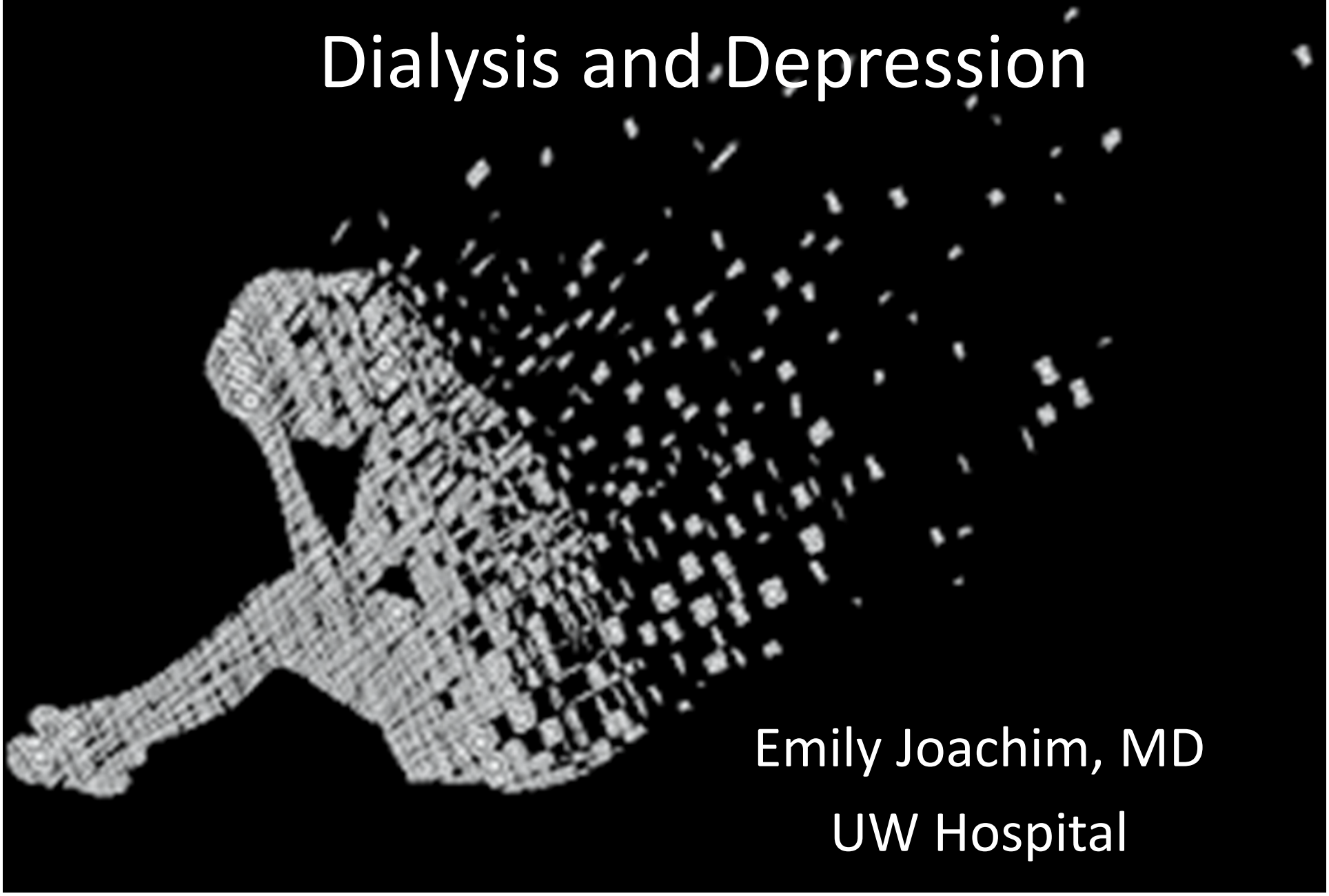
Dialysis and Depression



Emily Joachim, MD
UW Hospital

Goals

- Understand the prevalence of depression in patients on dialysis and how this affects patient outcomes
- Be able to discuss how to screen for depression in ESRD patients
- Describe which medications are most effective and be aware of dose adjustments
- Discuss alternative therapies that might be helpful for patients

Case

- You are seeing J.S, a 57 year old with a history of diabetes type 2, HTN, osteoarthritis, GERD who is starting on dialysis on your shift.
- She has been endorsing increased fatigue, lack of appetite, and weight loss, which is why dialysis is being started. She hasn't been able to do the things she normally likes to do because of these symptoms.
- She is nervous about starting dialysis, but otherwise says her mood is "ok".

Would you screen her for depression?

A. Yes

B. No

C. Maybe

Which screening tool would you use?

A. PHQ-9

B. Beck Depression inventory

C. Hamilton rating for depression

D. Cognitive depression inventory

E. Center for Epidemiologic Studies Depression Scale

Which screening tool to use?

- **Beck Depression Inventory (BDI)**
- 21 item questionnaire
  - <9 no depression
  - 10-15 mild depression
  - 16-23 moderate depression
  - >24 severe depression

- **Cognitive depression inventory (CDI)**
  - Subset of BDI which removes somatic symptoms

Which screening tool to use?

- **PHQ-9**
- 9 item questionnaire
  - 1-4 minimal depression
  - 5-9 mild depression
  - 10-14 moderate depression
  - 15-19 moderately severe depression
  - 20-27 severe depression

- **Center for Epidemiologic Studies Depression Scale (CES)**
- 20 item questionnaire
  - >16 is considered depressed

Beck Depression Inventory in ESRD patients

- 45.4% of dialysis patients were depressed if 10 was used as a cutoff
  - vs 12.2% based on DSM criteria
- Cutoff of 15 was found to be best
  - 92% sensitivity and 80% specificity
- Another study: BDI score >/= 16
  - 91% sensitivity and 86% specificity
  - PPV 59% and NPV 98%

Craven et al. *Int J Psych Med* 1988
Watnick et al. *AJKD 2005*

What about somatic symptoms?

