We Need to Talk about Depression and Dialysis: but What Questions Should We Ask, and Does Anyone Know the Answers?

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Depression is common in people with CKD. When diagnosed *via* a gold standard semistructured psychiatric interview by culturally competent staff, depression affects one fifth to one quarter of people with CKD, regardless of whether in receipt of maintenance dialysis, with nondialysis-treated CKD, or with a functioning transplant (prevalence rates, 22.8%; 95% confidence interval (95% CI), 18.6% to 27.6%; 21.4%, 95% CI, 11.1% to 37.2%; and 25.7%, 95% CI, 12.8% to 44.9%, respectively) (1). These frequencies are clearly in excess of the average population lifetime risk of approximately 9% (2). Potential reasons for the high rates of depression in ESRD include the overlap of some risk factors for both conditions, the alteration of physiologic processes associated with ESRD, and the psychosocial consequences of living with ESRD (3). Depression in people receiving dialysis is associated with lower quality of life, increased hospitalizations, and likely, shortened survival (3).

Despite its frequency and effect, we have little evidence to guide management of depression in people with CKD. There are two Cochrane systematic reviews on antidepressant treatment (4) and psychosocial interventions (5) for depression in people on hemodialysis to guide practice. Unfortunately, the psychosocial interventions review includes no trials. The antidepressant review includes one randomized, placebo-controlled trial with depression as an end point. This trial of sertraline included only 43 participants (6) and showed a statistically significant lower Beck Depression Inventory (BDI) scale (7) mean score at the end of treatment in the sertraline group of −7.50 (95% CI, −11.94 to −3.06). In one other trial, 44 participants were randomized to receive citalopram or psychologic training and showed no differential evidence of benefit (8).

Therefore, it was with great anticipation that we read the two trials in this issue of the *Clinical Journal of the American Society of Nephrology*. Friedli *et al.* (9) explored the feasibility of conducting a randomized, controlled trial (RCT) of sertraline in people on hemodialysis with major depressive disorder diagnosed *via* a structured psychiatric interview (the M.I.N.I. International Neuropsychiatric Interview) (10). The results of their pilot RCT outline the difficulties of conducting trials of depression in people with CKD in agonizing detail. After screening 1353 patients, 231 participants were identified on the basis of high scores on the BDI-II. Of these, 30% were on some form of pharmaceutical or nonpharmaceutical therapy—a figure that further reduced the eligible population but one that also indicates the number receiving ineffective treatment strategies. With only 50% of the recruitment target of 60 able to be randomized to sertraline or placebo, the next challenge was the immediate drop in BDI-II scores in all participants at the first post-randomization follow-up, indicating spontaneous recovery, regression to the mean, or possibly, the therapeutic advantage associated with involvement in a trial. The next challenge was the uneven dropout, with nearly one half of intervention participants (seven of 15) dropping out by 4 months compared with only two of the 15 control patients. The small numbers involved prevent speculation on the degree to which this was due to drug tolerability or the play of chance. Given the challenges, the authors correctly identify that the negative result of their study is not definitive and conclude that additional trials on the treatment of major depression in this population are warranted.

Pena *et al.* (11) report secondary analyses of data from the Symptom Management Involving End-Stage Renal Disease (SMILE) Trial, an RCT comparing the effectiveness of two 12-month pain, sexual dysfunction, and depression symptom management strategies in adults receiving chronic hemodialysis: a feedback intervention (not covered in this article) and a management intervention. The SMILE Trial began with monthly observational surveys documenting participants' symptoms of pain, sexual dysfunction, and depression (12) (assessed using the interviewer-administered nine-item Patient Health Questionnaire [PHQ-9] [13]). The feedback intervention included feedback of participants' symptom scores for those with one or more symptoms of pain, sexual dysfunction, or depression and their respective guideline–based treatment modifications to participants' renal providers. Five written guideline–based treatment algorithms were used for nociceptive pain, neuropathic pain, erectile dysfunction, sexual dysfunction in women, and depression (12). The renal provider (nephrologist and/or renal nurse practitioner/physician assistant) decided whether to implement the algorithm-defined treatment recommendations.

In this issue, Pena *et al.* (11) report the acceptance (by participants) and uptake (by renal providers) of depression symptom management recommendations made by trial-specific nurses for those in the management intervention following the aforementioned treatment algorithm for depression. A trial-specific nurse performed a history and medical examination, reviewed participants' symptoms, and generated treatment recommendations for each symptom. The nurse contacted the renal provider to review participants' symptoms and discuss the treatment recommendations. The patient or the renal provider could refuse the recommendations. Both interventions in the SMILE Trial achieved the same small but statistically significant decrease in depression symptoms from the observation phase to the end of the intervention (14).

