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REVIEWS

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Managing nirmatrelvir/ritonavir (Paxlovid) interactions in general practice

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Summary Nirmatrelvir/ritonavir (Paxlovid) is indicated in patients who are at high risk of progressing to severe COVID-19. Many of these patients are concomitantly prescribed various medications for other indications. Ritonavir has no activity against SARS-CoV-2, but, administered with nirmatrelvir, acts as a pharmacokinetic booster, increasing nirmatrelvir's efficacy. Ritonavir can simultaneously change other medicines' plasma levels, affecting their safety and therapeutic effects. Ritonavir's potential to cause clinically significant interactions is well documented, as it has a long history of being used as a pharmacokinetic enhancer with other antiviral agents. Pharmacokinetic drug-drug interactions (DDIs) are a well-known phenomenon, but data on the clinical impact of Paxlovid DDIs is still insufficient. Ritonavir in the treatment of COVID-19 is only administered for 5 days; therefore, uncertainty exists on how the coadministration of various medicines should be managed. Numerous Paxlovid DDIs can lead to serious adverse drug reactions; therefore, careful analysis of all concomitantly prescribed medicines is essential to ensure treatment safety. This article aims to summarise currently available information on Paxlovid DDIs that may be relevant for general practitioners. It explains the main mechanisms leading to pharmacokinetic interactions and possible options for DDIs management. The authors indicate sources of information that may be helpful to prescribers when weighing the benefits and risks of Paxlovid co-administration with other medicines.
Key words: nirmatrelvir and ritonavir drug combination, patient safety, drug interactions.

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Background

Nirmatrelvir and ritonavir administered together, marketed under the name Paxlovid, are licenced for the treatment of SARS-CoV-2 infection in adults not requiring supplemental oxygen who are at increased risk of progressing to severe COVID-19 [1]. The drug was approved by European Medicines Agency in January 2022 [2]. Early administration (as soon as possible after a diagnosis of COVID-19 and within 5 days of symptom onset) has been shown to be effective in preventing hospitalisation and severe clinical outcomes [3, 4]. Nirmatrelvir inhibits the main protease of SARS-CoV-2 – an enzyme essential for viral genome replication. Ritonavir has no known activity against SARS-CoV-2 but acts as a pharmacokinetic enhancer. It slows down the metabolism of nirmatrelvir and therefore boosts its plasma levels [5]. The combination needs to be administered orally twice daily for 5 consecutive days [1]. Ritonavir's co-administration is essential to boost nirmatrelvir's effectiveness, but its ability to affect the metabolism of other drugs can be the cause of numerous significant DDIs [6]. Patients considered for Paxlovid therapy will most likely be treated with multiple medications, as risk factors for progression to severe COVID-19 include, among others, autoimmune conditions requiring immunosuppression, diabetes, cardiovascular or respiratory diseases [4]. Therefore, it is necessary to check for possible DDIs before prescribing Paxlovid. Understandably, to assess the potential for interactions, the prescriber must have a complete list of all medication that the patient is currently taking, including medications bought over the counter, traditional and complementary medicines, as well as food supplements.

Drug-drug interactions – sources of information and interpretation difficulties

There are several interaction databases available online [6–9]. The summary of product characteristics (SmPC) can be valuable source of information, but interaction databases are a timesaving and continuously updated option. They are useful for quick verification of potential interactions between concomitantly used drugs. In most cases, interaction databases, apart from warning about a potential interaction, provide comments on the mechanism that leads to its occurrence, as well as specific suggestions for management (e.g. avoiding combination, making a dose adjustment). However, in many instances, assessing the clinical significance of an interaction can be difficult, especially for newly marketed medicines with a short history of collection of real-world data. It is worth noting that various interaction databases may differ in the information provided due to the sources they use [9, 10].

Based on the knowledge of the drug's pharmacokinetics or *in vitro* studies, it is possible to predict that one drug will cause changes in the pharmacokinetic parameters of another drug, but whether this change will be clinically significant may be difficult to judge [11]. Published data on the clinical impact of DDIs is insufficient [12]. The prescriber is often faced with the difficult task of managing the benefits of prescribing several medicines concomitantly and the risks of these medicines interacting unfavourably. It is essential to interpret the information about possible interactions, taking into account the patient-related factors that can increase the risk of an adverse drug reaction, for example, reduced kidney function or malnutrition. Understandably,

physicians must also consider the specific indication for each interacting drug, as this can affect the decision on whether the drug can be stopped or withheld to avoid the negative consequences of a DDI. Pharmacokinetic interactions are of particular importance for drugs with a narrow therapeutic index, for which even small fluctuations in concentration may cause a significant change in the drug's effect.

