MEDIATING MEDICATION ADHERENCE IN RENAL TRANSPLANT RECIPIENTS: THE ROLES OF DEPRESSIVE SYMPTOMS AND COGNITION.

by

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ABSTRACT

Cognitive abilities and depressive symptoms have been previously linked to medication adherence following renal transplantation. To further elucidate these relationships, we assessed two potential mediational models: 1) depressive symptoms mediate the relationship between cognition and adherence; and 2) cognition mediates the relationship between depressive symptoms and adherence. Renal transplant recipients (*N*=101) completed a cognitive battery, the CES-D, and the Transplant Effects Questionnaire (TxEQ). Using a product-of-coefficients method, we compared the proposed models. Weaker cognitive performance was correlated with reduced adherence. Additionally, depressive symptoms (CES-D total score) and the CES-D Somatic Symptoms subscale, each partially mediated the relationship between cognition (PCA derived composite score) and TxEQ adherence scores. None of the other CES-D subscales were significant mediators. Conversely, cognition did not mediate the relationship between depressive symptoms and adherence. The CES-D Somatic Symptoms sub-scale (five questions) may have important utility as a predictor of medication adherence in renal transplant patients.

Keywords: kidney transplant; neuropsychological; medication adherence; depression; cognition; mediation.

DEDICATION

To Silvia, who has been patient throughout all of my work on this project.

To my Mother for her unending support and belief in my abilities.

Finally, to my Grandfather for all of the inspiration he has given me.

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INTRODUCTION

Chronic Kidney Disease (CKD) is a relatively common disorder among middle aged and older adults. CKD is a disorder in which the kidneys gradually cease proper functioning, and consequently, renal replacement therapy or renal transplant is eventually required (Gonzalez-Perez, Stearns, & Wordsworth, 2005). The incidence of CKD increased from approximately 119 per million people in Canada in 1996, to about 154 affected per million in Canada in 2004 (a 29% increase), while prevalence statistics indicate that at the end of 2005 over 32,000 Canadians had active diagnoses of this disorder (CIHI, 2008). Almost 1000 patients received kidney transplants in this country in 2005, with a remaining 3000 on transplant waitlists (CORR/CIHI, 2008). Renal replacement therapy, usually in the form of hemodialysis, is the most common treatment for this illness. Transplant, however, is the preferred treatment, as it can result in the return of normal kidney function for the patient (Gonzalez-Perez et al., 2005).

Although transplant may allow for a return to normal kidney function, there is evidence that not all symptoms and difficulties associated with CKD dissipate in relation. Recent studies indicate that cognitive dysfunction following successful renal transplantation is similar to that seen in CKD patients prior to renal failure (Gelb, Shapiro, Hill & Thornton, 2008), indicating that some longstanding cognitive weaknesses may persist. Depression is also commonly reported in CKD patients both prior to and following transplant; 15-30% of end stage renal

disease patients meet mood disorder criteria, while many more show symptoms of depression. While some research indicates a decrease in rates of depression following transplant, other studies indicate similar levels of depression post transplant (Christensen, Ehlers, Raichle, Bertolatus, & Lawton, 2000). The fact that decreased cognitive functioning and depressive symptoms remain following successful kidney transplant could have vast implications for quality of life and illness management for those receiving transplants. Nonetheless, the implications of these difficulties for 'real-world' functioning in this population have rarely been examined.

One important functional outcome that has received considerable attention in the transplant literature is medication adherence. Despite the possible dangers of failing to adhere to anti-rejection medications, studies have reported high rates of non-adherence following renal transplantation. For example, a study by Frazier, Davis-Ali, and Dahl (1994) indicates that approximately half of renal transplant recipients report some degree of non-compliance. To date, risk factors identified for non-compliance include being unmarried, female, young, re-transplanted, living alone, reporting an external locus of control, a lower belief of need for immunosuppressive medications, illegal drug dependency, and/or lower income (Denhaerynck et al., 2005; Frazier et al., 1994). Importantly, non-adherence to medications in this population is related to increases in graft rejection rates (Morrissey et al., 2005). A recent study specifically indicated that patients who are not adherent to their medications have a sevenfold greater chance of graft rejection than those who are (Butler, Roderick, Mullee, Mason, &

Peveler, 2004). Many issues exist in the assessment of medication adherence, which may also lead to confusion and discrepancies in results between studies using different techniques (Appendix A). However, given the high rates and potentially devastating consequences of medication non-compliance for these patients, it is important that the mechanisms underlying difficulties with medication adherence be understood and addressed in this population.

One potentially important mechanism underlying non-adherence in this population is reduced cognitive performance. Recent studies from our lab indicate that reductions in memory and executive functioning are common in adults with CKD, with decreases in cognition seen at various stages of the disorder (Thornton, Shapiro, Deria, Gelb, & Hill, 2007). Studies also indicate that CKD patients may be at increased risk for cognitive difficulties relatively early in the course of the disease, even before renal failure occurs (Kurella, Chertow, Luan, & Yaffe, 2004; Thornton et al., 2007). Although one may presume that if transplant negates the need for hemodialysis in CKD patients, and allows for normal kidney function, cognition should also return to normal, recent studies indicate that some degree of cognitive dysfunction persists following transplantation (Gelb, Shapiro, Hill, & Thornton, 2008). Previous research indicates that there may be some improvement in attention and verbal memory following renal transplant but not in other cognitive domains, such as executive functioning (Griva et al., 2004). More recently, we have reported that both CKD and renal transplant patients demonstrate lower verbal memory and inhibition ability than control participants (Gelb et al., 2008). It is thought that cognitive

difficulties in these patients may be related to cerebrovascular insufficiencies, which are commonly reported in CKD and in dialysis patients and which may not be reversed with transplantation (Pereira, Weiner, Scott, & Sarnak, 2005; see Appendix B).

Another variable potentially important to medication adherence is affect; symptoms of depression are actually quite prevalent in persons with CKD and those post-transplant (Christensen et al., 2000). In fact, Kimmel, Weihs, and Peterson (1993) report that depression is the most common psychological disorder among end stage renal disease patients. Although not as thoroughly examined, previous studies, using two different self-report measures of depressive symptoms, indicate that pre-dialysis CKD participants have higher ratings of depressive symptoms than controls (Thornton et al., 2007), and similar ratings to those of participants receiving dialysis (Shidler, Peterson, & Kimmel, 1998). Another study examining transplant and transplant waitlist patients indicates that depression may lead to a decrease in self-esteem, further leading to treatment non-compliance and affecting rates of patient survival. This same study found that 7.4% of renal transplant patients were severely depressed, and almost 15% were mildly depressed (Akman, Özdemir, Sezer, Miçozkaioğlu, & Haberal, 2004). In comparison to data from the National Institute for Mental health indicating that about 9.5% of the general US population suffers from any mood disorder (NIMH, 2009), it seems renal transplant patients are at greater risk of depression. Other research has indicated that those transplant recipients who report more depression, higher stress, and who believe that outcomes are

beyond their control, are less compliant with follow-up procedures and treatments (Frazier et al., 1994). In addition, studies indicate that specific aspects of depression and mood are related to adherence in other patient groups. A study undertaken with HIV+ patients indicates that increased positive affect is related to increased adherence (Bogart, Gray-Bernhardt, Catz, Hartmann, & Otto-Salaj, 2002). Recent research also indicates that somatic symptoms of depression are especially common in patients with CKD (Pivac, Muck-Seler, Barisic, Jakovljevic, & Puretic, 2001). As previous research indicates similarities in depression between CKD and transplant patients, somatic symptoms may play an important role in the lives of transplant patients as well.

Another important question involves the association between cognition and depression. Various studies indicate an association between poor performance on cognitive tests and a diagnosis of major depression in other populations. Chamelian and Feinstein (2006) looked at the relationship between subjective cognitive complaints, scores on objective cognitive measures, and diagnosis of depression in traumatic brain injury (TBI) patients. Just under 20% of patients reporting cognitive symptoms met the criteria for major depression, while none of those not reporting cognitive symptoms met these criteria. Patients who report cognitive symptoms also score significantly lower on various memory and executive functioning tasks compared to participants who do not report such problems. Negative relationships between performance on executive functioning tasks, and depressive symptoms are also found in CKD patients (Yount et al., 1998), and in the elderly (Kasahara et al., 2006). Some authors indicate that

depression may have a causal role in cognitive difficulties, especially in relation to memory, attention, and psychomotor speed (Gallassi, Morreale, & Pagni, 2001). It is also asserted that there are neuropathological causes of depression in addition to the possibly more recognized psychosocial causes. For instance, previous research has indicated that some cortical lesions can lead to depressed affect (Gallassi et al., 2001). Other authors indicate that some neurological disorders may concurrently cause both depressive symptoms and cognitive difficulty. These authors refer to research indicating that older adults who are depressed frequently have more severe subcortical and white matter irregularities (Comijs, Jonker, Beekman, & Deeg, 2001). On the other hand, it is also theorized that depression may occur as a reaction to cognitive difficulties (Comijs et al., 2001).

Both cognition and depression have additionally been shown to affect adherence in various illness groups, including renal transplant patients. In HIV+ populations, higher scores on neuropsychological tests predict increased medication adherence (Albert et al., 1999). Affective state is also seen to positively effect level of adherence in patients with Type 2 Diabetes (Gonzalez et al., 2008), and coronary syndromes (Rieckmann et al., 2006). As well, better cognitive functioning and lower depressive symptoms predict better scores on objective measures of treatment adherence in older adults (Mackin & Areán, 2007). Other studies indicate that increased depression is a significant predictor of non-adherence in adolescent HIV+ patients, and that better cognition predicts better adherence among older HIV patients (Hinkin et al., 2004). Recent research

also indicates that decreased everyday problem solving performance along with reports of more depressive symptoms predicts lower medication adherence in renal transplant patients (Gelb, Thornton, & Shapiro, submitted) Despite possible implications of findings linking cognition and depression for 'real-world' functioning in patients receiving kidney transplants, there is a paucity of research examining this issue with these patients. The objective of the current study was to extend previous research by examining the relationships between cognition and depressive symptoms, and to better ascertain how these may contribute to medication adherence in patients post successful renal transplant.

Toward these ends, we aimed to compare two possible relationships between cognitive abilities, depressive symptoms, and medication adherence in patients who have received kidney transplants. Two separate mediational models were examined to determine whether depressive symptoms mediate the effects of executive functioning, processing speed, and learning and memory abilities on medication adherence (i.e. ability to think influences depressive symptoms, effecting motivation to adhere to medications); or conversely, that executive functioning, processing speed, and memory mediate the relationship between depressive symptoms and adherence (i.e. depressive symptoms influence ability to think, thus effecting ability to adhere to medications). As different authors have presented theories outlining both of these potential relationships between depression and cognition (Comijs et al., 2001; Gallassi et al., 2001), the current study will hopefully offer some clarification regarding how depression and cognition relate to each other in a renal transplant population specifically, in

addition to furthering our understanding of medication adherence in this population.

Mediation analyses aim to provide information as to whether a third variable of interest acts as an intermediary between an independent and dependant variable, providing an indirect effect of the independent variable on the dependant variable. This is as opposed to moderation analyses, which indicate whether there is an interaction between the independent variable and a third variable of interest. These analyses indicate whether the presence of the third variable has an effect on the strength or direction of the relationship between the independent and dependant variables (Muller, Judd, & Yzerbyt, 2005). A third variable can provide either partial or complete mediation of the effect between an independent and dependent variable. Complete mediation occurs if the path between the independent variable no longer has any relationship with the dependant variable once the intermediary variable is also considered. Partial mediation occurs if the intermediary variable decreases the amount of variance in the dependant variable accounted for by the independent variable (but not completely to zero; MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002).

For the first mediational model to be supported (Kenny et al., 1998; MacKinnon et al., 2002), better cognitive abilities should predict decreased depressive symptoms. Additionally, increased depressive symptoms should predict worse medication adherence when cognition is accounted for. As a result, depressive symptoms may mediate the relationship between cognition and

medication adherence. For the second mediational model to be found valid, increased depressive symptoms should predict worse cognition. In addition, increased cognitive abilities should predict better medication adherence when depressive symptoms are accounted for. If this is the case, cognition may mediate the relationship between depression and medication adherence.

