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COLUMBIA UNIVERSITY
HIV MENTAL HEALTH TRAINING PROJECT

Hepatitis C and Mental Health

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Overview

- Epidemiology and course of Hepatitis C (HCV)
- Treatment of HCV
- Neuropsychiatric complications and other adverse reactions related to HCV and treatment
- Managing depression in HCV treatment
- Potential drug-drug interactions
- Nonpharmacologic interventions for HCV treatments

Three of the types of viral hepatitis

- Hepatitis A Virus (HAV)
  - Fecal/oral route, (anal/oral sex, close interpersonal contact, contaminated food / water)
  - Easily treated, 99% recover without treatment
  - Vaccination available
- Hepatitis B Virus (HBV)
  - Contact with infected blood (needles, sex, childbirth)
  - Vaccination available
- Hepatitis C Virus (HCV)
  - Contact with infected blood (needles, sex, childbirth)
  - No vaccination

www.hepatitisfoundation.org
Epidemiology of HCV Today

- 170 million infected worldwide
- U.S. 21-30 million infected
- cost: $5-10 billion annually
- Deaths outnumber HIV in US—12,000 deaths / year
- 75% do not know they are infected
- The majority of new HCV diagnoses will occur among “baby boomers”
- 60% of cases are due to injection drug use (IDU), sexual contact (15%), and blood transfusions (10%)

www.cdc.gov

High Prevalence HCV Populations

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>IDU</td>
<td>27-93%</td>
</tr>
<tr>
<td>Psychiatric D/O</td>
<td>38-81%</td>
</tr>
<tr>
<td>HIV Positive/IDU</td>
<td>60-80%</td>
</tr>
<tr>
<td>HIV Positive/Non-IDU</td>
<td>16-25%</td>
</tr>
<tr>
<td>Homeless</td>
<td>19-69%</td>
</tr>
<tr>
<td>Incarcerated</td>
<td>23-39%</td>
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Course of HCV Infection

If 100 people contract hepatitis C at the same time

- 75 people would not clear the virus — they will have chronic HCV infection
- 25 people will clear the virus within 2-6 months (but still carry antibodies)

- 20 of the 75 people may never experience any noticeable symptoms but can still pass the virus to others
- After about 15 years, 40–60% of the 75 people will experience some symptoms and develop some level of long-term liver damage
- After about 20 years, 5–10% of the 75 people will develop liver scarring (cirrhosis)
- Between 2–5 people will experience liver failure or liver cancer at which point they require liver transplantation

Goals of Treatment

- Eradicate HCV [measured by sustained virological response (SVR) 12 months after treatment]
- Delay fibrosis and progression to cirrhosis.
- Prevent hepatic decompensation and need for liver transplantation.
- Prevent hepatocellular carcinoma
HCV Treatment Before 2011

- Prior to 2011:
  - pegylated Interferon-alpha (weekly injection)
  - Ribavirin (nucleoside analogue), (daily pill)
  - Adverse side effects make treatment adherence challenging
  - Low success rate, especially people with HCV genotype I (30-40% success rate)
  - Most African-Americans and Latinos have genotype I

HCV Treatment Since 2011

- Two protease inhibitors
  - Boceprevir (Victrelis)
  - Telaprevir (Incivek)
  - Specifically for HCV genotype I
    - Success rate doubled (30-40% to 63-88%)
  - Taken IN ADDITION to IFN-alpha & Ribavirin
  - High pill burden (12-18 pills per day)
  - Cost: Boceprevir ($1100/week), Telaprevir ($4100/week)
  - Inadequate adherence will result in treatment resistance
  - Side effects are similar to or more severe than previous regimen

Yee et al., Am Jour of Gastoenterology, 4/2012)
Future of HCV Treatment

- Currently in trial (once-daily uridine nucleotide analogs)
  - Taken orally, without Interferon (potentially fewer side effects)
- Some recommend delaying treatment in certain cases (those without advanced liver disease, etc.)
- Trials suggest cure rate remains low for people with genotype I unresponsive to previous treatment

HCV and HIV

- High rates of co-infection:
  - 60-80% HIV + urban IDUs
  - 16-25% HIV + via sexual contact
- Increased serum & liver titers of HCV
- Increased cognitive impairment
- Increased perinatal HCV transmission
- Nearly half of deaths among HIV-positive persons due to liver disease
- Co-infection accelerates HCV disease progression
  - HCV mono-infection progression to end stage: 20-30 years
  - HCV/HIV co-infection: 10-15 years

Shire and Sherman, Oxford Journal of Medicine, 2011
World Health Organization, 2011
HCV and HIV: Treatment Considerations

- Co-infection may complicate HCV treatment
  - HCV treatment lowers the HIV CD4 T-cell count
  - HCV meds are not typically given if CD4 T-cells <200
- Length of treatment is twice as long
- Several HIV meds have adverse interactions with HCV meds

Predominant Neuropsychiatric Disturbances Related to HCV and/or its Treatments

- Depression
- Manic-spectrum disturbances
- Mixed mood disturbances
- Fatigue
- Neurocognitive Impairment
- Delirium

