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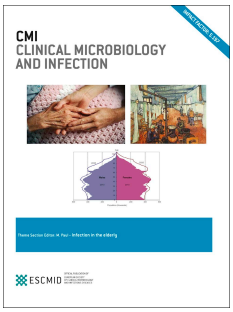

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Narrative review – April 13, 2022 – Version R2-1

First-Generation Oral Antivirals Against SARS-CoV-2

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Abstract

Background: Oral drugs against SARS-COV-2 have received emergency use authorization for the treatment of mild-to-moderate COVID-19 in nonhospitalized patients who are at high risk for clinical progression.

Objectives: To provide a clinical practice overview of first-generation oral antiviral agents against SARS-CoV-2.

Sources: References for this review were identified through searches of PubMed, Google Scholar, bioRxiv, medRxiv, regulatory drug agencies, and pharmaceutical companies' websites up to 16 February 2022.

Content: Molnupiravir and nirmatrelvir/ritonavir have been authorized for use in nonhospitalized individuals with mild-to-moderate COVID-19 who are at high risk for progression. In clinical trials, molnupiravir reduced the frequency of hospitalization or death by 3% (relative risk reduction 30%), and nirmatrelvir/ritonavir by 6% (relative risk reduction 89%). Their use in clinical practice requires early administration, review of drug-drug interactions (nirmatrelvir/ritonavir), considerations of embryo-fetal toxicity (molnupiravir), and compliance with ingestion of a high number of pills. Knowledge gaps include the efficacy of these agents in vaccinated, hospitalized, or immunosuppressed individuals with prolonged SARS-CoV-2 persistence.

Implications: First-generation oral antivirals represent progress in therapeutics against SARS-CoV-2, but also pose new challenges in clinical practice. Further advances in the development of new drugs are required.

Keywords: COVID-19; SARS-CoV-2; Coronavirus; Molnupiravir; Nirmatrelvir; Antivirals.

Background

Emergency use authorizations of oral drugs against SARS-COV-2 by regulatory authorities provide new options to treat high-risk outpatients with mild-to-moderate COVID-19. This progress represents a major advance, but also poses challenges in clinical practice. This review provides a clinical overview of the first-generation oral antiviral agents against SARS-CoV-2. Parenteral therapeutics, including anti-spike monoclonal antibodies and remdesivir, are outside the scope of this article and are reviewed elsewhere [1, 2].

Methods

Electronic searches were conducted in PubMed, ClinicalTrials.gov, bioRxiv, medRxiv, and Google Scholar databases until 16 February 2022 using the search terms "SARS-CoV-2," "COVID-19," "antivirals," "oral," "EIDD-2901," "MK-4482," "EIDD-1931," "β-d-N4-hydroxycytidine," "NHC," "NHC-triphosphate," "molnupiravir," "PF-00835321," "PF-00835321," "PF-07304814," "PF-07321332," and "nirmatrelvir." References were screened for relevance. Product fact sheets and the drug interaction resource www.covid19-druginteractions.org were consulted.

Targets for drugs

Targets for antiviral compounds include attachment inhibitors, host protease inhibitors, viral protease inhibitors, RNA-dependent RNA polymerase (RdRP) inhibitors, and maturation inhibitors [3]. **Table 1** shows oral compounds that are authorized for use or under development. The viral main protease M^{pro} and the polymerase RdRP are the current targets for oral antivirals against SARS CoV-2. Several health regulatory agencies have emergently authorized nirmatrelvir, a viral protease inhibitor, and molnupiravir, an RdRP inhibitor, for clinical use. Their pharmacological and other characteristics are summarized in **Table 2**.

