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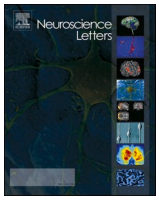

Minireviews

Mini-review: Anomalous association between lithium data and lithium use

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ABSTRACT

This mini-review aims to show a discrepancy between favorable data of lithium's therapeutic activity and the decreased use of the drug worldwide. The data point to lithium as the best mood stabilizer in the maintenance treatment of bipolar disorder for the prevention of manic and depressive recurrences. The second most encouraging psychiatric use of lithium is the augmentation of antidepressants in treatment-resistant depression. In addition to its mood-stabilizing properties, lithium is the most efficacious antisuicidal drug among all mood stabilizers. The drug also exerts antiviral, immunomodulatory, and neuroprotective effects which may be of major clinical value. On the other hand, the data of lithium use show that its therapeutic application in many countries has declined. A reason for this can be the introduction and heavy promotion of other mood-stabilizers, while lithium is an "orphan" drug with the minimal interest of any drug company. Probably, very important is also a perception of lithium as a "toxic drug", pointing to its side effects, mainly thyroid, renal and cognitive ones. In recent years, several proposals to turn back this anomalous association appeared, challenging a negative perception of lithium and optimizing its long-term administration. They show the data on lithium superiority over other mood stabilizers and point to the proper management of the lithium-induced side effects. This endeavor aims to allow a larger number of mood disorder patients to become beneficiaries of lithium use.

1. Introduction

1.1. Lithium data: Favorable effects extend beyond mood stabilization

Presently, lithium has been recognized as the best mood stabilizer in bipolar disorder for the prevention of manic and depressive recurrences. Three *meta*-analyses of the 21st century have fully confirmed the prophylactic effectiveness of lithium in bipolar disorder [1–3]. The studies also supported lithium prophylactic efficacy in recurrent depression [4]. Lithium augmentation of antidepressants in treatment-resistant depression can be regarded as a therapeutic indication for lithium in both bipolar and unipolar depressed patients, and a successful outcome may be expected in at least 50% of them [5]. The most recent review confirms lithium's usefulness against a broad spectrum of clinical issues in bipolar disorder [6]. In 1/3 of bipolar patients called "excellent lithium responders", lithium monotherapy can completely prevent affective recurrences. Such subjects can be mostly characterized by a moderate number of affective episodes with full remissions and the absence of psychiatric comorbidity which may correspond to the classic Kraepelin's description of "manisch-depressives Irresein". In a substantial proportion of the remaining bipolar patients, a combination of lithium with other mood stabilizers is also prophylactically very effective [7].

The experiences with ultra-long-term administration of lithium have exceeded several-fold those with other mood-stabilizers. Six years ago, we described two male and three female patients, aged 64–79 years, receiving lithium monotherapy with very good effect for more than 40 years. All patients had cognitive functions on a similar level as in healthy persons of comparable age, were professionally active until 55–65 years of age, and their family and social functioning were adequate [8]. In the last year, a 79-year-old female physician was described who has been taking lithium monotherapy for 50 years. It was a period of her optimal functioning in terms of mental, general, and social health [9].

In addition to mood-stabilizing properties, lithium exerts several other actions which can be of major clinical value. Probably the most important is its anti-suicidal effect, as suicide makes the main factor of mortality in mood disorders. Suicide prevention by lithium is the strongest among all mood stabilizers being the most conspicuous after two years of the drug administration. The evidence for this was substantiated by the *meta*-analyses performed in the 21st century [10,11]. The lithium's anti-suicidal effect is not correlated with mood stabilization which points to a specific aspect of lithium activity. [12]. Therefore,

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the necessary candidates for lithium monotherapy or combination would be patients with a high risk of suicide. In the recent decade, an astonishing negative correlation has been observed between lithium concentration in drinking water and suicides. Such relationship has been demonstrated in many countries, such as Japan [13], Austria [14], the USA [15], and Greece [16], and recently also in Argentina [17], Hungary [18], and Lithuania [19].

Experimental evidence for the antiviral effect of lithium started in 1980 when researchers from the University of Birmingham showed that the drug inhibits replication of the herpes simplex virus (HSV) in hamster kidney cells [20]. A decade later, the most important clinical research on labial herpes caused by HSV-1 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. Polish population consisted of 69 patients, among them 28 persons had recurrent labial herpes. During lithium therapy, the full cessation of recurrence of herpes occurred in 46% of patients, and the general decrease in recurrence frequency was 64%. The better effect was observed in patients in whom serum lithium concentration 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, age, and length of 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-years before the treatment decreased by 73%. In the second group, including patients with recurrent depression receiving antidepressant drugs, no significant difference was observed [21].

