

Short Report

Association between serum lithium level and incidence of COVID-19 infection

Livia J. De Picker, Marion Leboyer, John R. Geddes, Manuel Morrens, Paul J. Harrison and Maxime Taquet

Summary

An antiviral effect of lithium has been proposed, but never investigated for coronavirus disease 2019 (COVID-19). Using electronic health records of 26 554 patients with documented serum lithium levels during the pandemic, we show that the 6-month COVID-19 infection incidence was lower among matched patients with 'therapeutic' (0.50–1.00) versus 'subtherapeutic' (0.05–0.50) lithium levels (hazard ratio (HR) = 0.82, 95% CI 0.69–0.97, $P = 0.017$) and among patients with 'therapeutic' lithium levels versus matched patients using valproate (HR = 0.79, 95% CI 0.67–0.92, $P = 0.0023$). Lower rates

of infection were observed for both new COVID-19 diagnoses and positive polymerase chain reaction tests, regardless of underlying psychiatric diagnosis and vaccination status.

Keywords

COVID-19; lithium; valproate; bipolar disorder; psychopharmacology.

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Lithium is thought to have antiviral properties.¹ *In vitro*, lithium inhibits replication of several viruses, including coronavirus strains.^{1,2} In a national registry study using pre-pandemic data, lithium was associated with decreased risk of respiratory infections.³ As patients with mood disorders are at an increased risk of coronavirus disease 2019 (COVID-19)⁴ and of severe or fatal outcomes when infected,⁵ a protective effect of lithium against COVID-19 would be particularly welcome. However, no study to date has investigated the effect of lithium on COVID-19 incidence. This study used electronic health records (EHR) to compare the incidence of COVID-19 infections and positive polymerase chain reaction (PCR) tests for SARS-CoV-2 among patients with high versus low lithium serum concentrations, and versus patients using valproate.

Method

We used TriNetX Analytics, a federated EHR network with anonymised data from 81 million individuals (both insured and uninsured, mostly from the USA).⁶ Participating healthcare organisations include hospitals, primary care and specialist providers. De-identification data are formally attested as per Section §164.514(b)(1) of the HIPAA Privacy Rule, superseding TriNetX's waiver from the Western Institutional Review Board; no further ethical approval was thus needed. As we used anonymised routinely collected data, no participant consent was required. We followed STROBE reporting guidelines.

We compared all patients with a lithium level between 0.5 and 1 mmol/L (named 'therapeutic' for convenience) recorded between 19 January 2020 and 27 October 2021 in their EHR versus a matched cohort with a level between 0.05 and 0.5 mmol/L (named 'subtherapeutic') as our primary analysis, and versus a matched cohort using valproate during the same period, as our secondary analysis. The primary outcome was defined as a composite of confirmed COVID-19 diagnosis (ICD-10 code U07.1) or positive PCR test for SARS-CoV-2 between 1 day and 6 months after the lithium level was recorded.

Cohorts were propensity-score matched for 73 covariates: sociodemographic factors and comorbidities representing risk for COVID-19 and for more severe COVID-19 illness as in our previous studies,⁶ specific mood disorder diagnosis, personality disorder,

previous or concurrent use of any antipsychotics (and clozapine specifically), and previous or concurrent use of any antidepressant (and fluvoxamine specifically). In the analysis comparing lithium with valproate, patients with epilepsy were excluded from both cohorts.

Kaplan–Meier analysis and the Cox proportional hazard model (with log-rank test) were used to calculate the cumulative incidence and hazard ratio (HR) for the primary outcome. The proportional hazard assumption was tested with the generalised Schoenfeld approach. Sensitivity of the findings to unmeasured confounders was quantified with the *E*-value.⁷ Statistical significance was set at two-tailed *P*-values <0.05.

We tested the robustness of the primary association by separately analysing COVID-19 diagnosis and positive PCR test as outcomes and by restricting cohorts to individuals: (a) with all recorded lithium levels within the cohort's reference range during the 6-month follow-up, (b) who were not vaccinated before or within 6 months after the index lithium level, and (c) with a recorded diagnosis of bipolar disorder.

To rule out the confounding effect of concurrent antidepressant use, we compared cohorts of individuals on lithium with versus without concurrent antidepressant use. For completeness, we also restricted cohorts to individuals without antidepressants, although this analysis was underpowered (see Supplementary Data 1 available at <https://doi.org/10.1192/bjp.2022.42>). To assess the specificity of the association with COVID-19, we repeated the analysis for non-COVID respiratory infection. We used skin infection as a negative control outcome.

