

Supplementary Material: Drug interactions for patients with respiratory diseases receiving COVID-19 emerged treatments

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The supplementary file contains additional information as supplementary tables regarding the scientific data that were presented in the manuscript regarding detailed cases of PK and/or PD interactions that could lead in occurrence of ADRs for COVID-19 patients.

Table S1. Substrates, inducers and inhibitors for transport proteins, metabolic enzymes and plasma proteins for drugs that are discussed in this work. (X: inhibitor, S: substrate, I: inducer)

		Transport proteins				Metabolizing enzymes			Plasma proteins
Drugs for COVID-19		P-gp	OATP/ OCTP	MATE	BCRP	CYP3A	CYP2D6	Other CYPs or other enzymes	albumin
Antivirals									
	Darunavir	X				X	X		
	Fabifavir		X (OAT1 & OAT3)					X (CYP2C8, AO, XO)	
	Lopinavir/ Ritonavir	X	X OATP1A2, OATP1B1, OATP1B3, OATP2B1		X	X			
	Remdesivir		X (OATP 1B1/1B3)	X		X			
Antimicrobials									
	Azithromycin	X	X OATP1A2 OATP2B1			X			X UGT1A1
	Ivermectin	S				S			
	Nitazoxanide								S
Immunomodulators									
	Anakinra, Canakinumab, Sarilumab, Tocilizumab					Increasing enzymatic abundance			
	Baricitinib	S	S			S			
	Colchicine	S				S			
	Dexamethasone								
	Hydrocortisone	I	I (OATP2)			I (+CYP3A11)			
	Methylprednisolone								
	Ruxolitinib					S		S (CYP1A2, CYP2C9, CYP2B6)	
Medications for respiratory diseases									
	Xanthines					S		S (CYP1A2, CYP2C9,)	
	zafirlukast					S			
	Montelukast					S			
	Astemizole					S			
	Cetirizine/levocetirizine						S		

Table S2. Drug-Drug interactions between emerged treatments for COVID-19 and other medications (Clinical Significance: Serious–Use alternative= +++, Use with caution–Monitor= ++, moderate–minor=+)

Drugs in COVID-19		DDI	Biological Pathways involved/ Clinical result	Clinical significance	Examples of drugs that can be result in DDIs
Antivirals	Atazanavir	PK	CYP3A4, UGT1A1 (inhibitor)	+++	NRTIs, NNRTIs, anti-HCV, irinotecan, amiodarone, quinidine, diltiazem, bepridil, statins
	Darunavir	PK	CYP3A4, CYP2D6, P-gp (inhibitor)	+++	alfuzosin, DOACs, PAIs, anticoagulants, anticonvulsants SSRIs, TCAs, antipsychotics, voriconazole, colchicine, cisapride, β -blockers, Ca2+blockers, ranolazine, ivabradine, statins
	Favipavir	PK	AO, CYP2C8	+	amodiaquine, cerivastatin, dasabuvir, enzalutamide, imatinib, loperamide, montelukast, paclitaxel, pioglitazone, repaglinide, and rosiglitazone
	Lopinavir/ ritonavir	PK	CYP3A4, OATP1A2, OATP1B1, OATP1B3, OATP2B1, BCRP	+++	colchicine, alfuzosin, ranolazine, antiarrhythmics, statins, lomitapide, anticoagulants, astemizole, terfenadine, tadalafil
	Remdesivir	PK	CYP3A, OATP1B1, OATP1B3, MATE1	++	Dexamethasone, rifampicin, barbiturates, ACE inhibitors, antiviral agents, beta-lactam antibiotics, antineoplastics, metformin, NSAIDs, antiandrogens, barbiturates, statins, midazolam
	Ribavirin	PD	myelosuppression, hepatotoxicity, pancreatitis hypoprothrombinemic, anti-HIV	+++	6-mercaptopurine, azathioprine, didanosine, bexarotene, anticoagulants, NRTIs
Antimicrobial	Azithromycin	PK	P-gp, OATP1A2, OATP2B1, CYP3A	++	betrixaban, digoxin, antacids, nelfinavir, fluconazole, cyclosporin
	Azithromycin, Chloroquine, Hydroxychloroquine	PD	hERG -> QT-prolongation	+++	amifampridine; amiodarone; amisulpride; amitryptiline; apomorphine; bedaquiline; bosutinib; cabozantinib; ceritinib; chlorpromazine; ciprofloxacin; cisapride; citalopram; clarithromycin; clomipramine; crizotinib; dasatinib; delamanid; deofetilide; desipramine; disopyramide; dolasetron; doxepin; dronedarone; droperidol; efavirenz; encorafenib; eribulin; erythromycin; escitalopram; flecainide; fluconazole; fluoxetine; haloperidol; hydroxyzine; ibutilide; imipramine; inotuzumab; itraconazol; eketoconazol; elapatinib; lenvatinib; levofloxacin; levomepromazine; lithium; lofexidine; methadone; moxifloxacin; nilotinib; ondansetron; paliperidone; pazopanib; pimozone; procainamide; quetiapine; quinine; ranolazine; ribociclib; risperidone; saquinavir; sertraline; sildenafil; sorafenib; sotalol; sulpiride; sumatriptan; sunitinib; tetrabenazine; thioridazine; tizanidine; tolterodine; toremifene; vandetanib; vardenafil; vemurafenib; venlafaxine; voriconazole; ziprasidone; zolmitriptan
		PD	Convulsion threshold	+++	antiepileptics
		PD	Glucose homeostasis	++	Diabetes I drugs
		PD	ANS	+	parasympathomimetics
	Ivermectin	PK	P-gp, CYP3A	++	clarithromycin, erythromycin, diltiazem, ranolazine, itraconazole, ketoconazole, ritonavir, verapamil, grapefruit
	Nitazoxanide	PK	Protein binding affinity	++	benzodiazepines, warfarin, valproic acid

