Epilepsy and Acute Respiratory Syndrome – Related Coronavirus 2 (SARS-CoV-2): Are people with epilepsy at risk?

Epilepsia e síndrome respiratória aguda relacionada ao coronavírus 2 (SARS-CoV-2): as pessoas com epilepsia estão em risco?

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ABSTRACT

In February 2020, the pandemic disease designated COVID-19, caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has shown to be able to cause severe illness in some patients. Recent studies have hypothesized that the SARS-CoV-2 exploits the angiotensin-converting enzyme 2 (ACE2) receptor to gain entry inside the cells and so reach the central nervous system[1]. Amid this context, we have about 50 million people with epilepsy taking antiseizure drugs (ASDs) and or other medications (eg.: steroids, Cannabidiol, etc.) that are at risk to be infected by SARS-CoV-2 virus. So, we did an extensive review in the literature searching for recent studies that had explored the effects of the role of SARS-CoV-2 infection and epilepsy. We did not find evidence of poor outcomes between epilepsy and COVID-19. Regarding ASDs, we have found that enzyme inducers and inhibitors can have significant interactions with drugs that have been used to treat COVID-19 such as antiretrovirals, antibiotics, and antimalarial drugs. In contrast, others have fewer or no interactions with them as such as benzodiazepines, Lamotrigine, Levetiracetam, Topiramate, Perampanel, and so on. Besides that, the management of seizures in epileptic patients and status epilepticus should not be different from the usual protocol. However, the acknowledgment of these potential drug interactions could help in the right choice of ASDs, and also be aware of potential risk drug combinations and the importance in some cases of close monitoring of serum levels and adverse events.

Keywords: epilepsy, Coronavirus, SARS-CoV-2, COVID-19.

RESUMO

Desde de Fevereiro de 2020, a doença pandêmica conhecida como COVID-19, causada pelo Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) tem se mostrado capaz de acometer gravemente alguns pacientes. Estudos recentes levantaram hipóteses de que o SARS-CoV-2 explora o receptor da enzima conversora de angiotensina 2 (ACE2) para entrar no interior das células e atingir o sistema nervoso central[1]. Nesse contexto, temos cerca de 50 milhões de pessoas com epilepsia em uso de medicações antiepilépticas (DAEs) e ou outras medicações (como corticoesteroides, Canabidiol, etc.). Por isso, fizemos uma extensa revisão na literatura, buscando estudos recentes que exploraram os efeitos do papel da infecção por SARS-CoV-2 e da epilepsia. Até o momento, não há evidências de que pessoas com epilepsia apresentam prognóstico ruim no que se refere ao COVID-19. No que se refere aos antiepilépticos, foi encontrado que indutores e inibidores enzimáticos são os que apresentam mais interação medicamentosa com drogas utilizadas no tratamento do COVID-19, tais como antirretrovirais, antibióticos, e drogas antimaláricas, enquanto outras apresentam pouca ou nenhuma interação com esses. Além disso, o manejo de crises epilépticas e estado de mal epiléptico não deve diferente do protocolo usual. No entanto, o reconhecimento das potenciais interações medicamentosas nesse contexto pode auxiliar na escolha correta do antiepiléptico, e alertar sobre os potenciais riscos de combinação entre drogas e a importância de em alguns casos monitorizar de perto os níveis séricos e eventos adversos.

Palavras-chave: Epilepsia, Coronavírus, SARS-CoV-2, COVID-19.

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INTRODUCTION

The pandemic caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has brought changes in the world due to its high spread potential and severe evolution in some patients. The full understanding of the infection's pathophysiology is not known; it involves several human systems, including the nervous system, still a mystery. It is known that SARS-CoV-2 penetrates the host cell through the binding with the angiotensin--converting enzyme 2 (ACE2) receptor through the protein spike S1, which allows the virus to bind to the host membrane 1. In the central nervous system (CNS), glia and neurons express the ACE2 receptor making the CNS a target to SARS-CoV-2.

Epilepsy is one of the most prevalent neurological comorbidities in the world. About 1 % of the population has epilepsy and in Brazil and, more than 3 million people are affected by it. Understanding the vulnerability of this population during the SARS-CoV-2 pandemic setting is essential for the counseling and treatment of these patients.

