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# Epidemiology, Diagnosis, and Management of Depression in Patients With CKD

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## CASE PRESENTATION

A 58-year-old Hispanic man who has been dialysis dependent for 2 years because of diabetic nephropathy reports depressive symptoms during dialysis rounds. For the past 6 weeks, he has had reduced energy and difficulty sleeping and concentrating. He reports a loss of interest in his usual hobbies and family activities and notes an increasing sense of feeling worthless and guilty. He denies suicidal ideation. Medical history includes diabetic retinopathy and neuropathy, coronary artery disease treated with 4-vessel coronary artery bypass grafting 3 years ago, ischemic cardiomyopathy with an ejection fraction of 30%, and cerebrovascular disease. His wife recently has been given a diagnosis of breast cancer. His medications are aspirin, metoprolol, lisinopril, simvastatin, sevelamer, and epoetin alfa. His blood pressure is 130/75 mm Hg, pulse is 65 beats/min, and cardiac and pulmonary examination results are unremarkable. He is interviewed by the social worker in the dialysis unit, who diagnoses clinical depression by using standard *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) (*DSM IV*) criteria. The patient refuses to discuss his problems with the social worker and declines further psychiatric evaluation. His nephrologist discusses a trial of antidepressant medication, but the patient refuses to use additional medication. During the next month, the patient presents with greater interdialytic weight gains and begins to come late for dialysis sessions. He then presents to a dialysis session reporting dyspnea and orthopnea and is found to have a 10-kg weight gain. On physical examination, blood pressure is 196/96 mm Hg and he has increased jugular venous pressure and bibasilar crackles. He is admitted to the hospital with a diagnosis of congestive heart failure.

### INDEX WORDS

Depression; chronic kidney disease; end-stage renal disease (ESRD); treatment

## BACKGROUND

Depression is prevalent in patients with chronic kidney disease (CKD) and has been associated with increased morbidity and mortality. Whereas the point prevalence of



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depression is 2% to 4% in the general community and 5% to 10% in the primary care setting,[1] 20% to 30% of patients with CKD have clinical depression.[2–4] This prevalence is even greater than that reported for patients with other chronic diseases, such as 14% for congestive heart failure[5] and 16% for coronary artery disease after acute myocardial infarction.[6] Several studies have established that depressive symptoms are associated with recurrent cardiac events in patients with coronary artery disease and new cardiac events in those with no known coronary artery disease.[7–15] Depression is an independent risk factor for rehospitalization in patients with congestive heart failure and end-stage renal disease (ESRD)[3,5,16–19] and death in patients with recent myocardial infarction, congestive heart failure, or ESRD.[3,5,6,16,18–27] Patients with CKD and ESRD experience excessive rates of cardiovascular events and death.[28,29] Importantly, in patients with CKD, as in the general population, depression also results in substantial decreases in quality of life, functional impairment, and sexual dysfunction.[30–34] It therefore is important to better understand the problems and difficulties diagnosing and treating depression in patients with CKD and whether treatment of depression would improve medical outcomes and selected quality-of-life domains of patients with CKD.[16,35] Despite the large randomized placebo-controlled Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) that showed a trend toward benefit of the serotonin-selective reuptake inhibitor (SSRI) sertraline on cardiovascular outcomes in patients with acute myocardial infarction or unstable angina,[36] antidepressant medication treatment rates in patients with CKD are very low, in part because the efficacy and safety of antidepressant medications are not fully accepted by physicians caring for these patients.[2,37–39] Nevertheless, small studies have explored the use of antidepressant medications, as well as such nonpharmacological treatment of depression as psychotherapy, exercise therapy, cognitive behavioral therapy, and modifications in the dialysis treatment regimen in patients with ESRD.[40–44] It should be emphasized that treatment regimens for depression for patients need to be tailored to the individual patient, making it challenging to perform randomized treatment trials of depression in this complex patient population.

In this review, we emphasize the high prevalence of depression in patients with CKD, the association of depression with poor outcomes, and potential mechanisms for this association and review the data for pharmacological and nonpharmacological treatment of depression.

