Addressing SUD-related Comorbidities, such as Hepatitis, HIV, Depression, Anxiety, and PTSD

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  Suicide Prevention in Active Duty Soldiers
Medical co-occurring disorders: focus on Hepatitis C
Hepatitis C

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Learning Objectives

• Describe the epidemiology of HCV in the United States
• Interpret HCV testing
• Recognize the importance of addressing HCV in the primary care setting
HCV Deaths and Deaths from Other Nationally Notifiable Infectious Diseases,* 2003-2013

* TB, HIV, Hepatitis B and 57 other infectious conditions reported to CDC

Hepatitis C Prevalence in the United States

- NHANES (2003-2010)
  - 3.6 million chronically infected (anti-HCV)
  - 2.7 million currently infected (82% of anti-HCV positive)
- Populations not included in NHANES:

<table>
<thead>
<tr>
<th>Population</th>
<th>Estimated Size</th>
<th>Prevalence (anti-HCV, %)</th>
<th>Number Chronically Infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incarcerated</td>
<td>2,186,230</td>
<td>23.1</td>
<td>505,350</td>
</tr>
<tr>
<td>Homeless</td>
<td>691,899</td>
<td>32.1</td>
<td>222,100</td>
</tr>
<tr>
<td>Hospitalized</td>
<td>478,054</td>
<td>15.6</td>
<td>74,576</td>
</tr>
<tr>
<td>Nursing homes</td>
<td>1,446,959</td>
<td>4.5</td>
<td>65,113</td>
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<tr>
<td>Active-duty military</td>
<td>1,404,060</td>
<td>0.5</td>
<td>7,020</td>
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<tr>
<td>Indian reservations</td>
<td>1,069,411</td>
<td>11.5</td>
<td>123,224</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td><strong>997,384</strong></td>
</tr>
</tbody>
</table>

More than 80% of all HCV-infected adults are persons in the 1945-1965 birth cohort. It is estimated that 70% have moderate-severe liver disease. This is an ill cohort. These high rates of morbidity translate to high rates of mortality.

The number of reported cases of acute hepatitis C declined until 2003 and remained steady until 2010. However, from 2010-2015, there was an approximate 2.9-fold increase in the number of reported acute hepatitis C cases from 850 to 2,436 cases.

Injection drug use is the main risk factor for Hepatitis C virus (HCV) transmission in industrialized countries.

60–80% of new cases of HCV infection occur among PWID. Most (60%) of existing infections are among former and current PWID. Many of these patients will be seen by you for treatment of SUD.
Role of the Primary Care Clinician in HCV

- Screening for HCV
- Counseling on modifiable risk factors important in disease progression
- Staging of liver disease
- HCC surveillance
- Recognition of extra-hepatic manifestations
- HCV treatment (with mentoring) or referral
At least 50% of persons with chronic HCV are unaware of their infection. It is extremely important to screen in the setting of primary care. Other surveys have even more disappointing results: 45-85% unaware of their status. Among high-risk populations, testing rates are 17%-87%. ~70% of IDU's with HCV are unaware of their status.
Recommended Testing Sequence for Identifying Current Hepatitis C Virus (HCV) Infection

* For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended. For persons who are immunocompromised, testing for HCV RNA can be considered.

† To differentiate past, resolved HCV infection from biologic false positivity for HCV antibody, testing with another HCV antibody assay can be considered. Repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.

The Evolution of Highly Effective Treatment

Speaker Notes:

Treatment for HCV has evolved dramatically. For nearly two decades the standard of care was an interferon based regimen for 6-12 months, combined with ribavirin resulting in, at best, 50% of patients achieving cure with a year's worth of treatment. In 2011, the first generation of direct-acting antivirals were approved. Although these agents markedly improved SVR rates, in addition to the toxicities and laboratory abnormalities of interferon, these early agents were also plagued by substantial side effects and a high pill burden. By 2014, we entered a new era of therapy hallmarked by the ability to treat with an all-or-all regimen, sparing the need for interferon, with few side effects and, more importantly high cure rates with abbreviated courses of treatment.
WHAT DO WE GET WITH HCV TREATMENT?

