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REVIEW ARTICLE

Drug–Drug Interactions Between Direct-Acting Antivirals and Psychoactive Medications

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Abstract Treatment options for chronic hepatitis C virus (HCV) infection have drastically changed since the development and licensing of new potent direct-acting antivirals (DAAs). The majority of DAAs are extensively metabolized by liver enzymes and have the ability to influence cytochrome P450 (CYP) enzymes. Additionally, these DAAs are both substrates and inhibitors of drug transporters, which makes the DAAs both possible victims or perpetrators of drug–drug interactions (DDIs). There is a high prevalence of mental illnesses such as depression or psychosis in HCV-infected patients; therefore, psychoactive medications are frequently co-administered with DAAs. The majority of these psychoactive medications are also metabolized by CYP enzymes but remarkably little information is available on DDIs between psychoactive medications and DAAs. Hence, the aim of this review is to provide an overview of the interaction mechanisms between DAAs and psychoactive agents. In addition, we describe evidenced-based interactions between DAAs and psychoactive drugs and identify safe options for the simultaneous treatment of mental illnesses and chronic HCV infection.

Key Points

Escitalopram and citalopram have been studied in combination with most direct-acting antivirals (DAAs) and either of these drugs can be safely combined with hepatitis C virus (HCV) treatment.

No formal interaction studies between psychoactive agents and sofosbuvir or ledipasvir have been performed in humans. However, these DAAs are generally neither victims nor perpetrators of drug interactions and can therefore be safely used in combination with psychoactive drugs.

Boceprevir, simeprevir, and the combination paritaprevir/ritonavir plus ombitasvir with dasabuvir are most likely to cause drug interactions via the inhibition of cytochrome P450 (CYP) 3A4. Therefore, caution must be exercised when CYP3A4 substrates such as midazolam and/or quetiapine are co-administered with these DAAs.

1 Introduction

One of the components previously used in the treatment regimen for hepatitis C virus (HCV) is pegylated interferon; however, it has major adverse effects on mental

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health and depression was a commonly seen adverse event [1]. Since the development of novel direct-acting antivirals (DAAs), pegylated interferon is no longer used in the treatment of HCV infections in resource-rich settings. However, the prevalence of mental disorders remains high among untreated HCV-infected patients [2]. For example, a retrospective study reported that 86 % of HCV-infected patients had at least one psychiatric, drug-, or alcohol use-related disorder recorded in their patient charts. The most common conditions were depressive disorders (50 %), psychosis (50 %), anxiety disorders (41 %), post-traumatic stress disorders (34 %), and bipolar disorders (16 %) [3]. Another study reported a prevalence of 41 % for anxiety and 27 % for depression in HCV-infected individuals ($n = 395$) [4]. One explanation for this high prevalence was that patients with mental disorders are more likely to have a drug addiction, because intravenous drug use is a major route of HCV transmission [5].

The results from a cross-sectional study were in agreement with the high prevalence of mental disorders. In that study, 16 % of the HCV-infected patients were on antidepressants and 10 % were on antipsychotics ($n = 3716$) [6]. This corresponds with data from a Dutch nationwide survey in which benzodiazepines, drugs used for treating opioid dependence, and selective serotonin reuptake inhibitors (SSRIs) were among the drugs most frequently used by chronic HCV-infected patients [7].

The use of antipsychotics and antidepressants during DAA therapy increases the risk of drug-drug interactions (DDIs). Both DAAs and psychoactive agents are extensively metabolized in the liver and have the ability to affect the activities of various enzymes (e.g., cytochrome P450 [CYP]) and drug transporters (e.g., P-glycoprotein [P-gp]). This makes DAAs as well as psychoactive agents possible victims (objects of DDIs) and perpetrators (causes of DDIs) of drug interactions, which could negatively affect treatment outcomes as a result of adverse effects (increased plasma concentrations) or treatment failure (decreased plasma concentrations) [8, 9]. In order to interpret the DDIs between DAAs and psychoactive agents, it is important to have sufficient knowledge of their therapeutic ranges. Benzodiazepines, tricyclic antidepressants (TCAs), and antipsychotics have a narrow therapeutic range, while SSRIs have a broad therapeutic range. Generally, drugs with narrow therapeutic ranges are more likely to have clinically relevant DDIs than drugs with large therapeutic ranges [10]. DAAs have a large therapeutic range, which makes them less susceptible to the effects of an increase or decrease in their plasma concentrations caused by, for example, CYP inhibition or induction. However, extremely low plasma concentrations could lead to virologic failure.

Little information is available on interactions between DAAs and psychoactive agents. Therefore, the aim of this review is to provide an overview of the interaction mechanisms of DAAs and psychoactive agents. In addition, we describe evidenced-based interactions between DAAs and psychoactive drugs and identify safe options for treatment of the simultaneous treatment of mental illnesses and HCV infection.

2 Methods

We searched PubMed (1946–January 2016) and EMBASE (1947–January 2016) to identify peer-reviewed studies. The search covered all DAAs recommended in European and US guidelines [11, 12] and licensed by the European Medicines Agency (EMA) and US Food and Drug Administration (FDA). The DAAs included protease inhibitors (PIs) (boceprevir, simeprevir, paritaprevir, and grazoprevir), NS5A inhibitors (daclatasvir, ledipasvir, ombitasvir, and elbasvir), and NS5B polymerase inhibitors (sofosbuvir and dasabuvir). Telaprevir (PI) was excluded from the review because it has limited use in current therapy. We also referred to the work published by Kiser and colleagues [13] for more information about telaprevir and DDIs between DAAs and psychoactive drugs.

The psychoactive agents included were SSRIs, TCAs, typical and atypical antipsychotics, benzodiazepines, monoamine oxidase inhibitors, lithium, and St John's wort.

The Google and Google Scholar search engines, and ClinicalTrials.gov (http://www.clinicaltrials.gov) website and the Liverpool drug interaction database (http://www.hep-druginteractions.org) were used to identify conference papers and abstracts. All searches were performed in English. The search items contained generic and/or brand names of the drugs and included terms such as antidepressant, antipsychotic, sedative, and tranquilizer.

Information about the pharmacokinetics and metabolism of the DAAs and psychoactive agents were obtained from the Summary of Product Characteristics (SmPC) and FDA prescribing information for each drug as well as from the Lexicomp database (available via http://www.uptodate.com). Enzyme inhibitors and inducers were defined as being strong, moderate, or weak if they changed the area under the plasma concentration–time curve (AUC) of a substrate by 5-fold, >2 to <5-fold, and <2-fold, respectively. Substrates were also grouped as being minor and major substrates of enzymes. These groupings were based on the clinical relevance of the potential interaction described by Lexicomp (http://www.uptodate.com) [14, 15].

3 Drug-Drug Interaction (DDI) Mechanisms: Direct-Acting Antivirals (DAAs)

In this section, we elaborate on the mechanisms by which DAAs can be perpetrators and/or victims of DDIs. We focused on interactions through hepatic drug metabolism and drug transporters because they are the most important pathways underlying interactions between DAAs and psychoactive agents. These mechanisms are illustrated using examples of drug interactions between DAAs and psychoactive agents or non-psychoactive drugs, which were studied in healthy volunteers.

Tables 1 and 2 give an overview of the involvement of enzymes and drug transporters in the metabolism of DAAs and psychoactive agents, respectively. Table 3 shows the results of drug interaction studies performed between DAAs and psychoactive drugs.

