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Rationale and Design of the Chronic Kidney Disease Antidepressant Sertraline Trial (CAST)

Nishank Jain, MD, MPH^{1,2}, Madhukar H. Trivedi, MD³, A. John Rush, MD⁴, Thomas Carmody, PhD⁵, Benji Kurian, MD³, Robert D. Toto, MD², Ravindra Sarode, MD⁶, and S. Susan Hedayati, MD, MHS^{1,2}

¹Division of Nephrology, Veterans Affairs North Texas Health Care System, Dallas, Texas, USA

²Division of Nephrology, Department of Medicine, University of Texas Southwestern Medical Center, Dallas, Texas, USA

³Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, Texas, USA

⁴Office of Clinical Sciences, Duke-NUS, Singapore

⁵Division of Biostatistics, Department of Clinical Sciences, University of Texas Southwestern Medical Center, Dallas, Texas, USA

⁶Department of Pathology, University of Texas Southwestern Medical Center, Dallas, Texas, USA

Abstract

Major depressive disorder (MDD) affects one in five patients with Chronic Kidney Disease (CKD) and is an independent risk factor for hospitalization and death before and after dialysis initiation. However, it remains an under-recognized and under-treated problem, in part due to the lack of well-controlled studies that support or refute the efficacy and safety of antidepressant medications in CKD patients. Major trials of antidepressant treatment excluded patients with stages 3–5 CKD, precisely those at higher risk for both depression and increased mortality. The Chronic Kidney Disease Antidepressant Sertraline Trial (CAST) is a randomized, double-blinded, placebo-controlled trial of sertraline, a selective serotonin reuptake inhibitor (SSRI). It will enroll 200 adults with stages 3–5 CKD and MDD excluding kidney transplant and chronic dialysis patients. Sertraline will be administered at an initial dose of 50 mg once daily or matching placebo followed by a dose escalation strategy consisting of 50 mg increments at 2 weeks intervals (as tolerated) to a maximum dose of 200 mg. The primary outcome is improvement in depression symptom severity measured by the Quick Inventory of Depressive Symptomatology scale. Secondary outcomes include safety endpoints and improvement in quality of life. Changes in cognitive function, adherence to medications, nutritional status, inflammation, and platelet function will be explored as potential mechanisms by which depression may mediate poor outcomes. We discuss the rationale and design of the CAST study, the largest placebo-controlled trial aimed to establish safety and efficacy of a SSRI in the acute phase treatment of CKD patients with MDD.

Address correspondence to: S. Susan Hedayati, M.D. VA North Texas Health Care System Nephrology Section MC 111G1 4500 South Lancaster Road Dallas, TX 75216-7167 Phone: (214)857-2214 Fax: (214)857-1514 susan.hedayati@va.gov.

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Keywords

depression; chronic kidney disease; sertraline; randomized trial; treatment

INTRODUCTION

Chronic Kidney Disease (CKD) affects approximately 13% of the U.S. population and 21% of patients with CKD may suffer from a Major Depressive Disorder (MDD) episode, which is defined as a clinical syndrome characterized by depressed mood or anhedonia plus 5 of the 9 Diagnostic and Statistical Manual of Mental Disorders IV (DSM IV) criterion symptom domains for a period of 2 weeks [1–4]. This point prevalence is higher than that reported not only for the general population [5], but also for those with other chronic diseases [6–8]. Importantly, depression is associated with decreased quality of life (QOL), functional impairment, and an increased risk of hospitalization and death in End-Stage Renal Disease (ESRD) patients on chronic dialysis [9–15]. We reported that even in predialysis CKD patients, depression was associated with an increased hazard of death, hospitalization or progression to ESRD [16]. Potential mechanisms by which depression could lead to poor outcomes in this population include increased inflammation [2], cognitive impairment [17–18], abnormal platelet function [19–20], poor nutrition [21–22] and non-adherence to diet and interdialytic weight gain [23].

Despite growing literature in understanding the ill effects of depression, serious knowledge gaps exist in MDD treatment in CKD patients. Antidepressant medication treatment rates remain dismal, compounded by the unknown safety and efficacy of such therapy in CKD and ESRD patients [4, 24–26]. Safety concerns include possible drug-drug interactions, decreased metabolite clearance, and increased bleeding risk in these high risk groups [27–29]. Data to establish efficacy of MDD therapy or impact on outcomes in CKD patients is limited due to small sample sizes, lack of placebo-control, non-standard criteria for MDD diagnosis, high drop-out rates, or selection and refusal bias [30–33]. More recent data [34] suggest a trend towards improved cardiovascular outcomes when patients with acute coronary syndrome and MDD were treated with sertraline. However, those with moderate to advanced CKD, precisely the group of patients at higher risk for excessive rates of cardiovascular events and death, were excluded, likely due to safety concerns as delineated above.