## PREVALENCE OF DEPRESSION

Before discussing prevalence, a distinction must be made between depressive symptoms, assessed by using a score on a patient self-administered depression questionnaire, such as the Beck Depression Inventory (BDI), and a clinical diagnosis of major depressive disorder defined by using standard *DSM-IV* criteria. These criteria define a clinical syndrome lasting for at least 2 weeks, during which the patient experiences either depressed mood or anhedonia plus at least 5 of the 9 *DSM-IV* symptom domains (Box 1).[2,45,46] Patients with CKD may report symptoms of decreased energy, poor appetite, and sleep disturbance on self-report depression questionnaires that may not be confirmed as an episode of a major depressive disorder by using a *DSM-IV*–based structured clinical interview.[2,47] These increased somatic symptoms reported by a chronically ill patient therefore may be misdiagnosed as symptoms of a depressive disorder.[48] Furthermore, use of different self-report questionnaires in various studies has likely contributed to the varying estimates (from 15% to 60%) of the prevalence of depression in patients with ESRD.[2–4,17,20,30,37,47–51] The lack of consistency in these reports also could reflect different comorbid conditions, populations assessed at different times after the initiation of maintenance dialysis therapy, and different baseline characteristics of the sample population.[2]

**Box 1**

***DSM-IV* Criteria for Major Depressive Episode: Symptom Domains**

1. Depressed mood
2. Loss of interest or pleasure
3. Appetite disturbance
4. Sleep disturbance
5. Psychomotor agitation or retardation
6. Fatigue and tiredness
7. Worthlessness, feeling like a burden, or guilty
8. Difficulty concentrating
9. Recurring thoughts of death or suicide

Source: *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition).[46]

There is a large body of literature using self-administrated questionnaires, such as the BDI, as a screening tool for the identification of depressive symptoms in patients on maintenance dialysis therapy.[2,20,30,35,37,47,51] For example, mean BDI scores in large cohorts of patients with ESRD have averaged about 12 in several studies. Even higher scores were noted in patients at the initiation of dialysis treatment.[30,37] Other studies using different questionnaires, such as the Patient Health Questionnaire and the Center for Epidemiological Studies Depression Scale (CES-D), have emphasized the reporting of a large number of depressive symptoms by patients with CKD.[4,38]

However, few studies have used standard psychiatric criteria for diagnosing clinical depression in patients with CKD. Thus, 2 recent studies that used the health care provider–administered Structured Clinical Interview for Depression (SCID) as the *DSM-IV*–based standard for the diagnosis of a depressive disorder in cohorts of patients with ESRD deserve special mention.[2,4] The SCID is a structured interview that has been validated against the *DSM-IV* for establishing a psychiatric diagnosis of depressive disorder.[52,53] Hedayati et al[2] included a cohort that was 85% African American, and Watnick et al[4] included primarily white patients. The point prevalence of depressive disorder in patients with ESRD was 26% in both studies, with point prevalences of major depressive disorder of 17.3% and 19%, respectively. The remainder had dysthymia or minor depression based on the SCID.[2,4]

## ASSOCIATION OF DEPRESSION WITH POOR OUTCOMES

Although numerous studies have investigated the association of depression with outcomes in patients with ESRD, interpretation of these studies has been complicated by the lack of standardized criteria for diagnosing depression.[54] Documenting the association of depression with outcomes has been complicated further by the proximity of the depression measurement to the time of the outcome measure and persistence or change in depressive symptoms over time. Whereas a few studies involving small numbers of patients show no relationship between baseline depression scores and outcomes,[20,55,56] the majority of studies underscore the significance of this relationship.[17,20,21,32,57–64] The importance of examining the change in depressive symptom severity scores over time was emphasized in a prospective cohort study of 295 urban maintenance hemodialysis (HD) patients. Although baseline levels of depressive symptoms assessed by using the BDI were not a significant

