Management of Depression in Patients Receiving HCV Therapy

Blending Science and Clinical Practice

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What exactly are we treating?

What is Depression?
Depression – As A Symptom v Disorder

• Everyone occasionally feels blue or sad, but these feelings are usually fleeting and pass within a couple of days.
  – Common non-pathologic processes
    • Grief
    • Sadness
    • Demoralization
    • Disillusionment
    • Despondency

• When a person has a depressive disorder, it interferes with daily life, normal functioning, and causes pain for both the person with the disorder and those who care about him or her.

• Depression is a common but serious illness, and most who experience it need treatment to get better.

Major Depressive Disorder (MDD): Diagnostic Criteria

Five or more of the following symptoms are present most of the day, nearly every day, during a period of at least 2 consecutive weeks

At least 1 of these 2 symptoms

1. Depressed mood
2. Loss of interest or pleasure in all, or almost all, usual activities

3. Significant appetite or weight loss or gain
4. Insomnia or hypersomnina
5. Psychomotor agitation or retardation
6. Fatigue or loss of energy
7. Feelings of worthlessness or excessive or inappropriate guilt
8. Diminished ability to think or concentrate or indecisiveness
9. Recurrent thoughts of death or suicide

Symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

Is MDD Type Depression Ever “Appropriate”?

• Some patients are under stress
  – Stress is stress → no different
  – Stress can be a precipitant for depression

• Severe life stress increased the odds of developing depression

• Depression as a mood may be transient during stress

• Depressive Disorder (MDD) is never
  – Transient
  – Understandable or appropriate reaction
  – Warrants aggressive effective treatment
To Prevent Suicide ...

Only medical disorder that extinguishes natural instinct for survival …
Evaluating Depression

Using The PHQ-9 to Screen for Depression and Other Scales for Diagnosing and Managing
The PHQ-9 As An “MDD” Indicator

- Treatment guideline on depression suggests that screening for depression
  - Include at least 2 questions concerning mood and interest over the past 2-weeks (in UK, past month)

  Have you often been bothered by feeling down, depressed, or hopeless? and
  Have you often been bothered by having little interest or pleasure in doing things?

- A “yes” answer to either question is considered a positive test
- A “no” response to both questions makes depression highly unlikely

PHQ – Patient Health Questionnaire
Available at The McArthur Initiative on Depression In Primary Care Site:
http://www.depression-primarycare.org/clinicians/toolkits/materials/forms/phq9/.
Depression Rating Scales

• Self-rating scales
  – BDI (Becks Depression Inventory)*
  – Z-SDS (Zung Self-Rating Depression Scale)

• Rating scales
  – HAMD (Hamilton Depression Scale)+
  – MADRS (Montgomery-Åsberg Depression Scale)

*Not in public domain – must be purchased
+Deemed to be best scale
Making The Best Use of Scales

• BDI*, Z-SDS, HAMD, or MADRS
  – Try to quantify the severity of depressive symptoms
  – Show changes in depressive symptoms over time
• Diagnosis of “major depression” (MDD)
  – MDD has to be confirmed clinically by DSM-IV criteria


* Not in the public domain – must be purchased
Best Use of Scales - Examples

- Both patients received pre-HCV rx education
- Both patients not tolerating HCV rx
- Both patients severely depressed
  - Both patients w PPHx of MDD
- Both patients responded briskly
  - Both remitted in acute phase
  - Both maintained in remission
    - DS full remission
    - RP partial remission
- Both patients received supportive tx
  - HCRC group based rx
    - Planning ~ 6-10 mos of disability, work loss, financial hardship, emotional & physical distress
  - Unmanaged comorbidities
    - PTSD, irritability, anger, anxiety, mania, SA
    - Relapse plan, trigger & craving awareness, sponsor/support, injection issues
Best Use of Scales – Examples

- Patient with pre-existing severe, non-psychotic depression – melancholia
- Unresponsive to optimal medication management
- Serious suicide attempt x 2 → psychiatric hospitalization
- Failed course of ECT x 2
- Hepatology declared him ineligible for HCV-treatment
- Trial of repetitive, transcranial magnetic stimulation (rTMS) → Complete remission
Treatment Options for Depression In Context of HCV Therapy
The Good, The Bad and The Ugly
Approach to Managing Psychiatric Issues During HCV Treatment

- Education, monitoring, and support
  - Information and psychoeducation before and during treatment
  - Monitoring of patients and psychiatric issues
  - Supportive psychotherapy
  - Regulation of sleep

- Pharmaceutical strategies
  - Antidepressant treatment
  - Other treatments: antipsychotics, benzodiazepines (mood stabilisers, amphetamines, naltrexone, tryptophan, etc)
  - Antiviral therapy dose reduction, discontinuation
Current Treatment Practices in MDD

