■ Review article

Epileptic Disord 2021; 23 (2): 229-256

Epileptic Disorders

A review of pharmacokinetic drug interactions between antimicrobial and antiseizure medications in children

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Received June 29, 2020;
Accepted October 26, 2020

ABSTRACT – Comorbidity between epilepsy and infectious diseases in children is frequent. Pharmacokinetic drug-drug interactions (DDIs) between antiseizure medications (ASMs) and anti-infectives can occur and influence their efficacy or cause toxicity. All potential DDIs between ASMs and antimicrobial agents used in children were identified through consultation of drug compendia. Clinical studies, case reports and summaries of product characteristics of all identified drugs were also searched. A typical example of a DDI that is often observed in children is that involving valproate (VPA) and carbapenem antibiotics. This DDI has a unique mechanism of action (inhibits the enzyme that catalyses the hydrolysis of VPA-glucuronide) and leads to a fall of around 60% of VPA level, associated with seizure recurrence. An example of bidirectional DDI involves the antimycotic voriconzole and several ASMs. Voriconazole is metabolized and is a strong inhibitor of cytochrome (CYP)3A4, CYP2C9/10 and CYP2C19. There is clinical evidence of induction of voriconazole metabolism with possible loss of its efficacy by phenytoin (PHT), while voriconazole increases the levels of PHT. Other ASMs that are inducers of these enzymes, such as carbamazepine (CBZ), phenobarbital, stiripentol and to a lesser degree, oxcarbazepine, might be predicted to decrease the level of voriconazole. Voriconazole might also be predicted to increase levels of cannabidiol, CBZ, lacosamide, midazolam, and zonisamide. DDIs between ASMs and some antiviral agents are potentially even more frequent and clinically relevant.

Key words: antiseizure medicines; epilepsy; infectious diseases; antibacterials; antivirals; antimycotics; pharmacokinetic drug interactions

Epilepsy is one of the most common neurological disorders affecting children [1] and requires long-term treatment to prevent or limit seizure recurrence. Traditional antiseizure medications (ASMs) can exhibit several drug-drug interactions (DDIs) [2], and new compounds with high interaction potential such as stiripentol and cannabidiol have recently entered the market with indications for specific paediatric epileptic syndromes.

In the general population, infectious diseases have constituted the most serious health issue in the world up to the mid 20th century when, in developed countries, chronic degenerative diseases began to dominate the scenario [3]. Remarkably, infectious diseases still represent a major problem in children, and the COVID-19 emerging pandemia has renewed interest in the topic [4]. It has been estimated that a median of 14 infectious episodes occurs at age 0-3

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doi:10.1684/epd.2021.1261

years [5], and antimicrobial drugs constitute 60% of all medical prescriptions in children [6].
So far, several studies have assessed the DDIs occurring between ASMs and drugs used for treatment of diseases, most often comorbid with epilepsy in adults and elderly patients [7, 8]. Conversely, no updated systematic evidence exists for DDIs in paediatric age [9] despite the burden of the condition. According to one study performed almost 15 years ago, in primary care, 3.0% of children on chronic antiepileptic therapy were coprescribed therapeutic agents, which could give rise to clinically serious DDIs [10].
A few years ago, a review was performed on DDIs between ASMs and between ASMs and other drugs [2]. The aim of this review was to focus on a more specific aspect, that is the pharmacokinetic DDIs occurring between ASMs and drugs used for the treatment of infectious diseases in children. This focus relies on three specific aspects. First, while adult neurologists are generally aware of DDIs between ASMs and other drugs because of the high frequency of comorbidities in adult and elderly patients with epilepsy, paediatric neurologists are less aware of this issue. Second, although the pharmacokinetics in children is more similar to that in adults than neonates or infants, several differences exist. For several agents, children show higher drug clearance than adults and in general have higher pharmacokinetic variability that may be enhanced by enzyme induction or inhibition [11]. This also applies specifically to ASMs [12]. Third, antimicrobial drugs are the most frequently prescribed drugs in children [6] and are the source of a myriad of dangerous DDIs.
Identification of DDIs is an important component of preclinical development of any drug and is accomplished by *in vitro* and *in vivo* studies. This information, combined with that obtained from studies on healthy volunteers and from patients during clinical development, is stored in large data bases and used by drug compendia to allow prediction of DDIs that, in the majority of cases, are not verified through specific studies in humans.
Accordingly, in this review, as a first step, all potential DDIs were identified for all drugs, and as a second step, clinical confirmation was searched and concordance between these findings evaluated.

Search methods for systematic identification of drug interactions

We systematically searched all DDIs between ASMs and drugs pertaining to the class "anti-infectives for systemic use" (Class J) of the Anatomical Therapeutic Chemical (ATC) classification system [13].
ASMs searched were: brivaracetam (BRV), cannabidiol (CBD), carbamazepine (CBZ), clobazam (CLB), clonazepam (CNP), eslicarbazepine (ESL), ethosuximide (ETS), felbamate (FBM), gabapentin (GBP), lacosamide (LCM), lamotrigine (LTG), levetiracetam (LEV), midazolam (MDZ), oxcarbazepine (OXC), perampanel (PER), phenytoin (PHT), phenobarbital (PB), pregabalin (PGB), rufinamide (RFN), stiripentol (STP), topiramate (TPM), valproic acid (VPA), vigabatrin (GVG), and zonisamide (ZNS).
We searched all anti-infectives authorized for paediatric use (age< 16 years) for possible DDIs with ASMs in two leading publicly accessible drug compendia [14]. In the case of antiviral drugs, Liverpool Interaction checker and the list of interactions of experimental drug therapies for COVID-19 were also consulted [15]. Drugs with indication for rare disorders (for example, leprosy) were excluded. When a potential interaction between any anti-infective and ASM emerged, the literature was searched for available clinical evidence through MEDLINE (accessed by PubMed: name of the anti-infective drug AND antiepileptic drugs AND drug-interaction) and the Summary of Product Characteristics (SPC) for each drug were consulted.

Mechanisms of pharmacokinetic drug interactions of ASMs

Pharmacokinetic interactions occurring at the metabolic level

The most frequent and clinically significant DDIs of ASMs occur at the metabolic level and are consequent to their oxidative metabolism and/or glucuronidation and to their effect on the enzymatic systems involved in metabolism of drugs, mainly the cytochromes P450 (CYPs) and the uridine glucuronyl transferases (UGTs) [16, 17].
All CYPs function as mono-oxygenases. They are classified into several families and subfamilies, have a characteristic substrate specificity and their activity is genetically determined [16, 17]. The UGTs catalyse drug glucuronidation and are less substrate specific than CYPs. They include two enzymatic families (UGT1 and UGT2), each with eight isoenzymes [16].
The activity of these enzymes may be induced or inhibited by other drugs. Enzyme induction consists of enhanced metabolic clearance of the drug which is the substrate of the induced enzyme, consequently leading to a decrease in its serum concentration. This process is characterized by increased synthesis of the enzymes involved in drug metabolism and requires time before the new steady state concentration of the victim drug is reached. Enzyme inhibition results in

decreased metabolism and increased concentrations of the affected drug and takes place rapidly after the administration of the inhibiting agent [2, 17].
Although all pharmacokinetic DDIs can be predicted by the knowledge of the effects that perpetrators have on all CYP and UGT isoenzymes that metabolize the affected drug, the magnitude of the interaction is subject to high variability. The degree of interaction may be modulated by drug dose, genetic factors, different strength of the effect of perpetrators and the extent of the metabolic transformation of the enzymatic pathway of the affected drug that has been induced or inhibited as well as several other factors [18, 19].
Several traditional ASMs (PB, PHT, CBZ) are broad-spectrum strong enzyme inducers as they can induce the activity of many CYP450 enzymes and/or UGT isoenzymes; several second-generation ASMs are weak enzyme inducers (ESL, OXC, FBM, RFN, TPM at doses higher than 200 mg/day and PER at doses higher than 8 mg/day). VPA, FBM, STP, CBD, and BRV have enzyme inhibiting properties although some of them can also exert inducing effects on the same or other enzymes (OXC, STP, FBM, CBD) [20].

