Oral treatments for outpatient COVID-19: Effectiveness and value

A Summary from the Institute for Clinical and Economic Review's Midwest Public Advisory Council

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Coronavirus disease 2019 is an infectious respiratory disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of April 2022, there have been more than 81 million confirmed COVID-19 cases and 991,000 COVID-19 deaths in the United States.[1] Most symptomatic patients with COVID-19 have mild or moderate disease and do not require hospitalization, but many factors can increase the risk of developing severe or critical COVID-19, such as older age, obesity, cardiovascular disease, and chronic obstructive pulmonary disease.

The rise of more infectious variants and the failure to reach population vaccination goals highlight the need for outpatient treatment options for mild to moderate disease. Oral options could be particularly helpful in improving access to treatment across diverse communities in the United States. At the time of this article, there are 2 oral agents that have received Emergency Use Authorization from the US Food and Drug Administration (FDA): molnupiravir, an oral ribonucleoside analog that causes viral genome replication errors, and nirmatrelvir/ritonavir (Paxlovid), a combination oral drug that inhibits SARS-CoV-2-3-chymotrypsin-like (3CL) protease, an enzyme necessary to produce other functional SARS-CoV-2 proteins. The FDA declined to grant Emergency Use Authorization to another oral drug, fluvoxamine, an oral selective serotonin reuptake inhibitor that is licensed for the treatment of obsessive-compulsive disorder but has shown promise for mild to moderate COVID-19.

The Institute for Clinical and Economic Review (ICER) conducted a systematic literature review and cost-effectiveness analysis to evaluate health and economic outcomes of these 3 oral treatments in patients with mild to moderate COVID-19. Complete details of ICER's systematic literature search and protocol as well as the methodology and model structure for the economic evaluation are available on ICER's website at https://icer.org/assessment/covid-19-2022/. ICER considered this review to be a Special Assessment because the epidemiological landscape and evidence base for potential treatments for COVID-19 are both rapidly evolving and will continue to change beyond the publication of the final report. In this article, we present the summary of our findings and highlights of the policy discussion with key stakeholders held at a public meeting of the Midwest Comparative Effectiveness Public Advisory Council (CEPAC) on April 12, 2022.

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Summary of Findings

MOLNUPIRAVIR

Our systematic literature review on molnupiravir identified 1 phase 3 randomized controlled trial ("MOVE-OUT") 2 and a phase 2 dose-finding study that evaluated the effect of molnupiravir on viral load, safety, and tolerability.[2]

The pivotal MOVE-OUT trial was a double-blind, placebo-controlled trial that randomized 716 patients to molnupiravir and 717 patients to placebo. Patients in the treatment arm received

TABLE 1 Key Results of Randomized Controlled Trials of Molnupriavir, Paxlovid, and Fluvoxamine[3-8]

Intervention (trial)	Hospitalization or death from any cause, n/N (%)		Mortality, n/N (%)	
	Intervention	Placebo	Intervention	Placebo
Molnupiravir (MOVe-OUT)	48/709 (6.8)	68/699 (9.7)	1/709 (0.1)	9/699 (1.3)
Paxlovid (EPIC-HR)	8/1,039 (0.8)	66/1,046 (6.3)	0/1,039 (0.0)	12/1,046 (1.1)
Fluvoxamine (TOGETHER)	79/741 (11)[a]	119/756 (16)[a]	17/741 (2.3)	25/756 (3.3)

[a]*Observed in a COVID-19 emergency setting (for more than 6 hours) or hospitalized.*

COVID-19 = coronavirus disease 2019. EPIC-HR = Evaluation of Protease Inhibition for COVID-19 in High Risk Patients.

four 200-mg capsules (800 mg total) of molnupiravir twice daily for 5 days, whereas patients in the placebo arm received the matching inactive drug. Nonhospitalized patients with mild to moderate COVID-19 were eligible to participate in the trial if they were unvaccinated, had a laboratory-confirmed diagnosis of the disease, had symptom onset within 5 days of randomization, and had at least 1 risk factor for progression to severe disease.[3]