- Cognitive depression inventory (CDI)
  - Removes the somatic symptoms
  - Not good evidence it can actually be used this way
- Sensitivity 77.8% and specificity 80.6%

- BDI is better

Chilcot et al. *Nephron Clin Pract* 2008

PHQ-9

- Score of >/= 10 in dialysis patients
  - 92% sensitivity and 92% specificity
  - 71% PPV and NPV 98%

CES

- 62% sensitivity and 81% specific
- PPV 53% and NPV of 85%, so not recommended

Hedayati et al. *KI* 2006
Watnick et al. *AJKD* 2005

Screening for depression in ESRD

Table 1. Potential screening and diagnostic tools for depression in patients with ESRD[a]

Depression Screening Tools	Possible Cutoff Score for Depressive Affect
BDI	>14 to 16 (3–5)
Cognitive Depression Inventory	>7 to 8 (2); not validated or recommended in CKD
MAACL	>11 (2,11); not recommended in CKD
Hamilton Rating Scale for Depression	>10 (2); not validated or recommended in CKD
PHQ-9	>10 (4)
CES-D	>18 (5)
Structured Clinical Interview for DSM-IV-TR	N/A
Diagnostic Interview Schedule	N/A
Formal psychiatric examination	N/A

[a]BDI, Beck Depression Inventory; CES-D, Center for Epidemiological Studies Depression Scale; CKD, chronic kidney disease; DSM-IV-TR, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*; MAACL, Multiple Affect Adjective Check List; PHQ-9, Patient Health Questionnaire

- Many tools are not validated in CKD populations

Cohen et al. *CJASN* 2007

Best to use?

- Both **Beck Depression Inventory** and **PHQ-9** have been validated in ESRD patients
- PHQ-9 may be easier to administer (shorter)

- No data on PHQ-2 in dialysis patients

Beck's Depression Inventory

This depression inventory can be self-scored. The scoring scale is at the end of the questionnaire.

1.

0	I do not feel sad.
1	I feel sad
2	I am sad all the time and I can't snap out of it.
3	I am so sad and unhappy that I can't stand it.

2.

0	I am not particularly discouraged about the future.
1	I feel discouraged about the future.
2	I feel I have nothing to look forward to.
3	I feel the future is hopeless and that things cannot improve.

3.

0	I do not feel like a failure.
1	I feel I have failed more than the average person.
2	As I look back on my life, all I can see is a lot of failures.
3	I feel I am a complete failure as a person.

4.

0	I get as much satisfaction out of things as I used to.
1	I don't enjoy things the way I used to.
2	I don't get real satisfaction out of anything anymore.
3	I am dissatisfied or bored with everything.

5.

0	I don't feel particularly guilty
1	I feel guilty a good part of the time.
2	I feel quite guilty most of the time.
3	I feel guilty all of the time.

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

NAME:_____ DATE:_____

Over the last *2 weeks*, how often have you been bothered by any of the following problems?
(use "✓" to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3

How and when to screen

- Screening for depression in general is controversial
- KDIGO doesn't have any guidelines
- KDOQI:
  - Every dialysis patient should be seen by the dialysis social worker at initiation of dialysis, and at least biannually thereafter, to assess the patient's psychological state, with specific focus on the presence of depression, anxiety, and hostility. (C)
  - Recommend BDI

Case, continued

- On initial screen, her PHQ-9 total score is 4 and her BDI is 6.

- You see her at her care conference 1 year later, and the social worker has been concerned about her medication compliance and the fact that she is missing dialysis sessions

Case, continued

- She reports that she is not sleeping well, she has lost more weight, and is no longer going to her yoga classes.
- Her albumin has decreased now to 3.2 as well.

- Does she have depression?

DSM V: Major depressive episode

5 or more of the following present for the same two week period

1. Depressed mood most of the day
2. Markedly diminished interest or pleasure in all or almost activities
3. Significant weight loss or weight gain or decrease or increase in appetite
4. Insomnia or hypersomnia
5. Psychomotor agitation or retardation
6. Fatigue or loss of energy
7. Feelings of worthlessness, excessive or inappropriate guilt
8. Diminished ability to think or concentrate, or indecisiveness
9. Recurrent thoughts of death, recurrent suicidal ideation or plan

Prevalence of Depression in ESRD

- Depression is the most common psychiatric disorder in patient with ESRD
- True point prevalence is difficult to assess

- General population point prevalence of depression:
  - 5-9% for women
  - 2-3% in men

Cohen et al. *CJASN* 2007
Palmer et al. *KI* 2013

What do you think the point prevalence of depression in ESRD is?

A. 5%

B. 10%

C. 20%

D. 30%

E. 40%

Prevalence of Depression in ESRD

- Interview-based diagnosis: 22.5% (CI 18.6-27.6)
- Rating scale: 39.3% (CI 36.8-42)

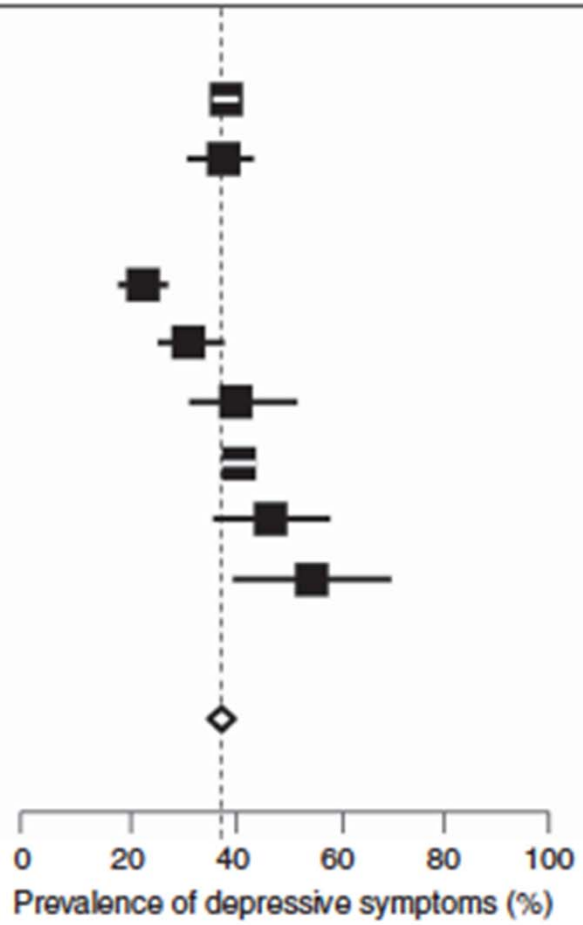
- Individual studies had prevalence between 5 to 54%!

