MAT in Patients with Liver Disease

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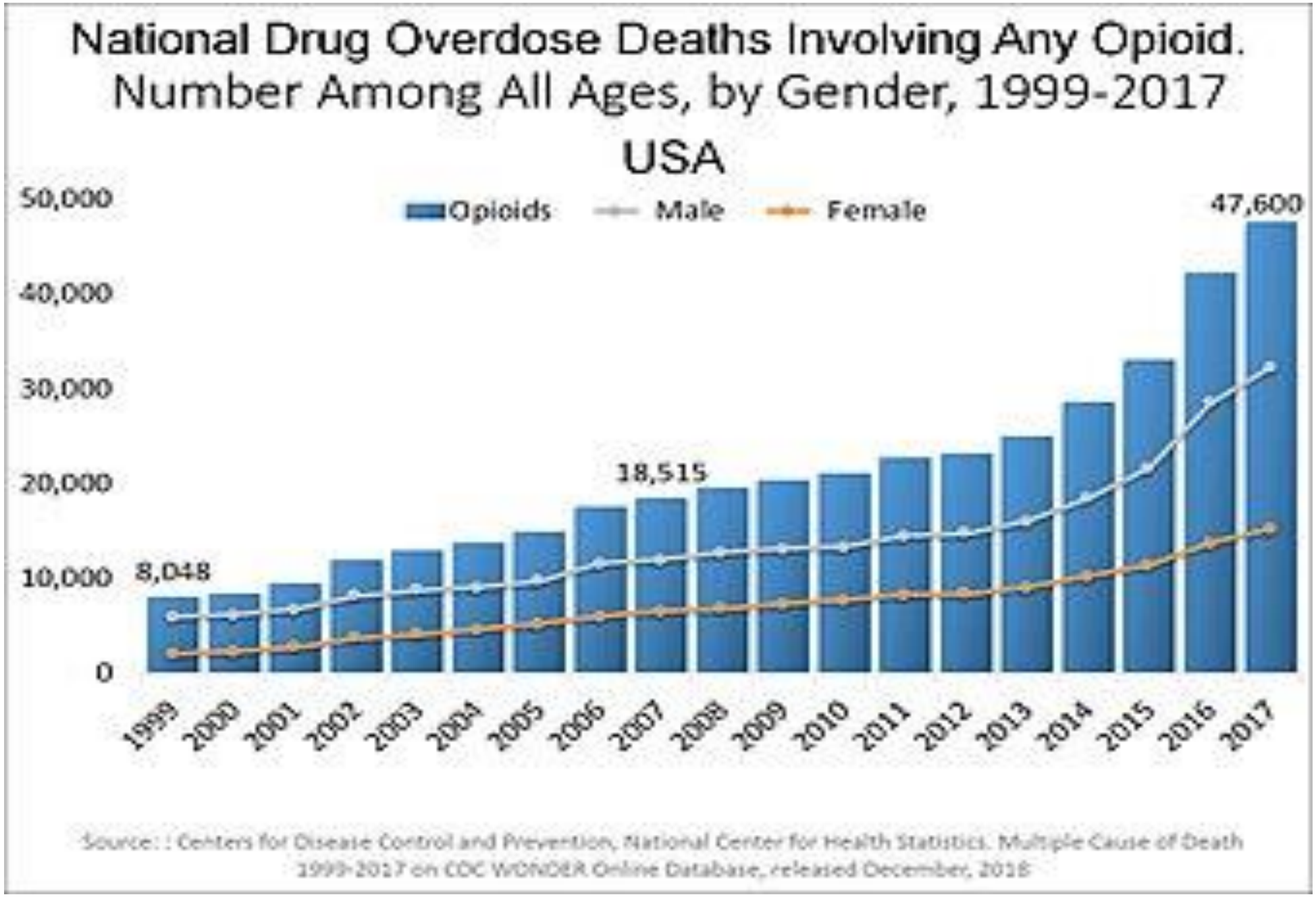

National Drug Overdose Deaths Involving Any Opioid.
Number Among All Ages, by Gender, 1999-2017
USA
Opioids
Male
Female
50,000
40,000
30,000
20,000
10,000
0
8,048
18,515
47,600
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
Source: : Centers for Disease 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.

