Direct-acting antiviral interactions with opioids, alcohol or illicit drugs of abuse in HCV-infected patients

ING LORENZINI, Kuntheavy, GIRARDIN, François

Abstract
The hepatitis C virus (HCV) prevalence is extremely high in patients who consume and inject illicit drugs. Concerns about poor adherence and fear of interaction with drugs of abuse could constitute further disincentive for treatment initiation in these patients. We discussed the pharmacokinetics (PKs) and pharmacodynamics (PD) of currently prescribed direct antiviral agents (NSA5 inhibitors: daclatasvir, elbasvir, ledipasvir, pibrentasvir, velpatasvir; NS5B inhibitor: sofosbuvir; NS3/4A protease inhibitors: glecaprevir, grazoprevir, voxilaprevir) and most common substances of abuse (opioids: buprenorphine, fentanyl, heroin, methadone, morphine, oxycodone; stimulants: amphetamines, cathinones, cocaine; cannabinoids; ethanol). Overall, most direct-acting antivirals (DAAs) are substrates and inhibitors of the transmembrane transporter P-glycoprotein (P-gp), and several of them are metabolized by cytochrome P450 enzymes. Clinically relevant interactions are associated with P-gp and CYP3A modulators. Most substances of abuse are eliminated by Phase I and Phase II metabolizing enzymes, but none of them are either major [...]
INTRODUCTION

Chronic viral hepatitis C infections are a major health problem, with approximately 1.75 million new cases worldwide (2015 estimation).1,2 The hepatitis C virus (HCV) prevalence is variable across the world: around 0.1%-1.0% in European countries, 2.0%-6.5% in Central Asia and up to 7.0% in African countries.3 In western countries, the major source of new HCV infections remains intravenous drug use, which
caused 390,000 new cases in 2015.² People with substance use disorders (PWSUDs) constitute the majority of incident (75%) and prevalent (80%) HCV cases in high-income regions.⁴ Thus, people who inject drugs (PWID) were more frequently HCV antibody (Ab) positive than non-intravenous (non-IV) drug users.⁵

Since 2014, the development of direct-acting antivirals (DAAs) revolutionized the management of chronic HCV infections, with higher rates of sustained virologic response (SVR) (>90%) and shortened treatment duration (8 to 12 weeks). Current available regimens consist of pangenotypic fixed-drug combinations (sofosbuvir/velpatasvir or glecaprevir/pibrentasvir), or of alternative genotype-specific regimen that includes sofosbuvir, ledipasvir, daclatasvir, grazoprevir/elbasvir and tritherapy with the fixed-dose association of sofosbuvir/velpatasvir/voxlaprevir.⁶,⁷

In PWSUD, the eradication of HCV could decrease the virus circulation community, reducing the infection rate.⁸ However, several barriers to HCV therapy have been identified, such as high rate of psychiatric disorders (psychosis and depression),⁹ poor adherence, ongoing substance use including alcohol use, lower responses to therapy, medication price and the risk of reinfection.¹⁰ The risk of interactions of DAAs with drugs used in substance disorders, such as opioid substitution therapy (OST), as well as with illicit or recreational substances (cocaïne, alcohol), can constitute a barrier to DAA access in PWSUD.

DAAs could be subject to drug-drug interactions (DDI), as they are transformed by metabolic enzymes and substrates of efflux transporters. They can also act as perpetrator of DDI if they modulate enzyme or transporter activity.⁷ The evidence regarding relevant DDI with most of the potential concomitantly prescribed drugs has been recently reviewed.⁷,¹¹

2 | METHODS

In order to review the main pharmacokinetic (PK) and pharmacodynamic (PD) characteristics and interaction potential of currently available DAAs (based on 2018 EASL recommendations⁶), and of selected substances of abuse, we performed a PubMed search of articles published until June 2019. The following keywords were used: drug-drug interaction, pharmacokinetics, pharmacodynamics, daclatasvir, elbasvir/grazoprevir, glecaprevir/pibrentasvir, sofosbuvir/ledipasvir, sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/voxilaprevir, substance of abuse, opioids, buprenorphine, fentanyl, methadone, morphine, oxycodone, amphetamine, ecstasy, cathinones, cocaine, cannabis and ethanol. The paritaprevir/ombitasvir/ritonavir ± dasabuvir combination was not considered in our review since this regimen is no longer recommended.¹¹

The following article types were eligible: PK/PD reviews, original articles, articles on physiologically based pharmacokinetic (PBPK) models and case reports. Only articles written in English or in French were selected. The following types of studies were eligible: in vitro PK studies, human clinical studies (PK phase 1 studies or phase 2/3 clinical studies) and post hoc or pooled analysis of clinical studies. Only studies regarding interactions of currently available DAAs with the selected substances of abuse were eligible.

For currently available DAAs, we included in our search the summary of product characteristics and the European public assessment report on the European Medicines Agency website (https://www.ema.europa.eu/en).

Finally, we performed a Google search to find congress abstracts or conference proceeding reporting unpublished interaction studies or data.

Papers involving other molecules than the keywords, and not considering PK, PD or drug-interaction data, were excluded.

3 | CLINICAL PHARMACOLOGY OF DAA

The currently available drugs in Europe are presented in Table 1, and their main PK and PD characteristics in Table 2, and in Figures 1 and 2.

3.1 | Daclatasvir

Daclatasvir (DCV) is an inhibitor of the HCV non-structural 5A (NS5A) protein approved for HCV genotypes 1, 3 and 4 in association with sofosbuvir, with or without ribavirin.¹³ It is readily absorbed after oral administration, with maximal concentrations (C_max) achieved after 1-2 hours, and an absolute bioavailability of 67%, and is highly bound to plasma proteins (99%). DCV is a substrate of the P-glycoprotein (P-gp) efflux transporter, and is metabolized by cytochrome P450 (CYP) 3A isoenzymes, predominantly CYP3A4. A majority of the dose (88%) is excreted in the faeces and 7% in urine. The mean terminal half-life after multiple dosing is 12-15 hours. DCV is an inhibitor of P-gp, organic-anion-transporting polypeptide (OATP) 1B1 and breast cancer resistance protein (BCRP) transporters.¹⁴ Interactions may occur when DCV is used concomitantly with CYP3A and P-gp inhibitor or inducers, and with P-gp, OATP and BCRP substrates.