Pharmacokinetic interactions affecting absorption and distribution

Although DDIs concerning drug metabolism are the most important, DDIs can also occur at the level of gastrointestinal absorption, renal excretion, or distribution of the drug [2, 20].
Drug absorption, disposition and elimination are influenced by some transmembrane polypeptides. These proteins are divided into an ATP-binding cassette (ABC) family and a solute carrier (SLC) family [19]. The ABC family include P-glycoprotein 1 (permeability glycoprotein, Pgp), also known as multidrug resistance protein (MDR1). This is a protein of the cell membrane that pumps many foreign substances out of cells and is extensively expressed in the intestinal epithelium, in excretory cells in the liver and kidney, and in endothelial cells related to the blood-brain barrier, thus regulating absorption, excretion and distribution of a wide range of compounds [21]. Breast cancer resistance protein (BCRP; ABCG2) limits intestinal absorption of low-permeability substrate drugs and mediates biliary excretion of drugs and metabolites [22]. SLC family transporters include several transporting polypeptides [23]. The activity of all these peptides can also be induced or inhibited [24]. Interestingly, while traditional ASMs (CBZ, PHT, PB) [19] are inducers, some of the newer ASMs (CBD [25], STP [26] and BRV [27]) are inhibitors of some of these protein transporters.

Mechanisms regulating pharmacokinetic interactions

Although the consequences of all these interactions are complex and cannot be easily predicted, it has recently been shown that there is some coordination between all these mechanisms. Pregnane X receptor (PXR) is a nuclear receptor whose primary function is to sense the presence of foreign and possibly toxic substances. This receptor up-regulates the expression of cytochrome P450 genes (mainly CYP3A4) and that of conjugating enzymes such as glutathione S-transferase as well as the expression of efflux proteins such as some OATP transporters and P-gp. Many P-gp substrates overlap with CYP3A4 substrates, and several drugs that are CYP3A4 substrates are also P-gp substrates [19].

Specific aspects of interactions in children

For some drugs, the level of interaction in paediatric patients might be different leading to a higher or lower DDI potential compared to adults [11, 28].
Studies conducted on the expression of drug-metabolizing enzymes during ontogeny show that in liver samples of subjects from 1 to 10 years, CYP2C9 and CYP2C19 expression is 40-50% of that reported in adults, while the expression of CYP3A4 increases over these years and adult levels are generally achieved after the third year of age [29].
In a systematic literature review conducted for all drugs, only 31 paediatric studies on DDIs were identified corresponding to only 24 cases, and comparisons were possible between studies conducted in adults and paediatric patients (also neonates and infants). The magnitude of the interaction, as measured by the area under the curve and the clearance of the affected drug in the presence and absence of the perpetrator, was higher than, similar to, or lower than the corresponding ratio in adults in 10, 15, and 8 cases respectively [11].
The main enzymes involved in the metabolism of ASMs authorized in children and their inducing or inhibiting properties on enzymatic systems and membrane transporter proteins are reported in *table 1*.

Identification of drug interactions

Among more than 400 drugs included in Class J of the ATC system, 147 were found in the compendia [14]. Of these, 47 have potential DDIs with at least one ASM and are authorized for paediatric patients (18 antibacterials, six anti-mychotics and 23 antivirals including drugs used for COVID-19). Analysis of the

▼ **Table 1.** Mechanisms of elimination of antiseizure medications and their effects on metabolism enzymes and transporter proteins.

Antiseizure drug	Maine route(s) of elimination	Effects on CYP, UGT and transporter proteins
Old-generation antiseizure medications		
Carbamazepine	Oxidation (CYP3A4; metabolite: epoxide hydrolase)	CYP induction (CYP3A4, 2C9, 1A2) UGT induction P-gp induction
Ethosuximide	Oxidation (CYP3A4)	-
Phenytoin	Oxidation (CYP2C9, 2C19, 2C18, 3A4)	CYP induction (CYP3A4, 2C9, 1A2) CYP inhibition (CYP2C19) UGT induction P-gp induction
Phenobarbital	Oxidation/conjugation (75%) (CYP2C9, 2C19, 2E1) Renal excretion (25%)	CYP induction (CYP3A4, 2C9, 1A2) P-gp induction
Primidone	Oxidation (CYP2C9)	CYP induction (CYP3A4, 2C9, 1A2)
Valproic acid	Oxidation (>50%) (CYP2A6, 2C9, 2C19 2B6, mitochondrial oxidases) Conjugation (30-40%) (UGT1A3, 2B7)	CYP inhibition (CYP2C9, *2C19, *3A4, epoxide hydrolase) UGT inhibition
New-generation antiseizure medications		
Brivaracetam	Hydrolysis (60%) Oxidation (30%) (CYP2C19)	*CYP induction (CYP2B6, 3A4) CYP inhibition (CYP2C19) Inhibition of epoxide hydrolase Inhibition of organic anion transporter (OAT)-3
Cannabidiol	Oxidation (CYP2C19, 3A4) Glucuronidation (UGT1A7, 1A9, 2B7)	CYP induction (CYP1A2, 2B6) CYP inhibition (CYP1A2, 2B6, 2C8, 2C9, 2C19) UGT inhibition (UGT1A9, 2B7) P-gp and BCRP inhibition
Clobazam	Oxidation (CYP3A4; CYP2C19)	-
Clonazepam	Oxidation (CYP3A4)	-
Eslicarbazepine acetate	Hydrolysis Glucuronidation (UGT1A4, 1A9, 2B4, 2B7, 2B17)	CYP induction (CYP3A4) *CYP inhibition (CYP2C19) UGT-induction
Felbamate	Oxidation (>50%) (CYP3A4, 2E1) Renal excretion (>30%)	*CYP induction (CYP3A4) CYP inhibition (CYP2C19)
Gabapentin	Renal excretion	-
Lacosamide	Demethylation (CYP3A4, 2C9, 2C19) Renal excretion (35% unchanged)	-
Lamotrigine	Conjugation (UGT1A4)	-
Levetiracetam	Hydrolysis (25%) (type-B esterase) Renal excretion (75%)	-
Midazolam	Oxidation (CYP3A4)	P-gp induction
Oxcarbazepine	Ketoreduction (arylketone reductase); Glucuronidation (UGT1A4, 1A9, 2B4, 2B7, 2B17) Renal excretion (<30%)	CYP induction (CYP3A4) *CYP inhibition (CYP2C19) UGT induction (UGT1A4) P-gp induction

▼ **Table 1.** Mechanisms of elimination of antiseizure medications and their effects on metabolism enzymes and transporter proteins (*continued*).

Antiseizure drug	Maine route(s) of elimination	Effects on CYP, UGT and transporter proteins
New-generation antiseizure medications		
Perampanel	Oxidation (CYP3A4)	*CYP induction (CYP2B6, 3A4/5) *CYP inhibition (CYP2C8) *UGT inhibition (UGT1A9)
Pregabalin	Renal excretion	-
Rufinamide	Hydrolysis (carboxyl esterases) Glucuronidation	CYP induction (CYP3A4)
Stiripentol	Oxidation/hydroxylation (CYP1A2, 2C19, 3A4; carboxyl esterases) Glucuronidation	CYP induction (CYP3A4) CYP inhibition (CYP1A2, 3A4, 2C19, 2D6) BCRP and P-gp inhibition
Topiramate	Oxidation (20-60%) Renal excretion (40-80%)	*CYP induction (CYP3A4) (>200 mg/day) *CYP inhibition (CYP2C19)
Vigabatrin	Renal excretion	-
Zonisamide	Oxidation, reduction, acetylation (>50%) (CYP3A4, N-acetyl transferase) Renal excretion (30%)	-

*Weak induction/inhibition. CYP= cytochrome UGT= uridine glucuronyl transferases; P-gp= P-glycoprotein efflux transporter; BCRP= Breast Cancer Resistance. Protein Data are from [2, 12, 16, 17, 20] and Summary of Product Characteristics for ASMs.

literature allowed the identification of 111 records on DDIs between the 47 identified antimicrobials and ASMs. All potential DDIs and a summary of clinical data concerning each interaction are reported in *tables 2, 3, 4*. Potential DDIs are ranked in parenthesis as "serious" (may result in potentially serious clinical consequences, and the combination should be avoided), "monitor" (not possible to avoid the combination, and clinical and laboratory monitoring is required which may lead to dosage adjustment), "minor" (limited clinical value, and dosage adjustment is usually not necessary). A list and a more detailed description of the clinical studies and case reports on the identified DDIs are presented in *supplementary tables 1, 2, 3* of the supplementary material. The most relevant DDIs are summarized in the following paragraphs.

Drug interactions between ASMs and antibacterials/antimycotics

Although antibacterials and antimycotics are usually taken for a limited amount of time and are rarely administered as a chronic therapy, there are examples of DDIs that can have very significant clinical consequences.