- Best estimate is likely 20-30% of dialysis patients have depression at any time.

Palmer et al. *KI* 2013

Study-level covariate	No. of cohorts	No. of participants	Prevalence of clinical depression Random effects (95% CI)	*P*-value for subgroup difference
Dialysis type				
Hemodialysis	134	36,369	38.5% (35.4–41.6)	0.73
Peritoneal dialysis	35	2796	37.3% (31.7–43.5)	
Diagnostic tool for depression				
Interview	28	2855	22.8% (18.6–27.6)	
HADS	23	3967	31.3% (25.5–37.6)	
CES-D	8	10,561	40.6% (30.5–51.6)	<0.001
BDI	87	9384	41.3% (37.9–44.7)	
Hamilton	9	592	46.9% (36.0–58.2)	
Zung	4	354	55.0% (39.1–70.0)	
All cohorts	198	46,505	36.8% (34.4–39.2)	

Heterogeneity Cochran Q=4236; I^2=95.3%, P<0.001



Palmer et al. *KI* 2013

Why is it so difficult to diagnose depression?

- Somatic symptoms of uremia and depression overlap
  - Fatigue, sleep disorders, reduced appetite, apathy, poor concentration
- Electrolytes disorders, anemia, underlying disease
- Medications – antihypertensive, sedative-hypnotics

Levensen *Psychosomatics* 1991
Israel *Can J Psychiatry* 1986

Can we differentiate somatic symptoms from depression?

- Non-depressed, medically ill patients:
  - Irritability
  - Sadness
  - Crying
  - Mild pessimism
  - Indecisiveness
  - Dissatisfaction
- Associated with MDD in ESRD:
  - Depressed mood
  - Loss of interest
  - Concentration difficulties

Chilcot et al. *Nephron Clin Pract* 2008

Can we differentiate somatic symptoms from depression?

- However, depressed dialysis patients reported more somatic symptoms than non-depressed dialysis patients

- Physical symptoms related more closely to depression than medical co-morbidities

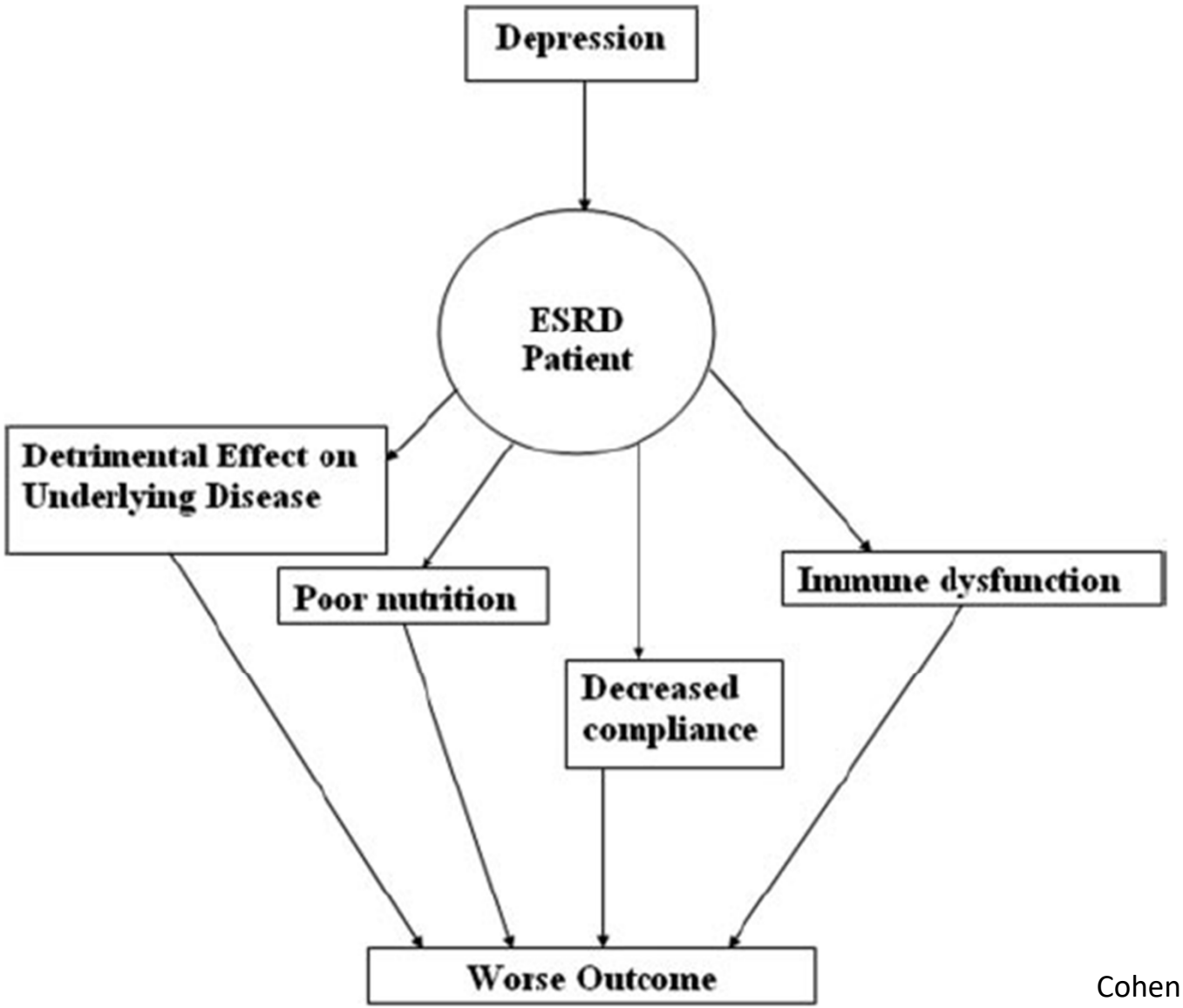
Why the high prevalence of depression in ESRD patients?

