NEWS

First real-world studies on COVID-19 oral antivirals emerge

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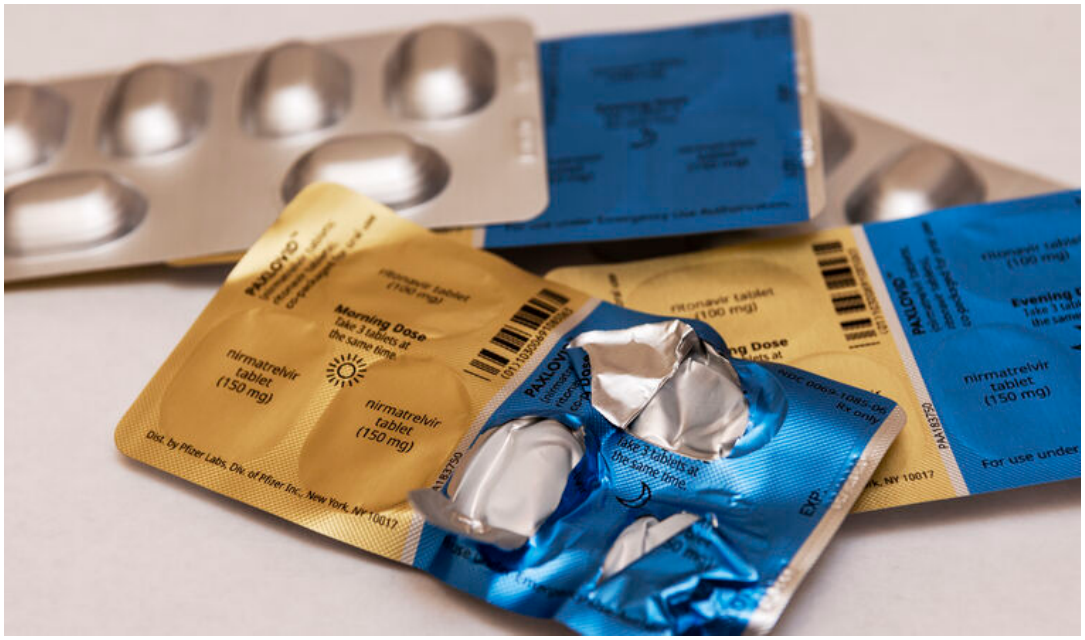
Pre-print studies are beginning to flesh out understanding of efficacy, suggesting Paxlovid may have a greater impact – particularly on at-risk older people.



Evidence on the real world application of oral antivirals has so far been lacking. (Image: AAP Photos)

The drugs do work – for some people at least.

That is the cautiously reassuring suggestion from two recent pre-print studies tracking outcomes for COVID-19 patients given two of the most widespread oral antiviral drug treatments.

They include the two oral antivirals treatments available in Australia, molnupiravir (sold as Lagevrio) and nirmatrelvir plus ritonavir (sold as Paxlovid), which have been approved for use on the Pharmaceutical Benefits Scheme (PBS) and can be prescribed by GPs.

But while clinical trials have led to the provisional approval of both treatments by the Therapeutic Goods Administration (TGA), there is still a lack of understanding of their impact in real-world settings, especially since the emergence of Omicron.

Both of the new studies set out to address that gap in knowledge.

One piece of research from Hong Kong suggests that both have a positive impact in reducing severe disease, with

nirmatrelvir/ritonavir seeming to offer the greater protection of the two.

Another new study from Israel focuses only on the outcomes for those treated with nirmatrelvir/ritonavir. That research concludes the oral antiviral is most effective in vulnerable people aged 65 and older, with 'no significant impact' on a younger cohort aged 40–64.

The Hong Kong research

The authors of a study from the University of Hong Kong claim their research as the first real-world study looking at the clinical use of oral antivirals while Omicron has been the dominant strain.

The observational, retrospective cohort study took place among 40,776 hospitalised patients in Hong Kong from 26 February to 26 April this year.

Among those patients, 2359 were given molnupiravir while 1000 were administered nirmatrelvir/ritonavir.

None of those patients required oxygen therapy at the point their treatment began. The outcomes of the study were measured by disease progression, mortality, whether patients required ventilation, and how quickly viral load faded.

The outcomes for oral antiviral users were compared with controls using propensity score matching.

Oral antiviral use was linked to a significantly lower risk of disease progression, with the study reporting a hazard ratio of 0.53 and 0.33 for molnupiravir and nirmatrelvir/ritonavir respectively.

Similar results were also seen for all-cause mortality, with the hazard ratio standing at 0.55 for molnupiravir and 0.32 for nirmatrelvir/ritonavir.

The study also looked at a head-to-head comparison of both treatments, with a higher relative risk of death reported among the molnupiravir group compared to nirmatrelvir/ritonavir.

Molnupiravir was also associated with a higher risk of longer hospital stays among surviving patients.