Interactions characterized by increased levels and/or effects of ASMs

Several antimicrobics are strong CYP inhibitors and may increase blood levels of ASMs with consequent risk of CNS toxicity [18, 20]. Among drugs used in children, ciprofloxacin, chlarythromicin, erythromycin, isoniazid, metronidazole, and fluconazole can increase levels of CBZ mainly through CYP3A4 inhibition; chloramphenicol, isoniazid, sulfamethoxazole and trimethoprim and the antimycotics fluconazole, voriconazole and isoniazid (in slow acetylators) can increase PHT concentrations with possible toxicity through CYP2C19 and/or CYP2C9/10 inhibition (*supplementary tables 1, 2*).
Given the lack of clinical studies, inhibition of metabolism of other ASMs by antibacterials can only be predicted (*tables 2, 3*).

Interactions characterized by reduced levels and/or effects of ASMs

The combination of antibacterials and ASMs may be less commonly associated with reduced ASM levels and possible loss of antiseizure activity. This effect generally derives from enzyme induction. Ciprofluoxacin and levofloxacin have been found to lower PHT levels with unknown mechanisms [2]. Rifampicine, a strong enzyme inducer of several cytochrome and glucuronidation enzymes and

▼ **Table 2.** Potential pharmacokinetic interactions between antibacterials and antiseizure medications in paediatric patients and related clinical data.

Class J. Antibacterials for systemic use	Mechanism of interaction[&]	Effects of ASMs on the antibacterial (affected drug)	Effects of the antibacterial (perpetrator) on ASMs
Amikacin	P-glycoprotein substrate and inducer	**Information from drug compendia** Midazolam, phenytoin and phenobarbital potentially decrease the levels of amikacin (monitor) **Clinical studies and case reports** None	Amikacin potentially decreases levels of phenytoin and phenobarbital (monitor)
Ciprofloxacin	P-glycoprotein substrate	**Information from drug compendia** Stiripentol potentially increases levels of ciprofloxacin (serious) **Clinical studies and case reports**	Ciprofloxacin potentially increases levels of carbamazepine (monitor), clonazepam and midazolam (minor). Ciprofloxacin potentially decreases levels of phenytoin (monitor) In a clinical study on healthy adult volunteers, ciprofloxacin increased Cmax, AUC and t½ of carbamazepine Case reports confirm DDI with phenytoin
Clarithromycin*	CYP3A4 strong inhibitor	**Information from drug compendia** Phenytoin, phenobarbital, oxcarbazepine and rufinamide potentially decrease levels of clarithromycin (minor). Zonisamide potentially increases the levels of clarithromycin (monitor) **Clinical studies and case reports**	Clarithromycin potentially increases levels of carbamazepine, midazolam (serious), lacosamide and valproate (minor). Clarithromycin potentially decreases levels of phenytoin, topiramate, oxcarbazepine, rufinamide (minor) Retrospective case series confirm DDI with carbamazepine. Three clinical studies confirm DDI with midazolam. In a case report, severe OXC toxicity was reported after starting clarithromycin. This observation is discordant with that predicted by drug compendia. It is suggested that clarithromycin inhibited the efflux of proteins of the blood-brain barrier which are potentially over-expressed in drug-resistant patients.
Chloramphenicol	CYP 3A4 and CYP 2C19 inhibitor	**Information from drug compendia** Phenobarbital potentially decreases levels of chloramphenicol (minor).	Chloramphenicol potentially increases levels of phenytoin, cannabidiol (monitor) and phenobarbital (minor)

▼ **Table 2.** Potential pharmacokinetic interactions between antibacterials and antiseizure medications in paediatric patients and related clinical data (*continued*).

Class J. Antibacterials for systemic use	Mechanism of interaction[&]	Effects of ASMs on the antibacterial (affected drug)	Effects of the antibacterial (perpetrator) on ASMs
Chloramphenicol		**Clinical studies and case reports** In a retrospective case series, PB decreased chloramphenicol levels (concordant) while PHT increased chloramphenicol levels (discordant with prediction based on drug compendia). In a paediatric patient, PB and PHT decreased chloramphenicol levels which is concordant with prediction	Two case reports signalled cases of PRI and of PHT intoxication induced by chloramphenicol in accordance with prediction
Doxycycline	Possible substrate and moderate CYP3A4 inhibitor	**Information from drug compendia** Carbamazepine, phenytoin, phenobarbital (monitor) and oxcarbazepine (minor) potentially decrease the levels of doxycycline **Clinical studies and case reports** In a clinical study, half-life of doxycycline was less than half in patients treated with phenytoin, carbamazepine or both drugs in subjects not treated with ASMs. In a further study, phenobarbital caused a similar fall of doxycycline levels which is in accordance with prediction.	Doxycycline potentially increases levels of, or effect, cannabidiol (monitor)
Erythromycin	CYP 3A4 substrate and moderate inhibitor. P-gp substrate	**Information from drug compendia** Carbamazepine, phenytoin, phenobarbital, oxcarbazepine, rufinamide, topiramate decrease the levels of, or effect erythromycin (serious). Stiripentol potentially decreases or increases erythromycin levels (monitor) **Clinical studies and case reports**	Erythromycin potentially increases levels of, or effect carbamazepine, cannabidiol, midazolam (serious) and valproic acid (minor) In 2 cross-over studies on healthy volunteers, midazolam and CBZ levels were increased by the agent while in 4 similar studies, erythromycin failed to increase levels of oxcarbazepine, felbamate, or phenytoin. Case reports confirm DDIs with carbamazepine and valproate

▼ **Table 2.** Potential pharmacokinetic interactions between antibacterials and antiseizure medications in paediatric patients and related clinical data (*continued*).

Class J. Antibacterials for systemic use	Mechanism of interaction[&]	Effects of ASMs on the antibacterial (affected drug)	Effects of the antibacterial (perpetrator) on ASMs
Ertapenem, imipenem and cilastin/ meropenem	Possible inhibition of hepatic acylpeptide hydrolase	**Information from drug compendia**	Ertapenem, imipenem and meropenem decrease levels of valproic acid (serious)
		Clinical studies and case reports	Clinical data: several retrospective studies, drug monitoring records and case reports confirm the clinical significant (50% to 90%) decrease of valproate levels induced by these antibiotics.
Gentamicin	Substrate of P-gp efflux transporter	**Information from drug compendia** Midazolam, phenytoin and phenobarbital potentially decrease the levels of gentamicin (monitor) **Clinical studies or case reports** None	Gentamicin potentially decreases the levels of phenytoin and phenobarbital
Isoniazid	CYP3A4 and CYP2C19 inhibitor	**Information from drug compendia**	Isoniazid potentially increases levels of carbamazepine, cannabidiol, clobazam, lacosamide, midazolam, phenytoin, valproic acid and zonisamide (monitor)
		Clinical studies and case reports In a retrospective study conducted on 60 patients with tuberculous meningitis and seizures, the combination of both phenytoin and isoniazide was associated with increased levels of both drugs in subjects who were slow acetylators as compared to rapid acetylators. The phenytoin-induced increase in isoniazid levels was not predicted by drug compendia. Several case reports confirm the prediction of increased levels of carbamazepine, phenytoin and valproate induced by isoniazid. A case is described of ethosuximide intoxication caused by isoniazid which is not reported in drug compendia.	
Levofloxacin	Unknown	**Information from drug compendia**	Levofloxacin potentially decreases levels of phenytoin (monitor) and increases the levels of clonazepam and midazolam (minor)
		Case reports	Levofloxacin decreased phenytoin levels in two patients.
Metronidazole	CYP3A4 and CYP2C9/10 inhibitor	**Information from drug compendia**	Metronidazole potentially increases levels of, or effect carbamazepine, cannabidiol, midazolam and phenytoin (monitor)

▼ **Table 2.** Potential pharmacokinetic interactions between antibacterials and antiseizure medications in paediatric patients and related clinical data (*continued*).