- "Multiple loss experience"
  - Loss of renal function
  - Time
  - Role in family
  - Work
  - Fear of death
  - Independence
  - Mobility
  - Medication effects
  - Dietary constraints
- Feelings of "loss of control"

Kimura
Chilcot et al. *Nephron Clin Pract* 2008

Why does depression matter?

Why does depression matter?



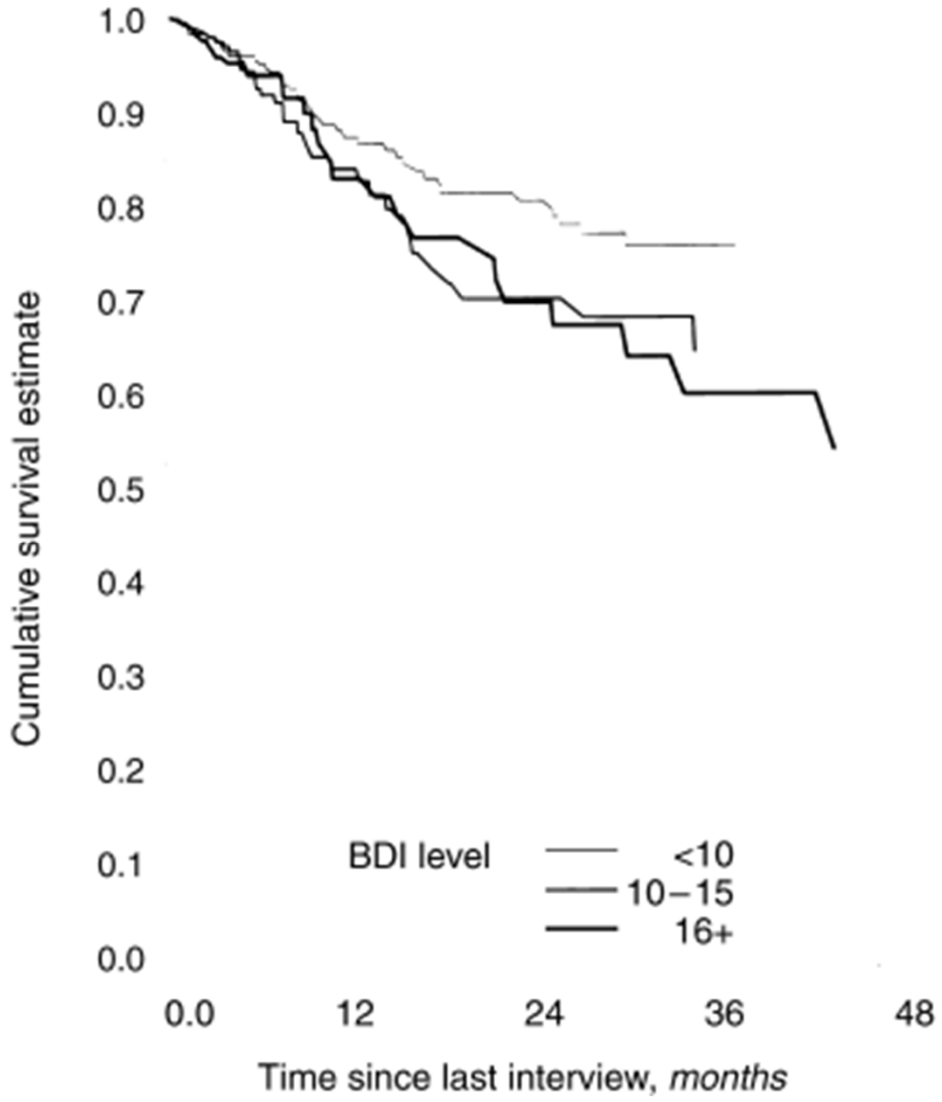
Cohen et al. *CJASN* 2007

Depression has been associated with:

- Altered immune system function (decrease cellular immunity, increased cytokines)
- Poor nutrition
  - Depression preceded low albumin in dialysis patients
- Increased cardiovascular disease
- Non-adherence to treatment
- Higher risk of suicide
- Dialysis discontinuation
- Hospitalizations

Farrokhi et al. *AJKD* 2014
Cohen et al. *CJASN* 2007

Survival is worse with more severe symptoms



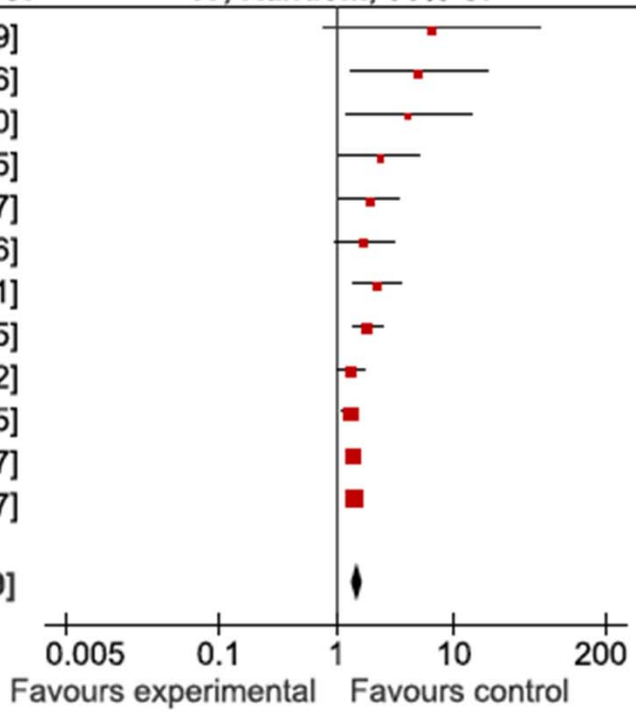
Kimmel et al. *KI* 2000

Depression increases mortality

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Diefenthaeler 2008	1.8718	1.0792	0.3%	6.50 [0.78, 53.89]
Riezebos 2010	1.6094	0.688	0.7%	5.00 [1.30, 19.26]
Drayer 2006	1.4109	0.623	0.8%	4.10 [1.21, 13.90]
Kojima 2010	0.859	0.398	1.9%	2.36 [1.08, 5.15]
Balogun 2011	0.647	0.304	3.1%	1.91 [1.05, 3.47]
Griva 2010	0.536	0.297	3.2%	1.71 [0.95, 3.06]
Boulware 2006	0.7975	0.248	4.4%	2.22 [1.37, 3.61]
van den Beukel 2010	0.604	0.15	9.6%	1.83 [1.36, 2.45]
Lacson 2012	0.278	0.136	11.0%	1.32 [1.01, 1.72]
Kimmel 2000	0.278	0.081	18.6%	1.32 [1.13, 1.55]
Lopes 2002	0.329	0.062	22.1%	1.39 [1.23, 1.57]
Lopes 2004	0.3506	0.0501	24.4%	1.42 [1.29, 1.57]
Total (95% CI)			**100.0%**	**1.51 [1.35, 1.69]**