Drug metabolism and transport proteins – basic information

Most medicines undergo metabolic biotransformation before being removed from the body. Human cytochrome P450 (CYP) enzymes are responsible for the majority of phase I reactions (mainly oxidation), which render drugs more polar and easier to excrete. Among a large variety of human CYPs, the isoforms belonging to the CYP1, 2 and 3 families are responsible for the metabolism of about 80% of drugs clinically used today. The CYP3A4 and CYP3A5 isoforms are involved in the metabolism of over 30% of currently used medicines [13]. Drugs (or their metabolites) can also undergo conjugation reactions, leading to the creation of polar compounds. These reactions are catalysed by a variety of transferases, including uridine diphosphate (UDP) glucuronosyltransferases. Various substances can inhibit or induce the enzymes involved in drug metabolism, leading to significant changes in drugs' concentrations and their clinical effects [12].

Several transport proteins play an important role in a drug's pharmacokinetics. Drug transporters include P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporting polypeptides (OATP) 1B1 and 1B3 or organic anion transporter (OAT) 1 and 3. A DDI resulting in the induction or inhibition of these transporters can lead to increased drug toxicity or reduced efficacy [12].

Enzyme inhibition

Medicines and other substances can inhibit several hepatic enzymes, including the cytochrome P450 complex isoenzymes [14]. Classifying a substance as a strong inhibitor means that it can cause a significant change in exposure to another drug metabolised by the same enzyme (greater than a 5-fold increase in the AUC of the substrate or more than an 80% decrease in substrate clearance) [15]. A weak enzyme inhibitor is a substance that causes a greater than 1.25-fold but less than 2-fold increase in the AUC values or a 20–50% decrease in substrate clearance [15]. AUC (i.e. the area under the blood concentration-time curve) is a parameter characterising the bioavailability of a drug [16]. It reflects the total exposure to the drug, taking into account both the drug concentration and the time during which the drug is present in the blood. A 5-fold increase in the AUC of a given drug as a result of an interaction can be compared to the effect obtained from a 5-fold increase in the drug's dose.

Enzyme inhibition can lead to an increase in an enzyme-substrate concentration and its increased clinical effect. In the case of a prodrug (a pharmacologically inactive substance that is converted in the body into an active metabolite), enzyme inhibition can cause reduced conversion into an active metabolite and therefore potentially reduce the drug's efficacy [12].

Enzyme induction

P450 complex isoenzymes can be induced by various medicines and substances [14]. Enzyme induction usually results in a decrease in the concentration of the drug metabolised by a given enzyme. Consequently, the therapeutic effect of a drug can be reduced. Conversely, inducing the metabolism of a prodrug can lead to its increased effect [11, 12].

Paxlovid pharmacokinetic interactions and their consequences

1. General information

The most important effects of Paxlovid interaction with other medicines are two-way:

a) altered drug metabolism leading to significant adverse reactions of the drug co-administered with Paxlovid (due to ritonavir's presence),
b) decreased therapeutic effect of Paxlovid (and potential for development of viral resistance) as a result of other drugs' influence on Paxlovid's metabolism.

Ritonavir has been used as a pharmacokinetic booster for a long time in the pharmacological management of HIV (human immunodeficiency virus) and HCV (hepatitis C virus) infections [17]. Therefore, a lot of data exists regarding its potential to cause DDIs. The doses of ritonavir used to boost other antiretrovirals were comparable to the current ritonavir dose used in combination with nirmatrelvir in COVID-19 treatment [1, 17]. The difficulty that may arise is assessing the interaction potential of the short nirmatrelvir/ritonavir treatment course (5 days only) and DDI effect duration after stopping COVID-19 therapy. Experts in pharmacology have been working on creating comprehensive resources for prescribers to help them manage Paxlovid's potential interactions [18–20]. Experts from the University of Liverpool manage an online database dedicated to COVID-19 treatment [21]. Apart from theoretical information on DDIs, this source uses available information from clinical DDI studies [22], as well as analytical tools designed to predict the magnitude of drug-drug interactions [23]. Recommendations tend to take into account the safety profile of interacting drugs and the potential consequences of altered pharmacokinetics in various clinical situations. However, data regarding DDIs is still insufficient, and therefore there are instances where no definite recommendation can be made regarding the coadministration of certain medicines with Paxlovid.