In this context, the profile of interactions between different drugs used to treat SARS-CoV-2 infection and the antiseizure drugs (ASDs) need to be comprehended to the safety of the patients. This review provides an overview of the current literature on the effects of SARS-CoV-2 on epilepsy.

METHODOLOGY

In this review, we conducted a review in the literature searching to provide an overview of studies that have so far explored the effects of the role of SARS-CoV-2 infection and epilepsy. We used a combined strategy of terms found in the controlled vocabulary of MeSH (Medical Subject Headings) as well as the terms representing synonyms with significant occurrences in major databases. The evaluation was according to the specifications of each database. Therefore, the Boolean operators "AND" and "OR" were used to combine keywords. Electronic searches were conducted on May 19, 2020, using the following databases: MEDLINE (via PubMed), Scopus, Web of Science, Cochrane Library, EMBASE, and Clinical Trials.org. All titles found in the survey were imported into Mendeley's web reference manager. Articles were promptly cataloged, and duplicate records were removed.

The titles and abstracts found in the research were subject to two researchers' independent ways to identify the articles of interest for this review. Besides that, we search for the mean concerning to clarify the concerns about it and show the recent recommendations to patients with epilepsy, their caregivers, and doctor.

RESULTS

Table 1 shows the recommendations and interaction profiles between ASDs and the drugs currently used in the treatment of SARS-CoV-2.

Is Epilepsy a risk factor for contracting SARS-CoV2? Is epilepsy a protective factor against this disease? Are people with epilepsy at risk of developing the most severe forms of SARS-CoV-2?

So far, there is no evidence that the presence of epilepsy increases or not the risk of contracting SARS--CoV-2 infection. The presence of seizures in critically ill patients seems to be related to other conditions, such as hypoxia and encephalopathy (2,3)

Regarding the evolution to more severe forms, patients with epilepsy are not, at first, part of the risk group with the highest chance of developing severe forms of the disease. However, specific epileptic syndromes (mainly in the pediatric population) require treatment with corticosteroids or adrenocorticotropic hormone (ACTH), leading to immunosuppression, for this reason, becoming part of the risk group, with a higher chance of progressing severely[3]. We should also pay attention to patients with tuberous sclerosis since they may have, in addition to epileptic seizures, reduced lung function, and use of immunological therapy[2].

What is the initial management of an epilepsy patient suspected or infected with SARS-CoV-2?

Initially, all the patients, with epilepsy or not, should receive the supportive treatment recommended according to his clinical condition.

What are the particularities of the drug management treatment for epilepsy patients with SARS-CoV-2?

In patients who evolve with severe forms of the disease or have an indication to start any of the treatments currently used for infection by SARS-CoV-2, such as Hydroxychloroquine, antibiotics, anticoagulants, immunobiological, antiretrovirals, among others, doctors should check the possible drug interactions between these drugs

and ASDs. These patients could have metabolic changes, such as renal and hepatic failure, blood dyscrasia, and hydroelectrolytic disorders due to systemic inflammatory state and also due to medications to treat COVID-19. Therefore, the need for dose adjustment, suspension, or replacement of the ASDs should be evaluated in each case.

A patient with epilepsy and SARS-CoV-2 infection had a seizure. What are the possible causes of the seizure (s)? In the context of viral infection in a patient with epilepsy, the answer to the following question should be: Is it an epilepsy decompensation or an acute symptomatic seizure?

Epilepsy decompensation: Any infectious condition can reduce the seizure threshold in patients with epilepsy; we should pay attention to medications to COVID-19 in use by the patient due to the possibility of reducing the seizure threshold and its possible drug interactions with the ASDs, which can reduce its serum levels; and also assess whether the patient is taking medications regularly (in Pandemic times many patients are unable to make appointments with a neurologist and prescriptions for antiepileptics are controlled).

- Stroke: Coagulation disorders, among other metabolic changes, have been observed in severe forms of SARSCoV-2, which may lead to a higher risk of stroke in these patients[4];
- Metabolic changes: Related to the severity of the infection itself, such as respiratory and hydroelectrolytic disorders, liver and kidney failure can be factors that trigger seizures, and hypoxia is a common disorder among these patients.
- The direct action of the virus in the CNS: SARS--CoV-2, as other respiratory viruses are at risk of invading and infecting the CNS - consider the need for cerebrospinal fluid collection for analysis in cases of altered consciousness[5];

How should be the management of the status Epilepticus in a suspected or confirmed patient for SARS--CoV-2?

