Potential Drug-Drug and Drug-Disease interactions of selected experimental therapies used in treating COVID-19 patients

Radhwan Nidal Al-Zidan
Department of Pharmaceutics, College of Pharmacy, University of Mosul, Iraq

ABSTRACT

At the end of 2019, the whole world was witnessing the birth of a new member of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) family in Wuhan city, China. Since then, the 2019 novel coronavirus (COVID-19) has rapidly invaded every corner of the world. Before the end of September 2020, nearly 32 million cases worldwide were recorded, with a death toll of approximately 1 million cases. As COVID-19 has spread across the world, certain groups of people prove more susceptible than others. Elderly patients and people with chronic medical conditions such as heart disease or diabetes are more likely to experience or even suffer from serious diseases. As a population, senior citizens take more medicines than young people. Similarly, people with chronic illnesses who are several taking drugs to control their illness. Generally, drug interactions are mechanisms in which one medication alters the absorption, distribution, metabolism, or elimination (ADME) of another drug and pharmacodynamics—in which one medication affects the response to another medication (apart from the pharmacokinetic effects). The effect of a patient’s condition on the disposition and reaction to a medication is of equal significance. Moreover, many medications adversely interfere with a variety of diseases, and vice versa. (i.e. drug-disease interactions). Unfortunately, this point has been scarcely addressed. Therefore, in addition to examining interactions between medications, this review also discusses interactions between the disease(s) and the experimental drugs used in COVID-19. An expanding number of studies have suggested that there is significant potential for ADIs occurrence in patients with COVID-19. Moreover, since the start of COVID-19 pandemic numerous studies and clinical trials, continuously, suggest the use of an even increasing number of potential and adjuvant drugs. Therefore, it is necessary to provide the healthcare providers with a comprehensive resource that contain all the possible drug-drug and drug-disease interaction in patients with COVID-19. To help health care providers locate the answers they need in the shortest possible time, the information contained in this review has been included in easy-to-read tables.

Keywords: Drug interactions; DDIs; Polypharmacy; SARS-CoV-2; COVID-19.

Introduction

Interactions between drugs could be described as the combination of two perhaps even more drugs, so that one drug’s potency, sometimes even efficacy, is substantially altered by the existence of another medication. Adverse drug reactions (ADRs) well-documented causes of increasing patient morbidity as well as rising medical costs and complaints of malpractice. Generally, drug interactions are known to include the effect(s) of one drug on the disposition and/or response to another. Normally such associations are addressed in pharmacokinetics—in which one medication alters the absorption, distribution, metabolism, or elimination (ADME) of another drug and pharmacodynamics—in which one medication affects the response to another medication (apart from the pharmacokinetic effects). The effect of a patient’s condition on the disposition and reaction to a medication is of equal significance. Moreover, many medications adversely interfere with a variety of diseases, and vice versa. (i.e. drug-disease interactions). Unfortunately, this point has been scarcely addressed. Therefore, in addition to examining interactions between medications, this review also discusses interactions between the disease(s) and the experimental drugs used in COVID-19. An expanding number of studies have suggested that there is significant potential for ADIs occurrence in patients with COVID-19. Moreover, since the start of COVID-19 pandemic numerous studies and clinical trials, continuously, suggest the use of an even increasing number of potential and adjuvant drugs. Therefore, it is necessary to provide the healthcare providers with a comprehensive resource that contain all the possible drug-drug and drug-disease interaction in patients treated for COVID-19. Currently, more than 200 thousand people are being infected with COVID-19 each day-worldwide. This extremely high number of cases is a huge burden on the healthcare personnel; therefore, the healthcare professionals may not have the sufficient time to go through all the relevant articles.
published about the safety of medications used in patients with COVID-19. That is why in this review all the information related to the drug-drug interactions as well as the drug-disease interactions was organized in easy-to-read comprehensive tables, as shown below in tables 1 & 2.

### Table 1: Drug-Drug interactions of selected experimental therapies for COVID-19

| Class of Drugs | Drug | Drug-Drug Interactions | Notes |
|----------------|------|------------------------|-------|
| Azithromycin  |      | Azithromycin stretches the QT interval, which raises the risk of developing cardiac arrhythmia and torsades de pointes. | Clinical monitoring, and likely serum digoxin levels, are recommended during and after azithromycin therapy is discontinued. |
| Chloroquine   |      | Chloroquine increases the hazard of prolonged QT interval in patients with COVID-19 who is also using Azithromycin. |       |
| Hydroxychloroquine |      | Hydroxychloroquine decreases metabolism of beta-blockers such as carvedilol and metoprolol. |       |
| Hydroxychloroquine |      | Hydroxychloroquine is an inhibitor of the transport system (P-gp). Therefore, increases the serum level of the substrates of this cellular pump inhibitor (such as cyclosporine and digoxin). | QT monitoring may be required. |
| Favipiravir    |      | Coadministration of paracetamol and favipiravir increases paracetamol C<sub>max</sub> and AUC. | In adults, the average dosage of paracetamol does not exceed 3 g/day (rather than 4 g/day). |

---

**Class of Drugs**
- Potential Antiviral Drugs
- Antihyperglycemic Drugs
- Anti-Inflammatory Drugs
- Nutritional Supplements
Lopinavir/Ritonavir (Kaletra®) 28–39

Kaletra is a strong CYP2D6 and CYP3A4 inhibitor. Therefore, Kaletra decreases the pharmacological efficacy of prodrugs that requires enzymatic transformation in the liver to their active metabolite such as prasugrel and clopidogrel. On the contrary, drugs that are metabolized by CYP2D6 or CYP3A4 their serum levels are anticipated to rise dramatically. For instance, coadministration of Kaletra with sildenafil increases the sildenafil’s AUC by 11-fold.

- Kaletra inhibits the metabolism of Rivaroxaban (Xarelto®) and Ticagrelor (Brilinta®); therefore, increasing the risk of bleeding.
- Kaletra accelerates the metabolism of Warfarin; therefore, Kaletra reduces the pharmacological action of Warfarin.
- Kaletra increases the QT interval, thereby raising the risk of cardiac arrhythmia. Due to the obvious potential for severe adverse reactions such as arrhythmia, co-administration of Kaletra and amiodarone, lidocaine, bepridil or quinidine should be avoided.
- Because of the high risk of severe adverse reactions such as rhabdomyolysis, co-administering simvastatin and Kaletra should be avoided.