From a safety point of view, the most common adverse events (AEs) in studies combining DCV and sofosbuvir were headache,
protease.

EBR and GZR’s bioavailability is 20% to 40%, and C is an intestinal BCRP inhibitor. Clinically relevant DDI are likely to CYP3A. EBR is a mild inhibitor of intestinal P‐gp and BCRP, and GZR achieved a half-life of 2–4 hours. Both compounds display extensive protein binding (free fraction: 1%). Excretion into faeces as parent drugs accounts for 75% to 80% of elimination of both EBR and GZR, the remaining 20% being excreted as oxidative metabolites formed via CYP3A. Both compounds are P‐gp substrates. In addition, GZR (but not EBR) is a substrate of OATP1B1 and OATP1B3. Their steady-state elimination half‐lives in HCV‐infected subjects were 24 and 31 hours for EBR and GZR respectively. Neither EBR nor GZR are potent inhibitors or inducers of CYP or uridine glucuronosyltransferase (UGT) enzymes in vitro, but GZR is a weak inhibitor of CYP3A. EBR is a mild inhibitor of intestinal P‐gp and BCRP, and GZR is an intestinal BCRP inhibitor. Clinically relevant DDI are likely to occur with moderate and strong CYP3A and P‐gp inducers (but not with CYP3A inhibitors), and when GZR is combined with OATP1B inhibitors. CYP3A and P‐gp/BCRP substrates with a narrow therapeutic range may be subject to DDI with EBR/GZR (increases in plasma concentrations).

The most frequently reported AEs were fatigue (17.0%), headache (16.4%), nausea and dose‐dependent increases in liver function markers.18,19

3.2 | Elbasvir/grazoprevir

Elbasvir (EBR) and grazoprevir (GZR) are available as a 50/100 mg fixed‐dose combination, approved for HCV genotypes 1a, 1b and 4. EBR is an inhibitor of the HCV NS5A while GZR inhibits NS3/4A protease. EBR and GZR’s bioavailability is 20% to 40%, and Cmax is achieved after 2–4 hours. Both compounds display extensive protein binding (free fraction: 1%). Excretion into faeces as parent drugs accounts for 75% to 80% of elimination of both EBR and GZR, the remaining 20% being excreted as oxidative metabolites formed via CYP3A. Both compounds are P‐gp substrates. In addition, GZR (but not EBR) is a substrate of OATP1B1 and OATP1B3. Their steady-state elimination half‐lives in HCV‐infected subjects were 24 and 31 hours for EBR and GZR respectively. Neither EBR nor GZR are potent inhibitors or inducers of CYP or uridine glucuronosyltransferase (UGT) enzymes in vitro, but GZR is a weak inhibitor of CYP3A. EBR is a mild inhibitor of intestinal P‐gp and BCRP, and GZR is an intestinal BCRP inhibitor. Clinically relevant DDI are likely to occur with moderate and strong CYP3A and P‐gp inducers (but not with CYP3A inhibitors), and when GZR is combined with OATP1B inhibitors. CYP3A and P‐gp/BCRP substrates with a narrow therapeutic range may be subject to DDI with EBR/GZR (increases in plasma concentrations).

The most frequently reported AEs were fatigue (17.0%), headache (16.4%), nausea and dose‐dependent increases in liver function markers.18,19

3.3 | Glecaprevir/pibrentasvir

Glecaprevir and pibrentasvir are available as a 100/40 mg fixed‐dose combination, approved for all HCV genotypes. The recommended dose is 300/120 mg once daily (three tablets) to be taken with a meal. Glecaprevir is HCV NS3/4A protease inhibitor while pibrentasvir inhibits HCV NS5A. Their Cmax is attained after 5 hours. Both drugs are extensively bound to plasma proteins (>95%). Glecaprevir undergoes limited CYP3A‐mediated metabolism, with 26% of the dose excreted as oxidative metabolites, whereas pibrentasvir is not metabolized. Both drugs are excreted in the faeces. Their elimination half‐lives are 6‐9 and 23‐29 hours respectively.

Glecaprevir is a substrate and inhibitor of P‐gp, BCRP and OATP1B1/B3. Pibrentasvir is a substrate of P‐gp and of BCRP, and inhibits P‐gp, BCRP and OATP1B1/B3. Clinical DDI studies have confirmed clinically relevant inhibition of P‐gp, BCRP and OATP1B1/B3. Finally, glecaprevir and pibrentasvir are weak inhibitors of CYP3A and UGT 1A1 in vitro and in vivo. Therefore, CYP3A, UGT1A1, P‐gp/BCRP and OATP1B substrates with a narrow therapeutic range are subject to DDI with glecaprevir and pibrentasvir.

The most frequently reported AEs were headache (13%), fatigue (11%) and nausea (8%).

3.4 | Sofosbuvir/ledipasvir

The fixed‐dose combination of sofosbuvir and ledipasvir contains 400 and 90 mg of each active substance respectively. It is approved for the treatment of HCV genotypes 1, 4, 5 and 6. Sofosbuvir is a prodrug that requires several steps bioactivation to GS‐461203, the pharmacologically active nucleoside analog triphosphate (11%) and nausea (8%). Their Cmax is attained after 5 hours. Both drugs are extensively bound to plasma proteins (>95%). Glecaprevir undergoes limited CYP3A‐mediated metabolism, with 26% of the dose excreted as oxidative metabolites, whereas pibrentasvir is not metabolized. Both drugs are excreted in the faeces. Their elimination half‐lives are 6‐9 and 23‐29 hours respectively.