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 18.33$, df = 11 (P = 0.07); $I^2 = 40\%$

Test for overall effect: Z = 7.34 (P < 0.00001)



Case, continued

- Her PHQ-9 is 16 now and BDI is 16.
- You are concerned that she has depression and it is affecting her health.

What to do next?

- Who should manage her depression?
  A. PCP
  B. Her primary nephrologist
  C. Psychologist or psychiatrist

- Do you feel comfortable prescribing medication?

Treatment of Depression in dialysis patients

- In one study, only 16% of depressed HD patients were being treated!
- Treatment options
  - SSRI
  - SNRI
  - Other: mirtazapine
  - Herbal supplements
  - ECT
  - Psychotherapy/CBT

Watnick et al. *AJKD* 2005
Cohen et al. *CJASN* 2007

SSRI therapy

- A general recommendation is to reduce the dose of SSRI by 1/3
- Can *decrease* orthostatic hypotension
- Can *increase* risk of bleeding
- Risk for mania or increased suicide risk (all antidepressants)

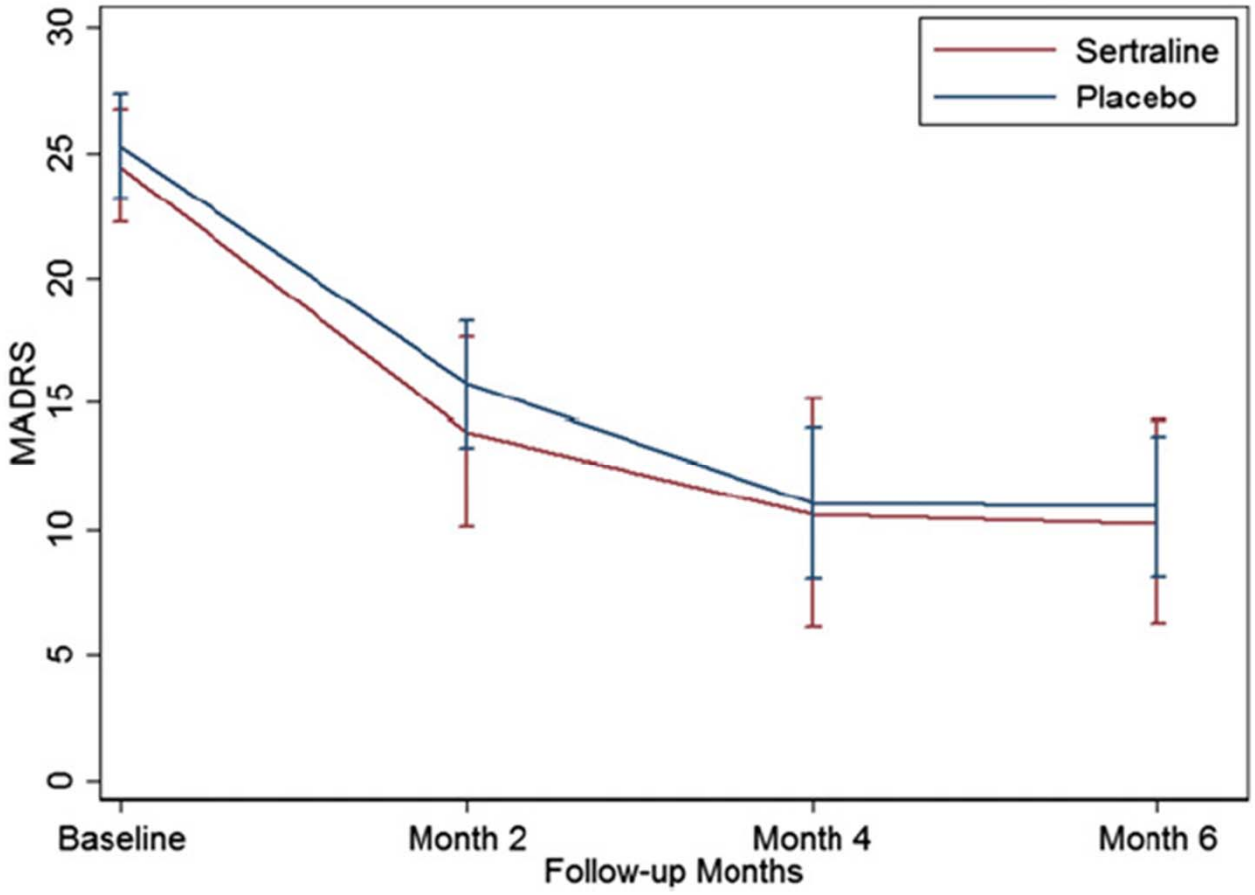
Cohen et al. *CJASN* 2007

Medication	Adult Starting Dosage in ESRD	Efficacy Data	Drug Interactions	Comments
Citalopram	10 to 60 mg/d	Wuerth *et al.* (87,88)	Contraindicated with MAOI, ergotamines, phenothiazines, pimozide, phenobarbital; may increase warfarin and phenytoin levels	In general, no dosage adjustment needed in ESRD
		Spigset *et al.* (95)		
Fluoxetine	20 mg/d	Blumenfeld *et al.* (85)	Same as citalopram	In general, no dosage adjustment needed in ESRD
		Levy *et al.* (86)		
Paroxetine	10 to 30 mg/d	Doyle *et al.* (96)	Same as citalopram	Reduction of dosage needed
Sertraline	50 to 200 mg/d	Wuerth *et al.* (87,88)	Same as citalopram	In general, no dosage adjustment needed in ESRD
Bupropion	100 mg every 8 h	Wuerth *et al.* (87,88)	MAOI	Increased risk for seizures in ESRD
Mirtazapine	7.5 to 22.5 mg/d		MAOI	Dosage reduced by 50% in ESRD
Nefazodone	50 to 150 mg/d	Seabolt *et al.* (97)		No dosage adjustment needed in ESRD
		Olyaei *et al.* (98)		
Venlafaxine	37.5 to 112.5 mg/d	Troy *et al.* (99)		No dosage adjustment needed in ESRD