To fill this large knowledge gap, we designed and initiated a double-blinded, randomized, placebo-controlled clinical trial (Chronic Kidney Disease Antidepressant Sertraline Trial or CAST), which will examine the safety, tolerability, and efficacy of sertraline treatment in CKD patients [35]. This trial will also elucidate mechanisms by which treatment may improve clinical outcomes. We hypothesize that short-term treatment of MDD with serotonin-selective reuptake inhibitor (SSRI) sertraline vs. placebo will result in improvement in depression symptom severity and QOL in patients with predialysis stages 3–5 CKD. We further hypothesize that short-term treatment of MDD with sertraline is safe and well-tolerated in such patients.

METHODS

Study Sample

Male or female adults ≥21 years with moderate to advanced CKD, defined as stages 3–5, with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m², and not yet on chronic dialysis who meet DSM IV criteria for a current MDD episode by the Mini International Neuropsychiatric Interview (MINI) are eligible for participation. Early in the

course of the study, based on National Institutes of Health feedback to reduce the disease status heterogeneity of the proposed sample, we changed the inclusion criteria to limit enrollment to those with an eGFR <45 mL/min/1.73 m² (CKD Stages 3b-5). Detailed inclusion and exclusion criteria are listed in Table 1.

Setting and Design

The CAST study is designed as a randomized, double-blind, placebo-controlled, flexible-dose 12-week trial. Patients are enrolled at the Dallas Veterans Affairs Medical Center and the University of Texas Southwestern Medical Center (UTSW) in Dallas, Texas. The UTSW includes clinics at Parkland Health and Hospital System, a large county hospital, and at St. Paul University Hospital, a tertiary care center. Institutional boards at all centers approved the protocol.

A schematic of the trial design is presented in Figure 1. During the screening period (Period A), eligible participants from prescreened clinic rosters are asked to fill out the Quick Inventory of Depressive Symptomatology-Self Reported depression scale (QIDS-SR₁₆), which takes 5–15 minutes to complete [36–37]. Those with scores ≥ 11 are invited to participate. After signing informed consent, eligibility is further assessed by the MINI structured psychiatric interview, administered by trained personnel blinded to participant medical history. The MINI is a DSM IV-based gold standard to determine the presence of a current MDD episode and elicit any psychiatric exclusion criteria, including bipolar disorder or psychosis [38–39].

Eligible participants enter a one-week single-blinded placebo run-in period (Period B) before randomization, designed to exclude placebo-responders and non-adherent patients, from randomization. Placebo-responders, defined as those who score ≥ 11 on the QIDS after the run-in period, are excluded to ensure that subjects still meet eligibility criteria and are not diagnostically misclassified as having MDD before randomization. Non-adherence to study drug is ascertained by pill count and defined as ingestion of $<65\%$ or $>120\%$ of study drug. If the participant successfully completes the run-in period and still scores ≥ 11 on the QIDS, they can enter the double-blinded randomization phase (Period C). Since not all participants can commit to return in exactly one week for randomization, a minimum of 6 and maximum of 12 days are allowed between the run-in period and double-blinded phase to be able to feasibly schedule all participants for randomization.

Rationale for screening tool—We previously validated the QIDS-SR₁₆ as a quick and reliable self-report measure of depressive symptomatology in 272 patients with pre-dialysis stages 2–5 CKD [2]. A receiver/responder operating characteristic curve was used to derive the optimal cut-off score on the QIDS-SR₁₆ by using the DSM IV-based MINI as the gold-standard comparator. The cutoff score with the best diagnostic accuracy for a Major Depressive Episode was 10, which had a sensitivity of 91% (95% CI, 80 to 97) and specificity of 88% (95% CI, 83 to 92). In addition, the positive and negative likelihood ratios were respectively 7.45 (95% CI, 7.23 to 7.66) and 0.10 (95% CI, 0.097 to 0.103) [2]. Furthermore, in this study, mean QIDS-SR₁₆ scores were not statistically different based on CKD stages. In order to best capture patients at high risk for MDD, a cutoff of ≥ 11 is being used for screening.

