Andrea Kattah

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An intervention trial for treatment of depression in dialysis patients

Study purpose and rational

Depression in the ESRD population is a common but routinely under-diagnosed problem. The incidence of depression in the general population is 2-4%, but the prevalence rate in the ESRD population is routinely placed at 20-30% (1). Though dialysis patients have frequent contact with the medical system, they are less likely to receive treatment for depression. One possible cause of this discrepancy is that ESRD patients commonly have many somatic complaints that have significant overlap with depressive symptoms, such as fatigue, sexual dysfunction and insomnia. If one adopts a strategy of aggressive treatment for all ESRD patients with these symptoms, this could result in overtreatment. In addition, practitioners often hesitate to prescribe anti-depressants to ESRD patients due to concern of medication side effects and safety. On the other hand, under-treatment of depression of can have a significant impact on both the quality of life and medical outcomes in these patients.

Several studies have shown the negative impact depression has on outcomes in ESRD patients. In a study by Hedayati et al, 98 patients with ESRD being initiated on hemodialysis (HD) were followed prospectively. 21/26 depressed vs. 31/72 non-depressed patients had died or were hospitalized at 6 months with a hazard ratio of 2.1 (95% CI 1.21-3.68) and the association remained after adjustment for several demographic factors including age, time on HD and number of co-morbid conditions (2). Other studies have confirmed the increased risk of mortality in the depressed ESRD population. The Pathways Study, a longitudinal prospective cohort study of patients with diabetes, showed that out of 110 patients with stage 5 chronic kidney disease in the 4,000 person study, 22% had major depression and this was associated with a 3-fold greater risk of death compared to patients with either no or few depressive symptoms (3). A large 15,000 patient study done by Soucie et al in 1996 evaluated what risk factors were associated with death in the first 90 days after initiation of HD and found many factors including age, male gender, smoking, congenital heart failure, as well as clinical depression (4). Perhaps not surprisingly, patients who are depressed are less likely to be compliant with their medication regimens. In one study by Cukor et al examining medication adherence in hemodialysis (HD) patients vs. transplant recipients found that patients on HD were more likely to be depressed and in multiple regression analysis, the variance in depression was the only significant predictor of medication adherence in both groups (5).

One potential difficulty in diagnosing depression in this population, as noted above, is that it is hard to differentiate between typical somatic symptoms and frank depression. A study by Watnick et al in 2005 validated two different depression scales, the Beck Depression Inventory (BDI) and the Patient Health Questionnaire 9 against the gold standard Structured Clinical Interview for DSM-IV (SCID-IV) in ESRD patients. Looking at the BDI specifically, a cutoff of 10 or greater is used in the general population to

diagnose possible depressive disorder. However, this study showed that a cutoff value of 16 or greater had sensitivity and specificity of 91% and 86% respectively (6).

Some randomized studies have been done to evaluate the efficacy of depression treatment in ESRD patients. A 2009 study by Duarte et al randomized approximately 40 patients each to either usual treatment for depression provided by the dialysis unit versus cognitive behavioral therapy and found that patients in the intervention group had a significant improvement in the BDI score at 9 months, with the average change being 13 with standard error of 2. Of note, the average completion rate in the intervention group was 80% (7). Another interesting study done in Turkey recruited 90 patients to participate in a theater play, of which 31 agreed and 60 refused to join. Of those who accepted, half were randomized to begin activities immediately and half were placed on a waiting list. The patients who immediately engaged in a social activity had a significant decrease in their BDI scale at 4 months versus the patients who did not (8). A study in 1997 study by Blumenfeld et al took 14 patients on dialysis and randomized them to fluoxetine or placebo and measured depression indices and serum drug levels. Patients on treatment had significantly improved symptoms at 4 weeks and serum drug levels were similar to patients without renal failure (9).

Models for interventions can be drawn from other studies of patients with chronic medical conditions. A 2010 study by Vera et al in Puerto Rico randomized patients with any one of a list of chronic medical conditions in primary care practices to either usual care, including information about the diagnosis, names of providers and encouragement to seek care, versus a collaborative care model that involved mental health specialists, physicians and care managers giving either cognitive behavioral therapy or pharmacotherapy based on patient preference. The intervention group in this study had significantly reduced depressive symptoms and an improvement in social function at 6 months (10).