The mechanisms of action of nirmatrelvir and molnupiravir have been described elsewhere [4, 5]. In brief, nirmatrelvir inhibits the main protease of SARS-CoV-2, M^{pro} (also called 3CL protease), which catalyzes the cleavage of viral polyproteins into nonstructural proteins that are essential for viral replication [4, 6]. For clinical use, nirmatrelvir is combined with ritonavir as a pharmacokinetic booster. By inhibiting cytochrome P450 CYP3A4, ritonavir boosts the concentration of nirmatrelvir sufficiently to inhibit SARS CoV-2 replication [4]. Ritonavir also prolongs the half-life of nirmatrelvir, supporting twice-daily administration. Molnupiravir is a prodrug of β-d-N4-hydroxycytidine (NHC) [7]. As a ribonucleoside analog, NHC is phosphorylated to NHC-triphosphate intracellularly, which is incorporated into viral RNA via RdRp. Elongation of viral RNA continues with incorporation of incorrect NHC bases, leading to multiple errors in the viral genome and loss of viable virus ("viral error catastrophe") [5, 8].

Data on nirmatrelvir/ritonavir

Nirmatrelvir/ritonavir was evaluated in the EPIC-HR (NCT04960202 [9]) and EPIC-SR (NCT05011513) clinical trials. In EPIC-HR study, 2246 nonhospitalized, nonvaccinated participants at high-risk of progression to severe disease were enrolled within 5 days of symptom onset (1126 in placebo arm, 1120 in nirmatrelvir/ritonavir arm). The modified intention-to-treat (mITT) analysis included participants within 3 days of symptoms who did not receive monoclonal antibodies (682 in placebo arm, 697 in nirmatrelvir/ritonavir arm). In the mITT analysis, the proportion of participants with COVID-19 related hospitalization or all-cause death by day 28 was 0.72% (5/697) in the nirmatrelvir/ritonavir arm and 6.45% (44/682) in the placebo arm (difference –5.73%; with Kaplan–Meier method and estimated event rates, the difference was –5.81%, 95% CI –7.78% to –3.84%; $P<0.001$, relative risk reduction 88.9%). No deaths occurred in the nirmatrelvir/ritonavir arm; 9 (1.32%) occurred in the placebo arm [9]. The EPIC-SR (NCT05011513) study enrolled 1140 study participants

with low or standard risk profiles (including some who had received COVID-19 vaccination) and assessed a different primary endpoint: sustained alleviation of all targeted COVID-19 signs and symptoms through day 28 [10]. In the interim analysis, no difference was seen in the proportion of individuals achieving sustained alleviation of symptoms between arms; the study is ongoing. Compared to the EPIC-HR study results [9], the proportion of participants who required hospitalization or died was similar in the nirmatrelvir/ritonavir arm (0.70%, 3/428), but lower in the placebo arm (2.4%, 10/426). The relative risk reduction for hospitalization or death was 70%, but this was not statistically significant (*P*=0.051) [10].

Data on molnupiravir

A phase 2a study demonstrated that administration of molnupiravir for 5 days cleared SARS-CoV-2 faster than placebo [11]. The study included 202 nonhospitalized, nonvaccinated participants with <7 days duration of symptoms. First, 46 patients were 1:1 randomized to receive placebo versus 200 mg molnupiravir every 12 hours, and then 156 patients were 1:3 randomized to receive placebo versus 400 mg molnupiravir versus 800 mg molnupiravir every 12 hours. Statistically significant faster clearance of viral RNA in nasopharyngeal swabs (defined as <1018 copies/ml) was observed with 800 mg twice daily. On day 3 of treatment, there was a significant difference in the proportion of patients from whom infectious virus was culturable (1/53 [1.9%] in participants treated with 800 mg versus 9/54 [16.7%] in the placebo group, *P*=0.016). In the phase 3 MOVe-OUT study, 1433 nonhospitalized, nonvaccinated participants with ≤5 days of symptoms and at least one risk factor for severe COVID-19 were randomized to receive placebo (n=717) or molnupiravir (n=716) [12]. In the interim analysis, which included about half of the eventual study participants, COVID-19 hospitalization or death by day 29 was observed in 7.3% (n=28/385) in the molnupiravir arm and in 14.1% (n=53/377) in the placebo arm (adjusted difference –6.8%; 95% CI –11.3% to –2.4%; *P* = 0.001, relative risk reduction 48%). Fewer

hospitalizations in the placebo arm were observed among participants enrolled during the second half of the study, leading in the final analysis to a diminishment in risk reduction: 6.8% (n=48/709) in the molnupiravir arm and 9.7% (n=68/699) in the placebo arm (adjusted difference –3.0%; 95% CI –5.9% to –0.1%; *P* = 0.02, relative risk reduction 30%). One death occurred in the molnupiravir arm (0.1%); 9 (1.3%) occurred in the placebo arm. The reason for the difference in risk reduction between participants enrolled in the first compared to the second half of the study is unclear. The authors suggest insignificant imbalances of multiple factors between the comparison groups that may have accumulated between the interim and final analysis (e.g., more females, more individuals with anti-SARS-CoV-2 antibodies and lower virological load in the placebo arm) [12].

