

## Screening, Diagnosis, and Treatment of Depression in Patients with End-Stage Renal Disease

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Depression is common in patients with end-stage renal disease and has been linked to increased mortality. Screening for depression in the general medical population remains controversial; however, given the high prevalence of depression and its significant impact on morbidity and mortality, a strong case for depression screening in patients with end-stage renal disease can be made. Several studies have been performed to validate the more common depression screening measures in patients with chronic kidney disease. The Beck Depression Inventory, the Hamilton Rating Scale for Depression, the Nine-Question Patient Health Questionnaire, and the Center for Epidemiologic Studies Depression Scale are some of the measures that have been used to screen for depression in patients with end-stage renal disease. Data suggest a higher Beck Depression Inventory cutoff score, of >14 to 16, will have increased positive predictive value at diagnosing depression in patients with end-stage renal disease. There are limited data on the treatment of depression in this patient population. Pharmacotherapy, including selective serotonin reuptake inhibitors, can be used if deemed clinically indicated, and no active contraindication exists. There are even fewer data to support the role of cognitive behavioral therapy, social support group interventions, and electroconvulsive therapy for treatment of depression in patients with chronic kidney disease. Larger randomized, controlled clinical trials aimed at the treatment of depression in patients with end-stage renal disease are desperately needed.

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Depression is prevalent in patients with ESRD (1–11). The true prevalence of depression in patients with ESRD, however, is unknown. A distinction must be made between levels of depressive affect and the diagnosis of a psychiatric disorder, such as major depression (2,7,9,10). Estimates of the prevalence of increased depressive affect in patients with renal disease vary between 0 and 100%, depending on the study and the assessment tool chosen for screening (1–3,5–11). Depression is common in general medical patients, approaching the prevalence of hypertension (12,13). In the general population, the point prevalence of depression in women ranges from 5 to 9% and is 2 to 3% in men (13). According to the National Comorbidity Survey, lifetime prevalence of depression in the general population is 21.3% among women and 12.7% among men (14). Screening for depression in dialysis centers is warranted given its high prevalence and association with increased morbidity and mortality (7,15–18).

As is the case with patients who have a diagnosis of other chronic medical illnesses, patients with ESRD have risk factors that predispose them to developing major depressive disorders (MDD) or increased depressive affect. Depression in patients

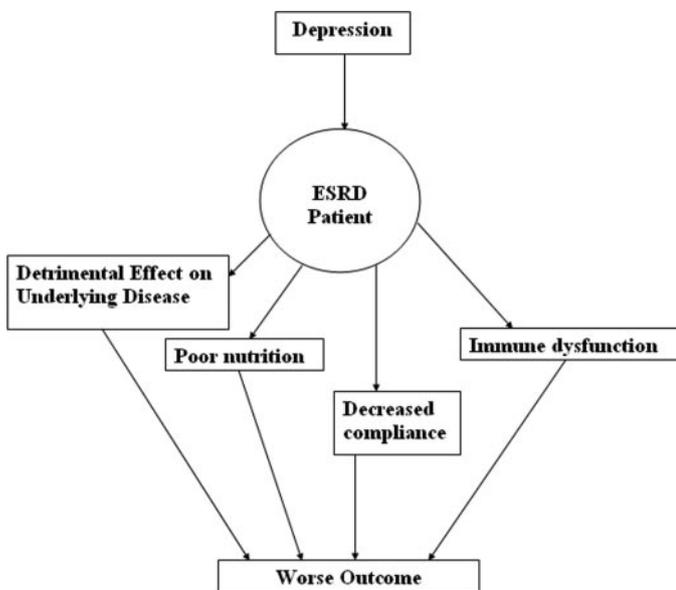
with ESRD can be secondary to loss of a primary role in their occupation or family, decreased physical function, diminution of cognitive skills, or a decline in sexual function (7,9,10). Depression may be more likely to result from the adjustment that is needed to cope with the long-term nature of renal replacement therapy, rather than be the consequence of the initial transition to dialysis therapy (8,10).

Depression has the potential to alter adversely the medical outcome of patients with ESRD through several mechanisms (Figure 1). Psychologic stressors can affect compliance with the medication regimen (7,9,10). In previous studies, increased depressive affect was associated with markers of poor compliance in dialysis patients (9,19,20). Depression has also been associated with altered immune system function, specifically decreased cellular immunity, and increased cytokine levels (10,21–24). Furthermore, depression is linked to poor nutritional status and has been shown to precede a decline in serum albumin levels in patients with ESRD (25,26).