Sofosbuvir/ledipasvir contains 400 mg and 90 mg of active substance respectively. It is approved for the treatment of HCV genotypes 1, 4, 5 and 6. Sofosbuvir is a prodrug that requires several steps bioactivation to GS‐461203, the pharmacologically active nucleoside analog triphosphate metabolite, which inhibits NS5B, and is ultimately dephosphorylated to an inactive metabolite, GS‐331007. Ledipasvir inhibits NS5A. Sofosbuvir and ledipasvir Cmax are reached after 1 and 4 hours respectively. Their protein bound fractions are, respectively, 65% and 99%. Sofosbuvir and its metabolites are not substrates of CYP or UGT enzymes. Ledipasvir and sofosbuvir itself are substrates for P‐gp and BCRP, but not GS‐331007. Sofosbuvir elimination is essentially non‐renal, whereas renal clearance is the major elimination pathway for GS‐331007. The latter has a half‐life of 27 hours. Ledipasvir half‐life is 50 hours and it is mainly excreted in faeces (>70%). Sofosbuvir and GS‐331007 do not display significant inhibition or induction of CYP, UGT1A1 and main drug transporters. Ledipasvir does not inhibit major human CYP, but has shown to inhibit the transporters P‐gp and BCRP.

### TABLE 1 Available drugs and fixed‐dose combinations according to the EASL 2018 recommendations

<table>
<thead>
<tr>
<th>Drug or fixed‐dose combinations</th>
<th>Brand name</th>
<th>Recommended dose</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daclatasvir</td>
<td>Daklinza®</td>
<td>60 mg qd</td>
<td>In combination with other drugs</td>
</tr>
<tr>
<td>Elbasvir/grazoprevir</td>
<td>Zepatier®</td>
<td>50/100 mg qd</td>
<td></td>
</tr>
<tr>
<td>Glecaprevir/pibrentasvir</td>
<td>Maviret®</td>
<td>100/40 mg qd</td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>Sovaldi®</td>
<td>400 mg qd</td>
<td>In combination with other drugs</td>
</tr>
<tr>
<td>Sofosbuvir/ledipasvir</td>
<td>Harvoni®</td>
<td>400/90 mg qd</td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir/velpatasvir</td>
<td>Epclusa®</td>
<td>400/100 mg qd</td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir/velpatasvir/voxilaprevir</td>
<td>Vosevi®</td>
<td>400/100/100 mg qd</td>
<td></td>
</tr>
</tbody>
</table>

Note: bid: twice daily; qd: once daily.
in vitro.23,26 The concomitant use of P-gp and/or BCRP inducers may result in virologic failure. P-gp and/or BCRP substrates with a narrow therapeutic range may see their exposure increase in the presence of sofosbuvir/ledipasvir.

Patients treated with the association may experience headaches, fatigue, insomnia, nausea and diarrhoea.24 In healthy volunteers, the corrected QT interval was not prolonged after single therapeutic (400 mg) and after supratherapeutic doses of sofosbuvir (1200 mg) and ledipasvir 120 mg (twice daily) in thorough QT studies.25,28

### 3.5 | Sofosbuvir/velpatasvir

The pangenotypic combination of sofosbuvir and velpatasvir contains 400 and 100 mg of each active substance respectively.29 Velpatasvir is an HCV NS5A protein inhibitor. Its $C_{\text{max}}$ is reached 3 hours after oral administration. Velpatasvir is extensively bound to plasma proteins (>99%), and undergoes minor metabolism by CYP2B6, CYP2C8 and CYP3A4, and is excreted (77% as parent drug) in the faeces with a median terminal plasma half-life of 15 hours. Velpatasvir is transported by P-gp and BCRP, and is also an inhibitor of P-gp, BCRP, OATP1B1/B3 and OATP2B1.30,31 There is a risk of therapeutic failure when the association is administered with P-gp and/or BCRP inducers. Substrates of P-gp, BCRP and OATP can be subject to an increase in their exposure when administered with sofosbuvir/velpatasvir.30

The most frequently reported AEs with this association are headache, fatigue, diarrhoea and nausea. Voxelaprevir was not shown to significantly prolong the QTc interval when given at nine times the recommended dose.33

### 3.6 | Sofosbuvir/velpatasvir/voxilaprevir

The pangenotypic combination of sofosbuvir, velpatasvir and voxelaprevir contains 400, 100 and 100 mg of each active substance.32 Voxelaprevir is a reversible NS3/4A protease inhibitor. It reaches $C_{\text{max}}$ 4 hours after administration. Food substantially increases the systemic exposure. It is extensively bound to plasma proteins (>99%) and undergoes metabolism by CYP3A4. Voxelaprevir is eliminated through biliary excretion, 40% as the parent drug, with a half-life of 33 hours.11,33 Voxelaprevir is a substrate of P-gp, BCRP and OATP1B1/B3.34 Inhibition of OATP1B1/B3 at clinically achieved concentrations is reported.34 There is a risk of therapeutic failure when inducers of CYP3A, P-gp and/or BCRP are co-administered. Concentrations of OATP1B1/B3 substrates can increase when administered with sofosbuvir/velpatasvir/voxilaprevir.33