predictor of mortality, depressive symptoms analyzed with a time-varying analysis were significantly associated with mortality in multivariable analysis.[20] Soucie and McClellan[57] reported a greater rate of death within 90 days of dialysis therapy initiation for depressed versus nondepressed patients. In a study of peritoneal dialysis patients using a time-varying analysis, patients with BDI scores of 11 or higher had a 2-fold greater peritonitis rate than patients with lower BDI scores.[64] In a multicenter study involving 9,382 HD patients from 12 countries using the CES-D questionnaire, elevated scores were associated with increased risks of mortality and hospitalization, and past physician diagnosis of depression ascertained from the medical chart was associated with mortality.[38] In another population-based study of 1,588 men receiving maintenance HD in US Veterans Affairs facilities, after adjusting for age, race, and comorbid conditions, a diagnosis of depression (noted in the medical records) was significantly associated with increased cumulative hospital days (rate ratio for adjusted model, 1.31; 95% confidence interval [CI], 1.04 to 1.66) and increased number of hospitalizations (rate ratio for adjusted model, 1.30; 95% CI, 1.11 to 1.52).[17] Analysis of the Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) Study showed that although baseline increased depressive symptoms were not associated with increased overall 2-year mortality, persistently greater levels of depressive symptoms over time were associated with increased risk of death and cardiovascular events.[21]

Perhaps the most compelling evidence for the independent association of depression with poor outcomes in patients with ESRD comes from a prospective observational study in which the diagnosis of depression was based on the *DSM-IV*–based SCID, administered blindly by a physician to 98 consecutively enrolled maintenance HD patients prospectively followed up for up to 1 year.[16] Survival analysis was used to investigate the association between depression and time to the first event, which was defined as either death or hospitalization. The prevalence of depression diagnosed by using the SCID was 26.5%.[16] Median time to first follow-up was 5.4 months. By first follow-up, 21 of 26 depressed patients and 31 of 72 nondepressed patients died or were hospitalized. In the unadjusted model, depression was associated with time to death or hospitalization with a hazard ratio of 2.11 (95% CI, 1.21 to 3.68).[16]

The association remained significant in multivariable models after adjusting for age, sex, race, time on dialysis therapy, and number of comorbid conditions (hazard ratio, 2.07; 95% CI, 1.10 to 3.90).[16] To our knowledge, no published data exist to examine the association of depression with poor outcomes in outpatients with CKD before dialysis therapy initiation. One study of inpatients with CKD admitted with a diagnosis of congestive heart failure examined the relationships among severe CKD, corresponding to creatinine clearance less than 30 mL/min/72 kg; depression, diagnosed by using the National Institute of Mental Health Diagnostic Interview Schedule (DIS); and 12-month mortality.[48,65] The point prevalence of major depressive disorder by using the DIS was 21.6% if severe CKD was present and 13.0% if absent.[48] Both depression by means of the DIS and severe CKD were significant predictors of mortality at 12-month follow-up in adjusted models.[48]

## RISK FACTORS ASSOCIATED WITH DEPRESSION

Younger age, white race, female sex, and longer duration of maintenance HD therapy were associated with a greater prevalence of physician-diagnosed depression in data from the Dialysis Outcomes and Practice Patterns Study (DOPPS).[3] Across studies of depression in patients with ESRD, there appears to be a relationship between various comorbid conditions, such as diabetes mellitus, coronary heart disease, cerebrovascular disease, peripheral vascular disease, lung disease, and hypoalbuminemia,[2,3,17,37] and depressive symptoms. This association between comorbidity and depressive symptoms is similar to that observed in the general medical population.[66] Severity of predialysis CKD also has been associated

with increased depressive symptoms.[48] This correlation of increased comorbidity and disease severity with depression reported in patients with CKD and ESRD is important to keep in mind when evaluating outcome studies and depression.[2,3,16,64] Not surprisingly, lower self-rated quality of life has been correlated with the presence of depressive symptoms.[2,30–34,37,67]

Depression also has been associated with problems with and disruptions of social interactions and relationships. These can result in an erosion of support provided by spouse and family, work, or community and religious organizations.[68–72] Marital and family difficulties for patients with ESRD are well documented.[70–72] Reasons for the disruption of social support networks for patients with ESRD and the isolation and withdrawal from social activities are complex and may be related in part to the patients' various comorbidities, time required for the dialysis treatment itself, postdialysis fatigue, cognitive impairment, and so on.