Intervention

Participants are randomly assigned to receive either sertraline at an initial dose of 50 mg once daily or matching placebo in a 1:1 ratio, stratified by CKD stage and study site. To minimize imbalance in treatment allocation and to maximize power, blocked randomization, using a computerized random number generator, will be used to create a randomization list

for each stage/site strata. We chose pharmacological treatment as an intervention for our study as non-pharmacological treatments of depression that were previously explored in dialysis patients, such as psychotherapy, exercise therapy, and cognitive behavioral therapy, have had variable efficacy [40–41], and such approaches may challenge providers given the organization and structure of CKD and ESRD care in most countries, such as insufficient resources available for and limited recognition of the significance of providing psychosocial support [42]. Further, pharmacological treatment of the acute phase of MDD can easily be done because CKD patients who require frequent clinic visits for the management of CKD may be more reluctant to spend additional time at therapy sessions. Among the various available antidepressant medications, we chose the SSRI sertraline as the antidepressant for our study.

Rationale for sertraline—Sertraline was chosen because it is metabolized by the liver; its active metabolite, *N*-desmethylsertraline, is further metabolized to an inactive form before being renally excreted [42]; and was shown to be safe in patients with cardiovascular disease in the Sertraline AntiDepressant Heart Attack Randomized (SADHART) Trial [34, 43]. Furthermore, it is available in the generic form and is easily accessible. Other antidepressants were rejected due to undesirable side effects [28, 42]: a) Other SSRIs—citalopram is not recommended for patients with advanced renal failure (GFR <20mL/min/1.73m²) due to its pharmacologically active metabolite; fluoxetine has a very long half-life; and dose reduction is advised for paroxetine use in CKD; b) Tricyclic and tetracyclic antidepressants prolong QTc and increase the risk of cardiac arrhythmias and orthostatic hypotension; c) Monoamine oxidase inhibitors have a poor safety profile and risk of drug-drug interactions; and, d) Serotonin-norepinephrine reuptake inhibitors, serotonin modulators and dopamine-norepinephrine reuptake inhibitors have toxic metabolites which may accumulate in predialysis CKD patients.

Initiation of dosing for sertraline is recommended at 50 mg/d as a single dose. During the titration phase of study drug, visits are performed every 2 weeks for 6 weeks; the dose may be escalated by 50 mg at each 2-week interval to a maximum of 200 mg daily at week 6. Dose escalation is based on “measurement-based care” [44–46] and involves the measurement of depressive symptoms by the QIDS-SR₁₆ [37] and side effects by the Frequency, Intensity and Burden of Side Effects Rating scale (FIBSER) [47]. Participants are also asked to rate if they believe the side effect they are reporting is due to study medication or not. If intolerable side effects occur, the dose is decreased by 50 mg per day. If side effects are deemed to preclude dose increases, the highest tolerable dose is used. Otherwise, the dose is increased as described.

No further dose escalations are permitted after 6 weeks, with follow-up visits occurring at weeks 9 and 12. A substantial portion of participants who achieved response or remission did so after 8 weeks of SSRI treatment in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, the largest “real-world” study of non-psychotic major depression [45–46]. Given that dosage escalation occurs for the first 6 weeks, treatment duration of 12 weeks was chosen to allow sufficient time for response while simultaneously minimizing loss to follow-up.

Washout Period

At 12 weeks, study drug is tapered at the rate of 50 mg per week (Washout Period, Period D). The rationale for tapering is to avoid potential withdrawal symptoms with abrupt discontinuation of sertraline, such as dysphoria, irritability, dizziness, sensory disturbances, anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, and seizures [48]. Further, continuation of study drug in those who respond to treatment would

not be easily accomplished as unblinding would occur for such participants at the end of 12 weeks, and we intend to keep the trial double-blinded until all participants complete the study. Since placebo may also result in improvement of symptoms and the study is to remain double-blinded, it would not be known whether the patient who is responding is on placebo or sertraline. Therefore, all participants go through a washout period where study drug is withdrawn and then get reassessed for depression. Subsequently, participants return 2 weeks after stopping all study medication for reassessment of depressive symptoms. If depression persists, the patient is started on unblinded antidepressant medication or referred to Mental Health or Primary Care provider for further management of depression, based on patient preference.