Indication and knowledge gaps

The effectiveness of molnupiravir and nirmatrelvir/ritonavir should be viewed in light of the circulating SARS-CoV-2 variant, as the efficacy endpoint – COVID-19-related hospitalization – may be lower with a viral strain that is responsible for less hospitalization in immune populations (e.g., the Omicron variant as opposed to Delta [13]). The population investigated in clinical trials consisted of nonvaccinated individuals, but vaccination (and boosting) is highly recommended especially in individuals with risk factors for severe COVID-19. The efficacy of oral antivirals is not yet quantified in fully vaccinated individuals and may also be lower. The interim analysis of the EPIC-SR trial (which included partially vaccinated individuals) indicated a non-significant difference between the nirmatrelvir/ritonavir and the placebo arms [10], although final results are awaited. Moreover, in a fully vaccinated and predominantly healthy population, the baseline risk of hospitalization may be lower and thus, the number needed to treat may be substantially higher. One commentary described a hospitalization rate of 0.15% among vaccinated Navy and Marine Corps populations [14]. The cumulative incidence of hospitalization for COVID-

19 among U.S. veterans vaccinated with BNT162b2 or mRNA-1273 was less than 0.15% over a 24-week period [15]. This is in contrast to the higher hospitalization rates of unvaccinated individuals in the placebo groups of the EPIC-HR, EPIC-SR (interim results), and MOVe-OUT studies of 7%, 2.4%, and 9.7%, respectively, which translated to numbers needed to treat of 17, 59, and 34, respectively [9, 10, 12]. When extrapolating the efficacy of oral antivirals to a vaccinated population, the absolute hospitalization rate decreases from 0.15% to 0.105% (i.e., 30% relative risk reduction) or to 0.015% (i.e., 90% relative risk reduction). Accordingly, the numbers needed to treat increase to 741, or to 2222, respectively. When estimating costs needed to prevent a COVID-19-related hospitalization [14], one therefore needs to consider the rapidly changing epidemiology of both the circulating viral variants of concern and population immunity.

Individuals with severe comorbidities (e.g., transplant patients, those receiving chemotherapy or immunosuppressive drugs) remain at risk for severe COVID-19 despite being fully vaccinated [16-18]. This argument favors the decision to use antiviral therapeutics despite the lack of data in vaccinated individuals with breakthrough COVID-19 [19]. Moreover, prolonged SARS-CoV-2 persistence occurs in immunocompromised individuals [20-25]. The optimal duration of oral antiviral treatment, their efficacy in viral clearance, and the risk of development of drug resistance in immunosuppressed patients are unknown. The efficacy of combination therapies (e.g., anti-SARS CoV-2 monoclonal antibody plus oral antivirals) in eliminating the virus and preventing drug resistance needs to be elucidated. The benefit of oral antivirals for post-exposure prophylaxis is not known and these drugs are not currently authorized for this indication. The efficacy of nirmatrelvir/ritonavir to prevent symptoms of COVID-19 in adults who have been exposed to household members with confirmed symptomatic COVID-19 is being investigated (NCT05047601, EPIC-PEP).

Finally, pharmacovigilance for new antivirals is of upmost importance to address long-term safety concerns. The antiviral mechanism of molnupiravir is lethal mutagenesis; therefore, the

mutagenic potential in human cells must be carefully monitored [26-28]. In their assessment report on molnupiravir, the European Medicines Agency concluded that lack of genotoxic potential cannot be definitively excluded, although the genotoxic risk could be considered justifiable in the context of the clinical benefit [29].