## POTENTIAL MECHANISMS FOR THE ASSOCIATION BETWEEN DEPRESSION AND OUTCOMES

A key question is whether depression itself has a direct mechanistic role in the development of morbidity and mortality in patients with CKD or whether depressive symptoms are merely a surrogate marker for increased comorbidity and disease severity. Specific biological and behavioral factors have been proposed as potential mechanisms by which depression may lead to cardiac events (Fig 1).[16,73–89] These factors include common genetic influences on depression and ischemic heart disease observed in twin studies,[74,75] altered autonomic tone such as lower heart rate variability,[76,77] enhanced hypothalamic-pituitary axis activity such as increased cortisol and norepinephrine excretion,[78,79] and alterations in inflammation and immune status.[47,80] Depressive symptoms also are associated with lower serum albumin levels.[88] The relationship between depression and inflammation appears to be bidirectional.[90] It now is well established that depression can result in upregulation of inflammatory mediators that can contribute to depressive symptoms.[91] For example, 50% of patients who receive interferon alfa treatment, which can result in decreased brain concentration of serotonin and dopamine, develop clinical depression,[92] and this depression can be ameliorated by paroxetine therapy.[93] Treatment of cytokine activation associated with inflammatory conditions alone without antidepressants can result in amelioration of depressive symptoms. For example, in 618 patients with psoriatic arthritis treated with etanercept, there was marked improvement in depressive symptoms independent of improvement in associated skin or joint problems.[94] Given the activated inflammatory state in many patients with CKD, the relationship between depression and inflammation deserves further exploration.

The relationship between the altered serotonin levels seen in depressed patients and increased platelet aggregation and vasoconstriction, which can lead to coronary events, deserves mention.[81–84] There are reports to suggest that depression is associated with changes in platelet function, and SSRIs may have antiplatelet activities.[82] Treatment of depressed patients after acute coronary syndrome with sertraline was associated with reductions in platelet activation and a trend toward improved cardiovascular outcomes in SADHART.[36,82–84]

Perhaps more compelling mechanisms in maintenance dialysis patients in particular are such behavioral factors as nonadherence, unhealthy lifestyle, poor nutrition, and lack of social support.[62,85–89] The relationship between depressive symptoms and withdrawal from dialysis therapy noted in the DOPPS is particularly noteworthy.[38] Depressive symptoms are associated with nonadherence to medical treatment in patients with ESRD, such as

nonadherence to diet and interdialytic weight gain.[62,95–99] There is an association between depressive symptoms and peritonitis rates in peritoneal dialysis patients.[64] Decreased behavioral compliance is associated in turn with decreased survival.[62] The strong correlation of depression with nonadherence suggests the importance of recognizing depression as a risk factor for poor outcomes in patients who may not be adhering to medical advice.[100]

## DIAGNOSIS OF DEPRESSION IN PATIENTS WITH CKD AND ESRD

Although it has been established that such self-report measures of depression as the BDI cannot be used for the diagnosis of a depressive disorder in HD patients,[2,4] these scales may serve as quick and easily administered screening tools to identify patients at high risk of depression.[2] This becomes especially pertinent given the increasing demands on clinical nephrologists to diagnose and treat medical comorbidities.[2] Based on the high prevalence of depression and its association with poor outcomes, we recommend that patients with ESRD be screened at the initiation of dialysis therapy, within 3 to 6 months after therapy initiation, and then yearly.[2] Patients who have high scores on depression screening questionnaires should then undergo a structured clinical interview to confirm the presence of a major depressive disorder before treatment options are considered. A challenge for dialysis facilities is how to implement the screening program; can this be done with existing personnel within the facility (social workers, nursing staff, and nephrologists) or do outside consulting personnel need to be used? Some investigators have suggested that a depression screening program can be carried out with existing personnel in the dialysis unit.[35]

It also should be noted that a higher cutoff score on self-report screening tools should be used in patients with ESRD for a depression threshold, based on previous studies that validated such screening tools in ESRD samples[2,4,51] (Table 1). For example, BDI cutoff scores of 14 and higher and 16 and higher were suggested as appropriate cutoff values using the SCID as the *DSM-IV*–based comparator[2,4] and 15 or higher in another study using the DIS as the *DSM-IV*–based comparator[51]; these are higher than the cutoff score of 10 or higher validated in the general non-ESRD population.[101] Similarly, the CES-D cutoff threshold score for depression of 18 or higher in data reported by Hedayati et al[2] is higher than the cutoff score observed for the general population.

