

Survival in Hemodialysis Patients: The Role of Depression¹

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ABSTRACT

Depression has been identified as the most prevalent psychological problem in patients with ESRD treated with hemodialysis (HD). Depression has been associated with mortality in HD patients; however, the similarity of the symptoms of depressive disorders to those of uremia and the difficulties in measuring depression and dissociating psychological from physical aspects of depression in such patients render these studies difficult to evaluate. Conflicting data regarding the effects of depression on survival in HD patients may be the result of using somatic symptoms in quantifying the extent of depression. In this review, studies regarding the diagnosis of depression in HD patients, the association of depression and survival in HD patients in light of recent work on factors related to the morbidity and mortality in the ESRD population, and aspects of therapy for depression in HD patients are considered. Specifically, depression may affect immunologic function, nutrition, and compliance factors that may affect the prescription and delivery of dialysis, which may, in turn, influence outcome. Alternatively, depression may be an independent factor in influencing survival. Cognitive depression measures may be more useful in predicting outcome in HD patients than standard measures used in nonmedically ill populations. Although there are few studies of the effect of treatment of depression on outcome in HD patients, it is reasonable to hypothesize that treatment of depressive disorders in HD patients might effect outcome. Further studies

on the association of depression and its treatment and mortality in ESRD patients are warranted.

Key Words: *Beck Depression Inventory, compliance, nutrition, delivery of dialysis, suicide*

Since the inception of long-term renal replacement therapy, practitioners and investigators have attempted to delineate the factors associated with prolonged and diminished patient survival. Within the first 10 yr of the institution of the ESRD Program, two main factors were established as important in determining patient survival: age at the initiation of treatment and the severity and number of underlying illnesses, including diabetes mellitus (1-9). It later became apparent that one of the Program's primary goals, rehabilitation of patients with advanced and incurable renal failure, was not optimal (10, 11). In addition to physiologic adaptations, dialysis patients make numerous social and psychological adaptations when incorporating regular dialysis therapy into their lives. A variety of psychological reactions have been reported in patients treated for ESRD (12-14). Depression has been highlighted as the most important clinical psychiatric problem in this population (15-17).

After those early reports, several other trends have been noted. More-refined predictors of outcome have been developed, focusing on the role of race—black patients younger than 30 yr of age have a higher mortality risk than young white patients, and older black patients have a lower mortality risk than older white patients (18); gender—lower mortality risk for females than males when adjusted for age, race, and diagnosis (18); nutrition (19-25); immunologic competence (25); and psychosocial status including compliance, personality, and coexistent family, social, and demographic parameters (26-28). The definition of outcome has moved beyond disease status with the development of measures such as quality of life indices (11, 29). Finally, high-efficiency dialysis techniques, first used in specific units and, in recent years, more generally across the United States, have been introduced (30). In spite of such improved understanding and technical advances, concern has been raised that the morbidity and mortality rates for the U.S. ESRD population have increased, both over time and when compared with those of other countries (31). Some have argued that these worsening statistics are not entirely accounted for by the increasing age and prevalence of diabetes mellitus in

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the ESRD population (31), but other assessments imply that the mortality rate is accounted for by case mix (32). A review of long-term data, moreover, indicated that survival for the 1988 cohort seems to have improved compared with survival for patients entering the ESRD program earlier (18).

The results of the National Cooperative Dialysis Study suggested that treatment time and hemodialysis (HD) efficiency of sufficient magnitude to maintain BUN levels below 100 mg/dL in patients improved outcome (19). The role of treatment time and the delivery of high-efficiency treatment affecting survival in the 1990s is currently unknown. Such prospective, controlled data are not, moreover, available in the era of more biocompatible dialyzer membrane materials and high-efficiency, short treatments (30). Several preliminary reports have suggested that increasing treatment delivery, in conjunction with maintaining patients' adequate protein calorie nutrition, can improve survival in newer therapeutic settings as well (33–37). However, data regarding improved survival in patients treated with high-efficiency techniques and bicarbonate dialysate solutions are often retrospective or based on historic controls. The current predictors of morbidity and mortality in the incident ESRD population remain unknown. Reports spanning the last 20 yr have suggested that depression may also be a factor associated with mortality in patients with ESRD treated with HD. The difficulties in measuring depression in patients with medical illness, and uremia in particular, and the probable interrelationship of depressive affect and the adequacy of dialysis have made this both a challenging and important subject for clinicians to appreciate. We will focus on a critical review of the data on the role of depression in the survival of patients treated for ESRD with HD and will present a theoretical schema for the relationship of cognitive depression to uremia, its treatment, and outcome.

CLINICAL ASPECTS OF DEPRESSION IN ESRD PATIENTS

"Depression," unfortunately, has been used to denote a wide range and various combinations of symptoms—ranging from irritability and changes in mood to hopelessness and suicidal behavior. The term has been variously used to describe a symptom, a syndrome, or a disease. This broad definition has led to reports of the prevalence of depression in studies of ESRD patients varying from estimates of 0 to 100% (15–17,38). High frequencies of depression have been typically reported in patients treated for ESRD with HD (15,39). Lower rates of depression are generally present when the diagnosis is based on DSM-III-R criteria for major depression; higher rates (including 30 to 50% of patients) are present when self-report measures of depressive symptoms are used

(38,39). Although there are varying estimates of its prevalence, it appears that a high frequency of moderate, debilitating levels of depression exists among patients with renal disease.

"Depressive disorder" may be used to designate patients who meet Diagnostic and Statistical Manual of Mental Disorders III-Revised (DSM-III-R) diagnostic criteria, whereas "depression" may describe characteristics in patients with the broader spectrum of symptoms of the disorder. The dissociation of the diagnosis of depression and depressive disorder from uremia may be difficult to establish in patients with ESRD. Depression may be thought of as having at least two aspects: a somatic component expressed as symptoms suggestive of medical illnesses and a psychologic component expressed in thoughts and feelings. Depressed patients may present the nephrologist with worsening somatic complaints that are not compatible with an unchanged medical status. The diagnosis of depressive disorder should be entertained if the results of the physical examination and laboratory studies do not offer an explanation for new symptoms of fatigue, anorexia, aches, and sleep and bowel disorders, particularly if they persist for more than 2 wk.