Challenges in clinical practice

Start early: Oral antivirals should be started as early as possible after symptoms develop and the diagnosis is confirmed (i.e.; within 5 days of COVID-19 symptom onset). However, early initiation is challenging when access to testing or medications is limited, rapid turnaround times of test results are not guaranteed, or the distance to healthcare services is long.

Accessibility/drug availability: Molnupiravir and nirmatrelvir/ritonavir are being rolled out to pharmacies and health centers in countries where they are authorized. The mode of distribution, monitoring of pills in stock, and availability for individuals qualifying for treatment, in association with the prescription process, reflect several challenges for authorities and providers. During times of high demand and limited supplies, equitable allocation strategies will be necessary (e.g., prioritizing those at highest risk for severe COVID-19), and should ensure access for disproportionately affected and vulnerable populations. Prescribers of oral antivirals should ascertain that the pills are available and can be provided before sending patients or their representatives to a pharmacy.

Drug-drug interactions: Molnupiravir is not anticipated to have drug interactions, based on limited data. In contrast, the concomitant use of nirmatrelvir/ritonavir and sensitive substrates of P-glycoprotein or drugs predominantly metabolized by cytochrome P450 CYP3A may result in clinically relevant drug interactions. Concomitant medications, including over-the-counter medicines, herbals, or recreational drugs (e.g., certain opioids such as fentanyl), must be reviewed for their potential for drug-drug interactions prior to prescribing nirmatrelvir/ritonavir [30]. Consultation with a specialist (e.g., pharmacologist), COVID-19

treatment guidelines, specialized drug-interaction website (e.g., Liverpool COVID-19 Interactions, www.covid19-druginteractions.org), or the fact sheet for nirmatrelvir/ritonavir is mandatory for providers prescribing this medication. Therapeutic drug monitoring (TDM) and/or dose adjustment of comedications are difficult to implement within this short 5-day treatment window for nirmatrelvir/ritonavir. Several strategies can be used to manage drug-drug interactions with nirmatrelvir/ritonavir:

(i) Temporary withholding of the interacting comedication (e.g., statins) and restarting 3 days after the last dose of nirmatrelvir/ritonavir because the effect of ritonavir takes several days to resolve. The impact of short cessation of comedications on chronic disease has not been evaluated, and therefore special attention should be paid to high adherence after restarting the comedication.

(ii) Not withholding the interacting comedication but patient counselling with symptom-driven pausing of drugs where appropriate (e.g., antihypertensives, HIV regimens that include cobicistat or ritonavir).

(iii) Dosage adjustment and clinical or TDM. However, TDM is frequently not feasible in an outpatient setting (at a time when patients are potentially highly contagious) and therefore necessitates a careful risk-benefit evaluation of nirmatrelvir/ritonavir versus an alternative COVID-19 treatment. Examples of drugs requiring complex monitoring are tacrolimus or digoxin.

(iv) Switch to an alternative medication (e.g., clopidogrel could be changed to prasugrel in patients with recent cardiac stents).

There are certain drug-drug interactions for which nirmatrelvir/ritonavir is not recommended and an alternative COVID-19 treatment must be sought. Stopping comedication characterized by a narrow therapeutic index and long half-life (e.g. amiodarone) will not prevent drug-drug interactions. Strong inducers of cytochrome P450 CYP3A4, such as rifampin, anticonvulsants, and the herbal product St. John's Wort will continue to induce for several

days even after the drug has been discontinued. They can decrease nirmatrelvir/ritonavir concentrations, causing potential loss of virologic response and risking resistance development. These examples underscore the importance of reviewing drug-drug interactions when considering nirmatrelvir/ritonavir therapy [30].

