Issues in Treatment of Pain and Opioid Use Disorders in those with HCV/HBV/HIV

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Dr. Kennedy, Disclosures

- Nothing to disclose

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After the presentation the learner will:

- Know the epidemiology of Pain in viral hepatitis and Human Immunodeficiency Virus (HIV)

- Know the complications of Pain and how these affect management issues in those with Opioid Use Disorders (OUD), and /or Hepatitis B Virus (HBV)/Hepatitis C Virus (HCV)/HIV
Learning Objectives (cont.)

After the presentation the learner will:

• Appreciate the physiologic complexities & risk related issues of multiple treatment regimens in those hepatitis, HIV or Substance Use Disorders (SUD)

• Appreciate the importance of knowing populations at risk, screening, treatment guidelines and resources available for those with hepatitis, HIV or SUD
Educational Content

- Epidemiology and Scope of the Problem
- Screening and Risk Groups
- Advances in Treatments for viral hepatitis and HIV
- Special Needs Populations and Considerations
- Principles and Pitfalls of Pain Management
- Resources

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Epidemiology-HCV

• 185 Million world wide with HCV
• 3-4 million in US; 2-6 % develop Hepato-cellular Carcinoma (HCC) each year (deOliveria et 2009)
• 80%+ develop chronic, often asymptomatic hepatitis C infection (CHC)
• 5-30% chronically affected develop cirrhosis
• Prevalence of decompensated cirrhosis doubled in 10 years
• Prevalence of HCC has increased 20-fold in 10 years (deLemos 2014).
Epidemiology-HBV

• 700,000 to 1.4 million persons in the US have chronic HBV (CHB) & an additional 5,000–8,000 persons become chronically infected each year.

• During 1990–2004, incidence of acute HBV in the US declined 75%

• Greatest decline (94%) among children & adolescents (increase in HBV vaccine coverage). A total of 3,405 cases of hepatitis B were reported in 2009

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Epidemiology of Co-Infection

• Estimate: 40% injection-drug users (IDUs) become infected with HBV after 1 year of drug use; More than 80% infected after 10 years.

• Co-Infection of HBV with HIV and or HCV is common, due to shared risk factors for transmission

• ~60,000 co-infected HBV and HIV in US

Scope of Problem

• Co-infection of HBV in those with HIV/HCV significantly increases liver-related morbidity and mortality.

• HBV and or HCV can push HIV to more rapid progression to AIDS

• 3,000 to 4,000 persons die of HBV-related cirrhosis annually in the US.
Scope of Problem

• Persons with CHB infection are at 12 to 300 times higher risk of HCC than non-carriers
• 1,000 to 1,500 persons die each year in the US of HBV-related liver cancer
• 60,000-80,000 persons will die each year in the US of HCV-related liver cancer—rates rising rapidly. (Mahajan 2013)
Pain in Hepatitis 1

Chronic HCV causes inflammation/pain with:

• Liver Enlargement (stretching of capsule)
• Liver Fibrosis
• Liver Cirrhosis
• Hepato-cellular Carcinoma (HCC)
• Liver Transplantation

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In one study of over 8000 HCV+ veterans, 67% had documented Pain Diagnoses (Dx). 56% had SUD Dx. Vets with co-occurring Pain & SUD less likely to get opioids than those with only Pain even though Indicators of prescription opioid misuse not associated in those with Pain and SUD.
PAIN in Hepatitis 3

Pain conditions common:

- Hepatology clinic estimates vary from 50-80% of patients with HCV
- Arthritis in up to 30% of HCV+
- Peripheral Neuropathy in 10% HCV+
- Severity of Depression predicts Pain Intensity
Pain in Hepatitis 4

- Frequent pain reports in acute HBV (nearly all) and chronic phase

- 25% patients with HBV report pain of Fibromyalgia type: chronic musculoskeletal pain and fatigue

(Ozsahin 2013)
Pain in HIV

• Higher incidence in those with HIV
• Even higher if any co-morbidities (HCV, HBV, SUD, DM, others)
• Estimated prevalence: 30-90% with higher prevalence as disease progresses
• Underestimated by those providing care
• 3 categories: Unrelated to HIV (low back)
  HIV related: Neuropathy,
  Opportunistic Infections
  (Krashin 2011)
• 2° HIV treatment (ART, chemo)
Opioid Abuse in Pain

Large Veterans study (n=4122) of non-medical use (NMU) of opioids & pain in those with or without HIV

• High prevalence of NMU associated with
  - SUD
  - medical status
  - pain interference

NOT HIV status
Screening for HIV

The US Prevention Services Task Force (USPSTF) recommends clinicians screen for HIV infection in:

• Adolescents and adults ages 15 to 65 years. Younger adolescents and older adults who are at increased risk should also be screened.

