

Depression in Patients with End-Stage Renal Disease Treated with Dialysis: Has the Time to Treat Arrived?

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The World Health Organization has highlighted depression as the second most common and economically costly chronic disease that will affect nonmedically ill people globally over the next decades (1). Depression in patients with another medical or psychiatric illness, or “compound depression,” is typically of greater intensity and more difficult to treat than depression occurring in patients without other underlying disorders (2–6). Depression has been identified as the most common psychiatric illness in patients with end-stage renal disease (ESRD), but its prevalence has varied widely in different studies, in different populations, using different assessment tools (2,3,7). Among the difficulties in evaluating the data has been the wide variety of assessment tools used to quantify depressive affect and for establishing the diagnosis of depression in patients with and without medical illness.

Depression is characterized by both cognitive and somatic features. The somatic characteristics of depression have an uncanny similarity to the symptoms of uremia, such as anorexia, sleep disturbances, fatigue, gastrointestinal disorders, aspects of volume overload, and pain (3,7–9). These similarities make the determination of the role of an association between depression and mortality potentially problematic (3,8,9).

Depression might mediate differential outcome in patients with chronic medical illnesses through effects on the underlying disease, compliance, nutrition, immune status, through marital and family dynamics, or through differential access to care (3,8,9). The association between depression and outcome in ESRD patients treated with dialysis has also been controversial. We showed that depression was associated with hospitalization in a substantial proportion of patients participating in the US ESRD Medicare program in 1993 (10). While early studies seemed to demonstrate a clear relationship between depression and mortality in patients treated with hemodialysis, more contemporary studies were unable to show a definitive relationship between depression and mortality, using adjustments for medical comorbidities and other factors associated with out-

comes (8,9,11). Few studies assessed patients at meaningful time points in the life cycle of the ESRD patients (12), usually performing evaluations at periods of investigator convenience, and even fewer studies employed longitudinal assessments. We developed a tool, the Cognitive Depression Index (CDI), a subset of the well-validated Beck Depression Inventory (BDI), to separate the somatic from the cognitive features of depression (3). Few studies, however, have evaluated treatment of patients with high levels of depressive affect, and few well controlled, randomized data exist to define treatment outcomes (13–18).

We showed correlations between depressive symptoms and many psychologic and quality of life variables in ESRD patients, as well as differences between correlates of depressive affect in patients of different genders. We were, however, unable to delineate a relationship between baseline level of depressive affect and mortality in a single-city, multicenter, study of primarily African-American incident and prevalent patients treated with hemodialysis for ESRD, regardless of whether standard measures of depression or cognitive depression indices were used (11). However, using data from the longitudinal measures in that patient population, we were able to show that time-varying covariate analyses, using multiple, pooled measurements of depression, were associated with increased mortality. Interestingly, the multiple measurement approach yielded similar results whether we used the BDI or the CDI in analyses, and the values of the relative risks were similar whether they were used in univariate analyses or analyses adjusted for various medical and treatment control variables (19). Levels of depressive affect varied over time in our patient population, increasing in about a third, decreasing in about a third, and remaining relatively stable in the remainder. We interpreted our findings as consistent with the notion that level of depressive affect assessed more closely to the outcome enhanced its predictive value.

More recently, Lopes *et al.* (20) showed, using data from the large Dialysis Outcomes and Practice Patterns (DOPPS) study, that a diagnosis of depression or increased level of depressive affect, even with crude measures such as the response to questions such as “Have you felt so down in the dumps that nothing could cheer you up?” or “Have you felt downhearted and blue?”, was associated with increased morbidity and mortality in an incident and prevalent population. Knight and colleagues

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(21), in a longitudinal study using Short Form 36 (SF-36) based measures, reported that the baseline Mental Component Score assessed one to three months after initiating ESRD therapy with hemodialysis, and decline of the score over time were associated with mortality.

In this issue of *CJASN*, Boulware and colleagues assess data from the Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) study, a large observational follow-up of incident hemodialysis and peritoneal dialysis patients from centers across the United States (22). They found a prevalence of depressive symptoms of 19 to 24% over time, in agreement with contemporary studies using BDI and SF-36 measures (8,9,11,20). Level of depressive affect assessed at the beginning of the study was not associated with increased overall mortality risk. Interestingly, the high level of baseline depressive affect was associated with increased risk for noncardiovascular deaths in adjusted analyses. Using several different time-dependent analyses, the investigators were able to confirm that persistently higher levels of depressive affect over time were associated with increased risk of death and cardiovascular events, in adjusted and unadjusted analyses. Analyses incorporating a 6-month lag period for assessment of high depressive symptom level did not demonstrate an association of depressive affect with morbidity or mortality in adjusted analyses. Using these time lag- and time-dependent analyses, the authors seek to make a case for “reverse causality,” suggesting that medical conditions worsened before the ascertainment of increased depressive affect in patients with poor outcomes in the study.

The strengths of this important study are its large and varied multicenter, nationwide population, the large number of covariates carefully assessed at baseline and over time, and the careful ascertainment of incident cardiovascular events and cause of mortality. Weaknesses include the use of a nontraditional measurement of depressive affect and the use of a cut-off, which was not previously evaluated in patients with chronic kidney disease, to determine a “high” level of depressive affect. Depressive affect was assessed at baseline and at 6, 13, and 18 months with the 5-item Mental Health Subscale of the Medical Outcomes Study SF-36. The only cited information regarding the validity of the Mental Health Subscale of the SF-36 in ESRD patients as a measure of depressive affect stems from a study by Troidle *et al.* (23), in which chronic peritoneal dialysis and daily hemodialysis patients were evaluated with both the BDI and the SF-36. The authors of the Troidle study expressed reservations regarding the use of the SF-36 scale questions and cautioned regarding implications of its use and associations with hard outcomes. The SF-36 set of questions cannot be construed as a scale of depressive symptoms, but is rather an assessment of depressive affect, anxiety, and distress, perhaps more accurately described as a distress scale.

