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Pharmacologic and Psychological Interventions for Depression Treatment in Patients with Kidney Disease

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Abstract

Purpose of Review—It remains controversial whether existing therapies, including pharmacologic and psychological interventions, are effective for treatment of depression in patients with chronic kidney disease (CKD) and end-stage kidney disease (ESKD).

Recent Findings—Most studies of depression treatment were underpowered or uncontrolled. The CKD Antidepressant Sertraline Trial (CAST) showed no benefit of a serotonin-selective reuptake inhibitor (SSRI), sertraline, over double-blind matched placebo for the treatment of depressive symptoms in patients with non-dialysis CKD. A Trial of Sertraline vs. Cognitive Behavioral Therapy (CBT) for End-stage Renal Disease Patients with Depression (ASCEND) showed improvement in depressive symptoms from baseline in both groups and a marginal benefit of sertraline over CBT that was of unclear clinical significance, given the lack of an active control group. SSRIs are associated with poor tolerability in clinical trials and serious adverse outcomes in large retrospective studies.

Summary—Although the data do not support unlimited use of SSRIs in patients with CKD or ESKD, it is reasonable to initiate a cautious trial of sertraline while closely monitoring for depressive symptom improvement and adverse effects. CBT is a low-risk, possibly effective intervention to treat major depressive disorder in patients with kidney disease who have access to such treatments.

Keywords

chronic kidney disease; depression; sertraline; cognitive behavioral therapy; selective serotonin reuptake inhibitor

INTRODUCTION

Major depressive disorder (MDD) is prevalent in 20–25% of patients with non-dialysis chronic kidney disease (CKD) and end-stage kidney disease (ESKD) and is associated with adverse outcomes including hospitalization, death, and cardiovascular events [1–8]. Despite

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this disproportionately high burden of disease, published data are limited in patients with CKD and ESKD to support the use of standard treatments for MDD that were proven effective in the general population, including pharmacologic and psychological interventions. The purpose of this review is to summarize existing literature evaluating the efficacy, tolerability, and safety of pharmacologic and psychological therapeutic options for MDD in patients with CKD and ESKD.

SCREENING FOR MDD

Current diagnostic algorithms begin with screening for MDD by self-reported patient questionnaires such as the Quick Inventory of Depressive Symptomatology (QIDS) [9] or the Beck Depression Inventory II (BDI) [10]. In patients with CKD, a QIDS score ≥10 and a BDI score ≥11 have been validated as thresholds to identify individuals who screen positive for MDD [11]. In patients with ESKD, validated cutoffs include BDI score ≥14–16 [2, 4, 12], Center for Epidemiologic Studies Depression Scale (CESD) score ≥18 [2], and Patient Health Questionnaire (PHQ) score ≥10 [4]. Formal diagnosis then requires more detailed evaluation to confirm the presence of sadness or anhedonia as an essential component of diagnosis, exclude other psychiatric diagnoses such as bipolar disorder, and identify the need for urgent intervention for suicidal ideation. Tools such as the Mini International Neuropsychiatric Interview [13] or the Structured Clinical Interview for DSM-5 [14] can facilitate this evaluation, but these require special training and may not be immediately clinically available. Thus, in the clinical setting it is often most practical to identify candidates for therapy by using a validated self-report screening measure such as the QIDS or BDI to see if the patient meets the validated cut-off, then confirming the presence of sadness, anhedonia, or suicidal ideation directly with the patient [15].

PHARMACOLOGIC THERAPY FOR MDD IN PATIENTS WITH KIDNEY DISEASE

Few clinical trials exist to guide therapy in patients with CKD and ESKD in whom MDD is confirmed. Recommendations should incorporate critical appraisal of several studies of varying quality that investigated the efficacy, tolerability, and safety of pharmacologic therapy for MDD.