The second aim of this study was to examine patient endorsements on the Centre for Epidemiological Studies – Depression Scale (CES-D), to determine whether particular types of depressive symptoms may predict medication adherence over and above other aspects of depression. Recent findings from our lab indicate that renal transplant patients with a greater number of depressive symptoms also report lower levels of medication adherence (Gelb et al., submitted). In the current study, we aimed to determine the relative contributions of specific types of depressive symptoms (utilizing previously established CES-D factor scores; Radloff, 1977) in predicting medication adherence in this population. Further, we wished to ascertain whether these factors would differentially mediate the relationships between cognition and adherence.

METHODS

Participants

One hundred and fifty post renal transplant patients were recruited from the Solid Organ Transplant (SOT) Clinic at Vancouver General Hospital (VGH). Data were collected in two phases. The cognitive findings from the first phase (i.e., October of 2004 until October of 2006) have been previously reported (Gelb et al., 2008). Participants were recruited either in person at the clinic (this was only done during the initial phase of recruitment - 64 participants recruited between 2004-2006), or via correspondence sent to them (86 participants recruited 2007-2008) identifying those involved in conducting the study, and providing some specific information regarding what participation would entail, followed by a phone call reminder of the details of the study (Gelb et al., under review). The overall recruitment success rates were approximately 64%. All participants signed letters of informed consent and received $40 compensation for their time and travel expenses. Testing was conducted individually by trained examiners, took approximately 2 hours, and occurred in a quiet room. Ethics boards at both the University of British Columbia, and Simon Fraser University, as well as Vancouver Coastal Health, approved the protocol for the current study.

To be eligible to participate in this study, prospective participants needed to be capable of providing informed consent. As well, participants had to have adequate vision (i.e. a minimum of 20/50 acuity, corrected or not), adequate

hearing (corrected or not), and be free of any other sensory impairments that could interfere with testing. Participants also needed to be fluent in English, and to have an education of at least a 6th grade level to ensure adequate reading ability. Finally, stable renal functioning and successful kidney graft for at least six months prior to recruitment was required. Exclusion criteria included the diagnosis of a psychotic disorder, an acute illness that could interfere with procedures, a neurological disorder, or any other major organ failure as indicated through self-report. After recruitment, 16 participants were excluded due to poor vision, or evidence of a previous stroke, brain injury, or similar concern. An additional 7 participants were excluded because of difficulty with the English language. Thus, 127 participants met inclusion/exclusion criteria and were eligible for participation in the study.

Measures

Demographics and Clinical Variables. Demographic information including age, gender, level of education, marital status, and living situation (alone or with someone else) was collected. Information on various illness variables was also collected via self-report and (when available) from medical records. Illness variables collected include time since transplant, number of transplants received, donor type (living or cadaveric), whether patients had a history of, or were currently diagnosed, with diabetes, and laboratory results such as estimated Glomerular Filtration Rate (a measure of kidney reserve; GFR; ml/minute/1.73 m^2) and hemoglobin levels (g/L; low levels are indicative of anemia). Descriptive statistics for these variables are provided in Table 1. As well, participants were

administered the Instrumental Activities of Daily Living scale (IADL; Lawton & Brody, 1969). This scale outlines 8 different aspects of daily living and asks participants how able they are to perform them, using a hierarchical scale for each task, which is then scored dichotomously (less vs. more able to perform the task).

The Center for Epidemiological Studies Depression Scale (CES-D; Radloff, 1977) was used to measure depressive symptoms. Depressive symptoms include feelings of helplessness, guilt, fatigue, and difficulty concentrating, as well as changes in sleep patterns and appetite, among other things. Although a combination of these symptoms, if causing significant impairment in areas of social functioning, may meet the criteria for a depressive disorder, this study is not specifically concerned with comparing those with a mood disorder to those without, but rather, simply looking at levels of depressive symptoms. With this caveat in mind, however, previous work from our lab has indicated that transplant patients endorse more symptoms of depression than controls (as determined from scores of the CES-D; Gelb et al., 2008).

The CES-D is a 20-item scale with items endorsed for occurrence during the past week on a Likert-type scale of 0-3 (0 = “rarely or none of the time” to 3 = “most or all of the time;” Hann, Winter, & Jacobsen, 1999). Reliability (internal consistency) of CES-D responses is α =.85 in the general population and α =.90 in clinical populations. Responses on this assessment also have good test–retest reliability, ranging from .51 to .67 within a 2-8 week period. This measure’s concurrent validity is supported by significant high correlations with other

measures of depression, and its construct validity is seen by differences in scores reported in the general population and in clinical populations (Hann et al., 1999).

Factor analysis of this measure in various populations has shown that four separate factors contribute significantly to measurement of depression as a higher-order construct (the factors have been named *Depressed Affect, Positive Affect, Somatic and Retarded Activity*, and *Interpersonal Relationships*, respectively, allowing for 4 separate subscales within this measure; McCauley et al., 2006; Radloff, 1977)[1]. The Depressed Affect subscale includes 5 items such as "I felt depressed," measuring negative mood. The Positive Affect subscale includes 4 reverse-scored items such as "I felt I was as good as other people," measuring lack of positive affect. The Somatic and Retarded Activity subscale (5 items) measures somatic symptoms of depression (e.g. "I did not feel like eating; my appetite was poor"). Finally, the interpersonal subscale, which includes 2 items (e.g. "I felt that people dislike me,") is thought to tap interpersonal aspects of depression. A recent study examining the factor structure of the CES-D in patients with systemic sclerosis reported reliability statistics for responses on the original Radloff (1977) CES-D factors as quite good. Internal consistencies were as follows: depressed affect factor, α = 0.88; positive affect factor, 0.82; somatic

[1] Radloff (1977) presents 4 factors of the CES-D in which all items had loadings greater than .40 in all three of the participant groups tested, as well as a more inclusive set of 4 factors, in which all items had loadings of .35 or greater in at least 2 of the 3 groups tested. The factors as outlined here are the more conservative groupings in which all items had loadings greater than .40 in all groups tested. This was the factor composition chosen for use in the current study.

factor, 0.80; and interpersonal factor, 0.67 (Thombs, Hudson, Schieir, Taillefer, & Baron, 2008).

The CES-D scale is designed to screen for depression and depressive symptomology. This self-report measure has been evaluated in many populations. There is, thus, research indicating this scale's utility for use with various ethnic groups, as well as with elderly and chronically ill populations specifically, the latter being of direct relevance to the current study. Validation studies on this measure tend to show a stable 4-factor structure, as well as indicating that the CES-D has quite stable psychometric properties across groups (Verdier-Taillefer, Gourlet, Fuhrer, & Alpérovitch, 2001). Of relevance to the current project, a study by Devins and colleagues (1988), which looked at the psychometric properties of the CES-D in healthy undergraduates, persons attending family physicians, persons with progressive renal disease, persons with end-stage renal disease, and cancer patients, has indicated that total scores on this measure have fairly good reliability with each of these groups. Specifically, internal consistency ranged from .63 to .93 among these groups, test re-test reliability over a 3 month period were .61, and the measure was seen to have a similar composite of factors in these groups as have been seen in other populations (Devins et al., 1988).

The California Verbal Learning Test - Second Edition (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000) was used to assess learning and memory. Many authors agree that the ability to remember instructions given or read concerning medications or dietary regimens is an important aspect of ability to adhere to

such regimens (Gould, 1999). In this test examinees are read a list of 16 words, and immediately asked to recall as many as they can (this is done for five consecutive trials). Following a delay period, they are again asked to recall as many items as possible. Total correct responses on trials 1-5 is thought to measure verbal learning ability (Delis et al., 2000). The Long Delay Free Recall score is an estimate of a participant's ability to retain verbal information. The total score on trials 1-5 and the score on the Long Delay Free Recall measure of this test are two of the most stable on the CVLT-II, with test-retest reliabilities of r = .82 and .88, respectively. The CVLT-II also has adequate reliability and validity overall, with internal consistency estimates usually in the range of .80 or higher (Delis et al., 2000; Hubley 2004).

The Delis – Kaplan Executive Function System (D – KEFS; Delis, Kaplan, & Kramer, 2001) assesses aspects of executive functioning. We used the *Trail Making Test* subtest from this battery, which has been shown to be sensitive to executive dysfunction (Yochim, Baldo, Nelson, & Delis, 2007), as a measure of set-shifting ability. In this study, we only looked at completion time scores from the 4th trial (letter-number sequencing), which introduces the need for set shifting. We also used the D-KEFS *Color-Word Interference* subtest, which is similar to the *Stroop* task, as a measure of cognitive inhibition. Scores on the *Color-Word Interference* subtest have been seen to be sensitive and reliable measures of this construct (Jefferson, Paul, Ozonoff, & Cohen, 2006). In this study, we examined only participants' scores for completion time of trial 3 of this subtest; the trial in which inhibition is introduced.

Reliability of scores on subtests from the D-KEFS battery are comparable to that published for other neuropsychological tests, and the utility of these instruments to detect neurocognitive deficits has been demonstrated in many studies. Although there is little new validity data on these tests, studies have demonstrated that they are sensitive to executive function deficits in various clinical populations, including frontal lesion patients, epilepsy patients, and persons with mild cognitive impairments (Delis, Kramer, Kaplan, & Holdnack, 2004; McDonald, Delis, Norman, Tecoma, & Iragui-Madoz, 2005). Reliability (internal consistency) for scores on these measures is in the range of .57 to .81 for the Trail Making subtest, and from .62 to .86 for the Color-Word Interference task (Dugbartey, 2004).

The *Digit Symbol-coding subtest - Wechsler Adult Intelligence Scale III* (WAIS III; Wechsler, 1997) is generally considered a measure of processing speed. Participants must match a set of 9 symbols with the numbers 1 through 9 in random order as quickly as they can for 120 seconds. Test-retest reliability of scores on this subtest is above 0.80 (Hess, 2003; average reliability is 0.84 according to Wechsler, 1997), indicating relatively high reliability. This subtest is also recognized as one of the neuropsychological tasks most sensitive to neurological impairment (Crowe et al., 1999), indicating its usefulness and utility in determining cognitive impairment.

Medication Adherence was measured by self-report using the *Adherence* subscale of the *Transplant Effects Questionnaire* (TxEQ; Ziegelmann et al., 2002). The TxEQ is a measure created specifically to assess functioning in

recipients of organ transplants. This scale consists of 5 subscales: *Worry about transplant, Guilt regarding donor, Disclosure, Adherence,* and *Responsibility*. An adequate internal consistency (Cronbach's α = .79) and test-retest reliability (r = .77) have been found for responses on this measure in previous research (Ziegelmann et al., 2002).

The Adherence subscale asks about level of medication adherence, and attempts to elucidate reasons patients may not be adhering. This subscale consists of 5 items (i.e. Sometimes I think I do not need my anti-rejection medicines," "Sometimes I forget to take my anti-rejection medicines;" "I find it difficult to adjust to taking my prescribed anti-rejection drug regime;" "When I am too busy I may forget my anti-rejection medicines;" and "Sometimes I do not take my anti-rejection medicines;" Ziegelmann et al., 2002). Responses to this subscale have been shown to significantly correlate with the SF-36 (a measure of quality of life related to health; Griva et al., 2002) in renal transplant patients (Jenkinson, Stewart-Brown, Petersen & Price, 1999). Items are endorsed on a 5-point Likert type scale ("Strongly Agree" to "Strongly Disagree"), allowing for a range of 5-25 in total-score on this subscale; low scores indicate low medication adherence, and high scores indicate high adherence. Test-retest reliability for scores on the Adherence subscale is .77, over a 1-month interval; validity information is not currently available (Ziegelmann et al., 2002). A study by Frazier and colleagues (1994) has indicated that measurement of non-adherence to medication regimens is improved by assessing non-adherent behaviours previous to onset of any complications that may occur as a result of such non-

adherence, and by measuring adherence as a continuous, as opposed to dichotomous, variable. The *Adherence* subscale of the *Transplant Effects Questionnaire* (TxEQ; Ziegelmann et al., 2002) allows for implementation of both of these recommendations.

