Antidepressant Use in Hepatitis C:
Level of Evidence for Prophylactic and Symptomatic Treatment of Depression in HCV and Actual/Potential Drug Interactions with Directly Acting Antivirals (DAAs)

Level of Evidence*	Antidepressant (route of metabolism)	Known or Potential Interactions with DAAs	Comments
Level 1[1, 2]	Escitalopram (Cipralex®) (CYP2C19, 3A4 >> 2D6)	21% ↓ AUC, 19% ↓ Cmax of escitalopram with boceprevir.[3] 35% ↓ escitalopram AUC with telaprevir.[4] 3% ↑ Cmax , no change in AUC or Cmin of escitalopram with simeprevir; 20%↓ Cmax, 25% ↓ AUC and 32% ↓ Cmin of simeprevir. These changes are not considered clinically significant.[5] No clinically relevant changes when coadministered with asunaprevir.[6]	Boceprevir: escitalopram dose may need to be adjusted.[7] Telaprevir: May need to titrate escitalopram dose according to clinical response.[8] Simeprevir: may be coadministered without dose adjustment. Asunaprevir: May coadminister escitalpram without dose adjustments.[6]
Level 2[9, 10]	Citalopram (Celexa®) (CYP2C19, 3A4 >> 2D6)	Potential for ↓ antidepressant concentrations with boceprevir and telaprevir based on escitalopram interaction data. No significant interaction predicted with asunaprevir.	Monitor and titrate dose according to clinical response.
	Paroxetine (Paxil®) (CYP2D6)	No interaction expected based on known pharmacologic characteristics.	Monitor and titrate dose according to clinical response. NB: Evidence in RCT for depressed mood component of major depression only
Level 4	Nortriptyline (Aventyl®) (CYP2D6)	No interaction expected based on known pharmacologic characteristics.	Monitor and titrate dose according to clinical response.
	Bupropion (Wellbutrin®) (CYP2B6) Fluoxetine (Prozac®) (CYP2D6)	No interaction expected based on known pharmacologic characteristics.	Monitor and titrate dose according to clinical response.

Level of Evidence*	Antidepressant (route of metabolism)	Known or Potential Interactions with DAAs	Comments
	Sertraline (Zoloft®) (CYP2B6 > 2C9/19, 3A4, 2D6, UGT1A1 - possible) Mirtazapine (Remeron®) (CYP2D6, 1A2, 3A4) Venlafaxine (Effexor®) (CYP2D6 > CYP3A4)	Potential for ↑ sertraline, mirtazapine, venlafaxine concentrations with boceprevir or telaprevir (clinical significance unknown). No clinically relevant changes when sertraline is coadministered with asunaprevir.[6]	Use with caution in the presence of boceprevir or telaprevir; monitor and titrate dose according to clinical response. Asunaprevir: May coadminister sertraline without dose adjustments.[6]
	Desvenlafaxine (Pristiq®) (UGT)[11, 12]	No interaction expected based on known pharmacologic characteristics.	Monitor and titrate antidepressant dose according to clinical response.
	Tricyclic antidepressants i.e. desipramine (CYP2D6>>UGT), imipramine (CYP2D6, 1A2, 2C19, 3A > UGT), trazodone (CYP2D6> CYP3A)	Potential increase in TCA concentrations resulting in dizziness, hypotension and syncope.	Use with caution with DAAs, lower TCA doses are recommended.[7, 8] NB: Trazodone is primarily used clinically for treating insomnia in HCV.
Inconclusive evidence as monotherapy	Modafinil (Alertec®) (CYP3A4; may induce 3A4)	Potential for ↑ modafinil concentrations and/or ↓ DAA concentrations.	Use with caution; monitor and titrate antidepressant dose according to clinical response. Monitor for efficacy to HCV therapy.
	Amantadine (Symmetrel®) (minimal metabolism)	No interaction expected based on known pharmacologic characteristics.	Monitor and titrate dose according to clinical response.
	St. John's Wort (hypericum perforatum); induces CYP3A4 and P-gp.[13]	Potential for ↓ DAA concentrations.	St. John's Wort is contraindicated with boceprevir and telaprevir.[7, 8]
Avoid (exceptional circumstances only)	Duloxetine (Cymbalta®) (CYP1A2, 2D6)	Duloxetine: risk of hepatotoxicity.	Duloxetine is contraindicated in liver disease.
	Nefazodone (Serzone®) (CYP3A4)	Nefazodone: potential for ↑ nefazodone and/or DAA concentrations; also risk of hepatotoxicity.	Nefazone was discontinued in the United States and Canada in 2003 due to hepatotoxicity concerns. Avoid use in liver disease.

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

***Level of Evidence for Prophylactic and Symptomatic Treatment of Depression in HCV**

	Criteria
Level 1	≥ 2 randomized controlled trials or meta-analysis
Level 2	1 randomized controlled trial
Level 3	Prospective open label study (n ≥ 10)
Level 4	Anecdotal or expert opinion

References:

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