The rationale behind this study is to try to make a meaningful intervention in patients with ESRD and to find a protocol that is applicable to an average dialysis unit. In order to this, there are two main questions this study aims to answer. One is simply whether a more aggressive intervention on ESRD patients on maintenance HD with newly diagnosed depression offers a benefit in depressive symptoms over a simple referral to mental health services. The second question is whether intensive collaborative care offers any additional benefit over a simple telephone caseworker model that involves periodic phone calls and new referrals if needed. The latter model is a simpler method to implement and therefore may be more applicable in the future.

Study Design and Statistical Analysis

All patients will be recruited from the outpatient dialysis unit associated with Columbia University Medical Center at 60 Haven Avenue. Patients must have a regular primary care physician who they foresee keeping for the next 6 months.

All subjects will be screened with a two-stage screening model to ensure only patients with persistent depressive symptoms are enrolled in the study. The Beck Depression Index (BDI) will be performed at enrollment and at 1 month. Patients with two scores greater than 16 and less than 55 will undergo

randomization for intervention. Those with positive tests on both screening tests and no exclusion criteria will be randomized to the following groups:

1. Usual care –Patients in this group that are screened in for possible depression will be told that they may have a diagnosis of depression based on their questionnaire results and should contact their primary care physician. They will also be provided with mental health services in their immediate area. Lastly, a with the patients consent, a note will be sent to the PMD to alert them of the questionnaire results.
2. Telephone Care model (TCM) – Patients will be provided with mental health services in their area and a note will be sent to the PMD with the test results. In addition, a social worker affiliated with the dialysis center will telephone the patients every month for 6 months and evaluate whether patients have accessed care for depression, to make a new referral if necessary, and to provide information on either social work services, community services, or medical and psychiatric care.
3. Collaborative care model (CCM) – Patients in this arm will be part of an integrated model involving physicians, mental health specialists and nurse practitioners. All patients will receive education about depression and will be offered a choice between pharmacotherapy and cognitive-behavioral therapy (CBT). Patients undergoing pharmacotherapy will have an initial visit with a psychiatrist that will recommend initial medication and dosage. They will meet weekly thereafter for brief visits targeted at medication adjustment. Any adverse effects of medications or side effects will be noted. Compliance will also be assessed. In the CBT arm, patients will have 12 sessions of CBT (approximately every 2 weeks) for 6 months. Each patient is assigned a 'care manager', which is either a psychologist or nurse practitioner that will contact the patient every 2 weeks for the first two months of the study and then monthly thereafter to answer questions and troubleshoot any adherence issues to therapy or side effects from medication.

The proposed length of study will be 7 months - 1 month of pre-randomization and 6 months of intervention.

Other demographic information of interest will be collected from patients prior to randomization including age, race, gender, marital status, living situation, education status and medical co-morbidities. We will also ask patients consent to access their medical records to gain information regarding medications and past medical problems.

For the first part of the study, to determine whether any intervention is an improvement over usual care, the number of subjects needed to detect a 10-point change in the BDI assuming an alpha of 0.05 and a power of 80% is approximately 20 subjects. This is assuming a standard deviation of the BDI of 10 drawn from other studies. Therefore, we will enroll 20 subjects into the usual care arm. The second question the study aims to answer is whether CCM offers any additional improvement over TCM, in other words, whether TCM is non-inferior to CCM. Therefore, assuming a difference in the two scores of no greater than 10%, again with alpha of 0.05 and 80% power, we need 250 subjects in both intervention arms. Assuming a 20% drop-out rate, we will enroll 300 subjects in both arms.

All demographic data will be analyzed using t-test for continuous variables and a chi-square analysis for categorical variables to look at differences between the usual care and intervention groups. To evaluate the primary outcome, BDI score at 6 months in usual care versus the two intervention arms, a t-test based on intention to treat will be performed. To evaluate the two interventions against each other, a t-test based on a per-protocol basis will be performed as we are trying to prove non-inferiority. In this analysis, all patients that dropped out of the study will be excluded. Multiple regression analysis looking at the interaction terms of age, number of co-morbidities and BDI score at study onset will be done as well.

Study Procedure

There are no procedures associated with this study.

Study Drugs

Patients randomized to intervention and who elect to initiate pharmacotherapy will be initiated on an anti-depressant determined by the consulting psychiatrist. The psychiatrist will contact both the nephrologist and PMD of the patient to inform them of his choice and ask if they have any concerns or recommendations. The psychiatrist will only prescribe drugs that are FDA-approved for the treatment of depression. If the patient experiences side effects, he may be switched from medication to another based on the psychiatrist's recommendations. Any adverse events or side effects will be recorded.