SVR (cure) of HCV is associated with:

• 70% Reduction of Liver Cancer
• 50% Reduction in All-cause Mortality
• 90% Reduction in Liver Failure

Lok A. NEJM 2012; Ghany M. Hepatol 2009; Van der Meer AJ. JAMA 2012
HEPATITIS C CASCADE OF CARE IN UNITED STATES

Now we know how widespread the HCV epidemic is. We have excellent tests to diagnose the disease and can cure it in over 90% of patients. However, the care cascade is dismal. You can help improve this situation by testing and treating these patients.

HCV Treatment in PWID

- Treatment of HCV in PWID has been very limited
  - Stigma
  - Drug use status as a criterion for treatment exclusion
  - Incarceration in prisons where treatment is limited
  - Concern for HCV reinfection
- Current AASLD/IDSA HCV Treatment Guidelines recommend HCV treatment for all persons including PWID
- PWID can be successfully treated for HCV on-site in an opioid treatment program rather than being referred

Mehta et al., 2008; Grebely, Oser, Taylor, & Dore, 2013; Oramasionwu, Moore, & Toliver, 2014; Wolfe et al., 2015; Butner, 2017.
Co-Occurring Psychiatric and Substance Use Disorder in OUD

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Questions for Co-Occurring Disorders in Primary Care Settings

• Are psychiatric symptoms present only during substance use disorder?
  → Likely psychiatric disorder due to substance

• Are psychiatric symptoms present before substance use disorder, and/or during extended periods of sobriety?
  → Likely co-occurring psychiatric disorder

• Are psychiatric symptoms present before substance use disorder, and/or during extended periods of sobriety, as well as during substance use disorder?
  → Likely co-occurring psychiatric disorder, +/- psychiatric disorder due to substance
Lifetime Prevalence of Psychiatric Disorders: General Population vs OUD

- Major Depression
- Dysthymia
- Bipolar I-II
- Panic Disorder
- Social Phobia
- Generalized Anxiety Disorder
- Personality Disorder
- PTSD

Lifetime Prevalence of Substance Use Disorders: General Population vs OUD

Data are from the National Epidemiologic Survey of Alcohol and Related Conditions

Psychiatric Disorders and Opioid Dependence Reciprocally Increase Risk

• Pre-existing psychiatric disorders:
  • Generalized anxiety disorder: 11x risk of developing opioid dependence
  • Bipolar I disorder: 10x risk of developing opioid dependence
  • Panic disorder: 7x risk of developing opioid dependence
  • Major depression: 5x risk of developing opioid dependence

• Pre-existing opioid dependence:
  • 9x risk of developing panic disorder
  • 5x risk of developing major depression
  • 5x risk of developing bipolar I disorder
  • 4x risk of developing generalized anxiety disorder

Martins et al 2009
Co-Occurring Psychiatric Disorders: Treatment Goals

• Acute Phase: 1-3 months
  • Non-response: <25% reduction in symptoms
  • Partial response: 25-50% reduction in symptoms
  • Response: >50% reduction in symptoms
  • Remission: no symptoms, e.g. PHQ-9 <5

• Continuation Phase: 3-12 months
  • Prevent relapse: another episode within 6 months of remission

• Maintenance Phase: 1-3 years
  • Prevent recurrence: another episode after 6 months of remission

• Treatment Goal: Durable remission
Co-Occurring Depressive Disorders

• Co-occurring depressive disorders treatment in OUD
  • Positive RCTs in methadone MAT: imipramine, doxepin
  • Negative RCTs in methadone MAT: imipramine, doxepin, bupropion, sertraline, fluoxetine
  • No RCTs in bup MAT

• Bup has empirical support as antidepressant outside OUD

• Lifetime major depression correlates positively with abstinence during bup MAT for OUD

• Depressive symptoms in OUD
  • Bup and methadone MAT equally improve depressive symptoms in patients with OUD – ~50% reduction
  • Naltrexone MAT does not appear to worsen depressive sx

Speaker Notes:
Note the mixed evidence for treatment of co-occurring depressive disorders in methadone MAT, and the dearth of studies on the treatment of co-occurring depressive disorders in buprenorphine MAT.