DATA ANALYSES

Missing Data & Outliers

As a method of substituting means can cause an artificial decrease in variability, possibly compromising regression analyses, we instead chose to delete data case-wise when data for a variable required for a given regression was missing. Over all, of the 127 participants from whom data were collected, data from 16 participants were excluded because of incomplete neuropsychological test scores, data from 1 participant were excluded because of a missing CES-D score, and data from 9 participants were excluded because of missing TxEQ scores. Thus, data from 101 participants were used in all regression analyses and some correlational analyses, while data from 100 participants were used in the remaining correlational analyses due to missing data from 1 additional participant (missing marital status and living situation data). Data points that were more than 3 times the inter-quartile range above or below the mean of a variable's distribution were considered outliers. These data points were changed to one unit below the lowest, and/or one unit above the highest non-outlier data point in the distribution.

Descriptive Statistics

Descriptive statistics including means, *SD's*, and percentages are reported for demographic and illness variables, and depression, in Table 1. Twenty-two percent of our sample (N = 22) had scores of 16 or greater on the CES-D, which

suggests clinically significant depressive symptomology (Radloff, 1977); this is generally in-line with previously reported rates of clinical depression in CKD and transplant samples (Akman et al., 2004; Christensen et al., 2000; Kimmel et al., 1993). In addition, Descriptive statistics for the CES-D total and subscales and for the TxEQ Adherence scale are presented in Table 2. Reliability (internal consistency) analyses for scores on the CES-D total score and each subscale score indicated relatively good reliability in our sample. Similar analyses examining each item on the TxEQ Adherence scale also indicated adequate reliability of scores on this measure (Table 2).

The descriptive analyses also indicated that the distribution of the outcome variable for our mediation analyses (TxEQ Adherence scores) was negatively skewed, which indicates an asymmetrical distribution. As the level of skew in this data did not fall within the range of 2 x the *SE* skewness (+/- .480; Tabachnick & Fidell, 2006), and as non-normality can violate the assumptions of regression, it was essential to decrease the level of skew by performing a reflected $\log_{10}$ transformation on the TxEQ Adherence variable. Conversely, positive skew was seen in the distributions of the CES-D total and subscale scores. We used square root transformations to decrease the amount of skew in each of these variables to within +/- 2 x *SE* skewness. These transformed variables were used in subsequent analyses. Table 3 shows the skew statistics before and after transformation for each variable considered.

Table 1. Demographic and Clinical Variables.

Participant Characteristics	
Age (mean ± *SD*)	50 ± 12.48
Female (*n*; %)	48 (47.5%)
Right Handedness (*n*; %)	93 (92.1%)
Ethnicity	
Caucasian (*n*; %)	*73 (72.3%)*
Asian (*n*; %)	*17 (16.8%)*
Other (*n*; %)	*11 (10.9%)*
Education (mean years ± *SD*)	13.97 ± 2.12
Depressive Symptoms (mean score ± *SD*)	10.68 ± 9.90
CES-D Score >15 (n; %)	22 (21.8%)
Hypertension (*n*; %)	79 (78.2%)
Diabetes mellitus (DM) (*n*; %)	17 (16.8%)
DM & History of DM (*n*; %)	27 (26.7%)
Coronary Artery Disease (*n*; %)	11 (10.9%)
Hypercholesterolemia (*n*; %)	36 (35.6%)
Anti-depressants (*n*; %)	14 (13.9%)
Benzodiazepines (*n*; %)	6 (5.9%)
Opiates (*n*; %)	1 (1.0%)
Anti-cholesterol agents (*n*; %)	39 (37.9%)
Anti-hypertensives (*n*; %)	74 (73.3%)
Anti-diabetic medications (*n*; %)	14 (13.9%)
Time since transplant (years; mean ± *SD*)	7.74 ± 6.10
Kidney and Pancreas transplant %	10 (9.9%)
Dialysis History %	91 (90.1%)
Hemodialysis	*50 (49.5%)*
Peritoneal Dialysis	*21 (20.8%)*
Both	*20 (19.8%)*
Time Spent on Dialysis (years; mean ± *SD*)	2.81 ± 3.04
Immunosuppressant Type	
Cyclosporine (n; %)	*20 (19.8%)*
Tacrolimus (n; %)	*71 (70.3%)*
Deceased Donor *(n; %)*	56 (55.4%)
Living Donor *(n; %)*	45 (44.6%)
# of Kidney Transplants	
1 Transplant (n; %)	87 (86.1%)
2 Transplants (n; %)	14 (13.9%)

Note: N = 101

Table 2. Internal Consistencies of Scores on Scales used in Analyses.

Scale	Cronbach's α	Min	Max	Mean	SD	Skew	Kurtosis
CES-D Full Scale	.913	.00	47.0	10.68	9.899	1.324	1.527
CES-D Depressed	.825	.00	12.00	2.25	2.985	1.447	1.406
CES-D Positive	.750	.00	11.00	2.63	2.656	.744	-.328
CES-D Somatic	.745	.00	12.00	3.22	3.045	1.252	1.217
CES-D Interpersonal	.750	.00	6.00	.55	1.091	2.429	6.843
TxEQ Adherence	.737	11	25	20.85	3.570	-.739	-.041

CES-D = Center for Epidemiological Studies Depression Scale; TxEQ = Transplant Effects Questionnaire.
N=101

Table 3. Amount of Skewness in Non-Transformed and Transformed Variables of Interest.

Variable	Untransformed Skew	Transformed Skew	2 x SE Skewness*
CES-D Total	1.326	.151	+/- .480
CES-D Depressed	1.445	.478	+/- .480
CES-D Positive	.731	-.074	+/- .480
CES-D Somatic	1.260	-.083	+/- .480
CES-D Interpersonal	2.446	1.378^	+/- .480
TxEQ Adherence	-.728	.392	+/- .480

* Range of skewness thought to be acceptable for variables used in regression analyses (+/- 2 x *SE* skewness)
^ Only the CES-D Interpersonal symptoms scale was not brought within range by transformation

Statistical Power

In consideration of statistical power, to decrease the number of cognitive variables considered in each regression equation, we used Principal Components Analysis to derive a neuropsychological composite score or scores. Given a sample size of N=101, according to Cohen (1992), using multiple regression with two or three predictor variables (1 CES-D score and 1 or 2 neuropsychological composite score(s)), our analyses are able to detect a medium effect size (f^2= .15) in both R^2 *and* ΔR^2 *respectively,* with significance level set at α = 0.05 and power set at 0.80 (Cohen, 1992).

Principal Components Analysis

We conducted a principal components analysis using the 5 neuropsychological variables of interest, the Trail Making test and Color-Word Interference test from the D-KEFS, trials 1-5 short delay and long delay free recall scores from the CVLT-II, and Digit Symbol Coding scores from the WAIS-III. This analysis indicated that one component accounting for approximately 60% of the variance in our sample was present with an Eigen value greater than 1 (*EV*= 2.97). We thus used this component score as a representation of cognitive performance in subsequent correlation and regression analyses.[2] Mean scores of this sample on individual cognitive tasks are provided in Table 4.

[2] We also looked at all of the individual traditional neuropsychological measures to determine whether these would provide better independent predictors of adherence in our sample. To examine this, we entered scores from Digit Symbol Coding, Trail making, Color-Word Interference, and the CVLT II immediate and long-delay tasks into a regression equation, with medication adherence as the outcome variable. Overall, this model was not significant (R^2 = .068, F = .235, p > .05) as well, none of these variables were seen to independently predict adherence using this analysis.

Table 4. Participants' mean performance on cognitive tests included in the principal components analysis derived cognitive composite score.[3]

Assessment	Mean (Unstandardized)	SD	Mean (Standardized)	SD
WAIS-Digit Symbol Coding	67.78	15.797	10.13	2.746
CVLT - Imm. Recall	47.670	11.3071	50.563	11.0938
CVLT - Long Delay Recall	10.699	3.4608	0.000	1.1440
Trails Number-Letter Switching	83.72	31.537	10.55	2.488
Color-Word Interference Inhibition	56.13	12.301	10.69	2.450

Note: N = 101.

Assumptions of Regression Analyses

One assumption made in regression analyses is normality of residuals, thus, we examined normal q-q plots of each variable to be entered in the regression analyses, along with normal probability plots of residuals for each regression equation, to determine whether any violations of normality were present. Normal q-q plots and normal probability plots of residuals examined did not show any severe departures from the diagonal, indicating that none of the variables or residuals had distinctly non-normal distributions. As the outcome variable and the depression symptom variables had been previously transformed to reduce skewness, near normality was expected for these variables. Another assumption is that there is a linear relationship between variables. We tested this

[3] Cognitive data from a good portion of our sample (*N* = 42) for all of these tasks except WAIS Digit Symbol Coding, has been previously compared to cognitive scores from a healthy control group (*N* = 49; Gelb et al., 2008). These comparisons indicated that transplant patients performed significantly worse than controls on learning and memory tasks (A composite score of both CVLT variables), and on one of the examined executive functioning tasks (Color-Word Interference). For learning and memory, the effect size was large (*d* = −0.74), while for both Color-Word Inhibition, and Trails Letter-Number tasks, effect sizes were medium (*d* = −0.56 and *d* = −0.44, respectively).

assumption for each analysis by plotting the standardized residuals against the standardized predicted value for each regression equation. In these plots, linearity is likely if the scatter is rectangular in shape. From examination of these plots, it was determined that linearity was indeed likely, as the scatterplots were approximately rectangular in shape. Examination of these graphs also allowed us to check that there was constant variance of error (homoscedasticity) in our data; there were no major violations of this assumption. The Durbin-Watson statistic was used to examine the independence of errors for the variables in this study. These analyses indicated no violations of this assumption. Finally, in regression analyses with more than one predictor variable, Variance Inflation Factor (*VIF*) was used to determine whether the level of multicolinearity between predictor variables was problematic. None of the VIF statistics examined indicated a high level of multicolinearity between predictor variables in an equation.

Regression and Mediation Analyses

Regression analyses were used to ensure that the minimum requirements were met for the causal steps model of mediation, in each mediational model tested (Kenny, Kashy, & Bolger, 1998; MacKinnon et al., 2002), and to obtain the statistics required to perform Sobel's test[4]. For the first mediational model, depressive symptoms were considered as the potential mediator. In testing this model, linear regression was used to determine whether cognitive abilities would

[4] Older, more stringent theories of mediation indicate that the relationship between the predictor variable and the outcome variable should also be significant, and that a test of this should be one step in a mediation analysis (Baron & Kenny, 1986). However, more recent theories indicate that this is not necessary, and that this step is not needed to establish mediation (Kenny et al., 1998; MacKinnon et al., 2002).

significantly predict depressive symptoms; this would indicate a significant path between the predictor variable and the potential mediator (the unstandardized regression coefficient from this analysis provides the *α* term in the product of coefficients assessment of mediation – Sobel's test). Next, for this same mediational model, hierarchical regression analyses were used to determine whether depressive symptoms predicted medication adherence, when cognitive ability was already considered on the first step of the regression; this would indicate that the path between the potential mediator and the outcome variable was significant (this unstandardized regression coefficient provides the *β* term required for Sobel's test). In testing the first series of mediational models the transformed CES-D total score and each of the depressed affect, positive affect, and somatic symptoms transformed subscales, were respectively considered as potential mediators in four separate models, while the neuropsychological component variable was always considered the predictor variable, and transformed TxEQ Adherence was always the outcome variable.