Class J. Antibacterials for systemic use	Mechanism of interaction[&]	Effects of ASMs on the antibacterial (affected drug)	Effects of the antibacterial (perpetrator) on ASMs
Metronidazole		**Clinical studies and case reports** Phenobarbital induced the metabolism of metronidazole in patients with Chron disease.	In a randomised, placebo-controlled, cross-over study conducted in 10 healthy subjects, metronidazole had no effect on the pharmacokinetics of midazolam which is *discordant* with prediction based on drug compendia. In an open-label, parallel study, metronidazole treatment significantly inhibited phenytoin levels. Carbamazepine metabolism was inhibited by metronidazole in a patient with diverticulitis
Sulfamethoxazole and trimethoprim	CYP2C9/10 substrate and inhibitor	**Information from drug compendia** Carbamazepine and phenobarbital potentially decrease the levels of, or effect sulfamethoxazole (minor). Valproic acid, cannabidiol and felbamate potentially increase levels of sulfamethoxazole or trimethoprim (minor) **Clinical studies and case reports**	Sulfamethoxazole potentially increases levels of phenytoin by affecting hepatic enzyme CYP2C9/10 metabolism (monitor) In old patients receiving PHT, treatment with sulfamethoxazole and trimethoprim was associated with a more than two-fold increase in phenytoin concentration. In a case report, phenytoin levels were increased by sulfamethoxazole and trimethoprim
Sulfadiazine	CYP2C9/10 inhibitor	**Information from drug compendia** Cannabidiol potentially increases levels of sulfadiazine (monitor) **Clinical studies or case reports** None	Sulfadiazine potentially increases the levels of phenytoin and lacosamide (monitor)
Sulfasalazine	BCRP substrate	**Information from drug compendia** Stiripentol potentially increases levels of, or effect sulfasalazine (monitor) **Clinical studies or case reports** None	

▼ **Table 2.** Potential pharmacokinetic interactions between antibacterials and antiseizure medications in paediatric patients and related clinical data (*continued*).

Class J. Antibacterials for systemic use	Mechanism of interaction[&]	Effects of ASMs on the antibacterial (affected drug)	Effects of the antibacterial (perpetrator) on ASMs
Tobramycin	P-glycoprotein (MDR1) efflux transporter substrate	**Information from drug compendia** Midazolam, phenytoin and phenobarbital potentially decrease levels of tobramycin (monitor). **Clinical studies or case reports** None	
Trimethoprim	CYP2C9 substrate	**Information from drug compendia** Cannabidiol potentially increases levels of trimethoprim (monitor) **Clinical studies or case reports** None	

▼ **Table 3.** Potential pharmacokinetic interactions between antimycotics/drugs for treatment of tuberculosis and antiseizure medications in paediatric patients and related clinical data.

J02. Antimycotic drugs and drugs for treatment of tuberculosis	Mechanism of interaction[&]	Effects of ASMs on the antimycotic (affected drug)	Effects of the antimycotic (perpetrator) on ASMs
Bedaquiline	CYP3A4 substrate	**Information from drug compendia** Carbamazepine, phenytoin, phenobarbital oxcarbazepine potentially decrease the levels of bedaquiline (serious). Stiripentol potentially increases or decreases bedaquiline levels (monitor) **Clinical studies or case reports** None	
Fluconazole	CYP3A4 and CYP2C9/10 moderate inhibitor	**Information from drug compendia** Phenobarbital potentially decreases levels of fluconazole (minor)	Fluconazole potentially increases levels of carbamazepine, cannabidiol, clobazam, midazolam, phenytoin, lacosamide (monitor) and zonisamide (minor)

▼ **Table 3.** Potential pharmacokinetic interactions between antimycotics/drugs for treatment of tuberculosis and antiseizure medications in paediatric patients and related clinical data (*continued*).

J02. Antimycotic drugs and drugs for treatment of tuberculosis	Mechanism of interaction[&]	Effects of ASMs on the antimycotic (affected drug)	Effects of the antimycotic (perpetrator) on ASMs
Fluconazole		**Clinical studies and case reports**	
			In a placebo-controlled, parallel study, the AUC of plasma PHT concentration was 75% higher in patients treated with fluconazole In patients treated with midazolam infusion, fluconazole determined a significant increase in levels of this drug. Several case reports confirm inhibition of phenytoin and carbamazepine levels.
Rifapentine	CYP3A4, CYP2C9/10 inducer	**Information from drug compendia**	
			Rifapentine potentially decreases levels of, or effect carbamazepine, cannabidiol, midazolam, phenytoin (monitor) and stiripentol (serious)
		Clinical studies or case reports	
		None	
Rifampicine	Strong inducer of CYP 1A2, 2B6, 2C8, 2C9, 2C19, and 3A4, UGT, and P-gp	**Information from drug compendia**	
		Stiripentol and cannabidiol potentially increase or decrease rifampicine levels (monitor)	Rifampicine potentially decreases levels of brivaracetam, cannabidiol, carbamazepine, midazolam, phenytoin, phenobarbital, lamotrigine, stiripentol (serious) and zonisamide (monitor)
		Case reports	
			In a patient treated with phenytoin, phenobarbital rifampicin and ethambutol, withdrawal of both antimicrobials caused an increase in phenytoin concentrations. A significant decrease in oxcarbazepine active metabolite was observed after rifampicin administration. This interaction is not predicted by drug compendia.

▼ **Table 3.** Potential pharmacokinetic interactions between antimycotics/drugs for treatment of tuberculosis and antiseizure medications in paediatric patients and related clinical data (*continued*).

J02. Antimycotic drugs and drugs for treatment of tuberculosis	Mechanism of interaction[&]	Effects of ASMs on the antimycotic (affected drug)	Effects of the antimycotic (perpetrator) on ASMs
Voriconazole	Substrate and strong inhibitor of CYP3A4, CYP2C9/10 and CYP2C19	**Information from drug compendia** Carbamazepine (serious), phenytoin, phenobarbital (monitor) potentially decrease levels of voriconazole. Oxcarbazepine (minor) and stiripentol (monitor) potentially increase or decrease voriconazole levels. Felbamate (minor) and cannabidiol (monitor) potentially increase voriconazole levels	Voriconazole potentially increases the levels of cannabidiol, carbamazepine, lacosamide, midazolam, phenytoin and zonisamide (monitor), and valproate (minor)
		Clinical studies and case reports In an open-label study on healthy volunteers, phenytoin decreased the mean steady-state Cmax and AUC of voriconazole by approximately 50% and 70%, respectively. In three seriously ill patients, phenytoin induced a dramatic fall in voriconazole levels that was not compensated by doubling the dose of the antimicrobial	In a double-blind, randomized clinical study on healthy volunteers, voriconazole increased the mean steady-state Cmax and AUC of PHT by approximately 70% and 80%, respectively.
Isoniazid	see *table 2*		

[&] Mechanism of interaction: route of elimination of the antimicrobial agent involved in the interaction or effect of the antimicrobial on CYP, UGT and P-gp. All searches were performed in Medscape Interaction checker [14] and Rx List [71].
Abbreviation: ASM=antiseizure medication.
Further details on reported clinical data and relative references are presented in *supplementary table 2*.

transport proteins, can be predicted to induce metabolism of several traditional and new ASMs. Amikacine and rifapentine have some inducing properties.
The fall of VPA levels with possible loss of seizure control induced by carbapenem is a case of antibacterial-induced reduction in the concentration of an ASM which is not due to enzyme induction [30].
Interestingly, this DDI was not predicted by *in vitro* studies and the first observation was in a child [31]. Moreover, this was also the only interaction that was assessed based on a retrospective study in a population of paediatric patients [32]. The suggested mechanism is the inhibition of acyl peptide hydrolase, a hepatic enzyme that catalyses the hydrolysis of VPA-glucuronide, leading to increased elimination of VPA [33, 34]. Ertapenem and meropenem seem to have greater effects on VPA levels than imipenem/cilastatin [35].

Interactions characterized by reduced levels/efficacy of antibacterials/antimycotics

There are also examples of ASMs that alter the metabolism of antibacterial and antimycotic drugs. These

DDIs usually involve induction of oxidative metabolism with a possible loss of antimicrobic activity. Lower levels of doxycycline levels have been found in patients treated with PB and/or PHT. Metabolism of metronidazole is induced by PB. In one study in healthy subjects, PHT caused a 70% reduction in voriconazole plasma levels, which led to a request to double the voriconazole dose in order to maintain effective antimycotic concentrations [16, 20].

Interactions characterized by increased levels/efficacy of antibacterials/antimycotics

More recently, new ASMs with strong inhibiting properties, namely CBD and STP, have been approved for use for specific paediatric syndromes. These drugs may potentially inhibit the metabolism of several antibacterials and antimycotics.

Concordance between prediction and clinical observations

In the vast majority of cases, concordance has been found between predicted and clinically observed DDIs. However, this is not always the case. One study failed to confirm the predicted DDI between metronidazole and MDZ [36] and there are also clinical studies or case reports signalling a DDI not predicted by drug compendia. PHT was found to increase chloramphenicol levels [37]. Primidone [38] and ETS levels [39] were increased by chloramphenicol and isoniazid, respectively, and rifampicine decreased the active OXC metabolite [40]. Importantly, cases of discordant findings also exist. OXC levels are predicted to be decreased by clarithromycin. However, a 10-year-old boy treated with OXC developed neurological signs clearly related to OXC toxicity a few days after the combination of this agent with clarithromycin, in the absence of any change in OXC plasma levels. Clarithromycin-induced inhibition of the efflux proteins of the blood-brain barrier, which are over-expressed in drug-resistant patients, may increase brain OXC concentrations with consequent toxic symptoms [41] (*see supplementary tables 1, 2*). All the potential DDIs between ASMs and antibacterials and antimycotic drugs and a summary of the clinical evidence for each identified DDI are presented in *tables 2, 3*.

