

EDITORIAL

PANDORA'S BOX: PAXLOVID, PRESCRIBING, PHARMACISTS AND PANDEMIC

Oral antivirals are a potential 'game changer' for healthcare provision during the ongoing coronavirus disease 2019 (COVID-19) pandemic. Whilst various parenteral treatments have been shown to prevent early disease progression – including casirivimab plus imdevimab, remdesivir and sotrovimab – the organisational requirements for these, including establishment of infusion clinics, are highly challenging and a barrier to access.^{1–3} Clearly, oral treatment regimens can be more feasibly and expediently prescribed, dispensed and administered. National treatment guidelines for use of all COVID-19 therapies are widely available and are evolving with the rapid availability of new evidence.⁴ All clinicians should follow this expert advice to ensure maximally effective and safe therapies for the management of COVID-19 patients. However, the new treatments are not without their own challenges.

Firstly, the pandemic continues to be characterised by the emergence of new variants for which antivirals may have altered potency. For the oral antivirals now available in Australia, nirmatrelvir/ritonavir (Paxlovid[®]) and molnupiravir (Lagevrio[®]), adequate potency is reported to continue in the presence of the Omicron variant.^{5,6} Secondly, the public health response has caused dramatic changes in the profile of the community in which the medications are to be potentially used, compared to when the early trial data was generated, where patients were unvaccinated. Of course, Australia currently enjoys very high vaccination rates. Given the uncertainty of effect of oral antivirals in fully vaccinated individuals, major guidelines recommend use in line with the clinical trial data and only in unvaccinated individuals with early COVID-19 symptoms, who do not require oxygen and who have one or more risk factors for disease progression.⁴ An extension to use in partially vaccinated or immunosuppressed individuals with early COVID-19 symptoms may be considered.⁴ Thirdly, the new oral antivirals are (mostly) novel drugs for which there is little existing clinical experience, thereby increasing the importance of establishing and adopting nationally consistent guidance on their safe and effective use. This is particularly important in the context of limited availability and access to these medications. Data collection of the effectiveness and safety of these agents is essential to generate a much stronger understanding of the risks

and benefits of these drugs in the patient population that are used.

The paradigm change for treatment of COVID-19 with oral antivirals is enthusiastically anticipated by many in the healthcare sector and the general public. Strong clinical data supports use of the oral antiviral drugs and in particular Paxlovid (nirmatrelvir/ritonavir), which is reported to reduce COVID-19-related hospital admission or death from any cause by 89% relative to placebo in unvaccinated adults with risk factors for disease progression.⁷ These data have led to endorsement by clinical practice guidelines globally, including in Australia (who received access to the unpublished clinical study report).⁴ However, specific considerations exist for the prescribing and dispensing of Paxlovid, a combination of nirmatrelvir and ritonavir. In the presence of ritonavir, nirmatrelvir, a severe acute respiratory syndrome coronavirus 2 3CL protease that inhibits viral replication, has a far more advantageous exposure profile allowing only twice daily drug administration (without ritonavir, dosing of only nirmatrelvir would require multiple doses throughout the day). In this sense, using ritonavir with nirmatrelvir makes therapy far more feasible. Classically, we know a lot about the presence of ritonavir as a pharmacokinetic enhancer from HIV therapeutics, where it is used to increase the exposure (concentrations) of protease inhibitors such as darunavir and atazanavir. The co-formulated product lopinavir/ritonavir (Kaletra[®]) was used prior to this for many years.

Ritonavir is a strong inhibitor of CYP 3A4, 2D6, p-glycoprotein and some transporter proteins (BRCP, OATP-C, MRP). Inhibition is fairly immediate and lasts several days post-withdrawal.^{8,9} Consequently, for many patients, there may be significant interactions to consider before they commence Paxlovid. Ritonavir also induces CYP 2C19, 2C8, 2C9 and 1A2. However, because enzyme induction has a longer onset (as new enzymes are created) and as Paxlovid is only a 5-day course, these interactions are less likely to be of clinical significance.⁹

Potential drug interactions can be very challenging to interpret, predict and manage. The risk of drug interaction will be different for some drugs with the short 5-day Paxlovid course than would be the case for chronic administration of ritonavir-boosted protease inhibitor.