The efficacy of oral lithium carbonate as a prophylactic treatment of genital herpes recurrences, caused by HSV-2, was demonstrated in two placebo-controlled studies [22–23]. Also, Amsterdam et al. [24] 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 caused mostly by RNA viruses in lithium- but not antidepressant-treated patients.

Shortly after the outbreak of the covid-19 pandemics, Nowak and Walkowiak [25] presented the experimental data on the possible antiviral effect of lithium in coronavirus infections. However, in most of these studies, lithium concentration exceeded several times the concentration of clinical lithium use (i.e. 0.5–1.0 mmol/l). They postulated that lithium could be useful clinically in coronaviral infections on account of its inhibition of GSK-3β which is indispensable for the production of viral genomic RNA [26]. Also, Murru et al. [27] 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 disputable. Gattner and Rybakowski [28] described a severe course of the COVID-19 in an inhabitant of Lombardy receiving lithium treatment for several years. On the other hand, Spuch et al. [29] treated six COVID-19 patients with lithium carbonate and observed an improvement in both inflammatory activity and the immune response in them. Recently, the author of this review presented the results of a naturalistic observation on the occurrence and course of COVID-19 infection in fifty patients treated with lithium from March 2020 to March 2021 and not receiving the vaccination against COVID-19 during this period. The study group included 23 men and 27 women aged 23–71 (mean 45) receiving lithium for 1–45 (mean 7) years. Bipolar disorder was diagnosed in 46 patients, which were treated with lithium to prevent manic and depressive recurrences. Four patients with schizophrenia receiving clozapine were given lithium to treat and prevent neutropenia. The COVID-19 infection occurred in one-fourth of lithium-treated patients (26%). In the majority of such subjects, the infection was benign. One patient died of COVID-19 related pneumonia. However, two patients developed lithium intoxication which suggests that COVID-19 infection and related circumstances may be a risk factor for such a complication [30].

Shortly after introducing lithium in modern psychiatry, Radomski et al. [31] reported an increase of leukocytes during lithium treatment. This effect was subsequently confirmed in clinical reports [32]. It can be employed for the prevention and treatment of neutropenia occurring during clozapine treatment [33] in schizophrenia, but also in bipolar disorder, where clozapine has been increasingly used. 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 bipolar disorder, the addition of lithium to clozapine augments the therapeutic effect. Lithium can also prevent neutropenia induced by carbamazepine, at the same time reinforcing mood-stabilization [34].

In recent decades, bipolar illness has been perceived as a condition characterized by a “low-grade inflammation”. In this process in the central nervous system (neuroinflammation), the cells most important are microglia [35]. 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–pituitaryadrenal axis [36]. A review of the anti-inflammatory effect of lithium was also published in 2014 [37]. Research carried out in Poznań has shown that in bipolar patients in sustained remission (6 months or more) during long-term lithium treatment, cytokine concentrations did not differ from those observed in healthy subjects [38].

We assessed the effect of long-term lithium treatment on VSELs (very small embryonic-like stem cells) and the expression of mRNAs of neuronal and glial markers in peripheral blood of bipolar patients with a long duration of the disease. Patients not treated with lithium had a significantly higher number of VSEL cells, proportionally to the duration of the disease, and higher expression of markers, in comparison to healthy individuals, matched by sex and age. This excessive mobilization of VSELs and higher expression of mRNA of neuronal and glial markers may cause an exaggeration of regenerative and inflammatory processes in the course of bipolar disorder. However, in lithium-treated patients, the number of VSELs did not differ from the healthy individuals and showed a negative correlation with the duration of lithium treatment and serum concentrations of the drug. Also, the expression of neuronal and glial markers was mostly similar to that of healthy individuals. The results indicate that long-term treatment with lithium for bipolar disorder may inhibit excessive regenerative and inflammatory processes in this disease [39].

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 two decades ago [40] and confirmed in several reports reviewed by Hajek and Weiner [41]. The brain structures influenced by either short-term or long-term lithium administration were the prefrontal cortex, anterior cingulate, and hippocampus. In our study, bipolar patients receiving lithium had larger hippocampal volumes than those not receiving lithium, and the volumes of lithium-treated subjects were similar to healthy controls [42]. The effects of lithium were also compared with anticonvulsants and antipsychotics, possessing mood-stabilizing properties. 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 for any other mood stabilizer [43–44].