Primary Outcome

The *primary outcome* measure is the change from baseline in depression symptom severity in the sertraline- as compared with the placebo-treated group ascertained by the 16-item Quick Inventory of Depressive Symptomatology-Clinician Rated (QIDS-C₁₆) scale (Table 2). This scale is administered by trained personnel, blinded to both treatment assignment and to measurement-based care for each participant. The QIDS-C₁₆ assesses the DSM IV-based 9 criterion symptom domains of major depression and is sensitive to detecting changes in depression severity [36]. Scores range from 0 to 27, with higher scores indicating a greater severity of depressive symptoms.

Secondary Outcomes

Secondary outcome measures include other efficacy, QOL, safety, and exploratory endpoints. *Secondary efficacy endpoints* are response to treatment (defined as a decline of 50% in the baseline QIDS-C₁₆ score) and remission of depression (defined as QIDS-C₁₆ score ≤ 5). *QOL endpoints* include assessment of overall function by the Work and Social Adjustment Scale (WSAS) and assessment of QOL by the Kidney Disease QOL survey (KDQOL-SF 1.3). The WSAS scale is a 5-item self-report Likert scale that assesses ability to work and maintain close relationships [49–50]. The KDQOL contains 8 generic subscales from the Medical Outcomes Study (SF-36) and 12 kidney disease-specific subscales [51].

The primary *safety and tolerability endpoint* is the proportion in each group experiencing serious adverse events (SAEs), including death, dialysis initiation, hospitalizations, or any bleeding episodes requiring blood transfusion. Additional safety and tolerability endpoints are: 1) type and severity of side effects reported on the Systemic Assessment for Treatment Emergent Effects scale (SAFTEE) [52]; 2) proportion in each group with side effects reported on the FIBSER [47]; 3) reduction in platelet function (platelet aggregation and activation) from baseline, and whether this reduction correlates with higher plasma sertraline levels.

Rationale for platelet function—Enhanced platelet activation is a potential mechanism leading to cardiac events in those with acute coronary syndrome and depression [20]. Data suggest that SSRIs may produce reductions in serotonin-mediated platelet aggregation [20]. Plasma levels of both sertraline and its active metabolite *N*-desmethysertraline showed negative correlations with platelet-activation markers such as platelet factor 4, β -thromboglobulin, and P-selectin in SADHART [53]. Therefore, platelet inhibition by SSRIs may represent an independent mechanism for the benefit of these drugs beyond their effects on depression in patients at risk for cardiovascular events, such as those with CKD. Alternatively, increased risk of bleeding reported with SSRIs may assuage these anti-platelet benefits in those with advanced CKD [54].

Exploratory aims will investigate potential mechanisms by which sertraline may affect outcomes. The following will be evaluated: 1) nutritional status, as measured by percent of standard body weight (SBW), albumin, prealbumin, and normalized protein nitrogen appearance (nPNA); 2) medication adherence using the Morisky Self-Reported Medication-Taking scale [55]; 3) markers of inflammation (high sensitivity C-reactive protein and Interleukin 6) and 4) cognitive function as assessed by *Continuous Performance Test*, (measures sustained attention); *Trail Making Test* (measures psychomotor speed and attention); *Stroop Color and Word* (measures attention response inhibition); *Controlled Oral Word Association* (test of verbal fluency); and *Rey Auditory Verbal Learning* (for short-term verbal learning and memory). Data will also be collected on death, hospitalizations, and dialysis initiation at 6 and 12 months after randomization, which will be used for power calculations to determine the feasibility of conducting a large-scale trial to investigate whether treatment of depression improves outcomes in CKD.

Rationale for exploratory aims—Percent of standard body weight is correlated with survival and recommended as a nutritional performance measure by the Kidney Disease Outcomes Quality Initiative in predialysis CKD patients. Prealbumin and albumin are indicators of visceral protein mass and have been extensively used in persons with and without CKD to assess nutritional status [56]. Deterioration in lean body mass and nutritional status occurs in patients with advanced CKD, which increases mortality [57]. Depressive symptoms are associated with lower serum albumin as well as non-adherence to diet and medications [21–23]. CAST is designed to explore the effect of sertraline treatment on nutritional status markers and adherence. In addition, depression may result in upregulation of inflammatory markers such as IL-6, and given the activated inflammatory state in CKD, the relationship between depression and inflammation will be further explored [4]. Finally, both CKD patients [18] and those with MDD [17] suffer from cognitive impairment. Relatively few studies have suggested that antidepressant medications may improve cognitive functioning in patients with MDD [17]. We aim to assess these outcomes.