## Table 2

<table>
<thead>
<tr>
<th>Drug</th>
<th>Metabolism and transport</th>
<th>Elimination</th>
<th>CYP/transporter inhibition or induction</th>
<th>Main adverse effects</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daclatasvir</td>
<td>CYP3A, P-gp</td>
<td>Faeces</td>
<td>P-gp, OATP1B1, BCRP inhibition</td>
<td>Headache, nausea, diarrhoea, arthralgia and cough</td>
<td>14</td>
</tr>
<tr>
<td>Elbasvir</td>
<td>CYP3A, P-gp</td>
<td>Faeces</td>
<td>P-gp, BCRP inhibition</td>
<td>Fatigue, headache, nausea</td>
<td>17,18</td>
</tr>
<tr>
<td>Ledipasvir</td>
<td>P-gp, BCRP</td>
<td>Faeces</td>
<td>P-gp, BCRP inhibition</td>
<td>Headache, fatigue, nausea</td>
<td>23,24</td>
</tr>
<tr>
<td>Pibrentasvir</td>
<td>No metabolism, P-gp (BCRP)</td>
<td>Faeces</td>
<td>CYP3A, UGT1A1, P-gp, BCRP, OATP1B1 and OATP1B3 inhibition</td>
<td>Headache, fatigue, nausea</td>
<td>19,20</td>
</tr>
<tr>
<td>Velpatasvir</td>
<td>Minor metabolism by CYP2B6, CYP2C8 and CYP3A4, P-gp, BCRP</td>
<td>Faeces</td>
<td>P-gp, BCRP, OATP1B1, OATP1B3, OATP2B1 inhibition</td>
<td>Headache, fatigue</td>
<td>29,30</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>P-gp, BCRP</td>
<td>Urine (GS-331007)</td>
<td>—</td>
<td>Headache, fatigue, insomnia, nausea, diarrhoea</td>
<td>23,24</td>
</tr>
<tr>
<td>Protease inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glecaprevir</td>
<td>CYP3A, P-gp, BCRP, OATP1B1 and OATP1B3</td>
<td>Faeces</td>
<td>CYP3A, UGT1A1, P-gp, BCRP, OATP1B1 and OATP1B3 inhibition</td>
<td>Headache, fatigue, nausea</td>
<td>19,20</td>
</tr>
<tr>
<td>Grazoprevir</td>
<td>CYP3A, P-gp, OATP1B1 and OATP1B3</td>
<td>Faeces</td>
<td>CYP3A, BCRP inhibition</td>
<td>Fatigue, headache, nausea</td>
<td>17,18</td>
</tr>
<tr>
<td>Voxelaprevir</td>
<td>CYP3A, P-gp, BCRP, OATP1B1 and OATP1B3</td>
<td>Faeces</td>
<td>P-gp, OATP1B1 and OATP1B3 inhibition</td>
<td>Headache, fatigue, diarrhoea, nausea</td>
<td>33,34</td>
</tr>
</tbody>
</table>

Abbreviations: BCRP, breast cancer resistance protein; CYP, cytochrome; DAA, direct-acting antiviral; PD, pharmacodynamic; Pk, pharmacokinetic.
The main PK/PD characteristics of selected substances of abuse are presented in Table 3.

### 4.1 Opioids

People often start with oral non-medical use of opioids, and move to more efficient routes of administration, such as insufflation, smoking or injection, and possibly initiate heroin use.\(^{35}\) Data on Drug Abuse Trends showed a first increase in the misuse of opioids between 2004 and 2011.\(^{36}\) Synthetic opioids, such as fentanyl, are major contributors to opioid-related overdoses.\(^{37}\) The management of opioid use disorder (OUD) requires an integrated treatment that includes opioid substitution therapy (OST). Methadone was the first medication approved in this indication, and buprenorphine is also approved. Other available options include intravenous diamorphine (medical heroin), levomethadone and slow-release oral morphine.\(^{38}\)

All opioids are metabolized through two major enzyme systems, CYP450 and UGT, but few of them are inhibitors or inducers of metabolizing enzymes or transporters; only methadone is identified as a CYP2D6\(^{39}\) and P-gp inhibitor.\(^{40}\) Excepted methadone, opioids are not expected to be significant perpetrator of CYP- or P-gp-mediated DDI with DAA.

Buprenorphine is a semisynthetic derivative of thebaine with partial opioid agonist properties, metabolized to norbuprenorphine by CYP3A (65%) and to a lesser extent by CYP2C8. Buprenorphine and norbuprenorphine undergo extensive Phase II metabolism by UGT, mainly UGT2B7 (>40%), followed by UGT1A1 and UGT1A3.\(^{41}\)
Fentanyl is a synthetic opioid agonist, 50 times more potent than morphine, metabolized to norfentanyl by CYP3A and transported by P-gp.41

Heroin is rapidly metabolized by a sequential hydrolysis/deacetylation to 6-acetylmorphine (6-AM) and morphine.42 The enzymatic metabolism is mediated mainly by human carboxylesterase 1 (hCE) and in part by hCE-2. Heroin has a very low affinity for μ-opioid receptors, and it acts as a highly lipophilic prodrug of its active metabolites 6-AM, morphine and morphine-6-glucuronide (M6G).43

Methadone is a synthetic opioid receptor agonist generally used as the racemic mixture of (R)- and (S)-methadone.41 It is extensively metabolized by CYP450 enzymes, CYP2B6 being currently recognized as the major isoform in human.44 Methadone is a P-gp substrate.41

Morphine is conjugated mainly by UGT2B7 to the inactive metabolite morphine-3-glucuronide (M3G) and, to a lesser extent, to the pharmacological active compound M6G.41 UGT1A1, 1A3 and 1A9 are also involved but to a lesser extent.43

Oxycodone is a semisynthetic opioid that is mainly (80%) metabolized by CYP3A to noroxycodone, and to a lesser extent (10%) by CYP2D6 to oxymorphone, which is pharmacologically active.41,45

All opioids share a common profile of potential AEs that include among others tolerance and dependence, cognitive effects, sedation, delirium, constipation, vertigo, nausea and respiratory depression.46,47 Reported AE also include cardiovascular effects, the most common being the prolongation of the QT interval, which can lead to torsades de pointes (TdP) and sudden death. The arrhythmogenicity

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### TABLE 3 Main PK and PD characteristics of substances of abuse