Start the treatment recommended protocol for epileptic status 6. You can find detailed information about some drugs used in the medication section of this manual. It is crucial to keep in mind that every critical patient with altered consciousness is liable to be in a non-convulsive state of illness, and an electroencephalogram (EEG) exam must be requested for correct diagnosis and management.

Should I request a specific exam for these patients?

The need for specific complementary exams such as lumbar puncture, CNS imaging exams, and EEG should be evaluated on a case-by-case basis, with no recommendation to perform them on a routine basis without a clinical-neurological picture that justifies them.

Treatment guide - ASDs X Drugs used in the COVID-19 treatment? - What is essential to know?

ASDs are a heterogeneous group of substances with distinct pharmacological characteristics. It is essential to be aware of its pharmacodynamic characteristics and possible interactions with other drugs or even with known adverse effects that can be aggravated by concomitant use with other medications. In this context of SARS-CoV-2, the risk of cardiac arrhythmias is noteworthy, highlighting that drugs such as Lacosamide can prolong the PR interval, as well as the Lopinavir/ritonavir antiretroviral regimen; Propofol that as used to treat refractory status epilepticus has high arrhythmic potential, and drugs such as Atazanavir, Chloroquine, Hydroxychloroquine, and Azithromycin can prolong the QT interval[7].

Therefore, it is emphasized the importance of performing pre / post-treatment ECG for all patients who need to use these medications, with particular attention when used in combination.

The ASDs with the most significant potential for drug interactions in patients undergoing treatment for COVID-19 are enzyme inducers (e.g., Phenobarbital, Phenytoin, Carbamazepine, Primidona, Rufinamide) and enzyme inhibitors (e.g., Sulthiame, Valproic Acid, Brivaracetam, and Cannabidiol). Medicines classified as either inducers or inhibitors (e.g., Oxcarbamazepine) can have variable enzymatic effects depending on each patient's metabolism. The class with little or no effect of enzyme induction or inhibition (e.g., Ethosuximide, benzodiazepines, Gabapentin, Lamotrigine, Levetiracetam, Pregabalin, Topiramate, Vigabatrin, Lasosamide, and Perampanel) would have fewer interactions with COVID-19 medication therapy and is the better choice in this context. However, in these cases, at first, the patients with refractory epilepsy should not stop their medication routine because of the potential risks such as seizures and status epilepticus.

Regarding the interaction between ASDs and the drugs used to treat SARS-CoV2 infection, it is essential

to notice that medications with hepatic metabolism suffer more changes than those with primarily kidney excretion. However, even these medications should be used carefully patients with severe SARV-CoV-2 infection evolve quickly with acute renal dysfunction.

CONCLUSION

It is worth mentioning that the pathophysiology of SARS-CoV-2 and its management is being discovered every day, so our knowledge about this subject is dynamic. At the moment, the person with epilepsy does not seem to belong to the higher risk group, but it is important to address issues of drug interaction and decompensation due to the infectious condition. Despite the drug interactions that evolve ASDs, there is no absolute contraindication to the uses of any them since, in some cases, mainly in underdeveloped countries, we do not have all the ASDs available, but we should be aware of the potential interactions to follow the best management.

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REFERENCES

1. Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. Severe Acute Respiratory Syndrome Coronavirus Infection Causes Neuronal Death in the Absence of Encephalitis in Mice Transgenic for Human ACE2 >. 2008;82(15):7264–75.
2. French AJA. Brodie MJ, Caraballo R, Devinsky O, Mph DD, Jehi L, et al. Keeping people with epilepsy safe during the Covid-19 pandemic. Neurology. 2020, 10.1212/WNL.0000000000009632;
3. Lu L, Xiong W, Liu D, et al. New-onset acute symptomatic seizure and risk factors in coronavirus disease 2019: A retrospective multicenter study [published online ahead of print, 2020 Apr 18]. Epilepsia. 2020;10.1111/epi.16524.
4. Asadi-Pooya AA, Simani L. Central nervous system manifestations of COVID-19: A systematic review. J Neurol Sci. 2020;413:116832.
5. Desforges M, Coupanec A Le, Dubeau P, Lajoie L, Dub M, Talbot PJ. Human Coronaviruses and Other Respiratory Viruses : Underestimated Opportunistic Pathogens of the Central Nervous System ? 2019;1–28.
6. Trinka E, Hößer J, Leitinger M, Brigo F. Pharmacotherapy for Status Epilepticus. Drugs. 2015;75(13):1499–521.
7. Russo E and Iannone L. Clinically relevant Drug-Drug interaction between AEDs and medications used in the treatment of COVID-19 patients https://www.ilae.org/Ples/dmPle/Antiepileptic-drugs-interactions_in_COVID-19.pdf. 20