Remdesivir (Veklury®) 40,41

- Remdesivir effect could be reduced by CYP3A4 inducers such as rifampicin, dexamethasone (at massive doses or with extended duration), phenytoin, carbamazepine, or phenobarbital.
- Chloroquine or Hydroxychloroquine can diminish Remdesivir’s antiviral activity. Therefore, it is not recommended to co-administer such medicines.

Anakinra (Kineret®) 42,43

- Enhances immunosuppression of other immunosuppressants. Therefore, it is not recommended to use it with TNF-blocking agents due to increased risk of infection

Convalescent plasma 44

- No known interactions. However, it may inactivate live vaccines and diminish vaccine effectiveness.

Dexamethasone 45–52

- Dexamethasone enhances the immunosuppression of other immunosuppressants drugs.
- On one hand, CYP3A4 inhibitors, (ex: cyclosporine, diltiazem, estrogens) increase the adverse effects/toxicity of Dexamethasone. On the other hand, CYP3A4 inducers (ex: phenobarbital, phenytoin, rifampicin) decrease the effect of Dexamethasone.
- Dexamethasone may reduce the effect of Isoniazid, Aldesleukin, Caspofungin, Salicylates, Vaccines, &Inhibitors of Cholinesterase.
- Dexamethasone may strengthen the effect and/or toxicity of Warfarin Cyclosporine, and Digoxin (by decreasing serum potassium).

Remdesivir effect could be reduced by CYP3A4 inducers such as rifampicin, dexamethasone (at massive doses or with extended duration), phenytoin, carbamazepine, or phenobarbital. Chloroquine or Hydroxychloroquine can diminish Remdesivir’s antiviral activity. Therefore, it is not recommended to co-administer such medicines.

Drugs should not be added to blood product IV infusion line.

There is a strong opportunity for multiple drug-drug interaction to occur as CYP2D6 and CYP3A4 are responsible for the vast majority of drug metabolisms. To prevent further complications, other antiviral medications like, Remdesivir or Favipiravir would be better alternatives for patients currently using prasugrel, clopidogrel or ticagrelor. ECG monitoring is recommended.

If treatment with an HMG-CoA reductase inhibitor is suggested, the safest alternative would be to use pravastatin. Or you can use a lower dose of the statin drugs to avoid the serious side effects.

No clinical studies have been performed on drug-drug interactions for Remdesivir.

In concurrent therapy with furosemide it is advisable to closely monitor the potassium levels as dexamethasone may cause hypokalemia, the effect of which will be enhanced by furosemide.

Patients taking NSAIDs must be supervised because gastrointestinal ulceration can occur and/or become more severe.
| Adjunctive Medications | Tocilizumab (Actemra®) | Ruxolitinib (Jakafi®) | Sarilumab (Kevzara®) | Acetaminophen (Panadol®) | Bromhexine (Solvodin®) | Famotidine (Pepcid®) | Vitamin C | Concurrent therapy monitoring is required for the CYP450-metabolized drugs.
Patients should be closely monitored for signs of neuropathy in the feet and hands, such as swelling, tingling, discomfort or numbness. Avoid concomitant use of DMARDs with tocilizumab. |
|------------------------|------------------------|----------------------|----------------------|--------------------------|-----------------------|----------------------|------------------|---------------------------------------------------|
| Tocilizumab (Actemra®) | - May increase CYP450 enzyme activity. Therefore, it could decrease the serum levels of many medications that are metabolized by the CYP450, such as Simvastatin.  
- The risk of peripheral neuropathy may be increased during concurrent use with hydroxychloroquine.  
- Coadministration of tocilizumab with immunosuppressive disease-modifying antirheumatic drug DMARDs (such as Leflunomide or Methotrexate) or corticosteroids may lead to serious infections. | - Using rivaroxaban together with Ruxolitinib can increase the risk of bleeding, including severe and occasionally fatal hemorrhage.  
- When Ruxolitinib administered with strong CYP3A4 inhibitors such as Ketoconazole, Fluconazole, And Erythromycin dose modifications is required.  
- Coadministration of Ruxolitinib with immunosuppressive disease-modifying antirheumatic drug DMARDs (such as leflunomide or methotrexate) or immunosuppressive agents (high-dose corticosteroids, tofacitinib, basiliximab, and mycophenolic acid) may lead to serious infections along with lymphoma. | - Using sarilumab together with adalimumab, baricitinib, etanercept, infliximab, may intensify the hazard of serious and potentially life-threatening infections.  
- Sarilumab may increase CYP450 enzyme activity. Therefore, it could decrease blood concentration & efficacy of many drugs that are metabolized by the CYP450, such as Simvastatin, atorvastatin, amiodarone, diazepam, sildenafil, vardenafil, tadalaflit, vinblastine, nifedipine, phenytoin, quinidine, alprazolam, theophylline, methylprednisolone, and dexamethasone.  
- Effects of Sarilumab on CYP450 can continue for weeks following its discontinuation. | - No clinically important unfavorable interactions have been reported with other medicines. | - Famotidine significantly increases the anticoagulant activity of warfarin and intensify the hazard of bleeding.  
- Famotidine reduces the hepatic metabolism of chloroquine, theophylline, phenytoin, propranolol, and lidocaine. | - Affects the excretion of drugs which are weak acids or bases can be diminished or increased, respectively. For instance, fluphenazine & Amphetamine are well-known examples for such interaction.  
- Vitamin C may reduce the anticoagulant activity of warfarin, and cyclosporine. | - The daily dose of paracetamol in adults should be no more than 3000 mg/day (rather than 4000 mg/day) when given with favipiravir.  
- Patients with hepatic impairment may be at increased risk of toxicity. Close monitoring is mandatory in patients concurrently using medications well-known to induce hepatotoxicity such as Remdesivir. |
Taking digoxin together with vitamin D can boost the effects of digoxin and lead to arrhythmia.

Taking large quantities of vitamin D along with diltiazem may reduce the efficacy of diltiazem.

- UFH: increased risk of bleeding with other anticoagulants, antiplatelets, NSAIDs.
- IV nitroglycerin may reduce heparin's anticoagulant effect.
- LMWH: increased risk of bleeding with other anticoagulants, antiplatelets, NSAIDs.

Zinc reduces the absorption of Quinolone & Tetracycline antibiotics (such as, Ciprofloxacin, Gatifloxacin, Moxifloxacin, Levofloxacin, Minocycline and Tetracycline). In addition, Zinc is implicated in hindering the absorption of other antibiotics—instance, Cephalexin. The doses used for COVID-19 in registered clinical trials differ among studies, with a maximum dose of 50 mg (elemental zinc) twice daily.