Efficacy of Pharmacologic Therapy

With a few notable exceptions, most prior studies of antidepressant medications in patients with kidney disease were limited by lack of an active control group, small sample size, and/or inadequate dosing or duration of treatment (Table 1) [16–27, 28*, 31]. Most investigated the effects of an SSRI, the class of antidepressant drug with the best cardiovascular profile [15]. Only one adequately powered placebo-controlled multi-center randomized clinical trial investigated the efficacy of pharmacologic antidepressant therapy in patients with non-dialysis CKD. The Chronic Kidney Disease Antidepressant Sertraline Trial (CAST) compared 12 weeks of sertraline with matching placebo for effect on depressive symptoms in 201 participants with non-dialysis CKD stages 3–5 [29*, 32]. Study drug was prescribed at an initial dose of 50 mg daily and dose-escalated every 2 weeks to a

maximum of 200 mg daily as tolerated [32]. Using an intention-to-treat analysis, there was a 4-point improvement in depressive symptoms from baseline to exit in both groups, but no benefit of sertraline over placebo, with a between-group difference (95% confidence interval [CI]) in depressive symptoms of 0.1 (−1.1, 1.3) points on the QIDS after 12 weeks of treatment. In subgroup analysis, there was no difference between depressive symptoms at study exit between the sertraline and placebo groups by CKD stage or study site. However, secondary analyses of this trial showed that inflammatory biomarkers were associated with somatic symptoms of depression and those with a higher baseline C-reactive protein (measured using a high-sensitivity assay) may be more likely to benefit from sertraline initiation [33*, 34*]. Although these hypothesis-generating results are promising, especially since depressive symptom severity is associated with increased levels of inflammatory biomarkers [35*], the use of inflammatory biomarkers to identify subgroup of patients with CKD who may benefit from sertraline needs to be validated prior to incorporation in clinical practice.

In patients with ESKD on chronic hemodialysis, well-powered, placebo-controlled data are lacking. Three small randomized trials compared SSRIs to placebo for the treatment of depressive symptoms in patients with prevalent ESKD on hemodialysis. In these studies participants were randomized to fluoxetine 20 mg daily for 8 weeks vs. placebo [18], sertraline 100 mg daily for 12 weeks vs. placebo [27], or sertraline, prescribed at an initial dose of 50 mg daily uptitrated to a maximum dose of 100 mg for 6 months, vs. placebo [28]. These trials reported significant decreases in depressive symptoms from baseline in both the SSRI and placebo groups but were underpowered to detect benefit of active drug over placebo. When taken in the context of the results of CAST, these studies suggest that placebo-treated individuals with ESKD demonstrate a decrease in depressive symptoms over time that paralleled the improvements seen in those treated with an SSRI, but potential benefit of these treatments over placebo has not been robustly investigated.

Another randomized trial compared sertraline to cognitive behavioral therapy (CBT) in patients with ESKD. A Trial of Sertraline vs. Cognitive Behavioral Therapy for End-stage Renal Disease Patients with Depression (ASCEND) randomized 120 participants receiving chronic hemodialysis to 12 weeks of either open-label sertraline, dose-escalated from 50 mg daily to a maximum tolerated dose of 200 mg daily, or ten 60-minute sessions of chair-side individualized CBT, administered during hemodialysis [30*]. This trial did not include an active control arm [36]. Participants in the sertraline group had an improvement in depressive symptoms as measured by the QIDS from 10.9 points at baseline to 5.9 points at 12 weeks. However, the absence of an active control calls in to question whether sertraline would have been more effective than placebo. In CAST, the placebo group had a 4-point improvement in depressive symptoms measured by the QIDS from baseline to study exit, which is similar to the improvement seen in ASCEND in the active treatment arms. Even the smaller placebo-controlled clinical trials in patients with ESKD showed improvements in depressive symptoms from baseline to exit in the control arms [18, 27, 28*]. Although there was a statistically significant but modest benefit of sertraline over CBT, with a between-groups effect estimate (95% CI) of −1.84 (−3.54, −0.13) points on the QIDS scale, it is unclear whether this difference is clinically meaningful, and it remains unknown whether

either of these treatments would have been more effective than no treatment, given the lack of active control.

Taken as a whole, randomized clinical trial data indicate that in patients with CKD and ESKD, sertraline is likely no more effective than placebo for improving depressive symptoms. However, given that some patients achieved clinical response to sertraline in CAST and ASCEND, and in the absence of evidence for alternative treatments, a cautious and closely monitored trial of sertraline at the minimally effective and tolerated dose is warranted in clinical practice. We suggest that sertraline be started at a dose of 50 mg a day, uptitrated by 50 mg every 2 weeks as tolerated, up to a maximum dose of 200 mg daily. The patient should be reassessed after 6 weeks of maximum dose, and drug titrated down and discontinued if there is no benefit.