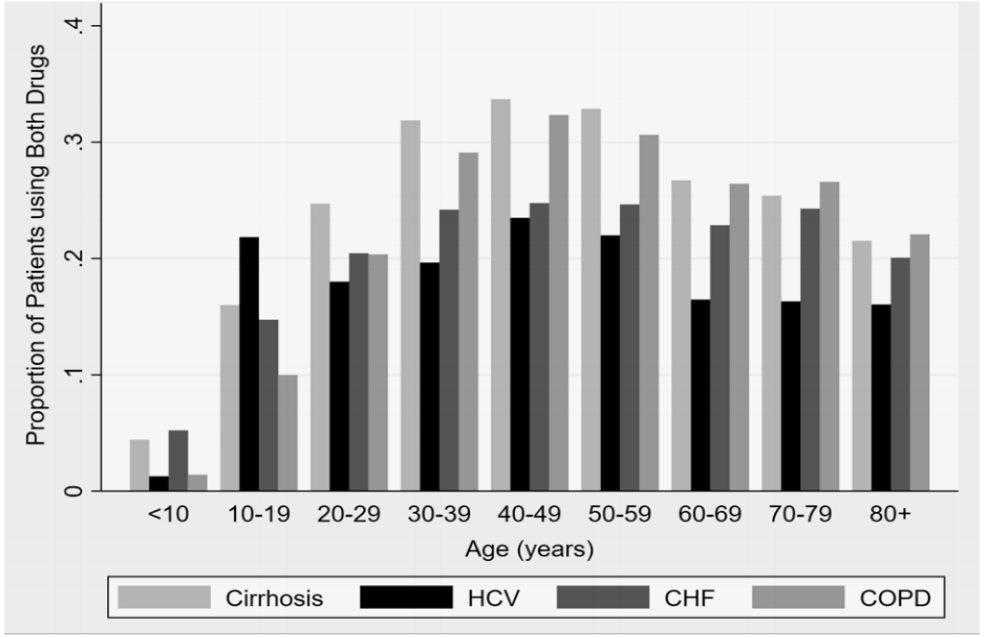
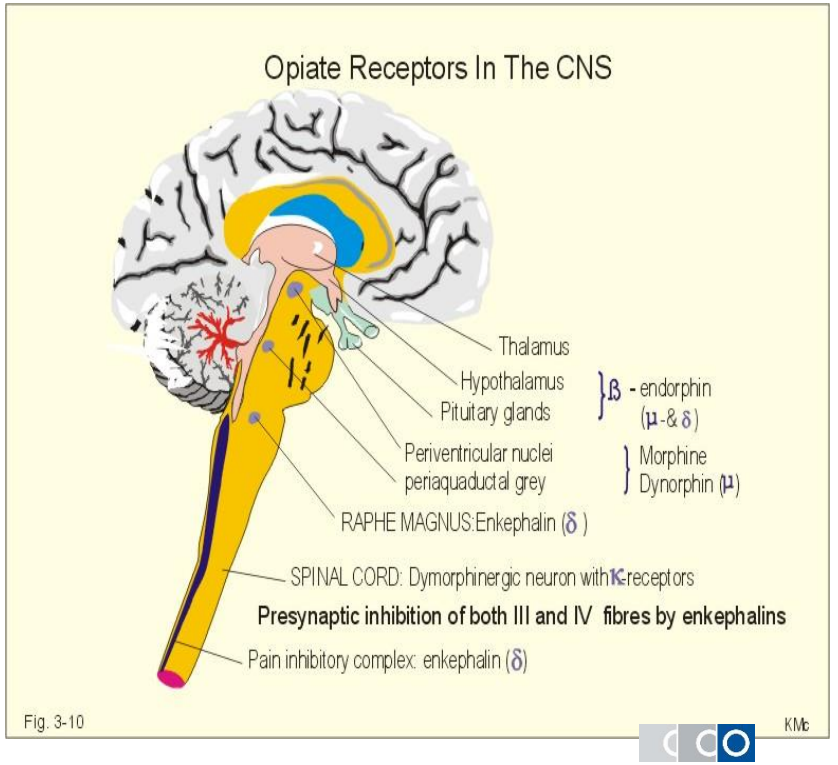


Figure 1 Proportion of patients using both opioids and benzodiazepines, years 2009–2015, by age and type of disease. CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; HCV, hepatitis C virus.

Konerman MA, et al. *BMJ Open Gastroenterol.* 2019 Apr 14;6(1):e000271.

