Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Management of COVID-19 in patients with seizures: Mechanisms of action of potential COVID-19 drug treatments and consideration for potential drug-drug interactions with anti-seizure medications

Shreshta Jain [a], Heidrun Potschka [b], P. Prarthana Chandra [c], Manjari Tripathi [d], Divya Vohora [a,*]

[a] Department of Pharmacology, School of Pharmaceutical Education and Research, Jamia Hamdard, New Delhi, India
[b] Institute of Pharmacology, Toxicology, and Pharmacy, Ludwig-Maximilians-University (LMU), Königinstr. 16, D-80539, Munich, Germany
[c] Hamdard Institute of Medical Sciences and Research, New Delhi, India
[d] Department of Neurology, All India Institute of Medical Sciences, New Delhi, India

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ABSTRACT

In regard to the global pandemic of COVID-19, it seems that persons with epilepsy (PWE) are not more vulnerable to get infected by SARS-CoV-2, nor are they more susceptible to a critical course of the disease. However, management of acute seizures in patients with COVID-19 as well as management of PWE and COVID-19 needs to consider potential drug-drug interactions between antiseizure drugs and candidate drugs currently assessed as therapeutic options for COVID-19. Repurposing of several licensed and investigational drugs is discussed for therapeutic management of COVID-19. While for none of these approaches, efficacy and tolerability has been confirmed yet in sufficiently powered and controlled clinical studies, testing is ongoing with multiple clinical trials worldwide. Here, we have summarized the possible mechanisms of action of drugs currently considered as potential therapeutic options for COVID-19 management along with possible and confirmed drug-drug interactions that should be considered for a combination of antiseizure drugs and COVID-19 candidate drugs. Our review suggests that potential drug-drug interactions should be taken into account with drugs such as chloroquine/hydroxychloroquine and lopinavir/ritonavir while remdesivir and tocilizumab may be less prone to clinically relevant interactions with ASMs.

1. Introduction

The catastrophic global pandemic of Coronavirus disease 2019 (COVID-19) has put large parts of the world on a transient standstill. COVID-19 was first discovered in December 2019 and the causative agent was a novel subtype of beta-coronaviruses, known as SARS-CoV-2 (Rothan and Byrareddy, 2020). The novel coronavirus is an enveloped non-segmented positive-sense RNA virus (Richman et al., 2016) that was transmitted to humans *via* zoonotic transmission, similar to its precursors, severe acute respiratory syndrome coronavirus (SARS-CoV) (Ksiazek et al., 2003) and the Middle East respiratory syndrome coronavirus (MERS-CoV) (Zaki et al., 2012). These viruses primarily affect the respiratory system, however, clinical literature also provides evidence for neuroinvasive and neurotropic properties of SARS-CoV-2 (Carod-Artal, 2020; Li et al., 2020b; Najjar et al., 2020). Neurological symptoms reported in patients with COVID-19 include febrile seizures, status epilepticus and complications including encephalopathy, cerebral haemorrhage (Asadi-Pooya, 2020; Asadi-Pooya and Simani, 2020; Carod-Artal, 2020; Yin et al., 2020). These clinical manifestations suggest that people with neurological disorders may be more vulnerable to experience severe symptoms of COVID-19 disease. However, that does not seem to be the case. The International League Against Epilepsy

Abbreviations: ACE, angiotensin-converting enzyme inhibitors; ASM, anti-seizure medication; CBD, cannabidiol; COVID, 19- Coronavirus disease 2019; CYP, cytochrome P; EMA, European Medicines Agency; FDA, US Food and Drug Administration; G-CSF, granulocyte-colony stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HDAC2, histone deacetylases; IL, interleukin; ILAE, International League Against Epilepsy; IMP, importin; MERS-CoV, Middle East respiratory syndrome coronavirus; NIH, National Institute of Health; NSAIDs, non-steroidal anti-inflammatory drugs; PWE, persons with epilepsy; SARS-CoV, severe acute respiratory syndrome coronavirus; T-705-RTP, favipiravir ibofuranosyl-5′-triphosphate; TGA, Therapeutic Goods Administration of Australia; TMPRSS2, type 2 transmembrane serine protease; TNF, tumor necrosis factor; UGT, uridine diphosphate glucuronosyltransferase.

* Corresponding author at: Department of Pharmacology, School of Pharmaceutical Education and Research, Jamia Hamdard, New Delhi, 110062, India.
E-mail address: dvohora@jamiahamdard.ac.in (D. Vohora).

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(ILAE) has informed that persons with epilepsy (PWE) are not likely to be more susceptible to get COVID-19 nor are they inclined to suffer through severe manifestations of SARS-CoV-2 infection (ILAE, 2020). Even if PWE are exposed to SARS-CoV-2, it is unlikely that the frequency of seizures increases (ILAE, 2020). Nevertheless, management of COVID-19 in PWE or with acute reactive seizures requires certain precautions and guidelines to avoid worsening of the condition. In particular, potential drug-drug interaction that may occur on concomitant administration of anti-seizure medication (ASM) along with the drugs for treatment of COVID-19 need to be taken into account.

The rapid spread of the SARS-CoV-2 pandemic with a high number of severe cases and high mortality rates has triggered almost desperate attempts to repurpose different types of drugs for treatment of patients with a severe course of COVID-19. At this point of time, it needs to be emphasized that no drug has been proven to be efficacious and safe for therapeutic management of COVID-19 based on sufficiently powered and controlled studies. This fact is also pointed out by an expert group of the National Institute of Health (https://www.covid19treatmentguidelines.nih.gov/). A substantial number of clinical studies are currently ongoing or planned with on today's date (15th March, 2021) 5017 clinical trials being registered at clinicaltrials.gov with a high percentage of these trials aiming to explore drug candidates for the management of COVID-19 (https://clinicaltrials.gov/ct2/results?cond=COVID-19). However, based on the current state-of-knowledge, only a number of drug candidates are classified by the NIH expert panel as 'therapeutic options for COVID-19 currently under investigation' along with the statement that there are 'insufficient data to either recommend for or against the use'. These drugs include immunomodulators such as interleukin (IL)-1 inhibitors (Anakinra). For other immunomodulatory drugs such as interleukin-6 inhibitors, interferons and janus kinase inhibitors along with anti-viral agents including lopinavir, ritonavir and other HIV protease inhibitors, and anti-malarial drugs such as chloroquine and hydroxychloroquine in combination with or without azithromycin, as well as for the recently reported anti-parasitic agent, ivermectin, the NIH expert panel clearly recommends against the use except in the context of a clinical trial (NIH, 2020). However, recommendations vary as per countries and these drugs are still used for COVID-19 in several other countries. The only drugs that are currently been recommended by the NIH include remdesivir and corticosteroids (dexamethasone) for the treatment of COVID-19 with a severe disease course (NIH, 2020).

