MAT in Patients with Liver Disease

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National Drug Overdose Deaths Involving Any Opioid. Number Among All Ages, by Gender, 1999-2017

USA

Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2017 on CDC WONDER Online Database, released December, 2018
Epidemiology of Opioid Use and Liver Disease

• Prevalence of opioid prescription among patients with cirrhosis was 37.1 per 100 person-years and greater than in the following in those ages 30-59.
  • HCV without cirrhosis
  • CHF and COPD

• High-dose opioids and dual opioid and benzodiazepines also higher in patient with cirrhosis.


Figure 1  Proportion of patients using both opioids and benzodiazepines, years 2009–2015, by age and type of disease. CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; HCV, hepatitis C virus.
Understanding Opioid Use Disorder

• Chronic, relapsing disease involving brain reward, motivation, and related circuitry characterized by **compulsive drug seeking and use despite harmful consequences**\(^1,2\)

• Abstinence-based programs have low success rates\(^3,4\)

• Best treated with long-term pharmacological therapies targeting the mu receptor, with longer-term retention on treatment resulting in the best treatment outcomes\(^5\)

Metabolism of Methadone and Buprenorphine
Methadone Metabolism

Fig. 1. Eleven methadone metabolites found in human excretion. *Indicates chiral carbon atom. ADH, alcohol dehydrogenase; CYP, cytochrome P450; EDDP, 2-ethyl-1,5-dimethyl-3,3-diphenylpyrroloidine; EMDP, 2-ethyl-5-methyl-3,3-diphenyl-1-pyrroline; p-HO, para-hydroxy.
Buprenorphine Metabolism

Fig. 5. The metabolism of buprenorphine to norbuprenorphine and inactive metabolites. Buprenorphine undergoes N-dealkylation to norbuprenorphine via CYP3A4 (and CYP2C8, CYP3A5, and CYP3A7, according to in vitro studies) and glucuronidation via UGT1A1, UGT1A3, and UGT2B7 to inactive metabolites. Norbuprenorphine also undergoes glucuronidation via UGT1A1, UGT1A3, and UGT2B7 to inactive metabolites.

Exposure of Buprenorphine/Naloxone in Mild, Moderate, and Severe Liver Impairment

Fig. 1 Mean plasma concentration-time profiles on linear scale of (a) buprenorphine, (b) norbuprenorphine, (c) naloxone, and (d) naloxone-3-β-D-glucuronide in subjects with mild, moderate, and severe hepatic impairment (groups 1, 2, and 3), HCV-infected subjects (group 4) and healthy subjects (group 5) after sublingual administration of Suboxone (2.0/0.5 mg).

Monitoring Recommendations

- LFTs, bilirubin, PT/INR and albumin should be drawn prior to initiation of MAT but it should not hold up treatment
  - No labs are necessary before starting naltrexone
- Obtain Hepatitis B and C panels before MAT
- Monitor LFTs on a periodic basis
  - No set guidance on how often
- Patients should be aware of signs/symptoms of acute liver failure
Drug Interactions with Hepatitis C Agents On the Market Before 2015

Table 2. Drug-Drug Interactions (DDIs)\(^a\) Between DAAs, Methadone, and Buprenorphine.\(^b\)

<table>
<thead>
<tr>
<th>HCV Antiviral Agents</th>
<th>Methadone</th>
<th>Buprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boceprevir</td>
<td>No clinically significant DDI(^{1,64})</td>
<td>No clinically significant DDI(^{1,64})</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>No clinically significant DDI(^{1,97})</td>
<td>NI (monitor for adverse events of buprenorphine)</td>
</tr>
<tr>
<td>Telaprevir</td>
<td>R-methadone AUC 21% ↓ Monitor for withdrawal; ↑ in dose may be required, S-methadone in the racemic mixture has potential for QT prolongation, ECG useful(^{1,70})</td>
<td>No clinically significant DDI(^{1,68})</td>
</tr>
<tr>
<td>Grazoprevir MK-5172 (investigational)</td>
<td>No clinically significant DDI(^{1,66})</td>
<td>No clinically significant DDI(^{1,66})</td>
</tr>
<tr>
<td>Paritaprevir/ritonavir</td>
<td>No clinically significant DDI(^{1,65})</td>
<td>No clinically significant DDI(^{1,65})</td>
</tr>
<tr>
<td>NSSB nucleoside inhibitor</td>
<td>No clinically significant DDI(^{1,65})</td>
<td>No clinically significant DDI(^{1,65})</td>
</tr>
<tr>
<td>Dasabuvir</td>
<td>No clinically significant DDI(^{1,98})</td>
<td>NI (DDI not expected)</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>No clinically significant DDI(^{1,98})</td>
<td>NI (DDI not expected)</td>
</tr>
<tr>
<td>NSSA inhibitors</td>
<td>No clinically significant DDI(^{1,99})</td>
<td>No clinically significant DDI(^{1,99})</td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>No clinically significant DDI(^{1,99})</td>
<td>No clinically significant DDI(^{1,99})</td>
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<tr>
<td>Ledipasvir</td>
<td>No clinically significant DDI(^{1,99})</td>
<td>No clinically significant DDI(^{1,99})</td>
</tr>
<tr>
<td>Elbasvir MK-8742 (investigational)</td>
<td>No clinically significant DDI(^{1,68})</td>
<td>No clinically significant DDI(^{1,68})</td>
</tr>
<tr>
<td>Ombitasvir</td>
<td>No clinically significant DDI(^{1,65})</td>
<td>No clinically significant DDI(^{1,65})</td>
</tr>
</tbody>
</table>

Abbreviations: AUC, area under the (concentration-time) curve; DAA, direct-acting antiviral; ECG, electrocardiogram; HCV, hepatitis C virus; NI, not investigated; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PK, pharmacokinetic.

