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PERSPECTIVE

COVID-19 and antiepileptic drugs: an approach to guide practices when nirmatrelvir/ritonavir is co-prescribed

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Abstract

Management and dose adjustment are a major concern for clinicians in the absence of specific clinical outcome data for patients on antiepileptic drugs (AEDs), in the event of short-term (5 days) nirmatrelvir/ritonavir co-exposure. Therefore, in this report, we identified drugs that require dose adjustment because of drug-drug interactions (DDIs) between nirmatrelvir/ritonavir and AEDs. We hereby used four databases (*Micromedex* Drug Interaction, *Liverpool* Drug Interaction Group for COVID-19 Therapies, *Medscape* Drug Interaction Checker, and *Lexicomp* Drug Interactions) and *DDI-Predictor*.

In the light of applying the *DDI-Predictor*, for carbamazepine, clobazam, oxcarbazepine, eslicarbazepine, phenytoin, phenobarbital, pentobarbital, rufinamide, and valproate as CYP3A4 inducers, we recommend that a dose adjustment of short-term nirmatrelvir/ritonavir as a substrate (victim) drug would be more appropriate instead of these AEDs to avoid impending DDI-related threats in patients with epilepsy.

Keywords SARS-CoV-2 · Seizure · Anticonvulsants · Nirmatrelvir · Ritonavir · Dosing · Drug interaction

We welcomed the recent paper on the safety profile of COVID-19 drugs in the real clinical setting in this journal, as the efficacy-safety balance is the key hallmark of pharmacotherapy [1]. As discussed by Chiu et al. in their review and randomized clinical trials (2 studies) and further supported by case reports (8), they show that a relevant portion of patients has adverse drug reactions exposed to concomitant ritonavir-boosted protease inhibitor therapy [1]. Based on this paper, we felt that some additional reflections on dose adaptations of either the AED co-medication or the COVID-19 targeted nirmatrelvir/ritonavir due to drug-drug interactions (DDIs) are warranted.

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For moderate-to-strong enzyme-inducing antiepileptic drugs (AEDs) that are cytochrome P450 (CYP3A4) substrates, it has recently been suggested that dose reductions of these AEDs are warranted when combined with nirmatrelvir/ritonavir to avoid overexposure of these AEDs [2]. As these effects are bidirectional, we aimed to highlight the short-term (5-day) dose adjustment of nirmatrelvir/ritonavir in patients co-exposed to some AEDs to further add to these recommendations.

Shortly after acceptance of the Chiu et al. paper [1], nirmatrelvir was approved with emergency use authorization in non-hospitalized patients (12 years of age and older) with mild and moderate COVID-19 (including Omicron variant) by the US Food & Drug Administration (FDA) on December 22, 2021, and the European Medicines Agency (EMA) on January 27, 2022. It is a peptidomimetic inhibitor of the SARS-CoV-2 main protease, resulting in the inhibition of viral replication [3, 4]. Ritonavir is an HIV protease inhibitor and used as a pharmacokinetic enhancer with no activity against SARS-CoV-2 [5]. It inhibits the CYP3A-mediated metabolism of nirmatrelvir, resulting in increased nirmatrelvir plasma concentrations. The irreversible inhibition of CYP3A4 by ritonavir is to a large extent mechanism-based and 100–200 mg of ritonavir results in (near) maximal inhibition of both gastrointestinal and hepatic CYP3A4 isoenzymes [2].

Nirmatrelvir/ritonavir (300/100 mg) is a potent CYP3A and P-glycoprotein (P-gp) inhibitor and poses significant challenges with clinically relevant DDIs. Due to the absence of comprehensive experimental data for nirmatrelvir/ritonavir, high study cost, and being the newest drug, the use of DDIs and substrate dose prediction is a valuable strategy to improve personalized medicine by non-invasive methods.

Therefore, in this paper, *Medscape* Drug Interaction Checker (WebMD Health, New York, USA), *Lexicomp* Drug Interactions (Wolters Kluwer Health, MA, USA), *Liverpool* Drug Interaction Group for COVID-19 Therapies (University of Liverpool, Liverpool, UK), and *Micromedex* Drug Interaction (Truven Health Analytics, MI, USA) databases, which are created by using the known DDI mechanisms and the current evidence-based literature, are strongly recommended to be used in clinical practice in the recognition and management of potential and clinically relevant DDIs [6–10].