Cohen et al. *CJASN* 2007

Sertraline Versus Placebo in Patients with Major Depressive Disorder Undergoing Hemodialysis: A Randomized, Controlled Feasibility Trial

Karin Friedli, Ayman Guirguis, Michael Almond, Clara Day, Joseph Chilcot, Maria Da Silva-Gane, Andrew Davenport, Naomi A. Fineberg, Benjamin Spencer, David Wellsted, and Ken Farrington



Friedli et al. *CJASN* 2017

Published in final edited form as:
Contemp Clin Trials. 2016 March ; 47: 1–11. doi:10.1016/j.cct.2015.11.020.

Rationale and Design of A Trial of Sertraline *vs.* Cognitive Behavioral Therapy for End-stage Renal Disease Patients with Depression (ASCEND)

S. Susan Hedayati[1,2], Divya M. Daniel[3], Scott Cohen[4], Bryan Comstock[5], Daniel Cukor[6], Yaminette Diaz-Linhart[7], Laura M. Dember[8], Amelia Dubovsky[9], Tom Greene[10], Nancy Grote[11], Patrick Heagerty[5], Wayne Katon[9], Paul L. Kimmel[12], Nancy Kutner[13], Lori Linke[3], Davin Quinn[14], Tessa Rue[5], Madhukar H. Trivedi[15], Mark Unruh[16], Steven Weisbord[17], Bessie A. Young[3], and Rajnish Mehrotra[3]

- 120 patients enrolled
- SSRI > CBT but both improved BDI score
- No control group

SNRI

- Bupropion
  - Increased risk of seizures in ESRD
  - Probably not a good choice
- Venlafaxine
  - Toxic metabolites, with ESRD and decreased renal clearance, “use with caution”

Cohen et al. *CJASN* 2007

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Cohen et al. *CJASN* 2007

Other antidepressants

- Mirtazapine
  - Can be helpful with sleep and appetite
  - Dose reduce by 50%

Cohen et al. *CJASN* 2007

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Cohen et al. *CJASN* 2007

Classes to avoid:

- Tricyclics and MAOIs
  - "adverse effects in general population"
  - TCAs have anticholinergic symptoms
    - Orthostatic hypotension
    - Arrhythmias
  - MAOI have *many* drug interactions

Cohen et al. *CJASN* 2007

Herbal supplements

- St John's Wort
  - Increased risk of drug interactions
  - CYP3A4 enzyme system
    - Can decrease drug levels of CNI in particular

Cohen et al. *CJASN* 2007

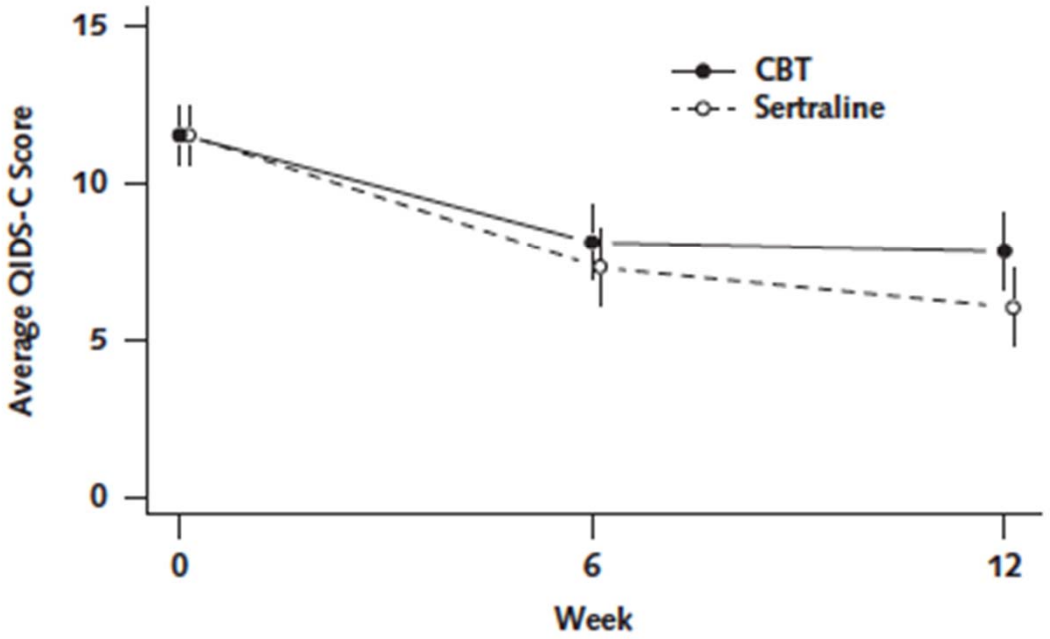
ECT

- One case report of a dialysis patient with bipolar treated with ECT successfully
- “Unique risks” with ESRD population
  - Hyperkalemia, acid-base alterations, general anesthesia, and the increased cardiovascular risk
- Not standard of care

Cohen et al. *CJASN* 2007

Psychotherapy/CBT

Figure 2. Longitudinal data on the primary outcome measure of QIDS-C scores among patients receiving hemodialysis with depression who were randomly assigned to CBT or sertraline treatment.



At each time point, for each treatment group, the data are presented as mean and 95% CI. CBT = cognitive behavioral therapy; QIDS-C = Quick Inventory of Depressive Symptoms-Clinician-Rated.