Participants in MOVE-OUT were primarily from Latin America (46%) and Europe (33%), and a minority were recruited in Africa (12%), North America (6%), and Asia (3%). Most participants in the trial were White (57%), 5% were Black, and 50% identified as Hispanic or Latino. The median age of participants was 43 years, and 51% were female. At the time of randomization, 48% of patients had signs and symptoms of COVID-19 within 3 days or less prior to randomization. The most common risk factors for progression to severe disease were obesity (74%), age over 60 years (17%), and diabetes (16%).[3]

The primary efficacy outcome in MOVE-OUT was the percentage of patients who were hospitalized and/or died from the time of randomization through day 29. As shown in Table 1, in the full population analysis (n = 1,433), 48 (6.8%) patients in the molnupiravir group and 68 (9.7%) patients in the placebo group were hospitalized or dead by day 29, a 30% relative risk reduction in favor of molnupiravir (no 95% CI reported). One death occurred in the treatment arm and 9 deaths occurred in the placebo arm; the patient who died in the treatment arm had metastatic cancer and died of multiorgan failure from COVID-19. In addition to the primary outcome, secondary outcomes in the MOVE-OUT trial included improvement or clinical progression of COVID-19 signs and symptoms through day 29, as measured by the World Health Organization 11-point scale. Superiority in patient-reported clinical progression among patients treated with molnupiravir was statistically significant on day 10 and day 15, with the maximum difference occurring on day 10 (odds ratio = 1.58; 95% CI = 1.14-2.20).[3]

Diarrhea, nausea, and dizziness were the most common treatment-related adverse events (AEs) in the MOVE-OUT trial. The incidence of AEs was higher in the placebo group because of the higher incidence of COVID-19 complications. A total of 216 patients (30.4%) in the molnupiravir arm had 1 or more AEs compared with 231 patients (33%) in the placebo arm.

PAXLOVID

The systematic literature review on Paxlovid identified 1 phase 3 randomized clinical trial in patients with mild to moderate COVID-19 with at least 1 risk factor for severe disease, the Evaluation of Protease Inhibition for COVID-19 in High Risk Patients (EPIC-HR trial), which was the focus of our review.[4] We also identified 1 phase 2/3 trial of Paxlovid in patients with mild COVID-19 at standard risk for progression to severe disease or vaccinated individuals with high risk, the Evaluation of Protease Inhibition for COVID-19 in Standard-Risk Patients (EPIC-SR) trial.[9]

EPIC-HR randomly assigned 2,246 patients to 400-mg tablets of Paxlovid or placebo twice daily for 5 days. Nonhospitalized adults were eligible to participate if they had a positive SARS-CoV-2 test with symptom onset no more than 5 days prior to randomization, were unvaccinated, and had at least 1 risk factor for progression to severe disease.[4] The mean age of participants was 46 years, and 49% were female. The majority (72%) of participants were White, 14% were Asian, a small minority (5%) were Black, and 50% were Hispanic or Latino. The most common risk factor for severe COVID-19 was obesity (31%). Approximately 41% of participants were recruited in the United States.

The primary endpoint of the EPIC-HR trial was hospitalization or death through day 29 calculated in the modified intention-to-treat analysis population, which was defined as the participants randomized within 3 days of symptom onset who did not receive previous monoclonal antibody treatment. To align the outcome reporting with the molnupiravir and

TABLE 2 Cost-Effectiveness Results

Intervention[a]	Cost per QALY gained	Cost per life-year gained	Cost per evLY gained	Cost per inpatient hospitalization averted
Molnupiravir	61,000	51,000	58,000	76,000
Paxlovid	21,000	18,000	20,000	26,000
Fluvoxamine	8,000	7,000	8,000	10,000

Values are represented as US dollars.

[a]*We advise against comparing the cost-effectiveness between interventions given the systematic differences in the trial populations and design.*

evLY = equal-value life-year; QALY = quality-adjusted life-year.

fluvoxamine phase 3 trials, we prioritized the outcome of hospitalization or death among participants randomized within 5 days of symptom onset (n = 2,085). In this population, the proportion of patients with a COVID-19–related hospitalization or death was 8/1,029 (0.8%) in the Paxlovid group and 66/1,046 (6.3%) in the placebo group (Table 1), an 88% relative risk reduction (no CI provided).[4]

In the EPIC-HR trial, AEs were more common in the placebo group. Discontinuation due to AEs occurred in 2% of participants in the Paxlovid group and 4% in the placebo group.[4]