<table>
<thead>
<tr>
<th>Drug</th>
<th>Metabolism and transport</th>
<th>Elimination</th>
<th>CYP/transporter inhibition or induction</th>
<th>Main adverse effects</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Opioids</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>CYP3A, CYP2C, UGT2B7, UGT1A1, UGT1A3</td>
<td>Faeces —</td>
<td>—</td>
<td>Tolerance, dependence, cognitive effects, sedation, delirium, constipation, vertigo, nausea, respiratory depression</td>
<td>41,45,46,47</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>CYP3A, P-gp</td>
<td>Urine —</td>
<td>—</td>
<td>As for buprenorphine</td>
<td>41,43,46,47</td>
</tr>
<tr>
<td>Heroin</td>
<td>hCE then as morphine</td>
<td>—</td>
<td>—</td>
<td>As for buprenorphine</td>
<td>43,46,47</td>
</tr>
<tr>
<td>Methadone</td>
<td>CYP2B6, P-gp</td>
<td>Faeces and urine CYP2D6, P-gp inhibition</td>
<td>As for buprenorphine, and QT prolongation, TdP</td>
<td>39,41,44,45,46,47</td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>UGT2B7, UGT1A1, UGT1A3, CYP3A, CYP2C, P-gp</td>
<td>Urine —</td>
<td>—</td>
<td>As for buprenorphine</td>
<td>41,43,45,106,46,47</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>CYP3A, CYP2D6</td>
<td>Urine —</td>
<td>—</td>
<td>As for buprenorphine</td>
<td>41,45,46,47</td>
</tr>
<tr>
<td><strong>Stimulants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amphetamine</td>
<td>CYP2D6, CYP2C</td>
<td>Urine —</td>
<td>—</td>
<td>Anorexia, insomnia, nausea, vomiting, increases in blood pressure and heart rate</td>
<td>49,52,53</td>
</tr>
<tr>
<td>MDMA</td>
<td>CYP2D6 CYP1A2, CYP2B6, CYP3A</td>
<td>Urine</td>
<td>CYP2D6 inhibition</td>
<td>Perceptual disturbances, increases in blood pressure and heart rate, mydriasis, derealization, panic attacks, delirium</td>
<td>54,54,55,56</td>
</tr>
<tr>
<td>Cathinones</td>
<td>CYP2D6</td>
<td>Urine</td>
<td>CYP2D6 inhibition</td>
<td>Tachycardia, hypertension, agitation, hallucinations confusion, creatine kinase elevation</td>
<td>50,56,57</td>
</tr>
<tr>
<td>Cocaine</td>
<td>hCE</td>
<td>Urine —</td>
<td>—</td>
<td></td>
<td>40,59</td>
</tr>
<tr>
<td><strong>Various</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>CYP2C9, CYP3A4</td>
<td>Faeces (65%-80%) and urine (20%-35%)</td>
<td>CYP450, P-gp inhibition (probably minor)</td>
<td>Asthenia, balance problems, confusion, dizziness, dry mouth, fatigue, hallucinations, nausea, vomiting, drowsiness</td>
<td>40,64,66,68</td>
</tr>
<tr>
<td>Ethanol</td>
<td>ADH, CYP2E1, CYP2A1, CYP3A4</td>
<td>Urine, sweat, saliva, tears, expired air</td>
<td>CYP450, P-gp induction?</td>
<td>Depressive effect on the central nervous system: anxiolytic effect, disinhibition of behaviour, sedation, respiratory depression</td>
<td>73-75</td>
</tr>
</tbody>
</table>

Abbreviations: CYP, cytochrome; PD, pharmacodynamics; Pk, pharmacokinetic.
of the main available opioids has been recently reviewed. The website https://credibled meds.org/, created and maintained by Arizona Education and Research on Therapeutics (AZCERT), is also a recommended source of information for drug-induced QT prolongation. This website defines three main categories of risk: known, possible and conditional risk.

Methadone is classified within the known risk category, buprenorphine within the possible risk category and fentanyl, morphine and oxycodone are not classified in any category. There have been many reports and studies showing the potential of methadone to induce QT interval prolongation and TdP even in low doses. Buprenorphine at conventional doses, by itself, does not appear to produce clinically significant QT interval prolongation or polymorphic ventricular arrhythmia.48

4.2 | Stimulants

4.2.1 | Amphetamine and derivatives

Amphetamine and its derivatives, which include 3,4-methylenedioxyamphetamine (MDMA) or ecstasy, belong to the class of β-phenylethylamines and show chemical similarity with the catecholamine neurotransmitters, noradrenaline and dopamine. After marijuana, these stimulants are the second most widely used group of illicit drugs worldwide. HCV infection is frequent among methamphetamine (N-methylated derivative of amphetamine) users as a consequence of unsafe injection methods, and as its use contributes to high-risk behaviours. One study in Veterans Affairs showed that 37% of HCV patients had a history of methamphetamine use. These patients were particularly prone to polysubstance use, alcohol and marijuana in particular.

Amphetamine is metabolized to 4-hydroxyamphetamine via CYP2D6, while isoenzymes of the CYP2C subfamily mediate its deamination pathway. Amphetamine does not exert significant inhibition towards main CYP enzymes or P-gp. Methamphetamine metabolism is also mediated by CYP2D6. Amphetamine and methamphetamine are excreted through the kidneys. MDMA metabolism occurs through two metabolic pathways. O-demethylation followed by catechol-O-methyltransferase (COMT)-catalysed methylation and/or glucuronide/sulphate conjugation; and N-dealkylation, deamination and oxidation to the corresponding benzoic acid derivatives conjugated with glycine. The involved enzymes are CYP2D6 and CYP1A2, and to a lesser extent CYP2B6 and CYP3A4. Moreover, MDMA is also a quasi-reversible inhibitor of CYP2D6, through the formation of a metabolite-intermediate complex.

As stimulants, amphetamines and derivatives can cause increases in blood pressure and heart rate, gastrointestinal symptoms such as nausea, vomiting and abdominal cramps. After high dose and frequent methamphetamine use, psychotic episodes and neurotoxic effects such as memory deficits and impaired psychomotor can occur. MDMA can produce panic attacks, delirium and brief psychotic episodes that usually resolve rapidly when the drug action wears off.

4.2.2 | Cathinones

Synthetic cathinones are derivatives of the parent compound cathinone, a naturally occurring psychostimulant found in the khat plant, Catha edulis. The most common AEs associated with the use of cathinones include tachycardia, hypertension, anxiety/agitation, hallucinations/delusions, confusion and creatine kinase elevation.

In vitro studies have shown that cathinones are mainly metabolized by CYP2D6, but the involvement of other enzymes is possible. For example, mephedrone is mainly metabolized by CYP2D6. A study in healthy users of khat showed that the use of this plant resulted in a CYP2D6 inhibition and a marginal effect on CYP3A4 and CYP2C19 activities, owing to competitive inhibition by cathinone.