Details of Paxlovid interactions and examples of interacting drugs are described below:

2. CYP3A4 inhibition

Ritonavir is a strong CYP3A4 inhibitor [15]. CYP3A4 isoenzyme is responsible for the metabolism of a large number of substances; therefore, a large number of potential interactions exist. An example of a significant interaction occurring in this mechanism is ritonavir affecting the metabolism of simvastatin or lovastatin – drugs primarily metabolised by CYP3A. This results in an increased level and effect of a statin, therefore increasing the risk of myopathy and rhabdomyolysis. Other examples of significant DDIs occurring as a result of CYP3A4 inhibition are hyperkalaemia associated with eplerenone or bradycardia associated with ivabradine. Administration of Paxlovid with simvastatin, lovastatin, eplerenone and ivabradine is therefore contraindicated [1].

The same mechanism will apply to the concomitant administration of Paxlovid with other medicines metabolised by CYP3A4, for example clozapine, quetiapine, diazepam or estazolam (concomitant administration is also contraindicated) [1]. In theory, it is possible to withhold and replace these medicines before administering Paxlovid, and this is one of the suggested options of management [19], but in an ambulatory setting, without the involvement of a specialist, this may not be feasible.

CYP3A4 enzyme inhibition can also contribute to reduced efficacy of clopidogrel if administered with Paxlovid, because clopidogrel's conversion to its active metabolite is dependent (although not exclusively) on this enzyme [24].

3. CYP3A4 induction

Both nirmatrelvir and ritonavir are substrates of CYP3A4 [15]. Administering Paxlovid with substances that induce CYP3A4 can lead to intensified metabolism, a significant reduction in nirmatrelvir/ritonavir plasma concentrations and a po-

tential loss of therapeutic response. Co-administration of Paxlovid with potent enzyme inducers is therefore contraindicated [1]. The list of CYP3A4 inducers is shorter than the list of CYP3A4 inhibitors and includes, for example, rifampicin, carbamazepine and St. John's wort (Hypericum perforatum) [15].

4. Onset and duration of altered CYP3A4 activity

Inhibition of CYP3A4 by ritonavir achieves its maximum within 48 h of initiating treatment [25]. It needs to be noted that this effect was observed for ritonavir given at a dose of 300 mg twice a day, and it is not clear if the same onset of enzyme inhibition applies to lower doses. Ritonavir blocks CYP3A4 irreversibly; therefore, newly synthesised enzyme molecules are necessary to reverse enzyme inhibition. As a result, the inhibitory effect can last for several days after stopping the drug [26]. This time may differ depending on the patient's individual response. A study investigating the duration of hepatic and intestinal CYP3A inhibition after stopping lopinavir/ritonavir (400/100 mg twice daily for 7 days) showed that although enzyme inhibition decreases significantly 24 h after stopping lopinavir/ritonavir, 5 days are needed to achieve greater than 80% disappearance of CYP3A inhibition across all age groups (taking into account population variability). Complete disappearance of CYP3A inhibition took 21 days in all age groups [27]. Because of this delayed effect, experts recommend that medication whose metabolism can be significantly inhibited by Paxlovid should not be restarted for at least 3 days (5 days if possible) after completing the course of Paxlovid [19, 24]. This comes to a total of 10 days of drug withdrawal, and a risk-benefit ratio should be individually weighed before recommending such approach.

CYP3A4 enzyme induction develops more slowly than inhibition. It requires the synthesis of new enzyme molecules, and it is expected to reach its peak after 5–7 days [19]. Enzyme induction also takes longer to reverse after stopping the inducer, taking up to 3 weeks to resolve [27].

Table 1 summarises the effects of CYP3A4 induction and inhibition, including duration of altered enzyme activity.

