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

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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?

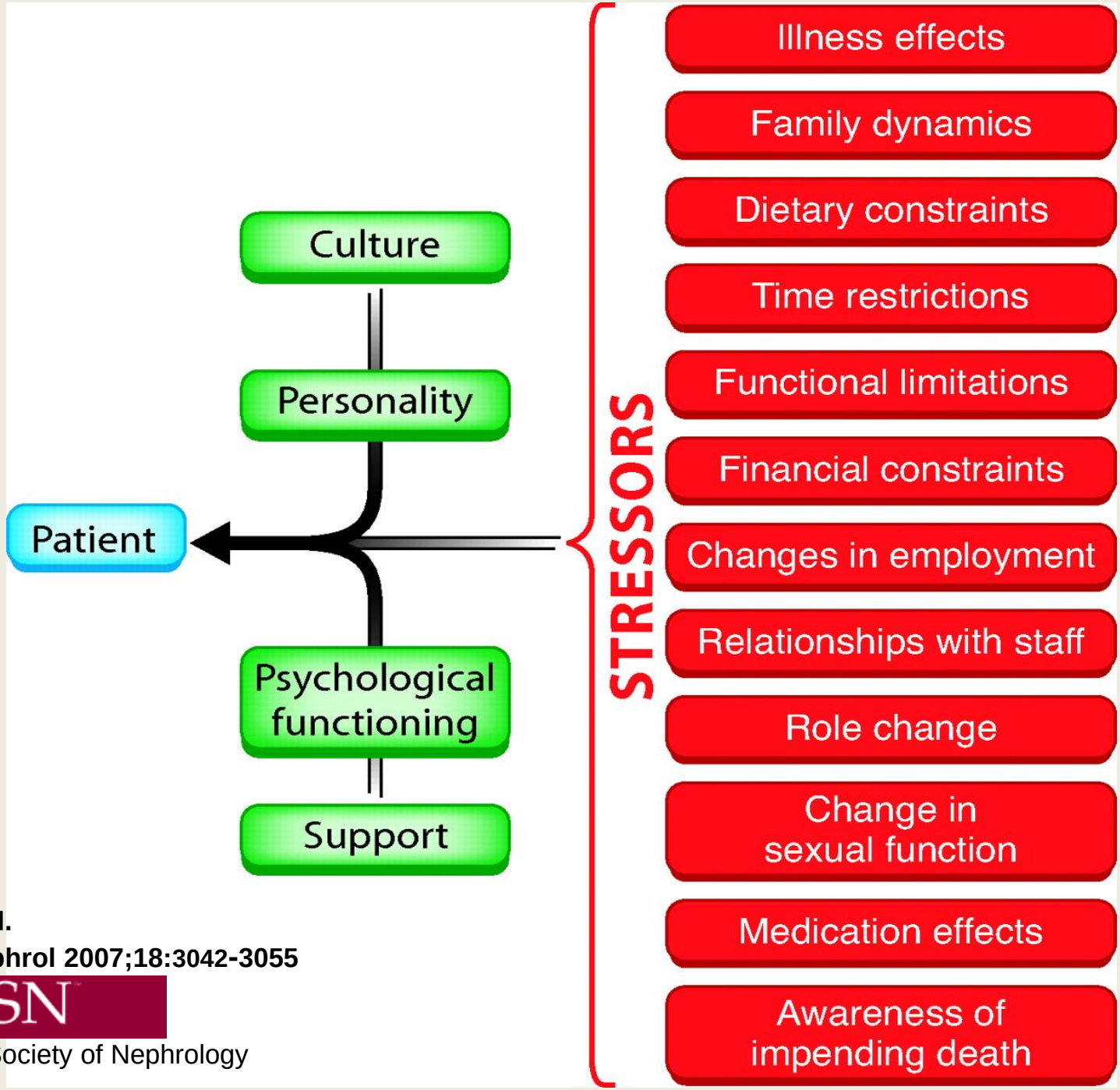
ASN 2013 -2014 – ~200 Dialysis Centers

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.