Drug interactions between ASMs and antivirals

In this section, antiviral drugs are classified according to their use against specific viral diseases, with special attention to chronic conditions such as HIV/AIDS, hepatitis C, hepatitis B and COVID-19.

Interactions between ASMs and antiretroviral therapies used as treatment for HIV/AIDS

Children may be infected in 0.7% cases through mother-to-child transmission [42]. This disease can be especially harmful to infants and children, with one study showing that 52% of untreated children born with HIV in Africa died by the age of two [43]. Notably, the WHO recommends treating all children less than five years old [43].

A guideline for patients who need to be treated with a combination of antiviral agents for HIV/AIDS and ASMs was delivered in 2012 [44]. Today, however, we can foresee more DDIs, mainly because of the introduction of new ASMs with strong inhibitory effects.

Several antivirals are comprised of a combination of two or more agents, one of which is a mechanistic inhibitor of CYP3A4 such as ritonavir or cobicistat. These agents are intended to enhance the effect of the combined protease inhibitor by inhibiting its metabolism [45, 46], but they have also some inducing properties on other enzymes. Hence, it is not surprising that these agents may have DDIs with a great variety of drugs, including ASMs undergoing oxidative metabolism.

Several clinical studies have documented two-way inducing effects between antivirals and ASMs. This is the case for DDIs between lopinavir/ritonavir and PHT, with increased clearance of both the antiviral, possibly via CYP3A4 induction, and PHT, possibly via CYP2C9 induction [47]. Coadministration of CBZ with efavirenz significantly reduces exposure to both drugs [2].

Documented examples of inducing effects of ASMs on antivirals include the effect of CBZ and OXC on the metabolism of atazanavir [48]; contrasting results are reported on the effect of OXC on dolutegravir [48, 49]. An example of an inducing antiviral is zidovuline, which has been shown to decrease PHT levels [18].

VPA has inhibiting properties and, as predicted, inhibits zidovuline metabolism and can double the level of the antiviral agent [2, 18]. However, in some patients, the combination of VPA and dolutegravir was associated with lower antiviral concentrations [50]. This unexpected finding may be due to reduced dolutegravir absorption by the excipients contained in some VPA gastro-resistant oral formulations.

Concerning the influence of antivirals on VPA metabolism, efavirenz or lopinavir/ritonavir have been shown to reduce VPA levels in one patient with bipolar disorder, possibly through the induction of VPA glucuronidation. However, in a pharmacokinetic study, the administration of a dose of VPA of 500 mg/day in

HIV-1 infected patients receiving efavirenz or lopinavir/ritonavir and in patients who had discontinued the antiretroviral therapy did not result in significant effects on efavirenz and lopinavir concentrations; further, no concerns arose that coadministration with these antivirals agents significantly influences trough concentrations of VPA [51].
The inducing effects of ritonavir on UGT enzymes may be responsible for the decreased levels of LTG observed in a clinical study conducted in healthy volunteers [52]. In this study, lopinavir/ritonavir led to a clear reduction in LTG levels, atazanavir/ritonavir had a moderate effect in reducing LTG exposure, and atazanavir alone did not significantly influence LTG concentrations [53].
An interesting example of the complexity of pharmacokinetic interactions is that between etravirine and CLB. Etravirine may reduce CLB levels through CYP3A4 induction. However, this antiviral is also a weak CYP2C19 inhibitor and may increase the concentration of desmethylclobazam, the active metabolite of CLB. Indeed, a case of etravirine-induced CLB toxicity has been described [54].
Clinical studies and case reports generally confirm predicted DDIs; some exceptions, however, have been documented. Notably, OXC was not found to reduce dolutegravir or efavirenz levels [50, 55].

Interactions between ASMs and other antiviral agents

Even in the case of hepatitis viruses, there is a risk of mother-to-child transmission. This risk is higher for hepatitis B than for hepatitis virus C [56]. Both hepatitis B and C place a child at high risk of subsequent chronic hepatitis. For hepatitis C, when treatment cannot be deferred, different first-line treatment options exist in the paediatric population [57]; as these agents are often substrates and inhibitors of P-gp, several potential DDIs with ASMs may be predicted [58]. Fewer drugs are available in children with hepatitis B and infrequently they cause DDIs [59]. Agents used to treat influenza do not show DDIs.
DDIs between ASMs and drugs used to treat COVID-19 are interesting. In the pandemia caused by Sars-CoV-2 infection, children usually present with mild clinical symptoms. Some patients, however, may progress rapidly and develop respiratory failure [4]. No drugs are currently approved and several agents already available on the market for other indications have been repurposed [60]. This is the case for atazanavir/ritonavir, darunavir/cobicistat and lopinavir/ritonavir (see section on HIV/AIDs drugs). Other drugs repurposed from other diseases (chloroquine, hydroxychloroquine, nitazoxanide) or not yet on the market (remdesvir) are reported in *table 4*. Some non-antiviral agents used for COVID-19, such as chloroquine and hydroxychloroquine, also exhibit important potential DDIs as their metabolism is induced by ASM enzyme-inducers.
Potential DDIs between antiviral drugs and ASMs in paediatric patients and a summary of the clinical evidence are reported in *table 5*. Additional details about clinical studies are reported in *supplementary table 3*.

Specific aspects of drug-drug interactions in children

An important clinical question is whether some DDIs have clinical characteristics that are specific to children. Although enzymatic systems in children are more similar to those observed in adults than in infants or neonates, the extent of DDIs has been shown to differ for several combinations of drugs used in paediatric patients [11]. We found only 11 clinical studies or case reports that describe DDIs in this population of patients, almost all concerning DDIs between ASMs and antibiotics, and these were generally concordant with findings in adults although no inference can be drawn on the degree of differences for any of the DDIs.

Discussion

There is a growing awareness of the importance of DDIs between ASMs and other drugs as a possible cause of drug-related toxicity or loss of efficacy for both classes of agents [61].
In this review, all DDIs between ASMs and antimicrobials authorized for paediatric patients have been evaluated. Among more than 400 antimicrobials, we eventually restricted the search to the 47 agents that have indications in paediatric patients and potential DDIs with at least one of the 24 ASMs. It is, however, worth noticing that potential DDIs have been confirmed by clinical data in only a few cases and these were often restricted to DDIs involving old-generation ASMs.
One major issue is that more than 60% of anti-infectives were not found in the consulted compendia and consequently no information is available on potential DDIs for these agents. Although we can speculate that the most frequently used drugs have more chance to be included in such compendia, for several antimicrobials, there remains a lack of information.
A further finding is that DDIs predicted on the basis of *in vitro* studies and reported in drug compendia

▼ **Table 4.** Potential pharmacokinetic interactions between antivirals and antiseizure medications in paediatric patients and related clinical data.

Class J. Antiviral drug for systemic use	Mechanism of interaction[&]	Effects of ASMs on the antiviral (affected drug)	Effects of the antiviral (perpetrator) on ASMs
Drug for HIV/AIDS			
Atazanavir/ritonavir, also used for COVID-19	Atazanavir is a CYP3A4 and a P-gp substrate, and also a CYP3A4 and UGT1A1 inhibitor. Ritonavir inhibits the major P450 isoforms 3A4 and 2D6. Liverpool checker: Atazanavir induces CYP2C9 and CYP2C19, and ritonavir induces UGTs	**Information from drug compendia** Carbamazepine (serious), phenytoin, phenobarbital, oxcarbazepine, topiramate and rufinamide potentially decrease the levels of atazanavir and ritonavir (monitor) Stiripentol potentially increases or decreases antiviral levels **Clinical studies and case reports** In 11 HIV-positive patients, atazanavir and dolutegravir concentrations were significantly lower in patients treated with carbamazepine or oxcarbazepine, than in patients not treated with ASMs.	Atazanavir/ritonavir potentially increases levels of carbamazepine, cannabidiol, clonazepam, ethosuximide, lacosamide, midazolam, perampanel and zonisamide (monitor) and decreases the levels of lamotrigine, phenobarbital, phenytoin and valproate In a study on healthy volunteers, atazanavir alone did not significantly influence glucuronidation of lamotrigine, while atazanavir/ritonavir moderately decreased lamotrigine levels. Toxic carbamazepine levels were observed in a patient after starting treatment with ritonavir.
According to the SPC, Darunavir/cobicistat must not be combined with drugs metabolized by CYP3A and with a narrow therapeutic window. Also used for COVID-19.	Darunavir is a CYP3A4 substrate. Cobicistat is metabolised via CYP3A (major)- and CYP2D6 (minor)-mediated oxidation. Darunavir is an inhibitor of CYP3A, a weak inhibitor of CYP2D6 and an inhibitor of P-gp. Cobicistat is an inhibitor of CYP3A, and a weak CYP2D6 inhibitor; it inhibits P-gp.	**Information from drug compendia** Carbamazepine, phenytoin, phenobarbital, oxcarbazepine potentially decrease cobicistat concentrations and consequently those of darunavir. **Clinical studies and case reports** None	Darunavir/cobicistat potentially increase levels of ASMs metabolized via CYP3A (cannabidiol, carbamazepine, ethosuximide, felbamate, lacosamide, midazolam, perampanel, phenytoin, stiripentol, zonisamide)