Mehrotra et al. *Annals* 2019

Group therapy

- Dialysis patients who participated in a social support group had improved survival

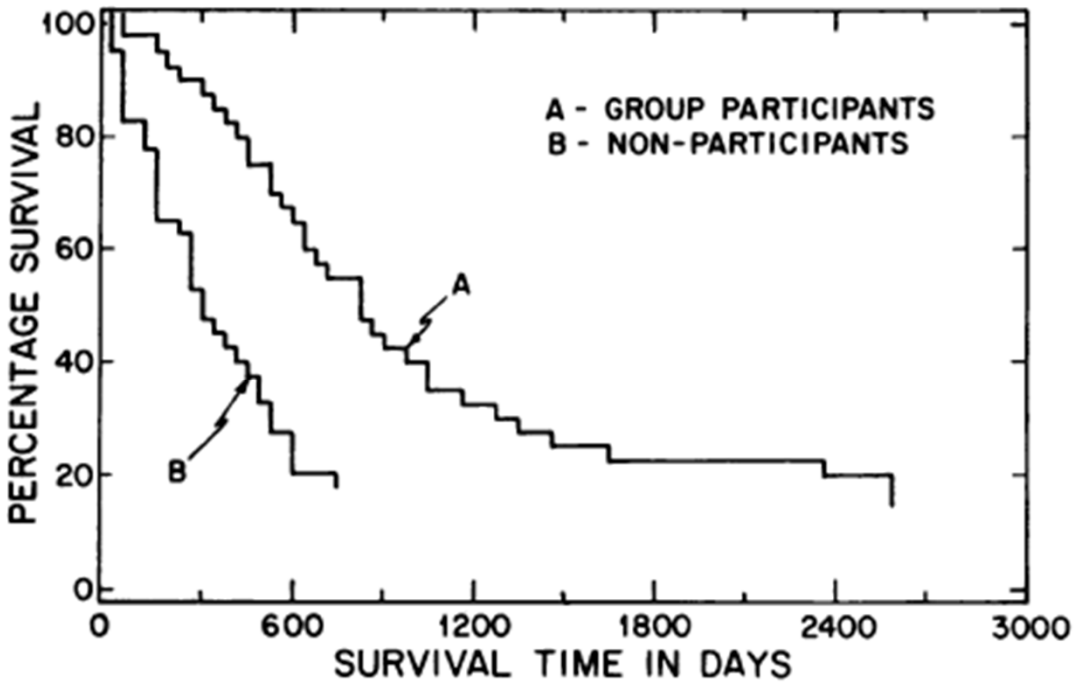


FIGURE 1—Kaplan-Meier Survival Curves for Group Participants and Non-Participants

Friend et al. *Am J Public Health* 1986

Group CBT led to decrease in depressive symptoms

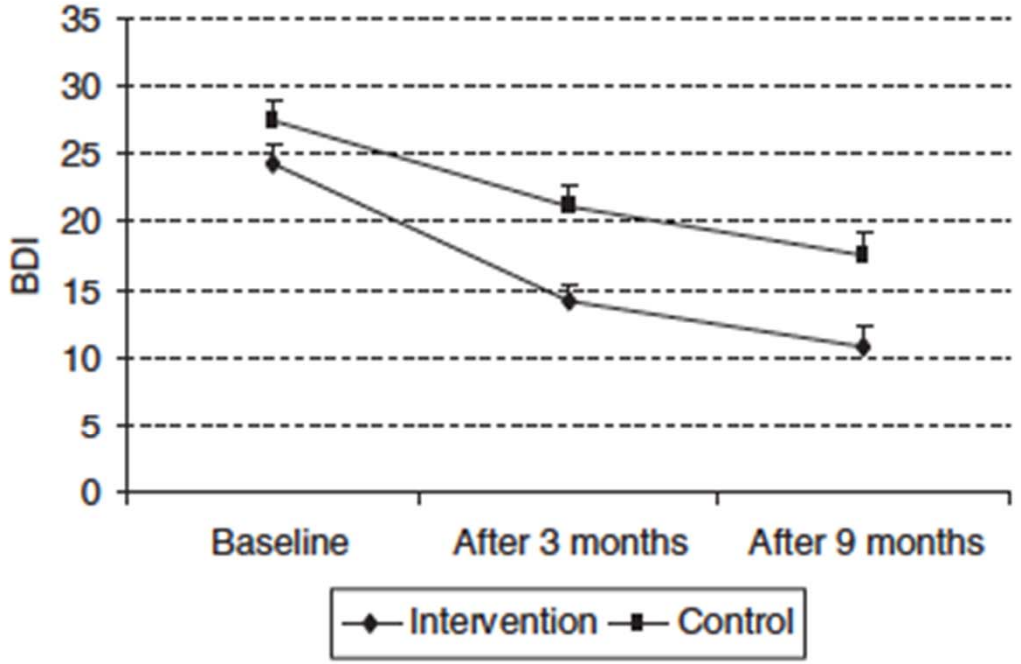


Figure 2 | Mean + s.e. of the Beck Depression Inventory (overall BDI score), according to time of study evaluation and group. $P = 0.001$ for the comparison between groups; $P < 0.001$ for the comparison within the intervention group; and $P < 0.001$ for the comparison within the control group.

Duarte et al. *KI* 2009

Exercise

- Randomized, controlled trial of 31 HD patients and “Exercise rehabilitation program”
  - BDI scores decreased from 21.0± 10.4 to 13.7± 9.5 in the exercise group

- Another study did not show any benefit

Kouidi et al. *Nephron* 1997

Case, continued

- How should we treat her?

