As nephrologists, we spend hours on monthly dialysis rounds examining and fine-tuning numbers: hemoglobin, iron saturation, ferritin, phosphorus, calcium, albumin, intact parathyroid hormone, and Kt/V, among others. Yet our dialysis patients are less concerned about whether they meet Kidney Disease Outcomes Quality Initiative guidelines and are more concerned about how they feel on a day-to-day basis, commonly bringing the presence of “nondescript” symptoms to our attention: symptoms we do not know exactly what to do about. We frequently encounter complaints about pain, erectile dysfunction (ED), sleeping disturbance, poor appetite, fatigue, and “Doc, I just don’t feel well;” symptoms that do not necessarily point us to a certain disease to diagnose or a laboratory value to intervene upon, but leave us with the relentless uncertainty of “Well, what do I do now?” This becomes particularly challenging when considering that adding another psychoactive, anticholinergic, or narcotic medication to the long list of medicines already prescribed to such patients may result in no benefit but may increase the risk of adverse events and drug-drug interactions.

ESRD patients treated with maintenance dialysis harbor a large burden of physical and psychologic symptoms that significantly impair their health-related quality of life (HRQOL) (1). Symptoms of pain, sexual dysfunction, and depression are especially commonly experienced by these patients and are associated with poor HRQOL (1). Pain is present in about 50% of hemodialysis patients, ED (80%) of men receiving chronic hemodialysis, and depression in about 20%-25% (2–4). Depression results in a substantial decrease in HRQOL and in functional impairment in ESRD patients (4,5), and levels of depression and functional and occupational impairment do not remit spontaneously in untreated depressed patients (6). Importantly, the presence of depressive symptoms is significantly associated with hospitalization and death in chronic dialysis patients, the independent effect of which on outcomes is of a higher order of magnitude than medical comorbidities (7–9).

However, these symptoms remain under-recognized and under-treated (4,10). For example, only a minority of hemodialysis patients receive adequate diagnosis and treatment for depression, perhaps due to concerns about adverse effects given the paucity of data regarding the safety of antidepressant medications, because ESRD patients were generally excluded from large randomized antidepressant trials due to concerns for safety (4). Serious knowledge gaps exist with respect to safety and efficacy of both pharmacologic and nonpharmacologic treatments for pain, sexual dysfunction, and depression in ESRD patients. Few clinical trials of pharmacologic symptom treatment in ESRD samples that do exist are fraught with serious limitations including small samples, short-term follow-up, and lack of placebo control. Observational data using antidepressant medications to treat depression in chronic peritoneal dialysis patients reported some improvement (11), but were limited by the lack of a control group, selection bias, refusal bias, and a 50% drop-out rate. In a double-blinded, placebo-controlled trial of 14 hemodialysis patients with depression, fluoxetine treatment was associated with a statistically significant improvement in depressive symptoms at 4 weeks, which was not sustained at 8 weeks (12). However, the short duration and small sample did not allow for adequate adverse event assessment. In another study, treatment with sertraline at 50 mg/d was associated with a decrease in depressive symptoms in 25 chronic peritoneal dialysis patients at 12 weeks (13), but the lack of a control group and small sample size were major limitations. A small but randomized, double-blinded, placebo-controlled trial reported efficacy of sildenafil use for treatment of ED in 41 chronic hemodialysis patients over a 1-month period (14). However, diabetic patients were excluded, and although the authors reported that sildenafil was well tolerated among the study participants, the study was too small and duration of follow-up too short to definitively establish long-term efficacy and safety of this agent in hemodialysis patients who are at high risk for cardiovascular events (14). Barakzoy et al. reported that using the World Health Organization three-step analgesic treatment ladder improved pain in chronic hemodialysis patients (15). Again, the study included only 45 hemodialysis patients, was of 4 weeks duration, and lacked a control group.

Nonpharmacologic interventions, such as alterations in the dialysis treatment regimen (16), exercise therapy (17), and cognitive behavioral therapy (18), have also been considered and tested for treatment of symptoms in ESRD samples. Although approaches such as...
cognitive behavioral therapy are promising for depression treatment, it will be challenging to universally implement such strategies given the structural organization of ESRD care in countries such as the United States, for example, with the limited resources available for providing psychosocial support (4).

