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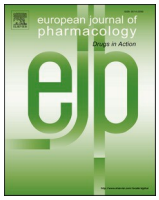

Review

# Potential repurposing of the HDAC inhibitor valproic acid for patients with COVID-19

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ABSTRACT

There is a need for therapeutic approaches to prevent and mitigate the effects of Coronavirus Disease (2019) (COVID-19). The histone deacetylase (HDAC) inhibitor valproic acid, which has been available for the therapy of epilepsy for many years, is a drug that could be repurposed for patients with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. This article will review the reasons to consider valproic acid as a potential therapeutic to prevent severe COVID-19. Valproic acid could reduce angiotensin-converting enzyme 2 and transmembrane serine protease 2 expression, required for SARS-CoV-2 viral entry, and modulate the immune cellular and cytokine response to infection, thereby reducing end-organ damage. The combined anti-thrombotic, anti-platelet, and anti-inflammatory effects of valproic acid suggest it could be a promising therapeutic target for COVID-19.

## 1. Introduction

The Coronarvirus Disease 2019 (COVID-19) pandemic has resulted in numerous hospitalizations and deaths around the world. While there are some promising new therapies such as dexamethasone (Group, 2020) and remdesavir (Beigel et al., 2020), it is likely that the risk of COVID-19 will remain an important risk for hospitalization and death until a vaccine is proven safe and widely disseminated. Although it is hoped that vaccines will be increasingly available, the pandemic is likely to last well into 2021, if not beyond. Thus, there is a need for further therapeutic approaches to prevent and mitigate the effects of COVID-19. The histone deacetylase (HDAC) inhibitor valproic acid, which has been available for the therapy of epilepsy for many years, has been suggested to be repurposed to patients with COVID-19 to prevent acute respiratory distress syndrome (ARDS) (Bhargava et al., 2020). This article will review the reasons to that valproic acid could both help to prevent severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) viral infection and in those infected, reduce ARDS, as well as other target organ damage, and decrease hospitalizations and death.

## 2. Prevention of COVID-19

The Severe Acute Respiratory Syndrome (SARS)-CoV-2 virus that causes COVID-19 requires angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (MPRSS2) to bind to the surface of respiratory and conjunctival epithelial cells. Gene profiling studies have identified the HDAC inhibitor valproic acid as one of the drugs that can reduce ACE2 (Cui et al., 2020). Recently, it was reported that valproic acid downregulated ACE2 in endothelial cells and inhibited the expression of IL-6 and ICAM-1 (Singh et al., 2020). Of equal or greater importance is the finding that valproic acid reduced the expression of TMPRSS2 in prostate cancer cells (Fortson et al., 2011). TMPRSS2 was increased by androgens (Lucas et al., 2014), possibly accounting for the increased risk of COVID-19 infection in males (Jin et al., 2020). Inhibitors of TMPRSS2 were found to be effective against the Middle East respiratory syndrome (MERS) Coronavirus (Shirato et al., 2013) and the SARS-CoV-2 virus (Hoffmann et al., 2020). Thus, there is reason to hypothesize that the administration of valproic acid in at risk individuals could reduce the risk of COVID-19 or reduce the viral load, both by an effect on ACE2 as well as TMPRSS2.

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## 3. Valproic acid-mediated reduction in target organ damage and inflammation

In a model of coxsackie B3 viral myocarditis, valproic acid attenuated myocardial damage by suppressing TH17 cells and inducing Treg cells (Jin and Guo, 2016). Valproic acid also diminished the replication of enveloped viruses (Vazquez-Calvo et al., 2011) and down-regulated inflammatory cytokines (interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α)) in human monocyte derived macrophages infected with the Dengue virus (Delgado et al., 2018). Increases in IL-6 were found to be an important predictor of disease severity and mortality (Wang et al., 2020). Valproic acid has been found to alter macrophage responses to lipopolysaccharide (LPS) by reducing IL-12p70 and TNF-α release while increasing IL -10 (Wu et al., 2012). The administration of valproic acid changed macrophages from a proinflammatory (M1) to an anti-inflammatory (M2) phenotype (Wu et al., 2012). Valproic acid also reduced macrophage infiltration in various models of inflammation. These effects on innate and adaptive immunity have recently been reviewed (Soria-Castro et al., 2019).

