metabolism of the amyloid precursor and tau proteins. However, it should be noted that in some instances, another GSK-3 isoform, namely GSK-3α, may be of importance [137]. An example can be the therapeutic effect of lithium on the pathophysiology in a mouse model of fragile X syndrome [138].

There has also been evidence for the contribution of the phosphatidylinositol and BDNF systems in both immunomodulatory and neuroprotective activity, involving the phosphatidyl-inositol-3-kinase/Akt (protein kinase B)/CREB/BDNF pathway [129]. Another mechanism can be the inhibition of excessive autophagy through mTOR signaling activation [100].

In conclusion, the antiviral, immunomodulatory, and neuroprotective effects of lithium constitute an important part of its biological properties. These mechanisms may add to the therapy of mood disorders and also repurpose lithium for other therapeutic indications.

Abbreviations

AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; BDNF, brain-derived neurotrophic factor; cAMP, cyclic ademosine monophosphate; CREB, cAMP response binding protein; G-CSF, granulocyte-colony stimulating factor; GSK-3β, glucogen synthase kinase-3-beta; MCI, mild cognitive impairment; HD, Huntington's disease; HSV, herpes simplex virus; IFN, interferon; IL, interleukin; LPC, lipopolysaccharide; PI, phosphatidylinositol; PKC, protein kinase C; PPV, porcine parvovirus; TLR4, toll-like receptor; TNF, tumor necrosis factor.

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Conflict of interest

The author declares no conflict of interest.

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