ANEXO:

Table 1. Summary of the main interactions between AEDs and COVID 19 treatments

Antiepileptic Drugs	Drug interactions with medications commonly used in the context of COVID-19	Antibiotic therapy interaction	Interactions with other medications	Observations in patients with renal or/and liver insufficiency
Clobazam	Use with caution Chloroquine > Its levels can be raised by Clobazam by affecting the hepatic metabolism of the CYP2D6 enzyme.	=	=	No adjustment or interruption is required. Contraindicated in cases of severe liver insufficiency
	No interaction Hydroxychloroquine; Ribavirin; Atazanavir; Lopinavir/ritonavir; Oseltamivir; Remdesivir*; Tocilizumab;	No interaction Piperacillin/tazobactam; Vancomycin; Polymyxin B; Meropenem; Amoxicillin/clavulanate; Ceftriaxone; Azithromycin	No interaction Enoxaparin; Nitazoxanide; Ivermectin; Hydrocortisone	
Lamotrigine	Use with caution Lopinavir/ritonavir > They increase the Lamotrigine metabolism, reducing levels up to 50%. Lamotrigine adjustment should be assessed.	=	=	Consider decrease dose in cases of severe renal insufficiency/renal failure (CrCl ≤ 30mL / min) or hemodialysis. Consider dose reduction in cases of moderate to severe liver insufficiency/failure.
	No interaction Chloroquine; Hydroxychloroquine; Ribavirin; Atazanavir; Oseltamivir; Remdesivir*; Tocilizumab	No interaction Piperacillin/tazobactam; Vancomycin; Polymyxin B; Meropenem; Amoxicillin/clavulanate; Ceftriaxone; Azithromycin	No interaction Enoxaparin; Nitazoxanide; Ivermectin; Hydrocortisone	
Levetiracetam				Adults and teenagers > 50 kg: CrCl > 80mL/min: 500-1500mg PO 12/12h CrCl 50-79 mL/min: 500-1000mg PO 12/12h CrCl 30-49 mL/min: 250 – 750mg PO 12/12h CrCl < 30 mL/min: 250-500mg PO 12/12h Hemodialysis: 500-1000mg PO once a day, with supplemental
				dose of 250-500mg after HD. Adults, adolescents and children over 6 months <50 kg: CrCl > 80mL/min: 10-30mg /kg PO 12/12h CrCl 50-79 mL/min: 10-20mg/kg PO 12/12h CrCl 30-49 mL/min: 5 – 15mg/kg PO 12/12h CrCl < 30 mL/min: 5-10m/kg PO 12/12h Hemodialysis: 10-20mg/kg PO once a day, with supllemental dose of 5-10mg after HD. Reduce 50% of the daily maintenance dose when creatinine clearance is below 60mL / min / 1.73 m² in cases of severe hepatic impairment.