• All pregnant women, including those who present in labor who are untested and whose HIV status is unknown
Screening for HIV

- Behavioral Risk: anal or vaginal sex; sharing injection equipment with infected persons

- Risk Groups: high rates of HIV infection in their communities; African Americans, American Indians, Asians, Hispanics/Latinos

(www.cdc.gov/hiv/risk/other/index.html)
Screening for HCV

USPSTF recommends screening for HCV infection in:

• Persons at high risk for infection
• One-time screening for HCV infection to adults born between 1945 and 1965
• Medicare & Medicaid will pay to screen at risk groups for HVC (AIDSmeds 6-24-14)
HI-Risk for HCV

• Currently inject drugs

• Ever injected drugs, including those who injected once or a few times many years ago
HI-Risk for HCV

• Have certain medical conditions, including persons:
  ○ who received clotting factor concentrates produced before 1987
  ○ who were ever on long-term hemodialysis
  ○ with persistently abnormal alanine aminotransferase levels (ALT)
  ○ who have HIV infection
HI-Risk for HCV

• Were prior recipients of transfusions or organ transplants, including persons who:
  o were notified that they received blood from a donor who later tested positive for HCV infection
  o received a transfusion of blood, blood components or an organ transplant before July 1992
HI-Risk for HCV

HCV- testing based on a **recognized exposure** is recommended for:

- Healthcare, emergency medical, and public safety workers after needle sticks, sharps, or mucosal exposures to HCV-positive blood
- Children born to HCV-positive women
- Note: IF exposure to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended

Screening for HBV

- Persons born in regions of high and intermediate HBV endemicity (HBsAg prevalence 2%):
  - Test for HBsAg, regardless of vaccination status in their country of origin, including
    - immigrants
    - refugees
    - asylum seekers
    - internationally adopted children

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Screening for HBV

- US born persons not vaccinated as infants with parents born in regions where HBV is endemic (HBsAg prevalence 8%)
- Test for HBsAg regardless of maternal HBsAg status if not vaccinated as infants in the United States
- If HBsAg-positive, refer for medical management.
- If negative, assess for on-going risk for hepatitis B and vaccinate if indicated.
Treatment Advancement Issues

Many differences complicate all treatments:

• Specific patient characteristics: co-morbidities, viral genotypes, hepatic function
• Duration of treatment
• Side effects
• Treatment costs
• Drug resistance

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Advances in Treatments for HCV

Current treatments for HCV infection:

• Pegylated and standard interferon alpha (IFN-α)
• Ribavirin (RBV)
• Protease inhibitors
  boceprevir
  telaprevir

 **SIMEPREVIR: Directly acting anti-viral (DAA)** (less side effects & toxicity, better sustained viral repression)

• NS5B nucleotide polymerase inhibitor **SOFOSBUVIR: DAA**
  (less side effects & toxicity, better sustained viral repression)

• **Simeprevir & Sofosbuvir combo** approved by FDA  2014
Advances in Treatment HBV

Effective medications available for HBV:

• Injectable interferon (IFN)-based therapies — both standard IFN α and pegylated (PEG)-IFN α

• Oral nucleos(t)ide analogues: adefovir dipivoxil (ADV), entecavir (ETV), lamivudine (LAM), telbivudine (LdT), and tenofovir disoproxil fumarate (TDF). (Marcellin 2011)
Future Hepatitis Treatments

• Additional antiviral compounds are expected to be licensed [WHO Guidelines 2013]

• Candidates with ‘Breakthrough Therapy Designation’ from FDA (fast track approval):
  o Daclatasvir (DCV) with Asunaprevir (ASV)
  o DCV, ASV & BMS-791325
  o Check www.hcvguidelines.org for updates
Advances in Treatment HIV

Barriers to advances:

• Long-lived latently infected cells
• Residual viral replication
• Anatomical Reservoirs may harbor unique long-lived infected cells
  o gastrointestinal tract
  o lymphoid tissue
  o central nervous system (CNS)
• Penetration of ART may be limited at these sites. (Lewin & Rouzioux 2011)
Advances in Treatment HIV

- **Sterilizing Cure**: eliminating all traces of HIV in all compartments, sanctuaries and reservoirs and for patients to have a plasma HIV RNA count of less than 1 copy/ml.