FLUVOXAMINE

The systematic literature review on fluvoxamine identified 1 phase 3 randomized trial, the TOGETHER trial, as well as 2 smaller trials (STOP COVID and STOP COVID 2).[5,10,11]

The TOGETHER trial randomized 1,497 participants to receive 100 mg fluvoxamine or placebo twice daily for 10 days.[5] Nonhospitalized adults were eligible to participate if they presented to an outpatient care site with COVID-19 symptoms that began within 7 days, had a positive rapid antigen test for SARS-CoV-2, and had at least 1 risk factor for progression to severe disease. Patients were excluded if they had been vaccinated for SARS-CoV-2 (in the second half of the trial, participants were allowed to be vaccinated), were currently using selective serotonin reuptake inhibitors, or had uncontrolled psychiatric disorders or suicidal ideation consistent with the FDA black box warning for fluvoxamine.

Mean age of the participants in the TOGETHER trial was 50 years, and 58% were female. The vast majority (96%) of participants were mixed race and all participants were recruited from multiple sites in Brazil. The most common risk factor for severe COVID-19 was age 50 years or older (44%).[5]

The primary outcome in the TOGETHER trial was a composite endpoint of COVID-19–related admission to an emergency setting (defined as observation for more than 6 hours) or referral to a tertiary hospital owing to COVID-19 progression within 28 days. Retention in a hospital-like setting was described as the best proxy for conventional hospitalization in the Brazilian health care system given that the wave of COVID-19 infection there during the study period (June 2020 to August 2021) exceeded conventional hospital capacity, leading many patients during that period to be cared for with hospital-level services in emergency settings. In the TOGETHER trial, 79/741 (11%) of participants in the fluvoxamine group (intention-to-treat analysis) had the primary outcome compared with 119/756 (16%) of participants in the placebo group, a 32% relative risk reduction (95% CI = 12%–48%).[5]

Limitations of the Clinical Evidence

Although the clinical trials of all 3 agents demonstrate statistically significant benefits of treatment, there remains substantial uncertainty regarding the comparative effectiveness of each drug in the current US landscape. Some of this uncertainty comes from the preliminary nature of the evidence base, which rests upon a single phase 3 randomized controlled trial for each drug, without an additional confirmatory trial. Further, in attempts to compare these drugs with each other, we note that there are some differences in the composite outcome measures used and differences in the spectrum of risk factors for progression to severe COVID-19 among different trial populations. But perhaps the most notable source of uncertainty is the difficulty in interpreting the generalizability of results of studies conducted during periods with different prevalent COVID-19 variants. The time periods for the pivotal trials occurred before the advent of the Omicron or Delta variants. Although clinical experts do not believe there are likely to be major differences in the relative effectiveness of these treatments among patients infected with more recent variants, only future research will be able to confirm this assumption.

The primary outcome in the fluvoxamine TOGETHER trial differed from that in the phase 3 trials for molnupiravir and Paxlovid, which makes comparison of absolute or indirect benefits of treatment more difficult. The population being treated in the studies we reviewed also differs from

TABLE 3 Votes on Comparative Clinical Effectiveness Questions

Question	Yes	No
Given the currently available evidence, is the evidence adequate to demonstrate that the net health benefit of molnupiravir is superior to that provided by symptomatic care alone?	2	**11**
Given the currently available evidence, is the evidence adequate to demonstrate that the net health benefit of Paxlovid is superior to that provided by symptomatic care alone?	**13**	0
Given the currently available evidence, is the evidence adequate to demonstrate that the net health benefit of fluvoxamine is superior to that provided by symptomatic care alone?	**7**	6

the full population of patients likely to be treated today in the United States. First, key trials for the drugs of interest were performed almost exclusively among individuals who were not vaccinated against SARS-CoV-2. Second, individuals enrolled in the phase 3 trials may be healthier than treated individuals in the real world. Lastly, study participants in the molnupiravir and fluvoxamine trials were primarily or exclusively outside of the United States.[2,5] This reduces the generalizability of results to the US population because countries may vary in prevalent SARS-CoV-2 variants, health care practices and infrastructure, and risk factors for developing COVID-19.