Raison C. CNS Drugs 2005
Henry C et al., Current Psychiatry 2006
### Interferon Induced Symptoms*

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Fatigue</td>
<td>54-64%</td>
</tr>
<tr>
<td>Depression</td>
<td>16-58%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>37-40%</td>
</tr>
<tr>
<td>Irritability</td>
<td>24-35%</td>
</tr>
<tr>
<td>Decreased appetite or</td>
<td>21-29%</td>
</tr>
<tr>
<td>weight loss</td>
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* Data derived from clinical trials of IFN alfa-2a and 2b combined with ribavirin in the treatment of HCV infection (Manns et al., Lancet 2001; Fried et al., NEJM 2002) Data reviewed extensively in Raison et al., CNS Drugs 2005

### Non-psychiatric Side Effects from HCV and/or its Treatment

- Anemia
- Type-II Diabetes
- Hair Loss
Cognitive Impairment

- Chronic HCV is associated with:
  - Impaired attention
  - Psychomotor slowing
  - Impaired working memory
  - Impaired executive function

- Potential Causes:
  - Direct HCV effects on the brain
  - Hepatic encephalopathy caused by severe liver damage
  - Substance Abuse
  - Psychopathology
  - Interferon-α

Differential Diagnosis

- Pre-morbid Psychiatric History
- Concurrent Substance Abuse
- Neuropsychiatric Symptomatology
- Long-term effects of Alcohol and Substance Abuse on CNS
- IFN-Ribavirin RX - Cytokines - Genetic predisposition
- HIV and Other Comorbidities
- CNS Invasion

Long-term effects of Alcohol and Substance Abuse on CNS
Risk Factors for IFN-induced Depression

- Patient-related Factors
  - Depressive symptoms before treatment is started
  - Depression during previous IFN treatment
  - Genetics
    - Age, gender, history of drug use, treated psychiatric disorder do not predict increased risk
- Medication-related Factors
  - Dose, Duration, and Route of IFN (and Ribavirin in one study)
    - Increased risk with greater exposure, IV > sub Q route of administration

Potential Mechanisms for IFN-induced Depression

- IFN alters metabolism of monoamine neurotransmitters (Asnis, De La Garza, 2006)
- IFN activates proinflammatory cytokines and the HPA axis (ibid)
- IFN alpha shunts tryptophan metabolism away from serotonin (Capuron et al., 2002)
- Genetic predictors of IFN depression
  - allele of apolipoprotein E (Gochee et al., 2004)
  - IFN-α receptor polymorphism increases risk of depression (Rifai & Sabouni, 2012)
Studies on Pretreatment of Depression in IFN-Treated Patients

Positive study on pretreatment
- Randomized, double-blind, prospective, placebo-controlled throughout IFN treatment (N=181)
- Escitalopram 10 mg vs placebo,
- Maj Dep 8% escitalopram vs 19% placebo

Negative study on pretreatment
- Randomized, double-blind, prospective, placebo-controlled (N=133) Only first 12 weeks of HCV treatment
- Escitalopram up to 15 mg vs placebo
- Rates of Maj Dep 5.4%,
- No difference between placebo (3.2%) and escitalopram (7.6%)—may have underpowered re rate of depression.

Antidepressant Prophylaxis

Pros
- IFN-induced depression is common
- Cannot be reliably predicted
- Significant cause of morbidity, treatment discontinuation, & treatment failure

Cons
- 50-70% of patients don’t get depressed
- SSRIs may cause side effects, including bleeding, in advanced liver disease
Pretreatment of IFN-Induced Depression

- Treat MDD before initiation of HCV therapy
- Consider pretreatment in patients with baseline sub-threshold depressive symptoms
  - Most likely to benefit from antidepressant prophylaxis
- Consider pretreatment in patients with a history of depression

Monitoring & Treatment of IFN-Induced Depression

- Prospective psychiatric assessment, reassessments of depression q 4-12 weeks
  - Rapid identification and treatment of depression
  - More frequent evaluations throughout HCV treatment in patients with a history of psychiatric illness or substance use disorders
- SSRIs: safe and effective in IFN-treated patients in multiple studies
- Decreased rate and severity of psychiatric illness increases adherence, decreases dropout rates
Reviews of Treatment of Depression in IFN-Treated Patients

- Systematic reviews with evaluation of the data:

Newer HCV Tx (PI) Drug Interaction Considerations-CONTRAINDICATED

- Both boceprevir (BOC) and telaprevir (TVR) have significant drug interactions
  - Inhibitors of CYP3A4/5 and p-glycoprotein
- Contraindicated medications are those:
  - Highly metabolized by CYP3A4/5
    - increased plasma concentrations may cause serious/life-threatening events
  - Potent inducers of CYP3A4/5.
    - Reduce HCV PI plasma concentration, lowers efficacy and/or increases drug resistance
**Newer HCV Tx (PI) Drug Interaction Considerations--SIGNIFICANT**