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]



Slide credit: clinicaloptions.com

1. American Society of Addiction Medicine. Definition of addiction. Adopted April 12, 2011. 2. NIDA. Drugs, brains, and behavior: the science of addiction. Updated July 2014. 3. Mattick RP, et al. Cochrane Database Syst Rev. 2003;2:CD002209. 4. Wegman MP, et al. Lancet Global Health. 2017;5:e198-e207. 65 Volkow ND, et al. N Engl J Med. 2016;374:1253-1263.

Metabolism of Methadone and Buprenorphine

Methadone Metabolism

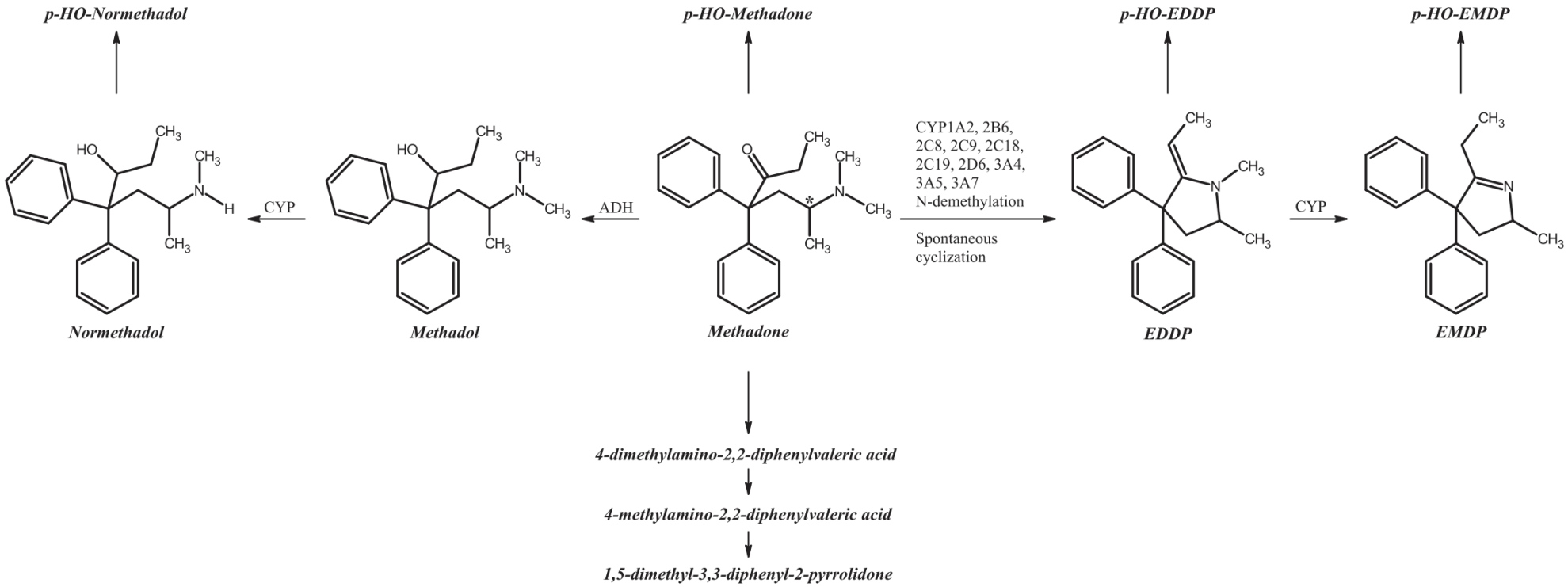


Fig. 1. Eleven methadone metabolites found in human excretion. *Indicates chiral carbon atom. ADH, alcohol dehydrogenase; CYP, cytochrome P450; EDDP, 2-ethyl-1,5-dimethyl-3 diphenylpyrrolidine; EMDP, 2-ethyl-5-methyl-3,3-diphenyl-1-pyrroline; *p*-HO, para-hydroxy.