For COVID-19 clinical studies, potential drug-drug interactions need to be considered for all patients with chronic diseases requiring continuous treatment. This in particular applies for PWE as several ASMs are prone to drug-drug interactions (Patsalos et al., 2018; Zaccara and Perucca, 2014). Information about drug-drug interactions is also of particular relevance for intensive care unit management of critically-ill COVID-19 patients who may develop acute seizures during a severe disease course. Here, we will discuss the mechanism of action of drugs currently under discussion as potential therapeutic options for COVID-19 management (referred to as COVID-19 candidate drugs). Further, we will also discuss the current state-of-knowledge about possible interactions between ASMs and COVID-19 candidate drugs.

2. Mechanisms of action of COVID-19 candidate drugs

The current understanding of the life cycle of the novel coronavirus SARS-CoV-2 suggests drug target candidates for the prevention and treatment of COVID-19. As it is known, the virus contains a single-stranded RNA, that upon entering the host cell unfolds and translates into polypeptides that further mitigate the synthesis of viral RNA strands *via* RNA-dependent viral RNA polymerase (Chen et al., 2020c). Furthermore, virus binding to ACE2 through the spike (S) protein and entering the host cell is facilitated by the host type 2 transmembrane serine protease (TMPRSS2). Based on knowledge about these viral invasion mechanisms, the targeting of viral entry is in the focus of current efforts to develop therapeutic treatments against COVID-19 (Hoffmann et al., 2020).

In the following, we highlight some of the potential drug candidates that have been or are assessed in first clinical trials (Tu et al., 2020). In this context, it is again emphasized that for all candidate drugs listed there is a lack of sufficient evidence supporting efficacy and tolerability for management of COVID-19 at this point of time. The outcome of future studies are awaited for final conclusions about the therapeutic value of these compounds. As mentioned in the introduction, an NIH expert panel even argues against the use of some of the compounds considered here due to tolerability issues and toxicity or negative clinical efficacy data (NIH, 2020). Considering registered clinical studies, we will discuss some of these compounds despite the above recommendations by NIH as potential drug-drug interactions might be relevant for studies that are currently ongoing in different countries.

It is also emphasized that none of the following drugs has been specifically developed for management of SARS-CoV-2, and that the potential therapeutic options are so far limited to repurposing of drugs, which were originally developed and designed for different indications.

Considering the discussed candidate therapeutic options, these can be categorized as those with antiviral or anti-inflammatory potential.

2.1. Antiviral drugs

2.1.1. Remdesivir

Remdesivir is a prodrug, previously known as GS-5734. It is a monophosphate that is metabolized to an adenosine nucleoside triphosphate analogue, which is integrated into the viral RNA prior to its replication (Amirian and Levy, 2020). As a consequence, the function of RNA-dependent viral RNA polymerase and RNA synthesis is inhibited (Warren et al., 2016). Due to its antiviral action and low EC_{50}, remdesivir was explored as a possible therapeutic agent during the Ebola virus outbreak (Siegel et al., 2017). An earlier experimental study suggested an efficacy of remdesivir against various coronaviruses including SARS-CoV and MERS-CoV (Sheahan et al., 2017). As the safety of the drug was previously validated in humans and due to its broad spectrum, remdesivir became the prime candidate for clinical trials against COVID-19 (Al-Tawfiq et al., 2020). *In vitro* evaluation confirmed inhibition of SARS-CoV-2 replication at a low EC_{50} value of 0.77 μM (Wang et al., 2020a). So far, first clinical reports and studies indicate a possible beneficial impact of remdesivir in patients with severe COVID-19 (Holshue et al., 2020) (Grein et al., 2020). Remdesivir has now been authorized by US Food and Drug Administration (FDA) for emergency use and has been approved by the European Medicines Agency (EMA) as well as Therapeutic Goods Administration of Australia (TGA) and has also been widely prescribed for patients in India, Japan and South Korea for the treatment of COVID-19.

2.1.2. Favipiravir

Favipiravir is the first oral antiviral drug that was approved by the Director General of India for the treatment of COVID-19. Apart from India, the drug has also been approved in Russia and on-going clinical trials are being conducted in the US and some parts of middle-east (Varadharajan, 2020). Favipiravir is a broad spectrum anti-viral drug that inhibits the replication of virus (Furuta et al., 2017). The pyrazine carboxamide derivative favipiravir serves as a prodrug that undergoes ribosylation and phosphorylation to form its active metabolite favipiravir ibofuranosyl-5′-triphosphate (T-705-RTP) (Furuta et al., 2017). T-705-RTP gets incorporated into the viral RNA thereby interfering with the process of viral replication and inhibiting the viral RNA-dependent RNA polymerase (Du and Chen, 2020; Furuta et al., 2017). It has already been demonstrated that T-705-RTP can limit influenza virus replication by inhibiting the RNA-dependent RNA polymerase without affecting the human DNA polymerases α, β, or γ subunit (Sissoko et al., 2016). Favipiravir has also shown its effectiveness against various other RNA viruses that cause hemorrhagic fever including arenavirus,

bunyavirus, flavivirus, and filoviruses (Du and Chen, 2020). Hence, favipiravir is being investigated globally in clinical trials as a potential therapeutic agent against SARS-CoV-2 (Karlsen et al., 2020). During an *in vitro* analysis, it was confirmed that at high maximum effective concentration (EC_{50} = 61.88 μM), favipiravir was able to inhibit SARS-CoV-2 viral infection (Wang et al., 2020a). An open-label non--randomized clinical study conducted in China, provided evidence that favipiravir exposure can result in therapeutic responses with a beneficial impact on progression of the disease and viral clearance in COVID-19 patients (Cai et al., 2020). Further clinical studies seem to confirm the promising results for favipiravir as an effective treatment against SARS-CoV-2 infection (Chen et al., 2020a; Ito et al., 2021; Noda et al., 2020). In Russia, favipiravir is marketed as AVIFAVIR for management of COVID-19 patients following first clinical studies indicating its efficacy, safety, and tolerability in phase II/III multicentric randomized clinical trials (Ivashchenko et al., 2020).

