

Mental Health, Depression, and Anxiety in Patients on Maintenance Dialysis

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Depression and anxiety are among the most common comorbid illnesses in people with end-stage renal disease (ESRD). Patients with ESRD face many challenges which increase the likelihood that they will develop depression or anxiety or worsen these conditions. These include a general feeling of unwellness; specific symptoms caused by ESRD or the patient's treatment; major disruptions in lifestyle; the need to comply with treatment regimens, including dialysis schedules, diet prescription, and water restriction; ancillary treatments and hospitalizations; and the fear of disability, morbidity, and shortened lifespan. Depression has been studied extensively in patients on maintenance dialysis, and much effort has been done to validate the proper screening tools to diagnose depression and to define the treatment options for patients on maintenance dialysis with depression. Anxiety is less well studied in this population of patients. Evidence indicates that anxiety is also common in maintenance dialysis. More attention should be paid to measuring the incidence and prevalence and developing methods of diagnosis and treatment approaches for anxiety in patients with ESRD. In this review, we attempted to underscore those aspects of depression and anxiety that have not been investigated extensively, especially with regard to anxiety. The interaction between racial/ethnic characteristics of patients on maintenance dialysis with depression and anxiety needs to be studied more extensively, in order to assess better approaches to healthcare for these individuals.

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INTRODUCTION

End-stage renal disease (ESRD) is defined as kidney failure sufficiently severe to require maintenance dialysis or kidney transplantation to maintain health or life. According to the United States Renal Data System report in 2008, there were 485 000 patients with ESRD in the United States, 61% of whom were Caucasian; 31.7%, African-American; 14%, Hispanic; 4.5%, Asian; and 1.3%, Native American (1.5% had no defined ethnicity).¹ Like many chronic diseases, ESRD may affect the psychological state of the patients (Table 1). Psychiatric illness in patients with ESRD has persistently intrigued healthcare workers due to its effect on the morbidity and healthcare

costs in patients with ESRD. Levy introduced the term "psychonephrology," to refer to psychiatric problems of people suffering from kidney disease, and particularly those with kidney failure who undergo maintenance dialysis or who are transplanted.²

Although there have been many estimates of the actual prevalence of psychiatric illness in patients with ESRD, these estimates may be erroneously low, because patients often fail to seek mental healthcare. Johnson and Dwyer reported that over 70% of patients on maintenance hemodialysis who had symptoms of depression or anxiety and described barriers to mental health treatment did not recognize their symptoms or did not perceive

Table 1. Patient Challenges Upon Starting Maintenance Dialysis

Patient Challenges Upon Starting Maintenance Dialysis
Medical management of their end-stage renal disease (requires compliance to dialysis and medicinal intake)
Adjustment to dietary prescription and reduced fluid intake
Maintaining meaningful life roles regarding jobs, family, and friends
Coping with the anger, fear, anxiety, frustration, and sadness of having a chronic illness
Accepting the disruption of their activities
Confronting their own mortality and probable shortened life span
Acceptance of recurrent hospitalizations, placement and repair of vascular or peritoneal access, and the discomfort of dialysis and other medical treatments

that they were in need of therapy for their mental health condition.³ Dialysis physicians and nurses, who are not psychiatrists, often fail to recognize such symptoms, and physicians may pay less attention to somatic complaints of psychiatric illnesses, and therefore, leave these comorbidities undiagnosed. In this review, we have tried to highlight those aspects of depression and anxiety in patients with ESRD which can be addressed to improve the life of patients undergoing maintenance dialysis therapy.