▼ **Table 4.** Potential pharmacokinetic interactions between antivirals and antiseizure medications in paediatric patients and related clinical data (*continued*).

Class J. Antiviral drug for systemic use	Mechanism of interaction[&]	Effects of ASMs on the antiviral (affected drug)	Effects of the antiviral (perpetrator) on ASMs
Dolutegravir	CYP3A4 and Pgp substrate Liverpool checker: UGT1A1 substrate	**Information from drug compendia** Carbamazepine, phenytoin, phenobarbital, oxcarbazepine potentially decrease dolutegravir levels (monitor) **Clinical studies and case reports** In 8 patients with HIV, oxcarbazepine failed to suppress the effect of dolutegravir. In one patient, combination of valproate with dolutegravir was associated with lower levels of the antiviral. In a patient with HIV infection, phenobarbital decreased dolutegravir levels.	
Efavirenz	CYP3A4, a substrate and inducer, is potentially an inducer or inhibitor of CYP2C9, CYP2C19 CYP2B6 and UGT1A4	**Information from drug compendia** Carbamazepine (serious), phenytoin, phenobarbital, oxcarbazepine, rufinamide, topiramate potentially decrease efavirenz levels. Phenytoin potentially increases efavirenz levels. Stiripentol potentially increases or reduces efavirenz levels **Clinical studies and case reports** In a randomized, open label, cross-over study on 36 healthy subjects, coadministration of efavirenz with carbamazepine significantly reduced the exposure to both drugs. In a single patient, a bidirectional interaction resulted in lower efavirenz concentrations and more elevated phenytoin concentrations than-expected.	Efavirenz potentially reduces levels of carbamazepine, ethosuximide, lacosamide, midazolam, zonisamide, stiripentol (monitor) and lamotrigine (minor), and increases clobazam and phenytoin levels (monitor). It also potentially decreases or increases phenobarbital and cannabidiol levels

▼ **Table 4.** Potential pharmacokinetic interactions between antivirals and antiseizure medications in paediatric patients and related clinical data (*continued*).

Class J. Antiviral drug for systemic use	Mechanism of interaction[&]	Effects of ASMs on the antiviral (affected drug)	Effects of the antiviral (perpetrator) on ASMs
Efavirenz			A case of carbamazepine toxicity was reported after starting ritonavir (almost certainly the causative agent) and efavirenz. In HIV-1 infected patients, efavirenz did not influence valproate levels. In a case report, efavirenz did not affect oxcarbazepine levels.
Etravirine	CYP3A4, CYP2C9, CYP2C19 and UDPGT substrate. Weak inhibitor of CYP2C9, CYP2C19 and P-glycoprotein. CYP3A4 inducer	**Information from drug compendia** Carbamazepine, phenytoin, phenobarbital (serious), topiramate and rufinamide (monitor) potentially decrease the levels of etravirine. Oxcarbazepine and stiripentol potentially decrease or increase etravirine levels (monitor). Valproate and cannabidiol potentially increase the level of etravirine (monitor). **Clinical studies and case reports**	Etravirine potentially increases levels of clobazam, phenytoin and stiripentol (serious). Etravirine potentially decreases lacosamide, midazolam (monitor) and zonisamide levels (minor). In one patient, etravirine increased the concentration of clobazam and its metabolite with consequent toxic symptoms.
Fosamprenavir (amprenavir)	CYP3A4 substrate and inhibitor Liverpool checker: Induction of glucuronidation	**Information from drug compendia** Carbamazepine, phenytoin, phenobarbital, oxcarbazepine, topiramate, rufinamide potentially decrease levels of fosamprenavir (monitor). Stiripentol potentially decreases or increases fosamprenavir effects. **Clinical studies and case reports** None	Fosamprenavir potentially increases levels of cannabidiol, carbamazepine, clonazepam, ethosuximide, lacosamide, midazolam, phenytoin, and zonisamide (monitor). Fosamprenavir potentially decreases valproate and lamotrigine levels

▼ **Table 4.** Potential pharmacokinetic interactions between antivirals and antiseizure medications in paediatric patients and related clinical data (*continued*).

Class J. Antiviral drug for systemic use	Mechanism of interaction[&]	Effects of ASMs on the antiviral (affected drug)	Effects of the antiviral (perpetrator) on ASMs
Indinavir	CYP3A4 substrate and inhibitor	**Information from drug compendia**	
		Carbamazepine, midazolam, phenobarbital and phenytoin potentially reduce indinavir plasma concentrations (monitor). Oxcarbazepine potentially decreases indinavir exposure (minor)	Indinavir potentially increases levels of carbamazepine, midazolam, phenytoin and phenobarbital (monitor), and ethosuximide (minor)
		Clinical studies and case reports	
		In one case, antiretroviral therapy failed after introduction of carbamazepine. In an HIV-positive man, indinavir levels decreased substantially leading to failure of antiretroviral therapy, after the introduction of carbamazepine.	
Lopinavir/ritonavir Also used for COVID-19	Lopinavir is a CYP3A substrate and inhibitor. Ritonavir is a CYP3A4 and P-gp inhibitor. These are also substrates of CYP2C9, CYP2C19 and either substrates and inducers of glucuronidation	**Information from drug compendia**	
		Carbamazepine, midazolam, phenytoin, phenobarbital, oxcarbazepine, eslicarbazepine, topiramate rufinamide potentially decrease levels of lopinavir and ritonavir (serious). Stiripentol potentially decreases or increases lopinavir and ritonavir levels (monitor). Valproic acid potentially increases lopinavir/ritonavir levels	Lopinavir/ritonavir potentially reduces levels of phenytoin and lamotrigine (monitor) and increases levels of carbamazepine, cannabidiol, clonazepam, ethosuximide, lacosamide, midazolam, perampanel and zonisamide (monitor). Lopinavir/ritonavir potentially reduces or increases plasma concentrations of felbamate
		Clinical studies and case reports	
		In a randomized, open-label study on healthy volunteers, there was a 2-way drug interaction. Phenytoin increased lopinavir clearance, and lopinavir/ritonavir decreased phenytoin levels	

▼ **Table 4.** Potential pharmacokinetic interactions between antivirals and antiseizure medications in paediatric patients and related clinical data (*continued*).

Class J. Antiviral drug for systemic use	Mechanism of interaction[&]	Effects of ASMs on the antiviral (affected drug)	Effects of the antiviral (perpetrator) on ASMs
Lopinavir/ritonavir Also used for COVID-19		In a pharmacokinetic study on HIV-1 infected patients, lopinavir concentrations were higher when this drug was combined with valproate.	In 24 healthy volunteers, lamotrigine levels decreased after starting lopinavir/ritonavir. In 13 healthy volunteers, midazolam levels were increased by ritonavir. In one patient, valproate levels were decreased and the clinical effect was abolished after starting lopinavir/ritonavir. Carbamazepine levels increased in a HIV-positive male patient after introduction of lopinavir/ritonavir.
Maraviroc	CYP3A4, CYP3A5 and P-gp substrate	**Information from drug compendia** Carbamazepine, midazolam, oxcarbazepine, phenytoin phenobarbital, rufinamide and topiramate potentially reduce maraviroc levels. Stiripentol is expected to increase or decrease maraviroc levels **Clinical studies and case reports**	In a randomized, double-blind, placebo-controlled study on healthy subjects, maraviroc had no clinically relevant effects on the pharmacokinetics of midazolam.
Nevirapine	CYP3A4 substrate and CYP3A inducer	**Information from drug compendia** Carbamazepine, phenytoin, oxcarbazepine potentially decrease levels of nevirapine. Stiripentol potentially decreases or increases nevirapine levels (monitor) **Clinical studies or case reports** None	Nevirapine potentially decreases cannabidiol, carbamazepine, felbamate, midazolam, stiripentol and zonisamide levels (minor)

▼ **Table 4.** Potential pharmacokinetic interactions between antivirals and antiseizure medications in paediatric patients and related clinical data (*continued*).