Kimmel *et al.* (15) evaluated the link between depression and mortality in chronic hemodialysis (HD) patients in a prospective cohort of 295 HD outpatients. Patients were screened for depression during a 2-yr period using the Beck Depression Inventory (BDI) and followed for cumulative survival during approximately 3 yr (15). Patients with ESRD and BDI scores >10 (signifying “mild” depression in the general population), assessed in a time-varying manner, had a significant increase in mortality compared with those with lower levels of depressive

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**Figure 1.** Depression and its effect on medical outcomes. Depression has the potential to modify medical outcomes through a number of mechanisms, including its effect on the underlying disease process, poor nutritional status, decreased compliance with medications/physician's prescriptions, and immunologic dysfunction.

affect (15). There was no significant difference in survival between patients who were classified as having "mild" or "moderate to severe" depression as measured by the BDI (15).

Additional data by Boulware *et al.* (17) support the potential link between depressive affect and survival in patients with ESRD. Using data from the Choices for Healthy Outcomes in Caring for ESRD (CHOICE) cohort of 1041 dialysis patients, depressive symptoms were evaluated at baseline and at 6, 12, and 18 mo. There was an association between scores on a five-item Mental Health Index, which measured depressive affect with all-cause mortality, when assessed in a time-varying analysis during a 2-yr follow-up period (17).

Not all studies consistently link depression with survival in patients with ESRD (2,9,10,27–29). The discrepancy in results may be from differences in study design or the populations studied; however, some of the earlier studies linking depression with mortality used crude analytic techniques, such as comparing mean values of depressive affect between deceased and surviving patients but not adjusting for certain key confounders, including comorbid illnesses (2).

## Epidemiology

Depression is believed to be the most common psychiatric disorder in patients with ESRD (2,7,9–11,18,30,31). Kimmel *et al.* (8) evaluated the hospitalization data from all Medicare-enrolled patients who had ESRD and received dialysis at any point in 1993 and found that 8.9% had been hospitalized with a psychiatric diagnosis. The Program Management and Medical Information System of the Health Care Financing Administration was used to identify patients who received dialysis at any

point in 1993. Patients with ESRD were evaluated when a mental health condition was identified as the primary diagnosis on admission to the hospital or when a psychiatric illness was a secondary diagnosis. The most frequent psychiatric disorder that required hospital admission in patients with ESRD was depression and other affective disorders. Schizophrenia and other acute psychoses accounted for an additional 22% of cases, and substance abuse made up 15% of cases (8).

Among outpatients who were treated with HD, Kimmel and colleagues (10,20,27,32) reported that approximately 25% of patients were depressed, with mean BDI scores that corresponded to mild levels of depression in the general population. A study (27) of 295 urban black HD patients from Washington, DC, revealed that approximately one quarter had a BDI score >15, a possible cutoff for the diagnosis of depressive disorder in patients with ESRD (2,3,5). More recent data by Hedayati *et al.* (5) found a 26.7% prevalence of depressive disorder and a 17.3% prevalence of major depression when measured using Structured Clinical Interview for the Diagnostic Statistical Manual-IV (SCID) modeled after the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria for MDD. Watnick *et al.* (4) found a 19% prevalence of major depression in a cohort of 62 dialysis patients from Oregon. Lopes *et al.* (33) studied 6987 HD patients who were enrolled in the Dialysis Outcomes and Practice Patterns Study (DOPPS II) and found a 13.9% overall prevalence of "physician-diagnosed depression" in this cohort. The highest prevalence rates for depression were found in the United States and Sweden, with rates of 19.8 and 21.7%, respectively (33). Japan had the lowest prevalence of the 12 countries represented in the study, with rates of only 2.0% (33).

Depending on the screening tool chosen, different results for depression prevalence in patients with ESRD have been found. For example, Smith *et al.* (11) studied the prevalence of depression among 60 patients with ESRD and found a 47% prevalence of depression using the BDI as a screening tool, a 17% prevalence with the Multiple Affect Adjective Check List, and a 5% prevalence using a structured psychiatric interview using DSM-III criteria. Lopes *et al.* (33) found a 43.0% prevalence of depression in the DOPPS II cohort when a Center for Epidemiologic Studies Depression Screening Index (CES-D) score of >10 was used as a cutoff value for depression, compared with a 13.9% prevalence of depression when diagnosed by a physician. This disparity in depression prevalence rates can largely be explained by the different screening measures used in each study. When the same screening measure is used, there is a high degree of reliability in the results for depression prevalence. Despite the variation in results, all screening measures confirm a high prevalence rate for depression in patients with ESRD. This underscores the importance of using appropriate diagnostic and screening techniques for evaluating depression in patients with ESRD.

