Treatment of Depression in CKD Patients with an SSRI

Why Things Don't Always Turn Out as You Expect

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An extensive literature has been developed over the last four decades regarding the associations of a diagnosis of major depressive disorder and extent of depressive symptoms with outcomes in patients with ESKD (1). The field has moved from descriptive studies and analyses evaluating comparisons between two groups to sophisticated observational studies using administrative databases as well as direct participant evaluation and participation (1). Depression has been strongly and consistently linked to mortality in this population (2), but of course, direct linkages and causality cannot be inferred from such research.

Although current nomenclature conventions link ESKD with CKD, the former patients represent only the numerical tip of the iceberg for the group. Patients with ESKD who require dialysis experience a substantial burden in terms of morbidity, mortality, prescribed medications, and diminished perception of quality of life in addition to financial concerns, role transformations, and potential disruption of occupational, marital, and financial obligations (1). The remaining overwhelming majority of patients with CKD make up an extremely heterogeneous group. The kidney diseases that they suffer from are multitudinous, and the range of kidney function in this population, conservatively estimated, spans mild decreases in function to almost total absence.

CKD extends from slight decreases in kidney function to severe decrements, usually termed uremia, a constellation of signs and symptoms, including lack of appetite, dysgeusia, nausea, and vomiting, and a diverse set of neurologic, psychologic, and behavioral impairments on a spectrum from lassitude and lack of interest to somnolence, delirium, coma, seizures, and ultimately, death. In most cases, however, uremia is only encountered with severe diminution in kidney function, and patients with greater levels of GFR have been considered relatively asymptomatic.

In general, less is known about the relationship of depression and affective disorders with outcomes in patients with CKD, perhaps in part because of the heterogeneity of the diseases. Specifically, the true prevalence of major depressive disorder in patients with CKD not ready for renal replacement is unknown but likely varies in populations worldwide. The consequences of depression in this population are also less clear than in patients treated with dialysis. The hypothesized pathways that link ESKD to worse medical outcome span common autonomic dysregulation and behavioral nonadherence (1). The degree to which these extend to patients with earlier-stage CKD is unclear. As an example, it is unknown if depression is associated with mortality in patients with CKD.

More saliently, the essential operative question seems to be, "Is depression in patients with CKD different from depression in a population of patients without chronic comorbid medical illness?" The construct of "comorbid" or "double" depression, in which depression coexists with another medical or psychiatric illness, is traditionally thought of as a condition of greater complexity and resistance to treatment. It is unknown whether the severity of coexistent CKD modifies outcomes in patients with the additional depression diagnosis or whether any treatment modifications are required. Related questions include the following. Is depression different in patients with CKD, perhaps rendering it more difficult to treat? Are there different neural pathways involved in the pathogenesis of this syndrome in patients with and without a specific chronic illness, such as CKD? Are such pathways modified by decrements in kidney function? Is the severity of depressive affect a determinant of outcomes with medical antidepressant therapy? Is the severity of kidney dysfunction a determinant of outcomes with medical antidepressant therapy? Might subtle symptoms associated with kidney disease, perhaps consistent with those attributed to major depressive disorder, affect patient therapeutic outcomes?

To provide answers to the types of questions raised above and elucidate mechanisms, well designed randomized, controlled trials are necessary. Hedayati *et al.* (3) presented a well designed, well conducted trial of pharmacologic therapy for depressed patients with CKD using the selective serotonin reuptake inhibitor (SSRI) sertraline. Rates of adherence were excellent. Unexpectedly, there was no difference between outcomes in the group of patients treated with the SSRI compared with the patients treated with placebo. Some of the purported reasons for this surprising outcome were addressed both by the investigators (3) and in an editorial accompanying the report (4), including assessment of the possible role of the placebo effect.