Diagnostic dilemmas in patients with ESRD may be encountered because of the prominence of somatic symptoms of uremia such as fatigue, anorexia, and sleep and bowel disorders, which are also important in establishing the diagnosis of depressive disorder. Other physical illnesses such as sleep apnea, which may be associated with renal disease (40), anemia, and medical therapy may produce symptoms that are similar to the somatic symptoms of depression (16,38,39,41–44). The classic symptoms of depression, used as psychiatric diagnostic criteria, closely mimic those found frequently in dialysis patients (Table 1) (38). It is therefore essential that the differential diagnosis of such symptoms in patients treated with HD include depressive disorder, along with the complications of ESRD and its treatment.

Physicians and nurses must look for indirect evidence of depression. Occasionally, patients may voice depressive symptoms directly, but often they may only allude to them. These symptoms include feeling sad, loss of interest in daily life, lack of pleasure, hopelessness, self-hate, indecisiveness, loss of libido, feelings of worthlessness or guilt, and in severe cases, a desire to die. The indirect presentation of depressive symptoms requires the professional staff to take note of changes in nonverbal behavior. Speech that is soft, slow, or flat in tone may indicate depressed mood. A less-common presentation is agitated speech, sometimes accompanied by disorganized thinking and distractibility. Body posture that is slumped, slowing of movements, and drowsiness are also diagnostic signs of depression. Lack of care with grooming, housekeeping, and social habits, such as

TABLE 1. Symptoms of uremia and depression^a

| Selected Symptoms of Uremia | DSM-III-R Criteria for a Major Depressive Episode |
|---|---|
| Apathy Anorexia; Volume Overload Sleep Disorder Sensorium Depression; Tremor Fatigue Cognitive Deficits | <p>At least five of the following symptoms must have been present during the same 2-wk period and represent a change from previous levels of function. At least one of the symptoms must be either depressed mood or loss of interest (133)</p> <p>(1) Depressed mood (or) (2) Loss of interest or pleasure, and (3) Appetite disturbance or significant weight change (4) Sleep disturbance (5) Psychomotor agitation or retardation</p> <p>(6) Fatigue (7) Problems in concentration (8) Feelings of guilt or worthlessness (9) Recurrent thoughts of death or suicidal ideation</p> |

^a Modified from reference 38 with permission of authors and publisher.

greetings and courtesies, and poor attendance at dialysis treatments may indicate apathy. Forgetfulness about otherwise routine activities may suggest problems with concentration. Increased requests for help, indecisiveness, or complaints that treatment is too burdensome or not useful may indicate feelings of helplessness. A desire to die may be acted out as noncompliance and failure to attend dialysis treatment regularly or for the full prescribed time. Only after direct questioning may the patient be able to express this destructive motivation. When the indirect presentation of symptoms is carefully sought, a greater detection rate of treatable depression may be the result.

Physicians can increase detection of depressive disorders by routinely asking how patients are feeling and following this question with one or two reflective statements, such as "So it's been a rough week for you and your wife?" or "You feel irritable because of the hustle and bustle of getting the kids back to school?" Such statements tell the patient the doctor wants to understand his or her situation and invite further disclosure and clarification of symptoms, which may aid in accurate diagnosis. Routine use of this approach establishes the depth of the physician-patient relationship, which may allow earlier diagnosis and treatment of depression.

The diagnosis of depression is at first often resisted by patients. The idea of yet another problem can be overwhelming to a person already feeling burdened with illness. It is therefore important to emphasize that undesirable symptoms can be alleviated with social, interventional, psychologic, or pharmacologic therapy. Specific examples of other patients who have benefitted from treatment may be important for engaging patients in treatment programs. Involvement of family members is imperative, both because

their understanding and cooperation may allow the patient to accept the diagnosis and because they can participate in the treatment plan. When patient, family, and medical staff work in a coordinated fashion to intervene with depressive symptoms or disorder, the probability of improvement may be maximized.

MEASURING DEPRESSION IN ESRD PATIENTS

Patients with a psychiatric, DSM-III-R diagnosis of major depressive disorder constitute a subgroup of all patients with depressive symptoms (38,39,41,43,45) (Figure 1). The clinical examination remains the gold standard for establishing a psychiatric diagnosis of depression (38,39,46), but it is a comprehensive task. Although Minnesota Multiphasic Personality Inventory (MMPI) scales and other scores have been used to assess depression in physically healthy and medically ill subjects, for screening and research purposes, the Beck Depression Inventory (BDI) is a well-validated and widely used index of depression (47,48), highly correlating with psychiatric diagnostic criteria. The BDI scores the subject within a range of depression (none, mild, moderate, and severe) rather than merely identifying if the person meets diagnostic criteria. The 21 items of the BDI are answered on a four-point likert scale that represents 0 as the absence of a problem and 3 as an extreme problem. The total scores range from 0 to 63.

In a recent validation study, a BDI score greater than or equal to 15 had maximal sensitivity and a high specificity and predictive value for the diagnosis of a major depressive disorder in a population of dialysis patients—i.e., distinguishing depressive symptoms from the presence of a true psychiatric disorder (46). The diagnostic accuracy of a BDI score

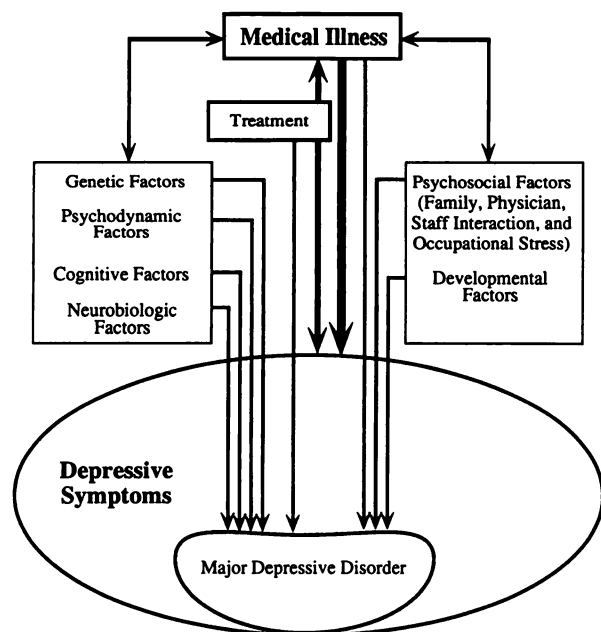


Figure 1. A theoretical schema for the interaction of medical and other factors producing depressive symptoms in patients treated for ESRD with HD. Patients with a psychiatric diagnosis of major depressive disorder are a subset of all ESRD patients with symptoms of depression. Medical illness can directly or indirectly be associated with symptoms of depression or may influence the outcome of depressive disorders in patients with ESRD. A single-headed arrow indicates a unidirectional influence. Bidirectional influences are indicated by double-headed arrows.