- **Functional Cure**: ‘cancer model:’ an individual would have long-term health in the absence of treatment, with low-level viremia at less than 50 copies/ml. (Lewin & Rouzioux 2011)
Advances in Treatment HIV

• Treatment intensification

• **Early Treatment** to reduce viral load early, e.g., initiate treatment during acute phase or **Prophylactic** treatment for some

• **Targeted treatments**: target organ systems with highest volume of residual virus with penetrating ART: Gastro-intestinal tract (most), CNS and Lymphoid tissue (less so) (Lewin & Rouzioux 2011)

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HIV and Hepatitis Prevention: Gold Standard

Changing Behaviors (when no vaccine):

- Testing on vaginally inserted ring with combination contraception and anti-retroviral therapy
- Changing risk behaviors of other groups: Men who have sex with men, especially those who abuse stimulants
- Changing behavior of IDUs
Treatment for Opioid Use Disorders

Medication Assisted Treatment:

OPIOIDS
- Methadone
- Buprenorphine/Naloxone (Suboxone®)
- Naltrexone (ReVia®, Vivitrol®, Depade®)

ALCOHOL
- Disulfiram (Antabuse®)
- Acamprosate Calcium (Campral®)
- Naltrexone

See Treatment Improvement Tip Series (TIP) No. 43 Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs for detailed guidance.
Special Needs Populations with HCV/HBV/HIV

Certain conditions, situations can increase risk for PAIN and complications of treating PAIN:

• Co-occurring disorders: Mental illness, SUDs
• Serious medical problems
• Housing, family or social problems
• Disabilities
• Pregnant Women
• Adolescents and young adults
Special Needs Populations

- Victims of sexual or physical abuse
- Parents
- Complex Medical Problems
- Gay, Bisexual, Lesbian, Transgendered
- Aging patients
- Patients with PAIN from other conditions
SAMHSA TIP #43

• Medical providers in Medication Assisted Therapy (MAT) for Opioid Use Disorder (OUD) should work collaboratively with Primary Care Providers, Hepatologists, HIV-Specialists, Pain and Palliative-care clinicians to ensure establishment of appropriate pain interventions for patients on MAT.
SAMHSA TIP #43

• Patients on MAT or with OUD are often undertreated or denied medication for acute or chronic pain management.

• Pain complaints maybe misperceived as drug-seeking behavior.

• Patients' have higher tolerance for opioids and often need for higher doses.
SAMHSA TIP #43

- Providers need education about maintaining current opioid levels while adding sufficient immediate-release treatment agents to manage acute or chronic pain.

- Pain Management Centers that have a FULL array of services may be best option.
BEFORE Prescribing OPIOIDS

Consider the many challenges and problems when there is non-malignant PAIN:

• Lack of evidence for efficacy, particularly with high dose opioid therapy
• Syndrome of rebound pain/hyper-algesic states produced by opioid use
• Withdrawal syndromes masquerading as or reported as ‘pain’
BEFORE Prescribing OPIOIDS

Consider:

- Opioid adverse events: QT prolongation, Torsade de Pointes (shown with methadone and risk for widened QTc with second generation anti-psychotic meds)
- Addiction rate underestimated
- Large increase in prescribed opioids in past 10 years mirrored by sharp increase in overdose deaths
- Consult Risk Evaluation Management Strategies (REMS) Guidance Documents (FDA approved) see Resources
Drug Interactions

• Pharmacokinetic and Pharmaco-dynamic drug interactions that affect methadone management or HIV medications have been demonstrated within every class of antiretroviral agents.

• Pharmacokinetic and Pharmaco-dynamic drug interactions affect adjuvant medications used in treatment for HIV/HCV/HBV.
Drug Interactions

- Drug interactions between methadone, buprenorphine and HIV medications are known (Consult SAMHSA TIP #43 Chapter 3 for detailed chart of interactions).
- Anti-viral Didanosine contra-indicated with anti-HCV therapy
- Avoid AZT, Combivir®, Trizivir®, d4T with anti-HCV therapy
- Abacavir (in Ziagen®, Kivexa®, Trizivir®) can reduce levels of Ribavirin
Drug Interactions

Co-administration of anti-hypertensive agents (HTN seen co-morbidly in liver disease & HIV):

• Angiotensin Converting Enzyme (ACE) inhibitors use with opioids has significant interactions possibly due to decreased metabolism of opioids thus potentiation and prolongation of opioid effects; dose adjustments may be in order.
Drug Interactions

• Research evidence supports that Ang II acts as anti-opioid peptide to decrease the actions of opioids.