Antiepileptic Drugs	Drug interactions with medications commonly used in the context of COVID-19	Antibiotic therapy interaction	Interactions with other medications	Observations in patients with renal or/and liver insufficiency
	No interaction Chloroquine; hydroxychloroquine; Ribavirin; Atazanavir; Lopinavir/ritonavir; Oseltamivir; Remdesivir*; Tocilizumab;	No interaction Piperacillin/tazobactam; Vancomycin; Polymyxin B; Meropenem; Amoxicillin/clavulanate; Ceftriaxone; Azithromycin	No interaction Enoxaparin; Nitazoxanide; Ivermectin; Hydrocortisone	
Lacosamide	Monitor / Modify therapy Lopinavir/ritonavir > They elevate serum levels of lacosamide through pharmacological synergism and reduce its hepatic / intestinal metabolism. Evaluate the dose reduction of lacosamide.	=	=	The maximum daily dose of 300mg in cases of severe renal insufficiency/failure (CrCl ≤ 30mL / min) or hemodialysis. Maximum daily dose of 300mg/day in cases of mild to moderate liver insufficiency. Contraindicated in cases of severe liver insufficiency/ failure.
	No interaction Chloroquine; Hydroxychloroquine; Ribavirin; Atazanavir; Oseltamivir; Remdesivir*; Tocilizumab	= No interaction Piperacillin/tazobactam; Vancomycin; Polymyxin B; Meropenem; Amoxicillin/clavulanate; Ceftriaxone; Azithromycin	= No interaction Enoxaparin; Nitazoxanide; Ivermectin; Hydrocortisone	
Topiramate	Use with caution Lopinavir/ritonavir > Topiramate increases their hepatic/intestinal metabolism		Use with caution Hydrocortisone > Topiramate increases the hepatic/intestinal metabolism of hydrocortisone.	Decrease to 50% of the initial dose in cases of CrCl below 70 mL/min. Administer dose after HD with serum monitoring when possible.
	No interaction Chloroquine; Hydroxychloroquine; Ribavirin; Atazanavir; Oseltamivir; Remdesivir*; Tocilizumab;	No interaction Piperacillin/tazobactam;Vancomycin; Polymyxin B; Meropenem; Amoxicillin/clavulanate; Ceftriaxone; Azithromycin	No interaction Enoxaparin; Nitazoxanide; Ivermectin	
Clonazepam	Monitor/Modify therapy Lopinavir/Ritonavir > They raise the serum levels of clonazepam by reducing its hepatic metabolism. Increase the risk of toxicity.	=	=	No adjustment or interruption is required.
	No interaction Chloroquine; Hydroxychloroquine; Ribavirin; Atazanavir; Oseltamivir; Remdesivir*; Tocilizumab;	No interaction Piperacillin/tazobactam;Vancomycin; Polymyxin B; Meropenem; Amoxicillin/clavulanate;Ceftriaxone; Azithromycin	No interaction Enoxaparin; Nitazoxanide; Ivermectin; hydrocortisone	
Valproic acid	=	Avoid/Assess therapy change Meropenem > Increases serum levels of valproic acid by an unknown mechanism related to absorption and increases its renal excretion.	Avoid/Assess therapy change Nitazoxanide > One increases the serum level of the other through protein binding competition.	Consider decrease dose in cases of severe renal insufficiency/ failure (CrCl ≤ 30mL / min) or hemodialysis. Contraindicated in cases of liver failure

Antiepileptic Drugs	Drug interactions with medications commonly used in the context of COVID-19	Antibiotic therapy interaction	Interactions with other medications	Observations in patients with renal or/and liver insufficiency
	No interaction Chloroquine; hydroxychloroquine; Ribavirin; Atazanavir; Lopinavir/ritonavir; Oseltamivir; Remdesivir*; Tocilizumab	No interaction Piperacillin/tazobactam;Vancomycin; Polymyxin B; Amoxicillin/clavulanate;-Ceftriaxone; Azithromycin	No interaction Enoxaparin; Ivermectin; Hydrocortisone	
Phenytoin Attention: In case of intravenous use, use sodium chloride solution 0,9%. Never use a glucose solution because of the risk of drug precipitation.	Monitor/Modify therapy Atazanavir, Lopinavir/ritonavir , Chloroquine, hydroxychloroquine, and Remdesivir* > Phenytoin increases their metabolism through enzyme CYP3A4, by decreasing their serum levels and effects. Weak drug interaction Tocilizumab > May decrease Phenytoin levels.	=	Monitor/Modify therapy Nitazoxanide > One increases the serum level of the other through protein binding competition. Risk of intoxication. Use with caution and monitor Ivermectin; Hydrocortisone; Enoxaparin	At First, adjustments are not necessary. However, it is recommended to monitor Phenytoin serum levels by dosing its free fractions, because of the risk of intoxication by the drug. Since most of its metabolism is hepatic (95%), the clearance of the medication may be reduced and it is, therefore, important to closely monitor its free serum fractions leading to an adjustment of dose.
	No interaction Ribavirin; Oseltamivir; Remdesivir*	No interaction Piperacillin/tazobactam;Vancomycin; Polymyxin B; Meropenem; Amoxicillin/clavulanate;Ceftriaxone; Azithromycin		
Phenobarbital	Monitor/Modify therapy Atazanavir, Lopinavir/ritonavir, Chloroquine, Hydroxychloroquine, and Remdesivir* > Phenobarbital increases the metabolism of these drugs through the enzyme CYP3A4, decreasing their serum levels and effects. Use with caution and monitor	=	Use with caution and monitor Ivermectin, Hydrocortisone; Enoxaparin	No adjustment or interruption is required.
	No interaction Ribavirin; Oseltamivir;	No interaction Piperacillin/tazobactam;Vancomycin; Polymyxin B; Meropenem; Amoxicillin/clavulanate;Ceftriaxone; Azithromycin	No interaction Nitazoxanide	
Carbamazepine	Monitor/Modify therapy Atazanavir, Lopinavir/ritonavir, Chloroquine, Hydroxychloroquine and Remdesivir* > Carbamazepine increases metabolism of these drugs through the enzyme CYP3A4, decreasing their serum levels and effects. Use with caution and monitor Tocilizumab	=	Use with caution and monitor Hydrocortisone; Enoxaparin	If glomerular Þltration rate below 10 mL/min or hemodialysis: administrate 75% of the dose and monitor.