of 15 is 0.63, indicating that 63% of patients who score at or above this level will meet diagnostic criteria for a major depressive disorder. The psychiatric diagnosis of a major depressive disorder in this study was based on the Diagnostic Interview Schedule III, a structured psychiatric interview from which DSM-III-R diagnoses of affective disorder and other psychiatric conditions may be derived (49). Establishing the psychiatric diagnosis is important, in that it indicates that the patient may be more likely to benefit from antidepressant medication and intensive psychiatric intervention.

The BDI measures both cognitive or psychologic and somatic symptoms of depression. The psychologic portion of the BDI places an emphasis on cognitive symptoms but also includes self-report of affective experience. The psychological, or cognitive, symptoms of depression, however, rather than the somatic symptoms of depression, discriminated clinically evaluated depressed from nondepressed patients with ESRD in one study (39). The inclusion of the somatic items of the BDI, which may be associated with the severity of medical disease, raises the question of whether the usual indices of depression are measuring somatic depression factors or symptoms of medical illness, thereby accounting both for

the high prevalence of depression in ESRD patients and the variability of its rates of prevalence. High levels of endorsement of somatic items of the BDI could confound somatic depression factors with the symptoms of medical illness.

A subset of the BDI, the Cognitive Depression Index (CDI), was created in order to control for the possible confounding contribution of somatic symptoms of physical illness and/or treatment effects to the symptoms of depression. The CDI is a subset of 15 cognitive depression items from the total 21 items of the BDI (47,48,50,51). Examples of psychologic characteristics or cognitive beliefs surveyed are guilt, disappointment, sadness, and failure and difficulties with decision making. The six somatic items of the BDI deleted to create the CDI deal with the symptoms of fatigue, sleep and sexual dysfunction, disordered appetite, and changes in weight and general health. The deleted somatic items are similar to the psychiatric diagnostic criteria somatic complaints, which have been shown to fail to discriminate between depressed and nondepressed ESRD patients, when the clinical interview was taken as the gold standard (39). Three of the four items from the BDI that have recently been characterized as identifying depression in medical patients are included in the CDI (52). The internal consistency of the CDI with ESRD patients obtained an $\alpha = 0.74$ (50). With medical patients, therefore, the CDI might be a better predictor of depression because of a reduction in the confound due to symptoms of physical illness that are similar to symptoms of depression.

PATHOGENESIS OF DEPRESSION

There are several possible explanations for the occurrence of psychologic depression in the ESRD population. Depression in ESRD patients may have multiple sources, including changes in a variety of biologic and psychosocial systems that may feed into a common pathway, culminating in the clinical disorder of depression (53).

Depression has classically been associated within the psychodynamic model with a patient's experience of loss (15) and with actual losses and the interpretation of loss within the cognitive-behavioral model (54). Patients treated for ESRD have undergone several kinds of losses: loss of renal function, loss of role in the workplace and the family, and diminution in quality of life. In addition, they may have suffered loss of sexual function. It is also conceivable that the quantity of dialytic therapy may physiologically modulate the expression of depressive symptomatology. This biologic view emphasizes the neuropsychiatric effects of uremic toxins, suggesting that uremia itself, especially if inadequately treated, may be a cause of depression (15). Psychosocial determinants of the pathogenesis of depression in patients treated

with HD have been emphasized by other workers—loss of control over crucial aspects of life activities and dependency imposed by the treatment on medical staff, family, and mechanical devices (12,28,55,56). Finally, a genetic predisposition to depression within the population of ESRD patients has been suggested (15). More recent analyses have suggested dynamic interactions between the aforementioned factors—with depressive symptomatology viewed as a resultant of stressors interacting with genetic, psychodynamic, developmental, cognitive, psychosocial, and neurobiologic patient variables (15,57). A theoretical schema for the interaction of psychologic and medical factors producing depressive symptoms in patients treated for ESRD with HD is outlined in Figure 1.

Recent research has focused on depression in the setting of patients with other medical or psychiatric disorders, termed compound depression (58). Patients with depression and another psychiatric or medical disorder have a greater magnitude of depressive affect and a poorer response to treatment than do patients with depression without another coexistent disorder (58). Poorer outcome and response to treatment are also found in depressed patients with concurrent illnesses, regardless of the nature of the coexistent diagnosis (59–61). Depression in patients with medical illnesses may be qualitatively different and distinguishable from the psychiatric illness (15,39,46). A study in medical inpatients demonstrated that cognitive aspects of depression were more prevalent and suicidal ideation was less common in medical compared with psychiatric patients (62).

DEPRESSION AND SURVIVAL IN ESRD PATIENTS

There are few data on the effect of HD treatment on depression in ESRD patients. Results from the National Cooperative Dialysis Study showed that low BUN groups (those with better survival) had lower depression scores on the MMPI (63). The short treatment time, low BUN group also showed a decline in depression scores over the study period. The long-term effects of depression on the course of ESRD are largely unknown, but depression has been associated with diminished survival of patients treated with HD for ESRD (51,64–68).