### Table 2: Drug-Disease interactions of selected experimental therapies for COVID-19

| Class of Drugs | Drug | Drug-Disease Interactions | Notes |
|----------------|------|---------------------------|-------|
| Potential Antiviral Drugs | Azithromycin | - Patients with noninfectious colitis or enteritis are at multiplied hazard of developing pseudomembranous colitis.  
- Azithromycin rises the hazard of prolonged cardiac repolarization and QT in patients with history of torsades de pointes, elongation of the QT interval, bradyarrhythmia, congenital-long QT syndrome, patients with uncorrected hypomagnesemia or hypokalemia, or patients using another drug that prolongs the QT interval.  
- In general, the use of macrolide antibiotics has been reported to worsen symptoms of myasthenia gravis.  

| Chloroquine | - Chloroquine use is commonly considered contraindicated in the presence of retinal or visual field changes.  
- The use of Chloroquine may exacerbate the medical condition in patients with porphyria.  
- Chloroquine rises the risk of elongated cardiac repolarization and QT in patients with history of torsades de pointes, elongation of the QT interval, bradyarrhythmia, congenital-long QT syndrome, patients with uncorrected hypomagnesemia or hypokalemia, or patients using another drug that prolongs the QT interval.  
- Chloroquine may provoke epileptic seizures in prone individuals. Therefore, patients with low seizure threshold or epilepsy may be at greater risk.  
- Chloroquine may provoke acute renal failure and hemolysis in patients with glucose 6 phosphate dehydrogenase (G6PD) deficiency.  
- The use of Chloroquine may incite a severe attack of psoriasis.  

Chloroquine should be ceased immediately if visual abnormalities (e.g., changes in visual acuity, loss of foveal reflex or pigmentary changes) develop.  
It is suggested to use ECG to monitor patients during therapy.  
Both of the hemoglobin and blood cell counts should be checked regularly. | Stool test for C. difficile toxin and stool cultures for C. difficile could be beneficial diagnostically.  
It is suggested to use ECG to monitor patients during therapy.  
If signs and symptoms of hepatitis occur, Azithromycin should be stopped immediately. |
| Drug                                      | Contraindications                                                                 | Caution                                                                                                                                 |
|------------------------------------------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| Hydroxychloroquine (Plaquenil®)          | - Use is commonly considered contraindicated in the presence of retinal or visual field changes.  
- The use of Hydroxychloroquine may exacerbate the medical condition in patients with porphyria.  
- Hydroxychloroquine rises the risk of elongated cardiac repolarization and QT in patients with history of torsades de pointes, elongated of the QT interval, bradyarrhythmia, congenital-long QT syndrome, patients with uncorrected hypomagnesemia or hypokalemia, or patients using another drug that prolongs the QT interval.  
- Hydroxychloroquine may provoke epileptic seizures in prone individuals. Therefore, patients with low seizure threshold or epilepsy may be at greater risk.  
- Hydroxychloroquine may provoke acute renal failure and hemolysis in patients with glucose 6 phosphate dehydrogenase (G6PD) deficiency.  
- The use of Hydroxychloroquine may incite a severe attack of psoriasis. |
| Chloroquine should be ceased immediately if visual abnormalities (e.g., changes in visual acuity, loss of foveal reflex or pigmentary changes) develop.  
- It is suggested to use ECG to monitor patients during therapy.  
- Both of the hemoglobin and blood cell counts should be checked regularly. |
| Favipiravir (Avifavir®)                   | - It is better to be avoided in patients with severely impaired renal or hepatic function |
| Lopinavir/Ritonavir (Kaletra®)           | - Lopinavir/Ritonavir is a known hepatotoxic. Therefore, Kaletra is better to be avoided in patients with hepatic impairment.  
- Patients with hemophilia are at an increased hazard of bleeding when given Lopinavir/Ritonavir.  
- Lopinavir/Ritonavir has been reported to elevate the blood glucose level. Therefore, it should be used with caution in patients with Diabetes Mellitus.  
- Second and third degree atrioventricular (AV) block have been reported with the use of Ritonavir. Therefore, in patients with pre-existing conduction irregularities, underlying heart disease, ischemic heart disease, or cardiomyopathies, Kaletra should be cautiously prescribed because such patients are at greater risk for developing cardiac conduction abnormalities. |
| Hepatic laboratory testing is crucial at baseline and on daily basis during Remdesivir administration.  
Stop Remdesivir if the level of Alanine Aminotransferase (ALT) becomes more than 5 times the upper limit of normal (ULN). |
| Remdesivir (Veklury®)                    | - The use of Remdesivir has been associated with Transaminase elevations in patients with COVID-19 and healthy volunteers. Therefore, Remdesivir should be used with caution in patients with hepatic impairment. |
| Immuno-modulators                        | - Anakinra impedes the immune response. Therefore, Anakinra should not be given to patients with active infections or those who acquire severe infections after administration of Anakinra.  
- Anakinra is mainly excreted by the kidneys. Therefore, in patients with renal dysfunction it should be used with vigilance to prevent toxic reactions.  
- Anakinra should be used with vigilance in patients with hepatic diseases. |
| Patients with severe renal dysfunction or end-stage renal disease should receive the dose of Anakinra every other day.  
Monitoring of renal function is recommended. |
| Medication | Summary | Dosage Adjustments/Advisories |
|------------|---------|-----------------------------|
| Dexamethasone (Decadron®) | - Dexamethasone might cause gastrointestinal hemorrhage and perforation. 
- Dexamethasone impedes the immune response. Therefore, Dexamethasone should not be commenced in actively infected patients or those who develop serious infections after its administration. 
- Dexamethasone can elevate blood glucose level by suppressing the secretion and antagonizing the action of insulin, which leads to augmented gluconeogenesis and suppression of peripheral glucose uptake. Therefore, Dexamethasone should be used with attentiveness in patients with Diabetes Mellitus. 
- Dexamethasone is mostly metabolized in the liver and may have higher pharmacological actions in patients with hepatic disease. 
- The use of dexamethasone in patients recently recovered from myocardial infarction can be related to left ventricular free-wall rupture. Hence, Dexamethasone should be used with extreme caution in myocardial infarction. | Dosage adjustments might be needed in patients with liver disease. |
| Tocilizumab (Actemra®) | - Tocilizumab impedes the immune response. Therefore, Tocilizumab should not be commenced in actively infected patients or those who develop serious infections after its administration. 
- Tocilizumab should be avoided or administered with great attentiveness in patients with hepatic impairment. | Dose adjustment is required in patients with renal impairment. |
| Ruxolitinib (Jakafi®) | - Ruxolitinib impedes the immune response. Therefore, it should not be started in patients with active infections or those who develop serious infections after Ruxolitinib administration. | Dose adjustment required in patients with renal impairment. |
| Sarilumab (Kevzara®) | - Sarilumab may increase the risk of potentially life-threatening infections. Therefore, it should not be started in patients with active infections or those who develop serious infections after Sarilumab administration. 
- Sarilumab is associated with transaminase elevations. Therefore, Sarilumab is not advised for patients with hepatic impairment or active liver disease. | |
| Acetaminophen (Panadol®) | Acetaminophen must be used cautiously in patients with hepatic impairment. | |
| Bromhexine (Solvodin®) | No clinically important unfavorable interactions have been reported with other medicines. | |
| Famotidine (Pepcid®) | Famotidine should be used with caution in patients with impaired kidney function. | Adjustment of the dose is important in patients with renal impairment. |
| Vitamin C | - Vitamin C should be used vigilantly in patients with G6PD. | It is worth mentioning that high circulating concentrations of vitamin C can affect the accuracy of glucometers. |
Vitamin D functions to increase the serum calcium concentration and can make arrhythmias worse, especially in patients taking digoxin. Therefore, high doses of vitamin D should be used cautiously in patients with arrhythmias.