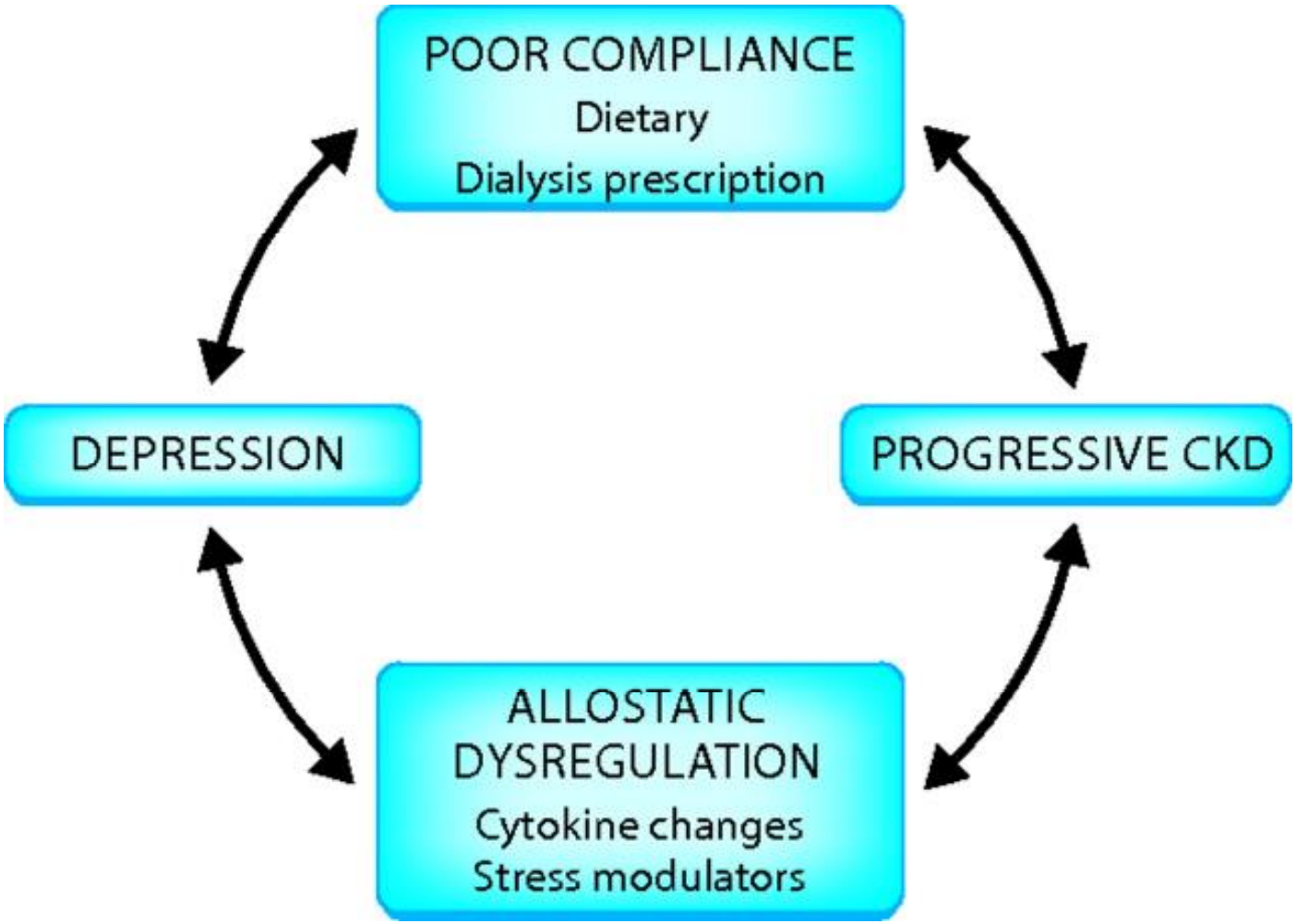
25% B. We screen for depression, but do not have the resources to adequately address all patients issues.

50% C. System for addressing depression? What system?