The population studies suggest an association between lithium treatment and a reduction of dementia risk [45]. The analysis of the Danish nationwide register of lithium prescriptions revealed that in patients taking lithium for a long time, the rate of dementia decreased to the same level as the general population while in persons treated with anticonvulsant drugs, the risk of dementia increased with the duration of treatment [46]. 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 [47]. In Denmark, a negative association between the

incidence of dementia and lithium concentration in drinking water was shown [48]. Also, an American study demonstrated that changes in the mortality of Alzheimer's disease (AD) were negatively correlated with trace lithium in drinking water [49]. The role of lithium microdose was supported in the study of Nunes et al. [50] assessing the effects of lithium, 300 μg per day, in a 15-month trial including 113 patients with AD. During this time, the lithium-treated group showed no decreased performance in the Mini-Mental State Examination test, in opposition to the lower scores observed for the control group. A possible procognitive effect of lithium in patients with mild cognitive impairment (MCI) and AD was suggested in a *meta*-analysis including three clinical trials with a total of 232 patients [51].

2. Lithium use: Relative decline all over the world

Paradoxically, these many favorable effects of lithium have not been reflected in the use of this drug all over the world. This has been indicated in the prescription analyses of mood-stabilizing medications. In the USA, an analysis of prescriptions in 2002–2003 for patients with bipolar disorder, published in 2007, showed less percentage of lithium use (7%), compared to mood-stabilizing antiepileptic drugs (17%), and antipsychotics (11%) [52]. In Britain, the paper of 2011 found the proportion of bipolar patients receiving pharmacological treatment in 2009 almost doubled compared with 1995 (78.5% and 40.6%, respectively). The percentages of those using the drug in 2009, compared with 1995, were for lithium 29.3 and 22.5%, respectively, for valproate 22.7 and 0%, for carbamazepine 7.3 and 6.5%, for lamotrigine 6.2 and 0%, and atypical antipsychotics 35 and 0%, respectively (the most frequent were olanzapine – 18% and quetiapine – 6%) [53]. In Australia, an assessment of prescription trends for psychotropic drugs has shown that in 2011, mood stabilizers such as lithium, valproate, carbamazepine, and lamotrigine accounted for 5.8% of daily doses of psychotropic drugs. Between 2000 and 2011 the number of prescriptions for lithium remained stable, while valproate and lamotrigine showed a significant increase [54]. In a large region of Italy, lithium use increased by 8% between 2000 and 2002, followed by a 13% decrease between 2002 and 2006, and a further increase of 11% in 2006–2010 [55].

In Scandinavia, using the country prescription data for the period July 2005-June 2006, it was found that 0.17, 0.21, and 0.25% of the respective population of Denmark, Norway, and Sweden, had at least one lithium prescription during this time [56]. However, in Sweden, a study of mood-stabilizing drugs' prescriptions in bipolar disorder between 2007 and 2013 showed a decrease of lithium from 51% to 41%, as well as that of valproate (from 18% to 14%) and olanzapine (from 21% to 17%). On the other hand, an increase was noted for lamotrigine (from 25% to 33%) and quetiapine (from 9% to 25%) [57]. Similarly, in Denmark, the rate of lithium prescription in 2000–2011 diminished from 41.1% to 34%, and in 2011, it was exceeded by lamotrigine (increase from 3.4% to 42.1%), and by quetiapine (the increase 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% [58].

A large drop in lithium and an increase in the use of valproate in the first decade of the 21th century prompted the investigators to make a systematic comparison of these two mood stabilizers. This was performed in the study having the acronym BALANCE (Bipolar Affective disorder Lithium/ ANtiConvulsant Evaluation). Three-hundred thirty bipolar patients were randomized to lithium (n = 110) or valproate (n = 110) monotherapy, or both drugs in combination (n = 110). During the two-year follow-up, 59 (54%) subjects from the combined lithium-valproate group, 65 (59%) from the lithium monotherapy, and 76 (69%) from the valproate monotherapy experienced a recurrence of a manic or depressive episode. The results showed the prophylactic superiority of lithium monotherapy over valproate and the best results of combination [59].