3.1 Phase I and II Reactions: DAAs as Perpetrators

Drugs that influence drug-metabolizing enzymes (perpetrators) such as CYP and uridine diphosphate glucuronyltransferase (UGT) have the ability to affect the plasma concentration of substrates of the enzymes (victims). Inhibitors of CYP and UGT generally cause an increased plasma concentration of the victim, while inducers usually lower the plasma concentration of the victim.

Ritonavir is included in the fixed-dose combination with paritaprevir, ombitasvir, and dasabuvir to 'boost' the pharmacokinetic characteristics of paritaprevir through the inhibition of CYP3A4; this opens the door for DDIs to occur. For example, the AUC and maximum plasma concentration (C_{max}) of orally administered midazolam, a CYP3A4 substrate, increased ~26-fold and ~4-fold, respectively, when midazolam was co-administered with ritonavir (note: the interaction between ritonavir and midazolam is studied in the absence of paritaprevir, ombitasvir, or dasabuvir) [16]. Increases in the plasma concentration of midazolam have also been observed when the drug was administered with boceprevir, simeprevir, and grazoprevir, which are also CYP3A4 inhibitors. Boceprevir is a strong inhibitor of CYP3A4, while simeprevir and grazoprevir are mild CYP3A4 inhibitors (Table 3) [17–19].

UGTs are inhibited by DAAs such as ombitasvir, dasabuvir, and paritaprevir. Lorazepam (benzodiazepine) is a UGT substrate; however, this interaction has not been studied. Interaction studies between furosemide (UGT1A1 substrate) and combination regimen paritaprevir/ritonavir, ombitasvir, and dasabuvir have indicated the importance of UGT inhibition. Results from these studies showed that the AUC and C_{max} of furosemide were increased by 8 and 42 %, respectively. As a result of this, a reduction in the dose of furosemide of up to 50 % might be required if the drugs have to be co-administered [20].

3.2 Phase I and II Reactions: DAAs as Victims

DAAs, e.g., daclatasvir, simeprevir, grazoprevir, and elbasvir, are predominantly metabolized by CYP3A4/5 in the liver and gastrointestinal tract. Thus, caution is needed when DAAs are administered with strong inducers or inhibitors of CYP3A4. A reduced plasma concentration of DAAs creates a potential risk of resistance of the virus to the administered drug and/or virologic failure, while elevated drug concentrations increase the risk of adverse events. Most psychoactive agents do not strongly inhibit or induce CYP3A4 and, thus, we do not expect DAAs to be victims of psychoactive agents. St John's wort, which is a psychoactive agent, is the exception; it is a strong CYP3A4 inducer. However, co-administration of boceprevir and St John's wort showed only a slight decrease in the plasma concentration of boceprevir (9 %) [21].

DAAs are not metabolized by UGT or other phase II enzymes; therefore, phase II-mediated DDIs with DAAs as victims are not usually expected.

3.3 Drug Transporters: DAAs as Perpetrators

DAAs inhibit various drug transporters such as the efflux transporters P-gp and breast cancer resistance protein (BCRP) (Table 1), which are, among other located at the blood–brain barrier (BBB). Little information is available on DDIs between psychoactive agents and drug transporters. However, it is known that amitriptyline and risperidone are P-gp substrates (Table 2). Accordingly, inhibition of these transporters increases substrate concentrations in the cerebrospinal fluid [22]. Since the pharmacological action of psychoactive drugs takes place in the brain, inhibition of P-gp can result in an increased pharmacological effect.

No formal interaction studies have been conducted between the P-gp substrates and DAAs. The effect of P-gp inhibition by DAAs has been studied using digoxin, which is a known P-gp substrate. Boceprevir had a minor influence on plasma digoxin concentrations (an increase in AUC and C_{max} by 19 and 18 %, respectively) [17]. Daclatasvir and simeprevir also affected digoxin plasma concentrations; the AUC of digoxin was increased by 27 and 39 %, and C_{max} was increased by 65 and 31 %, respectively [18, 23]. It should be noted that these interactions between the P-gp inhibitors and digoxin were driven by the concentration of digoxin in the intestinal lumen, which is high after oral intake. For psychoactive drugs,

Table 1 Overview of the route of metabolism, effects on enzymes, and transporters of direct-acting antivirals

Drug	Enzyme		Transporter		Comments	References
	Substrate	Inhibitor	Substrate	Inhibitor		
Protease inhibitors						
Boceprevir	AKR-mediated pathway CYP3A4/5	CYP3A4/5		P-gp (mild)		[17]
Simeprevir	CYP3A4	Intestinal CYP3A4 CYP1A2 (weak)		OATP1B1/3 P-gp		[18]
Paritaprevir	CYP3A4/5	UGT1A1	P-gp OATP1B1 BCRP	OATP1B1/3 OATP2B1 BRCP		[20]
Ritonavir	CYP3A4 CYP2D6 (lesser extent)	CYP3A4 CYP2D6 (?) *Inducer CYP2C19* *Inducer CYP1A*		OATP2B1 OCT1 (?) BRCP		[20]
Grazoprevir	CYP3A4	CYP3A4 (mild)	OATP1B1 OATP1B3	BCRP		[19]
NS5A inhibitors						
Daclatasvir	CYP3A4		P-gp	P-gp OATP1B1 OCT1 BCRP		[23]
Ledipasvir	Metabolism unknown, unchanged ledipasvir is the major compound in feces		P-gp BCRP	P-gp BCRP		[29]
Elbasvir	CYP3A4			BCRP		[19]
Ombitasvir	Hydrolysis followed by oxidative metabolism	UGT1A1				[20]
NS5B polymerase inhibitors						
Sofosbuvir/GS-331007	Hepatic non-enzymatic metabolism Elimination renally		Sofosbuvir: P-gp Sofosbuvir: BCRP GS-331007 is not a substrate of P-gp or BCRP		Sofosbuvir is a nucleoside analogue triphosphate. Sofosbuvir (prodrug) is metabolized in GS-461203 and GS-331007	[26]

Table 1 continued

Drug	Enzyme		Transporter		Comments	References
	Substrate	Inhibitor	Substrate	Inhibitor		
Dasabuvir	CYP2C8 CYP3A4	UGT1A1		BCRP	Main active metabolite is dasabuvir M1 which is formed by CYP2C8	[37]

Only drug enzymes and drug transporters that are thought to be involved in clinically relevant drug–drug interactions, according to the summary of product characteristics or prescribing label, are shown

AKR aldoketoreductase, *BCRP* breast cancer resistance protein, *CYP* cytochrome P450, *OATP* organic anion-transporting polypeptide, *OCT* organic cation transporter, *P-gp* P-glycoprotein, *UGT* uridine diphosphate glucuronosyltransferase

interactions with P-gp inhibitors take place at the BBB. This is affected by the systemic concentration of the P-gp substrate instead of the concentration in the lumen. Therefore, it is difficult to predict possible interactions between DAAs and psychoactive drugs from these results. Additionally, the clinical relevance of P-gp inhibition by DAAs depends on the inhibitory potential of the perpetrator and the therapeutic range of the victim (see Sect. 4).

Many DAAs are inhibitors of organic anion-transporting polypeptide (OATP) 1B1 and OATP1B3, which are uptake transporters. No psychoactive drug is a substrate of OATPs; hence, these transporters are not discussed in this review.

3.4 Drug Transporters: DAAs as Victims

Most DAAs are substrates of P-gp and OATPs; therefore, DAAs are possible victims when psychoactive agents inhibit or induce these transporters. However, there are limited data available on psychoactive agents and transporters. An example demonstrating the importance of a transporter-mediated interaction is the contraindication of the co-administration of grazoprevir with OATP1B1/3 inhibitors.

