Depression and Non-adherence Predict Mortality in Hemodialysis Treated ESRD Patients

Daniel Cukor, PhD
Associate Professor of Psychiatry and Behavioral Science
Research Scientist, Brooklyn Health Disparities Center
SUNY Downstate Medical Center, Brooklyn, NY
Daniel.Cukor@Downstate.edu
Learning Objectives

• The goal of the lecture is to highlight recent scientific advances in the assessment, outcomes, and treatment of comorbid depression in patients with end stage renal disease.

• To provide practical suggestions for the implementation of depression screening programs in dialysis centers
Question?

Which attitude best describes your center’s approach to depression treatment.

A. We regularly screen for depression and treat or refer as necessary, system works well.
B. We screen for depression, but do not have the resources to adequately address all patients issues.
C. System for addressing depression? What system?
Question?
ASN 2013 -2014 – ~200 Dialysis Centers

Which attitude best describes your center’s approach to depression treatment.

25%
A. We regularly screen for depression and treat or refer as necessary, system works well.

25%
B. We screen for depression, but do not have the resources to adequately address all patients issues.

50%
C. System for addressing depression? What system?
Figure 3. Potential mechanism of vicious cycle between depression and ESRD

Impact of Depression in Dialysis

Association of depressive symptoms and morbidity
– Increased mortality
– Higher peritonitis rates
– Increased hospitalization

Kimmel, KI, 2000
Troidle, AJKD 2003
Lopes, KI, 2004
Hedayati, AJKD 2005
Farrokhi, AJKD 2014

“the presence of depressive symptoms significantly increased the risk of death by 51% (adjusted HR, 1.51; 95% CI, 1.35-1.69; $I^2 = 40\%$)”
Cox Regression Survival Function Across Depression Severity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Full Sample (n=130)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>58%</td>
</tr>
<tr>
<td>Age (years)</td>
<td>57.6 ± 13.6</td>
</tr>
<tr>
<td>Afro/Caribbean American</td>
<td>84%</td>
</tr>
<tr>
<td>Born in the U.S.</td>
<td>48%</td>
</tr>
<tr>
<td>Currently Employed</td>
<td>17%</td>
</tr>
<tr>
<td>Dialysis Vintage (months)</td>
<td>54.8 ± 54.3</td>
</tr>
<tr>
<td>Diabetic</td>
<td>31%</td>
</tr>
<tr>
<td>≥ 2 hospitalizations in last year</td>
<td>39%</td>
</tr>
<tr>
<td>Urea Reduction Ratio</td>
<td>70.7 ± 10.5</td>
</tr>
<tr>
<td>Calcium Phosphate Product</td>
<td>49.5 ± 15.8</td>
</tr>
<tr>
<td>Serum Albumin g/dl</td>
<td>3.83 ± .86</td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>12.6 ± 10.2</td>
</tr>
<tr>
<td>Mild (&lt;15)</td>
<td>55%</td>
</tr>
<tr>
<td>Moderate (15-24)</td>
<td>32%</td>
</tr>
<tr>
<td>Severe (&gt;24)</td>
<td>13%</td>
</tr>
</tbody>
</table>

• The psychological response to dialysis treatment is individual and varied.
• Depression is the most prominently studied psychological response.
• Comorbid depression is associated with lower QOL, behavioral adherence, increased hospitalization and morbidity.
SCREENING FOR DEPRESSION
What is “Depression”?  

“Depression is characterized by feelings of helplessness, hopelessness, inadequacy, and sadness. However these are symptoms of several disorders and can also occur in normal individuals”

DSM 5

• Major depressive episode vs major depressive disorder
• Dysthymia
DSM 5 Criteria for Major Depressive Disorder (MDD)

- Depressed mood or a loss of interest or pleasure in daily activities for more than two weeks.
- Mood represents a change from the person's baseline.
- Impaired function: social, occupational, educational.
- Specific symptoms, at least 5 of these 9, present nearly every day:
  - 1. Depressed mood or irritable most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad) or observation made by others (e.g., appears tearful).
  - 2. Decreased interest or pleasure in most activities, most of each day
  - 3. Significant weight change (5%) or change in appetite
  - 4. Change in sleep: Insomnia or hypersomnia
  - 5. Change in activity: Psychomotor agitation or retardation
  - 6. Fatigue or loss of energy
  - 7. Guilt/worthlessness: Feelings of worthlessness or excessive or inappropriate guilt
  - 8. Concentration: diminished ability to think or concentrate, or more indecisiveness
  - 9. Suicidality: Thoughts of death or suicide, or has suicide plan
Dysthymia

• Now called ‘chronic depression’
• overwhelming yet chronic state of depression, exhibited by a depressed mood for most of the days, for more days than not, for at least 2 years.
• No more than 2 months without experiencing two or more of the following symptoms:
  – poor appetite or overeating
  – insomnia or hypersomnia
  – low energy or fatigue
  – low self-esteem
  – poor concentration or difficulty making decisions
  – feelings of hopelessness
Diagnosing Depression

• Most nephrologists not qualified to perform DSM-5 gold standard assessment
• You CAN assess patients yourselves
• – Screening tools identify high risk, not diagnostic
Criterion contamination: overlap of depressive symptoms & physical illness makes diagnosis difficult
Overlapping Symptoms

Medication Side Effects

Uremic Symptoms

Depression

How do we measure the unique variance?
Screening Instruments

**Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) Scale**
New scale can be self report or clinician administered, used in Star*D

**Beck Depression Inventory-II (BDI-II)**
21-item self-report instrument. High scores reflect the presence and severity of depressed mood.

