Actual and Potential Drug Interactions Between Directly Acting Antivirals (DAAs) and Narcotics

Narcotic	Narcotic Route of Metabolism[1] [2,3]	Boceprevir (Victrelis®, BOC) Merck	Telaprevir (Incivek®, TVR) Vertex Pharmaceuticals	Simeprevir (Galexos®, SMV) Janssen	Sofosbuvir (Sovaldi®) Gilead
		Boceprevir undergoes biotransformation by CYP3A4, CYP3A5 and aldoketoreductases.[4] It is a substrate of p-glycoprotein in vitro.[5] Boceprevir appears to be a strong, reversible inhibitor of CYP3A4/5 and p-glycoprotein.[6] In a healthy volunteer study, boceprevir does not appear to exert significant P-gp inhibition at clinically relevant concentrations.[7]	Substrate and strong inhibitor of CYP3A4 and p-glycoprotein.[8] Telaprevir inhibits renal drug transporters OCT2, MATE1, OATP1B1 and OATP1B3.[9]	Simeprevir mildly inhibits CYP1A2 and CYP3A4 (intestinal, not hepatic). Simeprevir does not induce CYP1A2 or CYP3A4 *in vitro*, and does not affect CYP2C9, CYP2C19 or CYP2D6 *in vivo*. Simeprevir inhibits Organic Anion Transporting Polypeptide 1B1 (OATP1B1; efflux transporter) and P-glycoprotein (P-gp) transporters.[10]	Sofosbuvir is a substrate of P-gp and BCRP. Sofosbuvir has no inhibiting or inducing effects on P450, UGT1A1 and drug transporters (P-gp, BCRP, OATP1B1, OATP1B3, OCT1, BSEP). GS-331007 (primary systemic nucleoside metabolite, accounts for >90% of systemic drug exposure) is not a P-gp substrate, and has no inhibiting or inducing effects on P450, UGT1A1 and drug transporters.
Alfentanil Alfenta®	Parent: CYP3A	Potential ↑ alfentanil concentration.	Potential ↑ alfentanil concentration. Careful monitoring of therapeutic and adverse effects (including respiratory depression) is recommended when telaprevir is coadministered with alfentanil.[8]	Simeprevir mildly inhibits intestinal CYP3A4 activity, while it does not affect hepatic CYP3A4 activity. Co-administration with drugs that are primarily metabolized by CYP3A4 may result in increased plasma concentrations of such drugs.[10]	
Buprenorphine *Partial agonist* BuTrans® (Transdermal Patch) Suboxone® (buprenorphine / naloxone)	Parent: CYP3A4, 2C8 Metabolite (active): norbuprenorphine inhibits CYP3A4, 2D6 (this inhibition is not likely to lead to clinically significant interactions);[11] buprenorphine and norbuprenorphine undergo glucuronidation.[12]	In HCV-negative volunteers on stable, maintenance doses (8/2 mg to 24/6 mg QD) of buprenorphine/naloxone, coadministration of boceprevir 800 mg q8h for 6 days did not have a clinically significant impact on the pharmacokinetics of buprenorphine (AUC ↑ 20%, Cmax ↑ 18%) or naloxone (AUC ↑ 30%, Cmax ↑ 9%).	In HCV-negative volunteers on stable, maintenance doses of buprenorphine/naloxone, coadministration of telaprevir 750 mg q8h for 7 days did not have a clinically significant impact on the pharmacokinetics or pharmacodynamic effects of buprenorphine. Telaprevir exposure was consistent with historical control when co-administered with buprenorphine/naloxone.	Although not studied, no clinically relevant drug-drug interaction is predicted when simeprevir is co-administered with buprenorphine and naloxone.[10]	