Patient serostatus: Both MOVe-OUT and EPIC-HR studies demonstrated a higher efficacy of antivirals in seronegative relative to seropositive participants. The number of seropositive individuals who achieved the primary endpoint was low in the molnupiravir study (n=5/136 in molnupiravir arm versus 2/146 in placebo arm) [12]. The absolute risk reduction of nirmatrelvir/ritonavir in comparison to placebo was –1.34% (95% CI –2.45% to –0.23%) in seropositive individuals [9]. These data indicate that naturally-acquired anti-SARS-CoV-2 antibodies diminish the magnitude of treatment effectiveness of oral antivirals. However, the data were generated prior to the emergence of the Omicron variant. Recent data from the U.K. and South Africa demonstrated that both naturally-acquired and vaccine-induced antibodies have limited protection against infection with the Omicron variant [31, 32]. These observations, together with the turn-around time of serology results and the necessity of early treatment, lessen the value of serostatus assessment in the treatment decision-making process.

Compliance: Although oral antivirals are administered for only 5 days, the number of pills that must be taken is considerable (**Table 2**). Such a high number of pills ingested per day may decrease adherence.

Individuals of child-bearing potential: There is a warning of potential embryo-fetal toxicity for molnupiravir. Individuals of child-bearing and reproductive potential should use contraception during and after treatment (**Table 2**). Prescribers of molnupiravir to males who are sexually active with females of child-bearing potential must remind their patients to use contraception during treatment and for ≥3 months after the last dose [33].

Pregnant women: Pregnant women are at a significantly greater risk of severe COVID-19 [34]. Molnupiravir is not recommended in pregnancy. There are no available human data on

the use of nirmatrelvir during pregnancy. Use of ritonavir during pregnancy has an acceptable safety profile. The American College of Obstetricians and Gynecologists recommends weighing the available data against the individual risks of COVID-19 in pregnancy in a shared decision-making process. Nirmatrelvir/ritonavir may be considered in pregnant individuals with mild-to-moderate COVID-19 if one or more additional risk factors are present (e.g., body mass index >25, chronic kidney disease, diabetes mellitus, cardiovascular disease) [35]. However, other treatment options may also be considered (e.g., monoclonal antibodies, remdesivir [36]).

Resistance development

Preclinical studies with molnupiravir and its parental nucleoside revealed high barriers to resistance [37, 38]. In the EPIC-HR trial, sequence analysis data suggested no significant associations between M^{pro} mutations and treatment failure. Substitutions in the M^{pro} emerged in 4 cases (A260V [n=3] and A260T [n=1]), although nirmatrelvir activity was not reduced in a biochemical assay [39]. Both molnupiravir and nirmatrelvir/ritonavir demonstrate preserved activity against variants of concern, including Omicron [40, 41]. Animal studies indicate similar antiviral activity against BA.1 and BA.2 Omicron lineages [42]. Evolution and constituent mutations of SARS-CoV-2 have hitherto mainly affected the genetic variability of the spike proteins, resulting in emergent SARS-CoV-2 variants and diminishment or loss of effect of anti-SARS CoV-2 monoclonal antibody therapies [2, 43]. There are questions about potential resistance development against RdRp and M^{pro} inhibitors. Monotherapies that focus on a single target may be more prone to resistance development than are combination therapies that attack multiple targets simultaneously. This concern derives from the observations made with first-generation antivirals against HIV and is in particular relevant to the treatment of immunocompromised individuals who may have prolonged SARS CoV-2

283 replication. *In vitro* studies with SARS-CoV-2 demonstrated promising results with
284 combination therapies [40].
285
286 **Outlook and Conclusion**
287 Oral antivirals provide an easier-to-administer option than anti-SARS CoV-2 monoclonal
288 antibodies and intravenous remdesivir. Current data indicate that RdRP and M^{pro} inhibitors
289 have a higher barrier to resistance development than that observed with anti-spike monoclonal
290 antibodies. Two compounds have been authorized for clinical use while several promising
291 candidates are still in the preclinical or early phase clinical trials (**Table 1**).
292 Although the newly authorized treatment regimens offer a more convenient option for
293 patients, they pose significant challenges in clinical practice. Strategies to overcome such
294 challenges should be implemented. The history of drug development against other viral
295 diseases holds promise that these first-generation antivirals against SARS-CoV-2 can be
296 improved upon in the future.

Transparency declaration

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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Contribution: PS performed the literature search, wrote the first draft, and revised and approved the final version. RRR, SBN, AS, and RTG revised the first draft, reviewed and completed the references, and approved the final version.