2.1.3. Lopinavir/ritonavir

The use of lopinavir/ritonavir has been discouraged recently and has also been recommended against by the NIH expert panel in their COVID-19 Treatment Guidelines, due to the adverse pharmacodynamics and no clinically beneficial outcome reported in COVID-19 patients (NIH, 2020). Lopinavir and Ritonavir are anti-retroviral agents that are used in combination against human immunodeficiency virus (Kujawski et al., 2020). They act by inhibiting the enzyme protease responsible for cleaving viral polypeptides, which are essential for viral replication. It has been described that lopinavir/ritonavir also acts on the 3CL protease enzyme involved in replication of coronaviruses (Nukoolkarn et al., 2008). Related to this effect, therapeutic effects have been previously assessed in patients with SARS-CoV or MERS-CoV infections (Yao et al., 2020a). A recent randomized clinical trial conducted by Cao and colleagues (2020) failed to confirm a benefit with lopinavir/ritonavir treatment in COVID-19 patients (Cao et al., 2020).

2.1.4. Ivermectin

Ivermectin is a broad-spectrum anti-parasitic agent that has been approved by the FDA for the treatment of internal and external parasitic infestations including tropical diseases such as onchocerciasis, helminthiases, and scabies (Crump and Ōmura, 2011; Omura and Crump, 2014). Ivermectin has also exhibited anti-viral potential *in vitro* with efficacy against RNA viruses such as dengue virus (DENV), Zika virus, HIV and influenza (Barrows et al., 2016; Götz et al., 2016; Wagstaff et al., 2012). Ivermectin inhibits the intracellular transportation of the virus in the host cells by targeting the host importin (IMP) α/β1 nuclear transport proteins (Wagstaff et al., 2012; Yang et al., 2020b). Based on corresponding evidence that IMPα/β1 seems to possess a role during SARS-CoV infection, an *in vitro* study was conducted by Leon Caly and co-workers that reported a 5000-fold reduction in the RNA levels of SARS-CoV-2 at 48 h post incubation with 5 μM of ivermectin in Vero/hSLAM cells (Caly et al., 2020). However, further reports were published that warned against the use of ivermectin in COVID-19 patients as the dose required to exhibit anti-viral activity as observed *in vitro*, was 100 fold more than the clinically approved dose (Bray et al., 2020; Chaccour et al., 2020). Conversely, a retrospective cohort study conducted in South Florida, reported a lower mortality rate in patients confirmed positive for SARS-CoV-2, who were on ventilatory support or required higher inspired oxygen and were treated with ivermectin (Rajter et al., 2020). Hence, these findings are required to be followed up by controlled randomized clinical trials aiming to further evaluate the efficacy and safety of ivermectin for treating COVID-19.

2.2. Drugs with anti-inflammatory or immunomodulatory potential

2.2.1. Chloroquine/hydroxychloroquine

The US Food and Drug Administration (FDA) along with WHO and NIH has warned and recommended against the use of chloroquine or hydroxychloroquine except for emergency use in hospitalized COVID-19 patients or in a clinical trial to avoid the risk of ventricular tachycardia and prolonged QT interval (Li et al., 2020a). However, in developing countries like India, the official guidelines recommend the use of hydroxychloroquine in combination with or without azithromycin, for treatment of mild to moderate symptomatic or asymptomatic COVID-19 patients and also as a prophylactic measure (Medina and Moncada, 2020). Chloroquine and hydroxychloroquine are anti-malarial agents that are also used as preventive treatment against chronic inflammatory diseases such as Systemic lupus erythematosus or rheumatoid arthritis (Fox, 1993). These drugs have also been repurposed for therapeutic management of viral infections. Chloroquine has been previously used against the structurally similar SARS-CoV due to its inhibitory action on the glycosylation of the ACE2 receptor (Vincent et al., 2005). Hydroxychloroquine also exhibits antiviral action by acidifying the endosomal pH and thereby blocking the fusion of virus with the host cell membrane (Savarino et al., 2003). Immunomodulatory effects are also observed in response to these drugs with a decrease in the production of pro-inflammatory cytokines, and an inhibition of autophagy and lysosomal action (Sanders et al., 2020). Recent *in vitro* studies have demonstrated inhibitory effects on SARS-CoV-2 at a half-maximal effective concentration (EC_{50}) of hydroxychloroquine and chloroquine in micromolar range (EC_{50} = 6.14 μM; EC_{50} = 23.90 μM, respectively) (Yao et al., 2020b). Few clinical trials have also validated the antiviral action of these drugs in COVID-19 patients (Chen et al., 2020b; Gao et al., 2020; Gautret et al., 2020). Tolerability concerns have been raised based on the pharmacodynamics of these compounds related to their effect on cardiac sodium channels (Frisk-Holmberg et al., 1983). Recent clinical studies exploring a potential benefit in patients with COVID-19 confirmed the occurrence of QTc interval prolongation in patients with COVID-19 (Chorin et al., 2020; van den Broek et al., 2020). Based on these findings, the need for ECG monitoring has been pointed out by the authors. The adverse effect potential has a particular relevance in the context of SARS-CoV-2 infections considering that patients with cardiovascular disease are considered patients with a high risk for a severe disease course, which therefore will also more often require pharmacotherapy.

2.2.2. Corticosteroids

According to the NIH COVID-19 treatment guidelines, the expert panel is currently recommending the use of dexamethasone, a glucocorticoid, for treating COVID-19 patients that are mechanically ventilated or require supplemental oxygen (NIH, 2020). The use of dexamethasone and other corticosteroids such as prednisone, methylprednisolone, and hydrocortisone has been advised based on their anti-inflammatory properties (Yang et al., 2020a). During the progression of SARS-CoV-2 infection, patients suffer from a “cytokine storm” that results from an abrupt release of cytokines and chemokines such as interleukins IL-6 and IL-1β, granulocyte-colony stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and tumor necrosis factor (TNF) (Huang et al., 2020; Nie et al., 2020; Shi et al., 2020; Xu et al., 2020b; Zhou et al., 2020).

Glucocorticoids can limit inflammatory signaling based on an interference with gene expression. Among other effects, glucocorticoids cause activation of histone deacetylases (HDAC2) by stimulating the transcription factors CREB, AP-1, and NF-κB (Ferner et al., 2020). This molecular mechanism is of particular interest as the SARS-CoV-2 Nsp5 protease can inhibit transport of HDAC2 into the nucleus, thereby impairing inflammation-associated cellular responses (El Baba and Herbein, 2020).