More details on the data and analyses are provided in Supplementary Data 1.

Results

A total of 14 008 individuals with a recorded therapeutic lithium level (mean level 0.741 (s.d. = 0.163) mmol/L) and 12 546 individuals with a recorded subtherapeutic lithium level (mean level 0.352 (s.d. = 0.141) mmol/L) were identified (see Supplementary Table 1 for baseline characteristics). In total, 11 791 individuals were selected from each cohort after matching. Adequate matching was achieved for all characteristics and all robustness analyses (Supplementary Tables 1–5). From 103 018 patients with

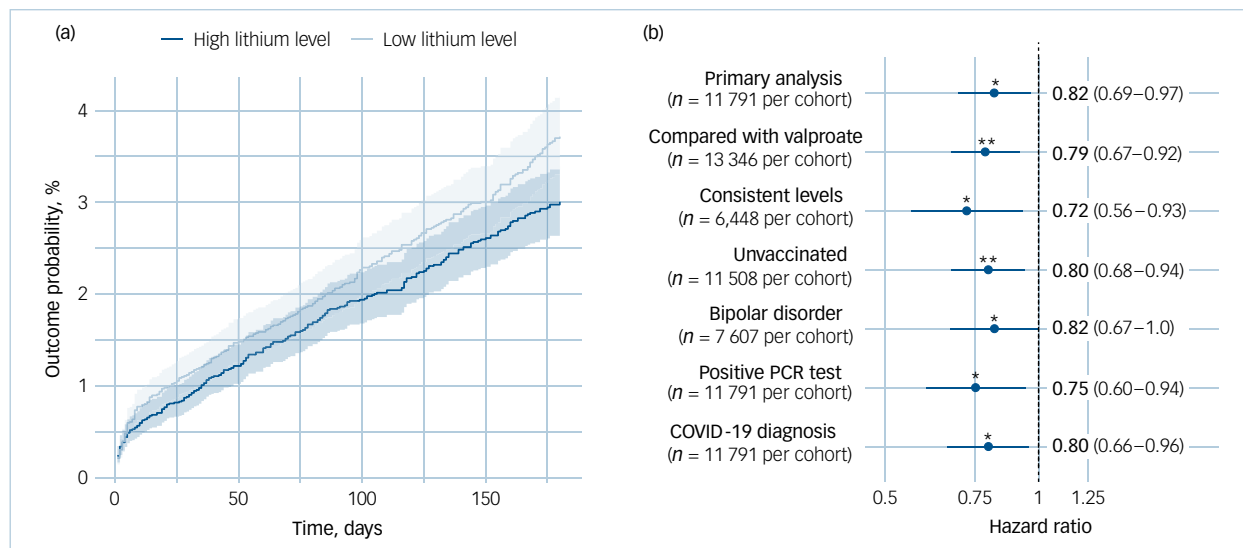


Fig. 1 (a) Kaplan–Meier curves for the primary analysis showing the cumulative incidence of confirmed coronavirus disease 2019 (COVID-19) diagnoses or positive polymerase chain reaction (PCR) test for SARS-CoV-2 after a therapeutic (dark blue) versus subtherapeutic (light blue) lithium level in matched cohorts. The shaded areas around the curves represent 95% confidence intervals. (b) Hazard ratios for the comparison between matched cohorts in the secondary and robustness analyses. Consistent levels refer to the analysis restricted to individuals with all recorded lithium levels within the cohort’s reference range during the 6-month follow-up. Unvaccinated and Bipolar disorder refer to the analysis restricted to individuals who had not received a COVID-19 vaccine and who had a diagnosis of bipolar disorder respectively. Positive PCR test and COVID-19 diagnosis refer to the analysis with the same cohorts as in the primary analysis but looking at each component of the composite outcome. * $P < 0.05$, ** $P < 0.01$.

documented valproate use during the pandemic, 13 346 were selected as a second control cohort after matching.

Therapeutic (versus subtherapeutic) lithium level was associated with a significantly lower risk of COVID-19 within the next 6 months (cumulative incidence 3.01%, 95% CI 2.66–3.39% v. 3.72%, 95% CI 3.32–4.16%, HR = 0.82, 95% CI 0.69–0.97, $P = 0.017$, E -value = 1.74, P -value for proportionality 0.35; Fig. 1a).