Buprenorphine Metabolism

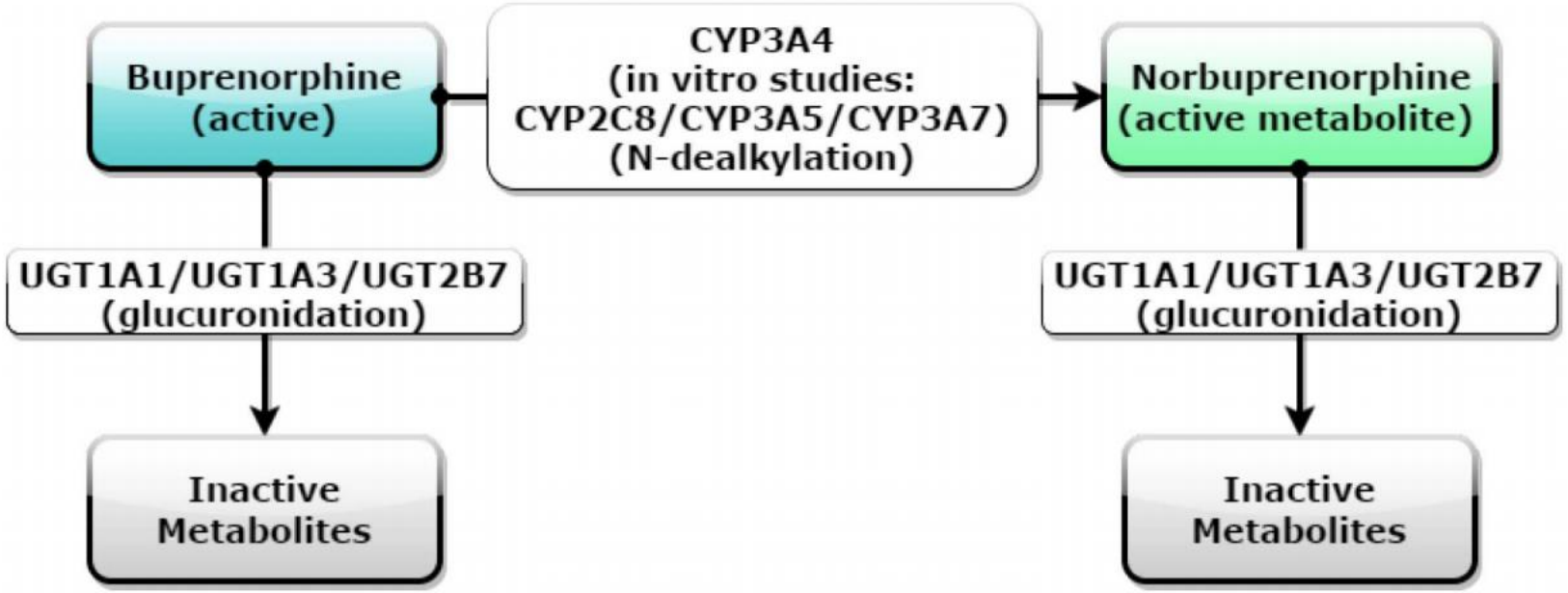


Fig. 5. The metabolism of buprenorphine to norbuprenorphine and inactive metabolites.Buprenorphine undergoes N-dealkylation to norbuprenorphine via CYP3A4 (and CYP2C8, CYP3A5, and CYP3A7, according to in vitro studies) and glucuronidation via UGT1A1, UGT1A3, and UGT2B7 to inactive metabolites. Norbuprenorphine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

Ettienne EB, et al. *Addict Behav Rep.* 2017 May 8;7:8-14.