For the second mediational model, cognitive ability was considered as the potential mediator, and each of the CES-D scores previously used was considered as a predictor variable, while TxEQ score was still considered the outcome variable. To test this model, linear regression was used to determine whether depressive symptoms would significantly predict cognitive ability; this would indicate a significant path between the predictor variable and the potential mediator (*α* term for Sobel's test). Next, hierarchical regression analyses determined whether cognition predicted medication adherence, when depression

was already considered on the first step of the regression; this would indicate that the path between the potential mediator and the outcome variable was significant (the β term required). SPSS statistical software, version 17.0 for Macintosh computer was used for all analyses conducted for the current project excluding Sobel's test (online software: http://people.ku.edu/~preacher/sobel /sobel.htm).

RESULTS

Participant Characteristics

After accounting for missing data, data from 101 renal transplant participants were used in all regression analyses, and correlational analyses for which this was possible, while data from 100 participants was included in the remaining correlational analyses. Characteristics of our sample such as previously mentioned demographic variables (e.g. age, gender, education) as well as information on ethnicity, number of transplants, time since transplant, and dialysis prior to transplant are presented in Table 1. The types of medications prescribed to members of our sample often included those prescribed for treatment of other illnesses in addition to the immunosupressants prescribed in relation to their transplants. Medications included those for high cholesterol, hypertension, and diabetes, among other things (also reported in Table 1). Performance on the IADL indicated that all participants reported functional independence, obtaining scores between 6 and 8 out of a possible total of 8 (M = 7.94; SD = 0.31).

Correlational analyses

Prior to conducting the regression analyses, the relationships between potential independent variables and the dependent variables were assessed by conducting Pearson and point biserial correlations. Correlations of demographic variables (age, gender, and education) with the transformed TxEQ Adherence

outcome variable were non-significant, thus, demographic variables were not entered as predictors into the regression analyses. Higher transformed CES-D total score, depressed, and somatic subscale scores, and lower positive affect subscale scores were significantly related to decreased TxEQ Adherence, $p < 0.05$ (CES-D total, depressed affect, and somatic scores, $p < 0.01$). Each of the transformed CES-D total, depressed affect, positive affect, and somatic symptoms scores were, thus, separately considered in the subsequent mediational analyses. Correlations between the variables used in these analyses are displayed in Table 5 (correlations between demographic variables and both non-transformed and transformed variables of interest are provided in Appendix C for reference – Tables A, B, and C). We also examined correlations with various illness variables. Interestingly, increased adherence correlated with diagnosis of diabetes, such that patients who had a diagnosis of diabetes were more likely to adhere. There was also a correlation between higher hemoglobin and increased adherence (these correlations are displayed in Table 6).

Table 5. Correlation table for all variables considered in analyses.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1. Age	--														
2. Gender	-.040	--													
3. Education	-.078	-.109	--												
4. CES-D Total (transformed)	-.061	-.143	-.098	--											
5. CES-D Depressed (trans)	-.138	-.031	.006	.807**	--										
6. CES-D Positive (trans)	-.062	-.193*	-.049	.768**	.517**	--									
7. CES-D Somatic (trans)	-.031	-.152	-.194*	.848**	.588**	.502**	--								
8. CES-D IP (trans)	-.103	-.156	.067	.561**	.470**	.336**	.428**	--							
9. WAIS-Digit Symbol Coding	-.394**	.161	.145	-.276**	-.177*	-.250**	-.203*	-.095	--						
10. CVLT Immediate Recall	-.419**	.350**	.063	-.232**	-.126	-.239**	-.265**	-.067	.464**	--					
11. CVLT Long Delay Recall	-.317**	.418**	-.003	-.220*	-.101	-.229*	-.271**	-.101	.402**	.845**	--				
12. Trails Switching	.328**	.119	-.158	.286**	.242**	.236**	.167*	.074	-.554**	-.408**	-.306**	--			
13. Color-Word Inhibition	.391**	-.107	-.067	.166*	.079	.229*	.057	.040	-.595**	-.468**	-.479**	.398**	--		
14. Neuropsych Composite	-.480**	.254**	.108	-.304**	-.183*	-.306**	-.253**	-.098	.776**	.842**	.803**	-.668**	-.760**	--	
15. TxEO Adherence (trans)	-.161^{+}	.088	-.071	-.313**	-.287**^	-.208*	-.386**	-.084	.076	.145	.131	-.199*	.019	.136^{+}	--

Note: As the pattern and magnitude of association was similar for non-transformed and transformed variables, only correlations with the transformed variables considered in the analyses are displayed.

^ Correlation between non-transformed variables was sig. at the 0.05 level; correlation between the transformed variables was sig. at the 0.01 level

$^{+}$ Correlation between non-transformed variables was sig. at 0.05 level; correlation between transformed variables was non-significant

** Correlation is significant at the 0.01 level 1-tailed.

* Correlation is significant at the 0.05 level 1-tailed.

Listwise N=101

Table 6. Correlations between demographic and illness variables of interest and transformed variables included in analyses.

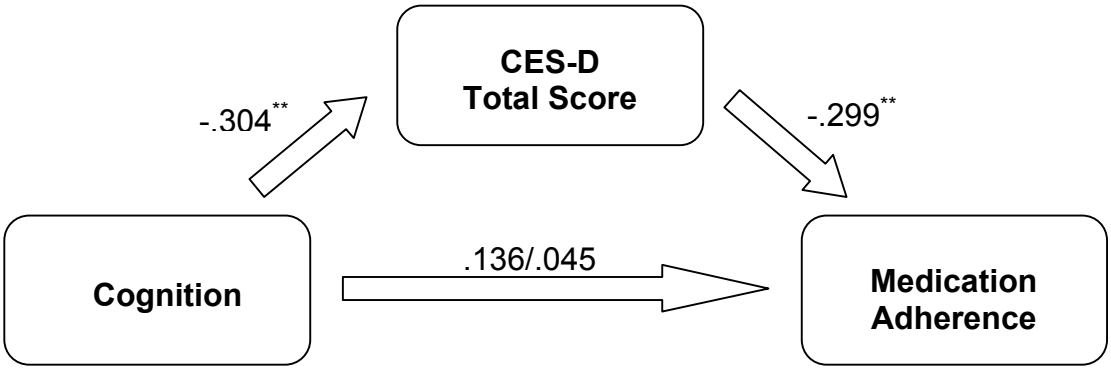
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1. Age	--															
2. Gender	-.036	--														
3. Education	-.078	-.110	--													
4. Marital Status	.132	.004	.011	--												
5. Living Situation	-.138	-.026	.032	.667**	--											
6. Time since transplant	.294**	.051	-.039	.026	-.067	--										
7. Donor type	-.215*	.053	.079	.097	.112	-.280**	--									
8. Diabetes #	.113	-.167	-.055	-.143	-.226*	-.161	-.221*	--								
9. Hemoglobin	-.010	-.368**	.006	-.046	.095	-.092	-.028	.011	--							
10. CES-D Total (trans)	-.055	-.164	-.100	-.112	-.029	-.013	-.052	.118	-.047	--						
11. CES-D Depressed (trans)	-.133	-.049	.006	-.175	-.052	-.026	-.060	.134	-.136	.801**	--					
12. CES-D Positive (trans)	-.056	-.213*	-.049	-.076	.056	.023	-.080	.072	.031	.762**	.504**	--				
13. CES-D Somatic (trans)	-.027	-.164	-.195	-.074	-.013	-.079	.052	-.001	-.062	.848**	.582**	.495**	--			
14. CES-D Interpersonal (trans)	-.097	-.176	.068	.002	-.029	.095	-.011	.089	.064	.549**	.455**	.319**	.419**	--		
15. Neuropsych Composite	-.479**	.248*	.108	.082	.172	-.074	.296**	-.185	-.021	-.321**	-.198*	-.321**	-.262**	-.111	--	
16. TxEQ Adherence (trans)	-.161	.089	-.071	-.049	-.128	-.139	.052	.205*	.169*	-.317**	-.290**	-.210*	-.387**	-.084	.137	--

**. Correlation is significant at the 0.01 level (2-tailed).
*. Correlation is significant at the 0.05 level (2-tailed).
Listwise N=100
The Diabetes variable indicates current or history of diabetes vs. no diabetes or history of diabetes.

Regression and Mediation Analyses

Regression results for all tests of the first model are included in Tables 7 through 10. In testing this model using the CES-D total score as the potential mediator, higher overall depressive symptoms predicted decreased adherence, when cognition was already accounted for (ΔR^2 = .08, $F(1, 98) = 5.44$, $p < .01$), while better performance on neuropsychological measures predicted decreased endorsements of depressive symptoms (R^2 = .09, $F(1, 99) = 10.05$, $p < .01$). As can be seen in Figure 1, addition of the CES-D total score variable partially mediated the relationship between cognition and medication adherence, as indicted by significant results using Sobel's test (Sobel's $Z = 2.18$, $p < .05$). Both the cognitive composite and depressive symptoms overall accounted for 10% of the variance in medication adherence in this sample (Table 7).

Figure 1. First mediation model with CES-D Total Score as the mediating variable.

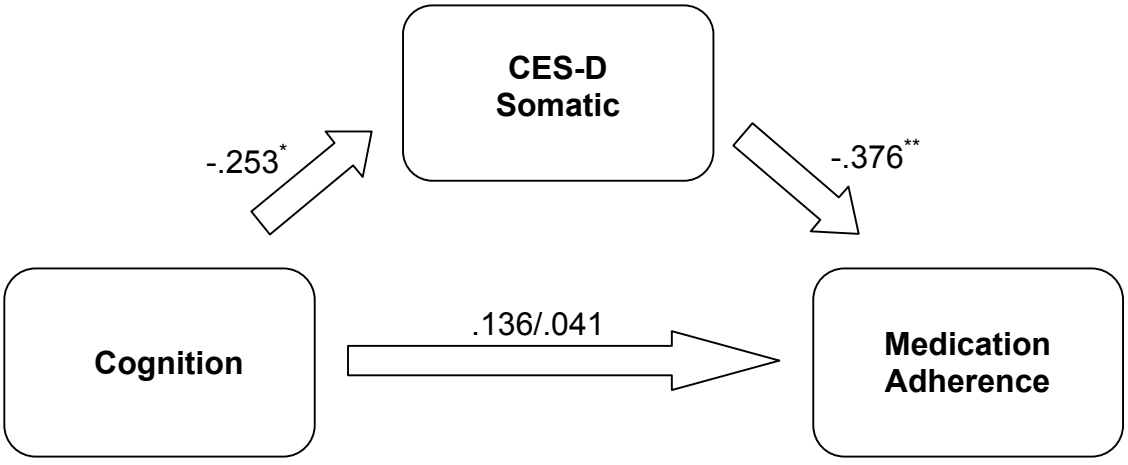


Sobel's $Z = 2.18$, $p < .05$

Note: numbers in the diagram reflect standardized regression coefficients; * p< .05, ** p < .01; standardized coefficient after the / indicates weight after inclusion of the specified mediator.

In examination of somatic symptoms as the potential mediator, greater somatic symptoms predicted decreases in adherence with cognition accounted for in the model (ΔR^2 = .13, F(1, 98)= 8.69, p < .001). As well, better cognitive scores predicted decreased somatic symptoms (R^2 = .06, F(1, 99)= 6.77, p < .05). The CES-D somatic symptoms subscale partially mediated the relationship between cognition and adherence (Sobel's Z = 2.17, p < .05), as seen in Figure 2. Cognitive scores along with somatic symptoms of depression accounted for 15.1% of the variance in adherence to medications. Thus, this model accounted for greater variance in adherence than did the model using the CES-D total score (Table 10).

Figure 2. First mediation model with CES-D Somatic Symptoms Score as the mediating variable.



Sobel's Z = 2.17, p < .05

Note: numbers in the diagram reflect standardized regression coefficients; * p< .05, ** p < .01; standardized coefficient after the / indicates weight after inclusion of the specified mediator.

Neither depressed affect, nor positive affect was seen to mediate of the relationship between cognition and adherence in this sample. In testing the second, opposing, series of mediational models, cognition was not seen to mediate the relationships between any of the depressive symptoms variables and medication adherence, in this sample (Tables 11 through 14).