## Diagnosis

It is important to distinguish between the diagnosis of MDD and the symptoms of depression or a high level of depressive affect (7,9,10,13,18,34,35). On the basis of criteria from the

DSM-IV (36), MDD is defined as a condition lasting for a period of at least 2 wk, during which a patient displays a depressed mood in addition to five other symptoms, including decreased interest in activities, changes in appetite, sleep disturbance, fatigue, psychomotor changes, guilty thoughts, decreased concentration, and suicidal ideation (13,36). Minor depression is a variant of MDD in which depression is present for at least 2 wk; however, it is associated with no more than three other symptoms of a depressive disorder (3,6,13,36).

Dysthymia is a variant of depression in which depressed mood is present for at least 2 yr; however, it typically lacks the suicidal ideation and changes in appetite, libido, and cognitive dysfunction that are associated with MDD (13,35,36). Three to 5% of the world population may be experiencing dysthymia by one estimate (35). Patients with dysthymia can have periods of MDD during their course. These may be characterized by being consumed by guilty thoughts, low self-esteem, and persistent or fluctuating depressive symptoms (35). Formal diagnosis of depression requires a structured clinical interview based on criteria from the DSM-IV, which is considered the gold standard in studies that assess the accuracy of a variety of potential screening tools that are used for depression.

When depression occurs along with another medical or psychiatric condition, the term “compound depression” is often used. Compound depression is in general more treatment resistant than depression in patients without another medical or psychiatric comorbid condition (7,10,34,37–39). Keitner *et al.* (37) compared the outcome of 37 patients with “major depression only” and 41 patients with “major depression plus an additional axis I, axis II, or axis III disorder.” Patients with compound depression had significantly worse scores for depression and “overall functioning” as measured by the Hamilton Rating Scale for Depression (HAM-D) and the Global Assessment Score during a 12-mo study period (37). All patients with ESRD and major depression would fall into the category of compound depression, highlighting the importance of proper screening and diagnosis.

A number of factors make the diagnosis of depression in dialysis patients challenging. These obstacles can be divided into three broad categories: Patient factors, physician factors, and issues related to syndromal diagnosis. A recent article by Wuerth *et al.* (40) examined the issue of properly identifying depression in patients with ESRD and the barriers that may impede formulation of a correct diagnosis. Reasons for diagnostic difficulties included patients’ denial of their illness, their unwillingness to consider antidepressant medications, and the stigma associated with a mental illness. This tendency to minimize symptoms, although challenging, can still be overcome. There are clues to assist the clinician with the diagnosis of depression in general populations and in patients with renal disease:

- Changes in behavioral and functional status: If a physician sees a patient withdrawing from care, not interacting, and starting to become noncompliant with dialysis, then these are potential clues that a depressive disorder could be present.

- Information from the family: Although patients may minimize symptoms, a supportive family member can frequently point out a patient’s change in mood and lack of engagement.
- Physical symptoms that are out of proportion to the current medical illness and functional status: Patients may experience depression as a worsening of their physical health. Speaking to patients in specific terms regarding their general medical condition may be more agreeable than using a psychiatric diagnosis that they may find stigmatizing.

Despite the potential barriers posed by any patient’s tendencies to minimize the mood symptoms that are associated with MDD, the biggest challenge to making the correct diagnosis may be encouraging health professionals to inquire about depressive symptoms in their patients (7). Physicians frequently do not inquire about the symptoms of MDD. Reasons for this may include reticence among medical staff when asking about depressive symptoms or making inquiries about suicidal ideations. There may also be a perceived lack of time for busy nephrologists to perform formal psychiatric evaluations in the dialysis unit. A frequently overlooked collaboration in establishing the diagnosis of depression is the primary nursing staff. Wilson *et al.* (41) compared the prevalence of depression as measured by the BDI-II, the primary nurse, and the nephrology team. Using the BDI-II as the gold standard, they found that nurses’ diagnoses of depression had an agreement of 74.6% with the BDI, compared with only 24.2% agreement between the depression screen and the nephrology team. Although the results of this study should be interpreted with caution, it seems that nursing staff have the ability to screen for depression and aid nephrologists in the diagnosis of depression. To address the need for brief assessment tools for health professionals who perceive that they have limited time to conduct evaluations, O’Donnell and Chung (42) evaluated the use of very brief screening questions in the assessment of depression. These studies have shown that one- or two-question assessments, focusing on the core symptom of depressed mood or anhedonia, can prove useful in the medically ill (42).

Another issue that may make formulating the diagnosis of depression difficult in patients with ESRD is the conceptualization of MDD as a syndrome. There is no known cause of MDD; therefore, it is diagnosed as a syndrome. The problem that this creates is that depressive symptoms can overlap with complications of uremia, as well as with other medical and psychiatric disorders. A discussion of the various types of unipolar affective disorders is beyond the scope of this article; however, the physician should be aware of three additional conditions when assessing patients for depression: Dementia, substance use, and bipolar disorder. The symptoms of dementia can frequently mimic MDD.