Cukor, D. et al.
J Am Soc Nephrol 2007;18:3042-3055

Figure 3. Potential mechanism of vicious cycle between depression and ESRD



Cukor, D. et al. J Am Soc Nephrol 2007;18:3042-3055

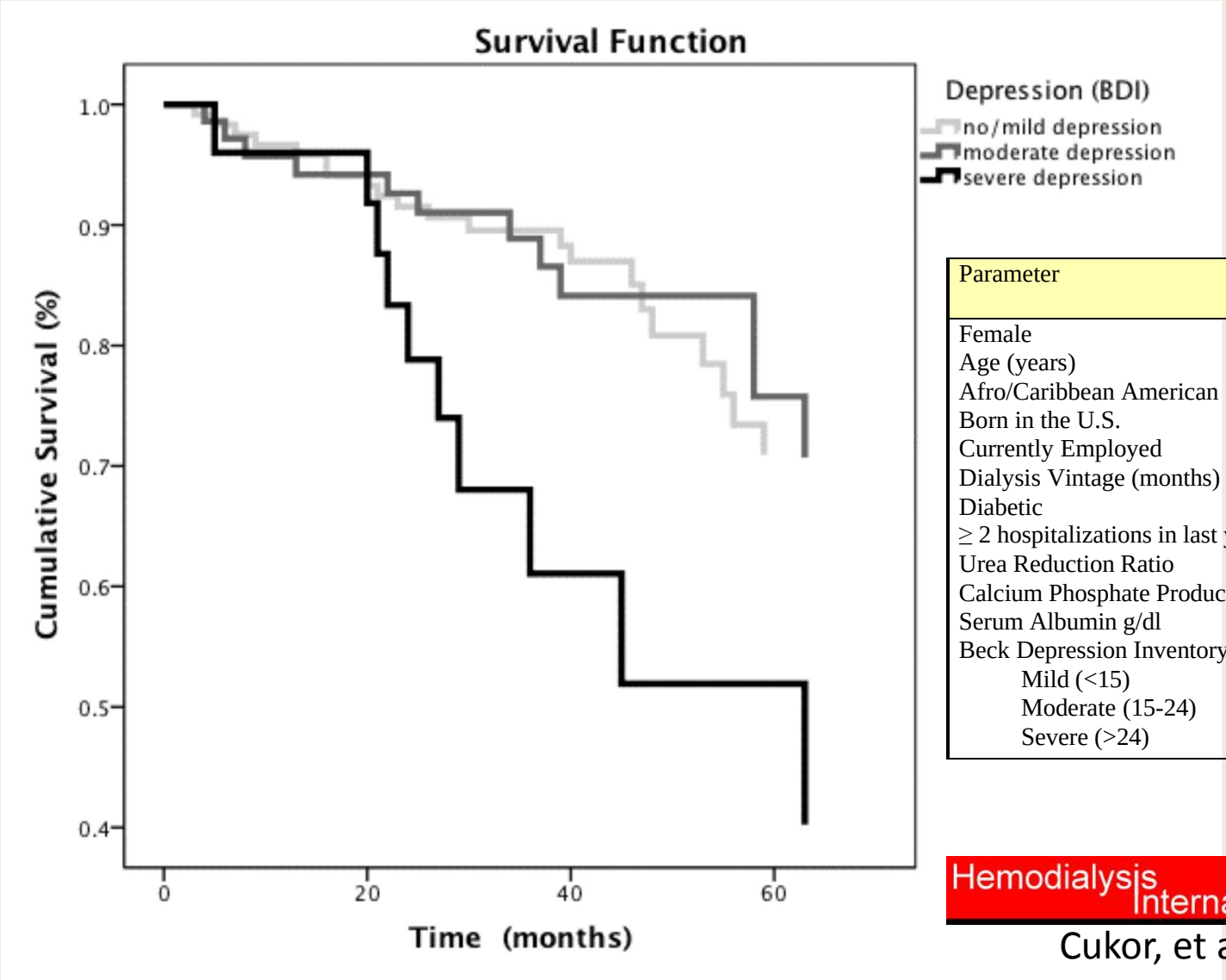
Impact of Depression in Dialysis

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



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

Hemodialysis International

Cukor, et al (2012)

Section Summary

- 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” -

Wolman, B. B. (1973). *Dictionary of behavioral science*

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

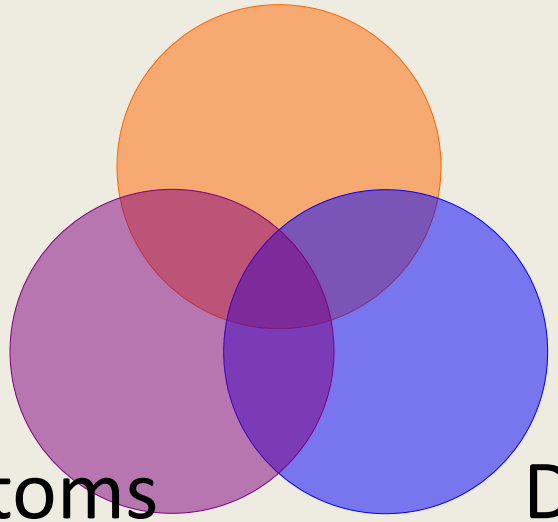
Diagnosing Depression

- 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



How do we measure the unique variance ?

Uremic Symptoms

Depression

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 selegiline, 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.