Class J. Antiviral drug for systemic use	Mechanism of interaction[&]	Effects of ASMs on the antiviral (affected drug)	Effects of the antiviral (perpetrator) on ASMs
Tipranavir	CYP3A is a substrate, inducer and inhibitor. It is also an inhibitor of CYP1A2, CYP2C9 and CYP 2C19	**Information from drug compendia**	
		Carbamazepine, phenytoin, phenobarbital, rufinamide, oxcarbazepine and topiramate potentially decrease the level of tipranavir (avoid). Stiripentol potentially decreases or increases tipranavir levels (monitor)	Tipranavir is expected to increase carbamazepine, cannabidiol, clonazepam, ethosuximide, lacosamide and midazolam levels (monitor)
		Clinical studies and case reports	
		In an early control study, tipranavir levels were 61% lower in subjects also treated with carbamazepine relative to patients not treated with ASMs.	In a case report, phenobarbital levels were lower and ineffective due to several antiviral agents, including tipranavir (study not informative).
Zidovudine	Primarily eliminated as a glucoronidated metabolite	**Information from drug compendia**	
		Valproic acid potentially increases levels of zidovudine (monitor)	Liverpool checker: zidovuline potentially increases carbamazepine concentration (minor)
		Clinical studies or case reports	
		In 6 patients infected with HIV, the combination of valproate and zidovudine led to an increase in zidovudine levels with a two-fold increase in AUC.	In 21 patients with AIDS, treated with zidovudine and phenytoin, phenytoin levels were significantly lower relative to 557 controls
Drugs for hepatitis B			
Tenofovir af and df*	BCRP and P-gp substrate	**Information from drug compendia**	
		Stiripentol potentially increases the level or effect of tenofovir df (monitor)	
		Clinical studies or case reports	
		None	
Peginterferon alfa 2b	CYP2C9 inducer		This agent is expected to decrease phenytoin levels (monitor)

▼ **Table 4.** Potential pharmacokinetic interactions between antivirals and antiseizure medications in paediatric patients and related clinical data (*continued*).

Class J. Antiviral drug for systemic use	Mechanism of interaction[&]	Effects of ASMs on the antiviral (affected drug)	Effects of the antiviral (perpetrator) on ASMs
Drugs for hepatitis C			
Glecaprevir/Pibrentasvir	Glecaprevir is a substrate of P-gp, BCRP. Pibrentasvir is a substrate of P-gp, and, possibly, of BCRP. Both glecaprevir and pibrentasvir are inhibitors of P-gp, BCRP, and OATP1B1/3, and weak inhibitors of CYP3A, CYP1A2, and UGT1A1	**Information from drug compendia** Carbamazepine, phenytoin, phenobarbital (serious), and oxcarbazepine (monitor) potentially decrease levels of glecaprevir/pibrentasvir. Stiripentol increases the levels of glecaprevir/pibrentasvir. **Clinical studies or case reports** None	
Ledipasvir/sofosbuvir Hepatitis C	Ledipasvir is a P-gp and BCRP substrate and inhibitor	**Information from drug compendia** Carbamazepine, phenytoin, phenobarbital and oxcarbazepine potentially decrease levels of sofosbuvir (serious). Stiripentol increases sofosbuvir levels.	
Sofosbuvir hepatitis C	BCRP and P-gp substrate	**Information from drug compendia** Carbamazepine, phenytoin, phenobarbital and oxcarbazepine potentially decrease levels of sofosbuvir (serious). Stiripentol increases sofosbuvir levels.	
Drugs used for COVID-19*			
Chloroquine and hydroxychloroquine. Not antiviral drugs.	CYP3A4, CYP 2C8, and CYP2D6 substrates. Moderate inhibitors of CYP2D6 and P-gp	**Information from drug compendia** Carbamazepine, phenytoin, phenobarbital (serious), oxcarbazepine, eslicarbazepine and rufinamide (monitor) potentially reduce plasma levels of chloroquine and hydroxychloroquine. Clobazam potentially increases chloroquine levels (monitor). Stiripentol potentially increases or reduces levels of chloroquine and hydroxychloroquine (monitor) **Clinical studies or case reports** None	Chloroquine and hydroxychloroquine potentially reduce the plasma concentrations of felbamate.

▼ **Table 4.** Potential pharmacokinetic interactions between antivirals and antiseizure medications in paediatric patients and related clinical data (*continued*).

Class J. Antiviral drug for systemic use	Mechanism of interaction[&]	Effects of ASMs on the antiviral (affected drug)	Effects of the antiviral (perpetrator) on ASMs
Nitazoxanide*	Prodrug of tizoxanide, strongly bound to plasma proteins. Plasma protein binding competition with strongly bound ASMs.	**Information from drug compendia** Phenytoin and valproate potentially increase free levels of nitazoxanide (serious) **Clinical studies or case reports** None	Nitazoxanide potentially increases phenytoin and valproate free concentrations (serious)
Remdesivir (not on the market)	Substrate of several CYP isozymes *in vitro*	**Information from drug compendia** Carbamazepine, phenytoin, phenobarbital (serious), oxcarbazepine, rufinamide (monitor) and topiramate potentially reduce the levels of remdesivir **Clinical studies or case reports** None	
Azithromycin (not antiviral, often used for bacterial complications of COVID-10)	Unknown mechanisms	**Information from drug compendia** **Clinical studies or case reports** None	Azithromycin potentially increases levels of phenytoin
Tocilizumab (not antiviral, often used for treatment of COVID-19	Tocilizumab potentially reverts the reduced activity of CYP450 caused by infectious diseases.	**Information from drug compendia** **Clinical studies or case reports** None	Tocilizumab potentially reduces the plasma concentrations of drugs that are substrates of CYP450 enzymes (especially phenytoin).

*Not found in Liverpool checker.
°Not found in Medscape.
[&] Mechanism of interaction: route of elimination of the antimicrobial agent involved in the interaction or effect of the antimicrobial on CYP, UGT and P-gp. All searches were performed in Medscape Interaction checker [14] and Rx List [71];
Abbreviation: ASM=antiseizure medication.
Further details on reported clinical data and relative references are presented in *supplementary table 1*.

▼ **Table 5.** Recommendations for preventing or minimizing the risk of serious complications due to drug-drug interactions.

1) At the beginning of the antiepileptic treatment, when possible, consider selecting an ASM with a low DDI risk in children with no other concomitant diseases. Epilepsy requires a chronic treatment, and intercurrent diseases, mainly infectious diseases, may appear thereafter.
2) In the case of infectious diseases in patients treated with ASMs with high DDI potential, check potential DDIs between the ASM and the antimicrobial based on the drug compendia and/or SPC for all drugs, and select an antimicrobial agent that is not indicated to interact with the ASM.
3) Avoid combinations of drugs associated with DDIs ranked as serious. In these cases, alternative drugs should be used.
4) In cases in which a combination requires monitoring or is ranked as serious, although considered inevitable, strict clinical monitoring of the affected drug is mandatory. Repeat monitoring of blood levels of both drugs may allow dosage adjustments in order to maintain their concentrations within therapeutic range. In the case of an antimicrobial affecting the level of an ASM, the aim of the drug monitoring may be to maintain the ASM at concentrations similar to those found to be effective before the administration of the added interacting agent (individual therapeutic concentration) [73].
5) Measures aimed at minimizing the effect of a DDI are different according to whether the mechanism of a DDI is inhibition or induction. a) Inhibition of drug metabolism is a rapid process in which clinical consequences are expected after four to five half-lives of the affected drug and may cause toxic symptoms. In such cases, a very slow titration of the perpetrator is recommended with early careful monitoring after the beginning of the drug combination or at a dose change. Clinically-driven dose reduction of the affected drug may be the consequent measure, shortly after the drugs are combined. b) Induction of metabolism is associated with a loss of efficacy, takes place slowly, and, most importantly, clinical effects can be appreciated over long periods (months or years). In those cases in which treatment with an antimicrobial can induce the metabolism of a coadministered ASM, duration of the antimicrobial treatment is critical. In fact, the effect of the interaction may not be apparent in the short term and no change in drug dose may be required over this period. Thereafter, the dose should be increased, according to information based on drug levels. The most subtle and perhaps most dangerous situation is derived from the induction of antibacterial metabolism, mainly in chronic infectious diseases, which may lead to antimicrobial failure. In this case, it is most important to increase the dose of the affected drug according to SPC recommendations and/or assessment of the antimicrobial efficacy.
6) One should not forget that withdrawal of a perpetrator from the combination also requires changes in the dose of the affected drug which should be made faster after inhibition than after induction of metabolism. In some cases, if known, it may be possible to re-establish the dose that was used before the drugs were combined.
7) Several bidirectional DDIs exist between ASMs and antimicrobials. In these cases, any agent behaves as a perpetrator and as a victim of the other drug, and the prediction of blood levels is even more difficult because the amplitude of the interaction changes with any variation in concentration of the perpetrator(s).
8) DDIs that involve different mechanisms (inhibition and induction of certain cytochromes or P-gp) are based on less easily predictable findings. When the mechanisms of DDIs oppose each other, the net final effect may be minimal or absent or vary in different subjects according to the dose, genetics or other individual variables. Strict clinical observation and clinically driven measurements of drug levels may be required in these cases.