Potential interactions between cathinones and DAA are limited.

4.2.3 | Cocaine

Cocaine, the main alkaloid of Erythroxylum coca, is a powerful stimulant whose metabolism is mainly mediated by three esterases, pseudocholinesterase, human carboxylesterase-1 (hCE-1) and 2 (hCE-2). HCE-1 mediates the formation of benzoylecgonine, the main metabolite excreted in the urine. Pseudocholinesterase and hCE-2 catalyse the formation of egonine methyl ester. Approximately, 85% to 90% of a dose are excreted in the urine, including 1% to 5% in unchanged form, and 75% to 90% of a dose as the metabolites benzoylecgonine and egonine methyl ester. Cocaine also undergoes oxidative metabolism by N-demethylation to pharmacologically active norcocaine. This metabolism is catalysed either by CYP3A4 or by a route involving both CYP and flavin-monoxygenases (2-step metabolism in the latter case). Oxidative metabolism to norcocaine represents less than 10% of the biotransformation of cocaine.

Cocaine did not inhibit P-gp and BCRP in vitro. The risk of interaction with DAA is, if any, very limited.

Cocaine blocks the presynaptic reuptake of norepinephrine and dopamine and acts as a powerful sympathomimetic agent. It has been associated with a variety of cardiac and other systemic complications. On the central nervous system, cocaine can cause cerebrovascular, neurological and psychological effects that include intracranial haemorrhage, seizures, movement disorders and psychiatric illness (such as psychosis, depression, decreased appetite). Among the many complications exhibited by cocaine use, cardiovascular toxicities are very prominent and comprise hypertension, coronary spasm, arrhythmias, myocardial infarction, cardiomyopathy, atherosclerosis and coronary artery disease. Pulmonary, hepatic and renal toxicities have also been reported.

4.3 | Various

4.3.1 | Cannabinoids

The cannabis plant (Cannabis sativa) contains more than 100 different cannabinoids. Among them, delta-9-tetrahydrocannabinol (Δ9-THC) and cannabidiol (CBD) are quantitatively important and of...
medical interest. Commonly observed AEs with cannabinoids included: asthenia, balance problems, confusion, dizziness, dry mouth, fatigue, hallucinations, nausea, vomiting and drowsiness.

THC is essentially stored in adipose tissue and is slowly released into the bloodstream, with a long terminal half-life of 25-36 hours. THC metabolism is catalysed by CYP2C9 and CYP3A4. CBD is metabolized by CYP3A4. At high concentrations, THC and CBD have demonstrated a potential inhibitory effect on CYP450 in vitro. Some data suggested that cannabinoids might inhibit P-gp but at high concentrations that are probably not achieved in vivo. Potential interactions with DAA have not been studied but probably appear limited without loss of DAA activity.

4.3.2 | Ethanol

The vast majority of ethanol (>90%) is metabolized by liver alcohol dehydrogenase (ADH), whereas a small fraction (<6%) occurs via CYP2E1. These enzymes are inducible. Even though they account for a small percentage of ethanol metabolism, induction of CYP activity can increase ethanol elimination by more than 25%. The impact of ethanol on drug-metabolizing enzymes seems to differ after acute and chronic ingestion. Several in vivo studies have shown that some components of red wine inhibited CYP3A, and eventually CYP2C19 at high concentrations. However, a study in healthy volunteers suggested the opposite. Indeed, acute red wine led to a 30%-40% decrease in the exposure of ciclosporine, a CYP3A substrate. The authors suggested that the mechanism could be a decrease in ciclosporine solubility and absorption. Consistent with in vitro data, a study in healthy volunteers showed that acute ethanol ingestion resulted in an average 30% increase in the area under the curve (AUC) of diazepam, a CYP2C19 (major pathway) and CYP3A substrate, although this observation was not confirmed by other studies. Other clinical studies have shown the lack of significant impact of acute alcohol ingestion on the PKs of CYP3A substrates (triazolam, zolpidem, felodipine, verapamil, maraviroc, vardenafil).

In an in vitro study, assessing the effects of chronic alcohol exposure on the expression of drug-metabolizing enzymes and drug transporters, ethanol strongly increased the mRNA expression of CYP2C19, CYP2E1 and ABCB1 after 1 and 3 weeks of exposure. Regarding ABCB1, this induction did not translate into an increase in efflux activity. In another in vitro study, ethanol was shown to induce CYP3A4. A study examining the liver biopsy from 12 patients with a history of excessive chronic alcohol consumption reported higher levels of CYP3A as compared to five patients with non-alcoholic hepatitis. In a clinical study involving 20 individuals with moderate chronic alcohol consumption (average 2-3 drinks per day), the disposition of intravenous midazolam, a CYP3A substrate, was not altered as compared to 20 individuals without alcohol consumption. However, the oral availability of midazolam was reduced by 26% in the alcohol group, suggesting CYP3A induction at the small bowel level. In another clinical study evaluating the PK of diazepam (CYP2C19 and CYP3A substrate), the AUC was lower in chronic alcohol drinkers than in healthy subjects, also suggesting an induced diazepam metabolism. In conclusion, a modest induction of CYP3A could be expected in chronic alcohol users, but the change in drug PK may be confounded by the alteration of CYP enzyme activities as a result of chronic liver disease or mild cirrhosis rather than the presence of ethanol in the blood alone.

Alcohol exhibits a dose-dependent effect on the central nervous system that can include disinhibition, sedation and respiratory depression. The cardiovascular effect can manifest as coronary vasodilation after acute consumption, whereas chronic use can lead to increased blood pressure as well as arrhythmias and cardiomyopathy. Other effects associated with alcohol use are pancreatitis and liver diseases such as hepatitis and cirrhosis.