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		Boceprevir exposures in the presence of buprenorphine/naloxone were similar (AUC ↓ 12%, Cmax ↓ 18%, Cmin ↓ 5%) to historical controls.[13] Dose adjustment is likely not necessary when boceprevir is co-administered with buprenorphine/naloxone.[13, 14]	Dose adjustment is not necessary when telaprevir is co-administered with buprenorphine/naloxone.[15]		
Butorphanol Apo®-Butorphanol *Agonist/ Antagonist*	Parent: Extensive liver metabolism via oxidation and conjugation to inactive metabolites	Unknown.	Unknown.	Unknown.	
Codeine	Parent: UGT (to codeine-6-glucuronide); >CYP2D6 (to morphine-active) >CYP3A (to norcodeine-active) Rapid metabolizers of codeine via 2D6 may lead to high levels of morphine and toxicity.	Potential ↑ codeine concentrations.	Potential ↑ codeine concentrations.		
Diphenoxylate Lomotil®	Parent: ester hydrolysis Metabolite (active): difenoxine (UGT)	No anticipated effect.	No anticipated effect.		
Fentanyl Duragesic®	Parent: CYP3A	Potential ↑ fentanyl concentrations. Careful monitoring (e.g. respiratory depression) is warranted.	Potential ↑ fentanyl concentrations. Careful monitoring of therapeutic and adverse effects (including respiratory depression) is recommended when telaprevir is coadministered with fentanyl, including extended-release transdermal or transmucosal preparations of fentanyl.[8]	Simeprevir mildly inhibits intestinal CYP3A4 activity, while it does not affect hepatic CYP3A4 activity. Co-administration with drugs that are primarily metabolized by CYP3A4 may result in increased plasma concentrations of such drugs.[10]	
Heroin	Heroin	Potential ↑ opiate	Potential ↑ opiate via	Potential ↑ opiate via	

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	(diacetylmorphine) undergoes deacetylation to 6-monoacetylase morphine and morphine. Morphine undergoes glucuronidation(UGT) to morphine-6-glucuronide. Parent: Deacetylase Metabolite: UGT (6-monoacetylase morphine) Morphine and morphine-6-glucuronide are also P-glycoprotein substrates.	via P-gp inhibition.	P-gp inhibition.	P-gp inhibition.	
Hydrocodone Hycodan®	Parent: CYP2D6, 3A Metabolite (active): hydromorphone via 2D6 Poor metabolizers of 2D6 will not produce hydromorphone and derive little/no analgesic benefit	Potential ↑ hydrocodone concentration.	Potential ↑ hydrocodone concentration.	Potential ↑ hydrocodone concentration.	
Hydromorphone Dilaudid® Jurnista®	Parent: UGT> ketoreductase	No anticipated effect.	No anticipated effect.	No anticipated effect.	
Levomethadyl (LAAM; levo-alpha-acetyl methadol) Orlaam® USA Note: product D/C due to severe cardiac events including QT prolongation (April 2004)	Parent: CYP3A4 Metabolites: norLAAM, dinorLAAM[16]	Potential ↑ LAAM concentration.	Potential ↑ LAAM concentration.	Potential ↑ LAAM concentration.	
Loperamide Imodium®	Parent: CYP 2C8, 3A4, UGT, Pgp	Potential ↑ loperamide concentration.	Potential ↑ loperamide concentration.	Significant interaction not anticipated.	
Meperidine Demerol®	Parent: CYP2B6>>3A4> 2C19	Potential ↑ meperidine concentration, but	Potential ↑ meperidine concentration, but	Significant interaction not anticipated.	