Antidepressants for depression in stage 3-5 chronic kidney disease: a systematic review of pharmacokinetics, efficacy and safety with recommendations by European Renal Best Practice (ERBP). Nagler, et al. Nephrol Dial Transplant. 2012

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
  - Duarte P, et al Cognitive-behavioral group therapy is an effective treatment for major depression in hemodialysis patients, Kidney Int 2009 76:4, 414-420.

Study Objective

To demonstrate the feasibility and effectiveness of a modified

Cognitive Behavioral Intervention in End Stage Renal Disease

Patients being treated with Hemodialysis.

K-23 NIDDK “Cognitive Behavioral Treatment of Depression in ESRD Patients on Dialysis” 2007-2012.

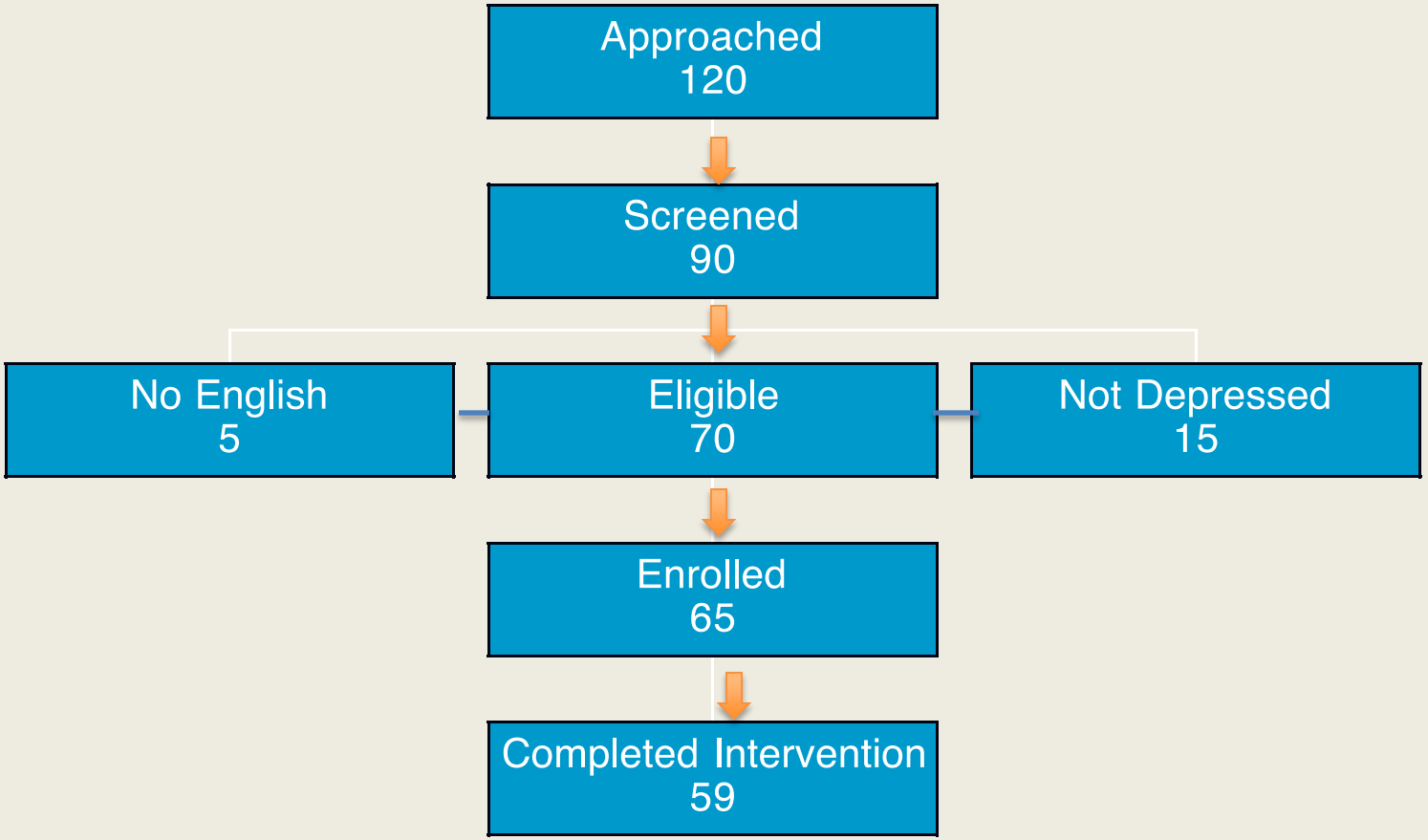
Cukor, et al. JASN, 2014

Study Design

Random Assignment

Baseline	3 Months	Assessment 2	3 Months	Assessment 3
Demographics[1] Psychological Measures[2] Medical Ratings[3]	Group A Intervention (10 sessions Of CBT) Group B Wait-list	Psychological Measures[2] Medical Ratings[3]	Group A No intervention Group B Intervention (10 sessions Of CBT)	Psychological Measures[2] Medical Ratings[3]