4 DDI Mechanisms: Psychoactive Agents

Table 2 provides an overview of the enzymes and transporters involved in the metabolism of psychoactive agents. In this section, we describe the mechanisms by which psychoactive agents can be victims and perpetrators of DDIs.

4.1 Psychoactive Agents as Perpetrators

In general, psychoactive agents are more often victims of DDIs than perpetrators. For example, benzodiazepines have limited influence on drug-metabolizing enzymes and transporters (Table 2).

Various antipsychotics, SSRIs, and TCAs have the potential to inhibit CYP2D6, which makes these drugs perpetrators of drug interactions. However, the currently available DAAs are not metabolized by CYP2D6 and therefore DDIs via this pathway are not expected (Tables 2, 3).

4.2 Psychoactive Agents as Victims

Most benzodiazepines are substrates of various CYP enzymes, such as CYP3A4, CYP2B6, CYP2C19, and CYP1A2; therefore, benzodiazepines are potential victims of DDIs. Benzodiazepines have a narrow therapeutic range

Table 2 Overview of the route of metabolism, effects on enzymes, and transporters of psychoactive agents

Drug	Enzyme		Transporter		References
	Substrate	Inhibitor	Substrate	Inhibitor	
Benzodiazepines					
Alprazolam	CYP3A4 (major)	CYP3A4 (weak)			[38]
Bromazepam	CYP1A2 (major)	CYP2E1 (weak)			
	CYP3A4 (minor)				
Brotizolam	CYP3A4				
Chlordiazepoxide	CYP3A4 (major)				[39]
Clobazam	CYP2C19 (major)	CYP2D6 (moderate)	P-gp		[40]
	CYP2B6 (minor)	CYP2C19 (weak)			
	CYP3A4 (minor)	*Inducer: CYP3A4 (weak)*			
Clorazepate	CYP3A4 (major)				[41]
Diazepam	CYP3A4 (major)	CYP2C19 (weak)			[42]
	CYP2C19 (major)	CYP3A4			
	CYP1A2 (minor)				
	CYP2B6 (minor)				
	CYP2C9 (minor)				
Flurazepam	CYP3A4 (major)	CYP2E1 (weak)			[43]
Lorazepam	Conjugation (UGT)				
Lormetazepam	Conjugation (UGT)				
Midazolam	CYP3A4 (major)	CYP2C8 (weak)			[44]
	CYP2B6 (minor)	CYP2C9 (weak)			
		CYP3A4 (weak)			
Oxazepam	UGT				
Temazepam	UGT (major)				[45]
	CYP2B6 (minor)				
	CYP2C19 (minor)				
	CYP3A4 (minor)				
	CYP2C9 (minor)				
Zolpidem	CYP3A4 (major)				[46]
	CYP1A2 (minor)				
	CYP2C19 (minor)				
	CYP2D6 (minor)				
Zopiclone	CYP3A4 (major)				
	CYP2C8 (minor)				
Selective serotonin reuptake inhibitors (SSRIs)					
Citalopram	CYP3A4 (major)	CYP2D6 (weak)			[47]
	CYP2C19 (major)	CYP2C19 (weak)			
	CYP2D6 (minor)	CYP1A2 (weak)			
		CYP2B6 (weak)			
Duloxetine	CYP1A2 (major)	CYP2D6 (moderate)			[48]
	CYP2D6 (major)				
Escitalopram	CYP3A4 (major)	CYP2D6 (weak)			[49]
	CYP2C19 (major)				

Table 2 continued

Drug	Enzyme		Transporter		References
	Substrate	Inhibitor	Substrate	Inhibitor	
Fluoxetine	CYP2C9 (major)	CYP2D6 (strong)			[50]
	CYP2D6 (major)	CYP2C19 (moderate)			
	CYP1A2 (minor)	CYP1A2 (weak)			
	CYP2B6 (minor)	CYP2B6 (weak)			
	CYP2C19 (minor)	CYP2C9 (weak)			
	CYP2E1 (minor)				
	CYP3A4 (minor)				
Fluvoxamine	CYP2D6 (major)	CYP2C19 (strong)			[51]
	CYP1A2 (major)	CYP1A2 (strong)			
		CYP2B6 (weak)			
		CYP2C9 (weak)			
		CYP2D6 (weak)			
		CYP3A4 (weak)			
Paroxetine	CYP2D6 (major)	CYP2D6 (strong)			[52]
		CYP2B6 (moderate)			
		CYP2C19 (weak)			
		CYP2C9 (weak)			
		CYP1A2 (weak)			
Sertraline	CYP2C19 (minor)	CYP2B6 (moderate)			[53]
	CYP3A4 (minor)	CYP2C19 (moderate)			
	CYP2B6 (minor)	CYP2D6 (moderate)			
	CYP2D6 (minor)	CYP1A2 (weak)			
	CYP2C9 (minor)	CYP2C8 (weak)			
		CYP2C9 (weak)			
Trazodone	CYP3A4 (major)			*Inducer: P-gp*	
	CPY2D6 (minor)				
Venlafaxine	CYP2D6 (major)	CYP2B6 (weak)			[54]
	CYP3A4 (major)	CYP2D6 (weak)			
	CYP2C9 (minor)	CYP3A4 (weak)			
	CYP2C19 (minor)				
Vortioxetine	CYP2D6 (major)		P-gp (minor)	P-gp (weak)	[55]
	CYP3A4/5 (major)				
	CYP2C9 (minor)				
	CYP2C19 (minor)				
	CYP2C8 (minor)				
	CYP2B6 (minor)				
	CYP2A6 (minor)				
Tricylic antidepressants (TCAs)					
Amitriptyline	CYP2D6 (major)	CYP1A2 (weak)	P-gp		
	CYP1A2 (minor)	CYP2C19 (weak)			
	CYP2B6 (minor)	CYP2C9 (weak)			
	CYP2C19 (minor)	CYP2D6 (weak)			
	CYP2C9 (minor)	CYP2E1 (weak)			
	CYP3A4 (minor)				

Table 2 continued

Drug	Enzyme		Transporter		References
	Substrate	Inhibitor	Substrate	Inhibitor	
Clomipramine	CYP1A2 (major)	CYP2D6 (moderate)			[56]
	CYP2C19 (major)				
	CYP2D6 (major)				
	CYP3A4 (minor)				
Dosulepin	COMT				
Doxepin	CYP2D6 (major)				
	CYP1A2 (minor)				
	CYP2C19 (minor)				
	CYP3A4 (minor)				
Imipramine	CYP2C19 (major)	CYP2D6 (moderate)			
	CYP2D6 (major)	CYP1A2 (weak)			
	CYP1A2 (minor)	CYP2C19 (weak)			
	CYP2B6 (minor)	CYP2E1 (weak)			
	CYP3A4 (minor)				
Maprotiline	CYP2D6 (major)				
Nortriptyline	CYP2D6 (major)	CYP2D6 (weak)	P-gp		
	CYP1A2 (minor)	CYP2E1 (weak)			
	CYP2C19 (minor)				
	CYP3A4 (minor)				
Other antidepressants					
Agomelatine	CYP1A2				
	CYP2C9				
	CYP2C19				
Bupropion	CYP2B6 (major)	CYP2D6 (strong)		OCT2	
	CYP1A2 (minor)				
	CYP2A6 (minor)				
	CYP2C9 (minor)				
	CYP2D6 (minor)				
	CYP2E1 (minor)				
	CYP3A4 (minor)				
Mianserin	CYP2D6				
Mirtazapine	CYP1A2 (major)	CYP1A2 (weak)			
	CYP2D6 (major)				
	CYP3A4 (major)				
	CYP2C9 (minor)				
Moclobemide	CYP2C19 (major)	CYP2C19 (moderate)			
	CYP2D6 (minor)	CYP1A2 (weak)			
		CYP2D6 (weak)			
		(MAO)			
St John's wort		*Inducer: CYP3A4*			
		Inducer: CYP1A2 (possible various CYP enzymes)			
Antipsychotics					
Aripiprazole	CYP2D6 (major)				[57]
	CYP3A4 (major)				
Bromperidol	CYP3A4				
	CYP2D6				