Regardless of the quality of the evidence that does exist for treatments to alleviate such symptoms in ESRD patients, until now no studies investigated clinical strategies to improve the provision of such treatments to chronic dialysis patients with the goal of improving these symptoms. In the Symptom Management Involving End-Stage Renal Disease (SMILE) study, the results of which are reported in this issue of CjASN, Weisbord and colleagues conducted a well-designed, unblinded, randomized controlled trial in which they compared two management strategies for pain, ED, and depression in ESRD patients receiving chronic hemodialysis at one of nine outpatient hemodialysis units in Pittsburgh, Pennsylvania (19). They randomized 220 patients to 12 months of either “feedback” or “nurse management.” In both groups, symptoms were assessed on a monthly basis. In the feedback group, the patient’s renal provider received a letter describing his or her patient’s symptoms along with algorithms that could be used to guide treatment. Any treatment was left to the discretion of the providers (20). In the nurse management group, trained nurses evaluated patients, provided recommendations for treatment directly to renal providers, and facilitated the implementation of those treatment recommendations. Although participants in both groups experienced small, statistically significant improvements in symptoms from their “usual care” baseline, nurse management did not provide additional benefit compared with feedback, resulting in yet another negative trial in ESRD samples.

The investigators are to be commended on their innovative approach of rigorously designing a comprehensive study to address this difficult clinical question in sick ESRD patients who, compared with the general population, disproportionately suffer from poor quality of life and dire outcomes. However, few limitations need consideration, some of which may have biased the results to the null. First, the intervention on ED only considered the treatment of men, whereas women with ESRD are also unfavorably affected by sexual dysfunction. Second, although the nature and mode of delivery of the interventions made blinding difficult, lack of at least single-blinding of the participants may have affected the results. Third, although all participants underwent an observational usual care phase to capture the prevalence and temporal stability of the symptoms and to establish a baseline comparator for the interventions, there was no simultaneous usual care arm control group during the randomization phase. A usual care arm may have allowed a difference to be observed for superiority of the nurse management intervention arm. In addition, having a usual care arm or standard of care to serve as the control group would have made the results more generalizable, had this been a positive study. Next, participants were randomized based on the day of their dialysis shift (Monday/Wednesday/Friday versus Tuesday/Thursday/Saturday) to avoid cross-contamination of the interventions if randomized at the level of the individual patient, as well as to avoid obscuring intervention differences if randomized at the level of the provider (20). However, there was still risk of cross-contamination, because the same individual providers were involved in both intervention arms, potentially leading to changing their treatment of patients in the feedback arm based on receiving direct recommendations from nurses in the nurse management arm, which could result in observing no difference in the interventions. Furthermore, the study did not formally assess adherence of participants to prescribed treatments, and the limited number of participants that were actually prescribed treatment or were adherent to treatment may have resulted in observing a lack of difference in intervention arms. Finally, the symptoms of pain, ED, and depression may be inter-related, and the treatment of one symptom may affect the other, potentially biasing results to the null. For example, treatment of pain may alleviate depression or, alternatively, worsen depressive symptoms due to side effects of narcotics, such as increased lethargy or sleep disturbance. Similarly, treatment of depression with antidepressant medications such as selective serotonin reuptake inhibitors may actually worsen ED.

In conclusion, the SMILE study did not show a difference in two management strategies designed to reduce symptoms of pain, ED, and depression among ESRD patients treated with maintenance hemodialysis. In addition, the clinical relevance of the small, although statistically significant, differences that were observed in symptoms from the usual care baseline is not clearly apparent. When addressing such symptoms during dialysis rounds, are we then left with the conundrum of adding yet another potentially harmful medication to the growing list of medicines we prescribe to our ESRD patients, or worse, dismissing such symptoms as untreatable nonspecific symptoms of chronic disease? However, data clearly suggest that such symptoms independently prognosticate poor HRQOL and survival in these patients. Therefore, such symptoms should not be ignored and should be addressed on an individual basis using best available evidence for treatment, until more data are available for symptom management in patients with ESRD treated with maintenance dialysis.

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References


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See related article, “Comparison of Symptom Management Strategies for Pain, Erectile Dysfunction, and Depression in Patients Receiving Chronic Hemodialysis: A Cluster Randomized Effectiveness Trial” on pages 90–99.