

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

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Summary

An antiviral effect of lithium has been proposed, but never investigated for 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) vs. ‘sub-therapeutic’ (0.05-0.50) lithium levels (HR 0.82, 95% CI 0.69-0.97, $p=0.017$) and among patients with ‘therapeutic’ lithium levels vs. 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 PCR tests, regardless of underlying psychiatric diagnosis and vaccination status.

Keywords: COVID-19, lithium, valproate, bipolar disorder, epidemiology, psychopharmacology

Introduction

Lithium has been proposed to have antiviral properties¹. In vitro studies have indicated that lithium inhibits replication of several viruses, including coronavirus strains^{1,2}. A national registry study using pre-pandemic data demonstrated that lithium is associated with decreased risk of respiratory infections³. Since patients with mood disorders are at an increased risk of COVID-19 infection⁴ and of severe or fatal outcomes when infected⁵, a protective effect of lithium against COVID-19 would be particularly welcomed. However, no study to date has investigated the effect of lithium on the incidence of COVID-19. This study used electronic health records (EHR) to compare the incidence of COVID-19 infections and positive PCR tests for SARS-CoV-2 among patients with high versus low lithium serum concentrations, and versus patients using valproate.

Methods

We used TriNetX Analytics, a federated EHR network with anonymised data from 81 million individuals (both insured and uninsured)⁶. Participating healthcare organisations include hospitals, primary care and specialist providers. Data de-identification is 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 the study uses fully anonymised routinely collected data, no consent from participants 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 January 19, 2020 and October 27, 2021 in their EHR versus a matched cohort with a level between 0.05 and 0.5 mmol/L (named 'subtherapeutic') as primary analysis, and versus a matched cohort using valproate during the same period, as 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 each of 73 covariates consisting of: sociodemographic factors and comorbidities representing risk for COVID-19 and for more severe COVID-19 illness as in our previous studies⁶, 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 to valproate, patients with epilepsy were excluded from both cohorts.

Kaplan-Meier analysis and the Cox proportional hazard model (with the 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. The E-value was used to quantify sensitivity of the findings to unmeasured confounders⁷. Statistical significance was set at two-sided 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 (1) with all recorded lithium levels within the cohort's reference range during the 6-months follow-up, (2) who were not vaccinated before or within 6 months after the index lithium level, and (3) 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 vs. without concurrent antidepressant use. For completeness, we also restricted cohorts to individuals without antidepressants, although this analysis was underpowered (see supplement). To assess the specificity of the association with COVID-19, we repeated the analysis with non-COVID respiratory infection. We used skin infection as a negative control outcome.

More details on the data and analyses are provided in the supplement.

Results

A total of 14,008 individuals with a recorded therapeutic lithium level (mean [SD] level 0.741 [0.163] mmol/L) and 12,546 individuals with a recorded subtherapeutic lithium level (mean [SD] level 0.352 [0.141] mmol/L) were identified (see Supplementary Table 1 for baseline characteristics). 11,791 individuals were selected from each cohort after matching. Adequate matching was achieved for all baseline characteristics and all robustness analyses (Supplementary Tables 1-5). From 103,018 patients with documented valproate use during the pandemic, 13,346 were selected as a second control cohort after matching.

Therapeutic (vs. subtherapeutic) lithium level was associated with a significantly lower risk of COVID-19 within the next six months in Cox regression (cumulative incidence 3.01%, 95% CI 2.66-3.39% vs. 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; Figure 1A). The risk was also lower compared to patients prescribed valproate (cumulative incidence 2.94%, 95% CI 2.62-3.30% vs. 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 (Figure 1B and Supplementary Fig. 1-2). We found no significant effect of concurrent antidepressant use on incidence of COVID-19 (HR 1.17, 95% CI 0.85-1.62, $p=0.17$; restricting cohorts to individuals without antidepressants resulted in a large 95% CI which includes the primary HR: 0.96, 95% CI 0.68-1.35), and no significant protective effect of lithium on rates of other respiratory or skin infections (Supplementary Fig. 1).