EPIDEMIOLOGY

Depression: a Greater Focus of Attention

Much attention has been given to depression in patients on maintenance dialysis during the past 3 decades. Considered to be the most common psychiatric abnormality in patients with ESRD,^{4,5} depression has been studied extensively in these individuals. The effect of depression on mortality, suicide, and hospitalization has been studied recently, and depression is established as an independent risk factor for mortality and morbidity.⁶⁻⁹ Drayer and colleagues found that patients with ESRD and depression have 4.1 times the mortality rate of patients with ESRD who do not have depression (Figure 1).¹⁰ Lopes and coworkers suggested a higher rate of withdrawal from maintenance dialysis in patients who developed depression while on dialysis than in those patients who were not depressed. These investigators also found a higher risk of mortality and hospitalization associated with depression.⁹ Einwohner and colleagues showed a similar increased risk of morbidity and mortality in depressed patients on maintenance peritoneal dialysis.¹¹

Suicide is highly linked with a depressed state of mind.^{4,12} It accounts for a death rate of 0.2% per 1000 dialysis patients-years at risk.¹³ Kurella and colleagues also found a strong association between alcohol dependence and hospitalization for substance abuse and mental illness with subsequent

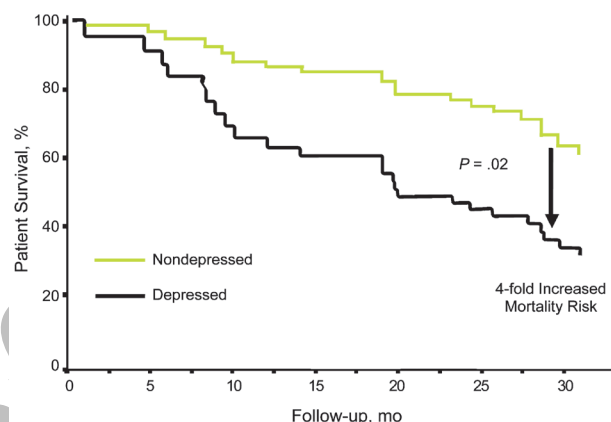


Figure 1. Survival possibilities for depressed and nondepressed patients on hemodialysis patients. Adapted from Drayer and colleagues.¹⁰

death by suicide.¹⁴ Patients with ESRD are often poorly adherent to their medical regimens, and Cukor and coworkers have reported depression as an independent factor for nonadherence in patients on maintenance dialysis.¹⁵

The prevalence rate for depression in patients with ESRD is around 3 times that of the general population. A national survey reported that the prevalence rate for major depressive disorders in the general population in the United States was 10.4% in Caucasians, 7.5% in African-Americans, and 8.0% in Mexican Americans.¹⁶ In contrast, Kutner and colleagues and Cukor and associates reported prevalence rates of 26.6% and 29% for depression, respectively, in patients with ESRD.^{17,18} Heydayati and colleagues demonstrated a point prevalence of depression of 26% and of major depression of 17% in patients on maintenance hemodialysis.^{19,20} Other studies, taken together, report a wider range for the prevalence of depression in patients with ESRD.^{7,20,21}

Anxiety: an Often Overlooked Disturbance

Anxiety has been an understudied aspect of

psychiatric illness in patients on maintenance dialysis. Most studies have focused on depression in these individuals. The National Institute of Mental Health defines an anxiety disorder as “an excessive, irrational dread of every day situations.” In the general population in the United States, the prevalence rate of anxiety disorders is 18%, which is tantamount to about 40 000 000 American adults aged 18 or older having this disorder.²² Precise data regarding the prevalence rate of anxiety disorders among patients with ESRD are unknown, but Kutner and colleagues,¹⁷ Taskapan and colleagues,²³ and Cukor and coworkers¹⁸ reported prevalence rates of 45%, 30%, and 45.7%, respectively. A review of 55 studies of the prevalence of symptoms of anxiety in patients with ESRD by Murtagh and coworkers found that 38% of patients with ESRD (12% to 52%) have substantial anxiety.²⁴

Because data are scarce regarding the prevalence of anxiety, the exact nature of its effects on patients with ESRD is also unknown. In the general population in the United States, the prevalence rates of social anxiety disorders over a 12-month period were reported to be 4.5% in African-Americans and 7.1% in Caucasians.²⁵

Sareen and associates established anxiety disorders as an independent risk factor for suicidal behavior and showed strong associations between the comorbidity of anxiety disorders and comorbid physical conditions, poor quality of life, and disability.^{26,27} Such associations have not been studied in patients with ESRD suffering from anxiety.