Antiepileptic Drugs	Drug interactions with medications commonly used in the context of COVID-19	Antibiotic therapy interaction	Interactions with other medications	Observations in patients with renal or/and liver insufficiency
	No interaction Ribavirin; Oseltamivir	No interaction Piperacillin/tazobactam;Vancomycin; Polymyxin B; Meropenem; Amoxicillin/clavulanate;Ceftriaxone; Azithromycin	No interaction Nitazoxanide; Ivermectin	
Primidone	Monitor/Modify therapy Atazanavir, Lopinavir/ritonavir, Chloroquine, Hydroxycloroquine, and Tocilizumabe > Primidone increases the metabolism of these drugs through the enzyme CYP3A4,	=	Use with caution and monitor Hydrocortisone; Enoxaparin	No adjustment or interruption is required.
	Decreasing their serum levels and effects.			
	No interaction Ribavirin; Oseltamivir; Remdesivir*; Tocilizumab	No interaction Piperacillin/tazobactam;Vancomycin; Polymyxin B; Meropenem; Amoxicillin/clavulanate;Ceftriaxone; Azithromycin	No interaction Nitazoxanide; Ivermectin	
Oxcarbazepine	Monitor/Modify therapy Atazanavir, Lopinavir/ritonavir, Chloroquine, Hydroxycloroquine and Tocilizumabe > Oxcarbamazepine increases the metabolism of these drugs through the enzyme CYP3A4, decreasing their serum levels and effects.	=	Use with caution and monitor Hydrocortisone	In cases of severe renal insufficiency / failure (CrCl below 30 mL/min): Administrate 50% of the initial dose and slowly increase until reach therapeutic response. No adjustment or interruption is required in cases of mild to moderate hepatic insufficiency. Contraindicated in cases of severe liver insufficiency/ failure.
	No interaction Ribavirin; Atazanavir; Oseltamivir; Remdesivir*; Tocilizumab	No interaction Piperacillin/tazobactam; Vancomycin; Polymyxin B; Meropenem; Amoxicillin/clavulanate; Ceftriaxone; Azithromycin	No interaction Enoxaparin; Nitazoxanide; Ivermectin	
Pregabalin	=	=	=	CrCl 30 -60 mL/min: Decrease to 50 % and divide into 2 or 3 doses per day. CrCl 15-30 mL/min: Decrease to 25 % and divide into 2 doses per day Hemodialysis > Administrate daily after hemodialysis.
	No interaction Chloroquine ; hydroxychloroquine; Ribavirin; Atazanavir; Lopinavir/ritonavir; Oseltamivir; Remdesivir*; Tocilizumab	No interaction Piperacillin/tazobactam;Vancomycin; Polymyxin B; Meropenem; Amoxicillin/clavulanate;Ceftriaxone; Azithromycin	No interaction Enoxaparin; Nitazoxanide; Ivermectin; Hydrocortisone	