5. CYP2D6 inhibition

Ritonavir inhibits CYP2D6, an enzyme responsible for the metabolism of several selective serotonin reuptake inhibitors (SSRIs), amitriptyline, risperidone, tramadol and many other substrates [15]. Ritonavir's inhibitory effect on this isoenzyme is weak; therefore, during a 5-day treatment course, it is unlikely to cause any clinically relevant changes to the pharmacokinetic parameters of medication metabolised by this isoenzyme [28]. However, the manufacturer of Paxlovid recommends careful monitoring of the therapeutic and adverse effects if Paxlovid and CYP2D6 substrates are concomitantly administered [1].

6. Ritonavir and nirmatrelvir as enzyme inducers

Ritonavir may induce CYP1A2, CYP2C8, CYP2C9 and CYP2C19 isoenzymes [1]. There is also some data indicating that ritonavir induces CYP2B6 and UGT1A1 (UDP-glucuronyl transferase 1A1), although sources vary about ritonavir's effects on these enzymes [1, 15, 29]. Nirmatrelvir may be an inducer of CYP3A4, CYP2B6, CYP2C8 and CYP2C9, but it is unknown whether this has any clinical consequences [1]. Most potential DDIs occurring in an enzyme-inducing mechanism are unlikely to be clinically significant if nirmatrelvir/ritonavir is given for 5 days only (induction develops more slowly) [12], but more studies are needed to expand upon the subject. A potentially significant DDI that can occur as a result of the drug's more intense metabolism via CYP1A2 and CYP2C9 is the reduced anticoagulant effect of warfarin [1] and acenocoumarol [30]. Induction of CYP2C9, CYP2C19 and UDP-glucuronyl transferase may lead to decreased plasma concentrations of some antiseizure medications (lamotrigine, valproic acid, lacosamide), but these interactions are unlikely to be clinically significant [31].

7. Transport proteins

Ritonavir can inhibit several transport proteins, including P-glycoprotein (P-gp), breast cancer resistance protein (BCRP) and organic anion transporting polypeptides (OATP) 1B1 and 1B3. Little is known about nirmatrelvir, but it may also inhibit P-gp, OATP1B1 and possibly other transporters [1].

P-gp is responsible for removing toxins and xenobiotics from cells. Inhibiting P-gp can lead to increased absorption and decreased excretion, therefore leading to an increased risk of adverse drug reactions (ADRs) of medicines that are P-gp substrates [12]. An example of an interaction occurring in this mechanism is increased exposure to digoxin (a significant raise in AUC) when administered with Paxlovid. As digoxin has a low therapeutic index, this can lead to significant clinical consequences. The manufacturer recommends avoiding concomitant use [1]. The Paxlovid-digoxin interaction can also be managed with the help of therapeutic drug monitoring [24]. The effect of

Table 1. CYP3A4 induction and inhibition – potential effects, their onset and duration [12, 19, 26–28]

	CYP3A4 inhibition	CYP3A4 induction
Potential effect of interaction	Increased exposure to drugs metabolised by the enzyme and increased risk of ADRs	Decreased effectiveness of drugs metabolised by the enzyme and increased risk of treatment failure
	Decreased effectiveness of prodrugs metabolised by the enzyme and increased risk of treatment failure	Increased exposure to prodrugs and increased risk of ADRs
Time to maximum effect	48 h	5–7 days
Time needed for enzyme to resume its baseline activity	1–3 days* (may take longer depending on individual response, up to 21 days)	Up to 21 days*

*It is difficult to establish the exact time based on current published evidence; ADRs – adverse drug reactions.

Table 2. Effects of ritonavir on the activity of enzymes involved in drug metabolism and on transport proteins [1, 15, 26, 29]

Influence on hepatic enzymes activity		Influence on transport proteins
Inhibition	Induction	Inhibition
CYP3A4 (strong)	CYP1A2	
CYP2D6 (weak)	CYP2C8	P-glycoprotein (P-gp)
	CYP2C9	Organic anion transporting polypeptides (OATP) 1B1 and 1B3
	CYP2C19	Breast cancer resistance protein (BCRP)
	CYP2B6	Other possible transporters
	UDP-glucuronyl transferase 1A1	

this interaction will depend largely upon the patient's renal function and the plasma level of digoxin before starting an interacting drug. The higher the starting level, the more likely the interaction is to lead to digoxin toxicity.