One co-author of this review (JDK) has personally observed that adult patients who are well established on maintenance hemodialysis therapy often describe higher anxiety levels during many of their thrice-weekly dialysis sessions. The prevalence of this problem is unknown. A possible temporal relationship between dialysis treatments and anxiety level was reported in 7 patients on maintenance hemodialysis in 1978 by Bedell and coworkers.²⁸ They reported that patients were more anxious on hemodialysis days, and that the intensity of their anxiety increased as their dialysis treatment session proceeded.²⁸ The small sample size and the lack of characterization of the patients were important limitations of this study.

Billington and coworkers reported that the degree of hope in 103 patients on maintenance dialysis, assessed from a self-report scale, correlated inversely

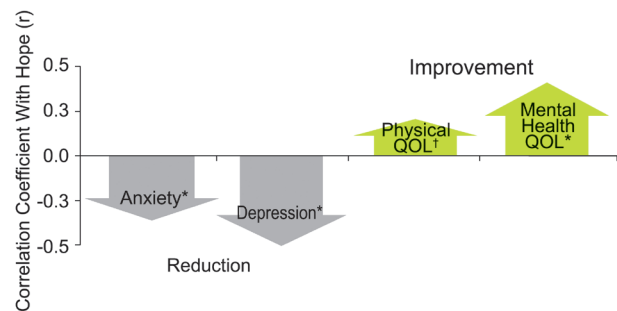


Figure 2. Correlation of hope with the quality of life in patients with end-stage renal disease. Adapted from Billington and colleagues (a cross-sectional study evaluating self-reported measures from 103 patients on dialysis in 5 dialysis centers in the Northwest United Kingdom).²⁹ Hope was defined as an active cognitive process of belief in one's capacity to produce goals, as well as goal-directed determination/energy and a positive sense of planning to meet goals. QOL indicates quality of life.

* $P < .001$

† $P < .05$

with the degree of depression and anxiety and positively with the disease effects, the burden of ESRD, and the physical and mental quality of life (Figure 2).²⁹

Race/Ethnicity and Its Association With Depression and Anxiety

Racial effects on depression and anxiety have been studied in the general population, and the results have been conflicting. Brown and colleagues showed no racial differences in the prevalence of anxiety disorders and comorbid major depression between African-Americans and Caucasians in the general population.³⁰ Himle and coworkers indicated in their study that most anxiety disorders are more prevalent among whites than African-Americans and Caribbean blacks.²⁵ Stephanie and colleagues reported a higher prevalence rate of major depressive disorders among whites than African-Americans and Mexican-Americans.¹⁶ No study has been conducted in patients with ESRD that clearly delineated racial effects of African-Americans and Caucasians on anxiety levels in patients on maintenance dialysis. The studies of Cukor and coworkers and Kimmel and colleagues consisted of 88.6% of the African-Americans; thus, they may not have had an adequate sample size to compare their findings to those of non-African-Americans.^{18,31,32}

Weisbord and associates reported the only available study on the association of race with depression in patients on maintenance hemodialysis. They reported that there were no racial differences in the prevalence of depression between Caucasian and African-

American patients on maintenance hemodialysis.³³

SCREENING

Validation of Practical Screening Tools

In the past decade, several questionnaires have been used to screen for depression and anxiety in patients with ESRD (Tables 2 and 3). The Beck Depression Inventory has been studied extensively, and its use has been validated to screen for depression in patients with ESRD.^{13,21,31,36} A higher cutoff value has been proposed to diagnose depression in patients on maintenance dialysis.^{19,21,37}

The Hospital Anxiety and Depression Scale is used as a screening tool for depression and anxiety and has been validated in the general population. A review by Bjelland and coworkers suggests that it has good internal consistency and validity.³⁸ Loosman and associates validated its use to screen depression in patients undergoing maintenance dialysis,³⁹ although Cukor and coworkers reported that the Hospital Anxiety and Depression Scale does

not serve as an effective screening tool for anxiety disorders in patients on dialysis.¹⁸ There is clearly a need for more effective screening tools, especially for anxiety, in patients on maintenance dialysis.