Substance use and bipolar disorders should always be considered before a diagnosis of MDD is made. Substance use disorders are frequently comorbid with mood disorders, and their presence can complicate treatment. Substance use was documented as a problem in dialysis patients both in small clinical studies (43,44) and in large studies using administrative

databases (8). Bipolar disorder is an affective illness that is characterized by periods of mania and depression. During manic periods, the patient may be restless and impulsive and often has a decreased need for sleep and increased energy. The patient's mood may be elevated or irritable. When screening for depression, the clinician should inquire about any reckless or impulsive behaviors during the patient's lifetime. If the clinician obtains a history that is suspicious for bipolar disorder, then the patient should immediately be referred to a psychiatrist, because the management of this disorder is frequently complex.

Risk for suicide is another key issue to assess when diagnosing depression in the ESRD population. Patients who are on dialysis may be able to commit suicide more easily through purposeful noncompliance with dialysis or medication prescription, dietary indiscretion, or disruption of their vascular access (7,9,10,45). Previous data suggested an extremely high rate of suicide in this patient population (45); however, the nature of the population sampled may have led to bias. It is also important to distinguish between dialysis withdrawal and suicide, because withdrawal from treatment is a far more frequent occurrence.

The association between dialysis withdrawal and depression remains to be elucidated. McDade-Montz *et al.* (46) studied the role of depression in dialysis withdrawal. A one-point increase in the total BDI score was associated with a 5.2% increase in the risk for withdrawing from dialysis in a predominately white population (46). Recently, Kurella *et al.* (47) sought to determine the incidence of suicide among patients with ESRD nationwide. With the exception of 15- to 29-yr-old patients, suicide rates among patients with ESRD were higher across all age groups compared with the national population (47). Dialysis patients were found to have an 84% higher rate of suicide compared with the general population (47). Risk factors for suicide among patients with ESRD in adjusted analyses included recent hospitalization for a psychiatric illness, male gender, white or Asian race, age >75 yr, and substance abuse (47). Suicide risk was found to be highest during the first 3 mo after dialysis initiation (47). The data highlight the importance of proper diagnosis and screening for depression in the ESRD population.

## Screening

A number of measures have been used to screen for depressive symptoms in patients with ESRD (Table 1). The optimal screening tool and diagnostic method to identify depression and depressive affect in patients with renal disease remain unknown, although several studies have been performed to determine the validity and accuracy of these tools in the ESRD population (3–5).

The BDI is a 21-item questionnaire that uses cutoff levels for depression in the general population as follows: <9, no depression; 10 to 15, mild depression; 16 to 23, moderate depression; >24, severe depression (2,3,7,48). The 21 items are scored on a four-point scale on which 0 signifies no problem and 3 represents an extreme problem, with a total score range of 0 to 63 (2,48). The HAMD is a 17-item questionnaire that is used to assess depressive affect (2,13). The questions are rated on a five-point scale with higher values indicating more severe depressive symptoms (2,13). The nine-question Patient Health Questionnaire (PHQ-9) consists of nine questions that assess severity of depression with each question based on a scale from 0 to 3 (2,4). Higher PHQ-9 scores correlate with increased depressive affect (2,4). The PHQ-9 has a maximum possible score of 27 (2,4,49). The Center for Epidemiologic Studies Depression Scale (CES-D) consists of 20 questions ranging on a scale from 0 to 60. A CES-D cutoff score of 16, in the general population, is used as a screening tool for possible depression (2,50). The Cognitive Depression Index is a subset of the BDI that consists of 15 items and excludes the somatic components of the survey (2,7,9). It showed a strong correlation with the BDI in HD patients surveyed at George Washington University (2,9). The SCID is considered the gold standard to make the diagnosis of depression for screening purposes and is used to compare the validity of the various screening tools for depression (2). The Diagnostic Interview Schedule (DIS) is similar to the SCID but is based on criteria from the DSM-III (2).

There is a concern that these self-report questionnaires may fail to distinguish between uremia and depressive symptoms, thereby potentially overestimating the actual prevalence of depressive disorders in patients with ESRD (5,7,9,10,15,30,34).