'Early initiation of oral antivirals within two days of admission was associated with significantly lower risks of disease progression and all-cause mortality, in addition to achieving low viral load faster than their respective matched controls,' the study states.

'Molnupiravir use was also associated with a significantly lower risk of requiring invasive mechanical ventilation than non-use'.

Despite both treatments having an impact in limiting severe outcomes, the authors set out a clear preference.

'Our findings also support the prioritisation of nirmatrelvir/ritonavir over molnupiravir use in COVID-19 patients whenever accessible and clinically appropriate, in view of the former's substantial mortality benefit,' they wrote.

Second study

Researchers from Israel's Clalit Health Services (CHS) and Ben-Gurion University of the Negev subsequently released a separate pre-print study this week, concentrating only on nirmatrelvir/ ritonavir.

Like the Hong Kong study, it was also an observational, retrospective cohort study, this time based on medical record data from CHS, which authors describe as 'a large healthcare organisation covering approximately 52% of the entire Israeli population and almost two-thirds of the older adults'.

The study, which included all CHS members with confirmed COVID-19 deemed as high risk from severe disease, also lasted two months from 9 January this year until 10 March. Omicron, once again, was the dominant strain in the country at the time.

The study included all CHS members, 40 years of age and older, with confirmed infection of SARS-CoV-2.

Of 42,819 eligible patients aged over 65 years, nirmatrelvir plus ritonavir were given to 2504, while there were 66,394

eligible patients aged 40–64 years, of whom 1435 received the treatment.

The study found hospitalisations and deaths were cut significantly among treated patients in those aged 65 and over.

'Nirmatrelvir therapy was associated with a 67% reduction in COVID-19 hospitalisations and an 81% reduction in COVID-19 mortality in patients 65 years and above,' the authors wrote.

'However, no significant benefit in avoidance of severe COVID-19 outcomes was shown in younger adults.'

The researchers found a lack of prior COVID-19 immunity and previous hospitalisation were the factors most linked to high rates of hospitalisations, with immunosuppression 'significantly associated' with those hospitalised among the 40–64 age group.

'Although this study is observational, we believe that its findings and the observed potential for avoiding severe COVID-19 could assist decision makers in prioritising the currently constrained supplies to those in whom nirmatrelvir was shown to be substantially effective,' they concluded.

While they also underline the strength of the data used, the researchers warned that their study is prone to 'confounding clinical and sociodemographic characteristics' that may have biased observations.

Evidence still emerging

Clinical trials for both the treatments being used in Australia took place in very different circumstances to the present situation.

Trials for both drugs took place during the Delta wave, before the Omicron variant of concern had been identified – and were conducted among unvaccinated patients.

In the real world, the oral antiviral treatments are largely being administered in a highly vaccinated population while Omicron is the dominant strain.

Senior pharmacists and clinicians highlighted in March an urgent need for greater understanding of how the new oral antivirals work.

The Head of the TGA, Professor John Skerritt, has also previously referred to a lack of evidence for the real-world efficacy of the oral antiviral drugs but stated that he thought accurate studies are likely to emerge this year.

The oral antiviral drugs are currently targeted at at-risk patients with mild-to-moderate symptoms, with the aim of reducing the burden on hospitals.

To have the most impact, the treatments need to start within five days of the onset of symptoms, prescribers are advised.

While these early studies suggest nirmatrelvir plus ritonavir is more effective, it has many more contraindications than molnupiravir.

Who is eligible in Australia?

According to PBS criteria, the drugs can be prescribed for those with mild-to-moderate COVID-19 confirmed by a PCR or rapid antigen test within five days of symptom onset, among the following patient groups:

- Those aged 65 or older, with two other risk factors for severe disease
- Those aged 75 or older with one other risk factor
- Those aged 50 and older who are of Aboriginal or Torres Strait Islander origin with two further risk factors for severe disease
- Those with moderate-to-severe immunocompromise

The RACGP's COVID-19 resources includes information relevant for every state and territory.

A guide with details relevant to general practice about the COVID-19 oral antivirals has also been published by newsGP.

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COVID-19 Lagevrio molnupiravir Paxlovid

NEWSGP WEEKLY POLL

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- 1.6% — 2%
- 5% — 15%
- Between 5–10% — 27%
- More than 10% — 54%

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Dr Ian **4/06/2022 11:12:26 AM**

It is reassuring that there is efficacy which means there is a need to offer more patients at risk the option of treatments as soon as diagnosis is established .
Some estimate only one third of eligible patients are receiving treatment despite available supplies .
And there are 50 deaths a day in Australia .
Another medication Remdesivir is recommended for pregame t women and the system is one day in hospital for the 200mg dose 100mg a day for two days hospital in the home .
There is also the Preexposure dual monoclonal Evusheld that is holding up still used for the very immunocompromised with over 70% protection and lasting for . 6 months .
The results were reported in a trial in the NEJM .