Patient Flow



Baseline Demographic Information (N=65)

Gender	65% women
Self-Identified Race	94% Afro/Caribbean American
U.S. Born	28%
Transplant History	14%
Dialysis Vintage	50 ± 31 months
Serious Comorbidity	94%

Baseline Medical Information (N=65)

		Referent
Diabetes	30%	8.3% in US
Hypertension	68%	24% in US
URR	71 ± 11	Goal > 70
Serum Albumin	4.0 ± .36	Goal > 4
Calcium phosphate	54.8 ± 17.5	Goal <55
Mini-mental	27.6 ± 2.3	Intact >25

Baseline Psychiatric Information (N=65)

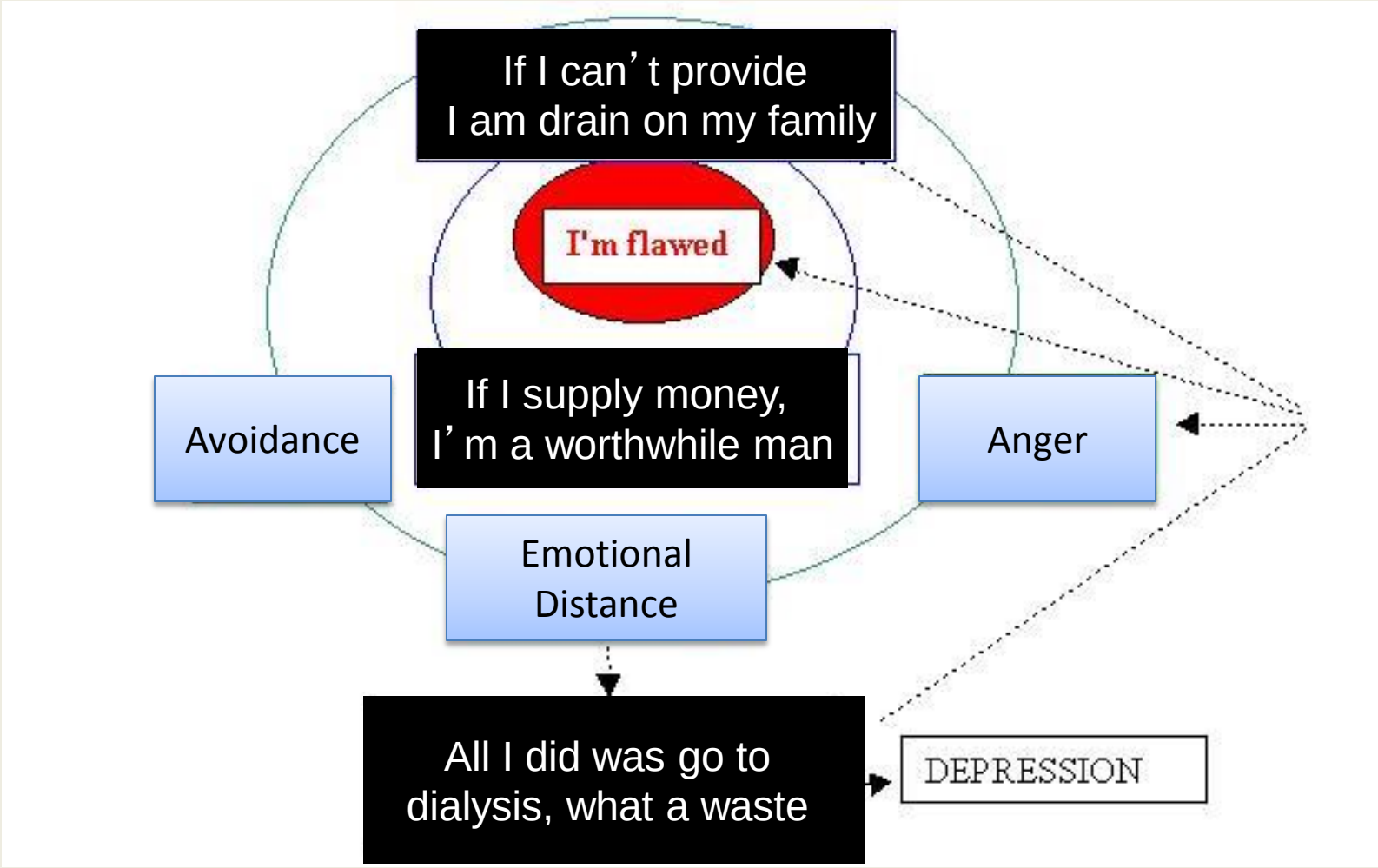
Any SCID Axis I	68%	
SCID MDD	55%	
Any SCID Axis II	50%	
Beck - Depression	23.3 ± 9.6	Moderate
Hamilton - Depression	15.2 ± 6.4	Low Moderate
Beck - Anxiety	14.4 ± 11.2	Mild
Quality of Life	101.6 ± 26.0	Poor (average for hemo samples)