Table 1. Potential screening and diagnostic tools for depression in patients with ESRD<sup>a</sup>

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

<sup>a</sup>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

Craven *et al.* (3) were the first to evaluate the validity of the BDI in patients with ESRD. They compared the BDI with the DIS-III, which uses the DSM-III criteria for diagnosis of depression. Ninety-nine Canadian patients who were receiving HD or peritoneal dialysis were included in the study (3). Patients were excluded from the study when they did not speak English, when they had recently received a renal transplant, or when they had severe cognitive dysfunction (3). The mean BDI score in this patient population was 11.7 (3). A total of 45.4% of patients scored in the depressed range for the general population, with 24 of 99 patients having mild depression, or BDI scores between 10 and 15 (3). Thirteen of 99 patients had moderate depression, or BDI scores between 16 and 23; and eight of 99 patients had severe depression, or BDI scores of >24 (3). When the DIS was applied to these patients, the prevalence of depression was 12.2% (3); therefore, a BDI cutoff of 10, used in the general medical population, was shown to have decreased specificity and a lower positive predictive value (PPV) for the diagnosis of depression (3). A BDI cutoff score of 15 was found to have the highest sensitivity, specificity, and accuracy for the diagnosis of depression, when compared with the gold standard DIS (3). They found that a BDI score of >15 had 92% sensitivity and 80% specificity for diagnosing depression (3).

Watnick *et al.* (4) studied the validity of the BDI and the PHQ-9 compared with a structured clinical interview based on the DSM-IV in 62 dialysis patients. Sixty-two patients who were treated with HD or peritoneal dialysis were enrolled from outpatient dialysis units in Portland, OR (4). Inclusion criteria were age >18 yr and at least 3 mo of dialysis therapy (4). Patients were excluded when they did not speak English, when they scored <17 on the Folstein Mini-Mental status examination, when they had a documented psychiatric diagnosis other than depression, when they were to receive a renal transplant in the next 4 wk, or when they were “unable to participate” according to the dialysis staff (4). Similar to the results of other studies, a BDI score of  $\geq 16$  was associated with a 91% sensitivity for depression, a specificity of 86%, PPV of 59%, and negative predictive value (NPV) of 98% (4). A score of  $\geq 10$  on the PHQ-9 was associated with 92% sensitivity, 92% specificity, 71% PPV, and NPV 98% for the diagnosis of depression (4). Watnick *et al.* (4) concluded that both the BDI and the PHQ-9 had validity in the dialysis population. In addition, the authors stated that the PHQ-9 might be more advantageous as a screening tool because of its shorter length and its relative ease of administration (4).

Hedayati *et al.* (5) sought to evaluate the validity of the BDI and the CES-D as depression screening tools in patients with ESRD by comparing the results of these surveys with an interview performed by a psychiatrist using DSM-IV criteria, known as the SCID. Ninety-eight predominately black HD patients underwent depression screening using the BDI and the CES-D scales (5). Patients were included in the study when they spoke English, were able to sign their own consent, or had a designated health care power of attorney (5). These results were compared with the SCID (5). Patients who met criteria for depression by the SCID had a higher mean score on the BDI and CES-D scales (5). Mean score for BDI was  $16.6 \pm 8.4$  in

depressed patients *versus*  $9.1 \pm 6.2$  for the nondepressed group (5). CES-D scores were  $24.1 \pm 9.8$  in depressed patients *versus*  $11.8 \pm 8.0$  for those who did not meet criteria for depression with the SCID (5). Hedayati *et al.* (5) found that a BDI score >14 was most accurate at predicting depression when compared with the gold standard SCID. This score had a 62% sensitivity and an 81% specificity for diagnosing depression (4). It also corresponded to a PPV of 53% and an NPV of 85% (5). A value of 18 on the CES-D was believed to be most accurate at diagnosing depression (5). This value had a 69% sensitivity and a 83% specificity for diagnosing a depressive disorder (5). It also has a PPV of 60% and an NPV of 88% (5).

Screening for depression remains controversial (12,51). There are conflicting data regarding the effectiveness of routine screening for depression in primary care populations. Schade *et al.* (52) reported that no studies “show that screening leads to measurable benefit.” In addition, several studies failed to demonstrate improved outcomes as a result of screening for depression (51,52); however, Coyne *et al.* (53) argued that screening is effective because it identifies depressed patients whose disorder may otherwise go undetected by health providers. Palmer and Coyne (54) pointed out that these screening tools may be more effective for monitoring the progression of depression in patients who have already received the diagnosis and who are currently receiving treatment, because it is not clear that increasing the number of patients with a potential diagnosis of depression will necessarily lead to appropriate treatment and care of these patients. Finally, Katon (51) stated that clinical trials should focus more on treating depression appropriately in patients who have depression already detected, because patients with undiagnosed depression tend to have milder illness at baseline. This screening controversy may not apply in patients with chronic kidney disease because of the increased prevalence and increased morbidity and mortality from depression in this population. An active as opposed to a minimal approach to the screening and treatment of depression may have a significant impact on the morbidity and mortality from disease (Figure 2). Again, further epidemiologic studies and randomized trials are needed to address this issue with sufficient depth.