## 4. Anti-thrombotic/anti-platelet effects

There is increasing evidence that thrombosis and a disseminated intravascular coagulopathy are important in the pathophysiology of the respiratory complications of COVID-19 as well as for many of its myocardial, renal, and cerebral complications (Giannis et al., 2020). The incidence of thrombosis in patients hospitalized with COVID-19 infection is thought to be around 30% (Klok et al., 2020b). The mechanisms responsible for the increase in thrombosis are as yet uncertain but include disseminated intravascular coagulopathy; direct effects of viral invasion with a resultant increase in inflammatory cytokines and proinflammatory M1 macrophages; activation of the complement cascade; the antiphospholipid syndrome; and endothelial dysfunction (Campbell and Kahwash, 2020; Li et al., 2020; Uthman and Gharavi, 2002; Zhang et al., 2020b). Recent data have emphasized the fact that COVID-19 is associated with an increase in platelet reactivity and thromboxane generation (Manne et al., 2020). Patients, especially older males, and those with cardiovascular risk factors such as hypertension, chronic kidney disease, coronary artery disease, traumatic brain injury, diabetes mellitus, and/or obesity are at an increased risk of thrombotic complications (Bilaloglu et al., 2020; Zhang et al., 2020a). Patients hospitalized with COVID-19 have been found to have an increase in biomarkers of thrombosis including D-dimer, von Willibrand factor (vWF), and fibrinogen (Panigada et al., 2020). Increased levels of these coagulation factors are associated with an increased risk of critical illness and death (Goshua et al., 2020; Wang et al., 2020). Valproic acid has proven antiplatelet effects (Larsson et al., 2016), reducing platelet aggregation, intercellular adhesion molecule-1 (ICAM -1), and E-Selectin, as well as down-regulating the conversion of arachidonic acid to prostaglandins by cyclooxygenase 1 and 2 (Bambakidis et al., 2017). It also increased tissue plasminogen activator (t-PA) and decreased plasminogen activator inhibitor (PAI-1) (Saluveer et al., 2014). Valproic acid reduced endothelial cell dysfunction through transforming growth factor-beta (TGF-β) and vascular endothelial growth factor (VEGF) pathways in a swine hemorrhagic shock model of ischemia reperfusion (Causey et al., 2012). The finding that valproic acid reduced the risk of endothelial dysfunction, while not in the setting of COVID-19, has important implications since endothelial dysfunction and subsequent thrombosis have been identified as being important mechanisms associated with target organ damage in patients with COVID-19 (Bikdeli et al., 2020). Thrombosis has also been identified as an important component of acute respiratory distress syndrome (ARDS) with both micro- and macro-thrombosis (Greene et al., 1987). The finding that increased angiogenesis is an important component of ARDS (Ackermann et al., 2020) and that valproic acid reduced VEGF and angiogenic factors (Iizuka et al., 2018; Zhao et al., 2016) suggests that valproic acid could play an important role in ameliorating pulmonary injury in ARDS due to COVID-19.

Valproic acid also suppressed IL-12 and TNF-α, changed the polarization of macrophages from T1 to the anti-inflammatory T2 type, and decreased macrophage infiltration, all of which would tend to reduce the risk of thrombosis (Van Beneden et al., 2011; Wu et al., 2012). The anti-platelet/anti-thrombotic effects of valproic acid are supported by large scale epidemiologic studies showing that epileptic patients treated with valproic acid had a significantly lower risk of stroke and myocardial infarction than those treated with other anti-epileptic drugs (Brookes et al., 2018; Dregan et al., 2014; Olesen et al., 2011). Thus, there is abundant evidence from experimental and epidemiologic studies that valproic acid has important anti-platelet and anti-thrombotic effects.

## 5. Potential benefits of valproic acid

### 5.1. Potential impact of valproic acid on the myocardium

In an experimental model of myocardial infarction, valproic acid significantly reduced infarct size through the Foxm1 pathway (Tian et al., 2019). Valproic acid also effected the acetylation of the mineralocorticoid receptor (MR) (Lee et al., 2013) and was associated with a reduction in fibrosis of the heart (Kang et al., 2015; Kee et al., 2006; Kook et al., 2003) as well as the lung (Cetinkaya et al., 2015; Kabel et al., 2016; Korfei et al., 2015), kidney (Khan et al., 2015; Van Beneden et al., 2011), and liver (Mannaerts et al., 2010). Valproic acid has also prevented the development of atrial fibrillation in an experimental model (Scholz et al., 2019). These studies support the hypothesis that valproic acid has cardioprotective effects.

Myocardial damage has been found in approximately 20–30% of patients hospitalized for COVID-19 as evidenced by an increase in troponin levels or cardiomyopathy (Arentz et al., 2020; Guo et al., 2020). Those with an increase in troponin levels have a worse prognosis than those without evidence of myocardial injury (Shi et al., 2020b). Thus, therapeutic strategies directed against COVID-19 induced myocardial injury deserve further investigation. The cause of the myocardial damage associated with COVID-19 is thought to be due to several factors including 1) myocardial localization of the virus with myo- or pericarditis (Guagliumi et al., 2020; Inciardi et al., 2020); 2) type 1 and 2 myocardial infarction (Klok et al., 2020a); 3) Takotsubo cardiomyopathy (Minhas et al., 2020); 4) endothelial damage with resultant microvascular dysfunction and infarction (Varga et al., 2020); 5) cytokine- and or autoimmune-induced myocardial damage (Fried et al., 2020; Prabhu, 2004); and 6) microthrombi (Guagliumi et al., 2020). Thus, valproic acid could be beneficial in preventing or ameliorating the extent of myocardial injury due to several of these mechanisms based on its proven cardioprotective, anti-inflammatory, immune; anti-thrombotic, and anti-platelet effects.