As such, the magnitude of changes in exposure (concentrations) can be major for some interacting drugs and minimal for others.

Clear guidance is available on the drug interactions for some medications that interact with Paxlovid – black and white recommendations exist to avoid co-administration. Examples of clearly contraindicated drugs include (but are not limited to):

- CYP3A4 enzyme inducers: for example, rifampicin, St John's wort, carbamazepine, phenytoin, phenobarbitone and enzalutamide
- CYP3A4 or 2D6 substrates where the drug cannot be easily withheld or safely adjusted: for example, amiodarone, flecainide, quinidine, colchicine, venetoclax, clozapine, phosphodiesterase type 5 inhibitors for pulmonary hypertension (e.g. sildenafil), bosentan, immunosuppressants (e.g. tacrolimus, cyclosporin) and direct-acting oral anticoagulants (e.g. rivaroxaban).

The main clinical challenge can be where the recommendations for drug interaction management fall into the 'grey' zone. In some situations, the contraindicated drug may be important, and with careful consideration of an individual's circumstances, use may be managed. The management principles for some other drugs are not as clear, with three examples provided in Table 1.

Where a healthcare team elects to use Paxlovid and change the dosing regimen of a usual chronic therapy because of potential drug interaction, it is essential to change back at the appropriate time after the Paxlovid course. It is important that this information is clearly documented and appropriate education be provided to patients and/or carers to minimise the risk of medication misadventure or harm.

Preliminary data suggest that the proportion of patients that may fit Paxlovid eligibility criteria but have interacting medication that preclude use, is substantial.

Highly specialised patient populations may be particularly challenging and problematic. The American Society of Transplantation have released a statement on oral antiviral therapy for COVID-19 for organ transplant recipients, preferencing alternative treatment options for this patient cohort (e.g. sotrovimab).¹⁰ A recent 3-year snapshot of over 11 000 immunocompromised patients at The Alfred Hospital (Melbourne, Australia) showed that up to one in three of these patients may not be suitable candidates for Paxlovid purely because of the presence of contraindicated drug interactions with key chronic drug therapies. The common interacting medications were direct-acting oral anticoagulants (apixaban and rivaroxaban), calcineurin inhibitors (tacrolimus and everolimus), lercanidipine and amiodarone (unpublished data).¹¹ On review of COVID-19-positive patients admitted recently for a sotrovimab infusion, 37% were receiving a regular medication that would exclude them from Paxlovid therapy (unpublished data).

To facilitate the safe prescribing of Paxlovid, an individual patient's risk of disease progression must be balanced with the potential for adverse outcomes associated with interacting medications. Key to this is the consideration of the following points in making the decision regarding the prescribing of Paxlovid as an early COVID-19 therapy, and each highlights the importance of expert multidisciplinary healthcare team collaboration:

1. Obtain an accurate, up to date and thorough medication history, including over-the-counter and complementary and alternative therapies
2. Consider Paxlovid in patients where a CYP3A4 or 2D6 substrate may be acceptably withheld or dose reduced during/after the course of Paxlovid
 - a. Enzyme inhibition resolves within 3 days of cessation in most cases and the medication may be re-introduced or dose up-titrated

Table 1 Examples of complex drug interactions and suggested management¹¹

Interacting drug	Indications for use	Effect of ritonavir	Comments
Clopidogrel	Antiplatelet agent	↓ production of clopidogrel active metabolite	Contraindicated if very high risk of thrombosis (e.g. stents placed in last 6 weeks). Could consider use in other situations
HMG Co-A reductase inhibitors	Hyperlipidaemia	↑ Simvastatin and atorvastatin levels	Simvastatin contraindicated: withhold and recommence 3 days after Paxlovid® ceased. Could use lower dose atorvastatin, or withhold during and 3 days after Paxlovid
Quetiapine	Psychotropic	↑ quetiapine area under the curve by five- to eightfold	Contraindicated. Could consider significant dose reduction during and 3 days after Paxlovid course with careful monitoring