A conservative assessment of hepatic uptake transporter-mediated maximum possible DDIs can be achieved with a simplified static model incorporating drug parameters to estimate the ratio of the area under the plasma concentration–time curve in the inhibited state (AUC_i) in comparison with the control (standard patient) state (AUC), AUC ratio (AUC_i/AUC) as predicted vs. observed victim drug plasma concentration–time profiles [11, 12]. *DDI-Predictor* is a website dedicated and validated to the quantitative prediction of the impact on drug exposure of DDIs mediated by CYP3A4, 2D6, 2C9, 2C19, and 1A2, used to calculate AUC ratios, which the parameters derived from Monte Carlo simulations or single calculation, and determine the substrate dose of DDI caused [13]. According to this in vivo mechanistic static model, estimation of the substrate dose to be given is very simple by the formula:

$$\text{Adjusted substrate dose} = (\text{Current or usual dose})/(\text{AUC ratio})$$

DDI-Predictor (www.ddi-predictor.org, accessed on 20 April 2022) is a recently developed, free, online decision-making tool for characterizing pharmacokinetic modifications that involve the main CYPs in the patient [14]. Thus, this tool cannot analyze all DDIs. Besides, it is estimated that DDI-Predictor might complement other databases and thus improve DDI screening in patients with epilepsy and nirmatrelvir/ritonavir treatment.

Here, we generate recommendations using the steady-state equations in physiologically based pharmacokinetic (PBPK) modeling, integrated as a valuable tool to investigate and predict DDI (www.ddi-predictor.org). Using this approach, dosage adjustment of nirmatrelvir/ritonavir and alternative AEDs mentioned and analyzed to avoid possible toxicity, AED treatment failure, or virologic resistance in patients with epilepsy treated with chronic AEDs are explored [15]. We hereby focus on carbamazepine, oxcarbazepine, eslicarbazepine, (fos)phenytoin, phenobarbital, pentobarbital, clobazam, and valproate as commonly used AEDs and with a high DDI risk.

According to the *Lexicomp* Drug Interactions database, nirmatrelvir/ritonavir was flagged because of potential DDI with 595 drugs varying in severity from B (no action needed) to X (avoid combination). Currently, 10 (1.68%) of these drugs are AEDs. Based on the *Medscape* Drug Interaction Checker, 105 drugs had a potential DDI varying in severity from "monitor closely" to "contraindicated," with 5 (4.76%) being AEDs. Exploring the *Liverpoo*l Drug Interaction module for COVID-19 therapies, nirmatrelvir/ritonavir was flagged for DDI with 265 drugs varying in severity from "potential weak interaction" to "do not co-administer," with 14 (5.28%) being AEDs. Finally, assessing the *Micromedex* drug interaction module, nirmatrelvir/ritonavir was flagged for potential DDI with 749 drugs varying in severity from "moderate" to "contraindicated," 11 (1.46%) of them were AEDs (Supplementary Table).

All of the potential DDIs obtained as output from these four DDI databases were classified as inducers in the *DDI-Predictor* PBPK application and displayed a (by PBPK) impact on nirmatrelvir/ritonavir clearance. To quantify this impact, the AUC ratio and high-risk (strong) DDIs (defines as a ratio of either ≤ 0.5 or > 2) were considered [13]. Then, it was aimed to determine the corrected substrate (nirmatrelvir/ritonavir) doses by using the AUC ratio based on the current dose of the substrate.

Today, it is known that 30 different AED drugs are used in the treatment of seizures [16]. Based on information from four DDI databases, the number of AEDs identified as potential DDIs in at least one database is 20 (67%) (Supplementary Table). Only 9 (45%) of these drugs are present in the *DDI-Predictor* in terms of PBPK. Among these DDIs with AUC ratios ranging from 0.47 to 1.00, only carbamazepine (0.47), phenytoin (0.40), and phenobarbital (0.50) are seen as high-risk DDIs as the AUC ratio is ≤ 0.5, with a potential risk to result in underexposure of nirmatrelvir/ritonavir (Table 1).

