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Paxlovid, friend or foe?

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In July 2022, FDA has authorised the emergency use of Paxlovid (co-package of nirmatrelvir and ritonavir) for the treatment of COVID-19 in eligible patient. Despite PAXLOVID showing potential in reducing mortality and hospitalisation rates in COVID-19 patients, interaction with several common drugs have been identified.

Ritonavir is a potent inhibitor of CYP3A4 isoenzyme and various drug transporters. While ritonavir and nirmatrelvir are both subtrates of CYP3A4, an important enzyme that accounts for up to 60% of the total CYP450 in adult liver, this increases the chances of interaction with various drugs, especially those being metabolised by CYP3A4.
This bulletin herein summarizes the recommendation given from 3 different guidelines in the management of drug-drug interaction with PAXLOVID.

Drug	Effect	Recommendation		
		FDA	French Society of Pharmacology and Therapeutics (SFPT) Guidelines	Ontario COVID-19 Science Advisory Table, Canada
HMG-CoA reductase inhibitors				
Simvastatin Lovastatin	Increased plasma concentration thus increasing the risk of myopathy	Co-administration contraindicated. Withhold at least 12 hours prior initiation of Paxlovid. Restart simvastatin or lovastatin 5 days after completing Paxlovid.	Contraindicated	Stop at least 12 hours before starting Paxlovid. Restart 5 days after completing Paxlovid.
Atorvastatin Rosuvastatin	Plasma concentrations may be increased due to lesser dependence on CYP3A metabolism.	Consider temporary discontinuation during treatment with Paxlovid. Withholding Atorvastatin and Rosuvastatin prior and after completing Paxlovid is not necessary.	Paxlovid is possible with the discontinuation of medication.	Hold and restart 2 days after completing Paxlovid. Alternatively, reduce dose Atorvastatin or Rosuvastatin to 10mg daily. Resume usual dose 2 days after completing Paxlovid.
Calcium channel blockers				
Amlodipine Diltiazem Felodipine Nifedipine	Plasma concentration are expected to increase.	A dose decrease may be needed for these drugs upon concomitant use. Clinical monitoring is recommended.	Paxlovid is possible without modification of the associated treatment except for Verapamil and Diltiazem. To discontinue Verapamil and Diltiazem.	Reduce dose by 50% or take dose every other day. Restart usual dose 2 days after completing Paxlovid. Monitor BP. May consider continuing with usual dose if at risk of bradycardia or hypotension.

Anti-platelet agent				
Clopidogrel	Active metabolite is reduced. Decrease in anti-platelet effect have been reported.	Avoid concomitant use with Paxlovid.	Paxlovid possible without modification of the associated treatment. In case of angioplasty <6 weeks, cardiologist advice is required.	If <3 months since ACS or <1 month since PCI (no ACS), considering switching to prasugrel and resume 2 days after completing Paxlovid (for age <75, weight >60kg and no history of stroke/TIA).
Ticagrelor	Increase in ticagrelor exposure resulting in increased bleeding risk.	Avoid concomitant use with Paxlovid.	Contraindicated.	If <3 months since ACS or <1 month since PCI (no ACS), switch to prasugrel (for age <75, weight >60kg and no history of stroke/TIA).
Anticoagulants				
Warfarin	Weak interaction expected.	Closely monitor INR.	Paxlovid possible without modification of the associated treatment. Monitor INR and adjust dosage if needed.	Monitor for signs of increased bleeding and bruising. Check INR if clinically indicated.
Antipsychotics				
Quetiapine	Increase concentration of quetiapine. Possible QTc prolongation.	If co-administration is necessary, reduce quetiapine dose and monitor for adverse reactions.	Contraindicated.	Reduce to one-sixth of original dose and resume usual dose 2 days after completing Paxlovid. Monitor for confusion, dizziness and sedation.
Clozapine	Quetiapine AUC increased by a factor of 6.5.	If co-administration is necessary, reduce clozapine dose and monitor for adverse reactions.	Contraindicated.	Contraindicated. Use alternative Covid-19 agent.
Risperidone	Risperidone AUC might be increased.	-	-	Reduce dose by 25-50% and resume usual dose after Paxlovid. Monitor for confusion, extrapyramidal symptoms and sedation.
Antigout				
Colchicine	Risk of colchicine accumulation and toxicity.	Contraindicated.	Contraindicated.	Reduce dose if practical. Treatment of gout flares: 0.6mg x 1 dose, then 0.3mg 1 hour later. Repeat dose no earlier than 3 days. Resume usual dose after 2 days of completing Paxlovid. Contraindicated in patients with renal and/or hepatic impairment.

Adapted from:

1. Lemaitre F, Grégoire M, Monchaud C, Bouchet S, Saint-Salvi B, Polard E, et al. Management of drug-drug interactions with nirmatrelvir/ritonavir in patients treated for Covid-19: Guidelines from the French Society of Pharmacology and Therapeutics (SFPT). Therapie [Internet]. 2022 Sep [cited 2022 Oct 19];77(5):509. Available from: /pmc/articles/PMC9020499/
2. Ontario COVID-19 Drugs and Biologics Clinical Practice Guidelines Working Group, University of Waterloo School of Pharmacy. Nirmatrelvir/Ritonavir (Paxlovid): What prescribers and pharmacists need to know. Ontario COVID-19 Science Advisory Table. 2022;3(58).
3. U.S. Food and Drug Administration. Fact sheet for healthcare providers Emergency Use Authorization (EUA) for Paxlovid. US Food Drug Adm. 2022;(1).

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