

Letter to the Editor. Therapy with lithium as a protective factor against SARS-CoV-2 infection? Observations from the disease outbreak

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Lithium is a medication with documented efficacy in the treatment and prevention of episodes of mood disorders (both in the course of unipolar and bipolar disorder), with antisuicidal and neuroprotective properties [1]. The antiviral action of lithium has also been known for over 40 years – the first reports concerned individual patients with bipolar disorder who had complete remission of recurrent herpes during lithium therapy [2–4]. In the following years, the antiviral activity of lithium has been reported (mainly in preclinical studies) not only against HSV (herpes simplex virus), but also, i.a., parvoviruses, cytomegalovirus, Epstein-Barr virus, adenoviruses, and viruses from the Coronaviridae family [5]. However, data from clinical studies are less numerous. The beneficial effects of lithium in preventing recurrences of labial and genital herpes has been described in several publications [6, 7]. During therapy with this drug a statistically significant reduction in the incidence of influenza-like infections was also observed in the group of patients with mood disorders [8]. On the other hand, in 2021 an analysis performed among the population of patients with bipolar disorder was published, the results of which indicate an average 28% reduction in the incidence of respiratory infections (viral or bacterial) during lithium therapy (compared to the control group of patients not receiving this drug) [9].

Among the proposed mechanisms of the antiviral and immunomodulatory effects of lithium are: (1) inhibition of the activity of glycogen synthase kinase 3 β (GSK-3 β) – it is a pro-inflammatory protein, inducing apoptosis and the expression of pro-inflammatory cytokines, e.g., IL-6 (interleukin 6) and TNF-alpha (tumor necrosis factor α); (2) competition of lithium ion with magnesium ions: magnesium is a cofactor of enzymes necessary in the process of viral replication – its substitution by lithium inactivates viral polymerases; (3) increased activity of B lymphocytes (stimulation of antibody production), increased proliferation of T lymphocytes, decreased ratio of

regulatory to cytotoxic T lymphocytes – possible influence of lithium on gene expression in lymphocytes; (4) inhibition of the phosphatidylinositol signaling pathway; (5) stimulation of autophagy; (6) inhibition of cyclooxygenase 2 expression [5, 10–15].

Taking into consideration the above-mentioned data on the antiviral activity of lithium, it is not surprising that after the outburst of COVID-19 pandemic hypotheses have emerged about the possible role of this drug in preventing or treating coronavirus infection. In 2020, a case report of six patients with COVID-19 in whom lithium was added to standard therapy was published [16]. There was a significant improvement in inflammatory and immune parameters [CRP (C-reactive protein), NLR (neutrophil-lymphocyte ratio), lymphocyte count], while these parameters were unchanged in the group of three analyzed control patients who used standard treatment only. The authors also verified that none of the patients receiving lithium in their catchment area (437 patients in total) were registered as infected with COVID-19.

In 2021, the results of a retrospective analysis of data from three American registries covering over 300,000 patients who underwent PCR (polymerase chain reaction) testing for SARS-CoV-2 infection were published [11]. Statistically significant lower risk of infection was observed in the group of patients treated with lithium [OR (odds ratio) = 0.51 (95% CI: 0.35–0.74)]. The authors also have demonstrated that the virus nucleocapsid protein (necessary for its replication) is phosphorylated by the GSK-3 enzyme – inhibition of the activity of this enzyme by lithium could theoretically lead to impairment of the virus replication process.

In 2021, Prof. Rybakowski presented observation of 50 patients under the author's outpatient care who were taking lithium for a year since March 2020 and did not receive the COVID-19 vaccine during that time (most patients were treated with the diagnosis of bipolar disorder) [17]. In the analyzed group, SARS-CoV-2 infection occurred in approximately $\frac{1}{4}$ of patients – in the majority of them the infection was mild, one patient died of pneumonia and two patients developed lithium intoxication. It is worth adding that so far four other cases of lithium intoxication in the course of COVID-19 have been described in the literature, and one of the mentioned risk factors for occurrence of this complication is dehydration during infection [12, 18].

In the context of still very few reports on the potential role of lithium in the treatment/prevention of COVID-19, in our manuscript we would like to present observations from the course of the SARS-CoV-2 infection outbreak which took place at the beginning of 2022 in the Clinical Department of Adult Psychiatry of the University Hospital in Krakow. During this period eight patients hospitalized in the ward were put under epidemiological supervision. Four of them tested positive for coronavirus infection during the monthly observation period. None of the infected patients were treated with lithium. On the other hand, among four patients who did not get infected throughout the observation period, one patient had been receiving lithium for several years and in the second one lithium had been discontinued a few days before the beginning of the outbreak. The clinical data of both patients are briefly presented below. Table 1 summarizes the most important clinical features for all patients hospitalized in our ward during the COVID-19 outbreak.