are not always confirmed by clinical studies. Different hypotheses may be proposed to explain these discrepancies. A negative finding in a clinical study does not necessarily mean that a DDI will not take place in any case as there are several factors that affect the likelihood that a known interaction will occur in a patient, such as drug dose, duration of combined therapy, age, genetic background and underlying diseases. In addition, different mechanisms of interaction can co-occur with uncertain final effects (for example, induction and inhibition of different enzymes that are involved in the metabolism of the affected drug). In the case of antimicrobials, the duration of drug co-administration is also relevant for the detection and assessment of the clinical consequences of a DDI. Enzyme induction requires synthesis of a new enzyme and the full effects of a DDI may be observed after several weeks; conversely, the effects of drug inhibition are evident relatively soon. Clinical consequences of the enzyme induction, often characterized by loss of

efficacy, are more frequently observed with drugs that are combined over long periods of time, such as ,for example, the antiviral agents used for HIV treatment. In contrast, signs of drug toxicity, as a consequence of the inhibition of CBZ metabolism by macrolide antibiotics, are observed within a few days [2, 20].

Other sources of concern in the field of pharmacokinetic interactions are derived from the literature. In the case of several drugs, discrepancies in reporting and evaluating severity of interactions have been noted between different compendia [62]. Most often, inconsistences are noted between the effect of a drug on oxidative metabolism or membrane proteins, as described in the SPC and for DDIs reported in the compendia [7].

A first important question is: what is the clinical relevance of DDIs? To what extent are DDIs associated with a failure in resolving clinical effects (seizure relapse or failure to achieve resolution of infection) or toxic effects? Sub-therapeutic antiviral drug levels [63] and a risk of failure in treating viral infection [64] have been reported in patients treated with highly-active antiretroviral therapy combined with strong enzyme-inducing ASMs. These effects were caused by induction of oxidative metabolism of antiviral drugs. As previously described, this DDI is bidirectional because inhibition of CYP3A4 by several antiviral agents causes serious DDIs with ASMs. Here, it may be interesting to note that some DDIs are also caused by induction of cytochromes 2C9 and 2C19 or by induction of glucuronidation. For example, in healthy volunteers treated with lopinavir/ritonavir, dose increments of 200% of LTG were required to achieve concentrations similar to those observed in patients treated with LTG alone [52]. In a patient treated with VPA, combination with lopinavir/ritonavir, zidovudine, and lamivudine resulted in a 48% reduction in VPA levels and recurrence of maniac disease [65]. In both cases, this DDI was probably caused by the inducing properties of ritonavir on glucuronidation.

From an historical point of view, the most known and clinically relevant DDIs are those between several antibiotics and CBZ. Among antibiotics used in children, clarithromycin, chloramphenicol, doxycycline, erythromycin, isoniazid and metronidazole are moderate or strong CYP3A4 inhibitors and CBZ is metabolized mainly by this cytochrome. There are several clinical studies and case reports that show that treatment with one of these antibiotics may cause an increase in CBZ blood levels, that may be even doubled, as reported with erythromycin [66] and clarithromycin [67] with consequent drug toxicity. This DDI is very frequent and often serious because CBZ is widely used, is metabolized almost only by CYP3A4 and exhibits dose-dependent adverse effects (diplopia, ataxia, dizziness) and a narrow therapeutic window. Several other ASMs, such as CLN, MDZ, PER, and to a lesser extent CLB, ETS, LCM and ZNS are metabolized by the same cytochrome and their metabolism may be inhibited. Nonetheless, clinical consequences of such DDIs may be less severe because of a different pattern of dose-dependent adverse effects, a larger therapeutic window, and/or a minor amount of drug metabolized through this pathway.

An example of a particular DDI specific to one ASM is that between VPA and carbapenem antibiotics, which was discovered based on observations from case reports. In this case, enzyme inhibition determines a fall in VPA blood levels which is described at around 60% or more (*see supplementary material*) and has been associated with seizure recurrence in several cases. Although the exact mechanism of this DDI is not known, it is supposed that the inhibition of the hepatic enzyme acylpeptide hydrolase (an enzyme that hydrolyses VPA glucuronide metabolite back to its active VPA molecule) determines an upregulation of VPA glucuronidation [68]. This mechanism would explain why this DDI takes place rapidly while induction is usually slower. Among carbapenem antibiotics, ertapenem and meropenem have a greater effect than imipenem/cilastatin [35]. A further example of a DDI may be that of the antimycotic, voriconazole. This agent is metabolized by CYP3A4, CYP2C9/10 and CYP2C19, but is also a strong inhibitor of these enzymes. Consequently, in this case, there is also a bidirectional DDI with several ASMs. CBZ, PHT, PB, STP and OXC (to a lesser degree) may decrease the level of voriconazole, leading to possible inefficacy of antimycotic. It has been observed that combination of this agent with PHT (300 mg/day) requires a doubling of voriconazole dose to maintain therapeutic levels [69]. On the other hand, voriconazole inhibits the metabolism of several ASMs (mainly CBD, CBZ, LCM, MDZ, PHT and ZNS). In a clinical study in healthy volunteers, this agent increased Cmax and AUC of PHT by approximately 70% and 80%, respectively [69].

We may speculate that there are thousands of DDIs that have little clinical relevance in the majority of cases, but may cause serious complications in some patients. On the other hand, in some cases, the effect of a DDI may be less evident than predicted because other metabolic pathways may compensate for the effect of the perpetrator. For example, the magnitude of inhibition of MDZ metabolism (metabolized mainly by CYP3A4) by ketoconazole and indinavir (CYP3A4 inhibitors) is partially compensated by an increase in MDZ glucuronidation, which may attenuate the magnitude of the interaction [70]. In other cases, a change in the concentration of an active metabolite, as a consequence of induction or inhibition of the metabolism of the parent drug, may compensate the change in level of the affected drug. This may be the case for

induction/inhibition of CBZ metabolism (for example, by the CYP3A4 inducer, rifapentine, or by the CYP3A4 inhibitor, clarithromycin). This may lead to increased or decreased levels of CBZ-epoxide, the active CBZ metabolite. In this case, the net effect of this DDI may not determine a corresponding change in CBZ efficacy or CNS toxicity.
Recommendations for prevention or minimization of the risk of serious complications from DDIs is provided in *table 5*. ■

Supplementary data.
Summary didactic slides and supplementary tables are available at www.epilepticdisorders.com.

Disclosures.
GZ has received speaker's or consultancy fees from Eisai, UCB Pharma and Jazz pharmaceuticals and has served on an advisory board for GW Pharmaceuticals. SL has received speaker's or consultancy fees from Eisai, UCB Pharma, and GW Pharmaceuticals and has served on an advisory board for GW Pharmaceuticals.

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TEST YOURSELF

(1) Which is the most important cytochrome for the metabolism of antiseizure medicines that can be induced or inhibited by both antiseizure and antimicrobial agents?

A. CYP2D6
B. CYP3A4
C. CYP2C9
D. CYP2C19

(2) Clarithromycin affects the metabolism of which of the following antiseizure medications?

A. Phenytoin
B. Eslicarbazepine acetate
C. Carbamazepine
D. All the above

(3) Lopinavir/ritonavir is expected to:

A. reduce lamotrigine levels
B. increase carbamazepine levels
C. reduce lamotrigine and increase carbamazepine levels
D. increase phenytoin levels

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".