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Embracing Uncertainties Over the Evidence of New Oral Antivirals for COVID-19: Challenges in Pharmacoepidemiologic Research

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Since the beginning of the COVID-19 pandemic, efforts have been made to develop new therapies for COVID-19.[1,2] The drugs developed in the meantime focus on completing a COVID-19 response strategy to prevent serious illness, hospitalization, and death from COVID-19, without constituting an alternative to vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[3] The first orally administered COVID-19 drug was the repurposed dexamethasone; in a large-scale trial, it was shown to be successful in reducing inflammation, which is known to lead to organ failure and death.[4] It must be noted that this drug is not an antiviral and does not kill or inactivate the virus. Its mechanism is mainly to modulate the immune response to the virus.

More recently, new drugs have been approved for oral use in patients with COVID-19. Merck Sharp & Dohme B.V. was the first company to produce an oral antiviral, molnupiravir, successfully and to license it in the UK market as Lagevrio. Molnupiravir is a prodrug that is metabolized to the ribonucleoside analogue *N*-hydroxycytidine (NHC). NHC distributes into cells, where it is phosphorylated to form the pharmacologically active ribonucleoside triphosphate. NHC triphosphate incorporation into viral RNA by the viral RNA polymerase results in an accumulation of errors in the viral genome, leading to the inhibition of replication.[5] The MOVe-OUT study[6] (Table 1), a phase 3 double-blind randomized controlled trial, found evidence to recommend the use of this drug in the treatment of adults with mild to moderate COVID-19 who are within 5 days of symptom onset. In this trial, molnupiravir was shown to reduce the chances of progressing to severe illness and death by about 30%. In addition, molnupiravir is also recommended for people for whom alternative antiviral therapies are not affordable or clinically appropriate. The proportion of adverse events (AEs) was similar in the molnupiravir group and the placebo group, at 30% and 33%, respectively. AEs that occurred in ≥2% of participants were COVID-19 pneumonia and bacterial pneumonia. Moreover, in the interim analysis of the MOVe-OUT study, the most common AE occurring in ≥1% of participants during treatment and 14 days after the last dose were diarrhea, nausea, dizziness, and headache.

Afterwards, Pfizer Europe MA EEIG announced their own oral antiviral, nirmatrelvir, which is marketed in combination with the already existing antiviral ritonavir (Paxlovid) and showed an impressive result of about 89% efficacy in preventing serious

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Table 1. Summary of Some Relevant Registered Clinical Studies of New Oral Antivirals Against SARS-Cov-2

Project/Study Title	Study Type	Country	Purpose	Status	Registration Database
EPIC-HR: Study of Oral PF-07321332/Ritonavir Compared With Placebo in Nonhospitalized High Risk Adults With COVID-19	Interventional (clinical trial)	United States	This study aims to determine whether PF-07321332/ritonavir is safe and effective for the treatment of adults who are ill with COVID-19 and do not need to be in a hospital, but are at an increased risk of developing severe illness. The total study duration is up to 24 weeks.	Completed	ClinicalTrials.gov (NCT04960202)
Efficacy and Safety of Molnupiravir (MK-4482) in Non-Hospitalized Adult Participants With COVID-19 (MK-4482-002)	Interventional (clinical trial)	United States	This study aims to evaluate the safety, tolerability, and efficacy of molnupiravir (MK-4482) compared to placebo. The primary hypothesis is that molnupiravir is superior to placebo as assessed by the percentage of participants who are hospitalized and/or die through day 29.	Completed	ClinicalTrials.gov (NCT04575597)
Platform Adaptive Trial of Novel Antivirals for Early Treatment of COVID-19 in the Community (PANORAMIC)	Interventional (clinical trial)	United Kingdom	This study aims to find new treatments that help those suffering with COVID-19 at home and in the community get better quicker and without needing to be treated in a hospital.	Recruiting	Not registered, although approved by the UK Medicines and Health Care Products Regulatory Agency and the Health Research Authority
COVID-19 International Drug Pregnancy Registry (COVID-PR)	Observational (prospective cohort study)	United States	This study aims to evaluate obstetric, neonatal, and infant outcomes among women treated with monoclonal antibodies or antiviral drugs indicated for mild, moderate, or severe COVID-19 from the first day of the last menstrual period (LMP) to the end of pregnancy. For monoclonal antibodies, the exposure period also includes 90 days prior to the first day of the LMP.	Recruiting	ClinicalTrials.gov (NCT05013632) EUPAS42517
TURN-COVID Biobank: The Dutch Cohort Study for the Evaluation of the Use of Neutralizing Monoclonal Antibodies and Other Antiviral Agents Against SARS-CoV-2 (TURN-COVID)	Observational (prospective cohort study)	Amsterdam	This study aims to establish a prospective cohort together with a biobank of patients treated with new SARS-CoV-2 therapies to evaluate their real-world effect and safety.	Recruiting	ClinicalTrials.gov (NCT05195060)
Postmarketing Surveillance Study of the Effectiveness and Safety of New Oral Antivirals for Outpatients With Mild-Moderate COVID-19 (ESOA-19)	Observational (prospective cohort study)	Portugal	This study aims to record the demographic and clinical history of adult individuals receiving oral antivirals against COVID-19 (nirmatrelvir/ritonavir and molnupiravir), providing real-world data on the effectiveness and safety of such therapies, as well as serving for as the starting point for collaborative clinical studies, enabling their planning and execution. The study is set up as a cohort event monitoring for 3 months after onset treatment and will be implemented in hospitals and primary health care centers.	Recruiting	EUPAS48186