- Both boceprevir (BOC) and telaprevir (TVR) have significant drug interactions
  - Inhibitors of CYP3A4/5 and p-glycoprotein
- Significant interactions:
  - Drugs primarily metabolized by CYP3A4/5 or p-glycoprotein.
    - Increase drug concentrations prolonging/ increasing effects, side effects
  - Inducers or inhibitors of CYP3A4/5 or p-glycoprotein
    - Could decrease or increase plasma HCV PIs
  - Package inserts contain information on dose adjustments

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**Important Psychiatric Drug Interactions**

- Pimozide
  - CONTRAINDICATED: BOC/TVR increases level of pimozide with potential for cardiac arrhythmia
- Carbamazepine/phenobarbital/phenytoin
  - CONTRAINDICATED BOC/SIGNIFICANT TVR-can lower HCV drug levels, alter levels of AEDs
- St John’s Wort (hypericum perforatum)
  - CONTRAINDICATED: BOC/TVR lowers HCV drug concentrations and reduce virologic response
- Trazodone, Desipramine
  - BOC/TVR ↑ antidepressants→dizziness, hypotension, syncope
  - Use with caution; consider lower doses
- Escitalopram
  - TVR ↓ escitalopram; adjust dose of escitalopram
- Zolpidem
  - TVR-lowers zolpidem
Drug Interactions

- For further information on drug interactions see:
  - www.hep-druginteractions.org
  - BOC and TVR package inserts

NONPHARMACOLOGIC INTERVENTIONS FOR HCV TREATMENTS
Goals of Intervention
Prior to HCV Treatment

- Adjustment to HCV Diagnosis
  - May be a shock, especially for non-IDU population
  - Person may learn that they have been infected for years/decades, hence the liver disease may be advanced at time of diagnosis
  - Dealing with stigmatization
  - Disclosure issues, including partners and family

- Decision to go on HCV meds or not
- Not everyone with HCV requires treatment
- Person may need additional support while making the decision with treating provider.
- Determining factors include:
  - General overall health
  - Stage of disease progression
  - Co-morbid medical conditions, e.g., in HIV/HCV co-infection CD4>200 to begin treatment
  - Discussion of potential side effects
Goals of Intervention
Prior to HCV Treatment

- Preparing for HCV medications
- Discussion of potential side effects and their management
- Assess for active mental illness
- If present, treat before beginning HCV treatment
- Assess for current substance use
- If present, treat before beginning HCV treatment

Goals of Intervention
During HCV Treatment

- Management of medication side effects
  - Especially psychiatric side effects.
  - Depression during treatment predicts early discontinuation of HCV medications
  - Developing strategies to cope with side effects (exercise, avoiding stress, timing of Interferon shots and pills)
- Improving sleep habits
- Adherence
- Addressing substance use issues
Reaction to Poor Treatment Response

- If patient does not meet certain clinical parameters by end of week 12, treatment is discontinued
- <12 months after treatment patient may have rebound of HCV (SVR maintained 12 months after completion of treatment considered a “success”)
- Patients may experience anxiety waiting for labs indicating response to treatment
- If patient cannot tolerate treatment regimen, in spite of interventions, it will be discontinued
- Discontinuation of treatment may lead patient to experience sadness, demoralization, anxiety, anger, frustration, hopelessness

Modes of Therapeutic Interventions

- Psych meds if indicated
  - Antidepressants may increase adherence rates in patients being treated with interferon

- Supportive Therapy
  - CBT/Motivational Interviewing to improve adherence and to help manage side effects
Modes of Therapeutic Interventions

- Group Therapy
  - Peer-support from those who have successfully maneuvered treatment
  - Educational component
- Alternative Therapies
  - Cautions against certain herbal treatments
  - No indication that any herbal treatment will reduce HCV viral load
- Meditation/Yoga/Visualization, etc.
  - Relaxation to deal with anxiety and agitation

Summary

- HCV is a worldwide epidemic
- The number of known cases in US will increase in the next decade
- There is no vaccination only treatment post-exposure
- The side effects from the treatment can be debilitating
- Mental health interventions can be an important part of treatment, including:
  - Treatment of symptoms (e.g. antidepressants to treat depressive symptoms)
  - Management of symptoms (e.g. relaxation techniques to cope with feelings of agitation and irritability)
  - Support before, during, and after treatment via individual and/or group psychotherapy
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OR visit us on the web at:

http://www.columbia.edu/cu/hivmentalhealthtraining
TOPICS

1. DIAGNOSTIC ASSESSMENT AND TREATMENT RECOMMENDATIONS
2. MEDICATION EVALUATION
3. OTHER CLINICAL/PSYCHIATRIC ASPECTS OF PRIMARY CARE
4. LEGAL/ETHICAL ISSUES
5. CARE OF THE TRIPLY DIAGNOSED
6. CROSS-CULTURAL PROFICIENCY IN PSYCHIATRIC DIAGNOSIS AND TREATMENT
7. MOTIVATIONAL INTERVIEWING IN PRIMARY CARE SETTINGS
8. COGNITIVE-BEHAVIORAL THERAPIES IN PRIMARY CARE SETTINGS
9. NEUROPSYCHIATRIC ASPECTS OF HIV INFECTION
10. HIV TESTING FOR PEOPLE WITH MENTAL ILLNESS

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