MANAGEMENT

In patients with ESRD, the symptoms of depression or anxiety may be similar to those that occur with kidney failure or uremia per se. Therefore, the diagnosis and treatment of depression and anxiety in these patients is often delayed or missed altogether because the symptoms are disguised by, or attributed to, uremia.^{12,13,36} This is especially true for the symptoms of depression. Insomnia is commonly reported in patients with either depression or uremia,⁴⁰ and drug-induced symptoms (eg, from glucocorticoid medicines) may also present in ways that overlap with the symptoms of anxiety, depression, or uremia. A team approach that includes psychologists, psychiatrists, or social workers is generally needed in order to identify,

Table 2. Assessment Tools and Prevalence Rates Reported in 6 Recent Studies of Depression and Anxiety in Patients on Maintenance Hemodialysis*

Author	Number of Patients	Study Tools	Prevalence Results	Additional Comments (Major Recommendations of Article)
Taskapan et al ²³	40	HDRS HARS PRIME-MD MMSE SF-36	Depression, 30% Anxiety, 35%	A negative correlation between interdialytic weight gain and quality of life domains of vitality and social function was found.
Weisbord et al ³³	160	BDI CDI DSI	Depression, 27% (in both races)	No racial differences were found in the prevalence of depression. Spiritual/religious belief in African-Americans seemed relevant to their better quality of life and survival.
Cukor et al ³¹	70	SCID BDI KDQOL-SF YSQ	Depression, 20% Anxiety, 27%	"Aloneness" and "ineffectiveness" were hallmarks of the depressogenic changes that were associated with end-stage renal disease treatment.
Cukor et al ³²	50	SCID BDI-2 KDQOL-SF LESS	Depression, 42% (depression on follow-up) Anxiety, 33% of the diagnosed patients from the above study ³¹ still had an anxiety disorder	Level of depressive affect is a more powerful predictor of depression 16 month later, than other psychological measures, including baseline depression diagnosis. It was a follow-up study in which patients were again interviewed after 16 months of their diagnosis.
Cukor et al ¹⁸	70	SCID HADS KDQOL-SF	Depression, 29% Anxiety, 45.7%	It was a single-center study with population not demographic representation of the United States.
Hedayati et al ⁶	98	SCID BDI CDI CESD	Depression, 26.7%	It was the first report on association between depression and poor clinical outcome in patients with end-stage renal disease.

*HDRS indicates Hamilton Depression Rating Scale; HARS, Hamilton Anxiety Rating Scale; PRIME-MD, Primary Care Evaluation of Mental Disorders; MMSE, Mini Mental State Examination; SF-36, Short Form Health Survey 36; BDI, Beck Depression Inventory; CDI, Cognitive Depression Index; DSI, Dialysis Symptom Index; SCID, Structured Clinical Interview for Diagnosis; KDQOL-SF, Kidney Disease Quality of Life-Short Form; YSQ, Young's Schema Questionnaire; LESS, Life Events Stress Scale; HADS, Hospital Anxiety and Depression Scale; and CESD, Center for Epidemiological Study of Depression.

Table 3. Assessment and Approach to Depressed Patients on Dialysis*

Intervention	Measures
Screening	<ul style="list-style-type: none"> • Beck Depression Inventory • Asking 2 basic questions: <ol style="list-style-type: none"> a. How much of the time have you felt so down in the dumps that nothing could cheer you up? b. How much of the time have you felt downhearted and blue?
Referral	Mental Health Professionals
Treatment	<ul style="list-style-type: none"> • Nonpharmacological therapy <ol style="list-style-type: none"> a. Psychotherapy b. Cognitive behavioral therapy c. Exercise training programs d. Treat Anxiety e. Counseling and psychotherapy for family members, significant others and caregivers f. Management of medical conditions that may contribute to depression, such as sleep deprivation, medicinal intake, and syndromes causing pain or other physical discomfort • Pharmacological therapy • Electroconvulsive therapy

*Adapted from articles by Lopes and colleagues,⁹ Cohen and colleagues,³⁴ and Hedayati and Finkelstein³⁵

comprehensively diagnose, and treat these illnesses.