Foster *et al.* (69), in a pioneering investigation of the relationship between psychologic factors and survival in the late 1960s, studied 21 patients with ESRD treated with HD in the early days of renal replacement therapy. There were 14 survivors, and 7 patients died during a 2-yr observation period. There was no difference in mean age, signs of organic brain syndrome, or psychosocial performance before dialysis between the two groups. There were com-

parable histories of psychiatric disorders in both groups. The survivor group exhibited less evidence of general psychopathology during the initial interview compared with nonsurvivors. The mean BUN in the survivor group was lower than that in the nonsurvivors. The investigators noted a correlation of psychopathology scores and level of BUN. Although there was a significant correlation of survival time and score on the "constraint scale" (which measured the tendency of subjects to refuse to identify themselves as members of a patient group, to deliberately abdicate responsibility for other patients, and to be unwilling to fulfill group tasks), depression was not specifically measured in this study. Such paradoxical factors have also been suggested to play a role in the survival of HD patients by subsequent investigators (27,28,55).

Wai *et al.* (64) and Burton *et al.* (65) both examined survival among home dialysis patients. Wai *et al.* (64) performed a discriminant analysis with social, psychologic, demographic, and medical variables over an 18-month follow-up period. Only four variables were significant: three psychologic or demographic factors (age, depression, and stress scores) and serum albumin level. Mean age and depression score were lower and stress score and albumin levels were higher in survivors compared with nonsurvivors. Other measured medical factors did not differentiate between the two groups. Burton *et al.* (65), using structured interviews, studied home dialysis patients starting ESRD therapy, measuring psychologic, physical, social function and support, personality profiles, and economic well being. After a 2-yr period, discriminant analysis techniques showed that a personality factor (feelings of self-depreciation) and a combined index of physiologic function were the most powerful discriminators of survival. The mean depression score was lower in the group of survivors compared with subjects who died shortly after the initial interview. Both patient groups had mean depression scores that were higher than the population norm. Further analysis without the use of the personality data suggested that depression was the most important factor associated with shorter survival, although the physiologic index score and age were also significant factors. In both studies, depression was significantly related to survival. In addition, depression and other psychologic factors were as important or more important predictors of survival than physical illness variables (except for age). The important aspects of depression, however, are difficult to determine from these studies because Wai *et al.* (64) did not identify how depression was measured and Burton *et al.* (65) used the Basic Personality Inventory, an infrequently used measure of depression.

Ziarnik *et al.* (66) studied 47 male patients treated

with HD who had either survived for more than 3 yr or who died within 1 yr after starting renal replacement therapy, chosen from a population of 87 patients. The MMPI was administered at the time of initiating HD therapy. There was no difference in age between the survivors and nonsurvivors. As expected, the nonsurvivors had a greater frequency of medical problems. Short-term and long-term survivors had differences in mean levels of hypochondriasis and depression. Short-term survivors had higher depression scores at entry to the ESRD program than the long-term survivors. There were no differences in these parameters between patients who survived 3 to 7 yr and those who survived 7 to 10 yr, but there were only a small number of subjects available for this secondary analysis. The MMPI scale does include some somatic items, but the majority measure cognitive aspects. Therefore, in this case, the measure of depression may have limited the confound with medical illnesses.

Somewhat in contrast, a recent study assessed psychologic variables, medical illness, and survival in 100 ESRD patients over a 4-yr observation period (70). Fewer comorbid illnesses, younger age, participation in leisure activities, and a perception of an even mixture of happiness and unhappiness in the patient's life were associated with greater survival. BDI scores did not correlate significantly with survival. The component of somatic items of the BDI may have obscured a relationship between survival and cognitive depression in this investigation. Lack of leisure activities and balanced happiness may have functioned as markers, albeit inexact ones, of psychologic depression.

In a major recent study, Shulman *et al.* used survival analysis and assessed biochemical parameters, comorbid medical illness, and cause of death in an attempt to present psychiatric parameters of depression in a medical perspective, in a 10-yr follow-up study of 64 patients with ESRD treated with dialysis (67). The study group consisted of in-center and home dialysis patients, with an average treatment time of 3.7 yr before assessment. None of the patients had diabetes mellitus. The patients' perception of health and dietary compliance, previous psychiatric history, present mental status, perception of adjustment to renal replacement therapy, presence of suicidal ideation, BDI score, cause of renal disease, and biochemical data were recorded. Approximately 30% of the population was thought to have major depression on the basis of the structured interviews or by BDI score. There was a higher ratio of observed to expected deaths in patients who perceived themselves as sick rather than well or disabled rather than functional. Patients who had an overt abnormality on the mental status examination also had a greater mortality risk, as did patients with suicidal thoughts. These differences, however, became insignificant when adjusted

for the BDI score. The BDI score and age, which were unrelated at original evaluation, were the significant predictors of mortality in the study. BDI scores greater than or equal to 14 were associated with diminished survival. Further separation of mortality risk was achieved when patients with BDI scores greater than or equal to 25 were considered separately. When patients with scores of greater than 25 were compared with those with scores of less than 14, 2-yr survival from the time of assessment was 25 compared with 85%. Ten-year survival for the same groups was 10 compared with 36%. There was no relation of compliance to survival. The presence of comorbid illnesses was associated with diminished survival, but only age, gender, and level of serum calcium had significant independent associations with mortality when adjusted for the BDI score.

None of these studies adequately assessed depression in relation to the delivery of dialysis and the effect of medical risk factors and comorbid illnesses that may affect survival. When medical parameters of renal disease were assessed, BUN levels were usually taken as the index of treatment effectiveness. This approach can be fraught with difficulty because a bimodal association of BUN level and survival has been noted (23). The potential confound of uremia with depression in such studies renders their interpretation problematic. None can truly discriminate whether uremia causes depression, or whether both uremia and depression are associated with poor survival.

COGNITIVE DEPRESSION: A BETTER SURVIVAL MARKER?

The use of the somatic items of the BDI, possibly associated with the severity of the ESRD patients' illness, suggests that classic markers of depression may measure both cognitive depression factors and aspects of medical disease severity. The etiology of fatigue, sleep disturbance, and changes in weight and appetite may be medical illness, psychiatric illness, or both, thereby accounting for the conflicting data regarding the effects of depression on survival in HD patients. Most previous studies linking the psychologic aspects of behavior and survival, however, did not control for the severity of medical illnesses in study populations, especially those comorbidity factors that might affect mortality. The relationship of depression, medical illness, and survival cannot be disentangled when these characteristics are not separated in studies of HD patients.