Dabigatran is also a substrate for P-gp. Concomitant administration with Paxlovid can result in an increased dabigatran plasma concentration. The manufacturer does not recommend concomitant use [1]. This interaction can also be managed by reducing the dose of dabigatran or switching dabigatran to enoxaparin [24]. Table 2 summarises the effects of ritonavir on enzymes involved in drug metabolism and transport proteins.

Managing interactions

General approach

The approach to managing Paxlovid interaction can be summarised as follows:

a) avoiding combination (withholding an interacting drug or avoiding Paxlovid),
b) adjusting the dose of concomitant medication while taking Paxlovid,
c) introducing additional monitoring measures, including patient counselling to minimise the risk of adverse events during concomitant administration of potentially interacting drugs.

Table 3 presents examples of Paxlovid DDIs that cannot be managed or require special measures in management. It includes situations where Paxlovid cannot be given even if the interaction drug is stopped. This will be the case with strong CYP3A4 inducers (because of the prolonged effect of enzyme induction) and amiodarone (because of its unusually long half-life). In these circumstances, the interaction cannot be managed by withholding the currently used drug – the only option to prevent DDI is avoiding Paxlovid administration. Interestingly, a recent case report suggests that the coadministration of amiodarone with Paxlovid can be managed using therapeutic drug monitoring [32]. Table 3 also includes examples of DDIs that are difficult to manage in an ambulatory setting and without a specialist's involvement, especially since Paxlovid administration should not be delayed.

Table 4 gives examples of DDIs that can be managed by temporarily stopping the interacting drug or adjusting its dose. If a currently prescribed medicine can be withheld, it is advisable to wait at least 3 days (preferably 5 days) from the last Paxlovid dose before reinitiating the treatment [19, 24]. Please note that if a particular drug is not listed in the tables, it should not automatically be assumed it is safe to co-administer with Paxlovid.

Table 3. Examples of Paxlovid DDIs that cannot be managed or require special measures in management [1, 19, 20, 24]

Co-administration with Paxlovid is contraindicated. It is necessary to consider other COVID-19 treatment options		
Drug name	**Mechanism of interaction**	**Comments**
Amiodaron	CYP3A4 inhibition	Due to amiodaron's long half-life, immediate withdrawal is impossible. DDI cannot be avoided.
Carbamazepine	CYP3A4 induction	The effectiveness of Paxlovid can be significantly reduced if co-administered with CYP3A4 inducers (due to inadequate nirmatrelvir and ritonavir levels). DDI cannot be avoided even if the enzyme inducer is stopped (enzyme induction persists for several days after stopping the inducer).
Phenobarbital		
Phenytoin		
Primidone		
St John's wort (*Hypericum perforatum*)		
Enzalutamide, apalutamide		
Rifampicin		
Paxlovid DDIs requiring special measures in management. Risk of serious ADRs if administered with Paxlovid		
Drug name	**Mechanism of interaction**	**Comments**
Cyclosporine, voclosporine, tacrolimus, everolimus, sirolimus	CYP3A4 inhibition	Co-administration with Paxlovid requires the implementation of therapeutic drug monitoring (TDM) – interaction can be managed by a specialist adjusting the immunosuppressant dose based on its plasma levels.
Dronedarone, flecainide, propafenone, quinidine, ivabradine, ranolazine, digoxin		Paxlovid can be administered if the drug is withdrawn, but this may require a multidisciplinary approach. If digoxin is administered with Paxlovid, TDM is recommended.
Clorazepate, diazepam, estazolam, flurazepam, midazolam, triazolam, alprazolam		Paxlovid can be administered if benzodiazepine is withdrawn, but in cases of long-term benzodiazepine use, withdrawal during COVID-19 infection may not be feasible. Benefits and risks of this approach need to be considered on a case-by-case basis.
Clozapine, lurasidone, pimozide, quetiapine		Paxlovid could be administered if the antipsychotic drug is withdrawn, but this may require a multidisciplinary approach.
Rivaroxaban, dabigatran, apixaban, clopidogrel, ticagrelor		DDI can be managed, but high-risk patients may require specialist input. Recommendations exist for dose reduction of dabigatran and apixaban if co-administered with Paxlovid. Rivaroxaban can be replaced by LMWH. Benefits and risks of this approach need to be considered on a case-by-case basis.
Several anticancer agents (examples include venetoclax, neratinib, ibrutinib)		Management may require a multidisciplinary approach. Several anticancer agents can be administered with Paxlovid. Please check the recommendations for individual drugs.