• Moreover, opioids-induced decline in angiotensin release and functioning has also been reported.
Opioid Use Disorders & HCV/HBV/HIV

Common overlap of conditions due to overlap of risk factors

- Changes in neurotransmitter signals, including dopamine, opioid peptides, and corticotropin-releasing factor

- Changes in the regulation of transcription factors within the neurons of the reward system

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Opioid Use Disorders & HCV/HBV/HIV

- Changes associated with the long-term neuro-adaptive motivational aspects of drug dependence may be from alterations in gene expression.

- “Overlapping and additive neurochemical mechanisms validate the concern that IFN-based treatment of HCV infection may exacerbate preexisting depression or drug use behaviors.” (Sylvestre 2004)
Chronic Pain in SUD & Hepatitis/HIV

• Develop non-pharmacologic methods for treatment for Stress, Depression & Anxiety

• Pain medications, MAT

• Transcutaneous Electric Nerve Stimulator (TENS)
Multiply affected patients need multiple modalities utilizing inter-professional teams of experts for better outcomes:

- Psychosocial interventions, Case Management
- SUD treatment, MAT if indicated
- Medication: skilled and knowledgeable to also manage co-occurring illness & side effects
- Support groups
- Relapse prevention education
- Education to prevent viral transmission
Buprenorphine for Chronic Pain

In opioid dependent patients with HBV/HCV/HIV & PAIN: Pain significantly reduced when study participants were maintained on Buprenorphine/Naloxone (Bup/Nx) compared to pre-Bup/Nx ratings.

Factors associated with oxycodone preference:
- lower Bup/Nx maintenance dose
- more withdrawal symptoms
- more pain (Roux 2013)
Buprenorphine/Naloxone effective in:

- Reducing pain
- Reducing supplemental oxycodone use
- Adequate management of pain
- Withdrawal symptoms

Bup/Nx may reduce oxycodone preference in opioid users in chronic pain.
All patients:
- Screen for risk of suicide: history, thoughts, behaviors
- Closely monitor for new or worsening symptoms of depression at all encounters
- Unusual changes in mood or behavior
SAMHSA TIP #53 Hepatitis Treatment

Anti-viral therapy for those with Mental Illness, SUD can be successful but requires:

• Expert psychiatric management, close monitoring
• Intensive case management by behavioral health case manager
• More frequent appointments for lab monitoring of liver function, drug interactions or non-prescriptive drug use
• Consideration of support network, services available and patient’s abilities

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SAMHSA TIP #53 Hepatitis Treatment

- Individualized, flexible treatment planning
- Time for patients to rest
- More frequent sessions or more intensive programs
- Longer durations of Substance Abuse Treatment
- Ongoing support
SAMHSA TIP #53 Hepatitis Treatment

Specialized attention to:

• Therapeutic alliance, Motivational Interviewing
• Periodic screening for depression, other viral conditions
• Periodic screening for cognitive disorders
• Regular medication adherence checks
• Frequent communication among provider team
• PREVENTION PLAN; CONTINGENCY MANAGEMENT

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In Summary…

- Patients with viral hepatitis and/or HIV with SUD are complex and require an interprofessional, team based approach utilizing multiple-modalities. MAT for those complex patients who cannot achieve abstinence from opioids and require pain management.
Resources

- [http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm111350.htm](http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm111350.htm):

  Buprenorphine Transmucosal Products for Opioid Dependence (BTOD) REMS

  Extended-Release and Long-Acting (ER/LA) Opioid Analgesics REMS
Resources

- Treatment Improvement Tip Series (TIP) No. 43 Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs. Center for Substance Abuse Treatment. Rockville (MD): Substance Abuse and Mental Health Services Administration (US) 2005

- Treatment Improvement Tip Series (TIP) No. 53 Addressing Viral Hepatitis in People with Substance Use Disorders. Center for Substance Abuse Treatment. Rockville (MD): Substance Abuse and Mental Health Services Administration (US) 2011
Resources


• See Reference List

• Thank You

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