Studies evaluating the use of such depression screening tools in predialysis patients with CKD are limited to a study in which Hedayati et al[102] reported the best BDI cutoff score for depression in predialysis patients with stages 2 to 5 CKD to be ≥10, similar to the general population. A likely explanation for higher BDI cutoff scores validated in dialysis patients may be the greater frequency of somatic symptoms assessed by using this tool, such as sleep disturbance, poor appetite, and low energy level, which may not be manifest at earlier stages of predialysis CKD.[2,39]

## PHARMACOLOGICAL TREATMENT OF DEPRESSION

Despite the high prevalence of depression and its association with poor outcomes, only a minority of patients with ESRD are given a diagnosis of and receive treatment for depression.[2,37–39] When BDI scores of 15 or higher were used as a marker for depression in patients initiating HD therapy, only 16% were being treated with antidepressants.[37] Using a *DSM-IV*–validated interview, less than half the depressed patients with ESRD were being treated with antidepressants[2] and about half of those on drug treatment were receiving subtherapeutic doses.[2] Undertreatment of depression and underdosing of antidepressant agents may be caused by nephrologists' concerns about adverse effects of medications[39] because little research has been performed regarding the safety of antidepressant medication

use in patients with CKD. Unfortunately, such patients generally are excluded from antidepressant treatment trials because of concerns for safety.[36,103]

Generally, antidepressant medications are highly protein bound, hepatically metabolized, and not removed significantly by dialysis.[104] Furthermore, the relative activity and mode of excretion of metabolites of these drugs in patients with kidney disease often are uncertain and may complicate the use of these drugs if adverse events occur. For example, the half-life of fluoxetine is 24 to 72 hours, and that of its active metabolite is even longer (7 to 9 days).[104] Concerns about the safety of antidepressant medication use in patients with moderate to advanced CKD include increased risk of drug-drug interactions for monoamine oxidase inhibitors, tricyclics, and SSRIs[104–106]; anticholinergic effects and corrected QT interval prolongation for tricyclics[104–106]; accumulation of toxic metabolites with decreased renal clearance for nefazodone, venlafaxine, and bupropion[105]; and sexual dysfunction, central nervous system depression, and increased risk of bleeding for SSRIs, which becomes particularly problematic in patients with advanced CKD.[39,107–110] SSRIs also have increased serotonergic activity in the gastrointestinal tract and may cause nausea.[39,111,112] For these reasons, the safety and efficacy of antidepressant drug therapy in CKD populations have not been clearly established, and this presents a challenge for nephrologists. Table 2 lists commonly used antidepressant medications and potential problems for patients with ESRD.

There are limited scientific data to clearly suggest that treatment of major depressive disorder is efficacious or that such treatment changes clinical outcomes in patients with CKD.[2,47,113–118] Few studies have examined this issue, and they are fraught with limitations, including insufficient sample sizes,[40,116–118] lack of placebo-control groups,[33,40,115–117] and lack of *DSM-IV*–based gold-standard criteria for the establishment of a diagnosis of clinical depression.[33,117,118] In 1 study, 14 HD patients with major depression were randomly assigned to fluoxetine or placebo.[118] No patient discontinued medication. There was a statistically significant improvement in depression at 4, but not at 8, weeks.[118] A nonrandomized observational study of antidepressant therapy in long-term peritoneal dialysis patients with a diagnosis of depression on the basis of a structured interview reported significant improvements in BDI scores with therapy (17.4 ± 6.6 at the start and 8.4 ± 3.0 at completion of treatment at 12 weeks).[114,115] However, only half the patients with increased BDI scores agreed to be interviewed, and only half of those with a diagnosis of depression agreed to accept pharmacological treatment.[114,115] Furthermore, only half of those started on medication successfully completed 12 weeks of treatment.[114,115] Reasons for failure to complete a treatment course included the development of acute medical problems unrelated to the use of antidepressant medication, medication side effects, substance abuse, and the presence of concomitant *DSM-IV* Axis 2 disorders.[114,115]

## NONPHARMACOLOGICAL TREATMENT OF DEPRESSION

Nonpharmacological treatments of depression in patients with ESRD have met with some success in small series (Box 2).[40–44] These studies have examined the use of psychotherapy, exercise therapy, cognitive behavioral therapy, and other strategies that basically are not different from those used in the general population.

