

Oral antivirals for mild-moderate COVID-19: a panacea or a logistical and clinical conundrum?

In Australia COVID-19 is currently characterised by the Omicron variant in a population with high rates of primary vaccination, but moderate rates of booster doses. Healthcare professionals and health systems are facing new challenges with the increasing spread of SARS-CoV-2 through the community, the potential emergence of new mutations and the relaxation of public health restrictions. Although vaccination has significantly reduced morbidity and mortality from COVID-19, high case numbers mean that interventions to reduce hospital admissions and prevent long-term complications remain highly desirable.¹ These interventions are particularly important in people who are not fully vaccinated, and those who are immunosuppressed and may not develop adequate antibody responses from immunisation.

The Omicron surge heightened the perceived need for drugs to prevent or treat severe disease in patients infected with SARS-CoV-2. Approval of new drugs was expedited by regulatory agencies, such as the Therapeutic Goods Administration (TGA) via the provisional approval pathway.

Multiple therapeutic options for COVID-19 are now available. These include parenteral anti-spike protein monoclonal antibodies ([sotrovimab](#), [casirivimab/imdevimab](#)), oral antivirals ([nirmatrelvir/ritonavir](#), [molnupiravir](#)) and parenteral antivirals ([remdesivir](#)). However, clinical trial data are limited and were usually collected before the Omicron variant emerged. The considerations about the use of these treatments are complex. Each drug has nuances related to the patient population they were studied in, the strength of their apparent effects and the practicalities of how these treatments could be used in different populations. This leads to uncertainty about how to facilitate access to effective therapies and how to use them safely.

Among the new oral drugs, nirmatrelvir/ritonavir is a potentially effective antiviral combination. It reduced the absolute risk of hospitalisation due to COVID-19 by 5.8% within 28 days of randomisation.² However, this combination is not without risk, with a high certainty for harm if potentially significant drug interactions with ritonavir are not mitigated.³ Molnupiravir had a marginal benefit of 2.9% in

reduced hospitalisation.⁴ The pharmacoeconomic benefits, in terms of hospital bed days saved for both treatments, remain to be shown.

Some of these new drug approvals appear to be based on preliminary clinical data from single placebo-controlled, drug company-sponsored clinical trials. The information that was available to clinicians and clinical practice guideline panels at the time of approval was sometimes in the form of pre-print articles, press releases or summary data from regulatory agencies, rather than peer-reviewed publications. However, the evidence of clinical effectiveness was mainly from a patient cohort that now forms only a small part of the community – unvaccinated people infected with the Delta variant. These rapid approvals create a situation where postmarketing surveillance is crucial to ensure any benefits are derived without harm. The feedback of data about outcomes will be essential to inform future clinical use and continuing TGA approval.⁵

The currently available evidence presents a challenge to the use of the new drugs. Their clinical effect was seen in unvaccinated patients, with infections confirmed by polymerase chain reaction, who had a high risk of developing severe disease. The trials took place before the emergence of the Omicron variant, which is thought to have a lower virulence than previous variants. Most Australians are vaccinated and confirmation of infection is now by self-administered rapid antigen testing, which may result in false positives. There are also no head-to-head studies comparing nirmatrelvir/ritonavir with molnupiravir to guide treatment recommendations and delineate which patient groups should have priority access to the new oral drugs. It is impractical to restrict the use of these drugs to patients with particular comorbidity profiles. Eligibility criteria may not be completely reflective of the inclusion criteria used in the trials. An additional challenge is the change to the definition of who is considered to be 'fully vaccinated'. The drugs are now being used in patients who have received two doses of vaccine but have not received a booster dose. It is unknown whether the drugs will remain clinically effective or cost-effective in these people.

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Access to the intravenous agents is limited by the location and capacity of infusion centres. This will encourage the use of oral antivirals in the community, despite many prescribers having little experience with these drugs and the absence of long-term safety data, including information about antiviral resistance. Current treatments for COVID-19 are predominantly used under supervision in highly resourced hospital settings with daily monitoring of patients. However, in order to enable wider and more rapid access in regional, rural and remote areas of Australia, the prescribing and dispensing of the new oral drugs will move from specialised COVID-19 units attached to hospitals to primary care, supported by the Pharmaceutical Benefits Scheme (PBS). Molnupiravir has been listed on the PBS⁶ with uncertain ease of access in the community. The PBS criteria ideally should complement the national evidence-based [COVID-19 Living Guidelines](#) to prevent inequity of access and the use of drugs in patients who are unlikely to benefit. However, the rapid distribution of oral drugs directly to residential aged care and health services for Aboriginal and Torres Strait Islander people, while intended to enable immediate access for vulnerable patient groups, may also have increased risks through a lack of guidance and education to support appropriate prescribing. These

risks need to be mitigated. Healthcare systems must therefore determine how to maximise the benefits and safety of the new drugs and create a sustainable multidisciplinary, collaborative and responsive hospital-community model.

Rapid TGA approval and PBS listing of oral drugs will lead to a significant shift in the way that COVID-19 patients have been managed up to this point. It potentially adds to the risk of medication misadventure when community prescribers have limited access to specialist advice and support. Comprehensive guidelines and decision support for GPs and community pharmacists are required to ensure the safe use of these oral antiviral drugs, particularly in relation to drug interactions.⁷

The COVID-19 Living Guidelines for using the new drugs will change when more evidence emerges. To further inform decisions around ongoing and future drug approvals, purchasing, distribution and access, it is essential to capture data to evaluate the real-world outcomes of these new therapies. ◀

Conflicts of interest: Andrew Henderson has participated in advisory board meetings for MSD. Jason A Roberts is on advisory boards for Pfizer, MSD and Gilead, and has received speaking fees from Gilead.

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