Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Short Communication

Assessing the proportion of the Danish population at risk of clinically significant drug-drug interactions with new oral antivirals for early treatment of COVID-19

Carsten Schade Larsen*

Department of Infectious Diseases, Aarhus University Hospital, Aarhus, Denmark

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ABSTRACT

Objectives: The oral antiviral drugs nirmatrelvir/ritonavir (NMV/r) and molnupiravir have been approved for early outpatient treatment of COVID-19 to prevent severe disease. Ritonavir, contained in NMV/r, is known to have significant drug-drug interactions (DDI) with several drugs frequently used by the elderly. This communication puts the problem with DDI with oral antiviral COVID-19 treatment into perspective by assessing the percentage of the elderly population at risk of severe COVID-19, using drugs with significant DDI with oral antivirals.

Methods: We estimated the size of the Danish population at risk of significant DDI with antiviral COVID-19 treatment using the number of claimed prescriptions for drugs predicted to interact with NMV/r in Denmark in 2020.

Results: Danish prescription data demonstrate the extensive use of drugs likely to interact with NMV/r. Anticoagulants contraindicated during NMV/r treatment were used by 20% of people ≥65 years and 30% of people ≥80 years. Statins that must be paused during NMV/r treatment were used by 15-18%. More than one in five used either analgesics, calcium channel blockers, or digoxin.

Conclusion: There is major potential for significant DDI with NMV/r in the elderly population at risk of severe COVID-19 disease. This calls for clear guidance for prescribers to ensure patient safety and treatment success.

Infection with SARS-CoV-2 usually causes mild to moderate respiratory disease. However, elderly patients and those with underlying chronic medical conditions are at high risk of progressing to severe COVID-19 (Ko et al., 2021; Thakur et al., 2021).

Until recently, intravenous remdesivir was the only antiviral drug approved for the treatment of COVID-19. Now, two oral antiviral drugs, nirmatrelvir/ritonavir (NMV/r) (Paxlovid) and molnupiravir (Lagevrio), are available for outpatient treatment of early-stage COVID-19; both are recommended by the World Health Organization (Agarwal et al., 2020). In clinical trials with unvaccinated adults at high risk for progression to severe COVID-19, treatment with NMV/r reduced the relative risk of hospitalization or death by 89% versus placebo (Hammond et al., 2022). Molnupiravir showed a 50% relative risk reduction versus placebo (interim analysis), with a 30% relative risk reduction when all patients were analyzed (Jayk Bernal et al., 2022). Emerging real-world data from Hong Kong suggest that both treatments are effective in a clinical setting (Wong et al., 2022).

Ritonavir is a strong inhibitor of cytochrome P450 (CYP) 3A4 inhibitor and P-glycoprotein. Therefore, NMV/r has a high potential for significant drug-drug interactions (DDI) (Marzolini et al., 2022). No clinically significant DDIs have yet been identified with molnupiravir (European Medicines Agency, 2022).

As polypharmacy is frequent in patients at risk of severe COVID-19, oral antiviral treatment of early-stage COVID-19 poses a risk of significant DDI in the target groups. DDI may result in toxicity or lack of efficacy if not adequately managed by the treating physician. Therefore, prescribers must be aware of the risks of DDI with COVID-19 treatment.

* Corresponding author: Carsten Schade Larsen Dept. of Infectious Diseases Aarhus University Hospital Palle Juul-Jensens Boulevard 99 8200 Aarhus N Denmark
E-mail address: Carsten.Schade.Larsen@vest.rm.dk

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Table 1
The proportion of patients in Denmark at risk of DDI with NMV/r based on the number of prescriptions in 2020.

Treatment recommendation based on DDI risk	Use another COVID-19 treatment than NMV/r[a]	Pause or replace drug during NMV/r treatment[b]	Proportion of patients at risk of interactions		Adjust dose and/or monitor closely during NMV/r treatmen[c]	Counsel patient during NMV/r treatment[d]	Proportion of patients at risk of interactions	
			Patient age group				Patient age group	
			≥65 years	**≥80 years**			**≥65 years**	**≥80 years**
Anticoagulants		Apixaban Clopidogrel Rivaroxaban	19.62%	29.83%	Warfarin	Edoxaban Dabigatran	4.83%	8.05%
Lipid-lowering agents		Simvastatin Lovastatin	15.45%	17.70%	Atorvastatin		19.91%	15.85%
Analgesics					Fentanyl Oxycodone	Hydromorphone Morphine Tramadol	19.99%	31.57%
Hypertension/Heart failure					Digoxin		20.97%	25.32%
Calcium channel blockers						Verapamil Amlodipine Nifedipine	20.82%	24.13%
Antipsychotics		Clozapine	2.69%	5.24%	Haloperidol Risperidone		1.23%	2.84%
Anticonvulsants	Carbamazepine Phenobarbital Phenytoin	Clonazepam			Ethosuximide			
Anxiolytics		Midazolam Diazepam						
Antiarrhythmics	Amiodarone		0.65%	1.02%	Lidocaine		-	-