It is not immediately obvious how we should interpret the results of the SMILE Trial (11). It is possible that considering five treatment algorithms on a monthly basis over and above the management of CKD was excessively complex. The sheer number of treatment recommendations may have diluted any additional benefit of a trial-specific nurse providing the information. With multiple symptom targets, it is possible that pain or sexual dysfunction may have been prioritized over depression by patients or clinicians. Alternatively, it may be that guideline-based algorithms are not effective for people with complex conditions.

We believe that trials in people with depression receiving dialysis are feasible, because the altered physiology of ESRD and its associated polypharmacy create clear equipoise on the efficacy and harms of depression treatment. The publications in this issue should further strengthen equipoise.

Recruitment presents the major challenge. Friedli *et al.* (9) recruited 30 patients from five units. The results are broadly comparable with those of the industry-sponsored Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events Trial, the largest completed dialysis trial, which recruited an approximate average of ten patients per site, with many sites recruiting fewer than five participants (15). Large investigator networks, considerable industry sponsorship, and/or substantial collaboration would be required for a definitive trial.

Another challenge in clinical practice is accurately identifying depression. The gold standard diagnostic method is not accessible in most nonmental health clinical environments, where simple and quick self- or clinician-administered depression screening tools are often used. Generic depression screening tools substantially overestimate the prevalence of depression in patients on dialysis by over 70% but only overestimate by 24% in patients with CKD and $<5\%$ in patients with transplants (1). Although depression screening tools are sensitive enough to identify fluctuations in depressive symptom burden, as illustrated in Friedli *et al.* (9) and Pena *et al.* (11), recruiting only participants with sustained high scores over multiple assessments would identify those with the greatest need of intervention. However, this would shrink the eligible trial populations further.

Depression screening tools perform poorly in people receiving dialysis, in part due to the overlapping constellation of symptoms common to depression and ESRD, which include fatigue, altered sleep, and suppressed appetite. Depression screening tools were developed in general populations and were not designed to identify the cause of symptoms. Another reason may be the high rates of intermittent, distressing events that may appropriately elicit negative feelings. Just about every negative medical experience, including cardiovascular events, cancer diagnoses, hospitalizations, and impaired physical function, are disproportionately higher among people with ESRD (16–18). It is intriguing to note that a portion of those in the SMILE Trial (11) with high scores on the PHQ-9 refused depression treatment on the grounds of intercurrent events. Perhaps they knew why they were experiencing a negative affect and were, in effect, refuting a diagnosis of endogenous depression. Lastly, people on dialysis experience substantial kidney disease–related losses, a phenomenon also associated with adverse scores on depression screening tools (19).

These competing factors of high symptom burden, intercurrent events, and kidney disease–related losses should not be dismissed purely as competing risks for high scores on depression screening tools. The association between these events and psychiatrist-diagnosed depression has been shown, suggesting that these events may be predisposing factors for depression (3,19). However, these competing factors do add to the complexity of identifying a pure depression trial cohort as these papers illustrate.

Although the reports in this issue highlight the challenges associated with conducting trials of depression treatments in patients on dialysis, both papers provide valuable information that should inform the design of future trials rather than dissuade researchers. The lack of observed differential benefit in the completed trials provides a clear justification for broadening future trials to include patients already on antidepressants, including recruiting those willing to undergo a washout period as suggested by Friedli *et al.* (9). A deprescribing trial model for patients on dialysis taking selective serotonin reuptake inhibitors is justifiable given their lack of clear efficacy and the potential for side effects. Participants could be recruited on the basis of sustained high screening tool scores rather than requiring formal psychiatric assessment. Apart from facilitating recruitment, this method would better reflect how patients are selected for treatment in most primary health settings. Other trial designs that may be appealing for participants may include randomization to immediate or delayed start.

The challenges facing depression treatment trials in people on dialysis may reflect the low priority placed on depression. In the wider context, there is poor recognition of depressive symptoms, an unwillingness of patients to seek help, and a stigma attached to a diagnosis of depression and its treatment. The presence of depression may be eclipsed for patients, carers, and clinicians by intensive medical intervention, intercurrent comorbidities, and high rates of unwelcome events. The deprioritization of depression and the challenges reported in this issue could understandably leave many feeling that trials of depression interventions in dialysis are not feasible. However, the patients' concerns vocalized through the Standardised Outcomes in Nephrology initiative ask for research into living well on dialysis rather than just surviving (20). Arguably, a safe, effective, low-cost treatment for managing depression would realize a substantial and significant improvement in the lived experience.

Disclosures

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See related articles, "Sertraline Versus Placebo in Patients with Major Depressive Disorder Undergoing Hemodialysis: A Randomized, Controlled Feasibility Trial," and "Acceptance of Antidepressant Treatment by Patients on Hemodialysis and Their Renal Providers," on pages 280–286 and 298–303, respectively.