CBT Intervention

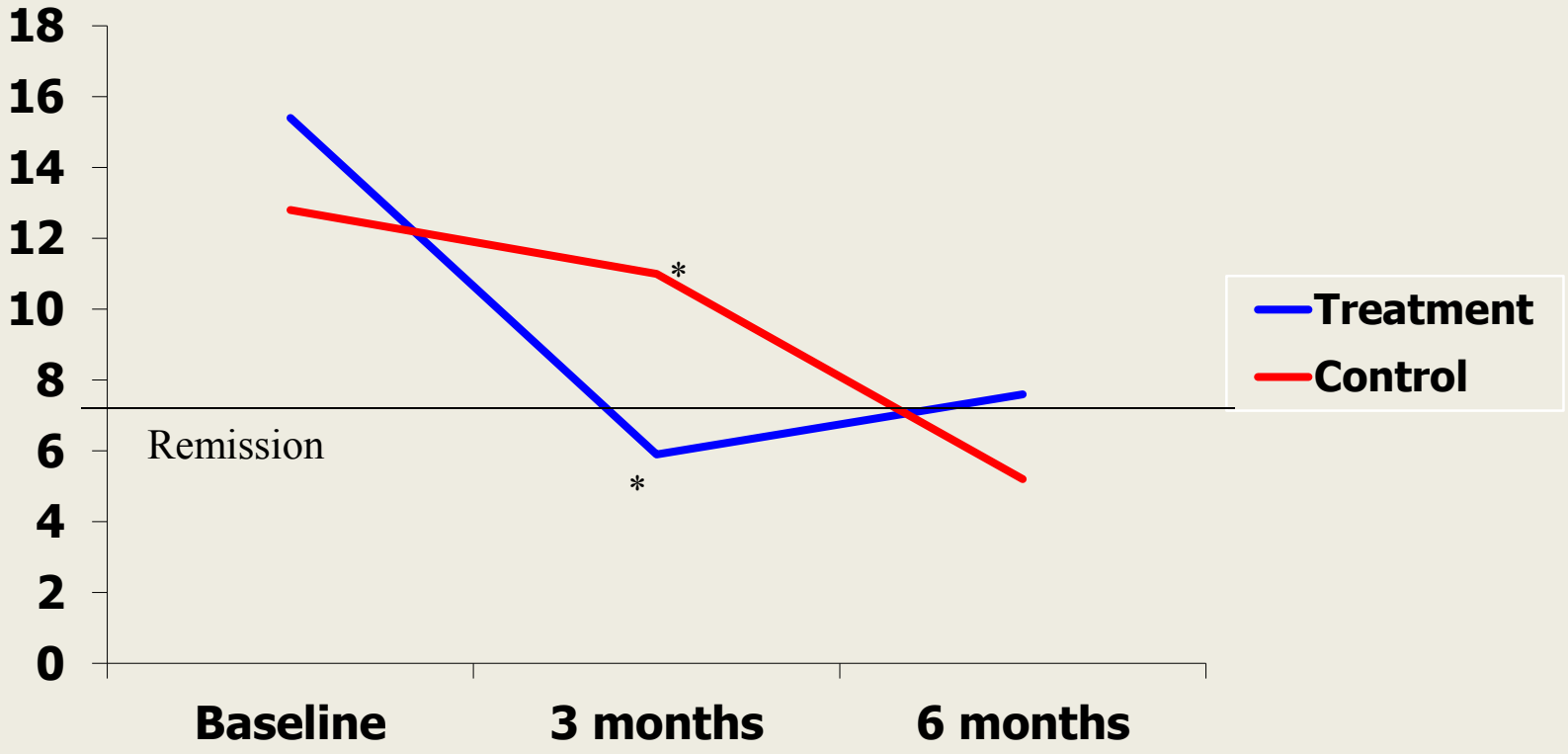
- Individual
- 10 sessions
- Chair-side
- Homework
- Focused on
  - Psycho-education (Depression vs. Illness)
  - Behavioral Activation (modified for HD)
  - Cognitive Restructuring (modified for HD)