Primary Care
- Initial Diagnosis
- Early Treatment Attempts

Psychiatry
- Improved Diagnosis
- Improved Dosing
- Psychotherapy
- New Treatment Options

Failed Treatment Attempts in Current Episode

Chronicity and/or Treatment-Resistance Continuum

In HCV-Related Depression, “Adequate” Treatment Is Difficult to Achieve

Factors contributing to inadequate treatment include:

- **Adequate Dosage**
- **Adequate Duration**
- **Minimum 4 weeks**

**Lack of Efficacy**
- Imipramine 150mg or equivalent
- Fluoxetine 20-40mg
- Paroxetine 20-40mg
- Sertraline 100-150mg
- Citalopram 20-40mg
- Escitalopram 10-20mg

**Poor Tolerability**
- Buproprion 300mg
- Venlafaxine 150-225mg
- Desvenlafaxine 50-100 mg
- Duloxetine 60 – 90 mg
- Mirtazapine 15mg

**Nonadherence**
- Safety Issues
- Comorbidities

How to best treat …

Achieving Remission Is the Name of the Game …
Definitions of Response and Remission

- **Remission**: >75%
- **Response**: 50% - 74%
- **Partial Response**: 25% - 49%
- **Nonresponse**: <25%
REMISSION

RECOVERY

NORMAL MOOD

DEPRESSION

100%

TIME

acute 6 - 12 weeks
continuation 4-9 months
maintenance 1 or more years
Recurrence Becomes More Likely With Each Episode of Depression

- **First episode**¹,²: >50%
- **Second episode**²: ≈70%
- **Third + episode**²,³: 80%-90%

*Patients were followed for 3 to 15 years following recovery of previous episode.*

NORMAL MOOD

DEPRESSION

RELAPSE

RECURRENCE

TIME

acute
6-12 weeks

continuation
4-9 months

maintenance
1 or more years

TIME

6-12 weeks

4-9 months

1 or more years
Since all ADs are created equal …

How do you pick one?
Considerations When Choosing AD

- Family history
- Past Psychiatric history
- Comorbidities
  - Active
  - Remission
- Ensuring compliance
## Considerations: Potential Side-Effects → Avoid v Advantage

<table>
<thead>
<tr>
<th>Type</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRIs</td>
<td>Sexual dysfunction, GI adverse effects, tremors</td>
</tr>
<tr>
<td>TCAs</td>
<td>Potential for lethal overdose; Alpha-adrenergic effects; Delirium risk from anticholinergic/antihistamine adverse effects; Cardiac conduction prolongation</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Minimal protein binding; Blood pressure risk</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Risk of decreased WBC count; Risk of weight gain; Sedation</td>
</tr>
<tr>
<td>Bupropion</td>
<td>May increase risk of IFN-associated seizures</td>
</tr>
</tbody>
</table>

Modified from CCO module 2007

Considerations: Potential for Drug-Drug Interactions

**Low P450 blockers:**
Likely to have little impact on metabolism of other drugs

**Potent P450 blockers:**
Potential for strong impact on metabolism of other drugs

*Not formal AD – both are stimulants

- Bupropion
- Citalopram
- Mirtazapine
- Venlafaxine
- Modafinil*
- Sertraline
- Methylphenidate*
- Paroxetine
- Fluoxetine
- Fluvoxamine

Etiology of IFN-Induced Depression: Possible Tryptophan-Serotonin Depletion

- IFNs
- L-Kynurenine
- Indoleamine hydroxylase
  - (mostly lung, placenta)
  - ~90%
- Tryptophan
- 2,3-hydroxylase (liver)
- Tryptophan hydroxylase
- ~10%
- 5-HTP
- BH4 (tetrahydrobiopterin)
- Aromatic amino acid decarboxylase
- 5-HT
- Serotonin

### Tryptophan Metabolic Pathway

# HCV Infection: Reduced Dopamine, Serotonin Transporter Binding

**Impact of HCV Infection on Transporter Binding**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Controls</th>
<th>HCV-Infected Patients</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAT</td>
<td>9.39</td>
<td>6.91</td>
<td>&lt; .0006</td>
</tr>
<tr>
<td>SERT</td>
<td>3.02</td>
<td>2.58</td>
<td>&lt; .0001</td>
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</tbody>
</table>

*DAT, dopamine transporter binding; SERT, serotonin transporter binding.*


Modified from CCO 2007
The Good News …

ADs Work In All Cases of MDD Depression …
Efficacy of Citalopram for Treatment Related Depression Associated With PegIFN and Ribavirin – *A Fighting Chance!*