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

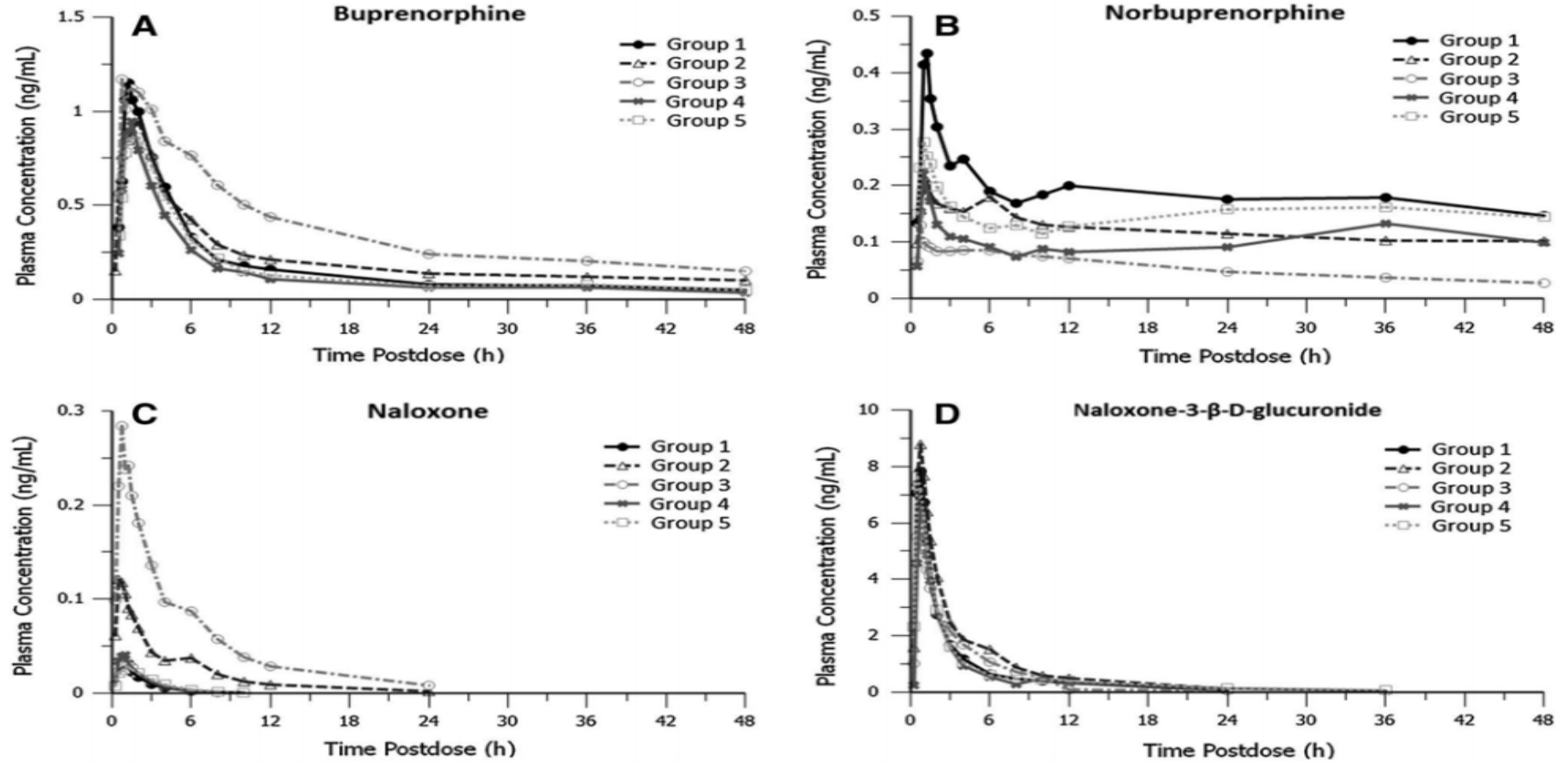


Fig. 1 Mean plasma concentration-time profiles on linear scale of **a** buprenorphine, **b** norbuprenorphine, **c** naloxone, and **d** naloxone-3-β-D-glucuronide in subjects with mild, moderate, and severe hepatic impairment (groups 1, 2, and 3), HCV-infected subjects (group 4) and healthy subjects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

Nasser AF, et al. *Clin Pharmacokinet.* 2015 Aug;54(8):837-49.

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]

HCV Antiviral Agents	Methadone	Buprenorphine
HCV protease inhibitors		
Boceprevir	No clinically significant DDI[c,64]	No clinically significant DDI[c,64]
Simeprevir	No clinically significant DDI[c,97]	NI (monitor for adverse events of buprenorphine)
Telaprevir	*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[c,70]	No clinically significant DDI[c,68]
Grazoprevir MK-5172 (investigational)	No clinically significant DDI[c,66]	No clinically significant DDI[c,66]
Paritaprevir/ritonavir	No clinically significant DDI[c,65]	No clinically significant DDI[c,65]
NS5B nucleoside inhibitor		
Dasabuvir	No clinically significant DDI[c,65]	No clinically significant DDI[c,65]
Sofosbuvir	No clinically significant DDI[c,98]	NI (DDI not expected)
NS5A inhibitors		
Daclatasvir	No clinically significant DDI[c,99]	No clinically significant DDI[c,99]
Ledipasvir	NI (DDI not expected)	NI
Elbasvir MK-8742 (investigational)	No clinically significant DDI[c,68]	NI
Ombitasvir	No clinically significant DDI[c,65]	No clinically significant DDI[c,65]

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,[8] Tseng,[9] and Gruber and McCance-Katz.[11]

[c]PK-study; drug-drug interaction between antiretroviral drug and DAAs has to be considered in HIV/HCV-coinfected patients.[100]

Meemken L, et al. *Ann Pharmacother.* 2015 Jul;49(7):796-807.