Please note that if a particular drug is not listed in the table, it should not automatically be assumed it is safe to co-administer with Paxlovid. Please refer to additional sources for details suggesting management strategies. DDIs – drug-drug interactions; TDM – therapeutic drug monitoring; LMWH – low molecular weight heparin.

Table 4. Examples of Paxlovid DDIs that can be managed by temporary withholding/avoiding introducing/adjusting the dose of the interacting drug. Co-administration may result in serious ADRs [1, 19, 20, 24]

Drug name	Administration with Paxlovid can potentially lead to:	
Simvastatin, lovastatin*	myopathy and rhabdomyolysis	Co-administration contraindicated according to Paxlovid SmPC
Eplerenone	hyperkalaemia	
Colchicine	bone marrow suppression	
Alfuzosin, silodosin	severe hypotension	
Cisapride	QT interval prolongation and ventricular arrhythmias	
Ergot derivatives (e.g. ergotamine)	acute ergot toxicity	
Eletriptan	serious adverse cardiovascular and cerebrovascular events	
Sildenafil and other PDE5 inhibitors	severe hypotension, prolonged erection and vision disturbances	
	Comment	
Lercanidipine and other calcium channel blockers	The manufacturer of Paxlovid recommends avoiding co-administration with lercanidipine, as the hypotensive effect of the drug can be significantly increased. Administration with amlodipine and other dihydropyridine calcium channel blockers is possible but may result in hypotension and may require dose adjustments. Administration with diltiazem or verapamil requires additional monitoring for bradycardia and hypotension and may require dose adjustments.	

* Temporary withholding of all statins should be considered. Please see the article text for more details.

Please note that if a particular drug is not listed in the table, it should not automatically be assumed it is safe to co-administer with Paxlovid. DDIs – drug-drug interactions; ADRs – adverse drug reactions; PDE – phosphodiesterase; SmPC – summary of product characteristics.

Comments on transplant immunosuppressants

Co-administration of Paxlovid with calcineurin inhibitors and mTOR inhibitors is possible but requires the implementation of therapeutic drug monitoring (TDM). Understandably, this will need specialist involvement and will be challenging in an ambulatory setting, especially if combined with home isolation and the short period available to introduce TDM intervention. Additional resources exist to aid in the co-administration of immunosuppressive drugs with Paxlovid [33, 34].

Comments on oral anticancer drugs

The risks and benefits of administering Paxlovid with medicines used in the treatment of cancer need to be carefully considered on an individual basis. Enzalutamide and apalutamide are CYP3A4 inducers; therefore, co-administration with Paxlovid is contraindicated according to the SmPC [1]. Administration of Paxlovid with venetoclax or neratinib can lead to a significant increase in exposure to these anticancer drugs [1, 19]. However, many anticancer treatments can be safely co-administered with Paxlovid (for example tamoxifen, capecitabine or lenalidomide) [19].

Comments on anticoagulants and antiplatelet drugs

Vitamin K antagonists can be co-administered with Paxlovid, but close monitoring of INR is recommended [1, 19, 24]. Warfarin is metabolised by several hepatic enzymes. Warfarin's effect can be potentiated as a result of CYP3A4 inhibition, but it is also possible that ritonavir will induce warfarin's metabolism via CYP1A2 and CYP2C9, contributing to a reduced anticoagulation effect [1, 19]. An inhibitory effect is more likely to occur with a short course of Paxlovid treatment. The effect of acenocoumarol can also be diminished if administered with an inducer of CYP2C9 or CYP2C19 [30]. Non-vitamin K antagonist oral anticoagulant (NOAC) effects can be increased by Paxlovid as a result of CYP3A4 and P-gp inhibition [1]. Co-administration of Paxlovid with a NOAC is therefore expected to increase the risk of bleeding [24]. The SmPC recommends avoiding concomitant use of Paxlovid with rivaroxaban and reducing the dose or avoiding dabigatran [1]. More data is needed to determine the significance of NOACs – Paxlovid DDIs, but currently suggested management strategies include dose reduction (for dabigatran or apixaban) or switching to an alternative anticoagulant (e.g. low molecular weight heparin) [24, 35].