Tolerability and Safety of Pharmacologic Therapy

Because of the high rate of comorbid medical conditions and polypharmacy in patients with kidney disease, randomized trial data are critical to evaluate adverse effects of antidepressant therapies. SSRIs, the most commonly used antidepressant medication in the general population, as well as the antidepressant class with the best cardiovascular profile, are known to cause somatic side effects including nausea, diarrhea, central nervous system effects such as headache, and sexual dysfunction. In CAST, those randomized to sertraline had a higher rate of gastrointestinal side effects such as nausea or vomiting (22.7% vs. 10.4%, P=0.03) and diarrhea (13.4% vs. 3.1%, P=0.02) than those receiving placebo [29*]. Prior to CAST, a meta-analysis of four small controlled clinical trials reported higher rates of nausea in patients with ESKD receiving an SSRI vs. control [37]. In ASCEND, sertraline was associated with higher rates of adverse effects, including nervous system effects, compared to CBT [30*]. In the placebo-controlled trial of 30 participants by Friedli, et al., dropout rate due to adverse events occurred in 0 of 15 participants randomized to placebo vs. 4 of 15 randomized to sertraline, attributed to death by cardiac arrest, insomnia, headache and dizziness, and nausea [28*]. Some of these adverse effects may not have been attributable to the study drug; for example, they report that the individual who died had only taken one tablet of sertraline. In the study comparing fluoxetine to placebo in 14 participants with ESKD, those randomized to fluoxetine had slightly higher rates of multiple adverse effects including hypotension, dyspepsia, nausea, and neurological symptoms such as headache and insomnia, but this study was underpowered to rule out sampling error as a source of these differences [18]. Taken in sum, SSRIs likely cause increased symptomatic adverse effects in patients with kidney disease. There are no randomized data in patients with CKD or ESKD to evaluate the adverse effects of non-SSRI classes of antidepressant medications, although these are known to cause serious side effects as well [16].

Furthermore, although clinical trials have not been powered to identify rare outcomes, recent large observational studies demonstrated that treatment with SSRIs was associated with several serious adverse events. One case control study showed that SSRI use was associated with increased odds of hip fracture among patients on chronic hemodialysis, adjusted odds ratio (95% CI) 1.25 (1.17, 1.35) [38*]. Although treatment with sertraline did not affect platelet aggregability in an *a priori* secondary analysis of CAST [39*], a retrospective cohort

study showed an increased risk of gastrointestinal bleeding in patients with non-dialysis CKD prescribed an SSRI, with an adjusted rate difference that increased across advancing stages of CKD [40*]. Finally, an active comparator new-user retrospective cohort study found that patients with ESKD receiving hemodialysis who were prescribed citalopram or escitalopram had a higher risk of 1-year sudden cardiac death, adjusted hazard ratio (95% CI) 1.18 (1.05, 1.31), and cardiovascular mortality, adjusted hazard ratio (95% CI) 1.11 (1.02, 1.22), compared to those prescribed SSRIs less likely to prolong the QTc (fluoxetine, fluvoxamine, paroxetine, or sertraline) [41*].

Based on these data, pharmacologic antidepressant therapy with an SSRI is associated with higher rates of somatic adverse effects such as gastrointestinal and nervous system symptoms, although it is less clear whether results of observational studies reporting more serious adverse events, such as hip fractures, frank gastrointestinal bleeding, and fatal cardiovascular outcomes, may have been confounded by indication bias. For individual patients who merit a trial of an SSRI, close monitoring for tolerability and adverse events is critical. Choosing an SSRI that is less likely to prolong the QT interval and need for dose adjustment in the setting of decreased glomerular filtration rate, such as sertraline, may be important to minimize the risk of cardiovascular mortality with these treatments.

PSYCHOLOGICAL INTERVENTIONS FOR MDD IN PATIENTS WITH KIDNEY DISEASE

Non-pharmacologic psychological interventions such as CBT are an alternative evidence-based strategy for managing MDD in the general population. However, psychological interventions are not universally acceptable to patients with kidney disease [36]. Compared to pharmacologic therapy, psychological interventions avoid prescribing additional medications for patients burdened by polypharmacy, adverse medication effects, and drug interactions. On the other hand, psychological interventions may not be accessible due to cost or regional availability and require investment of time and effort from patients who already frequently interface with the health care system. Some studies are attempting to improve access to psychological interventions using internet-based platforms for patients with ESKD [42, 43], but such interventions have not been widely implemented yet.