\(^a\)May not be all inclusive.

\(^b\)Modified from HEP-DrugInteractions.org,\(^b\) Tseng,\(^b\) and Gruber and McCance-Katz.\(^b\)

\(^c\)PK-study, drug-drug interaction between antiretroviral drug and DAAs has to be considered in HIV/HCV-coinfected patients.\(^c\)

OST and HCV Therapy: Drug–Drug Interactions

<table>
<thead>
<tr>
<th></th>
<th>EBR/GZR</th>
<th>GLE/PIB</th>
<th>LDV/SOF</th>
<th>SOF/VEL</th>
<th>SOF/VEL/VOX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine</td>
<td></td>
<td></td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Methadone</td>
<td></td>
<td></td>
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<tr>
<td>Naloxone</td>
<td></td>
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<tr>
<td>Naltrexone</td>
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</tbody>
</table>

- Do not coadminister
- Potential weak interaction
- No interaction expected
No Clinical Interactions Between Methadone with Glecaprevir/Pibrentasvir

Kosloski, MP et al. Animicrob Agents Chemother. 2017 Sep 22;61(10)/
No Clinical Interactions Between Buprenorphine with Glecaprevir/Pibrentasvir

Kosloski, MP et al. *Animicrob Agents Chemother.* 2017 Sep 22;61(10)/
Colocalized Drug and HCV Treatment: Buprenorphine Treatment Retention May Improve Cascade of HCV Care

![Bar chart showing the percentage of clients referred, evaluated, offered, and initiated HCV treatment, with associated p-values.]


Slide credit: clinicaloptions.com
Clinical Case Presentations:
Patient living with OUD, HIV, HCV

- 62 y/o Black Woman
- OUD for 35 years with episodes of remission for multiple years with abstinence only programs and recent relapse
- HIV well controlled with Abacavir/Dol/Lamivudine
- HTN, Nicotine Dependence, COPD

- 2 grown children, 3 grandchildren, works in social services
- Patient very committed to recovery process and starting treatment for HCV but was concerned that she would not remain in recovery without MAT
- Next step?
Enrolled in Methadone program
OUD/MAT group therapy
Continued individual counselling
Presented back in 3 months requesting to start HCV rx
UDS only positive for methadone

Routine LFTS, Hep B serology, HIV and HCV viral load repeated
Began Glecaprevir/Pibrentasvir
8 weeks completed with no complications, LFTS checked at 1 month rx
HCV vl undetectable at end of treatment
12 week SVR pending
Patient living with OUD, HCV, recent osteomyelitis

- 55 y/o White man
- OUD for 15 years, initially recreational use but now daily use, had episodes of reduced use but no sobriety
- Was seeing provider for treatment of osteomyelitis and epidural abscess
- Incidental discussion about abnormal LFTS leads to diagnosis of HCV

- Separated, 3 grown children, one daughter is a RN
- Felt that he wanted to "do well and was tired of being hooked on things"
- LFTS 2-3x upper limit of normal at base line, Genotype 1a, Fibroscan F2 moderate fibrosis, Hep B immune through vaccination, receives Hep A vaccine
- Next step?
Case presentation continued:

• Started buprenorphine
• By 2 months had cut down use of heroin but was still using 1-2 bags every other day
• Individual counselling
• Wanted to start HCV rx
• LFTS still 2-3 x upper limit of normal
• Started Glecaprevir/pibrentasvir

• One month on rx LFTS normalized
• Completed 8 weeks rx
• Still using heroin occasionally
• Began Emtricitabine/Tenofovir for HIV prevention
• 12 weeks SVR for HCV
• Remains on buprenorphine and is bringing in wife for HCV and MAT visit
Patient living with OUD, HIV, HCV, Laryngeal Cancer

<table>
<thead>
<tr>
<th>45 y/o Black woman</th>
<th>HCV associated chronic hepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>OUD for 25 years with periods of heavy use alternating with sporadic use, currently used heroin to also self-medicate for pain associated with invasive laryngeal cancer</td>
<td>Fibroscan with F3 severe fibrosis</td>
</tr>
<tr>
<td>Missed appointments with Radiation Oncology due to drug use-now with progression of disease</td>
<td>HIV viral load sub optimally controlled due to missed doses due to drug use</td>
</tr>
<tr>
<td></td>
<td>Team meeting with Oncology, ID, Advanced Case Management, ENT</td>
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<tr>
<td></td>
<td>Goals of care discussion with patient</td>
</tr>
</tbody>
</table>
Case presentation continued:

- Patient wanted to begin MAT to improve adherence with visits and treatment goals while still having pain control
- Base line LFTs, HIV viral load, CBC, CMP done
- Started Buprenorphine with planned titration to TID and improved pain control
- LFTs checked at one month and at 3 months-no increase
- HIV viral load undetectable at 6 weeks
- Patient able to present to appointments and to have total laryngectomy
- Still using Heroin sporadically but keeping appointments with ID and adherent to ENT Surgery and Oncology follow up
Thank you!
Any questions?