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COMMENTARY

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# Lithium as a candidate treatment for COVID-19: Promises and pitfalls

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## Abstract

The pandemic of respiratory illness caused by a novel coronavirus (SARS-nCoV-2) is a global health crisis. Despite numerous preliminary results, there is as yet no treatment of proven efficacy for this condition. In this context, the pharmacological properties of lithium, better known as a treatment for mood disorders, merit closer examination. Lithium has shown in vitro efficacy at inhibiting the replication of coronaviruses responsible for gastrointestinal and respiratory diseases in animals. It has immunomodulatory properties that may be of additional benefit in moderating the host inflammatory response to the novel coronavirus (SARS-CoV-2). Furthermore, there is evidence that lithium may exert a protective action against upper respiratory infections and influenza-like illnesses in patients taking it for other indications. These promising reports must be balanced against the narrow therapeutic index and high risk of toxicity associated with lithium therapy, its documented interactions with several commonly used drugs, and the absence of evidence of its efficacy against coronaviruses responsible for human disease. Nevertheless, naturalistic studies of the risk of COVID-19 in patients already receiving lithium could provide indirect evidence of its efficacy, and understanding the putative antiviral and immune-regulatory mechanisms of lithium in models of SARS-CoV-2 infection may provide leads for the development of safer and more effective treatments with a specific action against COVID-19.

**KEYWORDS**

COVID-19, lithium, nCoV-2

The global pandemic caused by a virus officially designated as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), and commonly referred to as COVID-19, has assumed the proportions of a worldwide public health crisis (Adhikari et al., 2020). To date, over 3.5 million cases of COVID-19, and over 250,000 deaths attributable to it, have been reported across the world. The mechanism of viral entry into host cells, using angiotensin-converting enzyme II (ACE-2) as a receptor, has been elucidated (Hoffmann et al., 2020) and has been shown to be dependent on a transmembrane serine protease enzyme designated as TMPRSS2. These molecular targets may be of therapeutic significance in the initial phase of infection. However, the later and more severe manifestations of COVID-19 appear to be immunologically mediated, through a pathway that may involve the endocytosis of ACE-2 along with SARS-CoV-2, followed by activation of angiotensin type 1 receptors (AT1R). Activation of AT1R causes a cascade of effects, including the activation of the transcription factors nuclear factor kappa B (NF-κB) and STAT-3, as well as the induction of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) (Spinelli, Conti, & Gadina, 2020). The latter can further stimulate the activation of these pro-inflammatory transcription factors, creating a positive feedback loop (Hirano & Murakami, 2020). The end result of this process, in vulnerable individuals, is what is known as a "cytokine storm" or "inflammatory storm," leading to lung damage as well as multiple organ dysfunction (Lipworth, Chan, Lipworth, & Kuo, 2020). Thus, the pathophysiology of COVID-19 is complex and involves both direct viral infection as well as immune/inflammatory mechanisms.

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A variety of treatments, including viral replication inhibitors, chloroquine and hydroxychloroquine, azithromycin, and immunotherapies, are being investigated as therapeutic options for COVID-19. Despite initial promising reports, there is insufficient evidence to recommend any of these, as well as substantial concerns about drug toxicity in some cases (Chary, Barbuto, Izadmehr, Hayes, & Burns, 2020). Given these limitations, as well as the time frame required for development of an effective vaccine, it is important to explore other therapeutic options (Ebrahimi, 2020).

Lithium salts, conventionally used in the treatment of bipolar disorder and related conditions, could represent one such alternative. The pharmacodynamics of lithium are complex and involve effects on genes related to the downstream effects of neurotransmitter cascades, as well as neural plasticity (Rybakowski, 2020). However, lithium has also been documented to moderate the immune-inflammatory activation seen during episodes of mood disorder, including the normalization of cytokine levels (Rybakowski, 2000; van den Ameele et al., 2016). In addition, lithium has been documented to have direct anti-viral effects. A close examination of these two properties reveals a conjunction of actions that may be of particular significance in treating infection with SARS-nCoV-2.