Data Collection and Measurements

Demographic and clinical variables are collected from electronic medical records at screening and confirmed with the participant. A brief physical examination is performed at each visit (Table 3). The primary outcome is assessed by the QIDS-C₁₆ as a repeated measure at randomization and at weeks 2, 4, 6, 9 and 12. At each visit, concomitant medications are assessed and adherence to study drug is monitored by pill count. Adverse events and tolerability are captured at each visit for the performance of measurement-based care and dose escalation. Cognitive function is tested at randomization and at the end of the randomization period (week 12). QOL measures are assessed at randomization, week 6 and week 12.

Blood and 24h urine samples are obtained at randomization and at week 12. Urinary creatinine and urea nitrogen are measured in the 24h urine to calculate nPNA as a measure of nutritional status. Whole blood platelet aggregation induced by 2 µg/ml collagen, 10 and 20 µM ADP, and 0.5 and 0.25 mM arachidonic acid is tested by ex vivo whole blood impedance platelet aggregometry via a Chrono-log aggregometer [58]. ATP secretion is tested with arachidonic acid, collagen and thrombin. Blood is analyzed within 4 hours of collection at the same reference laboratory at UTSW. Platelet factor 4 and β-thromboglobulin plasma levels will be tested using ELISA on samples stored at –70 C. Plasma sertraline and N-desmethysertraline levels are quantified at week 12 by using high-performance liquid chromatography with fluorescence detection (Mayo Medical Laboratories, Rochester, MN). C-reactive protein is tested using a high-sensitivity assay

(Quest Diagnostics, Irving, TX), and IL-6 by a highly sensitive ELISA (Quest Diagnostics, San Juan Capistrano, CA).

Statistical Analyses

Primary Outcome—All analyses will use the “intent-to-treat” sample of all available data from all randomized participants. QIDS-C₁₆ scores will be compared between treatment groups using a repeated-measures random-regression model with a random intercept term and time (visit weeks) as the within-participants factor and treatment group as the between-participants factor. The use of repeated-measures analysis provides more power to detect a difference and allows the best assessment of the primary outcome if there are drop-outs due to nonadherence or intolerability of the study medication [59]. The hypothesis will be tested by the significance of the treatment group by time interaction effect or the treatment group main effect. The baseline QIDS-C₁₆ will be a covariate along with site and demographic and clinical variables if they significantly improve the model fit.

Although every effort will be made to prevent dropouts, this analysis will allow for inclusion of those with missing data. Sensitivity analyses based on pattern mixture models will investigate the consequences of missing data. If the missing data conforms to the same pattern as the observed data (i.e., missing at random), then the random regression analysis will provide unbiased results and no imputation or other adjustment for missing data is required. If the data are missing not at random, the random regression model will yield biased results. However, to correct for the bias would require making strong and unverifiable assumptions about the missing data process. Instead, pattern mixture models will be used to impute missing data under a variety of assumptions about the missing data process in order to determine how sensitive the final results may be to missing data [60].

Secondary Outcomes—Each participant will be classified at each visit by response status (decline of 50% in the baseline QIDS-C₁₆ score) and remission status (QIDS-C₁₆ score of 5). A generalized linear mixed model (GLMM) will be employed using the same terms as described above. The changes in overall function and QOL will also be compared between groups using the random regression analyses described.

Safety Endpoints—The proportion of participants experiencing a SAE and also each type of side effect on the SAFTEE will be compared between groups using Chi-square tests. Presence or absence of a SAE will be assessed using logistic regression, with treatment group and appropriate clinical factors as covariates. The maximum SAFTEE global assessment of side effects (first item, 0–4 scale) will be analyzed using ordinal logistic regression, with treatment group and appropriate clinical factors as covariates. Presence or absence of side effects at each visit (as determined by the first item of the FIBSER) will be analyzed using a GLMM as described.

For platelet function, change from baseline will be compared between groups using a Student’s t-test or Mann-Whitney test as appropriate. The association of platelet aggregability and sertraline/*N*-desmethysertraline levels with bleeding episodes will be tested using logistic regression. Covariates will include hemoglobin, platelet count, eGFR, and concomitant therapy with antiplatelet agents. Spearman and Pearson correlations will identify a possible negative correlation between platelet function and sertraline/*N*-desmethysertraline.