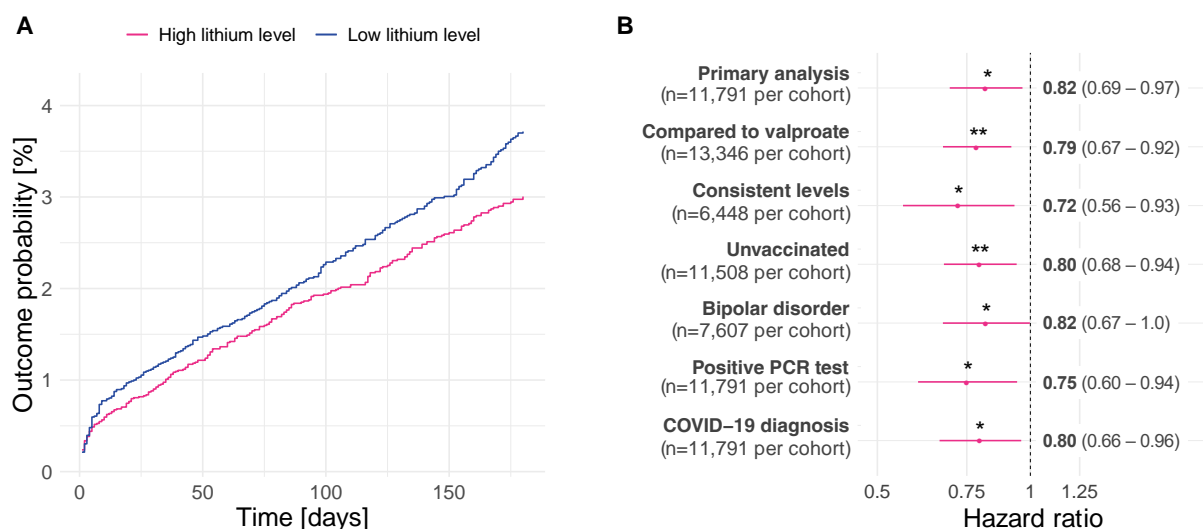


Fig. 1 (A) Kaplan-Meier curves for the primary analysis showing the cumulative incidence of confirmed COVID-19 diagnoses or positive PCR test for SARS-CoV-2 after a therapeutic (red) vs. subtherapeutic (blue) lithium level in matched cohorts. The shaded areas around the curves [see pdf version of figure below] represent 95% confidence intervals. (B) Hazard ratios for the comparison between matched cohorts in the secondary and robustness analyses. * $p < 0.05$, ** $p < 0.01$.

Discussion

Therapeutic lithium levels were consistently associated with lower risks of COVID-19 infection and a positive PCR test 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 replication². The weaker and non-significant association with other respiratory tract infections suggests some specificity of our finding to SARS-CoV-2. However, this might also result from lack of statistical power since only data from 2020-2021 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.

Our findings, while robust, come with inherent limitations of EHR data (see Supplement for discussion). Other sources of confounding might include differences in the nature and frequency of healthcare contacts in the pandemic context, as well as differences between patients who are able to maintain

adequate lithium serum levels versus those who are not. However, any unmeasured confounders would need to be associated 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. In addition, the use of lithium serum concentrations rather than prescriptions allowed us to reliably determine lithium exposure while avoiding confounding by indication. Furthermore, the lack of association with skin infection (used as a negative control), and the robustness of the finding in various scenarios also suggest that no major confounders were missed in our analysis.

While several psychopharmacological compounds have been claimed to exert either protective or detrimental effects on COVID-19 *outcomes* (e.g. fluvoxamine appears to improve COVID-19 prognosis⁸ whereas clozapine might worsen it^{5,9}), very few studies have investigated the effect of psychotropic medication against the *incidence* of COVID-19¹⁰ – 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, the reduced number of new infections can be reasonably expected to translate into a 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. While its tolerability profile excludes lithium from repurposing against COVID-19 in the general population, our findings can 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 in the pandemic context.

137

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143 **Declaration of interest**

144 The authors declare no conflict of interests. John R Geddes is a member of the BJPsych editorial board
145 but did not take part in the review or decision-making process of this paper.

146 **Author contributions**

147 LJDP, ML, JRG and MT formulated the research question. LJDP, PJH, and MT designed the study.
148 MT carried out the analyses. All authors contributed to interpretation of the findings. LJDP wrote the
149 first draft of the manuscript with input from MT. All authors revised the manuscript for content.

150 **Data Availability**

151 MT and PJH had full access to the data. The TriNetX system returned the results of these analyses as
152 csv files which were downloaded and archived. Data presented in this paper and the Appendix can be
153 freely accessed upon request to the corresponding author. Additionally, TriNetX will grant access to
154 researchers if they have a specific concern (via the third-party agreement option).

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