Table 2 continued

Drug	Enzyme		Transporter		References
	Substrate	Inhibitor	Substrate	Inhibitor	
Clozapine	CYP1A2 (major)	CYP2D6 (moderate)			
	CYP2A6 (minor)	CYP1A2 (weak)			
	CYP2C19 (minor)	CYP2C19 (weak)			
	CYP2C9 (minor)	CYP2C9 (weak)			
	CYP2D6 (minor)	CYP2E1 (weak)			
	CYP3A4 (minor)	CYP3A4 (weak)			
Flupentixol	CYP2D6				
Fluphenazine	CYP2D6 (major)	CYP1A2 (weak)			
	CYP1A2	CYP2C9 (weak)			
		CYP2D6 (weak)			
		CYP2E1 (weak)			
Haloperidol	CYP2D6 (major)	CYP2D6 (moderate)			
	CYP3A4 (major)				
	CYP1A2 (minor)				
Lurasidone	CYP3A4 (major)	CYP3A4 (weak)	P-gp		[58]
Olanzapine	CYP1A2 (major)	CYP1A2 (weak)			[59]
	CYP2D6 (minor)	CYP2C19 (weak)			
	UGT	CYP2C9 (weak)			
		CYP2D6 (weak)			
		CYP3A4 (weak)			
Paliperidone				P-gp (weak)	[60]
Perphenazine	CYP2D6 (major)	CYP1A2 (weak)			
	CYP1A2 (minor)	CYP2D6 (weak)			
	CYP2C19 (minor)				
	CYP2C9 (minor)				
	CYP3A4 (minor)				
Pimozide	CYP3A4 (major)	CYP2C19 (weak)			
	CYP1A2 (major)	CYP2D6 (weak)			
	CYP2D6 (major)	CYP2E1 (weak)			
Quetiapine	CYP3A4 (major)				
	CYP2D6 (minor)				
Risperidone	CYP2D6 (major)	CYP2D6 (weak)	P-gp		
	CYP3A4 (minor)				
Sertindole	CYP2D6				
	CYP3A4				
Zuclopenthixol	CYP2D6 (major)				
	CYP3A4 (minor)				

Note that most of these drugs have older registration files and, therefore, possible involvement of transporters and CYP enzymes may not be studied in sufficient detail per the current standards

Information in this table was compiled from the following sources: European Medicines Association summary of product characteristics, US Food and Drug Administration prescribing information, and data from Lexicomp, available through http://www.uptodate.com (October 2015)

Note: assignment of major/minor substrate status based on their clinically relevant drug interaction potential (http://www.uptodate.com)

No information about hepatic metabolism and/or drug tranporters were available for: Flunitrazepam, loprazolam, nitrazepam,prazepam, lithium salts, chlorprothixene, fluspirilene, penfluridol, pericyazine, pipamperone, sulpiride, and tiapride

COMT catechol-*O*-methyl transferase, *CYP* cytochrome P450, *MAO* monoamine oxidase, *P-gp* P-glycoprotein, *UGT* uridine diphosphate glucuronosyltransferase

and a strong concentration–effect relationship [24]; thus, increased plasma concentrations are likely to cause increased toxicity.

Midazolam is a model substrate of CYP3A4; therefore, interactions between midazolam and DAAs have been extensively studied. For example, oral co-administration of midazolam and boceprevir resulted in an increase in the midazolam AUC of 430 % and an increase in its C_{max} of 177 %. As a result, co-administration of midazolam and boceprevir is contraindicated [17]. Similarly, an increase in the plasma concentration of midazolam is expected when it is administered with paritaprevir/ritonavir, ombitasvir, and dasabuvir; therefore, this co-administration is also contraindicated [20]. Interactions between midazolam and simeprevir or grazoprevir have both been studied and increased midazolam AUC and C_{max} values were observed; thus, caution is needed with co-administration [18, 19]. On the other hand, daclatasvir has been shown to have little effect on midazolam exposure [23].

SSRIs are hepatically metabolized by various CYP enzymes (e.g., CYP3A4, CYP2D6, CYP2C9, and CYP2C19), particularly CYP3A4. Theoretically, this puts patients at risk when they are also taking DAAs. However, SSRIs have a broad therapeutic range; therefore, increased plasma concentrations of SSRIs are not likely to result in significant toxicities [10]. For instance, the co-administration of escitalopram (CYP3A4 substrate) and DAAs such as boceprevir, simeprevir, or the combination of paritaprevir/ritonavir, ombitasvir, and dasabuvir did not result in a clinically relevant increase in the escitalopram plasma concentration [17, 18, 20].

Antipsychotics are metabolized in the liver by a variety of CYP enzymes, as shown in Table 2. CYP3A4 and CYP2D6 are involved in this metabolism; however, they can be inhibited by DAAs. Most antipsychotics have a narrow therapeutic range. Therefore, DDIs involving antipsychotics can result in clinically relevant outcomes, especially with strong CYP3A4 inhibitors such as boceprevir and ritonavir. However, no interaction studies have been conducted so far. Theoretically, interactions might occur with, for example, strong CYP3A4 inhibitors such as boceprevir and ritonavir.

5 Clinical Guidance

In this section, we provide guidance for clinical decision making regarding the use of a combined treatment of DAAs and psychoactive drugs. Most potential drug interactions have not been subjected to rigid pharmacokinetic testing in humans, and recommendations are often based on theoretical interpretations of the pharmacokinetics characteristics of drugs.

We believe that a relevant interaction only occurs when a drug (victim) is metabolized to a 'major' or 'moderate' extent. Major or moderate substrate status is based on the potential clinically relevant drug interaction as described by Lexicomp [15]. A major status indicates that the regimen should be modified, whereas a moderate status implies that the therapy should be monitored. Consequently, a drug should have strong (>5-fold increase in substrate AUC) or moderate (2- to 5-fold increase in substrate AUC) influence on an enzyme/transporter (perpetrator) in order to cause an interaction (Tables 4, 5, 6, 7, 8, 9, 10).

5.1 Protease Inhibitors

5.1.1 Boceprevir

Table 4 shows benzodiazepines, antidepressants, and antipsychotics that are safe to combine with boceprevir. Of the currently available DAAs, boceprevir is one of the most potent CYP3A4 inhibitors. Therefore, we do not recommend combining boceprevir and drugs primarily metabolized by CYP3A4, especially if they have a narrow therapeutic range (a contraindication).

Co-administration of midazolam and boceprevir (both oral and parenteral) is contraindicated since the midazolam AUC and C_{max} are both significantly increased [17]. This exceptional increase was not observed with other DAAs, which emphasizes the strong inhibitory potential of boceprevir on CYP3A4.