Long-Term Cost-Effectiveness

We developed a 2-part decision analytic model to estimate the cost-effectiveness of molnupiravir, Paxlovid, and fluvoxamine for the outpatient treatment of COVID-19 from the health care sector perspective and over a lifetime time horizon. Cost-effectiveness was also estimated from the societal perspective that included patient productivity effects and an estimate of the benefits of improving hospital intensive care unit bed availability. The societal perspective may have particular relevance when the government is paying for the treatments outside of usual health care cost budgets. The model focused on an intention-to-treat analysis, with the relative effectiveness of each active treatment applied to a common hypothetical cohort representing the current mix in the United States of unvaccinated and vaccinated patients with mild to moderate COVID-19. All active treatments were compared with a common composite "usual care" arm. This comparator arm was based on a pooling of the usual care arms from all pivotal trials for outpatient COVID-19 treatments. The model also included estimates for the rates of long-term sequelae from COVID-19.

Health outcomes and costs were dependent on the highest setting of care received, respiratory support received if hospitalized, time spent in each health state, clinical events, AEs, and direct medical costs. Importantly, rates of death were modeled as a function of the rate of hospitalization and not taken directly from the very small numbers of actual death events in the pivotal trials. The price per treatment course was $707 for molnupiravir (based on the price negotiated in the government contract), $529 for Paxlovid (based on the price negotiated in the government contract), and $12 for fluvoxamine (based on the generic market price). Full details on ICER's cost-effectiveness analysis and model are available on ICER's website at https://icer.org/assessment/covid-19-2022/.

The cost-effectiveness findings are shown below in Table 2. Each intervention resulted in fewer hospitalizations and therefore resulted in life-years gained as well as improvements in quality of life. All incremental cost-effectiveness ratios were beneath $100,000 per quality-adjusted life-year or equal value of life-years gained. Results were particularly sensitive to assumptions regarding the background rate of hospitalization within the common usual care comparator arm. As the background rate of hospitalization falls, as data suggest it has during the Omicron wave of COVID-19, active treatments become less cost-effective. However, even if background rates fall to 2% from current estimates of 4%, all 3 treatments in this review, with pricing and effectiveness based on best current data, would remain highly cost-effective. Full results, including results from the societal perspective, are available on ICER's website at https://icer.org/assessment/covid-19-2022/.

Limitations of the Cost-Effectiveness Model

The primary limitation of our model is that many assumptions are based on the single pivotal trials available for each active treatment, whereas the background rates of hospitalization and other complications from COVID-19 infection continue to evolve. The model also uses estimates for the impact on improving hospital capacity that are impossible to validate. Our model does seek to include the long-term sequelae of COVID-19 through increased

TABLE 4 Votes on Other Contextual Considerations

Contextual consideration	Very low priority	Low priority	Average priority	High priority	Very high priority
Acuity of need for treatment of individual patients based on the short-term risk of death or progression to permanent disability	0	2	2	**7**	2
Magnitude of the lifetime impact on individual patients of the condition being treated	0	3	4	**6**	0

mortality, increased cost, and decreased quality of life for individuals that are discharged alive after being mechanically ventilated. This approach follows recently published recommendations, but we understand that uncertainty and variability in these long-term sequelae exist, and the evidence is continuing to evolve, especially as it relates to the prevalence, duration, associated consequences, and the influence of an outpatient COVID-19 treatment on these sequelae. Ongoing engagement with patients will be important to further inform the long-term sequelae associated with COVID-19.

POLICY DISCUSSION

The Midwest CEPAC is one of the independent appraisal committees convened by ICER to engage in the public deliberation of the evidence on clinical and cost-effectiveness of health care interventions. The CEPAC is composed of medical evidence experts, including clinicians, methodologists, and patient advocates. The ICER report on oral treatments for outpatient management of COVID-19 was the subject of a CEPAC meeting on April 12, 2022. Following the discussion, CEPAC panel members deliberated on key questions raised by ICER's report.

A majority of the panel (11-2) voted that current evidence is inadequate to demonstrate that molnupiravir is superior to symptomatic care alone. Panelists cited the uncertainty around potential harms as well as the dramatic change in efficacy between the interim and final data from the phase 3 trial. In contrast, the panel voted unanimously (13-0) that the evidence is adequate to demonstrate that Paxlovid is superior to symptomatic care alone. Panel members emphasized the greater relative risk reduction of 88% demonstrated in the phase 3 trial and the perception of fewer unknown risks in comparison to molnupiravir. A slight majority (7-6) of the panel voted that the evidence was adequate to demonstrate that fluvoxamine is superior to symptomatic care alone. Panelists who voted "Yes" cited the treatment's ability to reduce the risk of emergency observation and hospital stay, whereas those who voted "No" expressed concerns about the high discontinuation rate in the pivotal trial, wide CIs, and differences in health care management and outcomes in Brazil vs the United States (Table 3).