However, considering immunosuppressant effects related to the mechanism of action, the use of corticosteroids has been controversially discussed. So far there is insufficient clinical evidence, whether their administration helps to reduce the mortality of critically-ill COVID-19 patients (Singh et al., 2020). Nevertheless, application of dexamethasone has been associated with improved clinical outcomes when

administered to COVID-19 patients during the Randomized Evaluation of COVID-19 Therapy (RECOVERY) Trial. Similarly, few retrospective clinical studies have reported evidence for a beneficial impact of short-term use of the corticosteroid dexamethasone with a reduction of clinical respiratory symptoms and improvement in lung absorption (Singh et al., 2020; Wang et al., 2020b; Yang et al., 2020a). Further investigations with randomized controlled clinical trials are required to confirm the use of corticosteroids for the treatment of COVID-19 patients with a severe disease course (Nicolau and Bafadhel, 2020).

2.2.3. Tocilizumab

Tocilizumab is a monoclonal antibody that acts as an antagonist at the IL-6 receptor (Rose-John et al., 2017), and is used for therapeutic management of rheumatoid arthritis (Biggioggero et al., 2018). It inhibits the release of cytokine-storm related mediators (Borku Uysal et al., 2020). As mentioned above, there are a number of cases that report heightened levels of cytokines including IL-6 in patients with COVID-19 (Huang et al., 2020) (Zhou et al., 2020). Thus, first clinical trials have been conducted with tocilizumab. These provide limited evidence for a possible clinical improvement with reduced fever, improved respiratory functioning, and earlier discharge from the hospitals (Cao, 2020) (Xu et al., 2020a). Tocilizumab has been listed under the tentative 8th edition of the National Health Commission of the People's Republic of China COVID-19 Diagnosis and Treatment Guide, as a therapeutic agent for critically-ill patients with a severe COVID-19 course and increased levels of IL-6 (Wang, 2021; Anon, 2021b). On the contrary, the NIH expert panel has recommended against using interleukin-6 inhibitors including anti-IL-6 receptor monoclonal antibodies such as tocilizumab, sarilumab, *etc.* and anti-IL-6 monoclonal antibodies (siltuximab) for treating COVID-19, except in a clinical trial (NIH, 2020).

2.2.4. Anakinra

According to the NIH expert panel, there is insufficient data to recommend for or against the use of interleukin-1 inhibitors such as anakinra as a potential therapeutic option for COVID-19 management (NIH, 2020). While there seems to be no relevant clinical data supporting a benefit in patients with COVID-19, a possible use of anakinra has been brought up considering a subgroup of COVID-19 patients developing a cytokine storm syndrome (Cron and Chatham, 2020). In these patients, both, interleukin-6 inhibitors as well as the interleukin-1 receptor antagonist anakinra are discussed. This may be of particular future interest for patients with COVID-19 and seizure development, considering that first reports during recent years have indicated that anakinra may be efficacious in the management of a febrile infection-related epilepsy syndrome with development of a super-refractory status epilepticus (Dilena et al., 2019; Kenney-Jung et al., 2016; Sa et al., 2019).

3. Potential drug-drug interactions between ASMs and COVID-19 candidate drugs

First of all, we checked the literature regarding evidence for potential pharmacodynamic or pharmacokinetic drug interactions between the repurposed candidate drugs currently assessed for COVID-19 and available ASMs. Thereby, we considered potential pharmacokinetic interactions with a focus on an impact of the drugs on CYP450 enzymes. In addition, we also considered clinical reports about a possible impact of the compounds on seizure control in PWE. A brief summary of these case reports is provided in Table 1. The causal relationship between drug use and occurrence of seizures may of course not be established in all these cases. Nevertheless, some of the reports also point to the need for a more in-depth analysis of the potential for drug-drug interactions between COVID-19 candidate drugs and ASMs.

A list of probable drug-drug interactions of COVID-19 candidate drugs is provided by the following website https://www.covid19-druginteractions.org (Anon, 2021a) based on an initiative by the Liverpool Drug Interactions Group at the University of Liverpool. This list includes drug-drug interactions of COVID-19 candidate drugs with several ASMs. Table 2 lists the essential classes of drugs referenced from the website that indicates different degrees of drug-drug interactions. The classification distinguishes between drugs that are not to be co-administered, drugs that require dose adjustment and/or continuous monitoring if co-administered, and drugs that have a weak interaction potential with no need of monitoring. Justification for the above classification of the drug-drug interactions is, however, not provided by the

Table 1
Summary of case reports with evidence for possible seizure induction in patients exposed to drugs that are currently assessed as COVID-19 candidate drugs.

Patients' data (Age in years/ Gender)	Dosage	Indication	Duration of treatment before onset of seizures	Type of seizures observed	Previous history of seizures	References
CNhloroquine/ Hydroxychloroquine						
Case1−35yr/ Male; Case2−19yr/ Female	Chloroquine: 100 mg/day	Prophylactic anti-malarial treatment	2 days; 8 days	Generalized tonic-clonic seizures	None	(Schiemann et al., 2000)
17yr/ Female	Hydroxychloroquine: 200 mg/day	Systemic lupus erythematosus	14 days	Tonic-clonic seizures	Clinical history of complex partial seizure	(Malcangi et al., 2000)
49yr/ Male	Chloroquine: 150 mg three times daily for the first week; 150 mg twice for the second week; 150 mg daily for the third week	Erythema nodosum leprosum (Leprosy)	9 days	Tonic-clonic seizures	None	(Ebenso, 1998)
49yr/ Female	Chloroquine: 250 mg/day	Systemic lupus erythematosus	30 days	Complex partial seizures	None	(Krzeminski et al., 2018)
14yr/ Female	Chloroquine: 500 mg/day	Systemic lupus erythematosus	21 days	Tonic-clonic seizures	None	(Tristano et al., 2004)
26yr/ Female	Hydroxychloroquine: 500 mg/day	Systemic lupus erythematosus	30 days	Generalized tonic-clonic seizures	None	(Jafri et al., 2017)
Lopinavir/ritonavir						
10yr/ Female	Second line antiretroviral therapy (zidovudine-lamivudine-lopinavir/ ritonavir)	HIV	8 weeks	Generalized tonic-clonic seizures	None	(Otto et al., 2020)
54yr/ Male	Antiretroviral therapy with lopinavir/ ritonavir and abacavir/lamivudine	Pseudo-HIV	5 months	Non-convulsive *status epilepticus*	Alcohol-induced dementia, liver cirrhosis, epilepsy and psoriac arthritis	(Etgen et al., 2010)

Table 2
Potential drug-drug interactions between antiseizure drugs (ASMs) and COVID-19 candidate drugs*.