Exploratory Analyses—Paired t-tests will investigate whether %SBW, prealbumin, albumin, nPNA, CRP and IL-6 at week 12 are reduced from baseline, while student’s t-tests will be used to test for between group changes from baseline. The cognitive function

composite score at 12 weeks will be compared between groups using ANCOVA with the baseline score as a covariate.

Protection of Human Participants

The study was approved by Institutional Review Boards (IRB) at all study sites. Participants are enrolled after signing informed consent. A centralized and independent Data and Safety Monitoring Board (DSMB) provides oversight and monitoring to ensure the safety of participants and the validity and integrity of the trial. All SAEs are reported to the IRB and DSMB. Participation in the study is terminated if the participant encounters any of the following stopping points: 1) any adverse event attributed to study drug, such as bleeding requiring hospitalization, that would obviate the continuation of study drug; or intolerable side effects despite decreasing the dose to a minimum, and the participant decides to withdraw; 2) development of suicidal intent; 3) pregnancy; 4) the participant is unwilling or unable to continue with study procedures; 5) recommendation by the DSMB. An objective scale to measure suicidal ideation is administered to all participants at each visit that formally assesses suicide risk. Participants at risk for suicide based on their responses to the questions are identified and further queried while they are present at that visit. If a participant is discovered to have acute suicidal intent (that is, has a stated plan or needs inpatient care), specific referral actions are followed to ensure patient safety.

Estimation of Power and Sample Size

Based on the primary hypothesis, the relevant effect size was chosen to be the standardized difference between groups in change from baseline to exit in the QIDS-C₁₆ score, and power to be based on t-test comparison of the difference. No prior studies are available on which to base an estimate of this effect size in predialysis CKD patients. Therefore, the mean difference between groups was chosen to be the smallest clinically meaningful difference of 2 points on the QIDS-C₁₆. The standard deviation of the mean difference was chosen to be 4 points based on our pilot study, in which 15 participants with CKD and a current MDD episode started on a SSRI experienced a mean drop in QIDS score of 5.6 ± 4.1 . A difference of 2 ± 4 gives an effect size of 0.5. A t-test will have 80% power to detect a 0.5 effect size (assuming a two-sided- α of 0.05) with a sample of 128 participants or 64 per group. If the standard deviation turns out to be larger, for example 5 points, then an effect size of 0.4 will require a sample size of 200 or 100 per group. We took a conservative approach by proposing to randomize 200 participants.

Discussion

Major depression is an important and previously unappreciated common diagnosis that is independently associated with poor outcomes in CKD patients. We and others have reported that only a minority of CKD patients with depression are treated with antidepressant medications [25–26, 34]. Reasons for low treatment rates include a lack of well-controlled and adequately powered studies that clearly support or refute the efficacy and safety of antidepressant medications in CKD. We comprehensively reviewed the limited data that does exist about the use of antidepressant medications in CKD and ESRD, and unfortunately it is fraught with limitations, including selection bias, lack of placebo control, and small sample sizes [42]. CAST is a double-blind, placebo-controlled, randomized trial to assess pharmacological treatment of depression with a SSRI in CKD patients. It is unique and innovative in that we will also explore potentially modifiable mechanisms by which depression may lead to poor outcomes.

The SADHART study showed not only improvement in depression but also a trend towards better cardiovascular outcomes in patients with acute coronary syndrome treated with

sertraline as compared with placebo [34]. Although a large proportion of patients with CKD are affected with coronary artery disease, the results of SADHART cannot be reliably extrapolated to those with CKD for 2 reasons. First, this study excluded patients with moderate-to-advanced CKD, precisely those at higher risk for both depression and cardiovascular events. Second, other data suggest that depression in patients with chronic medical conditions may not respond to antidepressant medications as it does in those without chronic disease. For example, 2 depression treatment trials, one in patients with asthma and the other in patients with congestive heart failure (CHF), revealed that as compared with placebo, treatment with citalopram in asthma [61] and sertraline in CHF [62] did not provide greater reduction in depression. CAST will evaluate improvement in depression severity, overall function and QOL when CKD stage 3–5 patients are treated with sertraline vs. placebo. Importantly, it will generate preliminary data for power calculations needed for future studies investigating whether treatment of depression with an SSRI will improve cardiovascular outcomes in CKD patients.