The Midwest CEPAC also voted on important "potential other benefits" and "contextual considerations" (Table 4) that should be considered by policymakers as they make judgments regarding the value of these treatments. The CEPAC votes on long-term value for money at current prices (Table 5) showed a greatest number of panel members voting "high" value for Paxlovid, fluvoxamine garnering a split between high and intermediate value votes, and a majority voting "low" value for molnupiravir, largely driven by the underlying uncertainty in evidence regarding the relative effectiveness of molnupiravir.

Following the discussion of the evidence, a policy roundtable was convened to deliberate on how best to apply the evidence on the use of oral treatments for outpatient management of COVID-19. The policy roundtable members included 1 patient advocate, 2 clinical experts, 2 payer representatives, and 3 representatives from drug makers of COVID-19 treatments. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The full set of policy recommendations can be found in the Final Evidence Report on the ICER website: https://icer.org/assessment/covid-19-2022/.

Select key policy recommendations for outpatient treatment of COVID-19 are as follows:

Recommendation 1: Federal policymakers should view the advance market commitment strategy followed with outpatient COVID-19 treatments as a success that should be built upon. This approach substantially reduced manufacturer risk and resulted in multiple drugs becoming available at prices that were aligned with clinical benefit, in a relatively short time. The framework for drug price negotiation between the government and drug makers during a pandemic should be made more transparent so that the public is aware of the parameters that the federal government considers in pricing negotiations.

TABLE 5 Votes on Long-Term Value for Money at Current Prices

Question	Low	Intermediate	High
Given the available evidence on comparative effectiveness, incremental cost-effectiveness, and potential other benefits or disadvantages, what is the long-term value for money of treatment at current pricing with molnupiravir vs usual symptomatic care?	**8**	5	0
Given the available evidence on comparative effectiveness, incremental cost-effectiveness, and potential other benefits or disadvantages, what is the long-term value for money of treatment at current pricing with Paxlovid vs usual symptomatic care?	0	5	**8**
Given the available evidence on comparative effectiveness, incremental cost-effectiveness, and potential other benefits or disadvantages, what is the long-term value for money of treatment at current pricing with fluvoxamine vs usual symptomatic care?	1	**7**	5

Recommendation 2: The FDA needs to establish a clear and effective pathway for supporting evaluation of repurposed drugs. This may include proactive outreach to study investigators to invite applications and providing technical assistance during application development as well as consider internal FDA application initiation and development in cases where there is not a clear external sponsor.

Recommendation 3: The federal government should work with states and other policymakers to adopt policy changes needed to improve the effectiveness of its "test-to-treat" program. Test-to-treat sites are greatly needed to more immediately link diagnosis with treatment. Furthermore, test-to-treat sites, which offer the convenience of colocated services, may differentially benefit individuals with low incomes because these individuals may have lower means to make multiple visits to access testing and treatment. Given the need for rapid and broad distribution of treatment during a pandemic, the federal government should consider working with states and professional stakeholders to broaden the functional scope of practitioners who can prescribe COVID-19 treatments. It may be possible to use telemedicine or other means to accomplish this goal, but allowing pharmacists to prescribe under certain circumstances should also be considered.

Recommendation 4: When COVID-19 drug pricing and payment moves from federal contracts into private markets, manufacturers and payers should work together to explore innovative approaches for coverage and pricing that minimize the use of restrictive coverage access as a means of cost control. Manufacturers should price treatments so they are affordable to private insurance systems and patients. Given the need to treat COVID-19 rapidly upon symptom onset, payers should ensure that any prior authorization process leads to immediate coverage for an available and appropriate treatment and does not risk having patients not fill their prescriptions.

Recommendation 5: Future research is needed to understand the epidemiology of Long COVID and the impact of different prevention and treatment strategies on this condition as well as to define and measure the effects of treatments on a more inclusive set of patient-centered and societal outcomes.

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