### Minimal Approach



### Active Approach

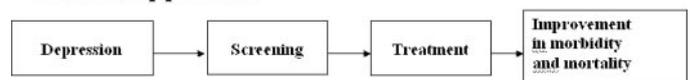


Figure 2. Approaches to depression screening and treatment. An active *versus* a minimal approach to screening and treatment of depression may have a significant impact on the morbidity and mortality of a patient’s underlying disease. Further clinical trials are needed to test this hypothesis and settle the screening controversy.

Questions of literacy remain critical each time screening questionnaires are used to assess depressive affect in dialysis patients. We perform psychological evaluations of patients in a face-to-face manner and recommend that all screening for depression be done verbally in person (27). All conversations with patients should be conducted while respecting patients' privacy as much as possible. Ideally, interviews should be private, before beginning dialysis sessions.

If a diagnosis of depression is suggested by a BDI score >14 on screening, then the nephrologist should perform a mental status examination on the patient and if confident in the diagnosis of depression should consider initiation of therapy or other interventions to treat depression. If the diagnosis remains uncertain or if the physician is uncomfortable with the prescription of psychotropic medications, then the nephrologist should refer the patient to a mental health provider. Practitioners who take responsibility for treatment of depression must determine whether the patient has any suicidal ideation when taking the medical history. If suicidal ideations are expressed, then an emergency mental health consultation is required. As with many other chronic illnesses, a team approach involving the nephrologist, psychiatrist, social worker, and dialysis nursing staff is optimal when dealing with any mental illness.

## Treatment

Limited studies have evaluated therapy for depression in patients with ESRD. Treatment options include psychotherapy, pharmacologic therapy, electroconvulsive therapy (ECT), or a combination of some or all of these modalities (10,13,55,56). The general medical literature suggests that the combination of psychotherapy and pharmacologic treatment for depression is ideal (55). Data from Lopes *et al.* (33) from the DOPPS II suggest that depression may be undertreated in the US ESRD population. Of patients in the United States who received a diagnosis of depression from a physician, only 38.9% were prescribed antidepressant medication. Watnick *et al.* (57) found that only 16% of depressed HD patients were being treated at the start of a prospective cohort study to estimate the prevalence of depression among incident HD patients. These data are concerning but may reflect the prominence of somatic symptoms in patients who are about to start renal replacement therapy for ESRD, as well as appropriate sadness regarding the loss of independence and loss of role function that usually accompany the start of therapy (7,9,10,18). Concern about adverse effects, noncompliance, and dosage adjustment in patients with ESRD may also play roles in physician hesitance to prescribe these medications.

Treating depression has the potential to modify other important complications of ESRD, including nutritional status, thereby affecting survival (2,7,9,10,18,26). Koo *et al.* (58) studied the effect of paroxetine compared with placebo on the nutritional status of 62 HD patients. Those who were treated with antidepressants had significant increases in key nutritional parameters, including the serum albumin concentration, predialysis blood urea nitrogen levels, and higher protein catabolic rates (58).

The different pharmacologic therapies that have been tried in

this patient population include the older tricyclic antidepressants plus newer agents, including selective serotonin reuptake inhibitors (SSRI) and selective serotonin and norepinephrine reuptake inhibitors (7,10,59–62). Other pharmacologic options for treatment of depression include monoamine oxidase inhibitors (MAOI), reverse inhibitors of MAO, and herbal supplements such as St. John's Wort (10,59,62) (Tables 2 and 3); however, these agents have increased risk for drug interactions, and special caution is advised in the ESRD population before prescribing herbal agents or MAOI. St. John's wort has the potential for numerous drug interactions because of its stimulation of the CYP3A4 hepatic enzyme system. St. John's wort can reduce the drug levels of calcineurin inhibitors, such as cyclosporine and tacrolimus, thereby increasing the risk for acute rejection in renal transplant recipients (63,64). Mai *et al.* (63) studied the effect of 600 mg of St. John's wort on 10 renal transplant patients who were taking tacrolimus and mycophenolate mofetil. The required dosage of tacrolimus to maintain consistent levels was almost doubled (63). MAOI and tricyclic antidepressants have adverse effects in general medical patients; therefore, caution with their use in patients with ESRD is advised (10,59). Tricyclic antidepressants may cause anticholinergic symptoms, such as orthostatic hypotension, and cardiac arrhythmias, which can be particularly problematic in the ESRD population (10,62). All psychotropic medications must be carefully monitored for potential prolongation of the QTc interval, and patients with a history of a prolonged QT interval or other arrhythmias should avoid or use caution with such agents (65,66).