A) List of drug-drug interactions with documented proof of evidence-

Antiseizure medication		COVID-19 candidate drug Relevant effect on enzymes	Lopinavir [b]/ Ritonavir Inhibition of CYP3A4^	Dexamethasone Inducer/ Inhibitor of CYP3A subfamily
Enzyme Inducers	**Carbamazepine**	**Induction of CYP3A4**	Decrease in concentration of LPV/RTV Increase in concentration of CBZ (83 %) (Burman and Orr, 2000) + + +	Decrease in concentration of DEX Decrease in concentration of CBZ (Clearance rate ↑ by 1.41) (Bénit and Vecht, 2015) ++
	Phenobarbital	**Induction of CYP3A4**		Decrease in concentration of DEX Decrease in concentration of PB (Clearance rate ↑ by 1.79) (Bénit and Vecht, 2015) ++
	Phenytoin	**Induction of CYP3A4**		Decrease in concentration of DEX Decrease in concentration of PHT (50 %) (Bénit and Vecht, 2015) ++
Enzyme Inhibitor	**Valproic acid**		Increase in concentration of LPV (38 %) (DiCenzo et al., 2004) + +	
Others	**Lamotrigine**		Decrease in concentration of LTG (50 %) (van der Lee et al., 2006) + +	
	Midazolam		Increase in concentration of MDZ (by a factor of 25) (Greenblatt et al., 2009) + +	

B) List of drug-drug interactions with potential risk hypothesized based on literature-

Antiseizure medication		COVID-19 candidate drug Relevant effect on enzymes	Remdesivir [c] –	Chloroquine/ Hydroxy-chloroquine [a] Inhibition of CYP3A4 –	Lopinavir [b]/ Ritonavir Inhibition of CYP3A4^ –	Ivermectin –	Dexamethasone Inducer/ Inhibitor of CYP3A subfamily –	Tocilizumab [d] Increase in CYP3A4 (indirect effect) –	Anakinra [e] Increase in CYP3A4 (indirect effect) –
Enzyme Inducers	**Carbamazepine**	**Induction of CYP3A4**	Decrease in concentration of RDV +	Decrease in concentration of CLQ/ HCLQ + + +		Decrease in concentration of IVM ++		Decrease in concentration of CBZ +	Decrease in concentration of CBZ +
	Eslicarbazepine	**Induction of CYP3A4**		Decrease in concentration of CLQ/ HCLQ + +	Decrease in concentration of LPV/ RTV + +	Decrease in concentration of IVM ++	Decrease in concentration of DEX Decrease in concentration of ESL ++		
	Oxcarbazepine	**Induction of CYP3A4**		Decrease in concentration of CLQ/ HCLQ + +	Decrease in concentration of LPV/ RTV + +	Decrease in concentration of IVM ++	Decrease in concentration of DEX Decrease in concentration of OXC ++		
	Phenobarbital	**Induction of CYP3A4**	Decrease in concentration of RDV +	Decrease in concentration of CLQ/ HCLQ + + +	Decrease in concentration of LPV/ RTV + + +	Decrease in concentration of IVM ++		Decrease in concentration of PB +	Decrease in concentration of PB +
	Phenytoin	**Induction of CYP3A4**	Decrease in concentration of RDV +	Decrease in concentration of CLQ/ HCLQ + + +	Decrease in concentration of LPV/ RTV + + +	Decrease in concentration of IVM ++		Decrease in concentration of PHT +	Decrease in concentration of PHT +
	Primidone								

(*continued on next page*)

Table 2 (*continued*)

B) List of drug-drug interactions with potential risk hypothesized based on literature-

Antiseizure medication		COVID-19 candidate drug Relevant effect on enzymes	Remdesivir [c] Decrease in concentration of RDV	Chloroquine/ Hydroxy-chloroquine [a] Inhibition of CYP3A4	Lopinavir [b]/ Ritonavir Inhibition of CYP3A4^	Ivermectin	Dexamethasone Inducer/ Inhibitor of CYP3A subfamily	Tocilizumab [d] Increase in CYP3A4 (indirect effect)	Anakinra [e] Increase in CYP3A4 (indirect effect)
		Induction of CYP3A4	Decrease in concentration of RDV	Decrease in concentration of CLQ/ HCLQ	Decrease in concentration of LPV/ RTV Decrease in concentration of PRM [$]	Decrease in concentration of IVM	Decrease in concentration of DEX Decrease in concentration of PRM	Decrease in concentration of PRM	Decrease in concentration of PRM
	Rufinamide	**Induction of CYP3A4**	+	+ + + Decrease in concentration of CLQ/ HCLQ	+ + + Decrease in concentration of LPV/ RTV	++ Decrease in concentration of IVM	++ Decrease in concentration of DEX Decrease in concentration of RFN	+	+
	Cannabidiol	**Inhibition of CYP3A4**	–	+ + Increase in concentration of CLQ/ HCLQ	+ + Increase in concentration of CBD	++	++ Decrease concentration of corticosteroid [#]	– Decrease in concentration of CBD	–
	Clonazepam Clobazam Diazepam (BZDs)		–	+ +	+ + Increase in concentration of BZDs	–	+	+	–
	Ethosuximide		–	–	+ + Increase in concentration of ESM	–	–	–	–
Others	**Felbamate**	**Induction of CYP3A4**	–	– Decrease in concentration of CLQ/ HCLQ	+ + Decrease in concentration of LPV/ RTV	–	–	–	–
	Perampanel		–	+ +	+ + Increase in concentration of PER	–	–	–	–
	Sultiame		–	–	+ + Increase in concentration of STM	–	–	–	–
	Tiagabine		–	–	+ + Increase in concentration of TGB	–	–	–	–

