BRIEF REPORT

Is lithium a potential treatment for the novel Wuhan (2019-nCoV) coronavirus? A scoping review [version 1; peer review: 1 approved with reservations, 1 not approved]

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Abstract
The current rapid spread of the novel coronavirus (2019-nCoV) originating from Wuhan, China, calls for a rapid response from the research community. Lithium is widely used to treat bipolar disorder, but has been shown to exhibit antiviral activity. This brief review took a systematic approach to identify five in vitro studies reporting on the influence of lithium on coronaviral infections. We propose that in the case of urgent need, lithium be explored as a potential treatment or prophylaxis for the novel Wuhan coronavirus (2019-nCoV).

Keywords
coronavirus, Coronaviridae, Wuhan, 2019-nCoV, lithium, lithium carbonate, lithium orotate, antiviral, apoptosis, glycogen synthase kinase 3-beta, GSK-3β,

This article is included in the Disease Outbreaks gateway.

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Introduction
The current rapid spread of the novel coronavirus (2019-nCoV) originating from Wuhan, China, calls for a rapid response from the research community. Lithium is known to exhibit antiviral activity, but the knowledge of its potential as a possible therapy for coronaviral infections has not been summarized yet. The aim of this brief report is to draw attention to lithium as potential 2019-nCoV treatment and prophylaxis.

Methods
On February 1st 2020 the following PubMed search was conducted with no language or time restrictions: (lithium and (coronavirus or *coronavirus or sarbecovirus or SARS or “severe acute respiratory syndrome” or MERS or “Middle East respiratory syndrome” or nobecovirus or merbecovirus or hibecovirus or embecovirus or andecovirus or buldecovirus or herdecovirus or maurecovirus or cegacovirus or “microhyla lentovirus” or milecovirus or alphaletovirus or tegacovirus or setracovirus or rhinacovirus or pedacovirus or “Rhinolophus ferrumequinum” or “transmissible gastroenteritis virus” or “feline infectious peritonitis virus” or “canine coronavirus” or “murine hepatitis virus”)). The search yielded 45 articles, of which all the abstracts were charted and reviewed by two researchers.

Results
Five studies reporting on the influence of lithium on coronaviral infections were identified (Figure 1).

In Vero cells, lithium chloride was shown to be effective in suppressing infection with the porcine epidemic diarrhea virus (PEDV), a member of the Coronaviridae family. Not only PEDV entry and replication were inhibited in the presence of LiCl, but apoptosis as well. In MAC-145 cells, LiCl reduced the production of RNA and proteins specific to the porcine reproductive and respiratory syndrome virus. The authors, however, cautioned that the effect might have been dependent on LiCl presence during the early stages of infection and the increase of tumor necrosis factor-α. In vitro studies of another porcine coronavirus causing transmissible gastroenteritis indicated that LiCl acts on both early and late stages of infection and inhibits apoptosis. The same research group from Harbin in China reported earlier that LiCl reduced the cytopathic effect of the avian infectious bronchitis virus (also a coronavirus) in primary chicken embryo kidney cells. In Vero cells, African green monkey kidney-derived epithelial cells, and immortalized chicken embryo fibroblasts LiCl suppressed the avian coronavirus infectious bronchitis. The antiviral activity of lithium was ascribed to a cellular effect.

Discussion
The possible molecular mechanisms of reduced apoptosis include the inhibition of glycogen synthase kinase 3-beta (GSK-3β). Moreover, PEDV requires the PI3K/Akt/GSK-3α/β pathway, which can be targeted at GSK-3β by lithium. Curiously, GSK-3β is required for template switching, a process seemingly indispensable for the production of coronaviral genomic RNA. The inhibition of GSK-3β prevents longer viral subgenomic mRNAs and the genomic RNA from being synthesized. Their production would require GSK-3β-dependent phosphorylation of the viral nucleocapsid and subsequent recruitment of helicase DDX1.

Lithium carbonate is an orphan drug widely used in the treatment of bipolar disorder. Its safety, when used correctly, is excellent. The main concern in the setting of an infectious disease unit would be the potential for interactions with other medication, possibly leading to the elevation of lithium levels and acute toxicity, mostly renal. This may be prevented by monitoring serum lithium concentrations. To our best knowledge, no interactions between lithium carbonate and ribavirin, lopinavir or ritonavir exist. In unconscious patients lithium carbonate could be given via a nasogastric tube. In case of lithium carbonate unavailability, lithium orotate could be explored, which, however, remains much less known to medical science despite being available as a dietary supplement.

Figure 1. Study flow chart.
Overall, we propose that in the case of urgent need lithium be explored by physicians as a potential treatment or prophylaxis for the novel Wuhan coronavirus (2019-nCoV).

Data availability
Underlying data
All data underlying the results are available as part of the article and no additional source data are required.

Reporting guidelines

The adapted reporting guidelines checklist is available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).