Inadequate data on the safety and tolerability of antidepressant medications in CKD patients has limited its use in this high risk group, and led to possible sub-therapeutic dosing of these medications [24]. Concerns have been raised due to potential accumulation of toxic metabolites in the presence of reduced GFR and risks of drug-drug interactions due to polypharmacy in this high risk group [28]. The list of adverse events noted in the literature range from nausea and vomiting and central nervous system depression to QTc prolongation and arrhythmias [63–64]. Bleeding risk from SSRI use is well-described, which becomes clinically relevant in patients with advanced CKD due to platelet dysfunction [27, 29]. CAST will assess the safety and tolerability of sertraline in CKD patients in hopes of providing more definitive, clinically meaningful results. CAST is also designed to elucidate potential mechanisms by which MDD may mediate poor cardiovascular outcomes in CKD, and whether treatment with sertraline will ameliorate these potentially modifiable factors.

A few limitations of the study are worth mentioning. First, CAST involves predialysis CKD patients and does not include those with ESRD. However, the majority of CKD patients die from cardiovascular disease before reaching ESRD, and CKD affects a larger proportion of the U.S. population. It is also not clear how dialysis initiation may affect the presence of depression due to the loss of bodily function, loss of role at work and in family, and dependence on dialysis. Second, the trial is of short duration and will not assess long-term effects of depression treatment. However, the duration was specifically designed to minimize any adverse events while maximizing the duration of exposure to sertraline. If treatment with sertraline proves efficacious and tolerable, future trials can investigate whether such treatment will improve morbidity and mortality in predialysis CKD, and extend these findings to ESRD. Although data on the number of deaths, hospitalizations and dialysis initiations will be collected, the occurrence of such events may not be large enough during this trial to definitively inform power calculations. However, we previously reported that the rate of such events was as high as 60% during 12 months of observation in CKD patients who were diagnosed with major depression at baseline. Therefore, outcome data collected here may be informative. In addition, it is realized that analyses aimed to elucidate mechanisms by which depression may lead to adverse outcomes in CKD patients, although novel, are exploratory in nature, and that the study was not powered to definitively address these additional aims. Finally, although the exclusion of placebo-responders during the run-in period is intended to avoid randomization of those patients misclassified as having MDD, it may slightly impact generalizability. However, we will compare patients excluded vs. those included in analyses to evaluate whether they are otherwise different and would have affected generalizability.

Conclusion

The CAST study is a double-blinded, placebo-controlled, flexible-dose randomized controlled trial that will generate novel data about the safety and efficacy of SSRI antidepressant sertraline in the treatment of depression in CKD stages 3–5 patients and advance clinical practice. This trial addresses the treatment of depression, an important and previously under-appreciated and under-treated diagnosis that is associated with decreased QOL, increased hospitalization rates and poor survival in CKD patients. There is an urgent need to determine the short-term safety and efficacy of antidepressant medications in CKD patients with MDD as a first step in order to determine the feasibility of conducting a large-scale trial designed to investigate whether the treatment of depression improves outcomes in patients with CKD, a population at disproportionately increased risk for poor cardiovascular events and death.

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Figure 1.
Schematic of Chronic Kidney Disease Antidepressant Sertraline Trial (or CAST) design.

Table 1**Inclusion and Exclusion Criteria**

INCLUSION CRITERIA
Male or female adults aged 21 years or older
Pre-dialysis stages 3, 4 or 5 CKD
Current Major Depressive Disorder Episode
QIDS-C ₁₆ [/] score of 11
Able to understand and sign informed consent
EXCLUSION CRITERIA
No health care power of attorney to sign informed consent
Unwilling or unable to participate
Kidney transplant recipient
Initiated on maintenance dialysis
Significant hepatic dysfunction or liver enzymes abnormalities 3 times the upper limits of normal
Terminal chronic obstructive pulmonary disease or cancer
Recent history of active bleeding
Current use of Class I antiarrhythmics
Use of pimozone, MAO inhibitors, reserpine, guanethidine, cimetidine or methylidopa;
tricyclic antidepressants, neuroleptics or anticonvulsants (excluding gabapentin)
Use of other serotonergic drugs or supplements such as triptans, tramadol, linezolid,
tryptophan, and St. John's Wort
Ongoing use of antidepressants
Past treatment failure on sertraline
Initiation of psychotherapy for depression in the three months prior to study entry
Alcohol or substance abuse or dependence that requires acute detoxification at study entry
Present or past psychosis or Bipolar I or II disorder
Dementia or Mini Mental Status Examination score of < 23
Suicidal ideation
Pregnancy, lactation and women of childbearing potential not using adequate contraception