SSRI are believed to be safer in patients with ESRD because of their more favorable adverse effect profiles (10,62). A general recommendation is to reduce the dosage of SSRI by one third in patients with ESRD (62,67). A 20-mg/d dose of fluoxetine tends to be well tolerated, although data on treatment are limited (62). One potential beneficial effect of SSRI in patients with ESRD is that they can decrease orthostatic hypotension, a common problem especially in HD patients (10,68); however, if the diagnosis of an MDD is uncertain, then caution is advised when prescribing SSRI, because they may enhance the risk for mania in patients who have bipolar disorder (69–72). There is also controversy regarding the use of SSRI and possible increased suicide risk (73–75).

Table 2. Treatment options for depression in patients with ESRD<sup>a</sup>

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Psychotherapy
ECT
SSRI
SNRI
Herbal supplements (St. John's Wort)
Other antidepressants: Bupropion, maprotiline, mirtazapine

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<sup>a</sup>ECT, electroconvulsive therapy; SNRI, selective serotonin and norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors

Table 3. Selected dosages, drug interactions, and evidence for antidepressant use in patients with ESRD<sup>a</sup>

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

<sup>a</sup>Further information can be obtained from Table 1 in reference (59), reference (57), and reference (100). This table is used as a general guide to therapy. Although many drugs do not need to be adjusted for level of renal function, a wise approach is to start low and go slow. Adapted with permission from Psychosomatics, Copyright (2004). American Psychiatric Association.

SSRI may exacerbate preexisting uremic symptoms. They may increase the risk for bleeding (76–79). This adverse effect can be particularly problematic in patients with ESRD and underlying qualitative platelet defects related to uremia. SSRI have also been associated with increased nausea as a result of increased serotonergic activity in the gastrointestinal tract (80–82). Antiemetic agents with serotonergic antagonist properties such as ondansetron may be necessary in such patients to reduce these symptoms (80–82); therefore, consultation with a mental health provider is advised if the diagnosis of depression is uncertain before prescribing therapies that have uncertain benefits and potential harmful effects. Patients need to undergo at least 6 wk of treatment with an antidepressant medication before assessing the potential outcome of therapy (10,60–62). There have only been a few studies using antidepressants in the ESRD population. The studies that do exist are limited by small sample size.

Steltzer *et al.* (83) assessed the effect of tricyclic antidepressants on five HD patients with depression. Three patients had a positive response to treatment (83). Kennedy *et al.* (84) treated 10 patients who had ESRD with desipramine or mianserin. Of

the six patients who finished the trial, five recovered from the depression (84).

Blumenfeld *et al.* (85) studied the effect of fluoxetine, an SSRI, on 14 HD patients. This was a double-blind, randomized, placebo-controlled trial conducted during an 8-wk period (85). Depression was assessed using the BDI, the Montgomery Asberg Depression Scale, the Brief Symptom Inventory, and the Hamilton Depression Scale (85). There was a statistically significant difference from baseline in all of the depression measures used in the treatment group compared with the group given a placebo (85). The authors concluded that fluoxetine was safe and effective in HD patients (85).

Levy *et al.* (86) also evaluated the safety of fluoxetine in patients with renal failure. Nine patients with depression and normal renal function and seven patients who had ESRD and were treated with HD were given fluoxetine 20 mg/d in an 8-wk study (86). All patients between 18 and 70 yr of age were included in the study when they met the criteria for MDD as outlined in the DSM-III clinical psychiatric interview and scored >16 on the HAMD scale (86). Patients also had normal liver enzymes, were free of chronic medical illnesses other than

ESRD or diabetes, and had no psychiatric disorders other than depression (86). Patients also could not receive a psychotropic medication for 1 wk after they were enrolled in the study (86). Depression was screened for using the HAMD-17, the BDI, the Montgomery Asberg Depression Rating Scale, the Brief Symptom Inventory, the Global Well-Being Scale, and the Electronic Visual Analog Scale before, during, and at the conclusion of the 8-wk study period. Six patients in each group completed the study (86). Five of six patients in both the ESRD group and the normal renal function group experienced significant decreases in their overall depression scores, with an approximately 25% reduction in the HAMD-17 score (86). Plasma concentrations of fluoxetine and its metabolite norfluoxetine over time were similar in the patients who were on HD and those with normal renal function (86). Adverse events were not significantly higher in the dialysis arm of the study (86).