Few studies have evaluated the efficacy of psychological interventions in individuals with CKD or ESKD (Table 2). Six small randomized controlled studies demonstrated efficacy of CBT compared to controls in patients with ESKD receiving chronic hemodialysis [44–49]. In one study, the control group received non-directive counseling [47], while the control groups in the other five studies received usual care [44–46, 48, 49*]. Despite the unblinded nature of the intervention, participants randomized to the control groups in three of the studies experienced improvements in depressive symptoms from baseline to study exit [45–47], although in all trials improvements in the CBT group were greater than in the control group. Small uncontrolled or non-randomized studies also showed a decrease in depressive symptoms after CBT or other psychological intervention [43, 50, 51*, 52]. A meta-analysis investigating this question also reported that CBT is likely effective for improving depressive symptoms in individuals with ESKD on hemodialysis [53*].

In the ASCEND trial, introduced above, individuals randomized to receive CBT also demonstrated an improvement in QIDS score from a mean (95% CI) of 12.2 (11.0, 13.9) at baseline to 8.1 (6.7, 9.4) after 10 sessions of individualized CBT delivered over 12 weeks [30*]. This was similar to the response seen in those randomized to receive sertraline, although depressive symptoms at 12 weeks were marginally better in the sertraline group. The absence of a control arm limits interpretation of this change in symptoms from baseline, particularly in light of the depressive symptom improvement seen in the placebo arm of CAST and the control groups in other studies of CBT [29*, 45–47]. However, CBT was associated with very low rates of adverse outcomes, so can be considered as a safe potential treatment for those with access to such interventions. Other non-traditional, non-pharmacologic treatments for depression, such as music therapy, exercise therapy, and more frequent hemodialysis reported variable results and met with more limited success in patients with ESKD [15].

Overall, small randomized controlled studies indicate that CBT may be an effective and low-risk intervention to treat MDD in patients with ESKD. No studies of psychological interventions have been conducted in patients with non-dialysis CKD or patients with ESKD on peritoneal dialysis. While psychological interventions such as CBT avoid some of the pitfalls of pharmacologic therapy, the primary limitation to their implementation is wide access to such treatments and willingness to participate. In the absence of these barriers, this is a promising therapeutic option.

KNOWLEDGE GAPS

Despite important advances made in recent years to our understanding of pharmacologic and psychological interventions to treat MDD in patients with CKD and ESKD, extensive knowledge gaps remain. First, adequately powered placebo-controlled randomized clinical trials of SSRIs other than sertraline, non-SSRI antidepressants, and CBT are needed to test clinical efficacy and safety in patients with kidney disease. Identifying clinical phenotypes or subgroups of patients more likely to benefit from SSRIs or other antidepressant therapies may improve the precision of clinical care and minimize exposing individuals to adverse effects of therapy if they are unlikely to experience clinical benefit. Although combination therapy for individuals who fail to respond to initial treatment is standard of care in the general population, no dual pharmacologic or combined pharmacologic/psychological therapies have been tested in randomized trials in individuals with kidney disease. To date no studies have been published measuring the effect of traditional interventions such as SSRIs on depressive symptoms in recipients of a kidney transplant, and few have enrolled patients with non-dialysis CKD or ESKD receiving peritoneal dialysis. Health services research incorporating social workers or psychologists in outpatient hemodialysis units to conduct CBT during dialysis treatment, as was done in ASCEND, may be an important and practical way to overcome barriers of access to care and time commitment that may prevent patients from participating in psychological interventions. Finally, it will be important to conduct well-powered studies and include long-term adverse outcomes such as cardiovascular events and all-cause death in future studies to measure whether these interventions affect the association of depression with such outcomes.

CONCLUSIONS

Many important questions remain to be answered regarding the best treatment strategies for MDD in patients with CKD or ESKD. Patient engagement in the choice between pharmacologic and psychological interventions is key, as patient preference is highly individualized [36]. Currently available evidence suggests that on average, sertraline is no more effective than placebo for improving depressive symptoms, but it is possible that subgroups of patients exist who may benefit from therapy. A cautious trial of sertraline can be considered, with continuation of treatment in those who experience improvement in depressive symptoms without intolerable side effects. CBT may be an effective and safe intervention for patients with kidney disease but is limited by availability and burden of responsibility on the patient. Future studies should focus on testing the safety and efficacy of alternative treatments for MDD such as non-SSRI medications and combination therapies to identify interventions that may address the high burden of MDD in patients with kidney disease.