Degree of drug-drug interactions:
Serious (+ + +)Potentially serious clinical consequences. Drugs not to be co-administered.
Moderate (+ +)Drugs that might require dose adjustment and periodic monitoring due to potential interaction.
Minor (+)Drugs expected to have potential weak interaction. Dose adjustment not necessary.
None (–)No clinical evidence exhibiting significant interaction.
enzymes that are relevant for a possible interaction between ASMs and COVID-19 candidate drugs based on the current state of knowledge.
For ASMs not mentioned in the above table including Gabapentin, Levetiracetam, Lorazepam, Pregabalin, Retigabine, Vigabatrin and Zonisamide, no significant evidence exists for drug-drug interactions with the COVID-19 candidate drugs.
BZD-Benzodiazepines; CLZ-Clonazepam; CBD-Cannabidiol; CBZ-Carbamazepine; CLQ/HCLQ-Chloroquine/ Hydroxychloroquine; DEX-Dexamethasone; ELS-Eslicarbazepine: ETS-Ethosuximide; IVM- Ivermectin; LPV/RTV-Lopinavir/Ritonavir; LTG-Lamotrigine; MDZ-Midozolam: OXC-Oxcarbazepine; PB-Phenobarbital; PER-Perampanel; PHT-Phenytoin; PRM-Primidone; RDV-Remdesivir; RFN- Rufinamide; STM-Sultiame; TGB-Tiagabine.

[*] The information summarized in this table considered information provided by Russo and Iannone at the International League Against Epilepsy (ILAE) website (Russo, 2020) and has been updated with information released by the Liverpool Drug Interaction Group (University of Liverpool, UK, in collaboration with the University Hospital of Basel (Switzerland) and Radboud UMC (Netherlands)) (http://www.covid19-druginteractions.org/). Please note that we only provide information about the compound's effects on metabolic.

[a] It is recommended that Chloroquine and Hydroxychloroquine are not administered in patients with recurring seizures. Both are metabolized by CYP3A4 and CYP2D6, and are also known to prolong QT interval and exhibit proarrythmic potential and hence, their administration should in general be closely monitored.

[b] Lopinavir is metabolized by CYP3A4.

[c] There is only limited clinical information for the investigational drug Remdesivir. However, it might be necessary to consider evidence suggesting that remdesivir is sensitive to CYP3A4.

[d] Tocilizumab causes suppression of IL-6 concentrations. IL-6 can reduce the expression of Cthe expression of P450 enzymes including CYP3A4, CYP2C9 and CYP2C19. As a consequence disease-associated increases in IL-6 as well as pharmacological reduction and control of IL-6 concentrations can affect the rate of hepatic metabolism in the opposite direction.

[e] Anakinra normalizes the increased concentration of metabolizing cytochromes (CYP450) due to inflammation, thereby it may decrease the systemic concentration of drugs metabolized by these enzymes.

[^] Ritonavir is a potent inhibitor of CYP3A4.

[$] Primidone is metabolized by CYP3A4 to phenobarbital, which induces CYP3A4.

[#] Cannabidiol inhibits CYP3A4 and thus concomitant administration with glucocorticoids like hydroxycortisone and prednisolone decrease glucocorticoid clearance, thereby increasing their systemic concentration (Wilson-Morkeh et al., 2019).

respective website. Hence, here we elaborate on the possible causes of the drug-drug interactions between commonly used ASMs and the COVID-19 candidate drugs.

3.1. Antiviral drugs

3.1.1. Remdesivir

Remdesivir is an investigational drug. Thus, only limited information is available about potential drug-drug interactions with remdesivir. It has been described that remdesivir is sensitive to CYP3A4 and hence, may act as a substrate to CYP3A4 enzyme (Streetman, 2020). However, considering the fact that it is metabolized predominantly by hydrolase *in vivo*, the risk for interaction with this nucleotide analogue compound is considered relatively low (Streetman, 2020).

Nevertheless, considering the limited clinical information, monitoring of remdesivir drug concentrations should be considered in case of co-administration of remdesivir with ASMs that induce CYP3A4 including carbamazepine, phenytoin, phenobarbital, primidone, oxcarbazepine, eslicarbazepine and rufinamide (Abou-Khalil, 2019).

3.1.2. Favipiravir

The active metabolite of favipiravir is metabolized in the liver by aldehyde oxidase and xanthine oxidase to form the inactive oxidative metabolite, T-705M1, which is then excreted *via* urine. There is insufficient to almost nil clinical data available for whether favipiravir or its active metabolite, T-705-RTP, affect hepatic metabolizing enzymes. However, pre-clinical studies have reported inhibitory effects of favipiravir on cytochrome isoenzyme, CYP2C8 (PMDA, 2014) and on aldehyde oxidase enzyme (Du and Chen, 2020). Available clinical data suggests that favipiravir has a low adverse effect potential and a favorable safety profile (Pilkington et al., 2020). Hence, even though favipiravir seems to have a low potential for drug-drug interaction, further studies are obviously required to evaluate the safety and tolerability of favipiravir, when co-administered with other drugs including ASM.

3.1.3. Lopinavir/ritonavir

Lopinavir is metabolized by the CYP3A group of cytochrome enzymes, whereas ritonavir is an inhibitor of CYP3A and, thus, is administered in combination with lopinavir to reduce the metabolism of lopinavir in plasma (Birbeck et al., 2012). This leads to a dual interaction between enzyme-inducing ASMs and lopinavir/ritonavir. The enzyme-induction property of ASMs such as carbamazepine, phenytoin, phenobarbital, primidone, oxcarbazepine, eslicarbazepine, felbamate and rufinamide, will lead to an increased metabolism of lopinavir, reducing its plasma concentration (Johannessen and Landmark, 2010). On the contrary, the enzyme inhibition property of ritonavir would block the metabolism of ASMs that are metabolized by CYP3A4, including carbamazepine, clonazapam, ethosuximide, perampanel, sultiame, and tiagabine, thereby, increasing their plasma concentration and consequently increasing their adverse effect potential (Abou-Khalil, 2019). Similarly, cannabidiol is also extensively metabolized by the cytochrome enzyme, CYP3A4, and hence, its co-administeration with patients treated with ritonavir will lead to an increase in the pharmacologically active concentration of CBD in the blood plasma (Yamaori et al., 2011).