Table 7. Regression Table for Model with CES-D Total Score as the Potential Mediator.

		Step 1				Step 2			
Outcome Variable	Predictor Variable	*B*	*SE*	*β*	*t*	*B*	*SE*	*β*	*t*
Regression 1 (Linear)									
CES-D Total	NP Composite	-.475	.150	-.304	-3.170**				
	F value	10.049**							
	R^2	.092**							
Regression 2 (Hierarchical)									
TxEQ Adherence	NP Composite	.049	.036	.136	1.368	.016	.036	.045	.451
	CES-D Total					-.069	.023	-.299	-2.975**
	F value	1.870				5.435**			
	ΔF					8.851**			
	R^2	.019				.100**			
	ΔR^2					.081**			

*$p < .05$, **$p < .01$. CES-D = Center for Epidemiological Studies Depression Scale. NP = neuropsychological composite. TxEQ = Transplant Effects Questionnaire. *F*-values represent the ANOVA for the full model. ΔF indicates the contribution of the second step (i.e., the variable added in Step 2).

Table 8. Regression Table for Model with CES-D Depressed Affect Subscale as the Potential Mediator

		Step 1				Step 2			
Outcome Variable	Predictor Variable	*B*	*SE*	*β*	*t*	*B*	*SE*	*β*	*t*
Regression 1 (Linear)									
CES-D Depressed	NP Composite	-.198	.106	-.183	-1.857				
	F value	3.447							
	R^2	.034							
Regression 2 (Hierarchical)									
TxEQ Adherence	NP Composite	.049	.036	.136	1.368	.031	.035	.087	.882
	CES-D Depressed					-.090	.033	-.271	-2.761**
	F value	1.870				4.809*			
	ΔF					7.621**			
	R^2	.019				.089**			
	ΔR^2					.071**			

*$p < .05$, **$p < .01$. CES-D = Center for Epidemiological Studies Depression Scale. NP = neuropsychological composite. TxEQ = Transplant Effects Questionnaire. *F*-values represent the ANOVA for the full model. Δ*F* indicates the contribution of the second step (i.e., the variable added in Step 2).

Table 9. Regression Table for Model with CES-D Positive Affect Subscale as the Potential Mediator.

		Step 1				Step 2			
Outcome Variable	Predictor Variable	*B*	*SE*	*β*	*t*	*B*	*SE*	*β*	*t*
Regression 1 (Linear)									
CES-D Positive	NP Composite	-.314	.098	-.306	-3.193**				
	F value	10.197**							
	R^2	.093**							
Regression 2 (Hierarchical)									
TxEQ Adherence	NP Composite	.049	.036	.136	1.368	.029	.037	.080	.775
	CES-D Positive					-.064	.036	-.183	-1.772
	F value	1.870				2.525			
	ΔF					3.138			
	R^2	.019				.049			
	ΔR^2					.030			

*$p < .05$, **$p < .01$. CES-D = Center for Epidemiological Studies Depression Scale. NP = neuropsychological composite. TxEQ = Transplant Effects Questionnaire. *F*-values represent the ANOVA for the full model. Δ*F* indicates the contribution of the second step (i.e., the variable added in Step 2).

Table 10. Regression Table for Model with CES-D Somatic Subscale as the Potential Mediator.

		Step 1				Step 2			
Outcome Variable	Predictor Variable	*B*	*SE*	*β*	*t*	*B*	*SE*	*β*	*t*
Regression 1									
(Linear)									
CES-D Somatic	NP Composite	-.242	.093	-.253	-2.602*				
	F value	6.769*							
	R^2	.064*							
Regression 2									
(Hierarchical)									
TxEQ Adherence	NP Composite	.049	.036	.136	1.368	.015	.035	.041	.428
	CES-D Somatic					-.141	.036	-.376	-3.904**
	F value	1.870				8.689**			
	ΔF					15.238**			
	R^2	.019				.151**			
	ΔR^2					.132**			

*$p < .05$, **$p < .01$. CES-D = Center for Epidemiological Studies Depression Scale. NP = neuropsychological composite. TxEQ = Transplant Effects Questionnaire. *F*-values represent the ANOVA for the full model. ΔF indicates the contribution of the second step (i.e., the variable added in Step 2).

Table 11. Regression Table for Model with CES-D Total Score as IV and Neuropsychological Composite Score as Potential Mediator.

		Step 1				Step 2			
Outcome Variable	Predictor Variable	*B*	*SE*	*β*	*t*	*B*	*SE*	*β*	*t*
Regression 1									
(Linear)									
NP Composite	CES-D Total	-.194	.061	-.304	-3.170**				
	F value	10.049**							
	R^2	.092**							
Regression 2									
(Hierarchical)									
TxEQ Adherence	CES-D Total	-.072	.022	-.313	-3.279**	-.069	.023	-.299	-2.975**
	NP Composite					.016	.036	.045	.451
	F value	10.753**				5.435**			
	ΔF					.203			
	R^2	.098**				.100**			
	ΔR^2					.002			

*$p < .05$, **$p < .01$. CES-D = Center for Epidemiological Studies Depression Scale. NP = neuropsychological composite. TxEQ = Transplant Effects Questionnaire. *F*-values represent the ANOVA for the full model. ΔF indicates the contribution of the second step (i.e., the variable added in Step 2).

Table 12. Regression Table for Model with CES-D Depressed Affect Subscale as the IV and Neuropsychological Composite Score as the Potential Mediator.

		Step 1				Step 2			
Outcome Variable	Predictor Variable	*B*	*SE*	*β*	*t*	*B*	*SE*	*β*	*t*
Regression 1									
(Linear)									
NP Composite	CES-D Depressed	-.170	.092	-.183	-1.857				
	F value	3.447							
	R^2	.034							
Regression 2									
(Hierarchical)									
Adherence	CES-D Depressed	-.096	.032	-.287	-2.976**	-.090	.033	-.271	-2.761**
	NP Composite					.031	.035	.087	.882
	F value	8.858**				4.809*			
	ΔF					.778			
	R^2	.082**				.089*			
	ΔR^2					.007			

*$p < .05$, **$p < .01$. CES-D = Center for Epidemiological Studies Depression Scale. NP = neuropsychological composite. TxEQ = Transplant Effects Questionnaire. *F*-values represent the ANOVA for the full model. ΔF indicates the contribution of the second step (i.e., the variable added in Step 2).

Table 13. Regression Table for Model with CES-D Positive Affect Subscale as the IV and Neuropsychological Composite Score as the Potential Mediator.

		Step 1				Step 2			
Outcome Variable	Predictor Variable	*B*	*SE*	*β*	*t*	*B*	*SE*	*β*	*t*
Regression 1									
(Linear)									
NP Composite	CES-D Positive	-.297	.093	-.306	-3.193**				
	F value	10.197**							
	R^2	.093**							
Regression 2									
(Hierarchical)									
TxEQ Adherence	CES-D Positive	-.073	.034	-.208	-2.114*	-.064	.036	-.183	-1.772
	NP Composite					.029	.037	.080	.775
	F value	4.467*				2.525			
	ΔF					.600			
	R^2	.043*				.049			
	ΔR^2					.006			

*$p < .05$, **$p < .01$. CES-D = Center for Epidemiological Studies Depression Scale. NP = neuropsychological composite. TxEQ = Transplant Effects Questionnaire. *F*-values represent the ANOVA for the full model. ΔF indicates the contribution of the second step (i.e., the variable added in Step 2).

Table 14. Regression Table for Model with CES-D Somatic Subscale as the IV and Neuropsychological Composite Score as the Potential Mediator.

		Step 1				Step 2			
Outcome Variable	Predictor Variable	*B*	*SE*	*β*	*t*	*B*	*SE*	*β*	*t*
Regression 1 (Linear)									
NP Composite	CES-D Somatic	-.265	.102	-.253	-2.602*				
	F value	6.769*							
	R^2	.064*							
Regression 2 (Hierarchical)									
TxEQ Adherence	CES-D Somatic	-.145	.035	-.386	-4.164**	-.141	.036	-.376	-3.904**
	NP Composite					.015	.035	.041	.428
	F value	17.338**				8.689**			
	ΔF					.183			
	R^2	.149**				.151			
	ΔR^2					.002			

*$p < .05$, **$p < .01$. CES-D = Center for Epidemiological Studies Depression Scale. NP = neuropsychological composite. TxEQ = Transplant Effects Questionnaire. *F*-values represent the ANOVA for the full model. ΔF indicates the contribution of the second step (i.e., the variable added in Step 2).

Additionally, as diagnosis of diabetes and hemoglobin levels were seen to associate with adherence in this sample, we ran a hierarchical regression with these two variables on the second step, and the transformed CES-D somatic symptoms subscale, and the cognitive composite variable on the first step, to determine whether inclusion of these variables would increase the amount of variance accounted for in medication adherence. Results indicated that inclusion of all four predictors accounted for 21.8% of the variance in adherence in this sample ($R^2 = .218$, $F(2, 98) = 6.69$, $p < .001$), providing a significant increase in variance accounted for in adherence ($\Delta R^2 = .067$, $F(2, 96) = 4.129$, $p < .05$); almost 5% more than our original analyses captured (see Table 15 for regression statistics).

Table 15. Regression Table For Hierarchical Regression Examining Illness Variables, CES-D Somatic Subscale, and Neuropsych Composite Score as Predictors of TxEQ Adherence.

		Step 1				Step 2			
Outcome Variable	Predictor Variable	*B*	*SE*	*β*	*t*	*B*	*SE*	*β*	*t*
TxEQ Adherence	CES-D Somatic	-.141	.036	-.376	-3.904**	-.132	.035	-.352	-3.758**
	NP Composite	.015	.035	.041	.428	.033	.034	.092	.961
	Diabetes					.177	.075	.218	2.370*
	Hemoglobin					.004	.002	.146	1.614
	F value	8.689**				6.686**			
	R^2	.151**				.218**			
	ΔF					4.129*			
	ΔR^2					.067*			

*$p < .05$, **$p < .01$. CES-D = Center for Epidemiological Studies Depression Scale. NP = neuropsychological composite. TxEQ = Transplant Effects Questionnaire. *F*-values represent the ANOVA for the full model. ΔF indicates the contribution of the second step (i.e., the variable added in Step 2).

DISCUSSION

As in CKD, both cognitive difficulties and depressive symptoms are issues faced by many patients post renal transplant (Christensen et al., 2000; Gelb et al., 2008). These burdens likely have real-world implications for quality of life and ability to manage illness. Medication adherence is one aspect of illness management that is a problem for many renal transplant patients (Frazier et al., 1994), to which cognitive difficulties and depressive symptoms have previously been related (Gelb et al., submitted). Given this background, our current aim was to further clarify the relationships among cognition, depression, and medication adherence by examining two potential mediational models, and by examining specific types of depressive symptoms in relation to cognition and adherence in these patients.

Our results indicate that lower reported depressive symptoms overall predicted increased adherence. Endorsement of greater symptoms of depressed affect, lower positive affect, and greater somatic symptoms, respectively also predicted decreased adherence. Furthermore, we found support for the first mediational model proposed, indicating that depressive symptoms partially mediate the relationship between reduced cognition and poorer adherence in renal transplant patients.

The results of the mediational analysis indicated that increased depressive symptoms predict decreased medication adherence, a result in agreement with

previous research in type 2 diabetes and coronary illness samples (Gonzalez et al., 2008; Rieckmann et al., 2006), and furthermore, these symptoms predict adherence when cognition is taken into account. As well, cognition accounts for some of the variance in depression among these patients, which is consistent with earlier research indicating a relationship between depression and cognition in other illness populations, and the elderly (Chamelian & Feinstein, 2006; Kasahara et al., 2006; Yount et al., 1998). Depressive symptoms overall were thus seen to partially mediate the relationship between cognition and adherence. This finding is supported by, and extends, previous research relating both depression and cognition to adherence in these patients (Gelb et al., submitted). See Figure 1 for a summary of the relationships between variables in this mediational model.