References

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The authors identified five previous studies reporting an effect of lithium (mostly LiCl) in coronavirus in cellular systems. This is obviously a very timely question. All studies point toward beneficial effects of lithium and thus underscore the possible beneficial effect of targeting lithium sensitive biochemical pathways, namely GSK3 mediated signaling for coronavirus treatment or prophylaxis.

As a technical issue lithium not only targets GSK3b but also GSK3-alpha and inositol monophosphatases. So the emphasis on GSK3-beta may be a bit premature.

A more important issue is that none of the studies shown an effect of lithium at a 1-1.5mM concentrations. Effects are reported at Li+ concentrations that are 5mM or higher. These concentrations are not toxic for cells in culture. However, in humans, serum lithium concentration above 1.5-2.0mM (or mEq, which stands for the mM concentration of the lithium ion) are considered toxic (Haussmann et al., 2015).

The prescription of lithium in the context of the current epidemic thus appears not to be supportable by the findings. The cure may kill the patients.

More detailed studies using lithium in animal models at tolerable concentrations would thus be needed.

Unfortunately these limitations are not addressed in the manuscript.

References

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Partly
Are sufficient details of methods and analysis provided to allow replication by others?  
Yes

If applicable, is the statistical analysis and its interpretation appropriate?  
Not applicable

Are all the source data underlying the results available to ensure full reproducibility?  
Yes

Are the conclusions drawn adequately supported by the results?  
No

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Gsk3 signaling

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 12 February 2020

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The wide spread of infection of 2019-nCoV has arouse an international concern since its original outbreak in Wuhan, China. Scientists and health workers around the world are currently working together to wipe out the virus and the novel coronavirus pneumonia (NCP), which has killed more than a thousand lives, by far, worldwide.

With the current epidemic being so severe, it is necessary and urgent to make potentially reasonable recommendations for the treatment or prevention for 2019-nCoV or NCP. The two authors clearly proposed that lithium might be a potential treatment or prophylaxis for 2019-nCoV or NCP based on a summary of existing literature that reported the in vitro effects of lithium on coronaviral infections and discussed potential mechanisms, which sound reasonable to some extent, but still not rigorous.

Specifically, there are few related studies available and only in vitro data have been reported. The authors may need more related studies and solid evidence to support their hypothesis to make it more scientific
and rigorous. As reported, lithium can be toxic due to its side effects, mainly thyroid, renal, and cognitive disturbances. Readers may wish to see more clinical information of lithium in treating viral infection cases, if not available, or in treating other diseases.

In terms of discussion, the authors reviewed some existing literature and suggested a potential mechanism of reduced apoptosis by lithium, the glycogen synthase kinase 3-beta (GSK-3β) inhibitor. The possibility that targeting at GSK-3β by lithium may potentially affect the coronavirus is an interesting topic. However, direct in vitro evidence is lacking regarding 2019-nCoV or related coronaviruses including severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) coronaviruses.

Moreover, relevant literature is still needed although the authors state that there is no interaction between lithium carbonate and ribavirin, lopinavir, or ritonavir exist. Another aspect worth noting is that the authors indicate that monitoring serum lithium concentration can be helpful in preventing side effects of lithium, however it should be emphasized that the in vivo relationship between the effective dose and toxic dose of lithium is still unclear, with some studies reporting a dose-dependent manner of the inhibitory effect of lithium in vitro. Thus, it warrants more data, both in vitro and in vivo, to clarify this issue.

Collectively, this study proposes a potential role of lithium in treating or preventing 2019-nCoV or NCP with some possible mechanisms. However, by far, solid evidence is lacking to validate this hypothesis. The time of developing lithium orotate for clinical use, even in emergency, is not yet.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Not applicable

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.
Reader Comment 21 Mar 2020

**Charlotte Ayley-Smith**, University of Greenwich, Student, UK

I am a Public Health BSc student and I have been undergoing Lithium therapy for 2 years now. I take 1000mgs of Priadel daily and I agree with a previous commenter - since therapy began I've been rarely ill. Even attending university I have not picked up any bugs. I am happy to help with any research should you need me. Thank you, Charlotte

*Competing Interests:* No competing interests were disclosed.

Reader Comment 21 Mar 2020

**Jim Meehan**, Personal, Liverpool, UK

As a mental health nurse in Liverpool UK I am very interested in this and hope endymologists are trialling it ASAP.
We need to data crunch correlations between people treated on lithium for many years and their h/o viral infection or resistance

*Competing Interests:* No competing interests were disclosed.

Reader Comment 17 Mar 2020

**Demis Cunningham**, Patient, Scotland, UK

As a lithium patient taking 800mg Li Carbonate I can vouch for its antiviral properties, I have not had a single cold or illness since commencing the drug for major depressive disorder in Dec 2019. I have passed this article on to relevant authorities in the hope someone takes note. I am happy to volunteer for research trials.

*Competing Interests:* Nil
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