Carbamazepine, oxcarbazepine, and eslicarbazepine: As a strong, persistent, and residual induction via CYP3A4, carbamazepine can significantly reduce nirmatrelvir/ritonavir exposure, potentially jeopardizing its efficacy [17]. In a PBPK study, co-administration of carbamazepine (300 mg twice daily for 16 doses) and nirmatrelvir/ritonavir (300/100 mg twice daily for 5 doses) decreased nirmatrelvir C_{max} and AUC by 43% and 55%, respectively, and causes inevitable DDIs [18]. However, depending on the clinical condition of the patients, it is known that the combination is continued by considering the benefit-harm relationship due to short-term nirmatrelvir-ritonavir (5 days) treatment. In such rare cases, dosage adjustment with close therapeutic drug monitoring (TDM) and target

Table 1 Dose adjustment of 9 AED drugs that can cause clinically relevant DDIs determined using *DDI-Predictor* [6, 7, 13]

Substrate	Inhibitor/inductor (usual dose)	AUC ratio (95% CI)	Recommended substrate dose	Clinical dose recommendations*	Quality of evidence	Summary
Nirmatrelvir/ritonavir	Carbamazepine (200–600 mg/day)	**0.47 (0.29–0.76)**	~600/200 mg (twice daily for 5 days)	2 × 2 tablets/day	Very low	CYP3A4 inducers (strong) may decrease the serum concentration of nirmatrelvir
Nirmatrelvir/ritonavir	Oxcarbazepine (900 mg/day)	0.87 (0.65–1.17)	~350/115 mg (twice daily for 5 days)	2 × 1 tablets/day	Very low	Oxcarbazepine is a moderate inducer of CYP3A4 and could potentially decrease nirmatrelvir/ritonavir exposure
Nirmatrelvir/ritonavir	Eslicarbazepine (800–1200 mg/day)	0.75 (0.54–1.05)	~400/150 mg (twice daily for 5 days)	2 × 1.5 tablets/day	Very low	Eslicarbazepine is a weak/moderate inducer of CYP3A4 and therefore could reduce nirmatrelvir/ritonavir concentrations
Nirmatrelvir/ritonavir	Phenytoin (300–400 mg/day)	**0.40 (0.24–0.67)**	750/250 mg (twice daily for 5 days)	2 × 2 tablets/day	Very low	CYP3A4 inducers (strong) may decrease the serum concentration of nirmatrelvir
Nirmatrelvir/ritonavir	Phenobarbital (100 mg/day)	**0.50 (0.32–0.79)**	600/200 mg (twice daily for 5 days)	2 × 2 tablets/day	Very low	CYP3A4 inducers (strong) may decrease the serum concentration of nirmatrelvir
Nirmatrelvir/ritonavir	Pentobarbital (100 mg/day)	0.59 (0.39–0.89)	~500/150 mg (twice daily for 5 days)	2 × 1.5 tablets/day	Very low	CYP3A4 inducers (strong) may decrease the serum concentration of nirmatrelvir
Nirmatrelvir/ritonavir	Rufinamide (800 mg/day)	0.84 (0.62–1.14)	~360/120 mg (twice daily for 5 days)	2 × 1 tablets/day	Very low	Rufinamide is a moderate inducer of CYP3A4 and may decrease nirmatrelvir/ritonavir concentrations
Nirmatrelvir/ritonavir	Clobazam (40 mg(day)	1.00 (0.76–1.32)	300/100 mg (twice daily for 5 days)	2 × 1 tablets/day	Very low	Induction of CYP2C19 by ritonavir may decrease N-desmethylclobazam
Nirmatrelvir/ritonavir	Valproate (400–800 mg/day)	1.00 (0.76–1.32)	300/100 mg (twice daily for 5 days)	2 × 1 tablets/day	Very low	Co-administration may decrease valproate concentrations due to induction of glucuronidation by ritonavir

Boldface fonts indicate high-risk DDIs as the AUC ratio is ≤ 0.5

CYP cytochrome P450, *AUC* area under the curve, *CI* confidence interval

*According to the FDA emergency use authorization, the tablets should be swallowed whole and not chewed, broken, or crushed. If the patient should use this as split tablets, the pharmacist should be informed

concentration intervention (TCI) should be considered. TCI is proposed as an alternative conceptual strategy to TDM. It is argued that the idea of a therapeutic range has limited the interpretation of measured plasma concentrations and diminished the anticipated clinical benefit to patients by use of an oversimplified PD model. TCI on the other hand embraces PK and PD concepts and uses the idea of a target effect and associated target concentration to make rational individual dose decisions [19]. According to the AUC ratio of this combination, twofold of daily dose of nirmatrelvir/ritonavir may be required. Oxcarbazepine (moderate inducer) and eslicarbazepine (weak/moderate inducer), which have structural similarity to carbamazepine with less DDI potential and no auto-induction, may also require dosage adjustment (Table 1).