In Poland, lithium use between 2004 and 2017 was assessed, using data provided by the Intercontinental Marketing Statistics, Poland, expressed as DOT (days of treatment) values. The current use of lithium in comparison to other mood stabilizers (valproate, carbamazepine, lamotrigine, olanzapine, quetiapine, aripiprazole) was evaluated by calculating the number of prescriptions for a given drug issued for patients diagnosed with bipolar disorder in the second half of 2017. It was shown that between 2004 and 2010 there was a slight increase (by 4%) in the use of lithium, while between 2011 and 2017, the increase reached 16%. However, in the second half of 2017, the use of valproate was almost three times higher, and of quetiapine, olanzapine, and lamotrigine about twice as high as lithium [60].

A recent American study assessed 20-year trends in the pharmacologic treatment of bipolar disorder by psychiatrists in outpatient care settings, using data from the 1997–2016 National Ambulatory Medical Care Surveys. Comparing the years 1997–2000 and 2013–2016, the most conspicuous was a great increase of the prescriptions for antipsychotics (12.4 and 51.4%, respectively), and a great decrease for classic mood-stabilizing drugs (62.3 and 26.4%, respectively). Among the latter, the use of lithium noted a decline from 30.4% to 17.6% [61].

In summary, these data indicate a relative decline in using lithium in recent two decades at the expense of other drugs having mood-stabilizing properties. There are several reasons for this. One is the introduction and heavy promotion of other mood-stabilizers, both first-generation (e.g. valproate) and second-generation (e.g. olanzapine, quetiapine, lamotrigine) [62], while lithium is an "orphan" drug with the minimal interest of any drug company. Another, and probably more important is a perception of lithium as a "toxic drug" among not only the non-psychiatrist physicians but also by the representatives of mainstream psychiatry. Lithium's side effects, such as renal, thyroid, and cognitive have been mainly indicated in this respect. The variation of this is perceiving lithium as a "difficult to use" drug due to the necessity of estimating serum concentrations.

3. How to turn back this anomalous association

There may be several possibilities to address and correct a discrepancy between favorable data of lithium's therapeutic activity and the decreased use of the drug worldwide. It is important to promote sound scientific evidence and provide an education that can facilitate the more extensive and long-term application of lithium in mood disorders. A negative perception of this drug as a first-line candidate for the prophylaxis of bipolar disorder can be challenged, showing the data of its clinical efficacy and successful managing its side effects.

The anticipated adverse effects of long-term lithium administration, mainly on kidney, thyroid, and cognitive function may pose a major barrier to the use of the drug. Probably, the most serious concern is the possibility of lithium-induced interstitial nephropathy, which can develop after 10–20 years of treatment and leads to increased creatinine concentration and a decreased glomerular filtration rate (GFR). This can even lead to a decision to discontinue lithium. However, such a choice should be made with extreme caution, especially in good responders, since replacing lithium with other mood stabilizers may not be equally efficacious. In the majority of these patients, discontinuing lithium results in a high risk of relapse and further treatment resistance.

We analyzed the data of 312 patients from 12 centers, treated with lithium for 8–48 (on average 18) years. With each year of lithium administration, a mean GFR decrease of 0.9% was found. Longer duration of treatment, a higher serum lithium concentration, older age, presence of comorbidities, and initiation of lithium treatment after the age of 40 were risk factors for lowered GFR. No person had end-stage renal failure [63]. During lithium administration, such preventive measures are recommended as to use a once-daily dosing schedule, target the lowest effective serum lithium concentration, and prevent lithium intoxication [64]. In another study, lithium responders with GFR as low as 40–50 monitored during five years were not showing significant progress [65]. Therefore, in patients with lithium-induced

nephropathy, renal function should be closely and frequently monitored. In case of progress, the lithium dose should be lowered. In lithium responders, even a very low dose can be helpful. Collaboration with a nephrologist may be recommended.

The most frequent lithium-induced thyroid adverse effects are goiter and hypothyroidism. The symptoms of hypothyroidism usually appear at the early stage of lithium treatment and are more frequent in women and persons with a family history of thyroid dysfunction. In our study of patients receiving lithium for at least three years (on average 19 ± 10 years), TSH concentration and thyroid volume were significantly higher compared with patients never treated with lithium, matched for the disease duration. The frequency of hypothyroidism was similar in both groups (24% vs 18%) and 3–4-fold higher in women than in men, which may suggest that bipolar illness itself may predispose to this disorder. The frequency of goiter in lithium-treated patients was similar in men and women (37 and 41%, respectively) and no correlation was found between goiter and thyroid hormones [66]. A comparison of thyroid autoantibodies between lithium-treated and lithium-naive patients revealed no significant differences [67]. Practical experience shows that symptoms of hypothyroidism and goiter can be successfully treated with levothyroxine, which dose can be consulted with an endocrinologist, and lithium administration can be well continued.