An extensive assessment of the interrelationship between the Mental Health Subscale measure of depressive symptoms and medical factors would have been useful for the assessment of this study. We have not been successful in identifying a scale that provides predictive power beyond that of a measure containing queries regarding the somatic aspects of depressive

affect. Several studies have suggested that the BDI has well-established cutoffs associated with a psychiatric diagnosis of a depressive disorder in hemodialysis patients (24–26). Therefore the BDI can be used to quantify depressive affect and establish the presence of a psychiatric diagnosis in ESRD patients. Although the prevalence estimates of this investigation regarding depression concur with those outlined by us and others (20,24), those estimates should be interpreted with caution because of the tool used in this study. However, this study clearly confirms the importance of depressive affect (and distress) rather than the more exclusive diagnosis of a depressive disorder as a risk factor for poor outcome in ESRD patients treated with dialysis.

It is not surprising that, using contemporary techniques, researchers have been unable to demonstrate an association between baseline level of depressive affect and outcomes. De Nour and Czaczkas (27) had opined many years ago that the time around the initiation of dialysis treatment for ESRD was turbulent and did not reflect a stable, steady state. Endurance of a debilitating medical illness and a time-intensive treatment over months and years may exact a price, especially in those less able to cope with such challenges (10). It is unclear whether the hypothesis regarding “reverse causality” suggested by the investigators in the study of Boulware *et al.* (22) is operational in that sample or in US ESRD patients treated with dialysis. Even with careful longitudinal assessments it may be difficult to infer causality because of measurement at investigator convenience and the association of different variables with depressive affect. The investigators are careful not to over-interpret their findings, correctly terming reverse causation a “possibility” from the data presented. Depressive symptoms were measured at set intervals, not at signal events in the life cycle of the ESRD patients, such as at a hospitalization, access revision, or interpersonal crisis. It is likely that the relationship between depression and physical decline or severity of illness is not simply unidirectional, but is intertwined. In some cases depression may lead to poorer health and higher mortality; in others, declining health may lead to increased depression, and in some instances, depression and/or declining health may be independently associated with mortality. This is consistent with the findings of several studies that the level of depressive affect varies in longitudinal studies of dialysis patients (19,22,28). The study by Boulware *et al.* (22) reemphasizes the importance of multiple measures in elucidating mechanisms in clinical studies. More frequent assessments of depression and depressive affect in longitudinal studies using refined tools may shed more light on this issue.

Longitudinal studies are more comprehensive, provide more statistical power, and allow the assessment of the contribution of change and stability to be quantified, but they incur increased costs. It is eminently clear now from the study by Boulware *et al.*, and from those that preceded it, that depression is a persistent problem, rather than an adjustment reaction, which does not necessarily improve with time in ESRD patients. High levels of depressive affect over time are associated with increased risk of morbidity and mortality. Analyses from

observational studies, however, do not necessarily imply causality.

Patients treated for ESRD exist in a complex environment, including family members, physicians, and dialysis personnel. The challenges in addressing the multiplicity of issues regarding depression in patients with ESRD include defining the nature of the interaction between medical illness, time, level of depressive affect and its variation, and outcomes. The role of age, gender, ethnic background and socioeconomic status (including residence), marital status and satisfaction, familial interactions, and interactions between patients, physicians and dialysis staff, corporations and payors, including patient compliance, should be investigated. The role of substance abuse, including alcohol dependence, and assessment of factors related to withdrawal should be elucidated. In addition, the role of interactions between dialytic treatment modality and outcomes remains to be more fully explored. Finally, the role of depression and its treatment and possible relationships with improved outcomes in patients (including children) treated with renal transplantation should be studied.

Therefore, while controversy exists regarding therapy of patients with ESRD with depressive symptoms, it is reasonable to believe that treatment of patients with high levels of depressive affect with the antidepressant drugs in the present armamentarium will result in improved outcomes. However, recent findings from well-designed, randomized, controlled trials (e.g., those of the Women's Health Initiative [29,30]), demonstrate that conventional wisdom gleaned from observational studies does not necessarily translate into valid practice recommendations.

We need the right tools for establishing a diagnosis, evaluating risk, and implementing guidelines for initiating and continuing treatment of depression in patients with chronic renal disease. We need to know the level of depressive affect at which treatment should be initiated and the safety and efficacy of treatment of patients with varying levels of depressive affect. We need to know the right approaches for therapeutic interventions. The time for a well designed, properly funded, randomized, controlled trial to show causality instead of associations is now. Randomized, controlled treatment trials of therapy directed at depression in patients with ESRD with high levels of depressive affect, using well validated measures such as the BDI, are desperately needed. This may be one of the last modifiable risk factors for poor outcomes we as nephrologists and mental health care workers can address.

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See related article, "Temporal Relation among Depression Symptoms, Cardiovascular Disease Events, and Mortality in End-Stage Renal Disease: Contribution of Reverse Causality," on pages 496–504.