5 | REVIEW OF CLINICAL EVIDENCES

5.1 | Interactions of DAA with opioids

The DDI between DCV and methadone, and the association buprenorphine-naloxone was assessed in a PK study including 25 subjects on stable OST (14 on methadone, 11 on buprenorphine/naloxone). This study showed no clinically relevant effect of DCV on methadone PK, whereas a raise in buprenorphine and norbuprenorphine exposure was observed (buprenorphine: AUC and C_max increased by 30%-40%). However, these increases were not considered to be clinically significant by the authors. None of the opioid had an impact on DCV PK as compared to historical data in healthy volunteers.

The DDI between elbasvir/grazoprevir and buprenorphine/naloxone has been assessed in two PK studies, one in healthy volunteers (13 subjects), and one in patients on stable buprenorphine/naloxone OST (12 subjects). Elbasvir/grazoprevir did not significantly affect the PK of buprenorphine, norbuprenorphine or naloxone. Similarly, the OST had no impact on the PK profiles of EBR and GZR.

The DDI between glecaprevir/pibrentasvir and methadone or buprenorphine/naloxone has been assessed in a PK study in 23 subjects on stable OST (11 on methadone, 12 on buprenorphine/naloxone). No significant impact of glecaprevir/pibrentasvir on methadone and buprenorphine/naloxone PK was observed. The exposures of glecaprevir and pibrentasvir when administered with methadone or with buprenorphine-naloxone were marginally lower than those observed in other studies of glecaprevir and pibrentasvir administered alone in healthy subjects, which could be explained by the reduced rate of gastric emptying induced by opioids, decreasing the absorption of glecaprevir and pibrentasvir. However, these changes in the PK of glecaprevir and pibrentasvir were not considered as clinically significant.

The lack of clinically relevant DDI between glecaprevir/pibrentasvir and OST has been recently confirmed based on data from eight international phase 2 and 3 trials of glecaprevir/pibrentasvir. Among 2256 enrolled patients, 157 patients (7%) were on OST, with 76% receiving methadone. With similar adherence frequencies between OST and non-OST patients (98% and 99% respectively), the SVR 12 rates were high in both groups (96.2% in OST vs 97.9% in non-OST).
patients). The safety profile was comparable, with a modestly higher percentage of patients on OST experiencing AE considered as possibly related to the study drugs (48% vs 40%).83

We did not find published PK studies on DDI between opioids and sofosbuvir-based combination. The lack of effect of sofosbuvir on methadone PK was already reported in the EMA reports of Sovaldi.84 The risk of a clinically relevant DDI with the addition of voxilaprevir is low.34 In a pooled analysis of phase 3 studies, 194 patients (4%) were on OST (113 on methadone, 75 on buprenorphine): the SVR 12 rates were high in both groups (94% in OST vs 97% in non-OST patients). The rates of AE were similar in both groups (78% vs 77%). These results suggest that sofosbuvir-based therapies are effective and safe in patients receiving OST.85 A Canadian cohort study that enrolled 5283 eligible PWSUD treated by sofosbuvir/ledipasvir (n finally treated = 3413) or sofosbuvir/velpatasvir (n treated = 1574) showed that patients with injection drug use (IDU) were less likely to achieve SVR as compared to other groups without IDU (adjusted odds ratio: 1.91 in patients not on OST, and 1.50 in patients on OST). The lower observed SVR among PWID was related to higher loss to follow-up, with a part of this loss related to deaths from drug overdose, rather than detrimental interactions between DAA and OST and/or drugs of abuse.86 Another cohort study compared the efficacy of DAA (sofosbuvir-based therapy as well as paritaprevir-ritonavir/ombitasvir ± dasabuvir and elbasvir/grazoprevir) in patients with or without a history of injecting drug use: among the 1752 patients enrolled, 47% reported no history of injecting drug use and 53% were PWID, with 42% not on OST and 11% on OST (mainly methadone). This study confirmed that the SVR rates were lower among PWID (92% in PWID not on OST, 89% in PWID on OST) compared to patients without a history of injecting drug use (95%). This observation was mainly attributable to higher rates of discontinuations after the occurrence of AEs and, especially, loss to follow-up in PWID, and not to virologic failure.87 The likelihood of potential interactions issues is not plausible.

5.2 | Interactions of DAA with stimulants

No detrimental outcome associated with potential interactions of DAA with stimulants was reported. Based on their respective metabolism and clearance, a clinically significant interaction is unlikely (see the website https://www.hep-druginteractions.org/checker).

5.3 | Interactions of DAA with ethanol

High-risk alcohol consumption was recognized as a factor associated with lower adherence to antiviral treatment and increased propensity of failure with former interferon and ribavirin treatment.88 Few comparable data are available with the DAA.89 Some authors suggested that alcohol consumption may be a risk factor in a lower response to DAA, through different mechanisms: decreased susceptibility of viruses to DAA and decreased immune response to eliminate remaining viruses.90

A study compared the SVR of 1515 veterans treated with DAA according to alcohol consumption. The DAA were as follows: sofosbuvir, ledipasvir/sofosbuvir or omibitasvir-paritaprevir-ritonavir and dasabuvir. Most patients were abstinent (10 387, 69%), while 3422 (23%) had low alcohol consumption, and 1342 (9%) had high-risk drinking. The proportion of patients with SVR was comparable between the three groups: 91.9% (95% CI: 91.3-92.5) vs 93.2 (95% CI: 92.2-94.1) vs 91.4% (95% CI: 89.5-92.9). These results suggested that the response to DAA remained regardless the level of alcohol use.91

A German registry study assessed the impact of alcohol and cannabis consumption on the efficacy of DAA (sofosbuvir-based therapy and paritaprevir-ritonavir/ombitasvir ± dasabuvir). Among the 7747 enrolled patients, 1015 reported alcohol consumption, and 631 of them were not on OST and did not use injected drugs. In these non-OST non-IDU patients with high alcohol consumption, the SVR rates were lower (85%) than in patients consuming no or less than 30 g/day (women) or 40 g/day (men) (91%-92%). Regarding cannabis consumption, SVR rates did not differ between the different patient groups.92

6 | DISCUSSION

The interactions between DAA and substances of abuse have been assessed in four PK phase 1 studies, all involving opioids.80-82 Even though a wide range of phase 3 studies including DAA were performed and taken into account in the review, we did not identify any adverse outcome associated with PK/PD interactions. PK studies with opioids were performed in a limited number of healthy volunteers or patients on OST, whereas no specific PK data on ethanol and stimulants were found. Hence, our hypothesis on the lack of interaction with alcohol and amphetamine derivatives is derived from in vitro PK considerations. Clinical data involving higher numbers of patients were mainly based on post hoc and pooled analysis of phase 2 or 3 studies, whose primary endpoint was SVR.