[/] QIDS-C₁₆: Quick Inventory of Depressive Symptomatology-Clinician Rated scale

Table 2**Outcome Measures**

Primary Outcome Variable	
QIDS-C ₁₆ ¹ score	Measures change in depression severity
Secondary Outcome Variables	
QIDS-C ₁₆ score	Assesses depression response to treatment
50% decline	
QIDS-C ₁₆ score ≥ 5	Assesses remission of depression
WSAS ²	Assesses overall function
KDQOL-SF 1.3 ³	Measures quality of life
Safety End Points	
SAE ⁴	Instances of hospitalizations, dialysis initiation, or death
FIBSER ⁵	Frequency of any side effects
SAFTEE ⁶	Types and severity of side effects
Platelet aggregation and activation markers	Measures platelet aggregability by whole blood impedance platelet aggregometry, and Platelet Factor 4 and β -thromboglobulin levels by ELISA
Plasma sertraline and N-desmethylertraline	Measures blood levels of study drug and its active metabolite
Exploratory Variables	
Nutritional markers	Percent standard body weight, albumin, prealbumin, normalized protein nitrogen appearance
Markers of Inflammation	Highly sensitive C-reactive protein and Interleukin-6
Cognitive function measures	Continuous Performance Test, Stroop color and Word, Trail Making Test, Controlled Oral Word Association, and Rey Auditory Verbal Learning
Morisky Scale	Measures medication self-reported adherence

¹QIDS-C₁₆: Quick Inventory of Depressive Symptomatology-Clinician Rated scale²WSAS: Work and Social Adjustment Scale³KDQOL-SF 1.3: Kidney Disease Quality of Life Survey Version 1.3⁴SAE: Serious adverse events⁵FIBSER: Frequency, Intensity and Burden of Side Effects Rating Scale⁶SAFTEE: Systemic Assessment for Treatment Emergent Effects Scale

Table 3

Variables and Measurements

Measurements	Time Performed
Depression Measures	
MINI	Screening visit
QIDS-C ₁₆ (blind assessor)	Randomization and weeks 2, 4, 6, 9, 12
QIDS-SR ₁₆ (self-reported)	Screening, randomization, and weeks 2, 4, 6, 9, 12, and end of washout period
Quality of Life Measures	
WSAS	Randomization and weeks 6 and 12
KDQOL-SF 1.3	Randomization and weeks 6 and 12
Safety and Tolerability Measures	
SAFTEE	Weeks 2, 4, 6, 9, 12
FIBSER	Weeks 2, 4, 6, 9, 12
SAE	Randomization, weeks 2, 4, 6, 9, 12, end of washout, 6 and 12 months
Cognitive Function Measures	
Mini Mental State Examination	Screening, randomization and week 12
Continuous Performance Test	Randomization and week 12
Stroop Color and Word	
Trail Making Test	
Controlled Oral Word Association	
Rey Auditory Verbal Learning	
Medication Adherence Measures	
Pill Count	Randomization, weeks 2, 4, 6, 9, 12, and end of washout period
Morisky Self-Reported Scale	Randomization, weeks 2, 4, 6, 9, and 12
Demographics and Co-morbidity Measures	
Demographics, past medical history,	Screening
Charlson Co-morbidity Scale	Screening
Concomitant Medication Use	Screening, randomization, and weeks 2, 4, 6, 9, 12, and end of washout period
Physical Examination	
Blood pressure, heart rate, weight, and general physical exam	Screening, randomization, and weeks 2, 4, 6, 9, 12, and end of washout period
Hip and waist circumference	Randomization and week 12
Blood Tests	
Comprehensive metabolic panel	Randomization and week 12
Complete blood count	
Glycosylated hemoglobin	
Lipid panel	
Uric Acid	
Phosphorus	

Measurements	Time Performed
Prealbumin	
25 α -hydroxy vitamin D	
Intact parathyroid hormone	
Prothrombin Time	
Partial Thromboplastin Time	
Interlukin-6 Level	
Highly sensitive C-Reactive Protein	
Sertraline and N-desmethylsertraline	Visit 6
Whole Blood Platelet Aggregation	Randomization and week 12
Platelet Factor 4 and β -thromboglobulin	Randomization and week 12
Urine Tests	
Urine microalbumin-to-creatinine ratio	Randomization and week 12
24-hour urine volume, total protein, creatinine, urea nitrogen	Randomization and week 12