On the other hand, no dose adjustment is required when escitalopram is administered with boceprevir. This is unexpected as escitalopram is a CYP3A4 substrate. It is possible that there is involvement of other unknown enzymes or transporters; hence, the underlying mechanism cannot be explained [17].

Boceprevir is also a P-gp inhibitor. Theoretically, this inhibition could have an impact on P-gp substrates; however, it seems to have minimal clinical relevance due to the mild inhibition of P-gp by boceprevir [17, 22]. Boceprevir may not be a victim of any DDIs with benzodiazepines, SSRIs, TCAs, or antipsychotics, as studies with midazolam and escitalopram have shown [17]. Additionally, interaction studies between St John's wort and boceprevir showed no alterations in the plasma concentration of boceprevir; hence, this combination is safe to use [17, 21].

Finally, physicians should take care when prescribing boceprevir in combination with drugs that might prolong the QT interval and are metabolized by CYP3A4 [17]. For instance, SSRIs and TCAs may influence the QT interval and serious pharmacodynamic interactions may occur when they are administered with boceprevir (Table 4).

Table 3 Overview of studied interactions between direct-acting antivirals and psychoactive agents

	DAA	Drug	DAA AUC	DAA C_{max}	DAA C_{min}	Drug AUC	Drug C_{max}	Drug C_{min}	Recommendation	References
Protease inhibitors	Boceprevir	Escitalopram (10 mg)	0.91 (0.81–1.02)	1.02 (0.96–1.08)		0.79 (0.72–0.87)	0.81 (0.76–1.87)		No dose adjustment DAA/drug	[17, 61]
		Midazolam po (4 mg)				430 % ↑	177 % ↑		Contraindicated	[17, 62]
		St John's wort (600 mg)	0.91 (0.87–0.96)	0.94 (0.81–1.07)	1.00 (0.79–1.26)	1.23 (1.10–1.38)	1.32 (1.16–4.52)	1.37 (1.19–1.58)	No dose adjustment DAA/drug	[21]
	Simeprevir	Escitalopram (10 mg)	0.75 (0.68–0.83)	0.80 (0.71–0.89)	0.68 (0.59–0.79)	1.00 (0.97–1.03)	1.03 (0.99–1.07)	1.00 (0.95–1.05)	No dose adjustment DAA/drug	[18, 63]
		Midazolam po (0.075 mg/kg)				1.45 (1.35–1.57)	1.31 (1.19–1.45)		Caution when co-administered	[18]
		Midazolam iv (0.025 mg/kg)				1.10 (0.95–1.26)	0.78 (0.52–1.17)		No dose adjustment DAA/drug	[18]
	Grazoprevir[a]	Midazolam (2 mg/mL)				1.34 (1.29–1.39)	1.15 (1.01–1.31)			[19]
NS5A inhibitors	Daclatasvir	Escitalopram (10 mg)	1.12 (1.01–1.26)	1.14 (0.98–1.32)	1.23 (1.09–1.38)	1.05 (1.02–1.08)	1.00 (0.92–1.08)	1.10 (1.04–1.16)	No dose adjustment DAA/drug	[23]
		Midazolam (5 mg)				0.87 (0.83–0.92)	0.95 (0.88–1.04)		No dose adjustment DAA/drug	[23]
	Ledipasvir	No DDIs studied								
NS5B polymerase inhibitors	Sofosbuvir	No DDIs studied								
Fixed-dose combinations	PTV/ritonavir, OBV, and DSV	Escitalopram (10 mg)[a]	PTV: 0.98 (0.85–1.14) OBV: 1.02 (1.00–1.05) DSV: 1.01 (0.93–1.10)	PTV: 1.12 (0.88–1.43) OBV: 1.09 (1.01–1.18) DSV: 1.10 (0.95–1.27)	PTV: 0.71 (0.56–0.89) OBV: 0.97 (0.92–1.02) DSV: 0.89 (0.79–1.00)	0.87 (0.80–0.95)	1.00 (0.96–1.05)		No dose adjustment DAA/drug	[20, 31]
		Duloxetine (60 mg)[a]	PTV: 0.83 (0.62–1.10) OBV: 1.00 (0.95–1.06) DSV: 0.92 (0.81–1.04)	PTV: 0.79 (0.53–1.16) OBV: 0.98 (0.88–1.08) DSV: 0.94 (0.81–1.09)	PTV: 0.77 (0.65–0.91) OBV: 1.01 (0.96–1.06) DSV: 0.88 (0.76–1.01)	0.75 (0.67–0.83)	0.79 (0.67–0.94)		No dose adjustment DAA/drug	[20, 31]
		Zolpidem (5 mg)[a]	PTV: 0.68 (0.55–0.85) OBV: 1.03 (1.00–1.07) DSV: 0.95 (0.84–1.08)	PTV: 0.63 (0.46–0.86) OBV: 1.07 (1.00–1.15) DSV: 0.93 (0.84–1.03)	PTV: 1.23 (1.10–1.38) OBV: 1.04 (1.00–1.08) DSV: 0.92 (0.83–1.01)	0.95 (0.74–1.23)	0.94 (0.76–1.16)		No dose adjustment DAA/drug	[20, 31]
		Alprazolam (0.5 mg)[a]	PTV: 0.96 (0.73–1.27) OBV: 1.00 (0.96–1.04) DSV: 0.98 (0.87–1.11)	PTV: 0.91 (0.64–1.31) OBV: 0.98 (0.93–1.04) DSV: 0.93 (0.83–1.04)	PTV: 1.12 (1.02–1.23) OBV: 0.98 (0.93–1.04) DSV: 1.00 (0.87–1.15)	1.34 (1.15–1.55)	1.09 (1.03–1.15)		No dose adjustment DAA/drug	[20, 31]
		Diazepam (2 mg)[a]	PTV: 0.91 (0.78–1.07) OBV: 0.98 (0.93–1.03) DSV: 1.01 (0.94–1.06)	PTV: 0.95 (0.77–1.15) OBV: 1.00 (0.93–1.08) DSV: 1.05 (0.98–1.13)	PTV: 0.92 (0.82–1.03) OBV: 0.93 (0.68–0.98) DSV: 1.05 (0.98–1.12)	0.78 (0.73–0.82)	1.18 (1.07–1.30)		No dose adjustment DAA/drug	[32]
	PTV/ritonavir and *OBV*	Duloxetine (60 mg)	PTV: 0.96 (0.70–1.32)	PTV: 1.07 (0.63–1.81)	PTV: 0.93 (0.76–1.14)					[20]

When possible, geometric mean ratios (with 90 % confidence intervals in parentheses) are presented; otherwise, percentages are shown

AUC area under the concentration–time curve, C_{max} maximum plasma concentration, C_{min} minimum plasma concentration, *DAA* direct-acting antiviral, *DDIs* drug–drug interactions, *DSV* dasabuvir, *iv* intravenous, *OBV* ombitasvir, *po* oral, *PTV* paritaprevir, ↑ indicates increase

[a] The interactions with midazolam are studied without elbasvir. No interaction studies with elbasvir/grazoprevir were performed

Table 4 Overview of safe options for and contraindicated psychoactive agents that have a potential interaction with boceprevir