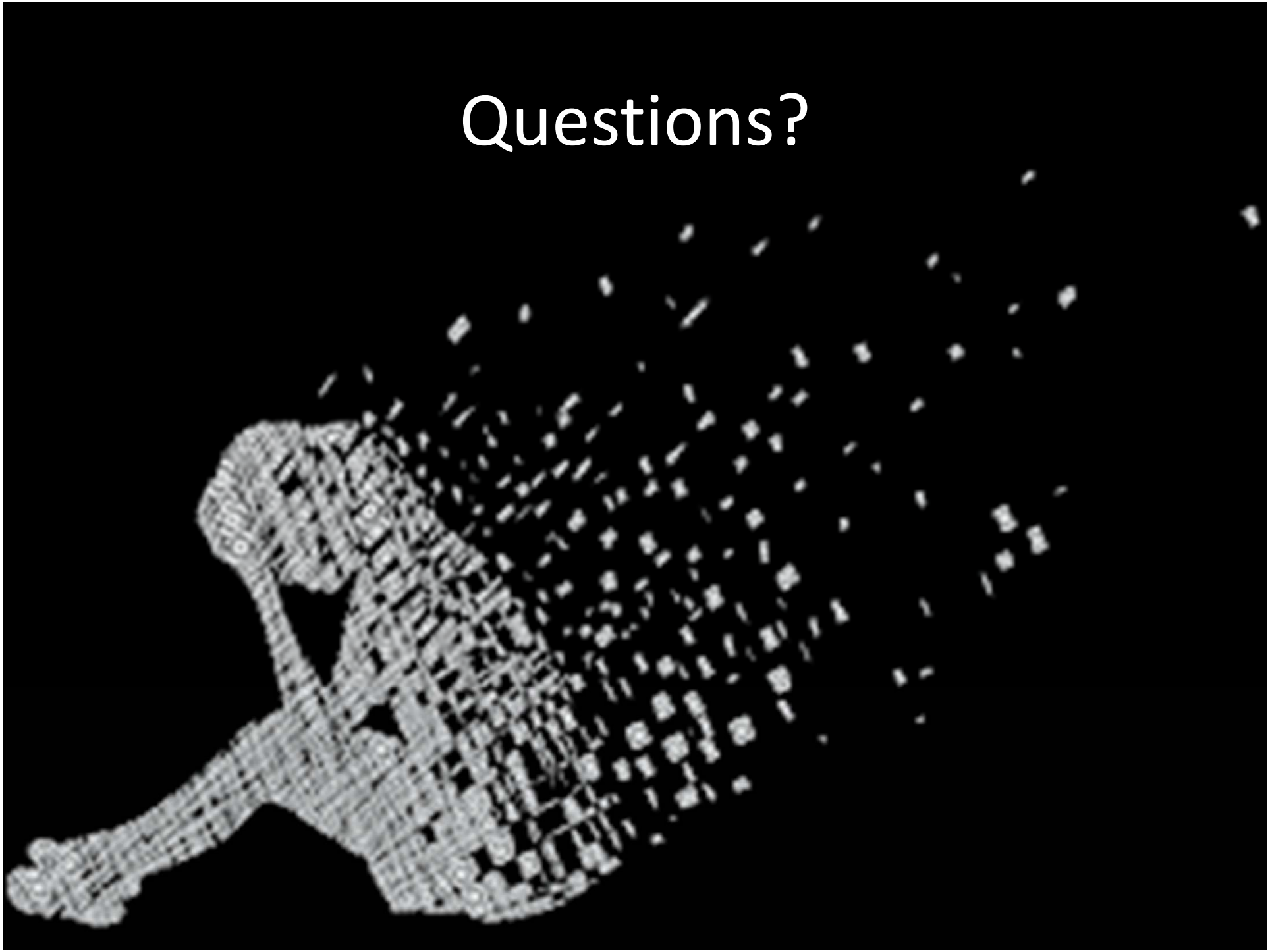
Case conclusion

- You start JS on fluoxetine, 20 mg daily and encourage her to restart her yoga instruction
- After 12 weeks, she did not report significant improvement and thus you refer her to a psychologist for further treatment

In Conclusion

- Depression is *very* common in your dialysis patients
- Associated with increased mortality and poor outcomes
- BDI or PHQ-9 are likely best screening tools
  - Adjusted cutoff of 14-16 with BDI
- SSRI is likely best class of medications, may need dose reduction
  - Efficacy not well studied in dialysis
- Need more studies but group therapy or exercise may be beneficial

Questions?



References

- Palmer S, Vecchio M, Craig JC, Tonelli M, Johnson DW, Nicolucci A, Pellegrini F, Saglimbene V, Logroscino G, Fishbane S, Strippoli GF. Prevalence of depression in chronic kidney disease: systematic review and meta-analysis of observational studies. Kidney Int. 2013 Jul;84(1):179-91.
- Levenson JL, Glocheski S. Psychological factors affecting end-stage renal disease: a review. *Psychosomatics* 1991;32:382–09.
- Israel M: Depression in dialysis patients: a review of psychological factors. Can J Psychiatry 1986; 31: 445–451.
- Hedayati SS, Bosworth HB, Kuchibhatla M, Kimmel PL, Szczech LA: The predictive value of self-report scales compared with physician diagnosis of depression in hemodialysis patients. *Kidney Int 69: 1662–1668, 2006*
- Watnick S, Wang PL, Demadura T, Ganzini L: Validation of 2 depression screening tools in dialysis patients. *Am J Kidney Dis 46: 919–924, 2005*
- Kimmel PL, Peterson RA, Weihs KL, Simmens SJ, Alleyne S, Cruz I, Veis JH: Multiple measurements of depression predict mortality in a longitudinal study of chronic hemodialysis patients. *Kidney Int 57: 2093–2098, 2000*
- Mehrotra R, Cukor D, Unruh M, Rue T, Heagerty P, Cohen SD, et al. Comparative Efficacy of Therapies for Treatment of Depression for Patients Undergoing Maintenance Hemodialysis: A Randomized Clinical Trial. Ann Intern Med. ;170:369–379.
- Friend R, Singletary Y, Mendell NR, Nurse H: Group participation and survival among patients with end-stage renal disease. *Am J Public Health 76: 670–672, 1986*
- Duarte PS, Miyazaki MC, Blay SL et al. Cognitive-behavioral group therapy is an effective treatment for major depression in hemodialysis patients. Kidney Int 2009; 76: 414–421.
- Kouidi E, Iacovides A, Iordanidis P, Vassiliou S, Deligiannis A, Ierodiakonou C, Tourkantonis A: Exercise renal rehabilitation program: Psychosocial effects. *Nephron 77:* 152–158, 1997
- Craven JL, Rodin GM, Littlefield C: The Beck Depression Inventory as a screen device for major depression in renal dialysis . *Int J Psychiatry Med 18:365–374, 1988*