In PWID (ie 0.34% of the total population in Western Europe), the prevalence of HCV is significantly higher (up to 50%).93 PWID are a key cluster and reservoir because of the interindividual dynamics of HCV transmission. However, only approximately 50% of PWID in Switzerland and in other European countries were adequately screened in the past with at least one antibody test, followed by the HCV RNA quantification if tested positive for antibodies.94

An increased access screening program using rapid antibody saliva test and dried blood spot testing to the PWID population is likely to be highly cost-effective, since the increased uptake of DAA could achieve significant reduction in this vulnerable population. (Incremental Cost-Effectiveness Ratio per Quality-Adjusted Life-Year (QALY); USD 8337 ~ net monetary benefit USD 99 192 per person).95 At a willingness-to-pay threshold approaching USD 100 000 per QALY, an increased access screening program linked to treatment scale-up with DAA is expected to have a 97.0% probability of being cost-effective compared to standard screening methods.

Treatment scale-up with DAA was identified as a requirement to achieve a significant reduction in HCV prevalence in
European countries, including custodial setting as a virus reservoir.

Similarly to the PWID population, comprehensive screening strategies in detention centres are likely to be very worthwhile, with 82.3% probability of cost-effectiveness. Extended screening strategies in the largest custodial setting of Switzerland are expected to achieve positive HCV-RNA identification in 63% instead of 35% of detainees and 117 instead of 65 cures per year compared with current practice.

Associations between blood-borne viral (BBV) diseases and severe mental illnesses were identified and more precisely documented. Before HIV (odds ratio = OR = 2.57) and HBV (OR = 2.29), HCV (OR = 6.18) appears to have the highest risk in people having severe mental illness in Sweden. A systematic review and meta-analysis indicated that pooled prevalence of HCV in people with mental illness was as high as 17.4% in North America (HIV 6%; HBV 2.2%) and 5% in Europe (HIV 1.9%; HBV 2.7%).

In psychiatric patients, the potential for interaction with DAA is particularly critical because of dose-dependent and life-saving AEs, such as torsades de pointes associated with long QT. In psychiatric setting, drug-induced long QT patients had more prevalent HCV infection (41.9% vs 9.8%, \( P < .001 \)) associated with additional T-wave abnormality frequencies (35.5% vs 15.4%, \( P = .003 \)). Independent predictors for long QT tend to cluster and correlate indirectly with chronic HCV infection, such as drug abuse (or uncontrolled intravenous administration), and opiate maintenance program.

This finding is likely explained by the higher number of prescribed drugs in patients with severe mental illness and HCV infection. Altered liver function is further an independent risk factor to develop repolarization abnormalities, including drug-induced long QT. Since the 1970s, patients under a methadone maintenance treatment appeared to have a lower heroin overdose mortality, lower probability of relapse, blood-borne infections (including chronic HCV infection) and criminal activities compared to those who did not receive treatment. Methadone is largely prescribed as maintenance treatment in patients suffering from dependence since it is considered as the most effective opiate substitution. In psychiatric patients and PWID receiving methadone in addition to psychotropic medications (antidepressants, antipsychotics), an impaired liver function with consecutive reduced cytochromes P450 enzymatic activity increases the likelihood of DDI and long QT interval to occur.

Moreover, methadone appears to be more effective than other opiate maintenance treatments in retaining patients in care.

In a cohort study of 1648 patients over a 3-year period, HCV colinfection nearly doubled the propensity of QTc of 470 ms or greater in patients with HIV infection (29.6% vs 15.8%, \( P < .001 \)). In contrast to HIV infection, it is not known whether the HCV viral load is associated with QT interval lengthening. Further, there are associated immunological mechanisms, such as liver kidney microsomal type 1 antibodies triggered by the HCV with reduction in the CYP2D6 activity, the most significant metabolic pathway that metabolizes a wide range of antipsychotics and antidepressants.

A still ongoing case-control study in the largest custodial setting in Switzerland shows a linear correlation between QT interval and methadone dose (personal communication). Initial analyses of the preliminary results suggest that methadone dose, HCV infection and patient age may have an influence that could provide further insight to envision indirect benefit of DAA, to optimize screening and medical management of vulnerable population. There is neither increased propensity of adverse drug reaction nor reported repolarization disorder (eg long QT) in detainees taking DAA.

Overall, it is reasonable to assume that treating chronic hepatitis infection with DAA does not significantly increase the risk of both PK and PD interactions. In high-risk patients such as PWIDs or patient with severe mental illness, the risk of serious drug AEs by adding DAA appears limited. It is expected that screening and treatment of chronic hepatitis C infection as early as possible before hepatic dysfunction are not only cost-effective (limited transmission and complication) but also safe even in the presence of QT interval lengthening drugs.

## 7 | CONCLUSION

The HCV prevalence is significantly elevated in detainees, patients with severe mental illness and PWID. Marginalized populations represent key clusters and reservoir with high dynamic interindividual BBV transmission. These populations further consume a wide range of medications and illicit drugs. Efficacy and safety are paramount during the prescription of DAA. Based on our literature review with PK and PD consideration, the interaction potential of DAA with most opioids and illicit drugs appears rather marginal. Taken together, most DAA mainly inhibit the transmembrane transporter P-gp and to a lesser extent the metabolizing enzyme subfamily CYP3A. Although, theoretically, interactions are plausible with opioids including methadone, these were not confirmed in PK studies. Large phase 3 and cohort studies did not show any clinically significant SVR decrease in PWID taking DAA.

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## CONFLICT OF INTEREST

The authors declared that they have no conflict of interest.

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