Pharmacological treatment, psychotherapy and cognitive behavioral therapy have been the mainstay for the treatment of depression and anxiety in the general population (Table 3).^{41,42} Similar options are available to treat the psychological disorders in patients with ESRD.³⁴ However, in patients with ESRD, more consideration may need to be paid to the appropriate doses of medicines to be used. Failure to treat with appropriate psychotropic medicines or underdosing of such medicines appears to be common in patients with ESRD who have depression. Hedayati and colleagues reported that less than 50% of patients with ESRD who were diagnosed with depression by the Structured Clinical Interview for Diagnosis were receiving antidepressants, and approximately 50% of whom were receiving subtherapeutic doses.¹⁹ Wartnick and coworkers reported an even lower rate of treatment for depression in patients commencing maintenance dialysis therapy.⁴³ No studies are available regarding the numbers of patients with ESRD who receive treatment for anxiety disorders or the appropriateness of the doses of psychotropic medicines that are employed for these individuals.

Selective serotonin reuptake inhibitors are the main category of medicines that are currently used to treat depression in such patients, because of their effectiveness and enhanced safety, including their potential for reducing the risk of orthostatic hypotension in patients on maintenance hemodialysis.⁴ Blumenfield and associates studied the effect of fluoxetine in patients on hemodialysis and reported both effectiveness and safety in

these individuals.⁴⁴ Citalopram and sertraline also have safe pharmacokinetics in patients with ESRD, and hence, are often prescribed.⁴⁵ Tricyclic antidepressants and monoamine oxidase inhibitors are other treatment options, but they have a higher side effect profile which limits their use (Table 4).

Benzodiazepines, such as diazepam, have been used to relieve acute episodes of panic and anxiety. Generally, an adjustment of the drug dose for the level of the glomerular filtration rate is not needed, as they are metabolized in the liver. However, the dosing of midazolam should be adjusted cautiously because the conjugate of main metabolite of medazolam; ie, alpha-hydroxymedazolam, causes prolonged sedation in patients with kidney failure.^{46,47} Buspirone, a partial serotonin agonist that acts on the 5HT(1A) receptor, is often recommended over benzodiazepines because of the greater incidence of unfavorable side effects with benzodiazepines.⁴⁸ There is an increase in the half-life of the parent compound, buspirone and its active metabolite, 1-(2-pyrimidinyl)-piperazine, in kidney impairment, especially in anuric patients on hemodialysis during the interdialytic interval; thus, the dose of this medication must be carefully titrated.^{49,50}

Nonpharmacological treatment of these disorders is an important component in the overall treatment of the mental health of these patients. Cognitive behavioral therapy has been shown to improve symptoms of depression in patients on maintenance dialysis.^{51,52} Exercise programs may also be effective at reducing depressive symptoms in these individuals.^{53,54}

The psychological, social, economic, and emotional

Table 4. Commonly Used Psychotropic Medications in End-stage Renal Disease (ESRD)