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KEY POINTS

- Although clinical trials do not support the indiscriminate use of pharmacologic antidepressant therapy, a trial of an SSRI is reasonable to evaluate for depressive symptom improvement, with careful dose titration and monitoring for adverse effects.
- In patients with kidney disease, SSRIs are associated with poor tolerability, including gastrointestinal and nervous system symptoms, and adverse effects such as hip fracture and gastrointestinal bleeding, and some SSRIs are associated with cardiovascular mortality.
- In the absence of barriers to access to psychological interventions, CBT is a potentially effective and low-risk treatment option for depression in patients with kidney disease.

Table 1.

Studies of pharmacologic treatments for depressive symptoms in patients with kidney disease

Study	Sample	Pharmacologic Intervention	Comparator	Result
Kennedy 1989 [16]	ESKD on HD (n=8)	Open label desipramine, maprotiline, or mianserin for 7 weeks	None	Depressive symptoms improved in 6 of 8 participants
Levy 1996 [17]	ESKD on HD (n=7)	Open label fluoxetine 20 mg/day for 8 weeks	None	Depressive symptoms improved from baseline to 8 weeks
Blumenfield 1997 [18]	ESKD on HD (n=14)	Fluoxetine 20 mg/day for 8 weeks	Placebo (random allocation)	Depressive symptoms improved in both groups from baseline to 8 weeks; no benefit of sertraline over placebo at 8 weeks
Wuerth 2001 [19]	ESKD on PD (n=11)	Open-label sertraline, bupropion, or nefazodone for 12 weeks	None	Depressive symptoms improved from baseline to 12 weeks
Wuerth 2003 [20]	ESKD on PD (n=23)	Open-label sertraline, citalopram, bupropion, paroxetine, or nefazodone for 12 weeks	None	Depressive symptoms improved from baseline to 12 weeks
Lee 2004 [21]	ESKD on HD (n=28)	Open-label fluoxetine 20 mg/day for 8 weeks	None	Depressive symptoms improved from baseline to 8 weeks
Koo 2005 [22]	ESKD on HD (n=62)	Open-label paroxetine 10 mg/day and psychotherapy for 8 weeks	Usual care (non-random allocation)	Depressive symptoms improved from baseline to 8 weeks in the paroxetine group; depressive symptoms not measured in the control group
Turk 2006 [23]	ESKD on HD (n=40)	Open-label sertraline 50 mg/day for 8 weeks	None	Depressive symptoms improved from baseline to 8 weeks
Kalender 2007 [24]	CKD or ESKD on HD or PD (n=34)	Open-label citalopram 20 mg/day for 8 weeks	None	Depressive symptoms improved from baseline to 8 weeks
Atalay 2010 [25]	ESKD on PD (n=25)	Open-label sertraline 50 mg/day for 12 weeks	None	Depressive symptoms improved from baseline to 12 weeks
Hosseini 2012 [26]	ESKD on HD (n=44)	Open-label citalopram 30 mg/day for 3 months	Psychological training, 6 sessions (random allocation)	Depressive symptoms improved from baseline to study exit in both groups; no between-groups difference
Taraz 2013 [27]	ESKD on HD (n=50)	Sertraline 100 mg/day for 12 weeks	Placebo (random allocation)	Depressive symptoms improved from baseline to 12 weeks in both groups; the improvement was greater in the sertraline group
Friedli 2017 [28*]	ESKD on HD (n=30)	Sertraline 50–100 mg/day as tolerated for 6 months	Placebo (random allocation)	Depressive symptoms improved in both groups from baseline to 6 months; no benefit of sertraline over placebo
Hedayati 2017 (CAST) [29*]	CKD stages 3–5 (n=201)	Flexible dose sertraline 50–200 mg/day as tolerated for 12 weeks	Placebo (random allocation)	Depressive symptoms improved in both groups from baseline to 12 weeks; no benefit of sertraline over placebo
Mehrotra 2019 (ASCEND) [30*]	ESKD on HD (n=120)	Open label flexible dose sertraline 50–200 mg/day as tolerated for 12 weeks	CBT, 10 sessions over 12 weeks (random allocation)	Depressive symptoms improved in both groups from baseline to 12 weeks; marginal benefit of sertraline over CBT at 12 weeks

CBT, cognitive behavioral therapy; CKD, chronic kidney disease; ESKD, end-stage kidney disease; HD, hemodialysis; PD, peritoneal dialysis

Table 2.