In the presence of hyperphosphatemia, Vitamin D administration may lead to the precipitation of calcium-phosphate deposits within the renal or vascular systems.

Heparin & Low Molecular Weight Heparins (LMWH) significantly increases the risk of bleeding in patients suffering from hemophilia, severe liver disease, hypertensive or diabetic retinopathy, subacute bacterial endocarditis, or severe renal impairment.

The trace metals, chromium and zinc, are excreted primarily in the urine. Supplemental doses of zinc may need to be reduced, or adjusted in patients with renal impairment.

Malabsorption syndromes reduce the amount of absorbed zinc. Therefore, larger dosages may be needed when zinc is given orally.

Long-term zinc intake may cause copper deficiency with associated reversible hematological defects (i.e., leukopenia, anemia) and possibly permanent neurological implications (i.e., paresthesia, myelopathy, spasticity, and ataxia).

**Discussion**

Comorbid patients need several pharmacological treatments, which in turn may lead to issues that physicians are expected to handle rapidly by recognizing potential drug-drug interactions that could arise in order to prevent diminished efficacy or increased adverse event burden. To put simply, the issue of whether concurrent pharmacological therapies that compromise patient safety is typically answered in a context that recognizes the treatment choices for each particular disease, enabling reasonable handling of interactions based on reliable clinical evidence. However, in the case of comorbid conditions happening in COVID-19 patients, healthcare professionals now are needed to consider the hard question as to whether interactions between COVID-19 pharmacological treatments, which are not yet well-defined, and various therapeutic agents are possible. Moreover, while waiting for the results from more than 300 ongoing clinical trials aimed at identifying successful treatments against the COVID-19 virus, how drugs used in COVID-19 patients (e.g., various Antiviral Agents, Azithromycin, Hydroxychloroquine, and Monoclonal Antibodies) that redundantly disturb the pharmacodynamics and pharmacokinetics of other drugs, and vice versa, remains a topic of investigation. Therefore, focus is put on the interactions between the medications most widely used for COVID-19 and various classes of medications (Table 1) and the most important drug-disease interaction in (Table 2).

Given the range of potential interactions with hepatic metabolism systems, such as Cytochromes P450 (CYPs), as most of the existing antiviral medications used in COVID-19 infection are expected to affect various CYP450 isozymes. Therefore, dose adjustments may be needed. Some of the most challenging drug-drug interactions are between investigational COVID-19 medicines and cardiovascular medicines, including anti-arrhythmias, beta-blockers, calcium channel blockers, anti-coagulants, and lipid-lowering statins. Antibacterial medications are another significant class; many have a defined effect on the QT interval, and others may alter the level of a COVID-19 drug, a co-medication, or both in the body. For instance, Rifampicin can reduce the serum level of the experimental COVID-19 medication ritonavir/lopinavir by 75%.
References