Phenytoin, phenobarbital, and pentobarbital: As strong CYP3A4 inducers, these drugs reduce ritonavir plasma concentrations by 30%. Therefore, patients with epilepsy receiving (fos)phenytoin and nirmatrelvir/ritonavir may require a ritonavir dosage increase of about 50% to maintain unchanged serum concentrations [5]. A 1.5- to 2.5-fold of daily dose of nirmatrelvir/ritonavir may be required based on the AUC ratio (Table 1). This variation is perhaps due to the impact of pharmacogenetics or ethnicity on pharmacokinetics and pharmacodynamics for patients with epilepsy [20]. However, while there are some pharmacogenetic variants of CYP3A4 that are of relatively limited influence on enzyme activity, the role of ethnicity besides the distribution of these genetic variants remains uncertain. Therefore, close TDM and TCI is also required for these drugs. However, pentobarbital seems more suitable in that it has a shorter half-life, as it reduces the risk of residual DDI after discontinuation, making it the treatment of choice [21].

Clobazam and valproate: Dose reduction may be recommended for clobazam during the nirmatrelvir/ritonavir treatment period and 24 h after termination of nirmatrelvir/ritonavir treatment if signs of AED toxicity are observed [2]. Fortunately, after stopping nirmatrelvir/ritonavir, the CYP3A4 inhibitory effect of nirmatrelvir/ritonavir is predicted to mostly disappear after 3 days for clobazam [7]. A study in HIV-infected patients reported a non-statistically significant trend toward lower valproate concentrations (250 mg twice daily for 7 days) with lopinavir/ritonavir [22]. Therefore, there is only a need to monitor the response to valproic acid and derivatives closely when continuing nirmatrelvir/ritonavir for 5 days. Also, according to the AUC ratio of these combinations, it appears that the daily dose of nirmatrelvir/ritonavir should not be changed and that these combinations are relatively safe (Table 1).

Rufinamide is metabolized by hydrolysis and does not undergo significant CYP-mediated metabolism. However, rufinamide is a weak to moderate inducer of CYP3A4 and may lead to increased metabolism of nirmatrelvir/ritonavir, reducing its plasma concentration [23]. According to the *DDI-Predictor*, the AUC ratio of 0.84 also indicates that the severity of DDI is weak to moderate and dose adjustment may be needed according to clinical response.

The major limitation of this brief report is that these recommendations have been constructed based on evidence-based primary sources, with still limited in vivo clinical evidence or a systematic review. At least, these recommendations may be helpful to prioritize clinical research or may assist clinicians on precision medicine, with a more focused assessment of effects and side effects (including failed viral suppression) in specific scenarios.

The above-mentioned information pertains to the high-risk DDIs that may require dose adjustments with known AUC ratios based on PBPK studies. In addition to these AEDs, close TDM/TCI and PBPK studies are required in concomitant use of having the high potential risk of DDI such as clonazepam, primidone, ethosuximide, and perampanel, sultiame, and tiagabine metabolized by CYP3A4 with nirmatrelvir/ritonavir. Due to the short-term use of nirmatrelvir/ritonavir, its short half-life (about 6 h), and the routine assessment of TDM/TCI for AED drugs, it is considered that it can be prescribed with dose adjustment, if necessary, without concern in patients with epilepsy.

Because of the bidirectional of DDIs, CYP3A inducers and CYP3A activity are constantly increased in chronic AED treatment, while the addition of ritonavir leads to suicidal inhibition of the enzyme and thus also alters the metabolism of most AED CYP inducers as they induce their own metabolism. Furthermore, these DDIs between induction and inhibition change over time, so that dose modifications adjusted by TDM probably need to be done daily. In this context of clinical practice, we recommend daily TDM of AED drugs (5 days) during the concurrent use of AED and nirmatrelvir/ritonavir.

These recommendations serve as a suggested starting point for the management of dosage adjustments for nirmatrelvir/ritonavir in cases co-exposed to some specific AEDs in the absence of published in vivo observations. Further clinical trials applying physiologically based and population pharmacokinetic modeling are immediately needed for patients on AEDs who are prescribed nirmatrelvir/ritonavir.

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Declarations

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