Separation of the somatic from the nonsomatic items of the BDI, when the relationship of depression and survival in ESRD patients is studied, is one strategy for solving this problem. Shulman *et al.* (67) separately analyzed an 8-item "somatic" score and a 13-item "nonsomatic score" of the BDI. Although the

somatic items contributed disproportionately to total BDI scores, they could not account for abnormally elevated scores. In patients in this study with major physical complications, nonsomatic scores were elevated in addition to somatic scores. There was no independent assessment, however, of the relationship of nonsomatic scores to survival in this study.

We designed a study with the goal of dissociating psychologic depression, perception of illness, severity of medical illness, and survival. We studied (51) 57 patients, examining the relationship between several variables suggested previously to affect levels of depression in ESRD patients, including several disease severity measures and perception of the effects of illness (50). Disease severity in this study was defined by mortality risk. The ESRD severity coefficient (50,51), previously validated in a large sample of ESRD patients as directly related to patient mortality rates (9), was used as the measure of severity of illness. The coefficient is based on the product of the patient's age and the prognosis of additional concurrent medical illnesses such as cancer, collagen-vascular disease, cerebrovascular disease, and heart disease as comorbidity measures, hierarchically scaled. It was used as an overall measure of the severity, in terms of mortality risk, of the ESRD patient's chronic illness, taking into account comorbidity factors.

Perception of illness was surveyed using the Illness Effects Questionnaire (IEQ) (71), a scale that assesses the individual's perception of ways in which the illness interferes with or affects personal and social behavior. Questions range from perceived family and personal disruption to physical problems and fears about illness effects, e.g., "My illness disrupts how I get along with family or friends," "My illness disrupts my appetite," and "My illness prevents me from enjoying myself."

Depression in this study was measured by use of the BDI, and separate analyses were performed by use of the CDI. Cognitive depression scores correlated with BDI measurements. The BDI also correlated with the severity coefficient, an index of medical illness. In contrast, CDI scores were independent both of disease severity and of measures of renal insufficiency, nutrition, and dialysis efficiency such as levels of serum creatinine or BUN (50). In addition, ESRD patients' perception of illness correlated highly with CDI scores. These correlations suggest that the CDI reflects more of the patient's personal and emotional state and is less confounded by the severity of medical illness than the BDI. Furthermore, such findings would suggest that the CDI may be a better measure of psychiatric depression than the BDI in patients with renal disease.

To investigate whether depression or perception of illness was associated with mortality in patients with

ESRD, we prospectively evaluated survival in the 57 patients with ESRD 1 and 2 yr after initial psychologic testing (51). Forty three patients were treated with maintenance HD, whereas 14 were treated with continuous ambulatory peritoneal dialysis (CAPD). Voluntary participation was more than 80% of those eligible. No patient was acutely ill at the time of the clinical evaluation.

The BDI and the IEQ were administered to the patients by psychologically trained personnel. The mean BDI score of the patient population was in the range of mild depression (47,48). There were no significant correlations of disease or dialysis duration with cognitive depression at the outset (50,51). At initial testing, BDI scores correlated significantly with the cognitive measure of depression, CDI, and the IEQ scores. IEQ scores did not correlate with age or severity coefficient but correlated with CDI (50,51). The CDI scores were slightly positively skewed (skewness = 0.8), with a cluster of scores at the 3, 4, and 5 levels; six subjects fell in the range of 13 to 15. The median score was 5. These results suggest a skew towards greater symptom levels in the population.

Of the original patients tested, 47 survived 1 yr. Ten had died, constituting 14.3% of the CAPD and 18.6% of the HD patients in the original sample. Although the patients in the HD sample had a significantly higher mean severity coefficient score, HD and CAPD patients did not have different death rates at 1 yr. The only significant difference in initial assessments between survivors and nonsurvivors was for the initial CDI scores of nonsurvivors (7.9 ± 4.1) compared with the mean CDI score (5.2 ± 3.5) in patients who survived. The median CDI score for the nonsurvivors was between 6 and 7, whereas it was between 4 and 5 for the survivors. For the 25 subjects who were reevaluated, there were no changes in their mean CDI, BDI, or IEQ scores, when evaluated initially and 1 yr later, suggesting that psychologic status remained stable in the tested subpopulation (51).

At the 2-yr follow-up, 21 patients died and 36 were alive. The unadjusted death rates were 16.7% for CAPD patients and 25.5% for HD patients. Similarly to the 1 yr assessment, mean initial CDI scores were significantly different between the groups; at 2-yr follow-up, however, mean age, BDI scores, and severity coefficient scores were also significantly higher in the nonsurvivors. Hazards analysis demonstrated that higher CDI scores were associated with a greater risk of death within the following 2 yr (51).

Despite a lack of differences in measures of disease severity, total depression, physical symptoms of depression, and perception of illness, the initial measure of cognitive aspects of depression provided a prospective discrimination between survivors and nonsurvivors (51). Although the mean difference in CDI scores between groups was not large, such a

result is consistent with the findings of previous studies (64–67). Cognitive depression had an important relationship to survival, even when severity of medical illness failed to be a discriminating factor during the first year of follow-up. A 1-yr assessment was initially selected because the first year or two of treatment in a noncritically ill patient population should be the period most sensitive to nonmedical variables, as suggested by Burton *et al.* (65) and demonstrated by Shulman *et al.* (67). Few patients were expected to die because of medical complications during the early follow-up. As expected, the disease severity measures were significantly different between the groups at the 2-yr evaluation, but surprisingly, cognitive depression was still significantly associated with mortality. Over time, severity of illness should become the major predictor of mortality, especially if an increased number of the more cognitively depressed patients have died.

Depression, and in particular its cognitive aspects, appears to be an important predictor of mortality in patients with ESRD, as demonstrated in patients with relatively long treatment duration. Cognitive depression may be a more sensitive marker of psychologic status in medical patients, who have a wide variety of physical symptoms associated with medical illness that may confound measures on standard tests of depression including both cognitive and somatic symptom items. Alternatively, cognitive depression may play an important independent role in modulating the patient's response to illness and subsequent success of treatment.