Class of psychoactive agent	Safe options	Contraindicated	Potential interaction	Unknown
Benzodiazepines	Bromazepam	Midazolam (oral and intravenous)	Alprazolam	Loprazolam
	Clobazam		Brotizolam	
	Flunitrazepam		Chlordiazepoxide	
	Lorazepam		Clorazepate	
	Lormetazepam		Diazepam	
	Nitrazepam		Flurazepam	
	Oxazepam		Zolpidem	
	Prazepam		Zopiclone	
	Temazepam			
Antidepressants	SSRIs	N/A	SSRIs	N/A
	Citalopram[a]		Trazodone	
	Duloxetine		Venlafaxine	
	Escitalopram[a]		Vortioxetine	
	Fluoxetine[b]		TCAs	
	Fluvoxamine		N/A	
	Paroxetine[b]		Others	
	Sertraline[b]		N/A	
	TCAs			
	Amitriptyline[b]			
	Clomipramine[c]			
	Dosulepin			
	Doxepin[b]			
	Imipramine[c]			
	Maprotiline			
	Nortriptyline[c]			
	Others			
	Agomelatine			
	Bupropion			
	Lithium salts[c]			
	Mianserin			
	Mirtazapine[c]			
	Moclobemide			
	St John's wort			
Antipsychotics	Clozapine[c]	Pimozide[a]	Aripiprazole[c]	Chlorprothixene
	Flupentixol	Quetiapine	Bromperidol	Penfluridol
	Fluphenazine		Haloperidol[a]	Pericyazine
	Fluspirilene		Lurasidone	Pipamperone
	Olanzapine[c]		Risperidone[c]	
	Paliperidone[c]		Sertindole[c]	
	Perphenazine			
	Sulpride[a]			
	Tiapride			
	Zuclopenthixol			

N/A not applicable, *SSRIs* selective serotonin reuptake inhibitors, *TCAs* tricyclic antidepressants

[a] Known risk for prolongation of the QT interval (http://www.crediblemeds.org)

[b] Conditional risk for prolongation of the QT interval (http://www.crediblemeds.org)

[c] Possible risk for prolongation of the QT interval (http://www.crediblemeds.org)

Table 5 Overview of safe options for and contraindicated psychoactive agents that have a potential interaction with simeprevir

Class of psychoactive agent	Safe options	Contraindicated	Potential interaction	Unknown
Benzodiazepine	Bromazepam	N/A	Alprazolam	Loprazolam
	Flunitrazepam		Brotizolam	
	Lorazepam		Chlordiazepoxide	
	Lormetazepam		Clobazam	
	Midazolam iv		Clorazepate acid	
	Nitrazepam		Diazepam	
	Oxazepam		Flurazepam	
	Prazepam		Midazolam po	
	Temazepam		Zolpidem	
			Zopiclone	
Antidepressants	SSRIs	N/A	SSRIs	N/A
	Citalopram		Trazodone	
	Duloxetine		Venlafaxine	
	Escitalopram		Vortioxetine	
	Fluoxetine		TCAs	
	Fluvoxamine		Amitriptyline	
	Paroxetine		Nortriptyline	
	Sertraline		Others	
	TCAs		Mirtazapine	
	Clomipramine		St John's wort	
	Dosulepin			
	Doxepin			
	Imipramine			
	Maprotiline			
	Others			
	Agomelatine			
	Bupropion			
	Lithium salts			
	Mianserin			
	Moclobemide			
Antipsychotics	Clozapine	N/A	Aripiprazole	Chlorprothixene
	Flupentixol		Bromperidol	Penfluridol
	Fluspirilene		Haloperidol	Pericyazine
	Fluphenazine		Lurasidone	Pipamperone
	Olanzapine		Paliperidone	
	Perphenazine		Pimozide	
	Sulpride		Quetiapine	
	Tiapride		Risperidone	
	Zuclopenthixol		Sertindole	

iv intravenous, *N/A* not applicable, *po* oral, *SSRIs* selective serotonin reuptake inhibitors, *TCAs* tricyclic antidepressants

5.1.2 Simeprevir

Table 4 shows psychoactive medications that can be safely combined with simeprevir. Simeprevir inhibits intestinal CYP3A4 and therefore only interactions with orally administered medications are relevant. Thus, intravenous midazolam can be used safely with simeprevir but oral midazolam should be used with caution, as the AUC and C_{max} of midazolam are increased by 45 and 31 %, respectively, when the two are co-administered [18].

Studies have been conducted of escitalopram and it can be safely used in combination with simeprevir [18].

Simeprevir inhibits P-gp and OATP1B1. Simeprevir has a higher impact than boceprevir on the transport activity of

Table 6 Overview of safe options for and contraindicated psychoactive agents that have a potential interaction with daclatasvir

Class of psychoactive agent	Safe options	Contraindicated	Potential interaction	Unknown
Benzodiazepine	Alprazolam	N/A	Clobazam	Loprazolam
	Bromazepam			
	Brotizolam			
	Chlordiazepoxide			
	Clorazepate			
	Diazepam			
	Flunitrazepam			
	Flurazepam			
	Lorazepam			
	Lormetazepam			
	Midazolam			
	Oxazepam			
	Nitrazepam			
	Prazepam			
	Temazepam			
	Zolpidem			
	Zopiclone			
Antidepressants	SSRIs	St John's wort	SSRIs	N/A
	Citalopram		N/A	
	Duloxetine		TCAs	
	Escitalopram		Amitriptyline	
	Fluoxetine		Nortriptyline	
	Fluvoxamine		Others	
	Paroxetine		N/A	
	Sertraline			
	Trazodone			
	Venlafaxine			
	Vortioxetine			
	TCAs			
	Clomipramide			
	Dosulepin			
	Doxepin			
	Imipramine			
	Maprotiline			
	Others			
	Agomelatine			
	Bupropion			
	Lithium salts			
	Mianserin			
	Mirtazapine			
	Moclobemide			

Table 6 continued

Class of psychoactive agent	Safe options	Contraindicated	Potential interaction	Unknown
Antipsychotics	Aripiprazole	N/A	Lurasidone	Chlorprothixene
	Bromperidol		Paliperidone	Penfluridol
	Clozapine		Risperidone	Pericyazine
	Flupentixol			Pipamperone
	Fluphenazine			
	Fluspirilene			
	Haloperidol			
	Olanzapine			
	Perphenazine			
	Pimozide			
	Quetiapine			
	Sertindole			
	Sulpride			
	Tiapride			
	Zuclopenthixol			

N/A not applicable, *SSRIs* selective serotonin reuptake inhibitors, *TCAs* tricyclic antidepressants

P-gp, as indicated in Sect. 3.3. Therefore, inhibition of P-gp by simeprevir may lead to a small increase in concentrations of P-gp substrates (e.g., risperidone and nortriptyline) in the brain. However, the clinical relevance seems limited [18].

Simeprevir is a possible victim of DDIs as it is primarily metabolized by CYP3A4 [18]. St John's wort may therefore cause a decrease in the plasma concentration of simeprevir as it is a CYP3A4 inducer. Nevertheless, this change might not be clinically relevance since simeprevir exhibits high inter-individual variability in its plasma concentrations [25].

5.2 NS5A Inhibitor

5.2.1 Daclatasvir

Daclatasvir has a negligible influence on the activities of CYP3A4 and other CYP enzymes and no dose adjustments were required when it was studied with midazolam [23]. Based on this information, it is expected that most benzodiazepines, antidepressants, and antipsychotics can be used safely in combination with daclatasvir, as shown in Table 6. Daclatasvir is metabolized by CYP3A4 and thus inducers and inhibitors of CYP3A4 have the ability to affect the plasma concentrations of daclatasvir [23]. Most psychoactive drugs do not influence CYP3A4, with the exception of St John's wort; therefore, co-administration of St John's wort and daclatasvir is contraindicated [23].

