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 chronic kidney disease (CKD). When diagnosed via a gold standard semi-structured psychiatric interview by culturally-competent staff, depression affects one fifth to one quarter of people with CKD, whether in receipt of maintenance dialysis, with non-dialysis treated CKD, or with a functioning transplant (respective prevalence rates 22.8 (95% confidence interval (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)%)[1]. These frequencies are clearly in excess of the average population lifetime risk of ~ 9%[2]. Potential reasons for the high rates of depression in end stage kidney disease (ESKD) include the overlap of some risk factors for both conditions, the alteration of physiological processes associated with ESKD and the psychosocial consequences of living with ESKD[3]. Depression in people receiving dialysis is associated with lower quality of life, increased hospitalisations and, likely shortened survival[3].

Despite its frequency and impact 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 haemodialysis to guide practice. Unfortunately, the psychosocial interventions review includes no trials. The antidepressant review includes one randomised, placebo-controlled trial (RCT) with depression as an endpoint. 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 randomised to receive citalopram or 'psychological training' and showed no differential evidence of benefit[8].

So it was with great anticipation that we read the two trials in this edition of CJASN. Friedli et al[9] explored the feasibility of conducting a RCT of sertraline in people on haemodialysis with major depressive disorder diagnosed via a structured psychiatric interview (the MINI)[10]. The results of their pilot RCT outline the difficulties of conducting trials of depression in people with CKD in agonising detail. After screening 1,353 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 non-pharmaceutical 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 randomised to sertraline or placebo, the next challenge was the immediate drop in BDI-II scores in all participants at the first post-randomisation 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 drop-out with nearly half of intervention participants (7/15) dropping out by 4 months compared with only 2 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 the negative result of their study is not definitive and conclude further trials on the treatment of major depression in this population are warranted.

Pena et al[11] report secondary analyses of data from the SMILE trial; an RCT comparing the effectiveness of two 12-month pain, sexual dysfunction and depression symptom management strategies in adults receiving chronic haemodialysis: a feedback intervention (not covered in this edition's 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 9-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, female sexual dysfunction, and depression[12]. The renal provider (nephrologist and/or renal nurse practitioner/physician assistant) decided whether or not to implement the algorithm-defined treatment recommendations.

In this edition 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 preformed 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 SMILE 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 study[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 pain or sexual dysfunction may have been prioritised over depression by patients or clinicians. Alternatively, it may be that guideline-based algorithms are not effective for people with complex conditions.

We believe trials in people with depression receiving dialysis are feasible because the altered physiology of ESKD 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. Friedl et al recruited 30 patients from 5 units. The results are broadly comparable with that of the industry-sponsored EVOLVE trial, the largest completed dialysis trial, which recruited an approximate average of 10 patients per site with many sites recruiting fewer than 5 participants[15]. Large investigator networks, considerable industry sponsorship and/or substantial collaboration would be required for a definitive trial.

A further challenge in clinical practice is accurately identifying depression. The gold standard diagnostic method is not accessible in most non-mental health clinical environments where simple, quick, self- or clinician-administered depression screening tools are often used. Generic depression screening tools substantially overestimate the prevalence of depression in dialysis patients by over 70%, but only by 24% in CKD patients and <5% in transplant patients[1]. While depression screening tools are sensitive enough to identify fluctuations in depressive symptom burden, as illustrated in Friedl[9] and Pena[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 ESKD 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. A second 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, hospitalisations and impaired physical function are disproportionately higher among people with ESKD[16-18]. It is intriguing to note that a portion of those in SMILE[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 demonstrated suggesting 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.

While the reports in this edition highlight the challenges associated with conducting trials of depression treatments in dialysis patients, 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 wash-out period as suggested by Friedl et al[9]. A de-prescribing trial model for dialysis patients taking SSRIs 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 randomisation 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 deprioritisation of depression and the challenges reported in this edition could understandably leave many feeling trials of depression interventions in dialysis are not feasible. However the patients' concerns vocalised through the SONG 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 realise a substantial and significant improvement in the lived experience.

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