**Hamilton Rating Scale for Depression (HAM-D)**
The total HAM-D provides an indication of depression and, over time, provides a valuable guide to progress.

**Center for Epidemiologic Studies Depression Scale (CES-D)**
includes 20 items that survey mood, somatic complaints, interactions with others, and motor functioning.

**SF-36 Health Survey**
A 36-item short-form was constructed to survey health status in the Medical Outcomes Study.

**Kidney Disease Quality of Life Questionnaire (KDQOL-SF)**
assesses the quality of life of patients with kidney disease.
Section Summary

• Depression can be difficult to define
• Screening instruments can identify high levels of depressive affect
• Outstanding questions
  – how often should we screen? (at initiation and every 6 months)
  – At what level of depression should we intervene?
    • Complex algorithm including: Depression severity, Depression length, suicidality, patient willingness, available resources
Question

Have you ever encountered a dialysis patient who had a comorbid depression?

A. Yes, and I attempted to treat the depression
B. Yes, and I made a referral.
C. Yes, but wasn’t sure what to do.
D. No, I haven’t encountered a depressed patient
Question
ASN ~ 200 Dialysis Centers
Have you ever encountered a dialysis patient who had a comorbid depression?

21% A. Yes, and I attempted to treat the depression
23% B. Yes, and I made a referral.
53% C. Yes, but wasn’t sure what to do.
3% D. No, I haven’t encountered a depressed patient
Depression Treatment in General

- Psychopharmacological Interventions
- Psychotherapy Interventions
- Other interventions
Pharmacological Interventions

• Identified 28 studies evaluating pharmacokinetic parameters in CKD for 24 antidepressants.
• Drug clearance in CKD 3-5 was markedly reduced for selegilene, amitriptylinoxide, venlafaxine, desvenlafaxine, milnacipran, bupropion, reboxetine and tianeptine.
• There were nine non-randomized trials, all suggesting benefit for the antidepressant under investigation. Side-effects were common, but mild in most patients.
• Conclusions: The evidence on effectiveness of antidepressants versus placebo in patients with CKD is insufficient, and in view of the high prevalence, a well-designed RCT is greatly needed.

Pharmacological Intervention

• 1 RCT in dialysis patients – 14 patients Fluoxetine vs Placebo (effect at 4 weeks, no effect at 8 weeks)

• Observational studies show moderate reductions in depression scores, but plagued by high rates of drop out, expectancy effects, and non-blinded assessment

  • Up To Date (2015) “Unipolar major depression in dialysis patients” Cukor, Pencille, Kimmel
Recommendations

• Citalopram or Sertraline – SSRI’s with fewest identified complications for ESRD. R/O Mania

• Common side-effects include: Sexual dysfunction, weight gain, GI & CNS symptoms, Risk of bleeding

• Typical treatment – initiation at ½ recommended dose – will not work until reach adequate dose
Other Interventions

• Exercise – Very modest effect in general, smaller for patients with increased comorbid illness/disability
  • Cochrane Review of Exercise Interventions for Depression
  • Exercise Training in Patients Receiving Maintenance Hemodialysis: A Systematic Review of Clinical Trials

• Frequent hemodialysis – no significant impact on BDI score
  • Chertow G, NEJM 2010
Psychotherapy

• Group CBT in Brazil 85 subjects with high BDI
• RCT
• Stronger effect for CBT than standard care at 12 weeks.
• Strong attendance
Study Objective

To demonstrate the feasibility and effectiveness of a modified Cognitive Behavioral Intervention in End Stage Renal Disease Patients being treated with Hemodialysis.


Cukor, et al. JASN, 2014
## Study Design

<table>
<thead>
<tr>
<th>Baseline</th>
<th>3 Months</th>
<th>Assessment 2</th>
<th>3 Months</th>
<th>Assessment 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics¹</td>
<td>Group A Intervention (10 sessions Of CBT)</td>
<td>Psychological Measures²</td>
<td>Group A No intervention</td>
<td>Psychological Measures²</td>
</tr>
<tr>
<td>Psychological Measures²</td>
<td>Group B Wait-list</td>
<td>Medical Ratings³</td>
<td>Group B Intervention (10 sessions Of CBT)</td>
<td>Medical Ratings³</td>
</tr>
<tr>
<td>Medical Ratings³</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹ Random Assignment
Patient Flow