5.3 NS5B Polymerase Inhibitor

5.3.1 Sofosbuvir

Sofosbuvir is an NS5B inhibitor and not a perpetrator of DDIs as it has no influence on CYP enzymes or drug transporters; therefore, it has no impact on the plasma concentrations of psychoactive drugs [26]. However, an unexpected interaction has occurred involving sofosbuvir and the antiarrhythmic agent amiodarone. This indicates that not every DDI can be predicted based on the activities of CYP, UGT, or drug transporters. The mechanism and the specific role of sofosbuvir in the interaction was uncertain because other DAAs (daclatasvir, simeprevir, and ledipasvir) were simultaneously administered and could have been involved in causing the interaction [27, 28]. Additionally, it could also be caused by a pharmacodynamic interaction.

Sofosbuvir is metabolized in the liver and intestine; the drug is not a victim of enzymatic DDIs because it is not metabolized by, for example, CYPs or UGTs [26]. Sofosbuvir is a substrate for P-gp and BCRP; hence, interactions may occur with inducers and inhibitors of P-gp. P-gp inducers, e.g., St John's wort, could potentially decrease

Table 7 Overview of safe options for and contraindicated psychoactive agents that have a potential interaction with ledipasvir

Class of psychoactive agent	Safe options	Contraindicated	Potential interaction	Unknown
Benzodiazepine	Alprazolam	N/A	Clobazam	Loprazolam
	Bromazepam			
	Brotizolam			
	Chlordiazepoxide			
	Clorazepate			
	Diazepam			
	Flunitrazepam			
	Flurazepam			
	Lorazepam			
	Lormetazepam			
	Midazolam			
	Prazepam			
	Nitrazepam			
	Oxazepam			
	Temazepam			
	Zolpidem			
	Zopiclone			
Antidepressants	SSRIs	St John's wort	SSRIs	
	Citalopram		N/A	
	Duloxetine		TCAs	
	Escitalopram		Amitriptyline	
	Fluoxetine		Nortriptyline	
	Fluvoxamine		Others	
	Paroxetine		N/A	
	Sertraline			
	Trazodone			
	Venlafaxine			
	Vortioxetine			
	TCAs			
	Clomipramine			
	Dosulepin			
	Doxepin			
	Imipramine			
	Maprotiline			
	Others			
	Agomelatine			
	Bupropion			
	Lithium salts			
	Mianserin			
	Mirtazapine			
	Moclobemide			

Table 7 continued

Class of psychoactive agent	Safe options	Contraindicated	Potential interaction	Unknown
Antipsychotics	Aripiprazole	N/A	Lurasidone	Chlorprothixene
	Bromperidol		Paliperidone	Penfluridol
	Clozapine		Risperidone	Pericyazine
	Flupentixol			Pipamperone
	Fluphenazine			
	Fluspirilene			
	Haloperidol			
	Olanzapine			
	Perphenazine			
	Pimozide			
	Quetiapine			
	Sertindole			
	Sulpride			
	Tiapride			
	Zuclopenthixol			

N/A not applicable, *SSRIs* selective serotonin reuptake inhibitors, *TCAs* tricyclic antidepressants

plasma concentrations of sofosbuvir and result in a decrease in the pharmacological effects of sofosbuvir. Therefore, co-administration of the two drugs is contraindicated. Trazodone is also a possible P-gp inducer and may affect the plasma concentration of sofosbuvir (Table 8). Inhibition of P-gp could increase the plasma concentration of sofosbuvir; however, the interaction studies have not been performed in humans [26]. Lastly, the main (inactive) metabolite of sofosbuvir (GS-331007) is not a P-gp substrate [26].

5.4 Fixed-Dose Combinations

5.4.1 Ledipasvir and Sofosbuvir

Ledipasvir inhibits P-gp and BCRP and may cause interactions with P-gp and BCRP substrates (e.g., risperidone, and nortriptyline) [29]. P-gp inhibition at the BBB could potentially increase the exposure of these P-gp substrates in the brain. No interaction studies have been performed between ledipasvir and psychoactive agents. Table 7 shows the psychoactive agents that can be safely used with or potentially interact with ledipasvir.

The metabolism of ledipasvir is unknown but it is mainly excreted unchanged through bile. Thus, ledipasvir is not expected to be a victim of DDIs [29].

Sofosbuvir is discussed in Sect. 5.3.1.

5.4.2 Paritaprevir/Ritonavir, Ombitasvir, and Dasabuvir

Ritonavir is a strong CYP3A4 inhibitor but it also influences other CYP enzymes and drug transporters. Consequently, caution is needed if combining drugs metabolized by CYP3A4 with this fixed-dose regimen (paritaprevir/ritonavir, ombitasvir, and dasabuvir). Psychoactive agents such as duloxetine, escitalopram, zolpidem, alprazolam, and diazepam can be safely administered with this regimen as previous studies have not shown any clinically relevant interactions (Table 9) [20, 30–32].

The plasma concentrations of duloxetine did not alter when it was co-administered with the combination regimen [20]. Duloxetine is a substrate for CYP2D6 and CYP1A2, and ritonavir inhibits CYP2D6 and induces CYP1A2. As no effect was observed when combined with paritaprevir/ritonavir, ombitasvir, and dasabuvir, it was suggested that the inhibition of CYP2D6 and induction of CYP1A2 occurred to similar extents. We recommend that this combination regimen be used with care in patients receiving medications that are metabolized by CYP2D6 and/or CYP1A2, especially as a previous interaction study on the co-administration of olanzapine (CYP1A2 and CYP2D6 substrate) and ritonavir resulted in decreased olanzapine concentrations [33].

It is important to note that CYP2D6 inhibition by ritonavir is dose dependent [34]. Low-dose ritonavir (100 mg twice daily) had only a mild effect on CYP2D6, as shown with the CYP2D6 substrate desipramine (26 % AUC increase), but the therapeutic dose of ritonavir (600 mg twice daily) had a stronger effect (desipramine AUC increase of 145 %) [34–36]. However, this fixed-dose HCV regimen contains only 100 mg of ritonavir. Therefore, we expect DDIs only with co-administered drugs that are primarily metabolized by CYP2D6 and that have a narrow therapeutic range. Such drugs are not

Table 8 Overview of safe options for and contraindicated psychoactive agents that have a potential interaction with sofosbuvir

Class of psychoactive agent	Safe options	Contraindicated	Potential interaction	Unknown
Benzodiazepine	Alprazolam	N/A	N/A	Loprazolam
	Bromazepam			Nitrazepam
	Brotizolam			
	Chlordiazepoxide			
	Clobazam			
	Clorazepate			
	Diazepam			
	Flunitrazepam			
	Flurazepam			
	Loprazolam			
	Lorazepam			
	Lormetazepam			
	Midazolam			
	Oxazepam			
	Prazepam			
	Temazepam			
	Zolpidem			
	Zopiclone			
Antidepressants	SSRIs	St John's wort	SSRIs	N/A
	Citalopram		Trazodone	
	Duloxetine		TCAs	
	Escitalopram		N/A	
	Fluoxetine		Others	
	Fluvoxamine		N/A	
	Paroxetine			
	Sertraline			
	Venlafaxine			
	Vortioxetine			
	TCAs			
	Amitriptyline			
	Clomipramine			
	Dosulepin			
	Doxepin			
	Imipramine			
	Maprotiline			
	Nortriptyline			
	Others			
	Agomelatine			
	Bupropion			
	Lithium salts			
	Mianserin			
	Mirtazapine			
	Moclobemide			

Table 8 continued

Class of psychoactive agent	Safe options	Contraindicated	Potential interaction	Unknown
Antipsychotics	Aripiprazole	N/A	Lurasidone	Chlorprothixene
	Bromperidol			Penfluridol
	Clozapine			Pericyazine
	Flupentixol			Pipamperone
	Fluphenazine			
	Fluspirilene			
	Haloperidol			
	Olanzapine			
	Paliperidone			
	Perphenazine			
	Pimozide			
	Quetiapine			
	Risperidone			
	Sertindole			
	Sulpride			
	Tiapride			
	Zuclopenthixol			

N/A not applicable, *SSRIs* selective serotonin reuptake inhibitors, *TCAs* tricyclic antidepressants

contraindicated with this combination regimen; however, plasma drug concentrations and adverse events should be monitored after co-administration [34].