The SmPC provides no recommendations on co-administration of Paxlovid with antiplatelet agents [1]. The most significant DDI is expected to occur with ticagrelor – the antiplatelet effect of ticagrelor can be potentiated, leading to an increased risk of bleeding [20, 24]. Clopidogrel's effect can be reduced increasing the risk of thrombosis [19, 20, 24]. The significance of this DDI is not fully understood, but it is likely to be most relevant for patients who underwent recent percutaneous coronary intervention [20, 24]. No DDI is expected if Paxlovid is administered with acetylsalicylic acid (ASA) [19].

Comments on statins

Simvastatin and lovastatin are metabolised primarily by CYP3A4; therefore, administration with ritonavir may predispose patients to ADRs, including rhabdomyolysis. Atorvastatin metabolism is less dependent on CYP3A4, and rosuvastatin is not metabolised by CYP3A4. However, ritonavir may still increase the risk of ADRs of these statins, most likely through inhibition of OATP1B1. Pravastatin and fluvastatin are the least likely to interact with Paxlovid [1, 19]. Experts in clinical pharmacology suggest that if Paxlovid is indicated in a patient currently taking simvastatin or lovastatin, the first Paxlovid dose can be given at least 12 h after the last statin dose. Statin can be resumed at least 3 days (preferably 5) after completing the Paxlovid course [19, 24]. Although administration of Paxlovid is not contraindicated with statins other than simvastatin and lovastatin [1], since temporary discontinuation of a statin is not likely to have a negative impact on a patient's outcome, it may be reasonable to avoid administering all statins during the 5 days of Paxlovid treatment and for 5 days afterwards [19].

Comments on antibacterials

Paxlovid should not be administered with rifampicin (CYP3A4 inducer) [1]. Co-administration is also contraindicated with fusidic acid [1], although the interaction is expected to be significant in cases of systemic administration only. Paxlovid is unlikely to cause any clinically significant DDIs with other antibacterials. Understandably, the use of antibacterials is not recommended in COVID-19 treatment. However, if an anti-infective agent is needed because of other indications, significant DDIs

are not expected [21]. The Paxlovid's SmPC warns that Paxlovid may increase the level of clarithromycin, but it is unlikely to cause problems if standard doses of clarithromycin are given (up to 1,000 mg/day).

Comments on medicines of plant origin and food supplements

St John's wort compounds are potent CYP3A4 and P-gp inducers; therefore, coadministration with Paxlovid is contraindicated [1]. Other interactions with medicines of plant origin or food supplements are difficult to predict, and it is therefore reasonable to withhold any herbal remedies or food supplements while taking Paxlovid and for 5 days after finishing the course.

Conclusions

Although the Paxlovid's SmPC includes a long list of potential DDIs, the drug should be considered in every case when the patient meets the criteria for its use. The potential risks and benefits of prescribing the drug should be assessed on a basis, especially in populations of patients at risk of a severe clinical course of COVID-19. It is essential to minimise DDI-related risks but also not to automatically deny treatment with Paxlovid to eligible patients taking multiple medications without considering DDI management options. In certain situations, to prevent the negative consequences of a DDI, short-term discontinuation of a currently prescribed medicine or temporary dose adjustment may be considered as a possible option. Some complex cases may require a multidisciplinary approach (for example consulting an oncology or transplant specialist, a clinical pharmacist or clinical pharmacologist). It should be stressed that knowledge about significant risks associated with Paxlovid DDIs will be verified and updated while the drug is present on the market; therefore, it is important to be aware of sources of information on this subject other than SmPC. One of the important elements related to the management of DDIs is counselling patients to be cautious when deciding about the use of available over the counter medicines or food supplements.

Paxlovid is currently being monitored closely by regulatory authorities, as it is included in the European Medicines Agency's additional monitoring (AM)/black triangle list [36]. Healthcare professionals can contribute to gathering safety information about the drug by reporting any suspected adverse drug reactions (ADRs). These adverse reactions may be the consequences of DDIs; therefore, reporting ADRs can indirectly contribute to gathering real-world data on clinically important interactions that contribute to ADRs.

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