The risk was also lower compared with patients prescribed valproate (cumulative incidence 2.94%, 95% CI 2.62–3.30% v. 3.69%, 95% CI 3.33–4.10%, HR 0.79, 95% CI 0.67–0.92, $P = 0.0023$, E -value 1.86, P -value for proportionality 0.50). The association remained significant in all robustness analyses (Fig. 1b and Supplementary Figs. 1 and 2). We found no significant effect of concurrent antidepressant use on COVID-19 incidence (HR 1.17, 95% CI 0.85–1.62, $P = 0.17$; restricting cohorts to individuals without antidepressants resulted in a large 95% CI that included the primary HR = 0.96, 95% CI 0.68–1.35), and no significant effect of lithium on risks of other respiratory or skin infections (Supplementary Fig. 1).

Discussion

Therapeutic lithium levels were consistently associated with lower risks of both COVID-19 and positive PCR tests for SARS-CoV-2. The mechanisms underlying this observation remain to be determined. *In vitro* studies have suggested that lithium exerts its antiviral effect by inhibiting RNA replication.² The weaker and non-significant association with other respiratory infections suggests some specificity of our finding to SARS-CoV-2. However, this might also result from lack of statistical power as only data from 2020 to 2021 were used (a significant association was observed in pre-pandemic data³). Larger samples are also required to estimate the individual impact of lithium and antidepressants on COVID-19 incidence.

Limitations

Our findings, although robust, come with inherent limitations of EHR data (see Supplementary Data 1). Other sources of confounding might include differences in the nature and frequency of health-care contacts during the pandemic, and differences between patients who can maintain adequate lithium levels versus those who cannot. However, any unmeasured confounders would need to associate with both the difference in lithium serum concentration and COVID-19 infection with a relative risk of 1.74-fold each (i.e. the E -value) to explain away the observed association, which seems unlikely. Furthermore, the use of lithium serum concentrations rather than prescriptions allowed us to reliably determine lithium exposure while avoiding confounding by indication. Finally, the lack of association with skin infection (used as a negative control), and the robustness of the finding in various scenarios suggest that no major confounders were missed in our analysis.

Implications

Although several psychopharmacological compounds have been claimed to exert protective or detrimental effects on COVID-19 outcomes (for example fluvoxamine appears to improve prognosis⁸ whereas clozapine might worsen it^{5,9}), very few studies have investigated the effect of psychotropic medication against COVID-19 incidence¹⁰ – with evidence on the effects of lithium lacking altogether. The number of patients exposed to lithium at the time of COVID-19 infection in the current study was too low to evaluate infection outcomes in any robust way. However, a reduced infection incidence likely translates into reduced burden of COVID-19-associated complications.

In summary, our results provide the first real-world evidence that therapeutic lithium levels are consistently associated with lower risks of COVID-19. These findings shed more light on the antiviral effects of lithium. Although its tolerability profile excludes lithium from repurposing against COVID-19 in the general population, our

findings inform the risk–benefit balance of lithium prescription for psychiatric indications. Head-to-head comparisons with other psychopharmacological compounds are needed to provide definite clinical recommendations, but the observed protective effect of lithium might offset clinicians' reluctance to prescribe lithium and monitor serum concentrations during the pandemic.

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First received 22 Nov 2021, final revision 10 Feb 2022, accepted 16 Feb 2022

Supplementary material

To view supplementary material for this article, please visit <https://doi.org/10.1192/bjp.2022.42>

Data availability

M.T. and P.J.H. had full access to the data. The TriNetX system returned the results of these analyses as csv files, which were downloaded and archived. Data presented in this paper and the Supplementary material can be freely accessed upon request to the corresponding author. Additionally, TriNetX will grant access to researchers if they have a specific concern (via the third-party agreement option).

Author contributions

L.J.D.P., M.L., J.R.G. and M.T. formulated the research question. L.J.D.P., P.J.H. and M.T. designed the study. M.T. carried out the analyses. All authors contributed to interpretation of the findings. L.J.D.P. wrote the first draft of the manuscript with input from M.T. All authors revised the manuscript for content.

Funding

Work supported by the National Institute for Health Research (NIHR) Oxford Health Biomedical Research Centre (grant BRC-1215-20005). M.T. is an NIHR Academic Clinical Fellow and NIHR

Oxford Health BRC Senior Research Fellow. The views expressed are those of the authors and not necessarily those of the UK National Health Service, NIHR or the UK Department of Health.

Declaration of interest

J.R.G. is a member of the *BJPsych* editorial board but did not take part in the review or decision-making process of this paper. The other authors declare no conflict of interests.

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