CBT of Depression in ESRD Patients

Challenging the Depressed Dialysis Patient
Form 4.3



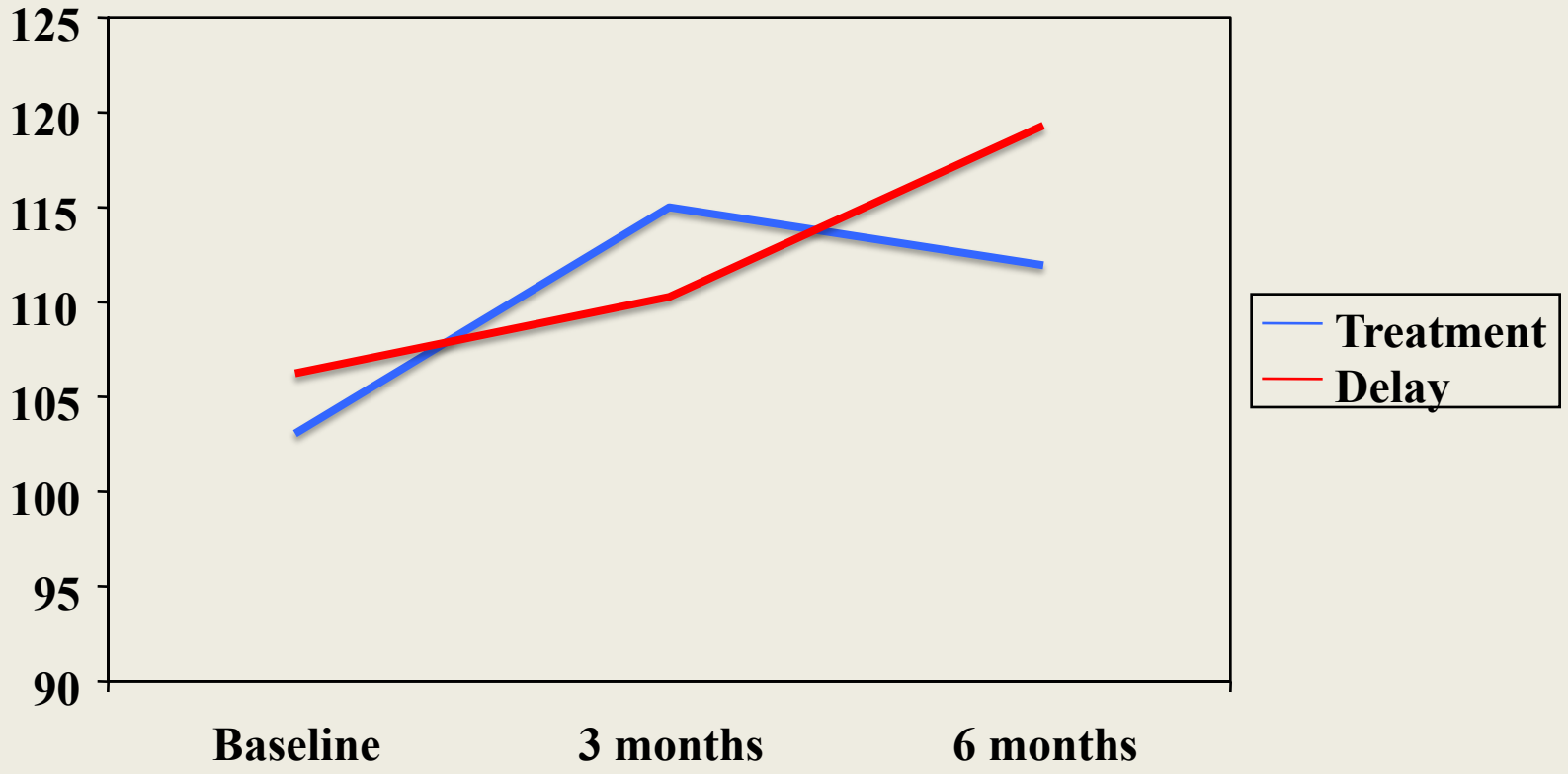
Hamilton-D ratings pre and post treatment for the treatment (n=31) and control (n=29) groups



