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.	(de Wit et al., 2020; Malin et al., 2020)
		• Showed superior effect over placebo in shortening the recovery time of hospitalized COVID-19 patients.	(Madsen, 2020)
		Evidence for chronotherapy	
		• Host clock components regulate viral replication either directly or indirectly thereby modulate the viral load.	(Edgar et al., 2016)
		• In a retrospective study, CRP levels reduced significantly when the antiviral drug was administered in the morning compared to the evening.	(De Giorgi et al., 2020)
		• 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.	(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.	(Channappanavar and Perlman, 2017)
		• 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.	(Mammen et al., 2020; Sterne et al., 2020)
		Evidence for chronotherapy	
		• Elevated levels of pro-inflammatory cytokines throughout the nighttime.	(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.	(De Silva et al., 1984; Buttgereit et al., 2008)
	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 F_{1+2}, and D-dimer. • Rivaroxaban and Aspirin both have been shown to exert better effects when taken in the evening compared to the morning.	(Malas et al., 2020) (Health, 2021) (Rentsch et al., 2021) (Kapiotis et al., 1997) (Bonten et al., 2015; Brunner-Ziegler et al., 2016; van Diemen et al., 2020)
	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.	(Salata et al., 2015) (Gehring et al., 2014; Salata et al., 2015) (Madrid et al., 2015)

		• Amiodarone also inhibits other viruses like the Arenavirus, the SARS-CoV-1, and Hepatitis C virus.	(Stadler et al., 2008; Cheng et al., 2013; Gehring et al., 2014)
		• Arrhythmias are common among COVID-19 patients, and it is associated with higher morbidity and mortality.	(Babapoor-Farrokhran et al., 2020)
		• Chlorpromazine exhibits antiviral activity against the Crimean-congo hemorrhagic fever virus, Adenovirus, Ebola virus, MERS-CoV, and SARS-CoV.	(Bhattacharyya et al., 2010; Diaconu et al., 2010; Dyall et al., 2014; Ferraris et al., 2015)
		• Chlorpromazine blocks the formation of clathrin-coated pits and thus prevents viral entry into the cells	(Daniel et al., 2015)
		• Selective estrogen receptor modulators (SERMs) have protective functions against MERS-CoV, Ebola virus, HSV-1, and HCV	(Johansen et al., 2013; Murakami et al., 2013; Zheng et al., 2014)
		• SERM, clomiphene possess antiviral activity against the Ebola virus by interfering with the late-stage fusion of the viral envelope and the endosomal membrane.	(Nelson et al., 2016)
		• 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	(Ghasemnejad-Berenji et al., 2020)
		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.	(Portaluppi and Hermida, 2007)

		• 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).	(Nagayama et al., 1978)
	Janus-associated Kinase Inhibitor (Baricitinib)	• 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.	(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. • Independently 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.	(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).
	Antihypertensive drugs (ACE inhibitors and ARBs)	• Acute lung damage can be reduced by renin-angiotensin-aldosterone system inhibitors. • Case fatalities are much higher in COVID-19 patients due to pulmonary hypertension. Hypertensive drugs are associated with decreased mortality. ***Evidence for chronotherapy*** • Blood pressure (BP) is higher during early mornings. Increased nighttime ambulatory BP is related to fatal and non-fatal cardiovascular events.	(Baral et al., 2020) (Surveillances, 2020) (Elliott, 1999)

		• Lessing BP at night and early morning hours markedly reduce cardiovascular events by administering hypertensive drugs before bedtime or in the evening.	(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)
Chronotherapeutic drugs that may be used against SARS-CoV-2	**REV-ERBα agonists (e.g., SR9009 and GSK2667)**	• Boost the endurance performance by increasing mitochondria numbers/counts in skeletal muscles and significantly reduce cholesterol and body weight.	(Solt et al., 2012; Woldt et al., 2013)
		• Lower anxiety to a level as effective as benzodiazepine.	(Banerjee et al., 2014)
		• Reduces inflammation by interfering with the production of inflammatory cytokines like TNFα, CCL2, and MMP-9 *in vitro* in nerve cells and *in vivo* rat lungs.	(Li et al., 2014; Morioka et al., 2016)
		• Reducing blood vessel lesions and hardening of arteries.	(Sitaula et al., 2015)
		• SR9009 can successfully inhibit positive-strand RNA viruses such as the Flaviviridae family (e.g., Hepatitis C virus, Dengue, and the Zika virus).	(Zhuang et al., 2019)
		• Regulate HIV-1 replication by inhibiting promoter activity in $CD4^+$ T cells and macrophages.	(Borrmann et al., 2020)
		• Successfully inhibits the replication of alphaviruses like Chikungunya and o'nyong'nyong virus by suppressing the synthesis of the structural proteins.	(Hwang et al., 2018)
		• Selectively regulate pro-inflammatory cytokines like IL-6, which has been considered as a prognostic marker for mortality among SARS-CoV-2 infected patients.	(Gibbs et al., 2012; Liu et al., 2020)