Ritonavir also inhibits P-gp; therefore, ritonavir may modify plasma concentrations of P-gp substrates such as risperidone and amitriptyline.

Paritaprevir, ombitasvir, and dasabuvir are inhibitors of UGT and thus benzodiazepines (e.g., lorazepam, lormetazepam, and oxazepam) conjugated by UGT could be victims of interactions (Table 6) [20].

5.4.3 Grazoprevir and Elbasvir

Table 10 shows safe options for psychoactive drugs that can be administered with grazoprevir and elbasvir. Grazoprevir is a mild CYP3A inhibitor as it was observed to increase the plasma concentration of midazolam by only 30 % [19]. Therefore, CYP3A4 substrates are not contraindicated for co-administration with grazoprevir. However, we recommend that prescribers be aware of possible interactions with drugs that are primarily metabolized by CYP3A4 and have a narrow therapeutic range. There are no reported studies on drug interactions between the grazoprevir/elbasvir combination and psychoactive agents [19]. Grazoprevir and elbasvir are mainly metabolized by CYP3A4; thus, they should not be administered with St John's wort and other CYP3A4 inducers or inhibitors [19] (Table 10).

6 Conclusion

In this review we have shown that there is a paucity of experimental data on drug interactions between psychoactive agents and DAAs. Many mechanisms are involved in the metabolism and transport of both classes of drugs, making it difficult to predict which drugs can be safely co-administered to patients.

In our opinion, safe options for concomitant administration should be combinations that have actually been studied in humans, or combinations that are not based on theoretical pharmacokinetic interactions. In addition, all medications used at the start of and during HCV treatment should be inventoried, so that possible DDIs can be evaluated before clinically relevant effects arise. Physicians should also be aware of possible interactions and their consequences. These may include adverse effects caused by increased plasma drug concentrations or reduced efficacy due to decreases in drug exposure. These are of great importance as such issues may also affect adherence to both

Table 9 Overview of safe options for and contraindicated psychoactive agents that have a potential interaction with paritaprevir, ritonavir, ombitasvir plus dasabuvir

Class of psychoactive agent	Safe options	Contraindicated	Potential interaction	Unknown
Benzodiazepine	Alprazolam	Midazolam	Brotizolam	Loprazolam
	Bromazepam		Clorazepate	
	Clobazam		Chlordiazepoxide	
	Diazepam		Flurazepam	
	Flunitrazepam		Lorazepam	
	Prazepam		Lormetazepam	
	Nitrazepam		Oxazepam	
	Zolpidem		Temazepam	
			Zopiclone	
Antidepressants	SSRIs	St John's wort	SSRIs	N/A
	Citalopram		Fluoxetine[a]	
	Escitalopram		Fluvoxamine[a]	
	Duloxetine[a]		Paroxetine[a]	
	TCAs		Sertraline	
	Dosulepin		Trazodone	
	Others		Venlafaxine[a]	
	Lithium salts		Vortioxetine[a]	
	Moclobemide		TCAs	
			Amitriptyline[a]	
			Clomipramine	
			Doxepin[a]	
			Imipramine[a]	
			Nortriptyline[a]	
			Maprotiline[a]	
			Others	
			Agomelatine	
			Bupropion	
			Mirtazepine	
			Mianserin[a]	
Antipsychotics	Fluspirilene	Pimozide	Aripiprazole[a]	Chlorprothixene
	Sulpride	Quetiapine	Bromperidol[a]	Penfluridol
	Tiapride		Clozapine	Pericyazine
			Flupentixol[a]	Pipamperone
			Fluphenazine[a]	
			Haloperidol[a]	
			Lurasidone	
			Olanzapine	
			Paliperidone	
			Perphenazine[a]	
			Risperidone[a]	
			Sertindole[a]	
			Zuclopenthixol	

N/A not applicable, *SSRIs* selective serotonin reuptake inhibitors, *TCAs* tricyclic antidepressants

[a] Substrates of CYP2D6 (Sect. 5.4.1)

DAAs and psychoactive agents. Our final recommendation is that physicians contact pharmacists or clinical pharmacologists for support in managing these interactions.

This review provides an overview of the mechanisms of interactions between DAAs and psychoactive agents. Based on interaction studies, we give recommendations for

Table 10 Overview of safe options for and contraindicated psychoactive agents that have a potential interaction with grazoprevir plus elbasvir

Class of psychoactive agent	Safe options	Contraindicated	Potential interaction	Unknown
Benzodiazepine	Alprazolam	N/A	Diazepam	Loprazolam
	Brotizolam		Midazolam	
	Chlordiazepoxide			
	Bromazepam			
	Clobazam			
	Flunitrazepam			
	Lorazepam			
	Lormetazepam			
	Clorazepate			
	Flurazepam			
	Nitrazepam			
	Oxazepam			
	Temazepam			
	Prazepam			
	Zolpidem			
	Zopiclone			
Antidepressants	SSRIs	St John's wort	SSRIs	N/A
	Citalopram		N/A	
	Duloxetine		TCAs	
	Escitalopram		N/A	
	Fluoxetine		Others	
	Fluvoxamine		N/A	
	Paroxetine			
	Sertraline			
	Trazodone			
	Venlafaxine			
	Vortioxetine			
	TCAs			
	Amitriptyline			
	Clomipramine			
	Dosulepin			
	Doxepin			
	Imipramine			
	Maprotiline			
	Nortriptyline			
	Others			
	Agomelatine			
	Bupropion			
	Lithium salts			
	Mianserin			
	Mirtazapine			
	Moclobemide			

Table 10 continued

Class of psychoactive agent	Safe options	Contraindicated	Potential interaction	Unknown
Antipsychotics	Aripiprazole	N/A	Lurasidone	Chlorprothixene
	Bromperidol			Penfluridol
	Clozapine			Pericyazine
	Flupentixol			Pipamperone
	Fluphenazine			
	Fluspirilene			
	Haloperidol			
	Olanzapine			
	Paliperidone			
	Perphenazine			
	Pimozide			
	Quetiapine			
	Risperidone			
	Sertindole			
	Sulpride			
	Tiapride			
	Zuclopenthixol			

N/A not applicable, *SSRIs* selective serotonin reuptake inhibitors, *TCAs* tricyclic antidepressants

the co-administration of DAAs and psychoactive agents. The administration of various combinations of drugs results in different potential interactions. It is therefore necessary that theoretical predictions of DDIs be backed with actual drug interaction studies, in order to obtain more conclusive and useful data for clinical applications.

Compliance with Ethical Standards

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