In examination of our secondary aim, we further found that somatic symptoms alone partially mediate this same relationship (Figure 2). While there has been limited work to date examining the question of whether specific types of depressive symptoms may relate variably to medication adherence, somatic symptoms of depression are common in patients with CKD (Pivac et al., 2001). As rates of depression are similar before and after transplant in this patient population, it is likely that somatic symptoms carry unique importance in transplant patients as well, which may explain their specific mediational properties in the relationship between cognition and adherence.

The converse mediational model was not supported. Cognitive ability was not seen to mediate the relationship between depressive symptoms and

adherence. Better cognitive abilities were related with decreased overall depressive symptoms and somatic symptoms specifically, as well as increased positive affect. However, there was no support for a relationship between cognition and adherence when depressive symptoms were considered.

Depressive symptoms and somatic symptoms specifically, may thus be important modifiers of adherence in renal transplant patients. Results show that the CES-D total score and Somatic symptoms subscale, which contains five questions (Table 15), are each partial mediators of the relationship between cognition and medication adherence in this sample, indicating the potential usefulness of the CES-D as a brief screening measure in assessing renal transplant patients. As well, as the somatic symptoms subscale actually accounted for more of the variance in adherence than general depressive symptoms (15.1% versus 10% when considered with cognitive composite scores), it is possible that the five questions this scale asks provide pertinent information concerning the ability of renal transplant patients to adhere to their medications. It may be that somatic symptoms of depression in general make adherence to medication more onerous and difficult for patients following transplant, or it may be that the specific questions utilized by the CES-D somatic symptoms subscale tap into specific deficits common in patients post renal transplant, which may or may not be inherently related to depression. As somatic symptoms examined by the CES-D include not being able to “get going,” feelings of irritability, restless sleep, and sluggishness, it is understandable that patients

endorsing many of these symptoms may find it difficult and extremely effortful to keep up with their medication regimens.

Table 16. Items included on the Somatic Symptoms subscale of the CES-D as outlined by Radloff (1977), and as used in the current analyses.

CES-D Item Number	Item
1.	I was bothered by things that usually don't bother me.
2.	I did not feel like eating; my appetite was poor.
7.	I felt that everything I did was an effort.
11.	My sleep was restless.
20.	I could not get "going."

As somatic symptoms of depression could be similar to feelings of illness following surgery and transplant it is possible that patients may confound these feelings and sensations with those of somatic depression. However, given that the patients in our sample had maintained stable graft functioning, and were at least 6 months post transplant, post-operative residual issues are somewhat unlikely. As well, there were no significant correlations between GFR and medication adherence in this sample, indicating that kidney function was not related to level of adherence. It will, nonetheless, be important for future research to examine potential mechanisms underlying this association. One variable of interest may be hemoglobin, as in this sample higher hemoglobin levels were correlated with better adherence, indicating that anemia may be a contributing factor that prevents patients from adequately adhering to their medications.

Additionally, future research should further investigate the specific symptoms of depression that seem most related to medication adherence.

Our results also suggest a need for future research into techniques that could increase medication adherence, and thus quality of life in patients who have received kidney transplant, as well as those with other disorders. As depressive symptoms are clearly related to adherence in this patient group, it would be beneficial to examine the usefulness of different treatments for depression in enhancing medication adherence in these patients.

Risk factors for non-adherence in renal transplant patients examined in previous studies, which include being unmarried, female, young, re-transplanted, and living alone (Denhaerynck et al., 2005; Frazier et al., 1994) were also examined in the current study. In this sample, however, none of these variables were related to adherence. These risk factors, however, were originally reported in a much larger sample (N=241; Frazier et al., 1994), and thus, power to detect these effects may have been an issue in the current research. Hemoglobin levels and diagnosis of diabetes were associated with medication adherence in our sample, however. Variables correlated with adherence in this sample may provide some insight into specific groups of transplant patients that could benefit greatly from programs focused on increasing medication adherence. As well, clearly, further research is needed to clarify those variables most associated with non-adherence in this population.

The current study also examined cognition as a principal components analysis derived composite score, as opposed to looking separately at different

types of cognitive performance in relation to depressive symptoms and adherence. As our models did not account for all of the variance in adherence in this sample, it would be interesting for future research to further examine the relationships between specific aspects of cognition (e.g. processing speed, memory, executive functioning), depression, and adherence, in greater detail. Although our correlational results do not support a relationship between the cognitive measures used in this study and medication adherence in this sample, previous research has indicated effects of cognition on adherence in renal transplant patients, and thus, this discrepancy should be further explored. As well, this study only considered traditional assessments of cognition, not more familiar, everyday cognitive measures. Recent research has indicated that everyday cognitive tasks are specifically predictive of medication adherence in transplant patients (Gelb et al., submitted), these should, thus, be considered in addition to traditional cognitive measures in future examination of the relationship between cognition and adherence in this population.

The current study relied on the factor structure of the CES-D previously found by Radloff (1977) in determining the relationships between factors of this scale and adherence. Although similar factor structures have been found in other samples, such as mild and moderate TBI sufferers (McCauley et al., 2006), no such studies have been conducted in renal transplant recipients. Thus, future research should explore the factor structure of the CES-D in renal transplant populations. Future research should also examine the reliability and validity of the CES-D for renal transplant patients specifically. As well, the somatic

symptoms subscale of the CES-D contains only 5 questions, and thus, likely does not cover all aspects of somatic depressive symptoms. It would thus be useful to examine other measures of the somatic symptoms of depression in future studies to determine whether similar results are found.

In relation to the number of items included in the CES-D Somatic subscale, there are 5 items on this scale, allowing only for scores in the range of 0-15. Some previous research has indicated that abridged versions of the CES-D total scale show less reliability in responses than the full 20 item scale (scores ranging 0-60), and thus, that it is better to use the full scale format of the CES-D (O'Rourke, 2004). Reliability estimates in our sample do indicate lower reliability of scores on the somatic and other subscales of the CES-D than on the full measure (Cronbach's α for scores on the Somatic Subscale was .75, whereas for the full scale, α was .91), however reliability estimates for the subscales examined in this study were still adequate. Nonetheless, it will certainly be useful for future research to examine a wider array of questions concerning somatic symptoms. It is also possible that reliability estimates may be increased by inclusion of a greater number of somatically related items on future scales tested for prediction of adherence in renal transplant patients. As the length of each subscale on this measure also differed (ranging from 2-5 questions), there is some chance that shorter subscales (the Positive Affect and Interpersonal subscales) may not have shown as great of a relationship with adherence due to range of variance issues related to their low number of questions. If this were the case, it is possible that some questions contained on these scales may also be

important in the prediction of medication adherence in these individuals, despite the subscales themselves not showing a relationship to adherence. Thus, future research examining all questions on the CES-D for relation to medication adherence in this population will also be important.

There are various potential limitations to the current study. The measures used both to quantify depressive symptoms, and to measure medication adherence, are self-report questionnaires, and are thus susceptible to issues surrounding self-report, such as demand characteristics. However, studies have shown that self-report measures of medication adherence are often highly concordant with other estimates of adherence such as electronic monitoring, pill counts, and drug levels in blood, indicating the utility of such measures (Garber, Nay, Erickson, Likens, & Lawrence, 2004). Research has also indicated that self-reports of medication adherence provide a better approximation of adherence as measured by electronic monitoring techniques than other methods, such as clinician ratings or blood serum concentrations (Butler et al., 2004). Given these previous findings, use of self-reported adherence ratings to assess medication adherence in this study was considered warranted (Appendix A).

Research conducted to date has also not considered the temporal relationship between depressive symptoms and cognitive difficulties in transplant or CKD patients. Longitudinal research will likely be required to further untangle the relationships between cognitive performance and depression in renal transplant patients. As well, by only looking at depressive symptoms themselves, this study does not specifically address transplant patients with depressive

disorders. On the other hand, this technique allows us to look at a larger proportion of patients, and to indicate whether depressive symptoms sub-threshold of those that would qualify as a disorder affect medication adherence. It is possible that the results of this study may also apply to patients with depressive disorders specifically, although further research specifically examining these populations is surely needed.

Our exclusion criteria also limit the generalizability of results to renal transplant patients on the whole, as many of these patients do have concurrent psychological or medical disorders. For instance, although the majority of participants were able to complete the Color-word subtest, a few transplant patients were unable to distinguish the colours used in this measure, likely due to diabetic retinopathy. However, it is also quite possible that cognitive impairments and depressive symptoms are greater among those not meeting inclusion criteria for this study, and thus the current findings may provide some information of relevance to these individuals.

Finally, the use of a cross-sectional design such as this is a good first step in this area of research. Although looking at changes in executive function and depressive symptoms over time and monitoring medication adherence could allow for a more comprehensive picture of the interactions between these different variables, we believed that the expense both in time and resources was unwarranted unless there were preliminary findings indicating a need for further study. As our first series of hypotheses was supported, it is likely that a longitudinal study examining the relationships between adherence, cognition, and

depression in these patients is warranted. Such research could enhance our understanding of medication adherence, and depressive symptoms, as well as providing information as to whether cognitive ability and depressive symptoms improve or otherwise change over time following transplant.

Our findings indicate the importance of considering depressive symptoms in the prediction of medication adherence in renal transplant patients. In this sample, it seems that depression may play a greater role than cognitive factors in understanding why patients fail to adhere to their medications. This said, it will be important for future research in this population not to discount the potential importance of cognition in predicting other real-world outcomes for these patients. Previous research from our lab and others indicates a role for cognitive factors in CKD, which certainly bears greater examination both in this population, and in patients post-transplant. It will be important that both depression and cognition are considered as potential predictors of various outcome variables, for research to adequately progress in these populations. Nonetheless, the current findings provide some support for the utility of the CES-D, particularly those questions making up the somatic subscale, to identify renal transplant patients at risk for potential difficulties with medication adherence.

APPENDICES

Appendix A

Medication Adherence Assessment Techniques

Of the various techniques available to assess medication adherence, each carries its own advantages and disadvantages. Blood serum concentrations are able to indicate whether a medication was in fact ingested, however, these concentrations are only reliable for a period related to the half-life of the drug ingested, making these measurements less than ideal for assessment of adherence under most outpatient circumstances (DeGeest, Abraham, & Dunbar-Jacob, 1996). In renal transplant patients specifically, for instance, authors believe that serum level measurements underestimate medication adherence as a result of this drawback (DeGeest et al., 1996).

Prescription refill methods have the advantage of being objective like serum concentrations, and also of being relatively inexpensive (Wetzels et al., 2006). Unlike serum concentrations, however, this method does not provide proof that the medications were indeed ingested. Thus, while serum concentrations may underestimate adherence, refill data may provide an overly optimistic assessment of adherence (as patients will not necessarily use all of their medications once they have filled a prescription; Wetzels et al., 2006).

Measures that rely on self-report, are obviously not affected by medication half-life, and may, unlike refill data, provide an indication of whether medications that have been picked up were in fact used. On the other hand, these methods can be susceptible to recency effects (in that patients may not accurately remember their prior adherence levels) and social desirability biases (such that patients want to look as though they are adhering better than they actually are). However, as mentioned above, recent research has indicated that self-report measures of adherence better approximate adherence as measured via electronic pill-top monitoring devices than do other forms of medication adherence assessment in renal transplant patients (Butler et al., 2004). As well, as indicated by a recent meta-analysis, self-report measures of adherence are the most commonly used adherence assessment in renal transplant populations, and of the studies examined, this method actually provided the most conservative estimate of adherence (highest rates of non-adherence; Dew et al., 2007). Thus, given the prevalence of their use, the cost effective nature of these methods, and the track record that self-report measures have in assessing medication adherence in renal transplant patients, this method was chosen for use in the current study.