Co-occurring major depression appears to be a positive prognostic feature for buprenorphine MAT.
Co-Occurring Depressive Disorders: Treatment

- Recommend first stabilizing OUD on MAT for ~6 weeks
- Depressive disorder remits?
  - Continue MAT as treatment of OUD and depressive disorder
- Depressive disorder persists?
  - Treat depressive disorder per established guidelines
    - Measurement based care: track and respond to depression using serial PHQ-9s
    - Shared decision making and patient activation: educated patient chooses treatment direction, team uses behavioral activation
    - Systematic follow up: team contacts patient proactively to address symptoms and concerns
    - Stepped care: proactive treatment titration, consultation with behavioral health in resistant illness
    - Treat to target: remission defined as PHQ-9 score <5

Co-Occurring Major Depression: Treatment

• Major Depressive Disorder
  • Psychotherapy, e.g.: IPT, CBT, Behavioral Activation
  • Medication
  • Psychotherapy plus medication
  • General treatment sequence: Psychotherapy → SSRI → SNRI → Bupropion → Mirtazapine → TCA → rTMS → ECT → MAOI

Huhn et al 2014, Rush et al 2006
Co-Occurring Anxiety Disorders: Treatment

- Panic Disorder
  - Psychotherapy
  - Medication
  - General treatment sequence: Psychotherapy → SSRI → SNRI → Imipramine

- Social Phobia
  - Psychotherapy
  - Medication
  - General treatment sequence: Psychotherapy → SSRI → SNRI

- Avoid benzos in MAT: 2x risk of all-cause mortality
- Avoid MAOIs in MAT: risk of serotonin syndrome

Huhn et al 2014, Abrahamsson et al 2017
Co-Occurring Anxiety Disorders: Treatment

- Generalized Anxiety Disorder
  - Psychotherapy
  - Medication
    - Pregabalin
    - Hydroxyzine
    - SNRI or SSRI
    - Buspirone
  - General treatment sequence: Psychotherapy → Hydroxyzine → SNRI → SSRI → Pregabalin → Buspirone

- Avoid benzos in MAT: 2x risk of all-cause mortality
- Caution pregabalin in MAT: 3x risk of overdose death

Co-Occurring PTSD: Treatment

- Psychotherapy, e.g.: CBT, PE, EMDR, SS
  - Positive RCT of PE for PTSD in methadone MAT
  - CBT for PTSD in buprenorphine MAT reduces positive urines

- Medication
  - Prazosin reduces nightmares and hyper-arousal assoc w PTSD
  - Note: prazosin only studied as augmentation of other PTSD treatment

- General treatment sequence: Psychotherapy → SSRI → SNRI → Prazosin Augmentation → TCA

Insomnia

• Reported in up to 21% of patients on buprenorphine MAT
  • Central sleep apnea demonstrated in 33%
  • Nocturnal hypoxemia demonstrated in 39%
  • No RCTs examining insomnia treatment in buprenorphine MAT

• Reported in up to 84% of patients on methadone MAT
  • Central sleep apnea in up to 60%
  • Positive RCTs of insomnia treatment in methadone MAT
    • Cognitive behavioral therapy for insomnia (CBTI)
    • Suan Zao Ren Tang (sour jujube concoction) *GABA-ergic
    • Acupuncture
  • Negative RCTs of insomnia treatment in methadone MAT
    • Trazodone

Insomnia: Treatment

• Assess for sleep disordered breathing and treat!

• Psychotherapy
  • CBT-I: stimulus control, sleep restriction, sleep hygiene, relaxation, cognitive restructuring

• Medication

• General treatment sequence: Psychotherapy → Doxepin → Ramelteon → Trazodone → Melatonin

• Caution z-drugs in MAT: 1.6x risk of overdose death

Summary

• Psychiatric disorders strikingly common in OUD
• Psychiatric disorders and OUD reciprocally increase risk
• Limited direct literature on psychiatric disorders treatment in OUD or MAT
• Stabilize OUD with MAT
• Psychotherapy first line in major depression, anxiety disorders, PTSD, and insomnia
• Medication first line in dysthymia
• Caution pregabalin, z-drugs
• Avoid benzos
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