Supplementary Table 1. Drugs that may be repurposed for the treatment of SARS-CoV-2 and associated chronotherapy.

| Category                                      | Drug Names / Classes | Evidence and scientific rationale for the treatment of SARS-CoV-2 infection and associated chronotherapeutic mechanisms | Citations                                      |
|-----------------------------------------------|----------------------|-----------------------------------------------------------------------------------------------------------------|------------------------------------------------|
| Drugs that inhibit or block the life cycle of SARS-CoV-2 | Antiviral (Remdesivir) | • Effective against other coronaviruses such as MERS-CoV and SARS-CoV.  
• Showed superior effect over placebo in shortening the recovery time of hospitalized COVID-19 patients.  

**Evidence for chronotherapy**  
• Host clock components regulate viral replication either directly or indirectly thereby modulate the viral load.  
• In a retrospective study, CRP levels reduced significantly when the antiviral drug was administered in the morning compared to the evening.  
• The dose of acyclovir needed to prevent HSV-2 infection during the active phase was four times more compared to the resting phase in mice. | (de Wit et al., 2020; Malin et al., 2020)  
(Madsen, 2020)  
(Edgar et al., 2016)  
(De Giorgi et al., 2020)  
(Matsuzawa et al., 2018) |
| Drugs that counteract the insidious effects caused by SARS-CoV-2 | Corticosteroids (Dexamethasone, Prednisone and Methylprednisolone) | • Corticosteroids are anti-inflammatory drugs that suppress the activation of the immune system, thus prevents cytokine storm.  
• Meta-analysis of clinical trials showed that corticosteroids reduced the risk of mortality and the duration of mechanical ventilation in patients suffering from ARDS and COVID-19.  

**Evidence for chronotherapy**  
• Elevated levels of pro-inflammatory cytokines throughout the nighttime. | (Channappanavar and Perlman, 2017)  
(Mammen et al., 2020; Sterne et al., 2020)  
(De Silva et al., 1984) |
- Prevents the nighttime rise in pro-inflammatory cytokines, particularly IL-6, which may be beneficial for COVID-19, as reported in studies from rheumatoid arthritis patients.

**Blood thinners**  
(anticoagulants or antiplatelet drugs)

- Increased rate of blood clots among hospitalized COVID-19 patients.
- Full dose anticoagulants when given to moderately ill hospitalized COVID-19 patients, the requirement for vital organ support such as ventilation and ICU was significantly reduced.
- Prophylactic anticoagulation administration did not increase the risk of serious bleeding in COVID-19 patients.

**Evidence for chronotherapy**

- Hypercoagulatory and hypofibrinolytic conditions are more frequent in the morning because of increased platelet activity and concentration of coagulation factors like Factor V, VII, and prothrombin fragment F1 + 2, and D-dimer.
- Rivaroxaban and Aspirin both have been shown to exert better effects when taken in the evening compared to the morning.

**Cationic Amphiphilic Drugs**  
(Amiodarone, Chlorpromazine, and SERMs)

- The anti-arrhythmic drug, amiodarone prevents the fusion of the viral envelop with the endosomal membrane and accumulates in late endosomes/lysosomes, and disrupts the viral endocytic pathway.
- Amiodarone prevents entry of the Filovirus and methyldiethanolamine (metabolite) was able to inhibit Ebola virus entry.
- Amiodarone increased the survival of mice infected with the Ebola virus.
Amiodarone also inhibits other viruses like the Arenavirus, the SARS-CoV-1, and Hepatitis C virus.

Arrhythmias are common among COVID-19 patients, and it is associated with higher morbidity and mortality.

Chlorpromazine exhibits antiviral activity against the Crimean-congo hemorrhagic fever virus, Adenovirus, Ebola virus, MERS-CoV, and SARS-CoV.

Chlorpromazine blocks the formation of clathrin-coated pits and thus prevents viral entry into the cells.

Selective estrogen receptor modulators (SERMs) have protective functions against MERS-CoV, Ebola virus, HSV-1, and HCV.

SERM, clomiphene possess antiviral activity against the Ebola virus by interfering with the late-stage fusion of the viral envelope and the endosomal membrane.

Clomiphene blocks the Ebola virus entry by inhibiting the NPC1-dependent pathway, which has been hypothesized to increase cholesterol accumulation in the late endosomes and impair viral entry for SARS-CoV-2.

Evidence for chronotherapy

Prior studies suggest that cardiac arrhythmia peaks mostly between 6:00 am and 12:00 noon. Arrhythmogenesis appeared to be less frequent or suppressed during the nighttime.