Antiepileptic Drugs	Drug interactions with medications commonly used in the context of COVID-19	Antibiotic therapy interaction	Interactions with other medications	Observations in patients with renal or/and liver insufficiency
Gabapentin	=	=	=	CrCl > 60 mL/min: 300-1200 mg divided into 3 doses per day. CrCl 30-60 mL/min: 200-700 mg dividided into 2 doses per day. CrCl 15-29 mL/min: 200-700 mg in 1 dose per day CrCl <15 mL/min : 100-300 mg in 1 dose per day.
				Hemodialysis > Administrate supplementary dose (125-350 mg) after hemodialysis.
	No interaction Chloroquine ; hydroxychloroquine; Ribavirin; Atazanavir; Lopinavir/ritonavir; Oseltamivir; Remdesivir*; Tocilizumab	No interaction Piperacillin/tazobactam;Vancomycin; Polymyxin B; Meropenem; Amoxicillin/clavulanate;Ceftriaxone; Azithromycin	No interaction Enoxaparin; Nitazoxanide; Ivermectin; Hydrocortisone	
Sultiame (Ospolot)	Monitor/Modify therapy Lopinavir/Ritonavir > They raise the serum levels of Sulthiame.	=	=	No adjustment or interruption is required
	No interaction Chloroquine; hydroxychloroquine; Ribavirin; Atazanavir; Oseltamivir; Remdesivir*; Tocilizumab	No interaction Piperacillin/tazobactam;Vancomycin; Polymyxin B; Meropenem; Amoxicillin/clavulanate;Ceftriaxone; Azithromycin	No interaction Enoxaparin; Nitazoxanide; Ivermectin; Hydrocortisone	
RuÞnamide	Monitor/Modify therapy Atazanavir, Lopinavir/ritonavir, Chloroquine, and Hydroxychloroquine > RuÞnamide increases the metabolism of these drugs through the enzyme CYP3A4, decreasing their serum levels and effects.	=	Use with caution and monitor Hydrocortisone	Hemodialysis: Consider dose adjustment. Contraindicated in cases of severe liver insufÞciency/ failure.
	No interaction Ribavirin; Oseltamivir; Remdesivir*; Tocilizumab	No interaction Piperacillin/tazobactam; Vancomycin; Polymyxin B; Meropenem; Amoxicillin/clavulanate; Ceftriaxone; Azithromycin	No interaction Enoxaparin; Nitazoxanide; Ivermectin	
Vigabatrin (Sabril)	=	=	=	CrCl > 50 – 80 mL/min: Decrease dose in 25 %. CrCl > 30-50 mL/min: Decrease dose in 50 %. CrCl >10-30 mL/min: Decrease dose in 75 %. Hemodialysis > no studies at the moment.
	No interaction Chloroquine ; hydroxychloroquine; Ribavirin; Atazanavir; Lopinavir/ritonavir; Oseltamivir; Remdesivir*; Tocilizumab	No interaction Piperacillin/tazobactam;Vancomycin; Polymyxin B; Meropenem; Amoxicillin/clavulanate;Ceftriaxone; Azithromycin	No interaction Enoxaparin; Nitazoxanide; Ivermectin; Hydrocortisone	

Antiepileptic Drugs	Drug interactions with medications commonly used in the context of COVID-19	Antibiotic therapy interaction	Interactions with other medications	Observations in patients with renal or/and liver insufficiency
Cannabidiol	Monitor/Modify therapy Lopinavir/ritonavir, Chloroquine and Hydroxychloroquine > They increase its serum levels. Risk of toxicity	=	=	No adjustment or interruption is required. At Þrst, no adjustment is necessary for hepatic dysfunction. Use with caution and monitor.
	No interaction Chloroquine ; hydroxychloroquine; Ribavirin; Atazanavir; Lopinavir/ritonavir; Oseltamivir; Remdesivir*; Tocilizumab	No interaction Piperacillin/tazobactam;Vancomycin; Polymyxin B; Meropenem; Amoxicillin/clavulanate;Ceftriaxone; Azithromycin	No interaction Enoxaparin; Nitazoxanide; Ivermectin; Hydrocortisone	

CrCl: Creatinine clearance; PO: peroral;

*Due to the current absence of pharmacokinetic studies in humans, these data concerning Remdesivir have been interpreted from their in vitro behavior.