Since lopinavir/ritonavir are antiretroviral agents used in the treatment of HIV, clinical information is available for potential drug-drug interactions of these antiretroviral drugs with ASMs (Birbeck et al., 2012). A study with 24 patients receiving lamotrigine reported a 50 % decrease in the plasma concentration of lamotrigine following addition of lopinavir/ritonavir to the treatment schedule (van der Lee et al., 2006). In a cohort study, it was observed that co-administration of lopinavir/ritonavir with valproic acid, increased the plasma concentration of lopinavir by 38 % over a course of seven days (DiCenzo et al., 2004). A case report also confirmed carbamazepine toxicity due to the administration of ritonavir, whereby an 83 % dose reduction was

necessary to establish a therapeutic concentration of carbamazepine (Burman and Orr, 2000). A pharmacokinetic study conducted in healthy subjects reported increased concentrations of midazolam by a factor of 25 (400 %) in the presence of ritonavir (Greenblatt et al., 2009). The increase seems to be due to inhibition of intestinal CYP3A as a consequence of lopinavir/ritonavir co-administration (Yeh et al., 2006).

Thus, reciprocal drug-drug interactions need to be considered, when administering lopinavir and ritonavir in patients with exposure to different ASMs.

3.1.4. Ivermectin

Ivermectin has been administered in PWE as an adjuvant along with phenobarbital. The combination has even been encouraged in patients with onchocerciasis-associated epilepsy (Mandro et al., 2020).

However, ivermectin is known to be metabolized by the cytochrome CYP3A4 in human liver microsomes (Zeng et al., 1998). Hence, the plasma concentration of ivermectin should be monitored when co-administered with ASMs that induce CYP3A4 including carbamazepine, phenytoin, phenobarbital, primidone, oxcarbazepine, eslicarbazepine and rufinamide (Abou-Khalil, 2019).

3.2. Drugs with anti-inflammatory or immunomodulatory potential

3.2.1. Chloroquine/hydroxychloroquine

Both chloroquine and hydroxychloroquine are metabolized by cytochrome P450 (CYP450) enzymes, namely, CYP2C8, CYP3A4 and CYP2D6. They also act as inhibitors of CYP2D6 (Schrezenmeier and Dörner, 2020). Hence, co-administration of enzyme inducers or inhibitors will affect the plasma concentration of, both, chloroquine and hydroxychloroquine, resulting in the need for dose adjustments. ASMs such as carbamazepine, phenytoin, phenobarbital, primidone, oxcarbazepine, eslicarbazepine acetate, felbamate and rufinamide are all inducers of CYP450 enzymes including CYP3A4 (Johannessen and Landmark, 2010). Thereby, co-administration of these ASMs may lead to increased metabolism of chloroquine and hydroxychloroquine, which may require elevated dose administration of the latter. However, chloroquine and hydroxychloroquine are reported to possess a potential risk for QT prolongation, which has recently been also confirmed related to its use in patients with COVID-19 (Chorin et al., 2020; van den Broek et al., 2020). Thus, dose adjustment will be quite challenging considering respective tolerability issues.

Although the patient information leaflet states an increased risk of seizures associated with the intake of the drug, a systematic review suggests that there is no class I evidence to support this notion (Pati, 2020).

Furthermore, a critical drug-drug interaction may exist between chloroquine/hydroxychloroquine and cannabidiol (CBD), the latter being a potent inhibitor of the cytochrome P450 enzyme CYP3A4. The potential interaction might lead to increased plasma concentrations of chloroquine/hydroxychloroquine, thereby increasing the risk of arrhythmia in patients co-administered with these medications. (Browning, 2014; Yamaori et al., 2011).

In conclusion, the co-administration of ASMs including cannabidiol, carbamazepine, phenytoin, phenobarbital, primidone, oxcarbazepine, eslicarbazepine, felbamate and rufinamide, with chloroquine and hydroxychloroquine should rather be avoided. Dose adjustments would require extreme care considering the proarrhythmic potential for chloroquine and hydroxychlorquine.

3.2.2. Corticosteroids

Corticosteroids like dexamethasone can act as enzyme inducers for the CYP3A cytochrome family (Zhou, 2008). This effect is mediated by an interaction with cytosolic glucocorticoid receptors, which upon activation translocate to the nucleus, where they affect transcription levels of several target genes. Hence, the concomitant use of dexamethasone and ASMs that are metabolized by CYP3A cytochrome (carbamazepine, phenytoin, phenobarbital, primidone, oxcarbazepine, eslicarbazepine and rufinamide) can result in decreased concentrations of the ASMs. Thus, it might be necessary to control and carefully adjust the dosing of ASMs.

Accordingly, clinical evidence indicates that co-administration of enzyme-inducing ASMs such as phenytoin (plasma concentration is decreased by 0.5), phenobarbital (clearance rate is decreased by 1.41 and 3.09) and carbamazepine (clearance rate is decreased by 1.79 and 4.42) can lead to an increase in the clearance time of corticosteroids with a subsequent decrease in their elimination half-life (Bénit and Vecht, 2015; Chalk et al., 1984; Griffiths and Taylor, 2018; Olivesi, 1986; Stjernholm and Katz, 1975). This suggests that administration of ASMs with corticosteroids, can cause a decrease in the plasma concentration due to increased metabolism of corticosteroids such as methylprednisolone, prednisolone, and dexamethasone (Bénit and Vecht, 2015).

3.2.3. Tocilizumab

Tocilizumab is a monoclonal antibody targeting cytokine IL-6 that is degraded by proteases. As expected, there is no evidence for any relevant direct interaction with cytochrome P450 enzymes. However, it may indirectly affect the expression of selected enzymes related to its effect on IL-6 function. It has previously been reported that increases in IL-6 concentrations can cause suppression of CYP450 enzymes such as CYP3A4, CYP2C19, CYP2C9 and CYP1A2 (Kim et al., 2012). As a consequence, concentrations of free drug substrates that are metabolized by these enzymes may increase (Abou-Khalil, 2019). This may also affect concentrations of ASMs such as carbamazepine, phenytoin, phenobarbital, clobazam, clonazepam, ethosuximide, tiagabine, topiramate, zonisamide. In turn, administration of tocilizumab will reduce IL-6 levels, thereby normalizing the expression of metabolizing cytochromes and the concentrations of affected drugs.

Taken together, tocilizumab possesses a weaker interaction potential than other COVID-19 candidate drugs and may not require dose adjustment or special monitoring, when co-administered with ASMs.

3.2.4. Anakinra

It has been reported that increased levels of cytokines such as IL-1 during chronic inflammation may result in reduced CYP450 enzyme activity. Thus, anakinra being an antagonist of IL-1 receptors, is theoretically expected to normalize CYP activity that was previously reduced due to release of inflammatory mediators. In view of this, dose-adjustments may be required for ASMs metabolized by CYP450 enzymes. However, we did not come across any clinical evidence for drug-drug interactions between ASMs and Anakinra (Bialer et al., 2018).