EFFECTOR MECHANISMS OF THE INFLUENCE OF DEPRESSION ON SURVIVAL

The manner in which depression may affect survival in HD patients is unknown at this time. It is not certain whether depression is an independent mortality risk factor, or if it exerts its effects through interactions and associations with intervening mediating medical variables. Depression, moreover, may simply be a marker of the severity of the underlying medical illnesses. Alternatively, the patient's level of depression may modify physiologic factors, such as nutrition, immunologic function, and compliance with treatment, or family dynamics, which could conceivably affect the course of medical illness and the patient's ultimate survival (Figure 2).

Depressive affect may interfere with compliance with a prescribed medical or dialytic regimen, which might negatively affect survival (27,28,72,73). Depression may therefore be associated with decreased administration of dialysis time. Anorexia, secondary to depression in patients with ESRD, may limit patients' protein and caloric intake and may be associated with diminished protein catabolic rate (74). Such responses may result in a vicious cycle of

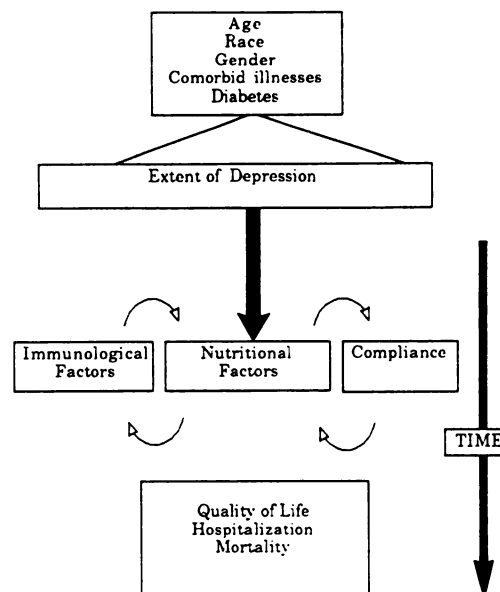


Figure 2. Depression and medical outcome in HD patients. Depression may influence the effect of traditional determinants of mortality in HD patients. A proposed mechanism involves the effect of depression on immunologic competence, nutrition, and compliance with the treatment and medication regimen. These mediators may interact. Over time, depression may influence morbidity and mortality outcomes. See Text for details.

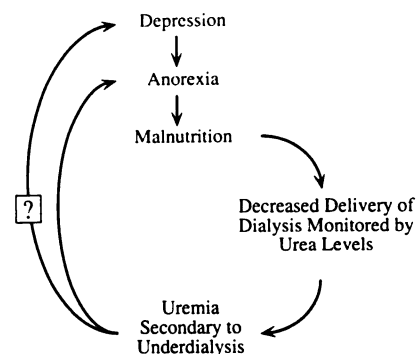


Figure 3. Relationship of depression, nutrition, and adequacy of dialysis: a vicious cycle. Depression may be associated with anorexia, resulting in decreased caloric intake, lowered BUN levels, and subsequent iatrogenic diminution of dialytic therapy, especially if the protein catabolic rate is not assessed. Uremia may result in increasing anorexia and worsening of depressive symptoms, completing a vicious cycle. The relationship of quantity of dialysis to depressive symptomatology has not been elucidated, as indicated by the question mark.

malnutrition, decreased delivery of dialysis because of lowered BUN levels, underdialysis, worsening anorexia, and poor outcome (20,74) (Figure 3). Therefore, uremia might underlie the association of depression with poor survival as a final common pathway.

Alternatively, depression may affect patient immune responses. Psychologic stress, and the subse-

quent anxiety and depression, can modulate immunologic responses in normal subjects (76,77). Psychologic states may directly affect lymphocyte subsets and responses (78). Cell-mediated immune responses are particularly susceptible, and responses such as lymphocyte mitogenesis (79,80), mitogen-induced lymphocyte proliferation (81), natural killer cell function (82), and neutrophil activity (83) are all decreased during periods of depression. In a similar manner, physiologic stress has been shown to lead to the dysfunction of many different cellular systems, including down-regulation of active immunologic activity, thus creating a greater potential susceptibility to bacterial infections and sepsis (84).

Immune dysfunction may be observed in populations of HD patients (84–98). The cause is unknown, but several investigations have suggested that adequacy of dialysis may mediate changes in the immune response in patients with ESRD (94–98). There may also be an indirect, but independent effect of depression's association with anorexia, resulting in the disordered immune function seen in HD patients (25,99,100). The problem of immune dysfunction in patients treated with HD for ESRD may be heightened in the face of the increasing age of the population and incident patients (101–104). Little attention, however, has been given to the notion that psychologic status or stress may be associated with the variations in immunologic function noted in patients treated with renal replacement therapy. ESRD therapy, without doubt, is certainly a stressor because of both its physiologic and psychologic demands (57). Of great interest is the similarity of reported abnormalities in depressed patients and those with ESRD: relative lymphopenia, impaired lymphocyte function, and anergy (87,91). There is also a decreased level of cell-mediated immunity in association with increased T suppressor cell activity (87,104) in patients with renal disease.

Such defects may be critical determinants of survival because infection is the second largest cause of mortality in the ESRD population (18). In addition, infection is the major cause of death most likely to be acquired after the initiation of dialysis, in contrast to the most prevalent cause of death, cardiovascular illness, the antecedents of which are likely to date from a substantial time before the initiation of renal replacement therapy or, in fact, may be related to the underlying cause of the ESRD. Studies, however, have also suggested the important role psychologic status may have on the outcome of cardiovascular disease (105).

Finally, depression may lead to mortality through suicide, its gravest complication. The role of suicide in the mortality statistics of ESRD patients has been noted since the early days of renal replacement therapy (14,106). Interestingly, one study of patients treated with HD suggested that suicidal ideation is

frequent but can be dissociated from classic markers of depression (107). Although the absolute death rate by suicide for the ESRD patient population has not been a large percentage of the total (18), its prevalence may be underestimated. Suicide as coded on Health Care Financing Administration death notification forms accounted for a death rate of less than 1.5 per 1,000 patient years (18). This compares with a suicide rate of 12.4 per 100,000 in the United States for 1988 (108). Investigators have pointed out that modes of suicidal behavior in ESRD patients may be more subtle than in a nonmedically ill population and that the means of accomplishment may be easily attainable and disguisable, for example by slow, steady decrease in dialysis time by noncompliance, lack of adherence to dietary prescriptions, or manipulation of the hemoaccess. In addition, the role of withdrawal from HD treatment as a cause of death in the ESRD population has recently been highlighted (109). That study, in a predominantly white population, suggested a relatively high rate of withdrawal from dialysis in the elderly and in patients with diabetes mellitus. Withdrawal from dialysis accounted for a death rate of 11.2 per 1,000 patient years in the U.S. ESRD program (18). Black patients had a death rate from suicide and withdrawal that was roughly half of that of white patients (18). The death rate from withdrawal was higher in diabetic patients and rose dramatically in older groups of patients (18).