Evidence for a direct effect of lithium against some members of the coronavirus family has accumulated over the past decade. Initially, lithium was thought to exert an antiviral effect mainly on DNA viruses, particularly herpes simplex viruses (Bach, 1987; Skinner, Hartley, Buchan, Harper, & Gallimore, 1980). This was confirmed by evidence that lithium therapy, at doses similar to those used in the maintenance treatment of bipolar disorder, was effective in treating recurrent genital herpes (Amsterdam, Maislin, Potter, & Giuntoli, 1990) and labial herpes (Amsterdam, Maislin, & Rybakowski, 1990). Similarly, topical application of lithium succinate proved efficacious in some patients with anogenital warts caused by the human papillomavirus (Ward et al., 1997). Subsequently, lithium was been shown to significantly reduce the rates of influenza-like illnesses in patients with mood disorders; this effect, like its effects against herpes, was specific to lithium and was not seen with antidepressants (Amsterdam, Garcia-Espana, & Rybakowski, 1998). This raised the possibility that lithium could possess meaningful in vivo activity against RNA viruses. More recent research suggests that lithium has at least in vitro activity against several coronaviruses, including both gastrointestinal and respiratory pathogens (Harrison, Tarpey, Rothwell, Kaiser, & Hiscox, 2007; Li et al., 2018; Ren et al., 2011). A recent review (Nowak & Walkowiak, 2020) examined these studies critically and concluded that lithium, either alone or in combination with chloroquine, merited further investigation as a treatment for SARS-CoV-2. The mechanism of lithium's antiviral action may involve the inhibition of RNA polymerases (Harrison et al., 2007). This effect appears to be exerted through lithium's inhibition of the enzyme glycogen synthase kinase-3 beta (GSK-3β), which inhibits the phosphorylation of co-factors needed for the action of viral RNA polymerase (Asenjo, Gonzalez-Armas, & Villanueva, 2008). Lithium also appears to possess aprotective effect against apoptosis triggered by viral infection (Ren et al., 2011).

From the perspective of immune modulation, lithium appears to exert an inhibitory action on NF-κB (Troib & Azab, 2015) which plays a key role in the initiation of the "cytokine storm" triggered by infection with SARS-nCoV-2. It has also been shown to reduce levels of TNF-α and IL-6, which are also crucial parts of this pathway, in an animal model of sepsis (Albayrak et al., 2013). Furthermore, lithium appears to inhibit the process by which IL-6 activates the transcription factor STAT-3 in an animal model of joint inflammation (Minashima, Zhang, Lee, & Kirsch, 2014), which means that it could potentially interrupt the self-reinforcing inflammatory cascade described above. At least some of these effects appear to be related to the inhibitory effects of lithium on the enzyme glycogen synthase kinase-3-beta (GSK-3β) (Beurel, Michalek, & Jope, 2010; Wang et al., 2013), which has also been identified as a molecular target for the action of chloroquine and hydroxychloroquine in reducing inflammation triggered by SARS-nCoV-2 (Embi, Ganesan, & Sidek, 2020). Besides its effects on this particular pathway, lithium also seems to have more widespread anti-inflammatory effects, including the inhibition of interleukin-1 beta (IL-1β) production and the reduction of cyclooxygenase-2 expression (Nassar & Azab, 2014). Taken together, these findings suggest that lithium may exert a beneficial effect on the "inflammatory storm" that seems to underlie some of the more severe manifestations of COVID-19.

Evidence for a direct effect of lithium against some members of the coronavirus family has accumulated over the past decade. Initially, lithium was thought to exert an antiviral effect mainly on DNA viruses, particularly herpes simplex viruses (Skinner et al., 1980). However, more recent research suggests that lithium has at least in vitro activity against several coronaviruses, including both gastrointestinal and respiratory pathogens (Harrison et al., 2007; Li et al., 2018; Ren et al., 2011). The putative mechanisms of this antiviral action may involve the inhibition of RNA polymerases (Harrison et al., 2007) or a protective action against apoptosis triggered by viral infection (Ren et al., 2011). More anecdotally, lithium has been shown to significantly reduce the rates of influenza-like illnesses in patients with mood disorders; this effect was specific to lithium and was not seen with antidepressants (Amsterdam et al., 1998). Thus, it is at least plausible that lithium may have an effect against respiratory infections caused by RNA viruses, including SARS-nCoV-2.