1. Jagadeesan M, Manikandan R, Sudha NSS. The drug-drug interactions: Affecting the rationality of prescriptions. Research Journal of Pharmacy and Technology 2018; 11:3077–80.
2. Pallierà C, di Paolo A, Griefò C, et al. Pharmacokinetic drug-drug interaction and their implication in clinical management. Journal of Research in Medical Sciences. 2013; 18:600–9.
3. Kafeel H, Rukh Q, Qamar H, et al. Possibility of Drug-Drug Interaction in Prescription Dispensed by Community and Hospital Pharmacy. Pharmacology & Pharmacy 2014; 5:041.
4. Back D, Marzolin C, Hodge C, et al. COVID-19 treatment in patients with comorbidities: Awareness of drug-drug interactions. British Journal of Clinical Pharmacology. 2020. DOI:10.1111/bcp.14358.
5. Patil PA, Jain RIKs. Theoretical Study and treatment of Novel COVID-19. Research Journal of Pharmacology and Pharmacodynamics 2020; 12:71.
6. Worldometer. Coronavirus Cases. Worldometer 2020; 1–22.
7. Gauthret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. International Journal of Antimicrobial Agents 2020; 56. DOI:10.1016/j.ijantimicag.2020.105949.
8. Saleh M, Gabriès J, Chang D, et al. Effect of Chloroquine, Hydroxychloroquine, and Azithromycin on the Corrected QT Interval in Patients with SARS-CoV-2 Infection. Circulation: Arrhythmia and Electrophysiology 2020; 13:496–504.
9. Nachimuthu S, Assar MD, Schussler M. Drug-induced QT interval prolongation: Mechanisms and clinical management. Therapeutic Advances in Drug Safety. 2012; 3:241–53.
10. Sears SP, Getz TW, Austin CO, Palmer WC, Boyd EA, Stancampiano FF. Incidence of Sustained Ventricular Tachycardia in Patients with Prolonged QTc After the Administration of Azithromycin: A Retrospective Study. Drugs - Real World Outcomes 2016; 3:99–105.
11. Glaskow SS, Fugil KV, Prochazka AV. The risk of overtreatment with antibiotic use in outpatients on stable warfarin regimens. Journal of General Internal Medicine 2005; 20:653–6.
12. Smit C, Peeters MYM, van den Anker JN, Knibbe CAJ. Chloroquine for SARS-CoV-2: a comprehensive literature review of its Unique Pharmacokinetic and Safety Properties. Clinical Pharmacokinetics 2020; 59:659–69.
13. Mercuro NJ, Yen CF, Shim DJ, et al. Risk of QT Interval Prolongation Associated with Use of Hydroxychloroquine with or without Concomitant Azithromycin among Hospitalized Patients Testing Positive for Coronavirus Disease 2019 (COVID-19). JAMA Cardiology. 2020. DOI:10.1001/jamacardio.2020.1834.
14. Bessière F, Roccia H, Delinière A, et al. Assessment of QT Intervals in a Case Series of Patients with Coronavirus Disease 2019 (COVID-19) Infection Treated With Hydroxychloroquine Alone or in Combination With Azithromycin in an Intensive Care Unit. JAMA Cardiology. 2020. DOI:10.1001/jamacardio.2020.1787.
15. Hasler JA, Johansson I, Masmimsembwa CM. Inhibitory effects of antiparasitic drugs on cytochrome P450 2D6. European Journal of Clinical Pharmacology 1995; 48:35–8.
16. Gupta A. Real-World Clinical Effectiveness and Tolerability of Hydroxychloroquine 400 Mg in Uncontrolled Type 2 Diabetes Subjects who are Not Willing to Initiate Insulin Therapy (HYQ-Real-World Study). Current Diabetes Reviews 2019; 15:510–9.
17. Nangoumeo HN, Nessim J, Gupta RK, Johny K. V. Drug interaction of chloroquine with cephosporin [1]. Nephron. 1992; 62:108–9.
18. Juurlink DN. Safety considerations with chloroquine, hydroxychloroquine and azithromycin in the management of SARS-CoV-2 infection. CMAJ. 2020; 192:E450–3.
19. Projean D, Baune B, Farpinetti R, et al. In vivo metabolism of chloroquine: Identification of CYP2C8, CYP3A4, and CYP2D6 as the main isoforms catalyzing N-desethylchloroquine formation. Drug Metabolism and Disposition 2003; 31:748–54.
20. Johnson MI, Radford H. CYP2D6 Polymorphisms and Response to Codeine and Tramadol. Analgésia & Reanudación: Current Research 2016; 05. DOI:10.4172/2322-2543.E100016.
21. Cazet L, Buleau S, Evin A, et al. Interaction between CYP2D6 inhibitor antidepressants and codeine: is this relevant? Expert Opinion on Drug Metabolism and Toxicology 2018; 14:879–86.
22. Stevenson A, Kireesh A, Conway S, White L, Ahmad M. Little C. Hydroxychloroquine use in COVID-19: is the risk of cardiovascular toxicity justified? Open heart 2020; 7. DOI:10.1136/openhrt-2020-001362.
23. Rosenberg ES, Dufort EM, Udo T, et al. Association of Treatment with Hydroxychloroquine or Azithromycin with In-Hospital Mortality in Patients with COVID-19 in New York State. JAMA - Journal of the American Medical Association 2020; 323:2493–502.
24. Bonov RO, Hernandez AF, Turakhia M. Hydroxychloroquine, Coronavirus Disease 2019, and QT Prolongation. JAMA Cardiology. 2020. DOI:10.1001/jamacardio.2020.1782.
25. reviews AG-C, diabetes 2019 undefined. Real-world clinical effectiveness and tolerability of hydroxychloroquine 400 mg in uncontrolled type 2 diabetes subjects who are not willing to initiate insulin therapy. ingestion. https://www.deaconnect.com/content/bcm/jcr/2019/00000015/00000006/art00010 (accessed Aug 25, 2020).
26. Shiraki K, Daikoku T. Favipiravir, an anti-influenza drug against life-threatening RNA virus infections. Pharmacology and Therapeutics. 2020; 209:107512–107512.
27. Zhao Y, Hartzett JS, Epstein CR, et al. Favipiravir inhibits acetaminophen sulfate formation but minimally affects systemic pharmacokinetics of acetaminophen. British Journal of Clinical Pharmacology 2015; 80:1076–85.
28. Ancrenaz V, Dégon J, Samei C, et al. Pharmacokinetic Interaction Between Prasugrel and Ritonavir in Healthy Volunteers. Basic and Clinical Pharmacology and Toxicology 2013; 112:132–7.
29. Hughes CA, Tseng A, Cooper R. Managing drug interactions in HIV-infected adults with comorbid illness. CMAJ. 2015; 187:36–43.
30. Hu S, Grammnan GR, Bertz RJ, Ritonavir: Clinical pharmacokinetics and interactions with other anti-HIV agents. Clinical Pharmacokinetics 1998; 35:275–91.
31. Elens L, Langman LJ, Hesselink DA, et al. Pharmacologic Treatment of Transplant Recipients Infected With SARS-CoV-2: Considerations Regarding Therapeutic Drug Monitoring and Drug-Drug Interactions. Therapeutic drug monitoring. 2020; 42:360–8.
32. Zeitlinger M, Koch BCP, Bruggemann R, et al. Pharmacokinetics/Pharmacodynamics of Antiviral Agents Used to Treat SARS-CoV-2 and Their Potential Interaction with Drugs and Other Supportive Measures: A Comprehensive Review by the PK/PD of Anti-Infectives Study Group of the European Society of Antimicrobial Agents. Clinical Pharmacokinetics. 2020. DOI:10.1007/s40262-020-00924-9.
33. ida, oner: KALIFTRA® (lopinavir/ritonavir) capsules. repository. https://www.drugs.com/medication/08698884.html.
34. Liebert MD, Rathbun RC, Warfarin-antiretroviral interactions. Annals of Pharmacotherapy. 2009; 43:322–8.
35. Bates DE, Herman RJ, Carbamazepine toxicity induced by lopinavir/ritonavir and nelfinavir. Annals of Pharmacotherapy 2006; 40:1190–5.
36. Pecora Fuku P, Zingoni NM, Higson RT. Possible antiretroviral therapy-warfarin drug interaction. Pharmacotherapy 2008; 28:945–9.
37. Hughes CA, Freitas A, Miedzinski LJ. Interaction between lopinavir/ritonavir and warfarin. CMAJ 2007; 177:357–9.
38. Experimental COVID-19 Therapy Combination Lopinavir/Ritonavir Is Implicated in a Complicated Set of Drug-Drug Interactions- Anesthesia Patient Safety
Radhwan Nidal Al-Zidan

Journal of Drug Delivery & Therapeutics. 2020; 10(6):219-230

QT-Prolonging and Torsadogenic Potential of Possible Pharmacotherapies for Coronavirus Disease 19 (COVID-19). Mayo Clinic Proceedings. 2020; 95:213–21.