The effect of depression on the rate of withdrawal from dialysis is unknown, but it presumably has a powerful negative influence. The role of depression in elderly subjects has recently been highlighted (108). Elderly patients, similar to those with compound depression, may frequently report somatic symptoms of depression, rather than aspects of depressed mood. Elderly patients living in nursing homes have a higher prevalence of depression, and the elderly have a higher suicide rate than the general population (108). Such findings become more compelling for nephrologists when it is noted that the elderly and patients with diabetes mellitus constitute the two most rapidly growing sectors of the U.S. ESRD population (18). It has been estimated that 60% of the U.S. ESRD population will be composed of patients over 69 yr of age by the year 2010 (7). Elderly dialysis patients had a withdrawal rate of 43% in one study (110). Interestingly, somatic predictors of mortality were not as good as psychosocial markers in that small study. The role of patient population and demographics and the association of racial and ethnic factors with the prevalence of withdrawal or suicide in the U.S. ESRD population have also not been intensively studied. This is an important research issue because the demographic composition of the U.S. ESRD population does not mirror that of the general population.

There has been no study of immune function in the ESRD population that has adequately normalized for nutrition, delivery of dialysis, and the effect of depression. There is no study that has prospectively assessed the effect of depression on survival, evaluating medical risk factors and comorbid illnesses and assessing nutritional parameters, immunologic function, and behavioral compliance simultaneously in the high-efficiency and erythropoietin era, or that has graded survival (in terms of these risk factors) for the quantity of dialysis delivered. Furthermore, previous studies of the relationship of depression and survival in the ESRD population have studied patients on different and mixed modalities of therapy, such as center HD, home HD, and CAPD, at various times after initiating renal replacement therapy, and at different stages of the ESRD life cycle. Because different treatment modalities can include patients with different personality characteristics (111) and because different treatment techniques with different populations may have different survival characteristics (18,112,113), it is imperative that study groups be well defined. The relationship of cognitive depression, in particular, to medical illness and treatment course in ESRD patients requires further study, including the concurrent assessment of adequacy of dialysis, nutritional status, and immune function.

THERAPEUTIC CONSIDERATIONS

An important step in assuring the best treatment of depression in HD patients is ensuring adequacy of dialysis. To the extent that medical outcome and somatic symptoms may be modified by the magnitude of clearance of uremic toxins, the somatic component of depression may be minimized with optimal dialysis. Another example of the potential of the medical approach is the improvement in the quality of life and cognitive function demonstrated in patients treated with erythropoietin (114–116). Although improvement in patients' hematocrit levels secondary to the use of erythropoietin may prove effective in modifying depressive affect in HD patients, this has not been demonstrated rigorously in clinical trials. If psychologic depression can be modulated by the clearance of uremic toxins, it is possible that the maximum delivery of dialysis can be important in modifying the level of cognitive depression as well. Finally, the effect of patients' medications on their cognitive functioning and level of depression should be considered.

Although the mechanisms of the effects of depression on survival are poorly understood, it is reasonable to hypothesize that the treatment of psychiatric depression might improve patient survival. An uncontrolled study that assessed participation in group therapy and survival in ESRD patients suggested that

psychologic factors are important in affecting outcome (117). Patients participating in a support group program enjoyed longer survival. Social support has been shown to reduce depression (118–120). Therefore, the salutary effects in the group participants may have been due to influences on depression. Because participants in the support group were self-selected, the results of this study may be biased and await controlled confirmation. The notions that therapy directed at changing attitudes in HD patients by classic psychotherapeutic techniques or that cognitive or rational-emotive therapies might affect cognitive depression and therefore survival are particularly exciting (40,121,122).

Studies regarding the response to pharmacologic therapy of depressive disorder in HD patients, however, are scanty, and the results are varied. A recent study on the treatment of depression in eight ESRD patients reported beneficial effects on psychologic functioning (123). In another study (124), nine patients with major depression were treated with a variety of therapies. No outcome was reported. Streltzer (125) studied five patients with ESRD and major depressive disorders treated with tricyclic antidepressant agents. Three had an excellent response, but two were nonresponders. There are, however, no studies of the effect of pharmacologic treatment of depression on survival in HD patients. Studies of the effects and comparative results of various treatments of depressive disorder in ESRD patients are warranted.

Patients with major depressive disorder, diagnosed by the use of standard psychiatric diagnostic interviews and satisfying DSM-III-R criteria, are candidates for a trial of antidepressant medication. Others in whom depressive symptoms are present, but who do not meet psychiatric diagnostic criteria for a depressive disorder, may be treated with social and psychologic interventions. Psychologic treatments for depression in various diagnostic populations have been described (126). Those patients whose symptoms have not responded to supportive and/or psychotherapeutic interventions or whose symptoms have not improved coincident with improvement in medical aspects of illness are also candidates for the pharmacologic treatment of depression.

A brief overview of the most commonly used antidepressant medications is given here as an orientation to the pharmacologic treatment of depressive disorder in ESRD patients. The *Handbook of Psychiatric Drug Therapy* (127) is recommended as a guide to practitioners prescribing these agents.

In light of the absence of validated treatment recommendations from controlled clinical studies, we suggest the following guidelines. The dose of antidepressant medication should be titrated for maximal reduction of specific symptoms, along with minimiz-

ing side effects. Target symptoms to be alleviated should be identified and discussed between the patient, family, and the physician before treatment is begun. In this manner, success in treatment can be accurately assessed.