**Box 2**

**Nonpharmacological Treatment of Depression**

Psychoeducation

Counseling, including cognitive behavioral therapy

| |
|---|
| Exercise programs |
| Modifications of the dialysis treatment regimen |
| Treating anxiety |
| Addressing difficulties in marital, family, and other supportive relationships, including caregiver burden |
| Exploring alternative therapies, such as sleep hygiene, meditation, muscle relaxation, and music |

Cognitive behavioral therapy, a well-documented evidence-based therapy for depression, is based on the premise that "automatic thoughts" in response to strong negative feelings/emotions can result in distorted or emotional thinking and reasoning and, in turn, poor decisions and ineffective problem solving. However, logical thinking lowers the intensity of strong negative emotions and allows for more effective problem solving. In a recent randomized trial of cognitive behavioral therapy (published only in abstract form), 85 dialysis patients with interview-diagnosed clinical depression were randomly assigned to standard care versus cognitive behavioral therapy with a psychologist.[119] Therapy considered the effects of kidney disease and its treatment on daily life, depressive symptoms, coping and cognitive remodeling techniques, relaxation activities, and so on. There was 80% adherence to the treatment regimen. After 3 months, there was a significant difference in BDI scores between the treatment and control groups (14.1 ± 8.7 versus 21.2 ± 9.1, respectively; $P < 0.01$).[119]

Exercise programs also may have a beneficial effect on depressive symptoms in patients with ESRD.[120,121] In a recent study, 35 HD patients were randomly assigned to a 10-month intradialytic exercise training program.[120] There was a 39% reduction in BDI scores in the exercise group after the 10-month study period.[120]

Considerable interest has been focused on the impact of alterations in the dialysis regimen on health-related quality-of-life assessments. Several studies have explored the impact of in-center nocturnal, home nocturnal, and short daily home or in-center HD on these measures. These studies often suggest improvements in selected health-related quality-of-life domains, including depression.[122] For example, one 12-month nonrandomized study of 6-times-weekly in-center short HD was associated with a reduction in BDI scores from 15 to 8 ($P < 0.01$).[123] In addition, an interim analysis of the Following Rehabilitation, Economics and Everyday-Dialysis Outcome Measurements (FREEDOM) study (published only in abstract form) indicated a significant reduction in BDI scores (from 12 to 7) in patients converted from conventional HD to 6-times-weekly short home HD.[124] Results of the National Institutes of Health–sponsored randomized trial of more frequent HD (short daily and nocturnal) that is using BDI score as a secondary end point should help clarify the impact of these therapies on depressive symptoms.[125] It should be emphasized that the impact of these newer therapies on BDI scores could indicate improvement in somatic symptoms and not affective symptoms. Future randomized trials investigating the effect of various interventions on depression in this chronically ill patient population should consider examining both the somatic and affective components of depressive symptoms.

The relationship between depression and various inflammatory markers has been discussed. Given the activated inflammatory state in many patients with CKD, this relationship deserves further exploration. One is led to wonder whether treatment of depression can ameliorate the inflamed state or, conversely, lessening the inflammation can result in an improvement in depressive symptoms.

Given the magnitude of the problem of depression in patients with CKD, additional therapeutic approaches need to be examined. Interventions that address the problems with social interactions of patients need to be explored in terms of family and marital counseling and involvement of community and religious organizations.[68–72] Support and education of caregivers and family members of patients may be helpful. The high incidence of anxiety in the ESRD population has been emphasized[126]; the well-documented relationship between anxiety and depression suggests that addressing anxiety may be another avenue of potential therapy.[127] In addition, there are lessons to be learned from other less traditional approaches to treating depression in patients with other chronic illnesses. For example, a recent Cochrane analysis suggested that music therapy, which is generally accepted by depressed patients, can result in an improved mood.[128] These findings were emphasized in a study involving 200 patients with a variety of chronic advanced illnesses who showed significant improvement in mood ($P < 0.001$) in response to music therapy.[129]

It should be emphasized that pharmacological and nonpharmacological treatment of depression can be used in combination. Combinations of medication and psychotherapy have been more efficacious than either treatment alone in patients with chronic major depressive disorders.[130]

## CONCLUSION

Recent studies have focused attention on the high prevalence of depression in patients with CKD. It is important to understand the methods used to evaluate depression and the differences between the presence of depressive symptoms and clinical depression. The association of both depressive symptoms and clinical depression with a variety of outcomes is well documented. Several promising studies have explored pharmacological and nonpharmacological approaches to treat depressive symptoms in patients with CKD. It remains to be determined how these treatments will impact on morbidity and mortality, hospitalizations, costs, and health-related quality-of-life measures in these patients.