Ghasemiyeh P, Borhani-Haghighi A, Karimzadeh, et al. Major neurologic adverse drug reactions, potential drug-drug interactions and pharmacokinetic aspects of drugs used in covid-19 patients with stroke: A narrative review. Therapeutics and Clinical Risk Management. 2020; 16:595–605.

Maus M V, Lionakis MS. Infections associated with the new "nibs and mabs" and cellular therapies. Current opinion in infectious diseases 2020; 33:281–9.

Antinori S, Bonazzetti C, Subburini G, et al. Tocilizumab for cytokine storm syndrome in COVID-19 pneumonia: an increased risk for candidacy? Autoimmunity Reviews. 2020; 19. DOI:10.1016/j.autrev.2020.102564.

Morel J, Constantin A, Baron G, et al. Risk factors of serious infections in patients with rheumatoid arthritis treated with tocolizumab in the French Registry REGATE. Rheumatology (United Kingdom). 2017; 56:1746–54.

XARELTO® (rivaroxaban): A Prescription Blood Thinner | JAXEL® (tofacitinib). 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209192s015lbl.pdf. (accessed Aug 26, 2020).

FDA. HIGHLIGHTS OF PRESCRIBING INFORMATION FOR JAKAFI® (ruxolitinib). 2017 https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/202192s015lbl.pdf. (accessed Aug 26, 2020).

Lee EB, Daskalakis N, Xu C, et al. Disease–Drug Interaction of Sarilumab and Simvastatin in Patients with Rheumatoid Arthritis. Clinical Pharmacokinetics. 2018; 57:607–15.

Hughes GP, Patel PN, Saxena N. Effect of acetylaminohep on international normalized ratio in patients receiving warfarin therapy. Pharmacotherapy. 2011; 31: 591–7.

Gebauer MG, Nyfort-Hansen K, Henschke PJ, Gallas AS. Warfarin and acetylsalicylic acid. Pharmacotherapy 2003; 23:109–12.

Sorkin EM, Darvey DL. Review of cimetidine drug interactions. Drug Intelligence and Clinical Pharmacy. 1983; 17: 110–20.

FDA. Cimetidine. 1998. https://www.accessdata.fda.gov/drugsatfda_docs/label/1998/75285s02.pdf. (accessed Aug 26, 2020).

A Multi-site, Randomized, Double-Blind, Comparative Trial of the Safety and Efficacy of Standard of Care (SOC) Plus Favipiravir vs SOC Plus Placebo for the Treatment of COVID-19 in Hospitalized Adults. 2020; published online April 7. https://clinicaltrials.gov/ct2/show/NCT04370262 (accessed Aug 27, 2020).

Holbrook AM, Pereira JA, Labiris R, et al. Systematic overview of warfarin and its drug and food interactions. Archives of Internal Medicine. 2005; 165: 1095–106.

FDA, Cider. HIGHLIGHTS OF PRESCRIBING INFORMATION OF ASCORB (ascorbic acid). 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/75285s02.pdf. (accessed Aug 26, 2020).

Robien K, Oppeneer SJ, Kelly JA, Hamilton-Reeves JM. Drug–Vitamin D Interactions. Nutrition in Clinical Practice 2013; 28:194–208.
76 Mousa SA. Comparative efficacy of different low-molecular-weight heparins (LMWHs) and drug intervention with LMWH: Implications for management of vascular disorders. In: Seminars in Thrombosis and Hemostasis. Semin Thromb Hemost, 2000: 39–46.

77 Cohen M. Combination of low molecular weight heparins with antplatelet agents in non-ST elevation acute Coronary syndromes: An update. Drugs. 2002; 62: 1755–70.

78 FDA. cder. Innohep (tinzaparin sodium injection). http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020480s014lbl.pdf (accessed Aug 26, 2020).

79 HIGHLIGHTS OF PRESCRIBING INFORMATION OF Lovenox (enoxaparin sodium injection). 1993 https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020164s051lbl.pdf (accessed Aug 26, 2020).

80 Ding Y, Jia Y, Li F, et al. The effect of staggered administration of zinc sulfate on the pharmacokinetics of oral cephalixin. British Journal of Clinical Pharmacology 2012; 73:22–7.

81 Uivarios V. Metal complexes of quinolone antibiotics and their applications. An update. Molecules. 2013; 18:11153–97.

82 Bartlett JG, Chang te W, Gurr with M, Gorbach SL, Onderdonk AB. Antibiotic-Associated Pseudomembranous Colitis Due to Toxin-Producing Clostridia. New England Journal of Medicine 1978; 298:531–4.

83 Farooq O, Memon Z, Stoianovski SD, Faden HS. Azithromycin-induced agitation and choreoathetosis. Pediatric Neurology 2011; 44:311–3.

84 Bhattacharyya S, Darby R, Berkowitz AL. Antibiotic-Induced Neuropathy. Current Infectious Disease Reports. 2014; 1: 1–6.

85 Pradhan S, Pardasani V, Ramteke K. Azithromycin-induced myasthenic crisis: Reversibility with calcium gluconate. Neurology India 2009; 57:352.

86 Chorin E, Wadhwa L, Magnani S, et al. QT interval prolongation and torsade de pointes in patients with COVID-19 treated with hydroxychloroquine/azithromycin. Heart Rhythm 2020; published online Sept 1.

87 Hancock JC, Vieweg WW, Harin N, Mousseau ELB, Baranchuk A. Azithromycin, cardiovascular risks, QTc interval prolongation, torsade de points, and regulatory issues: A narrative review based on the study of case reports. Therapeutic Advances in Infectious Disease 2013; 1:153–65.

88 Herman BE, Vargo JS, Phillips WS, Sweeney WB, Volpe RJ. Antibiotic-Associated Fulminant Pseudomembranous Colitis without Toxic Megacolon. The American Journal of Gastroenterology 1992; 87:1816–9.

89 FDA. ARALEN® CHLOROQUINE PHOSPHATE, USP. 2003 https://www.accessdata.fda.gov/drugsatfda_docs/label/2001/006002s043lbl.pdf (accessed Aug 27, 2020).

90 Vanheesbeke A. Retinal pigment epithelium—the point of safety about antimarial agents. Bulletin de la Société belge d’ophthalmologie. 2007; 47–58.