Some clinicians believe that lithium may exert an unfavorable effect on cognitive functions while experimental studies show a beneficial action of lithium in this respect. Bipolar patients may have primary cognitive dysfunction, intensified during the episodes of the illness, and treatment with lithium does not cause significant changes. In susceptible persons, to minimize possible negative effects of lithium, it is recommended to maintain serum lithium concentration at the lowest effective level, i.e., 0.4–0.6 mmol/l [68]. Our studies demonstrated that the effect of lithium on cognitive functions is connected with the quality of prophylactic efficacy. Non-responders to lithium had significantly worse performances on the neuropsychological tests compared with good responders and the healthy controls [69]. The excellent lithium responders obtained significantly better cognitive results than the remaining lithium-treated patients and were similar to healthy subjects [70].

Among other lithium side-effects which can be troubling, the tremor, occurring at the beginning of lithium therapy, as well as weight gain, can be mentioned. The tremor is usually mild and often disappears when the dose of lithium is reduced. However, if the reduction of the dose is not possible and this symptom interferes with the daily activities of the patient, beta-adrenolytic drugs, such as propranolol at a dose of 20–80 mg/day, can be used with good results. Weight gain is a common side-effect of mood-stabilizing drugs such as valproate, and atypical antipsychotics with mood-stabilizing properties such as olanzapine. It also occurs in a small percentage of lithium-treated patients and may be distressing, especially in women. In some of them, this can even be a reason to stop taking the medication. Therapy options include diet, physical activity, and/or co-administration of topiramate. However, a recent *meta*-analysis indicates generally a low impact of lithium on weight change [71].

The anomalous association between lithium data and lithium use has generated claims voiced by the prominent specialists in bipolar disorder and lithium therapy aimed to correct this trend. In 2018, the famous American researcher, Robert Post, deplored that lithium is greatly underutilized in the USA, even more than in Europe. He pointed to the multiple assets of lithium and argued that the fear of lithium's adverse effects is exaggerated [72]. In the same year, the author of this review published a paper titled "Challenging the negative perception of lithium and optimizing its long-term administration", where he demonstrated the advantage of lithium over other mood-stabilizing drugs, described the benefits of long-term lithium therapy, and the possibilities of effective management of side effects [73]. In 2020's editorial of the journal "Bipolar Disorders", titled "Make lithium great again!", the psychiatrists led by the Chief Editor of the journal, Gin Malhi, call upon a better utilization of lithium's therapeutic potential and for more frequent use of the drug [74].

Recently, a discussion was held on the Medscape webpage led by Steven Strakowski, the chair, and professor of psychiatry at Dell Medical School, University of Texas. Contributing discussants were Kay Jamison, professor of psychiatry at Johns Hopkins School of Medicine and the author of many books, among other the famous autobiographical "Unqiet mind", and Michel Ostacher, professor of psychiatry at Stanford University [75]. They all agreed that to improve the care of patients with bipolar disorder, the use of lithium should be resurrected. It is important to provide lithium education to both providers: the doctors should be persuaded before they can persuade patients. Targeting lower serum lithium should be considered as well as showing that adverse effects are manageable. The compelling data about reducing suicide by lithium should be strongly communicated. Kay Jamison even proposed that lithium therapy could be perceived as the ongoing care of the brain on account of lithium's neuroprotective properties.

In conclusion, it seems that the correction of the anomalous relationship between lithium data and lithium use may be possible. The advocates of this process, mainly psychiatrists, should be very persistent in their self-education and teaching others. The results of studies pointing to favorable action of lithium in mood disorders as well as fringe benefits of lithium therapy such as antisuicidal, antiviral and neuroprotective effects should be extensively promoted. Psychiatrists should continuously improve their knowledge of how to conduct lithium therapy and to handle possible side effects. This can enhance their confidence in giving the drug to patients and persuading them of the legitimacy of such a procedure. Such endeavor could allow a larger number of mood disorder patients to become beneficiaries of lithium use.

CRediT authorship contribution statement

Janusz K. Rybakowski: Conceptualization, Data curation, Writing – review & editing. **Ewa Ferensztajn-Rochowiak:** Conceptualization, Data curation, Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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