Hamilton x time $F(2) = 15.6$, $p<.001$

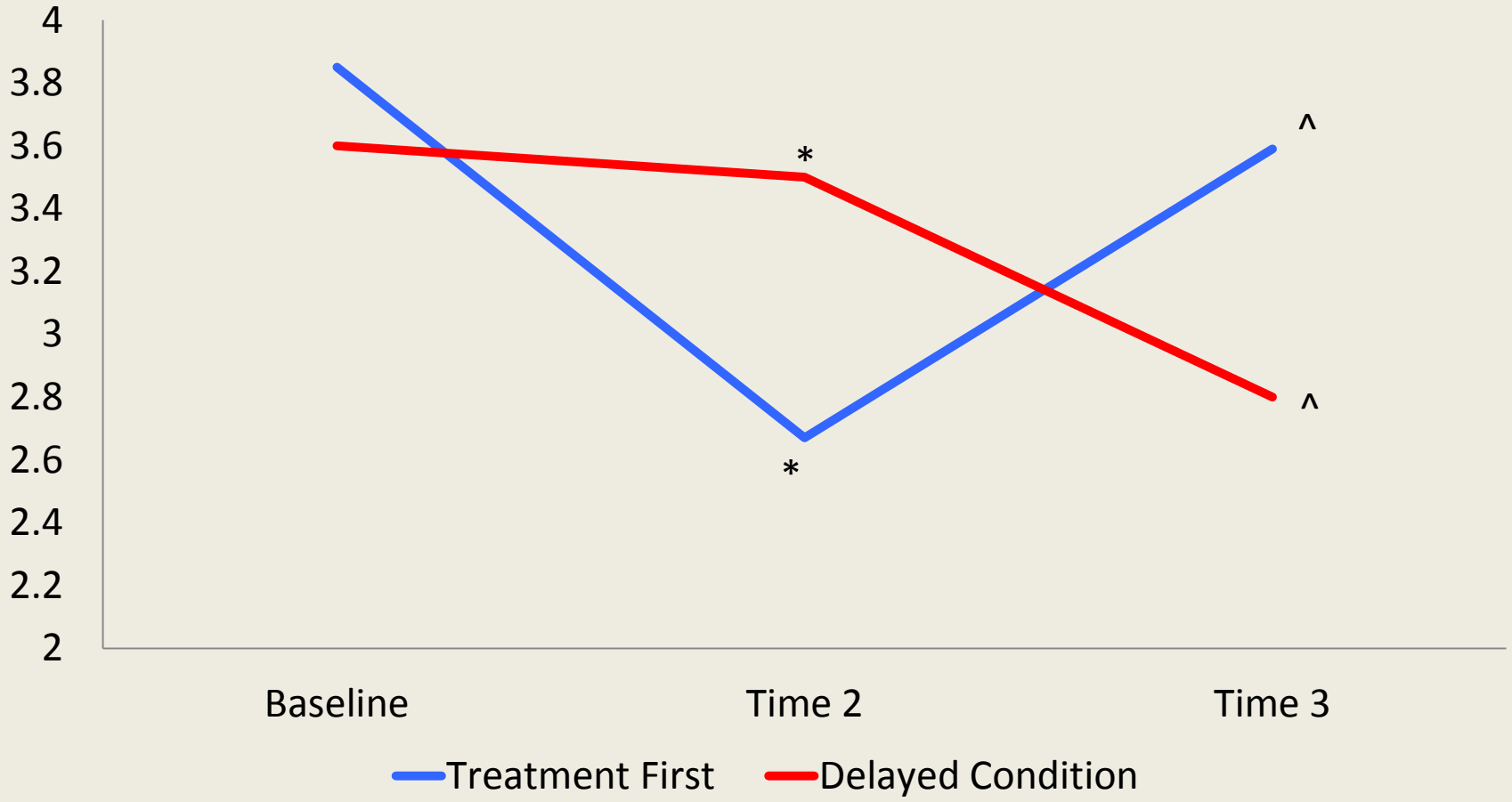
* $t(52)= -2.07$, $p < .05$

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

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PATIENT-CENTERED OUTCOMES RESEARCH INSTITUTE

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)
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  Scott Cohen (GW)
  Laura Dember (Penn)
  Tom Greene (U Utah)
  Paul Kimmel (NIDDK)
  Nancy Kutner (Emory)
  Steve Weisbord (U Pitt)
  Bessie Young (UW)

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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!