91 Cursiefen C, Grunert U, Jüenemann A. Chloroquine-induced bull’s-eye maculopathy without electrophysiologic changes. Klinische Monatsblätter für Augenheilkunde. 1997; 210:400–1.

92 Rossmann-Ringdahl I, Olsson R. Porphyria cutanea tarda: Effects and risk factors for hepatotoxicity from high-dose chloroquine treatment. Acta Dermato-Venereologica-2007; 87:401–5.

93 Fish DR, Espir MLE. Convulsions associated with prophylactic antimarial drugs: Implications for people with epilepsy. British Medical Journal 1988; 297:526–7.

94 Benbadis SR, van Ness PC, Mulhausen P, Alleman Y, Regamey C. Chloroquine and nonconvulsive status epilepticus. Annals of Internal Medicine. 1996; 124:614–5.

95 Vesty JP, Savin JA. Psoriasis worsened by antimarial prophylaxis. Journal of Infection. 1992; 24:211–2.

96 Balak D, Hajdarevigo C. Drug-induced psoriasis: clinical perspectives. Psoriasis: Targets and Therapy 2017; Volume 7: 87–94.

97 Okor RS. ONSET OF PRURITOGENNICY OF CHLOROQUINE AND THE IMPLICATION FOR THE TIMING OF SUPPRESSIVE THERAPY. Journal of Clinical Pharmacy and Therapeutics 1991; 16:463–5.

98 FDA. cder. UNILEN® HYDROXYCHLOROQUINE SULFATE TABLETS, USP. DESCRIPTION. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/009768s037s045s047lbl.pdf (accessed Aug 27, 2020).

99 Sanders [M, Monogue ML, Jedlowicz TZ, Catrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. JAMA – Journal of the American Medical Association. 2020; 323:1824–36.

100 CDC. Avigan (favipiravir) tablets. 2017 https://www.cdc.gov/govtv/File/Get/hr18j0ib_MI-akhntszwzv (accessed Aug 27, 2020).

101 Gorbett TH, Lim ML, Kashuba AD, Malnondao WT, Larouche M, Kaleatra (lopinavir/ritonavir). Annals of Pharmacotherapy 2002; 36:1193–203.

102 Pai VB, Koranyi K, Nahata MC. Acute hepatitis and bleeding possibly induced by zidovudine and ritonavir in an infant with HIV infection. Pharmacotherapy 2000; 20:1135–40.

103 Danner SA, Carr A, Leonard JM, et al. A short-term study of the safety, pharmacokinetics, and efficacy of ritonavir, an inhibitor of HIV-1 protease. New England Journal of Medicine 1995; 333:1528–34.

104 Hardy H, Fisch LD, Morse GD. Glucose disorders associated with HIV and its drug therapy. Annals of Pharmacotherapy. 2001; 35:343–51.

105 Calza L, Manfredi R, Chiado F. Insulin Resistance and Diabetes Mellitus in HIV-Infected Patients Receiving Antiretroviral Therapy. Metabolic syndrome and related disorders 2004; 2:241–50.

106 Fathallah N, Slim R, Larif S, Hmouda H, ben Salem C. Drug-Induced Hyperglycaemia and Diabetes. Drug Safety. 2015; 38:1153–68.

107 Grein J, Olmagni N, Shin D, et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. New England Journal of Medicine 2020; 382:2327–36.

108 Administration D. FACT SHEET FOR HEALTH CARE PROVIDERS EMERGENCY USE AUTHORIZATION (EUA) OF VEKLURY® (remdesivir). https://www.fda.gov/emergency- (accessed Aug 27, 2020).

109 Ahmed O, Brahmiana M, Alshahi M, Alkhawaiter S, Erb S. Anakina Hepatotoxicity in a Patient With Adult-Onset Still’s Disease. REPORTS JOURNAL acgcasereports.org. AGG Case Reports Journal 2015; 2.

110 Yang BB, Boughman S, Sullivan JT. Pharmacokinetics of anakinra in subjects with different levels of renal function. Clinical Pharmacology and Therapeutics 2003; 74:85–94.

111 Galloway JB, Hyrich KL, Mercer LK, et al. The risk of serious infections in patients receiving anakinra for rheumatoid arthritis: Results from the British Society for Rheumatology Biologics Register. Rheumatology. 2011; 50:1341–2.

112 FDA. DECADRON® (DEXAMETHASONE TABLETS, USP). https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/11664s062_decadron_lbl.pdf (accessed Aug 27, 2020).

113 Wong V, Lelfoch N, Crawford JR. Fatal gastrointestinal hemorrhage in a young boy with newly diagnosed metastatic medulloblastoma on high dose dexamethasone. Case reports in pediatrics 2014; 2014:478326.

114 Fadul CR, Leman W, Thaler HT, Posner JB. Perforation of the gastrointestinal tract in patients receiving steroids for neurologic disease. Neurology 1988; 38:348–52.

115 DeMaria EJ, Reichman W, Kenney PR, Armitage JM, Galloway JB, Hyrich KL, et al. Re: Fadul CR, Leman W, Thaler HT, Posner JB. Perforation of the gastrointestinal tract in patients receiving steroids for neurologic disease. Neurology 1988; 38:348–52.

116 DeMaria EJ, Reichman W, Kenney PR, Armitage JM, Galloway JB, Hyrich KL, et al. Re: Fadul CR, Leman W, Thaler HT, Posner JB. Perforation of the gastrointestinal tract in patients receiving steroids for neurologic disease. Neurology 1988; 38:348–52.

117 Ludvik B, Clodi M, Kautzky-Willer A, et al. Effect of desamethasone on insulin sensitivity, islet amyloid...
polypeptide and insulin secretion in humans. Diabetologia 1993; 36:84–7.

118. CUNFFI BJ, BURTON JL, HOLTI G, WRIGHT V. Hazards of steroid therapy in hepatic failure. British Journal of Dermatology 1975; 93:83–5.

119. Coloma PM, Schuermie MJ, Trifrìò G, et al. Drug-Induced Acute Myocardial Infarction: Identifying “Prime Suspects” from Electronic Healthcare Records-Based Surveillance System. PLoS ONE 2013; 8(1): e51771. DOI:10.1371/journal.pone.0072148.

120. Shokr M, Rashed A, Lata K, Kondur A. Dexamethasone-Associated ST Elevation Myocardial Infarction Four Days after an Unremarkable Coronary Angiogram—Another Reason for Cautious Use of Steroids: A Case Report and Review of the Literature. Case Reports in Cardiology 2016; 2016:1–6.