(Stadler et al., 2008; Cheng et al., 2013; Gehring et al., 2014)
(Babapoor-Farrokhran et al., 2020)
(Bhattacharyya et al., 2010; Diaconu et al., 2010; Dyall et al., 2014; Ferraris et al., 2015)
(Daniel et al., 2015)
(Johansen et al., 2013; Murakami et al., 2013; Zheng et al., 2014)
(Nelson et al., 2016)
(Ghasemnejad-Berenji et al., 2020)
(Portaluppi and Hermida, 2007)
| Janus-associated Kinase Inhibitor (Baricitinib) | - A relatively lower dose of chlorpromazine administered at 1:30 was able to show the same sedative effect than when administered at 7:30 (on a 24-hour clock).  
- JAK inhibitors can prevent the phosphorylation of proteins that are involved in the signal transduction cascade of the Jak-Stat pathway and thereby reduce cytokine-mediated inflammation and collateral damage in the vital organs.  
- Baricitinib significantly reduced the median number of days to recovery, from 18 to 10 days, in hospitalized COVID-19 patients requiring high-flow oxygen or non-invasive ventilation, when used together with remdesivir.  
- The need for ventilation support or death was reduced by > 50% (34.9% to 16.9%) using Baricitinib compared to the placebo/control group.  
- Baricitinib can successfully inhibit type-1 interferon response (exaggerated in COVID-19 patients) that increases ACE2 expression (in liver cells), the receptor that plays an essential role in the entry of SARS-CoV-2 in host cells to increase the viral load.  
- Baricitinib is a potent inhibitor of the Numb-associated kinase (NAK) family of proteins, particularly AAK1, that plays a pivotal role in clathrin-mediated endocytosis, which further prevents viral entry into the cells.  

**Evidence for chronotherapy**
- Studies have shown a peak in IL-6 levels during nighttime and early morning hours. |
  
  - (Nagayama et al., 1978)  
  - (Lin et al., 2020)  
  - (Kalil et al., 2020)  
  - (Stebbing et al., 2021)  
  - (Stebbing et al., 2021)  
  - (Conner and Schmid, 2002; Sorrell et al., 2016)  
  - (Vgontzas et al., 2005)
A better outcome was observed when Baricitinib was administered during the time (evening) when the cytokine production was at the highest. (Yaekura et al., 2020)

### Drugs that manage comorbidities and pleiotropic effects against SARS-CoV-2

| Hyperlipidemia drug (Statins) | Anti-inflammatory effects can block the infectious potential of enveloped viruses (*in vitro*) and considerably reduce the mortality risk among COVID-19 patients.  
Indepedently associated with lower ICU admission among COVID-19 patients.  
Reduce hyperlipidemia and decrease cytokine levels with its pleiotropic effects under different non-infectious conditions.  
**Evidence for chronotherapy**  
*Cholesterol synthesis peaks between 12:00 am and 6:00 am.*  
Administration of Statins in the evening is more effective than when taken in the morning.  
**Evidence for chronotherapy**  
*Blood pressure (BP) is higher during early mornings. Increased nighttime ambulatory BP is related to fatal and non-fatal cardiovascular events.*  
| (Rossi et al., 2020)  
(Tan et al., 2020)  
(Wassmann et al., 2003; Fang et al., 2005).  
NCT02056340  
(Izquierdo-Palomares et al., 2016)  
(Saito et al., 1991; Lund et al., 2002; Wallace et al., 2003; Ozaydin et al., 2006; Tharavanij et al., 2010).  
| (Baral et al., 2020)  
(Surveillances, 2020)  
(Elliott, 1999)  
|
| Chronotherapeutic drugs that may be used against SARS-CoV-2 | REV-ERBα agonists (e.g., SR9009 and GSK2667) |
|-----------------------------------------------------------|------------------------------------------------|
| • Lessing BP at night and early morning hours markedly reduce cardiovascular events by administering hypertensive drugs before bedtime or in the evening. | • Boost the endurance performance by increasing mitochondria numbers/counts in skeletal muscles and significantly reduce cholesterol and body weight. |
| [Hermida et al., 2007; Hermida and Ayala, 2009; Hermida et al., 2010; Hoshino et al., 2010; Zeng et al., 2011; Bowles et al., 2018; Hermida et al., 2020] | • Lower anxiety to a level as effective as benzodiazepine. |
| | • Reduces inflammation by interfering with the production of inflammatory cytokines like TNFα, CCL2, and MMP-9 \textit{in vitro} in nerve cells and \textit{in vivo} rat lungs. |
| | • Reducing blood vessel lesions and hardening of arteries. |
| | • SR9009 can successfully inhibit positive-strand RNA viruses such as the Flaviviridae family (e.g., Hepatitis C virus, Dengue, and the Zika virus). |
| | • Regulate HIV-1 replication by inhibiting promoter activity in CD4+ T cells and macrophages. |
| | • Successfully inhibits the replication of alphaviruses like Chikungunya and o’nyong’nyong virus by suppressing the synthesis of the structural proteins. |
| | • Selectively regulate pro-inflammatory cytokines like IL-6, which has been considered as a prognostic marker for mortality among SARS-CoV-2 infected patients. |
| | [Solt et al., 2012; Woldt et al., 2013] |
| | [Banerjee et al., 2014] |
| | [Li et al., 2014; Morioka et al., 2016] |
| | [Sitaula et al., 2015] |
| | [Zhuang et al., 2019] |
| | [Borrmann et al., 2020] |
| | [Hwang et al., 2018] |
| | [Gibbs et al., 2012; Liu et al., 2020] |