Patient 1

A 27-year-old patient treated psychiatrically for around 10 years with the diagnosis of paranoid schizophrenia was admitted to our ward due to deterioration of his mental state. Among somatic comorbidities he had hyperparathyroidism and rosacea. He was vaccinated against COVID with two doses (last dose – 20.07.2021). During the hospital stay, due to lack of remission during therapy with antipsychotics and accompanying affective symptoms (increased psychomotor drive, irritability, grandiosity), after endocrinological consultation, lithium was added to the treatment regimen reaching blood level of 0.36 mmol/l. However, after a few weeks of therapy the drug was discontinued due to the rapid increase in serum calcium level. Shortly, COVID-19 infection was detected in the ward. Due to his mental state, the patient was not able to fully comply with the epidemiological recommendations and the rules of isolation in the ward, he repeatedly contacted with other infected patients. Nevertheless, all swabs obtained from this patient during his stay were negative. He also did not show any signs of infection.

Patient 2

A 36-year-old patient was hospitalized due to a manic episode with psychotic features in the course of bipolar disorder. Among somatic disorders he had prediabetes, obesity, dyslipidemia, aortic valve regurgitation. He was vaccinated twice against COVID (last dose – June 2021). For several years, the patient had been treated with lithium, the dose of which was increased during hospitalization in our ward due to sub-therapeutic blood levels of the drug (after the modification, the blood level was 0.51 mmol/l). After the outbreak was detected, nasopharyngeal swabs for infection with coronavirus were performed several times in this patients, with all results negative and no infectious symptoms. Due to manic symptoms the patient did not fully comply with the epidemiological recommendations and did not self-isolate.

Table. Clinical features of patients hospitalized in the ward during the COVID-19 outbreak

Age (years)	Gender (F – female; M – male)	Psychiatric diagnosis	Comorbidities	Medications used during the COVID-19 outbreak, along with daily doses	Vaccination against COVID (YES/NO), type of vaccine taken, number of doses administered, date of the last dose	Compliance with sanitary recommendations during hospitalization
Patients who did not get infected with COVID-19 during the outbreak						
27	M	Schizophrenia with affective symptoms	Hyperparathyroidism, rosacea	Clozapine 400 mg, cariprazine 3 mg, estazolam 2 mg, bisoprolol 5 mg, torasemide 5 mg, vitamin D 1,000 IU	YES, Pfizer 2 doses, last 20.07.2021	NO

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36	M	Bipolar disorder	Obesity, prediabetes, dyslipidemia, aortic valve regurgitation	Olanzapine 15 mg, lurasidone 74 mg, lithium 1,000 mg, metformin 2,000 mg, lorazepam 2 mg	YES, Moderna 2 doses, last 14.06.2021	NO
20	M	Paranoid schizophrenia	-	Olanzapine 15 mg, lurasidone 74 mg, lorazepam up to 3 mg, propranolol 40 mg	NO	YES
78	F	Bipolar disorder	Hypertension, Buerger's disease	Haloperidol up to 12.5 mg, valproate 1,500 mg, dabigatran 300 mg, nebivolol 5 mg, doxazosin 4 mg, lercanidipine 20 mg, torasemide 10 mg, ramipril 10 mg, rosuvastatin 10 mg, zopiclone 7.5 mg	YES, Pfizer 3 doses, last 17.11.2021	YES
Patients who got infected with COVID-19 during the outbreak						
30	F	Paranoid schizophrenia	Pregnancy	Olanzapine 20 mg, haloperidol 5 mg, lorazepam 3 mg, iron supplementation 80 mg	NO	YES
65	F	Major depressive disorder	Non-insulin-dependent diabetes mellitus, hypothyroidism, dyslipidemia, hypertension	Agomelatine 50 mg, pregabalin 300 mg, duloxetine 60 mg, quetiapine XR 100 mg, levothyroxine 75 ug, metformin 1,000 mg, betaxolol 10 mg, perindopril 5 mg	NO (patient had COVID in March 2021)	YES
67	F	Organic mood disorder, organic delusional disorder	Parkinson's Disease	Clozapine 150 mg, duloxetine 30 mg, pramipexole 1.05 mg, mianserin 20 mg, levodopa + benserazide 375 mg, donepezil 10 mg,	YES, AstraZeneca 2 doses, last 14.06.2021	YES
28	M	Paranoid schizophrenia	-	Cariprazine 6 mg, paliperidone 150 mg intramuscular injection every 4 weeks	NO	NO

Conclusions

The patients of the ward treated with lithium did not get infected with COVID-19 during the outbreak. It is worth mentioning that the patients presented above, due to their mental state (manic symptoms), had significant difficulties in complying with the sanitary rules (isolation in a separate room with separate sanitary facility, keeping distance, disinfecting hands, wearing mask) – contrary to the recommendations, they were leaving their rooms, contacting with the infected patients, they were not using face masks. They both had comorbidities as well. The other two patients who did not get infected fully complied with the epidemiological recommendations, which may have helped them to avoid infection.

Obviously the above reports are casuistic. However, it seems reasonable to present our observations due to the scarcity of reports on the role of lithium in the prevention of SARS-CoV-2 infection. Perhaps this type of preliminary analysis will encourage scientists and clinicians to design and conduct research on the possibility of using lithium in the treatment of COVID-19 or other viral infections.

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