Medical Device

There are no medical devices associated with this study.

Study Questionnaires

Beck Depression Index (BDI) – The BDI has been shown in many studies to be a highly sensitive and specific test for depression (6). It includes 21 questions, each with a possible score of 0-3 with the summed range from 0 to 63. It measures several areas including affective symptoms and attitudes, impaired functional performance and somatic symptoms. It has been validated in the ESRD population with a higher cutoff of 16.

Other demographic data including age, race, gender, marital status, living situation, education status and medical co-morbidities will be obtained.

Study Subjects

- Inclusion criteria - Patients eligible for the study are those patients >18 or <60 years old with ESRD on hemodialysis for at least 1 year at Columbia University's outpatient dialysis unit. Patient s must consent for participation and have a primary care physician that they foresee keeping for the next 6 months.
- Exclusion criteria - Exclusion criteria – age< 18 or >60, unable to understand the study protocol or questionnaires, scheduled for renal transplant, psychotic symptoms, prior

diagnosis of depressive or anxiety disorder, prior psychiatric hospitalization or suicide attempt, active suicidal ideation, active substance use disorder, or BDI score >55

Of note, patients with active suicidal thoughts or psychosis, as well as patients with very elevated BDI score (>55), will be referred to emergent psychiatric care and excluded from the study.

Recruitment of Subjects

Patients will be approached by study personnel at the dialysis unit to ask if they would like to participate in the study. The questionnaire will be filled out while the patients are at the unit. As the patients spend the three days a week at the dialysis center, this is an ideal location to approach them to participate in the study. The patient's primary physician will be contacted and told that patient has been recruited for the study and will receive the results of the questionnaire. In addition, as mentioned above, the attending nephrologist and PMD will be notified of any medication changes made by the attending psychiatrist.

Confidentiality of Study Data

All study subjects will be assigned a unique study number. Data will be stored in a password-protected database that only the principal investigators will have access to.

Potential Conflict of Interest

No conflict of interest

Location of the Study

60 Haven Avenue dialysis unit and Vanderbilt Clinic

Potential Risks

Involvement in this study may include several additional appointments and may be an inconvenience to the study participants. In addition, filling out questionnaires and participating in telephone conversations may be a burden to some.

Those patients that are going to participate in the pharmacotherapy arm of the randomization arm may experience side effects of the medications, including stomach upset, diarrhea, fatigue, sexual dysfunction or increased wakefulness depending on the agent. The most common medications used for depression are the serotonin reuptake inhibitors (SSRIs). There may be an increased risk of bleeding during surgery with these medications. A more serious complication of these drugs that can occur when taken in conjunction with drugs that use a particular liver metabolism pathway, the cytochrome P450 pathway, is the serotonin syndrome, a disorder of the muscles that can be life-threatening. Lastly, there may be an increase in suicidal thoughts once the medications are initiated, though there has not been evidence to show an actual increase in the number of suicides.

There have been small studies of anti-depressants in patients on dialysis that have shown safety and efficacy, but there are no large clinical trials as ESRD patients have been excluded from the treatment trials in the past. While the studies have been encouraging, there is still a risk of having an adverse outcome as the evidence is still observational (1).

Potential Benefits

This study offers many potential benefits to the participants. The dialysis population has a high incidence of depression, but very few patients have been diagnosed or started on treatment. Participation in this study will familiarize them with the symptoms of depression and give them access to treatment. The potential benefits of treatment of depression include increased energy level, better quality of life and potentially fewer hospitalizations. However, you may or may not benefit as a result of your participation in this study.

Alternative Therapies

There are many alternative therapies for treatment of depression including different types of psychotherapy, exercise therapy, group therapy and many pharmacologic agents.

Compensation

There will be no monetary compensation for this study

Costs to Subjects

The patients will receive free metro cards to go to any additional appointments needed as a result of this study. When possible, sessions with the psychiatrist will be scheduled on the day the patient is on site for dialysis. The costs of the CBT sessions, the psychiatric evaluations and the anti-depressant medications will be covered by the study.

Minors as Research Subjects

No minors will be involved in the study.

Radiation of Radioactive Substances

No radiation or radioactive substances will be used in this study.

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