illness and death from COVID-19 when taken for 5 days after the beginning of symptoms. Nirmatrelvir is a peptidomimetic inhibitor of the coronavirus 3C-like (3CL) protease, including the SARS-CoV-2 3CL protease. Inhibition of the 3CL protease renders the protein incapable of processing polyprotein precursors, which leads to the prevention of viral replication. Ritonavir is not active against the SARS-CoV-2 3CL protease but inhibits the cytochrome P450 (CYP) 3A–mediated metabolism of nirmatrelvir, thereby providing increased plasma concentrations of nirmatrelvir.[7] The EPIC-HR study,[8] a phase 2/3 randomized, double-blind, placebo-controlled trial, found that the incidence of AE was similar between groups, with 23% experiencing AEs in the nirmatrelvir-plus-ritonavir group and 24% in the placebo group, leading to 2.1% and 4.2% of participants discontinuing treatment and placebo, respectively. AEs occurred in >1% of participants and included dysgeusia, diarrhea, headache, and vomiting.

According to World Health Organization VigiAccess database, the most commonly reported adverse reactions to pharmacovigilance systems are similar to those occurring in clinical trials, for both nirmatrelvir plus ritonavir, and molnupiravir.[9]

Good clinical practices that ensure equity in access to therapies are imperative. In the context of the COVID-19 pandemic, this has to take into account the evolution of the epidemiological situation, the high vaccine coverage achieved, and the currently limited availability of new oral antivirals. Moreover, it is also crucial to the adequacy and safety of health care provision, identifying patients with the most significant benefit for each available therapeutic option at each stage of disease severity.[10,11] Since there is public health, political, social, and economic pressure to prevent severity, hospitalization, and death from COVID-19, monitoring the effectiveness and safety of commercialized oral antiviral therapies against SARS-CoV-2 has become an emergent pharmacovigilance and public health task.[12] The scientific evidence regarding these drugs is still scarce, which justifies permanent monitoring and adaptation of the recommendations on therapy for COVID-19.

Uncertainties Over the Evidence

There are insufficient data on new oral antivirals in clinical practice, particularly from large-scale studies on the long-term efficacy or safety. Currently, the existing data are just supported by the clinical trials that led to the approval of these drugs, as well as some AE data that are now starting to be reported to regulatory agencies, as described above. Moreover, those trials have demonstrated significant differences between the results of the interim and final analyses and the clinical significance of the findings.

Based on current evidence, emerging challenges in the field of pharmacoepidemiologic research arise:

1. *Special populations*: Data during pregnancy and breastfeeding are lacking. As part of the authorization conditions attached to the approval of molnupiravir by the British regulator, the company is required to conduct a drug use study, collecting data on pregnancy outcomes for women exposed to this drug. For ethical reasons, conducting studies in a real-life context is unlikely, not least because they are not part of the eligible population. Thus, new clinical trials should be considered in this population. Further, patients with renal impairment are indicated to reduce the dose of nirmatrelvir by half for each dose. As each daily blister contains 2 nirmatrelvir and 1 ritonavir tablet, the potential for overdose error in these patients and putative clinical consequences should be considered. However, the Food and Drug Administration recently revised the emergency use authorization for nirmatrelvir plus ritonavir to authorize an additional dose pack with appropriate dosing for patients with moderate renal impairment. Thus, at this moment, it is already possible to find a nirmatrelvir-plus-ritonavir 150-mg/100-mg dose pack for patients with moderate renal impairment as an alternative to the 300-mg/100-mg dose pack for patients with normal renal function or mild renal impairment.[13] As the distribution of this new pack is not yet widely available in many countries, caution must be maintained when prescribing this combination drug.
2. *Drug interactions*: Nirmatrelvir plus ritonavir is described as a drug with great potential for drug–drug interaction. As described above, ritonavir is a potent CYP3A inhibitor aiming to boost the activity of nirmatrelvir by increasing its concentration in plasma to ensure persistence of antiviral concentrations during the 12-hour dosing interval. Both drugs may produce relevant interactions when coadministered with various other agents, such as CYP3A substrates, inducers, or inhibitors.[7] Currently, this potential is greater for nirmatrelvir plus ritonavir than for molnupiravir, not least because we already had previous data for ritonavir, which is already well known in clinical practice. The complexity of the interaction profile driven by the ritonavir booster dose could be a limiting factor in its use. New real-life data may condition the prescribing cascade for different patient populations with concomitant medications.