Appendix B

Cognitive Difficulties in CKD and Renal Transplant

It is believed that the cognitive difficulties reported by patients with CKD, and perhaps those who have received renal transplants, may be the result of brain metabolism or brain structure alterations (Pereira et al., 2005 reviews these findings). In support of this, imaging studies indicate larger ventricles and greater brain atrophy in dialysis patients, compared to controls. As well, this neural atrophy is positively related to the length of time a patient has needed dialysis. Dialysis patients are also seen to have focal ischemia, leukoaraiosis, and vascular calcifications, which are all brain abnormalities commonly associated with deficient cerebrovascular function (Pereira et al., 2005).

Previous research in other populations, including older adults, has indicated associations between cognitive decline and cerebral blood flow, atrophy, and white matter hyperintensities (Cook et al., 2002). As many CKD patients carry similar risk factors as do elderly individuals for cerebrovascular problems (such as hypertension and diabetes), it is possible that cognitive difficulties in CKD and, potentially in renal transplant populations as well, are a result of similar vascular issues. In support of such, recent reports indicate that diabetic nephropathy is, in fact the second leading cause of kidney failure among renal transplant patients in Canada (CORR/CIHI, 2008), and that accelerated age-related cognitive decline is related to diagnosis of type 2 diabetes (Hessing et al., 2004).

Appendix C

Reference Tables – Correlations between Variables Relevant to the analyses conducted

Table A. Correlation table for CES-D and cognitive variables of relevance to analyses.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1. Age	--														
2. Gender	-.040	--													
3. Education	-.078	-.109	--												
4. CES-D Total Score	-.110	-.074	-.102	--											
5. CES-D Depressed Affect	-.152	.001	-.040	.891**	--										
6. CES-D Positive Affect	-.071	-.153	-.061	.715**	.531**	--									
7. CES-D Somatic Factor	-.090	-.139	.068	.645**	.526**	.375**	--								
8. CES-D Interpersonal Factor	-.064	-.068	-.193*	.860**	.693**	.435**	.469**	--							
9. WAIS-Digit Symbol Coding	-.394**	.161	.145	-.240**	-.159	-.247**	-.217*	-.117	--						
10. CVLT Immediate Recall	-.419**	.350**	.063	-.209*	-.097	-.230*	-.243**	-.050	.464**	--					
11. CVLT Long Delay Recall	-.317**	.418**	-.003	-.184*	-.070	-.209*	-.241**	-.079	.402**	.845**	--				
12. Trails Switching	.328**	.119	-.158	.267**	.237**	.263**	.159	.111	-.554**	-.408**	-.306**	--			
13. Color-Word Inhibition	.391**	-.107	-.067	.082	.003	.253**	.014	.055	-.595**	-.468**	-.479**	.398**	--		
14. Neuropsych Composite	-.480**	.254**	.108	-.252**	-.142	-.309**	-.230*	-.105	.776**	.842**	.803**	-.668**	-.760**	--	
15. TxEQ Adherence	-.194*	.096	-.024	-.268**	-.210*	-.168*	-.342**	-.138	.105	.187*	.192*	-.195*	-.044	.187*	--

**. Correlation is significant at the 0.01 level (1-tailed).

*. Correlation is significant at the 0.05 level (1-tailed).

Listwise N=101

Table B. Correlation table for non-transformed and transformed variables of relevance to mediation analyses.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1. Age	--															
2. Gender	-.040	--														
3. Education	-.078	-.109	--													
4. CES-D	-.110	-.074	-.102	--												
5. CES-D Depressed Affect	-.152	.001	-.040	.891**	--											
6. CES-D Positive Affect	-.071	-.153	-.061	.715**	.531**	--										
7. CES-D Somatic Symptoms	-.064	-.068	-.193	.860**	.693**	.435**	--									
8. CES-D Interpersonal	-.090	-.139	.068	.645**	.526**	.375**	.469**	--								
9. CES-D (trans)	-.061	-.143	-.098	.950**	.811**	.739**	.829**	.565**	--							
10. CES-D Depressed (trans)	-.138	-.031	.006	.834**	.946**	.505**	.638**	.489**	.807**	--						
11. CES-D Positive (trans)	-.062	-.193	-.049	.708**	.519**	.954**	.467**	.337**	.768**	.517**	--					
12. CES-D Somatic (trans)	-.031	-.152	-.194	.799**	.610**	.456**	.934**	.422**	.848**	.588**	.502**	--				
13. CES-D IP (trans)	-.103	-.156	.067	.613**	.481**	.375**	.457**	.956**	.561**	.470**	.336**	.428**	--			
14. Neuropsych Composite	-.480**	.254*	.108	-.252*	-.142	-.309**	-.230*	-.105	-.304**	-.183	-.306**	-.253*	-.098	--		
15. TxEQ Adherence	-.194	.096	-.024	-.268**	-.210*	-.168	-.342**	-.138	-.286**	-.226*	-.172	-.366**	-.113	.187	--	
16. TxEQ Adherence (trans)	-.161	.088	-.071	-.304**	-.278**	-.206*	-.367**	-.121	-.313**	-.287**	-.208*	-.386**	-.084	.136	.934**	--

**. Correlation is significant at the 0.01 level (1-tailed).

*. Correlation is significant at the 0.05 level (1-tailed).

Listwise N=101

Table C. Correlations between demographic and illness variables of interest and non-transformed variables of interest to the analyses.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
1. Age	--																				
2. Gender	-.036	--																			
3. Education	-.078	-.110	--																		
4. Marital Status	.132	.004	.011	--																	
5. Living Situation	-.138	-.026	.032	.667**	--																
6. Time since Tx (months)	.294**	.051	-.039	.026	-.067	--															
7. Donor Type	-.215*	.053	.079	.097	.112	-.280**	--														
8. Diabetes #	.113	-.167	-.055	-.143	-.226*	-.161	-.221*	--													
9. Hemoglobin	-.010	-.368**	.006	-.046	.095	-.092	-.028	.011	--												
10. CES-D Total	-.105	-.097	-.104	-.109	.008	.029	-.051	.102	-.063	--											
11. CES-D Dep	-.147	-.020	-.041	-.159	-.018	.000	.044	.107	-.140	.886**	--										
12. CES-D Pos	-.064	-.179	-.062	-.039	.097	.087	-.120	.038	.048	.703**	.512**	--									
13. CES-D Som	-.061	-.079	-.194	-.074	-.018	-.022	.011	.058	-.087	.862**	.691**	.427**	--								
14. CES-D Int	-.085	-.155	.068	.004	-.009	.101	.023	.071	.042	.637**	.514**	.358**	.463**	--							
15. WAIS-Digit Symbol	-.398**	.169	.146	.182	.243*	-.006	.276**	-.346**	.002	-.232*	-.149	-.239*	-.213*	-.109	--						
16. CVLT Trial 1-5	-.418**	.343**	.063	.076	.204*	-.045	.197*	-.055	-.055	-.234*	-.119	-.257**	-.255*	-.064	.474**	--					
17. CVLT - Long Delay	-.314**	.412**	-.003	.039	.121	-.058	.221*	-.126	-.059	-.208*	-.091	-.234*	-.252*	-.093	.411**	.843**	--				
18. Trails Number-Letter	.327**	.124	-.158	-.030	-.022	.168	-.245*	-.029	-.028	.281**	.250*	.277**	.163	.118	-.558**	-.407**	-.304**	--			
19. Color-Word Inhibition	.389**	-.098	-.067	.017	-.052	.025	-.211*	.206*	-.012	.104	.022	.279**	.023	.068	-.606**	-.462**	-.474**	.396**	--		
20. Neuropsych Composite	-.479**	.248*	.108	.082	.172	-.074	.296**	-.185	-.021	-.272**	-.159	-.331**	-.238*	-.115	.785**	.841**	.802**	-.668**	-.758**	--	
21. TxEQ Adherence	-.193	.093	-.024	-.048	-.111	-.209*	.141	.217*	.192	-.280**	-.221*	-.179	-.347**	-.144	.107	.185	.190	-.194	-.041	.185	--

** Correlation is significant at the 0.01 level 2-tailed.

* Correlation is significant at the 0.05 level 2-tailed.

Listwise N=100

The Diabetes variable indicates current or history of diabetes vs. no diabetes or history of diabetes

REFERENCES

(2009). The Numbers Count: Mental Disorders in America. *National Institute of Mental Health.* Available Online at http://www.nimh.nih.gov/health/publications/the-numbers-count-mental-disorders-in-america/index.shtml#Mood. Retrieved August 25, 2009.

(2008). 2007 Report - Dialysis and Renal Transplantation. *Canadian Organ Replacement Register.* Canadian Institute for Health Information: Ottawa, Ontario.

Akman, B., Özdemir, F. N., Sezer, H., Miçozkaioğlu, H., & Haberal, M. (2004). Depression levels before and after renal transplantation. *Transplantation Proceedings, 36,* 111-113.

Albert, S., Weber, C., Todak, G., Polanco, C., Clouse, R., McElhiney, M. et al. (1999). An observed performance test of medication management ability in HIV: Relation to neuropsychological status and medication adherence outcomes. *AIDS and Behavior, 3,* 121-128.

Baron, R. M., & Kenny, D. A. (1986). The moderator-mediator variable distinction in social psychological research: Conceptual, strategic and statistical considerations. *Journal of Personality and Social Psychology, 51,* 1173-1182.

Bogart, L., Gray-Bernhardt, M., Catz, S., Hartmann, B., & Otto-Salaj, L. (2002). Social and temporal comparisons made by individuals living with HIV disease: Relationships to adherence behavior. *Journal of Applied Social Psychology, 32,* 1551-1576.

Butler, J. A., Roderick, P., Mullee, M, Mason, J. C., & Peveler, R. C. (2004). Frequency and impact of nonadherence to immunosuppressants after renal transplantation: a systematic review. *Transplantation, 77,* 769-776.

Chamelian, L., & Feinstein, A. (2006). The effect of major depression on subjective and objective cognitive deficits in mild to moderate traumatic brain injury. *Journal of Neuropsychiatry & Clinical Neurosciences, 18*, 33-38.

Christensen, A. J., Ehlers, S. L., Raichle, K. A., Bertolatus, J. A., & Lawton, W. J. (2000). Predicting changes in depression following renal transplantation: Effect of patient coping preferences. *Health Psychology, 19*, 348-353.

Clore, G., & Schnall, S. (2005). The Influence of Affect on Attitude. In D. Albarracín, B. T. Johnson, & M. P. Zanna (Eds.), The handbook of attitudes (pp. 437-489). New Jersey, US: Lawrence Erlbaum Associates.

Comijs, H. C., Jonker, C., Beekman, A. T. F. & Deeg, D. J. H. (2001). The association between depression and cognitive decline in community-dwelling elderly persons. *International Journal of Geriatric Psychiatry, 16*, 361-367.

Cook, S. E., Nebes, R. D., Halligan, E. M., Burmeister, L. A., Saxton, J. A., Ganguli, M., Fukui, M. B. et al. (2002). Memory impairment in elderly individuals with a mildly elevated serum TSH: The role of processing resources, depression, and cerebrovascular disease. *Aging Neuropsychology and Cognition, 9,* 175-183.

Crowe, S. F., Benedict, T., Enrico, J., Mancuso, N., Matthews, C., & Wallace, J. (1999). Cognitive determinants of performance on the digit symbol-coding test, and the symbol search test of the wais-iii, and the symbol digit modalities test: An analysis in a healthy sample. *Australian Psychologist, 34,* 204-210.

De Geest, S., Abraham, I., & Dunbar-Jacob, J. (1996). Measuring transplant patients' compliance with immunosuppressive therapy. *Western Journal of Nursing Research, 18*, 595-605.

Delis, D. C., Kaplan, E., & Kramer, J. H. (2001). Delis-Kaplan Executive Function System. San Antonio, TX: The Psychological Corporation.

Delis, D. C., Kramer, J. H., Kaplan, E., & Holdnack, J. (2004). Reliability and validity of the Delis-Kaplan Executive Function System: An update. *Journal of the International Neuropsychological Society, 10*, 301-303.

Delis, D. C., Kramer, J. H., Kaplan, E., Ober, B. A. (2000). Manual for the California Verbal Learning Test—Second Edition (CVLT–II). San Antonio, TX: The Psychological Corporation.