Immunomodulators	Anakinra, Canakinumab Sarilumab Tocilizumab	PK	CYP abundance	++	CYP substrates, especially drugs of narrow therapeutic index atorvastatin, calcium channel blockers, theophylline, warfarin, phenytoin, ciclosporin, benzodiazepines etc.
	Baricitinib	PK	OAT3	+++	probenecid
		PD	immunosuppression	+++	JAK inhibitors or other biologic DMARDs
	Colchicine	PK	P-gp, CYP3A (substrate)	++	clarithromycin, erythromycin, diltiazem, ranolazine, itraconazole, ketoconazole, ritonavir, verapamil, grapefruit
	Fingolimod	PD	immunosuppression	+++	immunomodulating agents
			hERG -> QT-prolongation	+++	amifampridine; amiodarone; amisulpride; amitriptyline; apomorphine; bedaquiline; bosutinib; cabozantinib; ceritinib; chlorpromazine; ciprofloxacin; cisapride; citalopram; clarithromycin; clomipramine; crizotinib; dasatinib; delamanid; deofetilide; desipramine; disopyramide; dolasetron; doxepin; dronedarone; droperidol; efavirenz ;encorafenib; eribulin; erythromycin; escitalopram; flecainide; fluconazole; fluoxetine; haloperidol; hydroxyzine; ibutilide; imipramine; inotuzumab; itraconazol; ketoconazol; elapatinib; lenvatinib; levoﬂoxacin; levomepromazine; lithium; lofexidine; methadone; moxifloxacin; nilotinib; ondansetron; paliperidone; pazopanib; pimozone; procainamide; quetiapine; quinine; ranolazine; ribociclib; risperidone; saquinavir; sertraline; sildenafil; sorafenib; sotalol; sulpiride; sumatriptan; sunitinib; tetrabenazine; thioridazine; tizanidine; tolterodine; toremifene; vandetanib; vardenafil; vemurafenib; venlafaxine; voriconazole; ziprasidone; zolmitriptan
			bradyarrhythmia	++	Cardiovascular medications
	Dexamethasone Hydrocortisone, methylprednisolone	PD	potassium homeostasis	++	diuretics, laxatives, digoxin
		PK	P-gp, OATP2, CYP3A11, CYP2B10, CYP3A4 (inducers)	+	CYP substrates, especially drugs of narrow therapeutic index
	Ruxolitinib	PD	heart rate (PR interval)	+++	antiarrhythmics, β -blockers, non-dihydropyridine calcium channel blockers, digitalis glycosides, cholinesterase inhibitors, sphingosine-1 phosphate receptor modulators, and HIV protease inhibitors
		PK	CYP1A2, CYP2B6, CYP2C9, CYP3A4	++	clarithromycin, erythromycin, diltiazem, ranolazine, itraconazole, ketoconazole, ritonavir, verapamil, grapefruit

Table S3. Drug-Drug interactions between emerged treatments for COVID-19 and respiratory medications (Clinical Significance: Serious–Use alternative= +++, Use with caution-Monitor= ++, moderate-minor=+)

Respiratory medications (ATC codes)		Interacting medications for COVID-19	Pharmacological Mechanism, Clinical outcome	Clinical Significance
R03AC Selective β-2- adrenoreceptor agonists	Salbutamol Terbutaline Fenoterol Rimiterol Hexoprenaline Isoetarine Pirbuterol Tretoquinol Carbuterol Tulobuterol Salmeterol	Azithromycin, chloroquine, hydroxychloroquine, lopinavir	PD, hERG -> QT-prolongation	++
	Formoterol Clenbuterol Reproterol Procaterol Bitolterol Indacaterol Olodaterol	Dexamethasone, hydrocortisone, methylprednisolone	PD, Hypokalemia	+
R03BA Glucocorticoids	Budesonide, Flunisolide, Betamethasone, Fluticasone, Triamcinolone	atazanavir, ritonavir,	PK, CYP3A4 elevated drug concentrations	++
	Mometasone Ciclesonide	anakinra, baricitinib, canakinumab	PD, myelosuppression, neutropenia	++
R03BB Anticholinergics	Revefenacin	atazanavir, lopinavir/ritonavir	PK, OAT1B1/ 1B3 elevated drug concentrations	++
R03DA Xanthines	Aminophylline, Theophylline	azithromycin, ritonavir, anakinra, canakinumab, sarilumab, tocilizumab	PK, CYP3A4 and CYP1A2 abundance	++
		dexamethasone, hydrocortisone, methylprednisolone	PD, Hypokalemia	+
R03DC Leukotriene receptor antagonists	zafirlukast	chloroquine, hydroxychloroquine, remdesivir, colchicine, tocilizumab	PD Neuropathy & hepatotoxicity (remdesivir)	++
	zileuton	atazanavir, lopinavir/ritonavir, ruxolitinib	PK, CYP3A4	++
	montelukast	Dexamethasone, hydrocortisone, methylprednisolone	PK, CYP induction decrease drug concentration	+

R06AD Phenothiazine derivatives	Thiethylperazine, Methdilazine	ribavirin	CYP2D6	++
R06AE Piperazine derivatives	Cyclizine Chlorcyclizine Cetirizine Levocetirizine	ribavirin	Renal elimination	++
R06AX Other antihistamines for systemic use	Astemizole, Terfenadine	atazanavir, ribavirin	CYP3A4 elevated drug concentrations	++
		azithromycin, chloroquine, hydroxychloroquine	hERG -> QT-prolongation	+++