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519 **Table 1:** Selected oral antivirals with activity against SARS-CoV-2 and their status in the
520 development for clinical use. Table adapted from [44].

521

Antiviral agent	Company	Status
RdRp Inhibitors		
Molnupiravir	Merck & Co.	Authorized for clinical use*
GS-5245 (Remdesivir oral)	Gilead/Jubilant	Phase 1 [45]
Prodrug of remdesivir parent compound (nucleoside GS-441524)		
ODBG-P-RVn	University of California San Diego	Preclinical [46]
GS-621763	Gilead/Georgia State University	Preclinical [47]
M^{pro} Inhibitors		
Nirmatrelvir/ritonavir	Pfizer	Authorized for clinical use*
S-217622	Shionogi	Phase 2/3 (Japan) [48-50]
PBI-0451	Pardes Biosciences	Phase 1 [51]
EDP-235	Enanta	Preclinical [52, 53]

522 *Several health authorities have authorized the emergency use of the compound. The list of
523 countries that have authorized one compound or both drugs is subject to change and not listed.

524 **Table 2:** The pharmacological and other important characteristics of molnupiravir and
525 nirmatrelvir/ritonavir. Table reused with permission and adapted from [54].

Compound name	**Molnupiravir**	**Nirmatrelvir/Ritonavir**
Trade name	Lagevrio	Paxlovid
Drug class	Nucleoside analog	SARS-CoV-2 protease inhibitor (nirmatrelvir) HIV-1 protease inhibitor and CYP3A inhibitor (ritonavir)
Dosing depending on age and body weight	≥18 years, no weight adaptation: 800 mg every 12 hours	≥12 years and ≥40 kg: 300 mg nirmatrelvir plus 100 mg ritonavir every 12 hours
Number of pills per dose	4 (4 × 200 mg)	3 (2 × 150 mg nirmatrelvir plus 1 × 100 mg ritonavir)
Duration of treatment	5 days	5 days
Influence of food on absorption	None listed	Fat-rich food reduced absorption by approximately 15%
Dose adaptation according to renal function	No dose adjustment[1]	eGFR ≥ 60 mL/min: no adaptation
		eGFR 30-60 mL/min: 1 × 150 mg nirmatrelvir plus 1 ×100 mg ritonavir every 12 hours
		eGFR ≤ 30 mL/min: not recommended
Dose adaptation according to liver function	No dose adjustment[2]	Not recommended in the case of severe liver function impairment (Child-Pugh class C)
Contraindication	None listed	Hypersensitivity to ingredients. Avoid in the case of drug-drug interaction that involves CYP3A4 metabolism
Warnings	Embryo-fetal toxicity; bone and cartilage toxicity; hypersensitivity to ingredients	Drug-drug interactions; hypersensitivity to ingredients; hepatotoxicity; individuals with HIV infection[3]
Warnings to individuals with reproductive potential	Females: Use contraceptives during treatment and for 4 days after the last dose	According to manufacturer's sheet, ritonavir may reduce the efficacy of hormonal contraceptives (ethinyl estradiol ↓). Clinically, this

	Males: Use contraception during treatment and ≥ 3 months after the last dose	interaction is unlikely to be relevant [55].
Pregnancy and lactation	Not recommended[4]	No data available
Most common side effects	Diarrhea, nausea, dizziness	Dysgeusia, diarrhea, hypertension, myalgia

[1]Little or no data on individuals with severe renal impairment (eGFR ≤ 30 mL/min).

[2]Little or no data on individuals with severe hepatic impairment (Child-Pugh class C).

[3]In the emergency use authorization, there is a warning about the possibility of HIV-1 resistance development in patients with HIV. In our view, the risk of developing resistance after 5 days of nirmatrelvir/ritonavir treatment is very low in people with HIV who are not receiving antiretroviral therapy and negligible in individuals with HIV who are receiving antiretroviral therapy and who are virologically suppressed.

[4]Based on findings from animal reproduction studies, molnupiravir may cause fetal harm when administered to pregnant individuals. There are no available human data on the use of molnupiravir in pregnant individuals to evaluate the risk to pregnant or lactating women.