Denhaerynck, K., Dobbels, F., Cleemput, I., Desmyttere, A., Schäfer-Keller, P., Schaub, S., & De Geest, S. (2005). Prevalence, consequences, and determinants of nonadherence in adult renal transplant patients: a literature review. *Transplant International, 18*, 1121-1133.

Devins, G. M., Orme, C. M., Costello, C. G., Binik, Y. M., Frizzell, B., Stam, H. J., Pullin W. M. (1988). Measuring depressive symptoms in illness populations: Psychometric properties of the Center for Epidemiologic Studies Depression (CES-D) scale. *Health Psychology, 2,* 139-156.

Dew, M. A., DiMartini, A. F., Dabbs, A. D., Myaskovsky, L., Steel, J., Unruh, M. et al. (2007). Rates and risk factors for nonadherence to the medical regimen after adult solid organ transplantation. *Transplantation, 83*, 858-873.

Dugbartey, A. T. (2004) Review of the Delis-Kaplan Executive Function System. *Mental Measurements Yearbook, 15.*

Faul, F., Erdfelder, E., Lang, A-G., & Buchner, A. (2006). G*Power 3 (version 3.0.1) [Software]. Dusseldorf: Heinrich-Heine-Universität Düsseldorf, Retrieved from http://www.psycho.uni-duesseldorf.de/abteilungen /aap/gpower3/download-and-register.

Frazier, P. A., Davis-Ali, S. H., & Dahl, K. E. (1994). Correlates of noncompliance among renal transplant recipients. *Clinical Transplantation 8*, 550-557.

Gallassi, R., Morreale, A. & Pagni, P. (2001). The relationship between depression and cognition. *Archives of Gerontology and Geriatrics, S7*, 163-171.

Garber, M., Nau, D., Erickson, S., Aikens, J., & Lawrence, J. (2004). The concordance of self-report with other measures of medication adherence: a summary of the literature. *Medical Care, 42,* 649-652.

Gelb, S. R., Shapiro, R. J., Hill, A., & Thornton, W. L. (2008). Cognitive and psychosocial outcome following kidney transplantation. *Nephrology Dialysis Transplantation, 23*, 1032-1038.

Gelb, S. R., Thornton, W. L., Shapiro, R. J. (submitted). Predicting medication adherence and employment status following kidney transplant: The relative utility of traditional and everyday cognitive approaches.

Gonzalez, J. S., Safren, S. A., Delahanty, L. M., Cagliero, E., Wexler, D. J., Meigs, J. B. & Grant, R. W. (2008). Symptoms of depression prospectively predict poorer self-care in patients with Type 2 diabetes. *Diabetic. Med. 25,* 1102–1107.

Gonzalez-Perez, L. V., Stearns, S. C., & Wordsworth, S. (2005). Hemodialysis for end- stage renal disease: A cost-effectiveness analysis of treatment options. *International Journal of Technology Assessment in Health Care, 21*, 32-39.

Gould, O. (1999). Cognition and affect in medication adherence. Processing of medical information in aging patients: Cognitive and human factors perspectives (pp. 167-183). Mahwah, NJ, US: Lawrence Erlbaum Associates Publishers.

Griva, K., Hansraj, S., Thompson, D., Jayasena, D., Davenport, A., Harrison, M., & Newman, S. P. (2004). Neuropsychological performance after kidney transplantation: a comparison between transplant types and in relation to dialysis and normative data. *Nephrology Dialysis Transplantation, 19*, 1866-1874.

Griva, K., Ziegelmann, J. P., Thompson, D., Jayasena, D., Davenport, A., Harrison, M., & Newman, S. P. (2002). Quality of life and emotional responses in cadaver and living related renal transplant recipients. *Nephrology Dialysis Transplantation, 17,* 2204-2211.

Hann, D., Winter, K., & Jacobsen, P. (1999). Measurement of depressive symptoms in cancer patients: Evaluation of the Center for Epidemiological Studies Depression Scale (CES-D). *Journal of Psychosomatic Research, 46*, 437-443.

Hassing, L. B., Grant, M. D., Hofer, S. M., Pedersen, N., L., Nilsson, S. E., Berg, S., Mcclearn, G. & Johansson, B. (2004). Type 2 diabetes mellitus contributes to cognitive decline in old age: A longitudinal population-based study. *Journal of the International Neuropsychological Society, 10*, 599-607.

Hess, A. K. (2003) Review of the Wechsler Adult Intelligence Scale-Third Edition. *Mental Measurements Yearbook, 14.*

Hinkin, C. H., Hardy, D. J., Mason, K. I., Castellon, S. A., Durvasula, R. S., Lam, M. N., Stefaniak, M. (2004). Medication adherence in HIV-infected adults: Effect of patient age, cognitive status, and substance abuse. *AIDS, 18,* S19-S25.

Hinkin, C.H., Castellon, S.A., Durvasula, R.S., Hardy, D.J., Lam, M.N., Mason, K.I., Thrasher, D., Goetz, M.B., & Stefaniak, M. (2002). Medication adherence among HIV+ adults: Effects of cognitive dysfunction and regimen complexity. *Neurology, 59,* 1945-1950.

Hubley, A. M. (2004). Review of the California Verbal Learning Test, Second Edition, Adult Version. *Mental Measurements Yearbook, 16*.

Insel, K., Morrow, D., Brewer, B., & Figueredo, A. (2006). Executive function, working memory, and medication adherence among older adults. *Journal of Gerontology, 61B,* 102-107.

Jefferson, A., Paul, R., Ozonoff, A., & Cohen, R. (2006). Evaluating elements of executive functioning as predictors of instrumental activities of daily living (IADLs). *Archives of Clinical Neuropsychology, 21*, 311-320.

Jenkinson C., Stewart-Brown, S., Petersen, S., & Paice, C. (1999). Assessment of the SF-36 version 2 in the United Kingdom. *Journal of Epidemiological Community Health, 53,* 46–50.

Kasahara, H., Tsumura, M., Ochiai, H., Furukawa, H., Aoki, K., Ito, T., Kada, H. et al. (2006). Consideration of the relationship between depression and dementia. *Psychogeriatrics 6*, 128–133.

Kenny, D., Kashy, D., & Bolger, N. (1998). Data analysis in social psychology. The handbook of social psychology, Vols. 1 and 2 (4th ed.) (pp. 233-265). New York, NY US: McGraw-Hill.

Kimmel, P. L., Weihs, K., & Peterson, R. A. (1993). Survival in hemodialysis participants: the role of depression. *Journal of the American Society of Nephrology, 4*, 12-27.

Leventhal, E., Leventhal, H., Robitaille, C., & Brownlee, S. (1999). Psychosocial factors in medication adherence: A model of the modeler. In D. C. Park, R. W. Morrell, & K. Shifren (Eds.), Processing of medical information in aging patients: Cognitive and human factors perspectives (pp. 145-165). New Jersey, US: Lawrence Erlbaum Associates.

Lawton, M.P., & Brody, E. M. (1969). Assessment of older people: Self-maintaining and instrumental activities of daily living. *Gerontologist, 9*, 179-186.

Mackin, R., & Areán, P. (2007). Cognitive and psychiatric predictors of medical treatment adherence among older adults in primary care clinics. *International Journal of Geriatric Psychiatry, 22,* 55-60.

MacKinnon, D., Lockwood, C., Hoffman, J., West, S., & Sheets, V. (2002). A comparison of methods to test mediation and other intervening variable effects. *Psychological Methods, 7*, 83-104.

McCauley et al. (2006). Confirmatory factor structure of the Center for Epidemiological Studies-Depression scale (CES-D) in mild-to-moderate traumatic brain injury. *Brain Injury, 20*, 519-527).

McDonald, C., Delis, D., Norman, M., Tecoma, E., & Iragui-Madoz, V. (2005). Is impairment in set-shifting specific to frontal-lobe dysfunction: Evidence from patients with frontal-lobe or temporal-lobe epilepsy. *Journal of the International Neuropsychological Society, 11*, 477-481.

Morrissey, P.E., Reinert, S., Yango, A., Gautam, A., Monaco, A., & Gohh, R. (2005). Factors contributing to acute rejection in renal transplantation: the role of noncompliance. *Transplantation Proceedings, 37*, 2044-2047.

Muller, D., Judd, C., & Yzerbyt, V. (2005). When moderation is mediated and mediation is moderated. *Journal of Personality and Social Psychology, 89*, 852-863.

O'Rourke, N. (2004). Reliability generalization of responses by care providers to the Center for Epidemiological Studies – Depression Scales. *Educational and Psychological Measurement, 64,* 973-990.

Pereira, A. A., Weiner, D. E., Scott, T., & Sarnak, M. J. (2005). Cognitive function in dialysis patients. *American Journal of Kidney Disease, 45*, 448 – 462.

Pivac, N., Muck-Seler, D., Barisic, I., Jakovljevic, M., & Puretic, Z. (2001). Platelet serotonin concentration in dialysis patients with somatic symptoms of depression. *Life Sciences, 68*, 2423-2433.

Radloff, L. S. (1977). The CES-D Scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement, 1,* 385-401.

Rieckmann, N. et al. (2006). Course of Depressive Symptoms and Medication Adherence After Acute Coronary Syndromes An Electronic Medication Monitoring Study. *Journal of the American College of Cardiology, 48*, 2218-2222.

Shidler, N. R., Peterson, R. A., & Kimmel, P. L. (1998). Quality of life and psychosocial relationships in patients with chronic renal insufficiency. *American Journal of Kidney Disease, 32,* 557-566.

Tabachnick, B. G., and Fidell, L. S. (2006). Using multivariate statistics. Boston, MA: Allyn & Bacon.

Thombs, B. D., Hudson, M., Schieir, O., Taillefer, S. S., & Baron, M. (2008). Reliability and validity of the center for epidemiologic studies depression scale in patients with systemic sclerosis. *Arthritis And Rheumatism, 59*, 438-443.

Thornton, W., Shapiro, J., Deria, S., Gelb, S., & Hill, A. (2007). Differential Impact of Age on Verbal and Executive Functioning in Chronic Kidney Disease. *Journal of the International Neuropsychological Society, 13*, 344-353.

Verdier-Taillefer, M. H., Gourlet, V., Fuhrer, R., & Alpérovitch, A. (2001). Psychometric properties of the Center for Epidemiologic Studies – Depression Scale in multiple sclerosis. *Neuroepidemiology, 20*, 262-267.

Wechsler, D. (1997). Wechsler adult intelligence scale manual (3rd ed.). New York: The Psychological Corporation.

Wetzels, G. E. C., Nelemans, P. J., Schouten, J. S. A. G., van Wijk, B. L. G., & Prins, M. H. (2006). All that glisters is not gold: A comparison of electronic monitoring versus filled prescriptions – an observational study. *BMC Health Services Research, 6,* 8.

Wingfield, A., & Stine-Morrow, E. (2000). Language and speech. In F. I. M. Craik & T. A. Salthouse (Eds.), The handbook of aging and cognition (2nd ed.) (pp. 359-416). London: Lawrence Erlbaum Associates.

Yochim, B., Baldo, J., Nelson, A., & Delis, D. (2007). D-KEFS trail making test performance in patients with lateral prefrontal cortex lesions. *Journal of the International Neuropsychological Society, 13*, 704-709.

Yount, S. E., Jacobs, C., Bustamante, V. A., & Brickman, A. L. (1998). Psychosocial and biomedical predictors of attention and memory in end-stage renal disease patients. *Journal of Clinical Psychology in Medical Settings, 5*, 497-510.

Ziegelmann, J. P., Griva, K., Hankins, M., Harrison, M., Davenport, A., Thompson, D., Newman, S. P. (2002). The Transplant Effects Questionnaire (TxEQ): The development of a questionnaire for assessing the multidimensional outcome of organ transplantation--example of end stage renal disease (ESRD). *British Journal of Health Psychology, 7*, 393-408.