3. Do not use Paxlovid in patients taking:
 - a. a CYP3A4 or 2D6 substrate medication which cannot be withheld/adjusted and high concentrations will be dangerous to the patient or has a long half-life or a narrow therapeutic window (such as some anti-arrhythmics, antipsychotics and antineoplastic agents)
 - b. a strong CYP3A4 enzyme inducer (for example rifampicin, St John's Wort and some anticonvulsants) in the past 28 days, which may significantly reduce concentrations of nirmatrelvir or ritonavir.

For complex cases, or where there is doubt, a specialist pharmacist opinion should be sought.

One of the many challenges associated with the interpretation of drug–drug interactions is the various sources available for drug interaction information. Whilst knowledge is power, the varying resources are not necessarily consistent, and on occasion, contradictory. Differences exist between the approved product information and resources such as the regularly updated University of Liverpool interaction website (<https://www.covid19-druginteractions.org>). This site has resources relevant to all COVID-19 therapies, including Paxlovid, however, at the time of writing, did not yet include all interacting medications (e.g. chemotherapy agents). For patients where Paxlovid cannot be used, other options such as molnupiravir or sotrovimab, for which some data now supports administration by IM injection, may be appropriate alternatives.¹² It is anticipated that future guidance regarding these alternative treatment options will be forthcoming, and will relate to ongoing access of these medications.

There are a number of patient populations in which the safety and efficacy of Paxlovid is not yet known. Pregnant and breastfeeding women, children and adolescents and patients with renal impairment (estimated glomerular filtration rate < 30 mL/min) were excluded from the Paxlovid trial.⁴ The recently updated Australian guidelines for the clinical care of people with COVID-19 are therefore, understandably, unable to make recommendations for these patients.

Whilst the timing and availability of access to Paxlovid and molnupiravir in Australia are not yet known, support for prescribers, community pharmacists, hospital pharmacists and – most importantly – patients is required. Development of a consistent and streamlined approach by a collaborating multidisciplinary team is required to support the safe prescribing of Paxlovid, and to avoid duplication of work and resources by clinicians working in this space.

ACKNOWLEDGEMENTS

JAR would like to acknowledge funding from the Australian National Health and Medical Research Council for a Centre of Research Excellence (APP2007007) and Australian National Health and Medical Research Council Investigator Grant (APP2009736) as well as an Advancing Queensland Clinical Fellowship.

CONFLICTS OF INTEREST STATEMENT

JAR and KAC are members of the Australian National COVID-19 Clinical Evidence Taskforce. JAR has provided consultancy for Pfizer and MSD in the last 3 years. JAR is an Associate Editor of the *JPPR*.

Jason A. Roberts PhD, BPharm (Hons), BAppSc, FSHP, FISAC
 Faculty of Medicine, The University of Queensland,
 University of Queensland Centre for Clinical Research,
 Brisbane, Australia;
 Metro North Health, Herston Infectious Diseases
 Institute (HeIDI), Brisbane, Australia;
 Departments of Pharmacy and Intensive Care Medicine,
 Royal Brisbane and Women's Hospital, Brisbane,
 Australia;
 Division of Anaesthesiology Critical Care Emergency
 and Pain Medicine, Nîmes University Hospital,
 University of Montpellier, Nîmes, France.
 E-mail: j.roberts2@uq.edu.au

Alison Duncan BPharm, GDipClinPharm and **Kelly A. Cairns** BPharm, GDipClinPharm, MCLinPharm
 Department of Pharmacy, The Alfred, Melbourne,
 Australia

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