OST and HCV Therapy: Drug–Drug Interactions

- Do not coadminister
- Potential weak interaction
- No interaction expected

	EBR/GZR	GLE/PIB	LDV/SOF	SOF/VEL	SOF/VEL/VOX
Buprenorphine					
Methadone					
Naloxone					
Naltrexone					

https://www.hep-druginteractions.org

Slide credit: clinicaloptions.com

No Clinical Interactions Between Methadone with Glecaprevir/Pibrentasvir

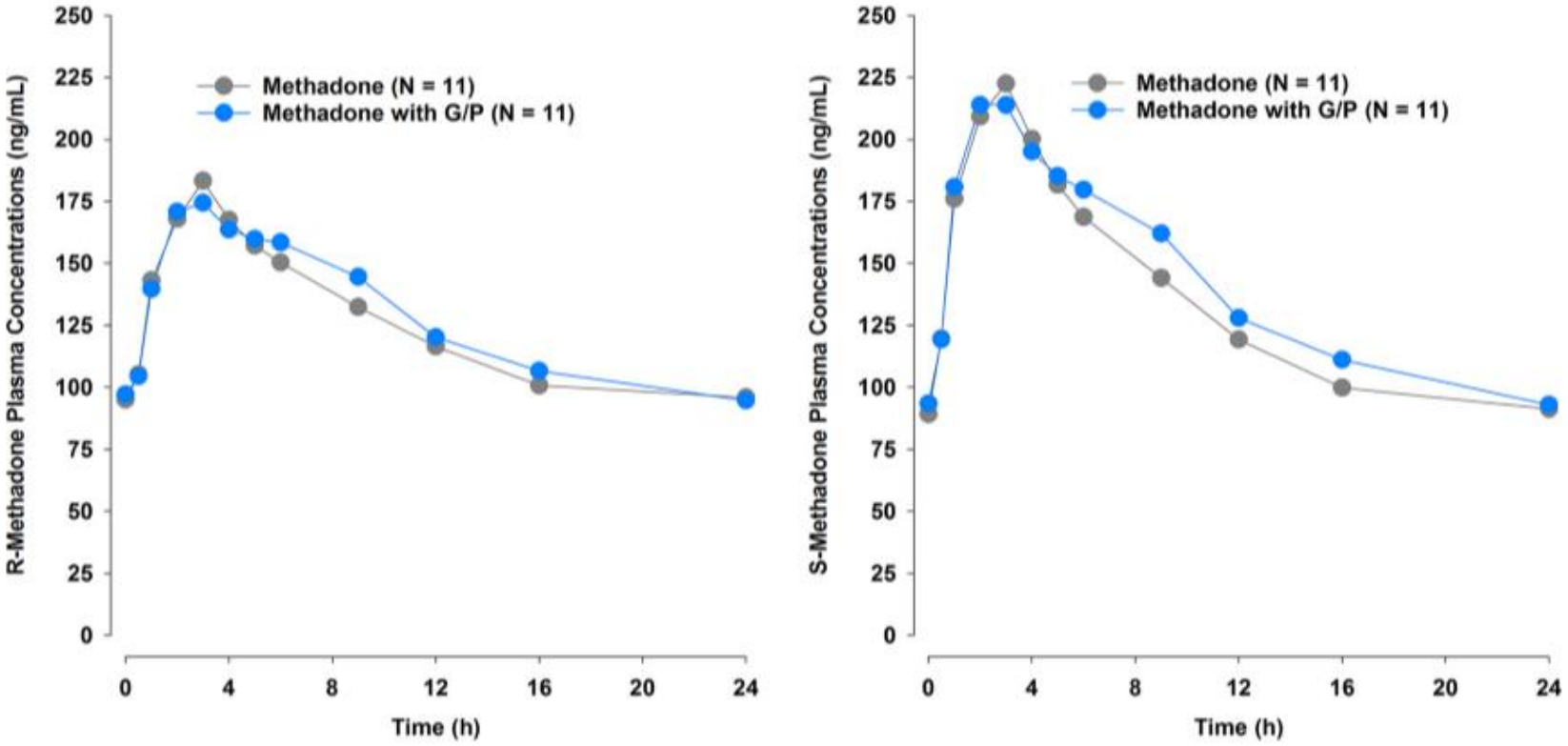


FIG 1 Mean (*R*)-methadone and (*S*)-methadone plasma concentration time profiles for methadone administered QD alone or with glecaprevir and pibrentasvir (G/P) QD.