3. *(Non)immunized populations*: Based on current evidence, no conclusions can be drawn regarding expected differences in efficacy among unvaccinated individuals or those with antibodies generated by natural infection (previous or recent infection) or immunization against SARS-CoV-2. There is still uncertainty regarding the circulation of new variants of SARS-CoV-2, so future pharmacoepidemiologic studies should consider this variable. It is worth investigating further whether an at-risk patient having had 2 or 3 vaccine doses might be better protected with the oral antiviral than a yearly booster. Another possibility is a patient with an increased risk of serious disease taking the oral antiviral drug prophylactically, especially before the period of the year most prone to respiratory diseases.
4. *Pharmacoeconomics*: There are no published data on treatment costs for health services or other comprehensive economic analyses such as cost-benefit and cost-effectiveness. There is an urgent need for cost-effectiveness studies to compare these drugs with other therapeutic alternatives, considering their costs and consequences or health effects.

Ongoing Real-Life Research

A real-life cohort event monitoring system allows for the monitoring of newly introduced oral antivirals, in addition to existing spontaneous reporting systems and health care database studies (ie, secondary data), as it is complementary to these systems in several ways. First, it is better suited to capture the more frequent AE, including those that are not medically attended. Then, it generates more comprehensive safety data, for example, on disease course and the impact of the AE.

Intending to address some gaps that exist in real-life data derived from the use in clinical practice of these new antivirals, the Porto Pharmacovigilance Center of the Portuguese Pharmacovigilance System, has an ongoing investigator-initiated study for pharmacoepidemiologic surveillance in the real-world setting. The study titled "Post-marketing Surveillance Study of the Effectiveness and Safety of New Oral Antivirals for Outpatients With Mild-Moderate COVID-19" (ESOA-19) is an open, prospective, multicenter, observational cohort study (patient registry), phase IV. The ESOA-19 intends to record the demographic and clinical history of adult individuals receiving oral antivirals against SARS-CoV-2, providing real-world data on the effectiveness and safety of such therapies and serving as the starting point of collaborative clinical studies, enabling their planning and execution. The study was registered in the EU PAS Register (EUPAS48186) of the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) and won the EnCePP Seal for considering the relevant methodological research standards described in the ENCePP Guide on Methodological Standards in Pharmacoepidemiology and conducted in line with the rules and requirements for independence and transparency. As such, the project is suitable to be replicated in other health institutions that may be considered in the regulations of each country as dispensing settings for oral antivirals.

Other studies are also being conducted in other countries. In the United Kingdom, the PANORAMIC study is a randomized trial of antiviral therapeutic agents for use by clinically vulnerable people in the community with confirmed acute symptomatic SARS-CoV-2 infection. Moreover, the COVID-PR is an observational study required by the European, American, Canadian, and Australian regulators, and aims to evaluate obstetric, neonatal, and infant outcomes among women treated with monoclonal antibodies or antiviral drugs indicated for mild, moderate, or severe COVID-19, from the first day of the last menstrual period to the end of the pregnancy. The TURN-COVID is an observational cohort study that includes a biobank of patients who receive neutralizing monoclonal antibodies and other novel antiviral agents against SARS-CoV-2; this study seeks to answer questions related to viral load kinetics, viral variants, spike mutations and immune escape, and the kinetics of the inflammatory response. Several other studies are ongoing for nirmatrelvir plus ritonavir in populations with particular clinical conditions. As such, most of the studies registered in ClinicalTrials.gov and the ENCePP registry seek to respond to specific clinical gaps but differ from those we aim at with the ESOA-19.

In conclusion, given the global impact of this disease, new therapeutic approaches are welcome. However, it should be noted that approvals by regulatory agencies were based on the limited data from clinical trials; therefore, new pharmacoepidemiologic studies must be promptly implemented in the ongoing active surveillance of these patients.

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Author Contributions

Renato Ferreira da Silva and Ana Marta Silva wrote the first draft of the manuscript. All authors contributed equally to the design, planning, discussion, and final review of the manuscript.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

Data Availability Statement

All data and information are publicly available through the references.

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