121. Varas-Lorenzo C, Rodriguez LAG, Maguire A, Castellsague J, Perez-Guthmann S. Use of oral corticosteroids and the risk of acute myocardial infarction. Atherosclerosis 2007; 192:376–83.

122. Dele Davies H. Infectious complications with the use of biologic response modifiers in infants and children. Pediatrics 2016; 138: DOI:10.1542/peds.2016-1209.

123. Drepper M, Rubbia-Brandt L, Spahr L. To clizumab-Induced Acute Liver Injury in Adult Onset Still’s Disease. Case Reports in Hepatology 2013; 2013:1–3.

124. Lussana F, Cattaneo M, Rambaldi A, Squizzato A. Ruxolitinib-associated infections: A systematic review and meta-analysis. American Journal of Hematology 2018; 93:339–47.

125. Sylvine P, Thomas S, Pirayeh B. Infections associated with ruxolitinib: study in the French Pharmacovigilance database. Annals of Hematology. 2018; 97:913–4.

126. Fleischmann R, Genovese MC, Lin Y, et al. Longterm safety of sarilumab in rheumatoid arthritis: an integrated analysis with up to 7 years’ follow-up. Rheumatology (Oxford, England) 2020; 59:292–302.

127. Yow CH, Gaber A, Choudhary M, Kutter M, Pyrsopoulos N. Acetaminophen-Induced Hepatotoxicity: a Comprehensive Update. Journal of Clinical and Translational Hepatology 2016; 4:131.

128. Inotsune N, Nishimura M, Fujiyama S, et al. Pharmacokinetics of famotidine in elderly patients with and without renal insufficiency and in healthy young volunteers. European Journal of Clinical Pharmacology 1989; 36:517–20.

129. Lin JH, Chremos AN, Yeh KC, Antonello J, Hessey GA. Effects of age and chronic renal failure on the urinary excretion kinetics of famotidine in man. European Journal of Clinical Pharmacology 1988; 34:41–6.

130. Halstenen CE, Abraham PA, Opsahl JA, Chremos AN, Keane WF, Matzke GR. Disposition of Famotidine in Renal Insufficiency. The Journal of Clinical Pharmacology 1987; 27:3–7.

131. Quan J, Gerber B, Fouche R, Kenyon K, Blom Z, Muthukaragai P. Effect of High-Dose Vitamin C Infusion in a Glucose-6-Phosphate Dehydrogenase-Deficient Patient. Case Reports in Medicine 2017; 2017: DOI:10.1155/2017/520660.

132. Liu X, Wang W, Tan Z, et al. The relationship between vitamin D and risk of atrial fibrillation: A dose-response analysis of observational studies. Nutrition Journal. 2019; 18:73.

133. Moe SM. Disorders Involving Calcium, Phosphorus, and Magnesium. Primary Care - Clinics in Office Practice. 2008; 35:21–37.

134. Michos ED, Blumenthal RS. Vitamin D supplementation and cardiovascular disease risk. Circulation. 2007; 115:827–8.

135. Hinnensteil JA, LaRiviere WB, Colbert JF, Langoët-Astrée C, Smith JP, Heparin as a therapy for COVID-19: current evidence and future possibilities. American journal of physiology. Lung cellular and molecular physiology. 2020; 319:L211–7.

136. Mika P, Béhounek J, Skoták M, Nevalimá L. Complications and risks associated with an anticoagulation therapy combining low molecular weight heparin and warfarin after total replacement of large joints - Our experience. Acta Chirurgiae Orthopaedicae et Traumatologicae Cechoslovaica 2004; 71:237–44.

137. FDA, cder. HIGHLIGHTS OF PRESCRIBING INFORMATION of HEPARIN SODIUM IN SODIUM CHLORIDE INJECTION. 2019 https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/018916s063,019339s052,019805s034lbl.pdf (accessed Aug 26, 2020).

138. Medicine I. of. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. National Academies Press, 2001 DOI:10.17226/10026.

139. Freeland-Graves JH, Friedman BJ, Wu-Hsin Han, Shorey RL, Young R. Effect of zinc supplementation on plasma high-density lipoprotein cholesterol and zinc. American Journal of Clinical Nutrition 1982; 36:988–92.

140. Johnson AR, Munoz A, Gottleib JL, Jarrard DF, High Dose Zinc Increases Hospital Admissions Due to Genitourinary Complications. Journal of Urology 2007; 177: 639–43.

141. Lewis MR, Kolan L. Zinc Glucorate: Acute Ingestion. Journal of Toxicology - Clinical Toxicology 1999; 36:99-101.

142. Pharmacology JS, B, 2008. undefined. A global view of drug-therapy interactions. search.ebscohost.com /http://search.ebscohost.com/login.aspx?direct=true&profile=ehost&site=ehost&scope=site&authtype=crawler&jrnl=14712210&bdata=J4K 2017/01039016.

143. Palleria C, Paolo A di, Giorel C, ... CC-J of research in, 2013 undefined. Pharmacokinetic drug—drug interaction and their implication in clinical management. ncbi.nlm.nih.gov https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3897029/ (accessed Aug 25, 2020).

144. Lorenzo G di, Trolis R di, Kozlakidis Z, ... GB-CR in, 2020 undefined. COVID 19 therapies and anti-cancer drugs: A systematic review of recent literature. Elsevier https://www.sciencedirect.com/science/article/pii/S104889402030030X (accessed Aug 25, 2020).

145. Sanders J, Monague M, Jodlowski T, Jama C-, 2020 undefined. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. jamanetwork.com https://jamanetwork.com/journals/jama/article-abstract/2764727 (accessed Aug 25, 2020).

146. Swapna G, Pravallika B, Poojitha J. A Review on Drug—drug interaction studies on Amiodarone and Levofoxicin. Research Journal of Pharmacology and Pharmacodynamics 2019; 11:147.

147. Radhwan N Al-Zidan, Ahmed S, Saadallah G, Ghyath M Abdulrahazzag. The public health dilemma of Self-Medication with Antibiotics: The undergraduate students of the College of Pharmacy in Mosul as an example. International Journal of Research in Pharmaceutical Sciences 2020; 11:3743–5.

148. Rabie MM, Paed H, Denti P, Melleron H, et al. Lopinavir-ritonavir super-boosting in young HIV-infected children on rifampicin-based tuberculosis therapy compared with lopinavir-ritonavir without rifampicin: A pharmacokinetic modelling and clinical study. 2018. DOI:10.1016/S2352-3018(18)30293-5.