4. Potential drug interactions between ASMs and antipyretic and anti-inflammatory drugs concomitantly used in COVID-19 patients

One of the initial symptoms observed in patients with COVID-19 is fever. The first line therapy for the management of fever includes antipyretic drugs such as paracetamol (acetaminophen) (Kakodkar et al., 2020). The use of other drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) has been controversially discussed in the context of COVID-19 management (Moore et al., 2020; Rinott et al., 2020). This discussion is for instance triggered by reports indicating that ibuprofen can increase the expression of ACE2 receptors (Fang et al., 2020) and can inhibit antibody production *in vitro* (Bancos et al., 2009).

However, the Food and Drug Administration later issued a statement addressing these reports and stated that there is no evidence for worsening of COVID-19 with the use of NSAIDs (FDA, 2020). Furthermore, according to the COVID-19 treatment guidelines provided by NIH, patients with COVID-19 are advised to continue taking NSAIDs as concomitant medication for any comorbid condition that has been previously directed by their physician. The expert panel has also

recommended that there is no difference in the use of anti-pyretic drugs including acetaminophen as well as NSAIDs between patients with or without COVID-19 (NIH, 2020).

NSAIDs such as ibuprofen, have been proposed to prevent the cytokine storm in patients with a severe disease course (Giollo et al., 2020). In particular, ibuprofen can reduce levels of the pro-inflammatory cytokine IL-6 (Gallelli et al., 2013). This effect is of interest as IL-6 levels can be elevated in patients with COVID-19 (Cao, 2020). Thus, effects of ibuprofen are also studied in ongoing clinical trials in patients with COVID-19 (Química Luar et al., 2021; University Hospital and Bordeaux, 2020).

Previous literature has reported various drug interactions between NSAIDs and commonly used anti-seizure drugs. A past study investigated the effects of administering antipyretic analgesics or NSAIDs including acetylsalicylic acid, phenylbutazone, paracetamol and tolfenamic acid in patients with epilepsy treated with phenytoin and carbamazepine (Neuvonen et al., 1979). Moreover, there have been several studies exploring a potential anti-convulsant action of NSAIDs given individually or in combination with anti-seizure drugs. Several of these studies pointed to a potential additive or synergistic interaction (Day et al., 2019; Srivastava and Gupta, 2001; Tandon et al., 2003; Zhu et al., 2017). This might be partly related to an impact on blood-brain barrier penetration of antiseizure drugs based on an inhibition of efflux transporter induction by NSAIDs (Potschka, 2010).

A strong drug-drug interaction potential needs to be considered, when deciding to combine an antipyretic analgetic drug or a NSAID in patients with epilepsy or acute reactive seizures.

As a consequence of paracetamol exposure, a clinical study reported a significant increase in the clearance of lamotrigine due to enhanced formation of glucuronide conjugates (Gastrup et al., 2016). The antagonistic interaction seems to be related to an interference of the drugs with uridine diphosphate glucuronosyltransferase (UGT), which catalyses the metabolism of lamotrigine and paracetamol through N-glucuronidation. Lamotrigine is metabolized by UGT enzymes, namely, UGT1A3, UGT1A4 and UGT2B7, while paracetamol is metabolized by UGT1A1, UGT1A6, UGT1A9 and UGT2B15 enzymes (Bock, 2010) (Zaccara and Perucca, 2014). Both, changes in expression and activity of enzymes or competitive inhibition may contribute to the specific interaction between paracetamol and lamotrigine. The clinical relevance was confirmed by a study reporting an enhanced potential for a decrease in lamotrigine exposure along with a detrimental effect on seizure control (Carnovale et al., 2019).

The co-administration of paracetamol with enzyme-inducing AEDs such as carbamazepine, phenobarbital, phenytoin and primidone is also not recommended due to a negative impact on paracetamol concentrations (Perucca, 2006). A drug interaction potential should also be considered for traditional NSAIDs and COX-2 inhibitors such as ibuprofen, diclofenac and celecoxib. These drugs are metabolized by the cytochrome enzyme, CYP2C9, that is induced by the above mentioned AEDs (Moore et al., 2015). Furthermore, clinical evidences suggest displacement of phenytoin, valproic acid and carbamazepine on administration of ibuprofen, thereby increasing the serum concentration of the anti-seizure drugs (Dasgupta and Volk, 1996; Nation et al., 1990). On the contrary phenobarbital is evidenced to induce metabolism of ibuprofen (Kantor, 1979).

Hence, following a careful weighing of potential beneficial and detrimental effects in individual patients, potential drug-drug interactions need to be kept in mind when co-administering NSAIDs with anti-seizure drugs in patients with epilepsy or acute reactive seizures.

5. Conclusion

Significant effort is currently underway to identify drugs that exert beneficial effects on the course and outcome of COVID-19. Considering the urgency associated with the rapid development of the pandemic, these efforts so far focus on the repurposing of licensed or investigational drugs including compounds with possible antiviral effects and immunomodulators. While efficacy and tolerability of none of these drugs has been confirmed yet in sufficiently powered and controlled clinical studies, numerous clinical trials are currently underway worldwide. Intense care management of patients that develop seizures during a severe COVID-19 course as well as management of patients with epilepsy and SARS-CoV-2 infection requires information about possible drug-drug interactions between COVID-19 candidate drugs and ASMs. The data provided in this review suggest that potential drug-drug interactions should be taken into account when considering the combination of selected COVID-19 candidate drugs with ASMs. This in particular applies for chloroquine/hydroxychloroquine as well as lopinavir/ritonavir. In contrast, other possible COVID-19 treatment options such as tocilizumab that may be less prone to clinically relevant direct interactions with ASMs. Furthermore, remdesivir is suggested to have minor drug-drug interactions with ASMs since no clinical evidence is available that may state opposite. The outcome of ongoing and future clinical trials should be waited for final conclusions recommending for or against the drug options currently discussed for therapeutic management of COVID-19. In case of confirmation of efficacy and tolerability, depending on the compound, more research might be necessary to improve our state-of-knowledge regarding the use in patients with exposure to ASMs.

Data availability statement

This is a review article and data sharing is not applicable to this article because no new data were created or analyzed in this study.

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