### 5.2. Potential anti-diabetic effects of valproic acid

Patients with diabetes mellitus are at increased risk of hospitalization for COVID-19 (Shi et al., 2020a; Williamson et al., 2020). Of interest is the finding that valproic acid attenuated diabetic-induced renal injury in a rat model of diabetic nephropathy (Sun et al., 2016). Valproic acid also reduced insulin resistance and gluconeogenesis in a type 2 diabetic rat model through inhibition of FOXO1 and promotion of glucagon like peptide (Khan et al., 2016). Valproic acid was effective in reducing blood glucose by potentiating insulin action and in streptozocin-induced type 1 diabetic mice (Terasmaa et al., 2011). There are potential anti-diabetic effects of valproic acid independent of COVID-19 (Rakitin, 2017).

### 5.3. Potential renal-protective effects of valproic acid

Patients with chronic kidney disease have been found to be at increased risk of COVID-19 infection and in those requiring hospitalization, to be at increased risk of renal failure and the need for dialysis (Cheng et al., 2020; D'Marco et al., 2020). The mechanisms contributing to renal failure in patients with COVID-19 are thought to include direct viral renal injury, as well as systemic hypoxia, thrombosis, and rhabdomyolysis (Su et al., 2020). Valproic acid has been studied in a murine model of adriamycin-induced nephropathy and prevented the development of proteinuria and the onset of glomerular sclerosis (Van Beneden et al., 2011). In this model, valproic acid decreased the deposition of collagen and the infiltration of macrophages into the kidney. It also reduced glomerular apoptosis and proliferation along with a reduction in podocyte damage. Thus, these findings suggest that valproic acid could potentially reduce the incidence of acute renal failure and therefore the need for dialysis in patients with COVID-19.

### 5.4. Potential neuroprotective effects of valproic acid

Although there is no evidence that the coronavirus directly attacks the nervous system, approximately 1 in 7 patients with COVID-19 infection have neurologic problems thought to be secondary to prolonged hypoxia (Frontera et al., 2021). Of interest is the finding that valproic acid decreased the vulnerability of motor neuron cells to cellular injury evoked by oxidant stress. The neuronal protective effects of valproic acid are related to an increase in sirtuin 3 (SIRT3) and coactivator associated arginine methyl transferase (CARM1), which regulate oxidative metabolism and mitochondrial biogenesis (Wang et al., 2013). Thus, valproic acid could protect against COVID-19 induced neuronal damage.

## 6. Safety of valproic acid

Valproic acid has been associated with a number of adverse effects including nausea, vomiting, hair loss, easy bruising, tremor, weight gain, insulin resistance, and metabolic syndrome (Abaci et al., 2009). Additional possible serious adverse effects include encephalopathy, acute hepatic failure, pancreatitis, and thrombocytopenia (Gerstner et al., 2007; Koenig et al., 2006). Valproic acid is a teratogen and should be avoided in pregnancy (Tomson et al., 2018). Valproic acid is metabolized by the liver, and dose adjustments are required in patients with hepatic insufficiency and in the setting of other drugs known to affect serum levels. However, the serious adverse effects are rare in adult patients (Gerstner et al., 2008). For example, in older patients with chronic obstructive pulmonary disease (COPD), the administration of valproic acid was not associated with any increase in the risk of pulmonary outcomes in comparison to phenytoin (Antoniou et al., 2015). Given the fact that patients were >65 years of age, males, and had cardiovascular risk factors (similar to those at increased risk of hospitalization and death from COVID-19), studies targeting valproic acid to these high risk patients should be possible. Nevertheless, liver enzymes and platelet counts should be serially monitored, and additional study to determine if the benefits of valproic acid would outweigh the risks in the setting of COVID-19 are required.

## 7. Future directions

Valproic acid effects on COVID-19 are currently being evaluated in clinical studies (e.g. Clinicaltrials.gov NCT04513314). In view of the long history of valproic acid's use in patients with epilepsy and neurologic disease and the mechanisms reviewed above that could affect the development and or severity of COVID-19, it would appear to be an excellent candidate for further repurposing to patients at risk of or with COVID-19. Proof of this hypothesis will, however, require evidence from prospective, adequately-powered, randomized trials.

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## Declaration of competing interest

B.P. is a consultant for Cereno scientific**, Bayer, Sanofi/Lexicon, Astra Zeneca, Boehringer Ingelheim/Lilly, Phasebio, CEVA animale, KBP Pharmaceuticals **, SC Pharmaceuticals **, SQinnovations, G3Pharmaceuticals **, and Relypsa/Vifor **. B.P. holds a U.S. Patent 9931412 on site specific delivery of eplerenone to the myocardium and a U.S. Patent is pending (63045784) on histone acetylation modulating agents for the treatment and prevention of organ injury. N.R.S. has received honoraria for speaking from Zoll and serves on an advisory committee for Cordis. M.H. has received research funding from Cereno Scientific and is a consultant and equity holder for Veralox Therapeutics, although no work presented here is associated with the relationship with Veralox Therapeutics. M.H. holds U.S. patent 10, 266, 488 on 12-lipoxygenase inhibitors. ** Denotes stock options. S.N.G. and Z.W. have no disclosures.

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