- Approached: 120
- Screened: 90
  - No English: 5
  - Eligible: 70
  - Not Depressed: 15
  - Enrolled: 65
- Completed Intervention: 59
### Baseline Demographic Information (N=65)

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage/Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>65% women</td>
</tr>
<tr>
<td>Self-Identified Race</td>
<td>94% Afro/Caribbean American</td>
</tr>
<tr>
<td>U.S. Born</td>
<td>28%</td>
</tr>
<tr>
<td>Transplant History</td>
<td>14%</td>
</tr>
<tr>
<td>Dialysis Vintage</td>
<td>50 ± 31 months</td>
</tr>
<tr>
<td>Serious Comorbidity</td>
<td>94%</td>
</tr>
</tbody>
</table>
# Baseline Medical Information (N=65)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Value</th>
<th>Referent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>30%</td>
<td>8.3% in US</td>
</tr>
<tr>
<td>Hypertension</td>
<td>68%</td>
<td>24% in US</td>
</tr>
<tr>
<td>URR</td>
<td>71 ± 11</td>
<td>Goal &gt; 70</td>
</tr>
<tr>
<td>Serum Albumin</td>
<td>4.0 ± .36</td>
<td>Goal &gt; 4</td>
</tr>
<tr>
<td>Calcium phosphate</td>
<td>54.8 ± 17.5</td>
<td>Goal &lt;55</td>
</tr>
<tr>
<td>Mini-mental</td>
<td>27.6 ± 2.3</td>
<td>Intact &gt;25</td>
</tr>
</tbody>
</table>
**Baseline Psychiatric Information (N=65)**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any SCID Axis I</td>
<td>68%</td>
<td></td>
</tr>
<tr>
<td>SCID MDD</td>
<td>55%</td>
<td></td>
</tr>
<tr>
<td>Any SCID Axis II</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>Beck - Depression</td>
<td>23.3 ± 9.6</td>
<td>Moderate</td>
</tr>
<tr>
<td>Hamilton - Depression</td>
<td>15.2 ± 6.4</td>
<td>Low Moderate</td>
</tr>
<tr>
<td>Beck - Anxiety</td>
<td>14.4 ± 11.2</td>
<td>Mild</td>
</tr>
<tr>
<td>Quality of Life</td>
<td>101.6 ± 26.0</td>
<td>Poor (average for hemo samples)</td>
</tr>
</tbody>
</table>
CBT Intervention

• Individual
• 10 sessions
• Chair-side
• Homework
• Focused on
  – Psycho-education (Depression vs. Illness)
  – Behavioral Activation (modified for HD)
  – Cognitive Restructuring (modified for HD)
Challenging the Depressed Dialysis Patient
Form 4.3

If I can’t provide, I am drain on my family

If I supply money, I’m a worthwhile man

I’m flawed

Avoidance

Emotional Distance

Anger

All I did was go to dialysis, what a waste

Depression
Hamilton-D ratings pre and post treatment for the treatment (n=31) and control (n=29) groups

Hamilton x time $F(2) = 15.6, p<.001$
* $t(52)= -2.07, p < .05$
Quality of Life ratings pre and post treatment for the treatment (n=31) and control (n=29) groups

QOL x time $F(2) = 3.5$, $p<.05$
Average Inter-Dialytic Weight Gain (IDWG) for the treatment (n=31) and delayed-control (n=29) groups

IDWG x time F(2) = 11.8, p<.01
* t(52)= -3.07, p < .05
Section Conclusions

• Pharmacotherapy is understudied, but probably effective – cautious approach warranted

• CBT holds promise for depression intervention

• Well-designed clinical trials are needed!
  – Can depression treatment be effectively integrated into dialysis care on a larger scale?
  – Does effective treatment mediate increased morbidity/mortality risk?
ASCEND:
A Trial of Sertraline vs. CBT for End-stage Renal Disease Patients with Depression

Treatment Options for Depression in Patients Undergoing Hemodialysis
Study Sites

• Seattle, WA:

• Dallas, TX:

• Albuquerque, NM:
Research Team

- Seattle Site PI: Rajnish Mehrotra (study PI)
- Dallas Site PI: Susan Hedayati (co-PI)
- Albuquerque Site PI: Mark Unruh
- CBT Core: Daniel Cukor (Downstate) co-PI
- Engagement Core: Nancy Grote (UW)
- Data Coordinating Center: Patrick Heagerty (UW)
  Bryan Comstock (UW)
- Research Team: Wayne Katon (UW)
  Scott Cohen (GW)
  Laura Dember (Penn)
  Tom Greene (U Utah)
  Paul Kimmel (NIDDK)
  Nancy Kutner (Emory)
  Steve Weisbord (U Pitt)
  Bessie Young (UW)
Conclusions

• Depression is a common comorbidity in ESRD
• Hemodialysis patients should be screened regularly
• Interventions should be made available that reduce barriers to care
• Treating depression is not only good mental health care, but good medical care
THANK YOU!