Kosloski, MP et al. *Animicrob Agents Chemother.* 2017 Sep 22;61(10)/

No Clinical Interactions Between Buprenorphine with Glecaprevir/Pibrentasvir

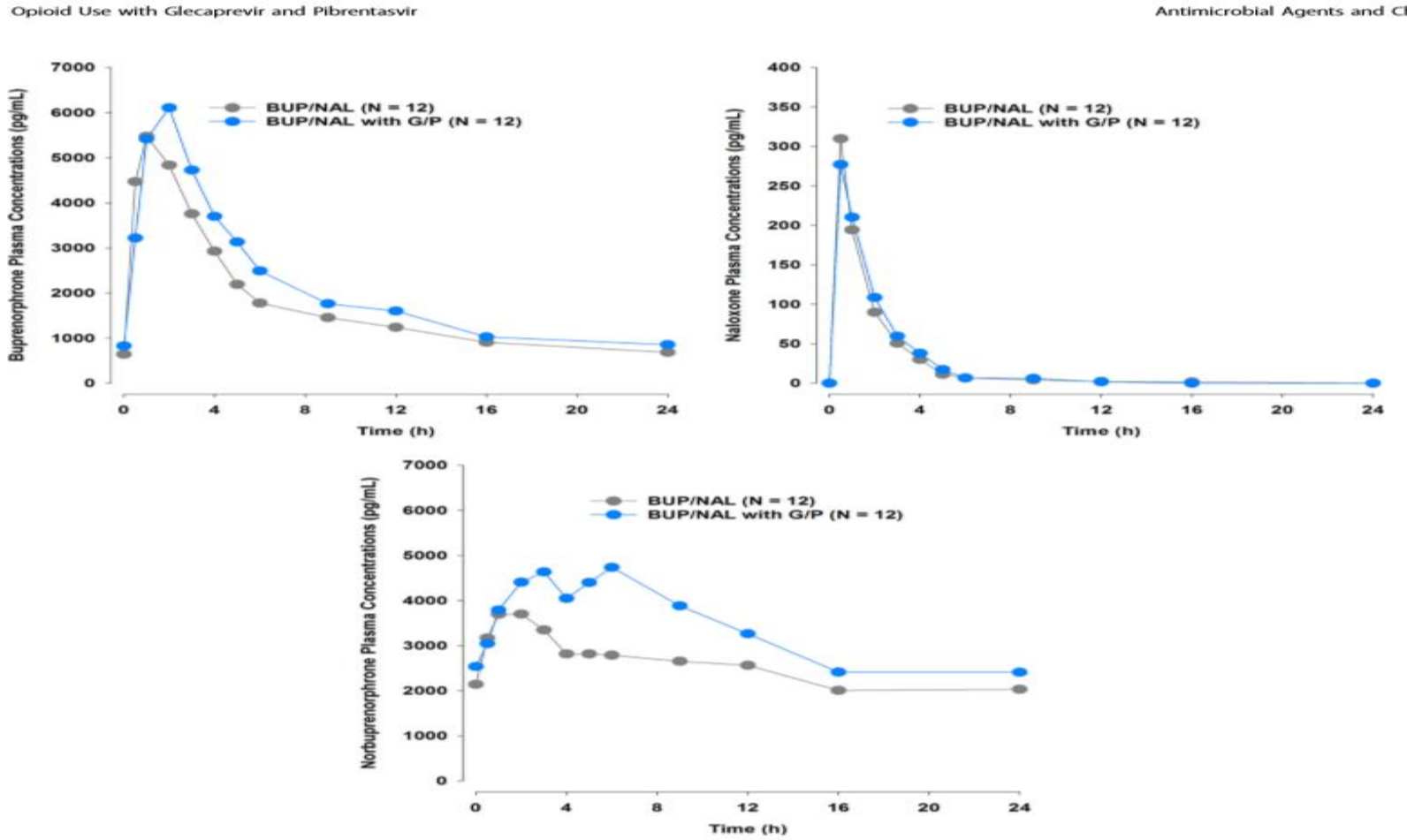
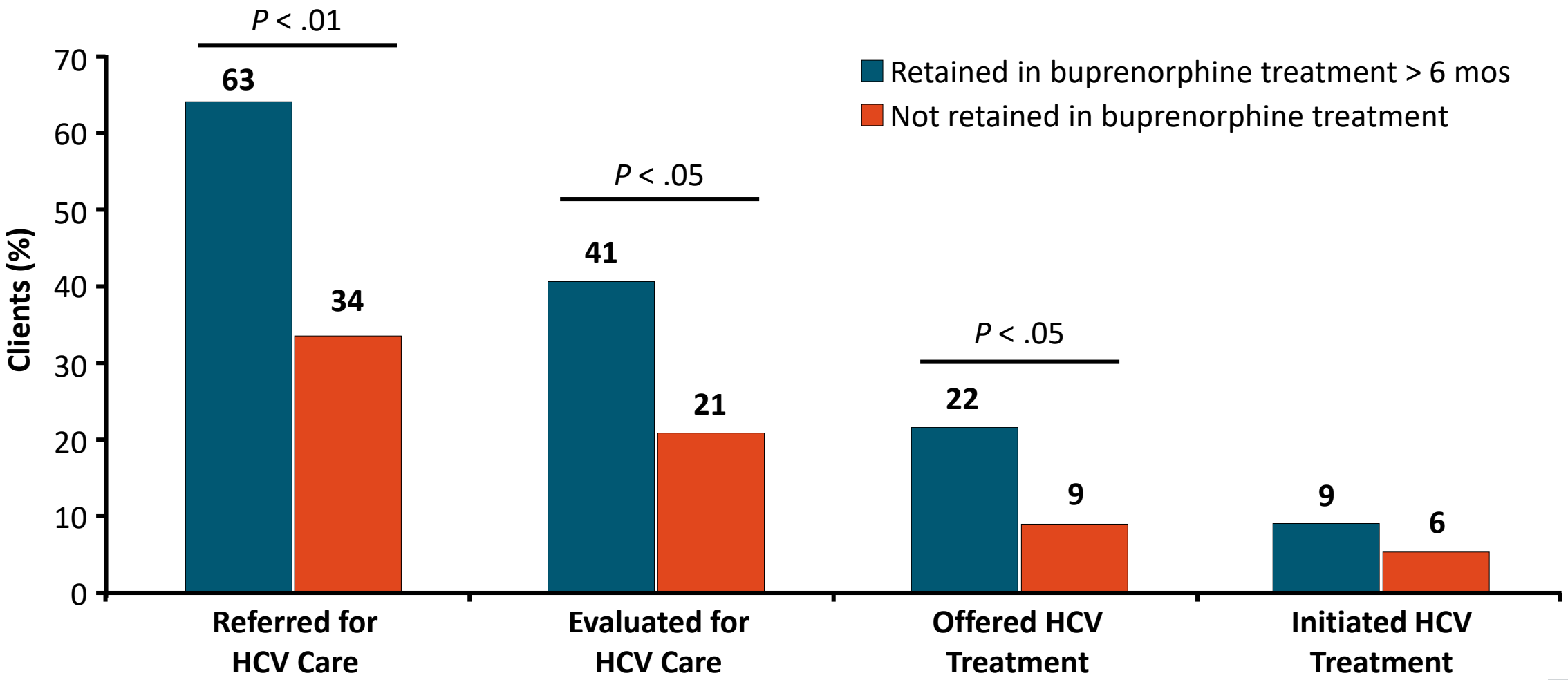


FIG 2 Mean buprenorphine, norbuprenorphine, and naloxone plasma concentration time profiles for buprenorphine-naloxone (BUP/NAL) administered QD alone or with glecaprevir and pibrentasvir (G/P) QD.

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



Norton. J Subst Abuse Treat. 2017;75:38.

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?

Case presentation continued:

- 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

- 45 y/o Black woman
- 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
- Missed appointments with Radiation Oncology due to drug use-now with progression of disease

- HCV associated chronic hepatitis
- Fibroscan with F3 severe fibrosis
- HIV viral load sub optimally controlled due to missed doses due to drug use
- Team meeting with Oncology, ID, Advanced Case Management, ENT
- Goals of care discussion with patient

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?