Wuerth *et al.* (87,88) evaluated the effects of antidepressant medication in 44 patients who had ESRD and were treated with long-term peritoneal dialysis. Patients were included in the study when they had been on peritoneal dialysis for at least 90 d, when they were free of acute medical conditions for at least 4 wk, and when they scored  $\geq 11$  on the BDI. Twenty-three of 44 patients recruited completed a 12-wk course of treatment (87). The 23 patients who underwent pharmacotherapy had significant improvement in their depressive affect (87). The medications used in this study included sertraline, citalopram, bupropion, nefazodone, and paroxetine (87). Potential weaknesses of this study include the possibility of selection bias in this sample and the BDI cutoff score of 11 that was chosen to screen for and treat depression. As previously discussed, higher cutoff scores of 14 to 16 have been shown to have more accuracy in identifying patients with depression in this patient population. There was also no control group in this study. Nevertheless, this study adds in an important way to the limited literature regarding pharmacologic treatment of depression in patients with ESRD.

Although fluoxetine is the oldest and best studied SSRI in both the general and ESRD population, the newer SSRI, including paroxetine, sertraline, and citalopram, are frequently prescribed for the treatment of depression (59,89). Sertraline undergoes hepatic metabolism, and pharmacokinetic studies in patients with advanced renal failure suggest a favorable safety profile (59,62). Citalopram is believed to have similar pharmacokinetics to both sertraline and fluoxetine with minimal dosage adjustment needed in patients with ESRD (59); however, paroxetine requires dosage reduction, because plasma levels are higher in patients with renal failure (59). Other antidepressant medications should be used with caution in patients with ESRD because of limited data or because of the possible consequences of subsequent accumulation of toxic metabolites in patients with decreased renal clearance. These include nefazodone, venlafaxine, and bupropion (59).

Group therapy is another potential treatment option for patients with ESRD and MDD. A study from Harlem Hospital by Friend *et al.* (90) found that dialysis patients who participated in a social support group had improved survival compared with those who did not participate, even after the effects of other

potential confounders were controlled for; however, this was not a randomized, controlled study, and therefore it likely suffers from selection bias (90). A larger randomized, controlled trial of a social support group intervention in patients with ESRD is needed to determine its potential effect on depression.

Exercise therapy is another potential option for patients with depression. Kouidi *et al.* (91) performed a randomized, controlled trial of 31 HD patients to study the impact of an exercise rehabilitation program on psychosocial parameters, including depression. Twenty patients were randomly assigned to the exercise intervention. BDI scores decreased from  $21.0 \pm 10.4$  to  $13.7 \pm 9.5$  in the exercise group (91); however, a study from The Netherlands by van Vilsteren *et al.* (92) failed to show a significant improvement in depression scores when a randomized, controlled trial of an exercise intervention in 96 HD patients was performed. Patients were excluded from the study when they were on  $\beta$  blockers or when they had orthopedic problems or “severe cardiovascular disease,” including unstable angina (92). Patients who participated in the exercise group did have significant increases in their “overall health perception and vitality” (92). Further studies are needed to investigate the role that exercise therapy may play in modulating depression in dialysis patients.

There are limited data on the role of electroconvulsive therapy (ECT) in the treatment of depression in HD patients. Williams *et al.* (93) described a case of a 60-yr-old male who had ESRD and severe bipolar depression and was successfully treated with ECT; however, there is concern that ECT may pose unique risks in this patient population, as a result of considerations regarding hyperkalemia, acid-base alterations, use of general anesthetic agents, and the increased cardiovascular risk that is associated with patients with ESRD (93).

Cognitive behavioral therapy is another potential therapeutic option for patients with chronic kidney disease and depression; however, as with other treatments in this patient population, data are limited. Cukor *et al.* (2,94) found that cognitive behavioral therapy may be an effective therapy for depression in HD patients.

## Conclusions

- Depression is prevalent in patients with ESRD and may be linked with mortality.
- It is likely that screening, diagnosing, and treating depression properly in this patient population will be associated with improvement in quality and quantity of life; however, confirmation of such notions awaits the design and performance of appropriate randomized, controlled trials.
- Several studies have been performed to determine the validity and optimal cutoff scores for depression screening tools, including the BDI, PHQ-9, and CES-D.
- A BDI score of 14 to 16 has been shown to have the most accuracy for making the diagnosis of depression in the ESRD HD patient population.
- The structured clinical interview, based on DSM-IV criteria for depression, remains the gold standard for making the diagnosis of depression.

- Limited trials have evaluated the safety and efficacy of antidepressants in this patient population.
- SSRI are believed to be safe and effective in patients with ESRD and may have other beneficial effects, including reduction of orthostatic hypotension.
- If the diagnosis of depression is uncertain, then caution is advised in prescribing any pharmacologic therapy before consultation with a mental health professional.
- Caution is advised when prescribing antidepressants in patients with ESRD, because dosage reduction may be necessary depending on the agent and class of medication chosen.
- Larger randomized, controlled clinical trials are needed to determine the optimal approach to treatment of depression in patients with ESRD.

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## Disclosures

None.

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