These promising indicators, summarized in Table 1, must, however, be weighed against several potential drawbacks of lithium therapy. First, lithium has a narrow therapeutic index and a wide range of drug interactions—including interactions with some antiviral drugs—that place the patient at risk of lithium toxicity (Finley, 2016). Second, the concentrations at which lithium exerts an antiviral effect in vitro are several times higher than the acceptable therapeutic levels (Li et al., 2018; Ren et al., 2011), meaning that achieving lithium levels sufficient to inhibit viral replication may not be possible in human patients; however, such a limitation may not apply to its immunomodulatory properties, and there is at least preliminary in vivo evidence for an antiviral effect of lithium at tolerable therapeutic doses (Amsterdam, Maislin, Potter, & Giuntoli, 1990; Amsterdam, Maislin, & Rybakowski, 1990). This may be due to the fact that lithium levels in

**TABLE 1** Potential anti-viral and immunomodulatory mechanisms of lithium relevant to SARS-CoV-2 infection

| Action | Mechanism | References |
|---|---|---|
| Antiviral effects | Inhibition of viral RNA polymerase, probably related to blockade of co-factor phosphorylation through inhibition of GSK-3β | Harrison et al., 2007; Asenjo et al., 2008 Ren et al., 2011 |
| | Protection of host cells from apoptosis triggered by viral infection | |
| Immunomodulatory effects | Inhibition of NF-κB | Troib & Azab, 2015 |
| | Inhibition of IL-6 induced activation of STAT-3, perhaps mediated through inhibition of GSK-3β | Beurel et al., 2010; Wang, Zhang, Li, et al., 2013; Minashima et al., 2014 |
| | Inhibition of IL-1β production | Nassar & Azab, 2014 |
| | Reduction in cyclooxygenase-2 expression | Nassar & Azab, 2014 |

Abbreviations: RNA, ribonucleic acid; GSK-3β, glycogen synthase kinase—3 beta; NF-κB, nuclear factor kappa B; STAT-3, signal transducer and activator of transcription 3; IL-6, interleukin-6; IL-1β, interleukin-1 beta.

some body compartments exceed those measured in plasma (Methaneethorn, 2018). Third, at least in the case of herpes viruses, the antiviral effects of lithium take weeks or months to manifest themselves fully; such a delayed onset of action would be of little use in COVID-19. Fourth, there is at least one report of lithium suppressing host defenses against infection with the Sendai virus, a paramyxovirus, in an animal model (Wang et al., 2013), although this may not be directly relevant to infection with SARS-nCoV-2. And finally, although indirect evidence from in vitro research on lithium is encouraging, such evidence does not always translate readily into efficacy in human clinical trials.

Such limitations preclude any direct plan for a controlled clinical trial of lithium monotherapy in patients with COVID-19 at the moment. However, studies of lithium in cell-based and animal models of SARS-nCoV-2 infection, particularly with reference to its ability to attenuate the "cytokine storm," could be planned. Such research could potentially lead to cautious trials of lithium as an adjuvant therapy in human subjects in the best case; failing this, it could shed further light on our understanding of the inflammatory cascade in COVID-19 and lead to the development of safer alternative treatments. There is also scope for naturalistic research of the sort conducted on influenza-like illnesses in patients with psychiatric disorders receiving lithium, in which any possible attenuation of the risk of SARS-nCoV-2 infection could be assessed. In other words, even if lithium does not directly prove to be an effective treatment for COVID-19, studies of its antiviral and immunomodulatory effects with reference to SARS-nCoV-2 could contribute substantially to the eventual development of effective treatments for this disease.

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## CONFLICT OF INTEREST

The author reports no current or potential conflict of interest.

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