Studies of psychological treatments for depressive symptoms in patients with kidney disease

Study	Sample	Psychological Intervention	Comparator	Result
Koo 2005 [22]	ESKD on HD (n=62)	Paroxetine 10 mg/day and psychotherapy for 8 weeks	Usual care (non-random allocation)	Depressive symptoms improved from baseline to 8 weeks in the paroxetine group; depressive symptoms not measured in the control group
Lii 2007 [44]	ESKD on HD (n=48)	Group CBT, 8 sessions over 8 weeks	Usual care and self-care booklet (random allocation)	Depressive symptoms decreased from baseline to 8 weeks in the CBT group and increased in controls; improvement in symptoms was greater with CBT than control
Duarte 2009 [45]	ESKD on HD (n=85)	CBT, 12 sessions over 12 weeks	Usual care (random allocation)	Depressive symptoms improved from baseline to 9 months in both groups; depressive symptoms were lower at 3 and 9 months for CBT than usual care
Hosseini 2012 [26]	ESKD on HD (n=44)	Psychological training involving stress management and problem solving, 6 sessions	Open-label citalopram 30 mg/day for 3 months (random allocation)	Depressive symptoms improved from baseline to study exit in both groups; no between-groups difference
Cukor 2014 [46]	ESKD on HD (n=59)	CBT, 10 sessions conducted chairside during HD over no more than 3 months	Wait-listed for CBT (random allocation, crossover study design)	Depressive symptoms improved from baseline in both groups; CBT was associated with greater improvement and controls who had improved from baseline had further improvement after receiving CBT
Valsaraj 2016 [47]	ESKD on HD (n=67)	CBT, 10 sessions over 10 weeks	Non-directed counseling, 10 sessions over 10 weeks (random allocation)	Depressive symptoms improved from baseline to 6 months in both groups; improvement was greater in CBT group than controls
Chan 2016 [42]	ESKD on HD (n=22)	Internet-based CBT, 5 sessions over 8 weeks	None	Depressive symptoms improved from baseline to 3 month follow up
Lerma 2017 [48]	ESKD on HD (n=60)	Group CBT, 5 sessions conducted after HD over 5 weeks	Usual care (random allocation)	Depressive symptoms improved from baseline to 9 weeks in the intervention but not control participants; improvement in depressive symptoms was greater in the CBT group
Hernandez 2018 [43]	ESKD on HD (n=14)	Internet-based psychological intervention, 7 online modules over 5 weeks	None	Depressive symptoms decreased from baseline to 5 weeks
Griva 2018 [49*]	ESKD on HD (n=235)	Group social cognitive theory-based intervention, 4 sessions over 8 weeks	Usual care (clustered random allocation)	Depressive symptom improved in the intervention group more than the usual care group
Sohn 2018 [50]	ESKD on HD (n=7)	Group CBT, 12 sessions over 12 weeks	None	Depressive symptoms improved from baseline to 12 weeks
Bargiel-Matusiewicz 2019 [51*]	ESKD on HD (n=139)	2 intervention groups: 1. Pre-recorded cognitive intervention for 4 weeks 2. Pre-recorded cognitive intervention and in-person narrative sessions with a psychologist twice weekly for 4 weeks	Usual care (non-random allocation)	Depressive symptoms improved in the cognitive/narrative intervention group but did not change from baseline to 4 weeks in the other two groups
Mehrotra 2019 (ASCEND) [30*]	ESKD on HD (n=120)	CBT, 10 sessions over 12 weeks	Open label flexible dose sertraline 50–200 mg/day as tolerated for 12 weeks (random allocation)	Depressive symptoms improved in both groups from baseline to 12 weeks; marginal benefit of sertraline over CBT at 12 weeks

CBT, cognitive behavioral therapy; CKD, chronic kidney disease; ESKD, end-stage kidney disease; HD, hemodialysis