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	Metabolite: normeperidine[17]	likely not significant.	likely not significant.		
Methadone	Parent: CYP3A, 2B6 (*S* isomer), 2C19 (*R** isomer), 2D6 Inhibits: CYP2D6 (weak) * The *R* isomer is more active The *S* isomer is more toxic	In HCV-negative volunteers on stable, maintenance doses (20-150 mg QD) of methadone, boceprevir 800 mg q8h was coadministered for 6 days. In the presence of boceprevir, exposures of R-methadone were decreased (AUC ↓ 16%, Cmax ↓ 10%) and S-methadone were decreased (AUC ↓ 22%, Cmax ↓ 17%). These changes did not result in clinically significant effects including withdrawal. Boceprevir exposures in the presence of methadone were similar (AUC ↓ 20%, Cmax ↓ 38%, Cmin ↑ 3%) to historical controls.[13] Dose adjustment is likely not necessary when boceprevir is co-administered with methadone.[13, 14] Clinical monitoring is recommended, with dose adjustments of methadone if necessary during concomitant treatment with boceprevir.[5]	In HCV-negative volunteers on stable methadone maintenance therapy (median methadone dose 85 mg, range 40-120 mg/day), telaprevir 750 mg q8h was co-administered for 7 days. In the presence of telaprevir, R-methadone Cmin ↓ 31%, Cmax ↓ 21% and AUC ↓ 21%. The AUC ratio of S-/R-methadone was comparable before and during coadministration of telaprevir. The median unbound fraction of R-methadone ↑ from 7.92% to 9.98% during coadministration with telaprevir, but the median unbound Cmin of R-methadone was similar before and during telaprevir coadministration. A priori methadone dose adjustments are not required when initiating telaprevir, but close monitoring is recommended, with dose adjustments if necessary.[5, 18]	The interaction between simeprevir and methadone was evaluated in clinical studies of healthy subjects; no dose adjustments are needed for either drug.[10]	In 14 HCV-negative subjects on stable methadone (30-105 mg daily), administration of sofosbuvir 400 mg QD did not result in a significant effect on the pharmacokinetics of either R-methadone (1% ↑ Cmax and AUC) or S-methadone (5% ↓ Cmax and AUC) and no subjects experienced symptoms of opiate withdrawal. Sofosbuvir and methadone may be coadministered without dose adjustment.[19]
Morphine	Parent: UGT Metabolite (active): morphine-6-glucuronide (renal)	No anticipated effect.	No anticipated effect.	No anticipated effect.	
Nalbuphine Nubain® *Agonist/*	Parent: liver metabolism to inactive	Unknown.	Unknown.	Unknown.	

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antagonist	metabolites				
Naloxone *Opioid antagonist* Suboxone® (buprenorphine / naloxone) Targin® (naloxone/ oxycodone)	Parent: UGT	In HCV-negative volunteers on stable, maintenance doses (8/2 mg to 24/6 mg QD) of buprenorphine/naloxone, coadministration of boceprevir 800 mg q8h for 6 days did not have a clinically significant impact on the pharmacokinetics of buprenorphine (AUC ↑ 20%, Cmax ↑ 18%) or naloxone (AUC ↑ 30%, Cmax ↑ 9%). Boceprevir exposures in the presence of buprenorphine/naloxone were similar to historical controls. Dose adjustment is likely not necessary when boceprevir is co-administered with buprenorphine/naloxone.[14]	In HCV-negative volunteers on stable, maintenance doses of buprenorphine/naloxone, coadministration of telaprevir 750 mg q8h for 7 days did not have a clinically significant impact on the pharmacokinetics or pharmacodynamic effects of buprenorphine. Telaprevir exposure was consistent with historical control when co-administered with buprenorphine/naloxone. Dose adjustment is not necessary when telaprevir is co-administered with buprenorphine/naloxone.[15]	No anticipated effect.	
Naltrexone *Opioid antagonist* ReVia®	Parent: Not via CYP450; metabolized via dihydrodiol dehydrogenase Metabolite (active): 6-B-naltrexol	No anticipated effect.	No anticipated effect.	No anticipated effect.	
Oxycodone OxyContin® OxyNEO® Supeudol® Endocet® Percocet® (acetaminophen/ oxycodone) Targin® (naloxone/ oxycodone)	Parent: CYP2D6, 3A4 Metabolites (active): oxymorphone via 2D6; noroxycodone via 3A4. Poor 2D6 metabolizers will not get analgesic effect.	Potential ↑ oxycodone concentration.	Potential ↑ oxycodone concentration.		
Pentazocine *Agonist/ antagonist*	Parent: extensive liver metabolism with inactive	Unknown.	Unknown.	Unknown.	

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Talwin®	glucuronide metabolite				
Propoxyphene Darvon-N® *(discontinued in 2010 due to risk of QT prolongation)*	Parent: extensive liver metabolism Metabolite (active): norpropoxyphene	Unknown.	Unknown.	Unknown.	
Tramadol Ralivia®, Tridural®, Ultram®, Zytram XL® Tramacet® (acetaminophen/ tramadol)	Parent: CYP 3A4, 2B6, CYP2D6 Metabolite (active): O-desmethyl tramadol via 2D6[20] Inhibition of 2D6 may lead to ↓ therapeutic response	Potential ↑ tramadol concentration.	Potential ↑ tramadol concentration.		

Legend: CYP = cytochrome P450, P-gp = p-glycoprotein, UGT = Uridine 5'-diphospho-glucuronosyltransferases

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