<table>
<thead>
<tr>
<th>Evaluation Time Points</th>
<th>Placebo (n = 14)</th>
<th>Citalopram (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 wk f/u</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 wk f/u</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 wk f/u</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After IFN therapy</td>
<td></td>
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</tbody>
</table>

*HAM-D Depression Score*

*P = .025*

(Modified from CCO in HCV 2007)
Use of SSRI Pretreatment in Patients Receiving HCV Retreatment

- Patients experiencing major depression during first course of HCV treatment received SSRI pretreatment when retreated for HCV (N = 8)


\[ P = 0.036 \]

(Modified from CCO in HCV 2007)
What to do when …

First Trial of AD Fails?
selective NRI
5HT1A IPT SARI T4 estrogen
DA / stimulants

ECT/TMS/VNS

SSRI TCA NDRI MAOI SNRI cognitive therapy

alpha 2 antagonists

DEPRESSION PHARMACY

Pharmacological Options After Failure of First Antidepressant

- Optimize dose and address adherence
- Change to another antidepressant
  - Same class
  - Different class
- Add a second antidepressant
- Add a non-antidepressant
  - Lithium or other mood stabilizer
  - Thyroid hormone
  - Psychostimulant
  - Atypical antipsychotic
Treatment of Major Depression: A Continuum of Care
<table>
<thead>
<tr>
<th></th>
<th>Male:</th>
<th>Female:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>16</td>
<td>8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th># of TMS</th>
<th>Initial Beck</th>
<th>Last Beck</th>
<th>Initial IDS-SR</th>
<th>Last IDS-SR</th>
<th>Initial QIDS</th>
<th>Last QIDS-SR</th>
</tr>
</thead>
<tbody>
<tr>
<td>27</td>
<td>34</td>
<td>23</td>
<td>45</td>
<td>25</td>
<td>30</td>
<td>22</td>
</tr>
</tbody>
</table>

- Off label: 4
- Remission: 10
- Response: 6
- Partial Response: 4
- Failure: 4
What if …

Depression Persists …
Persistence of Psychiatric Symptoms After Discontinuation of HCV Therapy

Discontinuation of interferon ± ribavirin

- Symptoms often reversible
- In some cases, symptoms persist over years (depression, cognitive disturbance)

Persistent adverse effects common up to 3 months after discontinuation

(Modified from CCO in HCV 2007)

Refer the Patient to a Psychiatrist

- Consider treatment discontinuation
- Diagnosis in question or complicated by other psychiatric factors
  - Comorbidities
    - Alcohol or substance abuse
    - Personality disorders
- Management is complex, response to medication is not optimal, or considering prescribing multiple agents in combination
- Hospitalization is indicated
  - Psychosis
  - Suspected risk of suicide
  - Homocidal ideation
- Complex psychosocial situation
- Psychotherapeutic treatment is required
- Neurostimulation is necessary
Is it true …

That ADs Are Forever …
Recurrence Becomes More Likely With Each Episode of Depression

- **First episode**¹,²: >50%
- **Second episode**²: ≈70%
- **Third + episode**²,³: 80%-90%

*Patients were followed for 3 to 15 years following recovery of previous episode.
How Long Should Patients Remain on Antidepressant Treatment?

• Case reports
  – 25-40% experience a recurrence
  – Recurrence of depression and suicidal thoughts can continue up to 6 months after end of antiviral treatment
  – 20-30% who experience depression go on to chronic state

• All possible efforts should be undertaken to prevent relapse and achieve remission
  – Select optimal treatments
  – Achieve remission in acute phase of depression (the first 10-12 weeks)
  – Continue treatment for 6-10 months beyond
  – Consider maintenance for at risk patients

Summary & Conclusions

• Depression is a painful and debilitating condition and deserves aggressive treatment

• Antidepressant treatment in patients with depressive symptoms during HCV treatment is highly effective

• Prophylactic use of antidepressants should be offered to:
  – Patients with pre-existing history of depression
  – Patients with a history of treatment-associated depression during previous HCV therapy

• Antidepressant treatment should be continued for at least
  – 10 months after achieving remission
  – 3 months after the end of antiviral treatment

• Most side-effects can be managed without dose reduction or discontinuation of antiviral therapy
**Muchas Gracias For Your Attention!**

**HCV On the Web**
- **USF Hep-C ETAC**
- **VA National Hepatitis C Program**
  - Info for patients & providers
  - [www.hepatitis.va.gov](http://www.hepatitis.va.gov)
  - Documents, video & tools for mood, SA, MI, and interventions
- **Centers for Disease Control & Prevention**
  - [www.cdc.gov/ncidod/diseases/hepatitis/c/](http://www.cdc.gov/ncidod/diseases/hepatitis/c/)
- **Hepatitis C Advocate**
  - [www.hcvadvocate.org](http://www.hcvadvocate.org)

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