Nortriptyline, desipramine, and imipramine are the drugs of choice in the group of tricyclic antidepressant medications (128). Amitriptyline, although effective, has a high level of anticholinergic side effects, making it less well tolerated. Nortriptyline, desipramine, and imipramine levels can be monitored via plasma concentration and, therefore, may be easier to evaluate for maximal effectiveness and minimal risk of toxicity in patients with renal disease. ESRD patients may require much lower doses of tricyclic antidepressant agents to reach therapeutic plasma levels than patients with normal renal function (123,129). Therapeutic strategies include increasing the dose interval or diminishing administered dose levels.

Desipramine is the least sedating of the tricyclic drugs and shares a low level of anticholinergic side effects with nortriptyline. For patients who would benefit from sedation, imipramine would be the drug of choice from this group. Treatment with either desipramine or imipramine should begin with 25 mg/day, increasing weekly by this amount up to 100 mg/day, as tolerated. A 12-h plasma level of more than 225 ng/dL of imipramine plus its active metabolite desipramine indicates a therapeutic level when the patient is taking imipramine. Dosing should be adjusted to maintain the therapeutic range for plasma levels as indicated in Table 2. A plasma level of more than 125 ng/dL is therapeutic when desipramine is prescribed.

For nortriptyline, initial dosing at 10 mg/day may be used. After 3 days, an increase of 10 to 25 mg/day may be used until the full dosage reaches 75 to 100 mg/day. After 1 wk of therapy at the full dosage, a plasma nortriptyline level should be obtained. A plasma concentration of 50 to 150 ng/dL indicates that the therapeutic range has been achieved. Monitoring for remission of symptoms after 4 wk of treat-

ment will confirm efficacy. If therapeutic plasma levels exist, but symptoms do not remit, a change in treatment is indicated.

The metabolism of tricyclic antidepressant agents is largely hepatic. Although drug dosages are usually unchanged in renal insufficiency (130) and the compounds are not generally dialyzable, lower doses may be administered effectively in patients with ESRD. Side effects include postural hypotension; anticholinergic effects such as dry mouth, blurred vision, and constipation; and quinidine-like effects on cardiac condition and rhythm (127,129,131). Sexual dysfunction may be associated with their use. These varied side effects may become more prominent in elderly patients. Drug interactions and changes in plasma protein binding may occur that alter circulating drug levels or worsen sedation, hypotension, cardiotoxicity, and anticholinergic effects (127). The use of tricyclic antidepressant agents in patients who have arrhythmias or who are taking cardiac drugs should probably be avoided if possible.

The newer antiserotonergic antidepressant agents fluoxetine (132) and sertraline have the advantage of minimal anticholinergic side effects, but nausea, headaches, nervousness, and insomnia are all commonly encountered side effects. Their metabolism is also largely hepatic. Sertoline has not been extensively studied in patients with renal disease; therefore, its use has not yet been recommended in this population. Doses are generally not changed for level of renal function, nor are they cleared by dialysis (129,130). Drug interactions with monoamine oxidase inhibitors may complicate therapy (127). Therapeutic serum levels have not been established for these drugs. Therefore, remission of clinical symptoms must be used to judge adequacy of treatment.

The importance of the physician-patient-family relationship cannot be overemphasized in the treatment of depression. Regular visits for education and support greatly enhance the patient's willingness to tolerate early side effects and await therapeutic effects, which often take a month to occur. Feedback from patient and family is essential for judging the

TABLE 2. Guidelines for antidepressant medication usage in HD patients

| Medication | Initial Dose (mg) | Usual Dose mg/day | Therapeutic Plasma Level | Sedative Effects | Anticholinergic Effects |
|---------------|-------------------|-------------------|--|------------------|-------------------------|
| Amitriptyline | 25 | 150–200 | >120 ng/ml (?) amitriptyline + nortriptyline | High | High |
| Imipramine | 25 | 150–200 | >225 ng/ml imipramine + desipramine level | Medium | Medium |
| Nortriptyline | 10 | 75–100 | 50–150 ng/ml | Low | Low |
| Desipramine | 25 | 150–200 | >125 ng/ml | Low | Low |
| Fluoxetine | 20 | 20–40 | None available | Low | Low |

adequacy of treatment related to target symptoms.

The augmentation of antidepressant medications with lithium or thyroid hormone, the adjunctive use of other antidepressant agents, or psychotherapy can all be helpful to some patients with depression that is relatively resistant to treatment. Consultation with a psychiatrist is usually warranted in treating resistant cases.

CONCLUSIONS

Reasonable evidence exists suggesting that the number of ESRD patients displaying moderate and severe levels of depression is of clinical significance and requires our attention. The confounding of psychologic depression with similar symptoms caused by biochemical factors suggests that the focus of definition and measurement of depression in ESRD patients should emphasize the cognitive and affective aspects of depression rather than the somatic symptoms. Recent studies substantiate this conclusion in terms of the accuracy of diagnosis and mortality outcomes.

The issue of how depression might influence mortality outcome, as well as quality of life, is a matter of speculation at this time. Major questions to be addressed and answered include: Does depression as a risk factor interact with classic risk factors (or is it relatively independent) in HD patients? Does depression function as a final common pathway for the effect of medical factors or family and social interactions, through effects upon nutrition, immunologic competence, or compliance, or is it an independent risk factor? Can early psychologic measurements predict patients at risk for withdrawal from HD or suicide? Is there a differential risk in patients receiving differing delivery of dialysis (in effect, is there a differential mortality risk of depression in patients who are more [or less] well dialyzed) or being treated with different dialysis membranes or therapies?

If depression is a factor in determining survival, it is possible that therapeutic efforts aimed at its treatment might have important salutary results in this population. Although the illness severity markers (age and coexistent medical illnesses) in the ESRD population are generally unmodifiable, depression is amenable to modification with drugs and cognitive behavior therapy among psychiatric patients. To the extent that cognitive aspects of depression are similar in both populations, such therapies could extend life in an ESRD population.

Continued research is needed regarding the associations between depression and mortality in patients with renal disease. First, additional efforts are needed to determine the factors related to and/or the causes of depression in HD patients. Second, to better understand the relationship of medical illness and

cognitive depression, the role of pharmacologic and psychologic therapy for depression, and their possible effects on patient survival, critically necessary, well-designed, and controlled clinical studies must be performed.

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