Some questions about the study require elucidation before key issues that have been raised can be addressed. Screening is a constant challenge in the design of studies of

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treatment of depression. The study by Hedayati *et al.* (3) screened 14,658 patients to arrive at a group of 201 patients with a median GFR of 27.5 ml/min per 1.73 m^2 to be randomized. This small selected group raises the issues of whether a biased study sample was created. It is not clear whether differences existed between the final study population and the eligible population. (Under current Institutional Review Board regulations, such detailed analyses probably cannot be performed.) Why did such a high percentage of people go through the screening process but not want to participate in the trial? (Weisbord and colleagues [5] addressed this in part in patients with ESKD treated with dialysis, but as noted, this is a very different patient group.) Why was there such a small proportion of women in the trial (approximately 27%), quite atypical for depression trials in particular? What is the significance of the high lifetime history of depression (approximately 40%) for this group? What were the patients' expectations for treatment? Was the choice of a cutoff of 11 or greater on the Quick Inventory of Depression Symptomatology scale as the inclusion criterion too low? Were changes in appetite, sleep, or sexual functioning present due to the comorbid medical illnesses in the population or their treatment with drugs for kidney and/or psychiatric disease, and were these changes, therefore, conflated with the presence of depression?

The final study population was not characterized by severe depression or stage 5 CKD. It would stand to reason that the study population would be skewed away from more severe depression, because patients with severe depression are likely to be treated and are not available for a clinical trial with equipoise. However, the efficacy of SSRIs in moderate depression, even in nonmedical populations, is controversial, with a treatment advantage being reliably shown only for those with severe depression (6).

Perhaps, due to the generally asymptomatic nature of earlier stages of CKD and the generally moderate levels of depression commonly found in outpatient populations, other treatment options should be considered. Individual cognitive behavioral therapy (CBT) of patients with increased depressive affect has had remarkably salutary results in the general population and in a small study of patients with ESKD treated with dialysis (7). This therapy holds the promise of addressing the maladaptive thoughts and feelings of patients with major depressive disorder in the absence of the kind of adverse effects associated with drug therapies. CBT may be a particularly good choice for patients with CKD due to its substantial empirical base, its effectiveness at treating moderate depression, and its flexibility, allowing adaptation to any potential unique challenges of the CKD population.

Nevertheless, the study by Hedayati *et al.* (3) is important in spite of its unexpected results, because it provides critical information for the design of more definitive research. Future studies might consider national, multicenter approaches with a registry, enrolling a broader spectrum of patients with CKD who are depressed in a trial of CBT versus drug therapy, which would test effectiveness. Perhaps pragmatic approaches may make such studies more feasible as well as affordable.

In addition, the results of the study by Hedayati *et al.* (3) raise the question of the homogeneity of the small group of patients available after screening. Precision medicine or the notion that specific markers, perhaps genetic or physiologic, might be used to determine individuals within populations more likely to respond to a given treatment or medication is currently vigorously advocated. Recently, the notion of endophenotype has been considered in evaluating studies that are inconclusive. Characteristics within a diagnostic class may prove useful in subcategorizing patients who will respond well or adversely to a specific therapy. Latent class analytic techniques have proven to be useful in identifying groups with particular outcomes in therapeutic studies (8). Such analyses should be applied to the data in this study, where it might be useful to evaluate the associations between severity of kidney disease and depression in relation to a variety of outcomes of drug therapy, although the database is relatively small. Finally, innovative therapeutic approaches, such as the use of drug combinations (such as an SSRI and bupropion or an atypical antipsychotic) or the combination of pharmacologic and talk therapies, should be considered.

We must, however, await the publication of subgroup analyses from the Systolic Blood Pressure Intervention Trial (SPRINT) (9), which assessed perceptions of quality of life and level of depressive affect in a large sample of patients with CKD compared with patients with hypertension in the absence of CKD to evaluate whether there is something unique about the relationship of depression to CKD, and A Trial of Sertraline versus CBT for End-Stage Renal Disease Patients with Depression (ASCEND) (10), which will determine if CBT and sertraline are equally effective in depressed patients with ESKD treated with dialysis to plan better studies for patients with CKD at less severe stages and patients with more moderate levels of depression.

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Disclosures

None.

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