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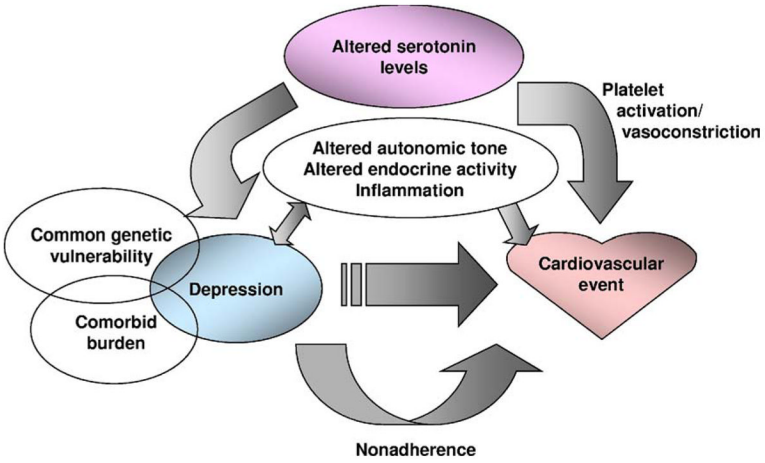


**Figure 1.**
Potential mechanisms by which depression may lead to cardiac events.

## Table 1

Depression Self-Administered Screening Scales Validated for Use in ESRD

| Depression Scale | Characteristics* | Non-ESRD† Cutoff Score | ESRD Cutoff Score |
|---|---|---|---|
| Beck Depression Inventory | 21 Items; score, 0–63 | ≥10 | ≥14—16 |
| Center for Epidemiologic Studies Depression Scale | 20 Items; score, 0–60 | ≥16 | ≥18 |
| Patient Health Questionnaire | 9 Items; score, 0–27 | ≥10 | ≥10 |

Abbreviation: ESRD, end-stage renal disease.

*Higher scores represent higher degree of depressive symptoms.

†Refers to cutoff scores validated in the general non-ESRD population.

## Table 2

Common Antidepressant Medications and Potential Side Effects in Patients With ESRD

| Antidepressant Medication | Side Effects | Use in Patients With ESRD |
|---|---|---|
| Selective serotonin reuptake inhibitors (citalopram, fluoxetine, paroxetine, sertraline) | Sexual dysfunction, GI symptoms, CNS symptoms, risk of bleeding | Citalopram: use cautiously in severe renal impairment due to metabolites<br>Fluoxetine: use with caution given long half-life<br>Paroxetine: use lower doses<br>Sertraline: no dose adjustment recommended |
| Serotonin-norepinephrine reuptake inhibitors (venlafaxine) | Accumulation of toxic metabolites, sexual dysfunction, hypertension | Reduce dose by 50% in mild to moderate renal impairment; use with caution |
| Serotonin modulators (nefazodone, trazodone) | Accumulation of toxic metabolites, liver failure (for nefazodone), CNS symptoms, hypotension and cardiac arrhythmias | Avoid use in patients with cardiac disease or hypotension |
| Noradrenergic and specific serotonergics (mirtazapine) | Sedation, weight gain | Give before sleep, reduce dose |
| Dopamine-norepinephrine reuptake inhibitors (bupropion) | Accumulation of toxic metabolites | Use with caution in renal impairment given metabolites |
| Tricyclics and tetracyclics (amitriptyline, desipramine, doxepin, nortriptyline) | CNS symptoms, anticholinergic effects, QTc prolongation, cardiac arrhythmia, orthostatic hypotension | Avoid if possible given cardiac side effects |
| Monamine oxidase inhibitors (phenelzine, selegiline, tranylcypromine) | Drug-drug interactions, enhanced sympathetic activity with ingestion of tyramine-containing foods | Avoid if possible given potential drug-drug interactions, significant side effects |

*Note:* Given the lack of large randomized well-controlled trials to test the safety of antidepressant medications in patients with ESRD, patients should be monitored closely for side effects, especially before dose escalation is considered.

Abbreviations: ESRD, end-stage renal disease; GI, gastrointestinal; CNS, central nervous system; QTc, corrected QT interval.