Psychotropic Medications	Important Considerations	Potential Side Effects	Effect of Dialysis	Pharmacokinetics in Kidney Impairment
Selective serotonin reuptake inhibitors (fluoxetine, citalopram, paroxetine, sertraline)	Effects are usually seen in 6 weeks.	Suicidal ideation, bleeding, weight gain, gastrointestinal symptoms	Fluoxetine: not removed by dialysis Citalopram: not studied Paroxetine: not studied Sertraline: not removed by dialysis	Citalopram in severe impairment (creatinine clearance < 20 mL/min): Use with caution. Paroxetine (creatinine clearance <30 mL/min): mean plasma concentrations is about 4 times that seen in normal function.
Serotonin-norepinephrine reuptake inhibitors (venlafaxine)	Serum half-life increases from 4 hours to 6 to 11 hours in patients with ESRD.	Accumulation of toxic metabolites, sexual dysfunction, hypertension	Not removed by Dialysis	Decrease total daily dose by 50% given after completion of dialysis.
Serotonin modulators (nefazodone, Trazodone)	Avoid use in cardiac patients due to accumulation of toxic metabolites.	Accumulation of toxic metabolites, liver failure (for nefazodone), central nervous system symptoms, hypotension and cardiac arrhythmias	Nefazodone: minimal removal Trazodon : no effect	Nefazodone: nonrenal elimination of drug. Serum half-life in ESRD: 3 to 5.8 hours. Trazodone: no data available.
Dopamine-norepinephrine reuptake inhibitors (bupropion)	They increase risk of seizures due to toxicity of drug level and accumulation of active metabolites.	Hallucinations, insomnia, agitation	Not known	Use with caution and consider a reduction in dosing frequency.
Partial Serotonin 5HT(1A) receptor agonists (buspirone)	Serum half-life in patients with ESRD is 1 to 5 hours. In normal adults, serum half-life is 0.5 to 2.5 hours.	Dizziness, nausea, headache, insomnia, tremor, and seizure on withdrawal	Not removed by dialysis	Usually 25% to 50% dose reduction is advised to prevent hypotension.
Tricyclics and tetracyclics (amitriptyline, desipramine, doxepin, nortriptyline)	Avoid if possible given cardiac side Effects.	Central nervous system symptoms, anticholinergic effects, QTc prolongation, cardiac arrhythmia, orthostatic hypotension	Amitriptyline: not removed by hemodialysis Desipramine: not removed by hemodialysis or CAPD Doxepin : not removed by hemodialysis or CAPD Nortriptyline: not removed by hemodialysis or CAPD	...
Benzodiazepines (alprazolam, lorazepam, diazepam, midazolam, chlordiazepoxide)	This group is used with care due to high rate of side effects.	Delusion, hallucination, prolonged sedation	Alprazolam: minimal removal Lorazepam: Not removed by hemodialysis Diazepam : Not removed by hemodialysis Midazolam: not known.	Alprazolam and diazepam: increased free fraction of plasma protein bound drug in ESRD. Minimal differences in dialysis-dependent patients is seen. Lorazepam: manufacturer does not recommend use in ESRD.

stresses of living with ESRD often are overwhelming or nearly so for the patients and their family or close associates. These factors, coupled with the extra physical workload that ESRD often brings to family and friends, can be major contributors to depression and anxiety in these individuals. Social support is also an integral way of providing better healthcare for patients with ESRD. Integration of psychological and material support for better

healthcare of the patient is the essence of the social support system. Social support has been shown to have an improved end result in a variety of chronic illnesses.^{55,56} Symister and Friend reported that social support decreased depression by improving the self-esteem of the patients with ESRD, which led to an increased degree of optimism in these patients.⁵⁶

A continuous care model, a native model for the Iranian society, was used by Rahimi and colleagues,⁵⁷

which appeared to make a significant difference in the levels of depression and anxiety of patients on maintenance hemodialysis. This model was based on the principle that continuous care requires an integration of the orientation, sensitization, control, and evaluation of the disease process. It also lays stress on the dynamic relationship among the healthcare team and the patients and their family.⁵⁷

CONCLUSIONS

Depression as a comorbid illness in patients with ESRD has been more extensively studied. Less attention has been paid to anxiety, and hence, the information in the medical literature is sparser with regard to information on practical anxiety screening tools, the potential effects of race/ethnicity on anxiety, and the preferred methods of treatment of anxiety in patients with ESRD. The psychiatric burden experienced by patients with ESRD may have profound effects on their quality of life and response to treatment. Such patients often develop depressive or anxiety disorders in response to these stresses, and of course, they may develop ESRD with underlying psychiatric illnesses that may not be directly related to kidney disease or kidney failure. The management plan for medical treatment as well as for possible psychotherapy of patients with ESRD should take these issues into consideration.

CONFLICT OF INTEREST

None declared.

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