For each drug category, the proportion of patients at risk of DDI with NMV/r is based on the total number of patients claiming at least one prescription in the year 2020 in relation to the number of individuals in Denmark in each age category by January 1, 2020.
Categorization of interactions is based on the Liverpool Drug Interactions Database: www.covid19-druginteractions.org (accessed 05 April 2022):
[a] Continued risk of severe toxicity or reduced NMV/r efficacy after pausing the drug.
[b] NMV/r treatment can only be started if the drug can be safely paused or replaced. The drug can be resumed three days after the end of NMV/r therapy.
[c] Potential clinically significant interaction that is likely to require additional monitoring, alteration of drug dosage, or timing of administration.
[d] Patient should be counseled about potential interactions and about temporarily pausing the drug if needed.DDI = drug-drug interactions; NMV/r = Nirmatrelvir/ritonavir.

Herein, we highlight the issue by assessing the percentage of the elderly Danish population at risk of DDI with oral antiviral agents for COVID-19 treatment.

As no DDI with molnupiravir has been identified (European Medicines Agency, 2021), we estimated the proportion of older people (aged ≥65 or ≥80 years) in Denmark who claimed prescriptions for drugs with potential DDI toward NMV/r (European Medicines Agency, 2022) in the year 2020 using data from medstat.dk (Medstat, 2021) and Year 2020 population statistics from Statistics Denmark (Statistics Denmark, 2022). DDIs were categorized using the University of Liverpool COVID-19 DDI database (University of Liverpool, 2022).

Danish prescription data demonstrate the extensive use of drugs likely to interact with NMV/r in people aged ≥65 and ≥80 years (Table 1). Anticoagulants contraindicated during NMV/r treatment were used by 20% of people aged ≥65 years and 30% of people ≥80 years. Statins that must be paused during NMV/r treatment were used by 15-18%, whereas statins requiring dose adjustment were used by up to 20%. Moreover, ≥20% used either analgesics, calcium channel blockers, or digoxin requiring dose adjustments or patient counseling during NMV/r treatment.

Our evaluation of Danish prescriptions demonstrates the extensive use of drug classes prone to significant DDI with NMV/r in elderly patients vulnerable to severe COVID-19 disease. The analysis covers only prescribed medicine purchased at pharmacies, excluding drugs administered at hospitals or handed out in outpatient specialist clinics. However, it may include individuals claiming prescriptions for several drugs.

Many DDIs can be managed by dose adjustments or temporarily withholding one or more drugs (Marzolini et al., 2022). Recovery of CYP3A activity after discontinuation of NMV/r may take 2-5 days, and paused medicine should not be resumed until 3 days after (Stader et al., 2020). According to the Liverpool DDI checker (University of Liverpool, 2022), the commonly prescribed simvastatin should not be co-administered during NMV/r treatment, whereas atorvastatin would demand a dose adjustment. Patients at low risk of atherosclerotic events could potentially pause the statin treatment during NMV/r administration. Alternatively, a switch to other statins/lipid-lowering agents or dose adjustments could be considered (European Society of Cardiology, 2022).

It is not recommended to stop anticoagulant treatment because of the risk of life-threatening embolic events (Nadkarni et al., 2020). Moreover, emerging evidence indicates the benefits of continued anticoagulation therapy to improve COVID-19 complications. Although some new oral anticoagulants (NOACs) do not interact with CYP3A4 and could be alternatives to apixaban and rivaroxaban, European Heart Rhythm Association guidelines do not recommend combining NOACs with ritonavir (Steffel et al., 2021).

Before prescribing NMV/r, the patient's full medical history, including herbals and over-the-counter and recreational drugs, must be known and co-treatment carefully managed by the treating physician or by a specialist to avoid detrimental effects. Such measures require additional utilization of healthcare resources and could be challenging to implement in areas strained by the COVID-19 pandemic. However, failure to manage DDI puts the patient at risk of serious toxicity or therapeutic failure. Oral molnupiravir, with no known DDI, or intravenous remdesivir, could be options to prevent progressing to severe illness.

General practitioners prescribing oral antivirals for COVID-19 may not have the specialist knowledge required to adjust the patient's other drugs during COVID-19 treatment safely. Limited experience and lack of treatment guidance increase the risk of clin-

ically significant DDIs being overlooked in the clinic. Therefore, in general practice, there is a need for clear and pragmatic treatment guidance for prescribing oral antiviral drugs for treating elderly or vulnerable patients with COVID-19. Guidance should include standardized dosing protocols for commonly used drugs, absolute contraindications, and suggestions for substituting or pausing treatments where DDI cannot be avoided.

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Ethical approval

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Declaration of Competing Interest

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