

SCIENTIFIC INVESTIGATIONS

A Novel Application of a Biopsychosocial Theory in the Understanding of Disturbed Sleep before and after Kidney Transplantation

Jacob M. Williams, PhD¹; Christina S. McCrae, PhD²; James R. Rodrigue, PhD^{3,4}; Pamela R. Patton, PA, MSP⁵

¹Department of Psychology/Neuropsychology, TIRR Memorial Hermann, Houston, TX; ²Department of Health Psychology, University of Missouri, Columbia, MO; ³Department of Surgery, Beth Israel Deaconess Medical Center, Boston, MA; ⁴Department of Psychiatry, Harvard Medical School, Boston, MA; ⁵School of Physician Assistant Studies, University of Florida, Gainesville, FL

Study Objectives: Sleep and fatigue difficulties appear to be highly prevalent among individuals with end-stage renal disease and individuals who have received a kidney transplant. While there is some evidence of biopsychosocial factors predicting sleep disturbance in these populations, previous studies have relied on single time point retrospective measurements.

Methods: The study utilized a 2-week prospective measurement approach, including one night of polysomnographic measurement, nightly sleep diaries, and self-report measures of health, sleep, and mood.

Results: The current study demonstrates that a number of psychological and behavioral factors, including negative mood, quality of life, napping, and caffeine consumption, are related to sleep disturbance among pre- and post-kidney transplant patients. This study also found that many of these factors have different relationships with sleep disturbance when comparing pre- and post-kidney transplant patients.

Conclusions: These results suggest that such factors may be worthwhile areas for intervention in treating the symptoms of insomnia among pre- and post-transplant recipients. A nuanced approach to understanding sleep problems is likely warranted when conceptualizing insomnia and developing a treatment plan.

Keywords: kidney transplantation, sleep disorders, insomnia

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INTRODUCTION

Sleep complaints are common among individuals with end-stage renal disease (ESRD) and patients who have received kidney transplantation (KTX).^{1–6} While on dialysis, patients report that sleep disturbance is one of their most prominent symptom complaints.¹ Compared to dialysis, kidney transplantation is considered the treatment of choice for ESRD due to longer patient survival, fewer morbidities, and better quality of life. Unfortunately, little is known about the relationship between ESRD and sleep or the impact of KTX on that relationship. The research that does exist suggests that the rates of common sleep disorders including insomnia (50% to 75% v 9%), restless legs syndrome (30% to 80% v 5% to 15%), and sleep apnea (~24%), are higher in ESRD than in the general population, and ESRD patients are also at risk for more severe sleep apnea.^{2–7} The rates of these disorders tend to decrease following KTX (except apnea), but nonetheless remain elevated compared to normative estimates.⁸ While considerable research has focused on predictors of sleep apnea and restless legs syndrome (RLS), relatively little research has focused on insomnia in these populations. Additionally, due to a reliance on cross-sectional designs and retrospective assessment of insomnia, previous research has been unable to provide greater insights into sleep's relationships with ESRD. Previous research has been largely atheoretical and has examined insomnia in relative isolation without consideration of important

BRIEF SUMMARY

Current Knowledge/Study Rationale: This study was conducted in order to explore the biopsychosocial factors contributing to sleep disturbance among patients before and after kidney transplantation. Prior research indicates that sleep problems are extremely common among individuals with end stage renal disease both before and after kidney transplantation but has not provided an explanatory model for these sleep problems.

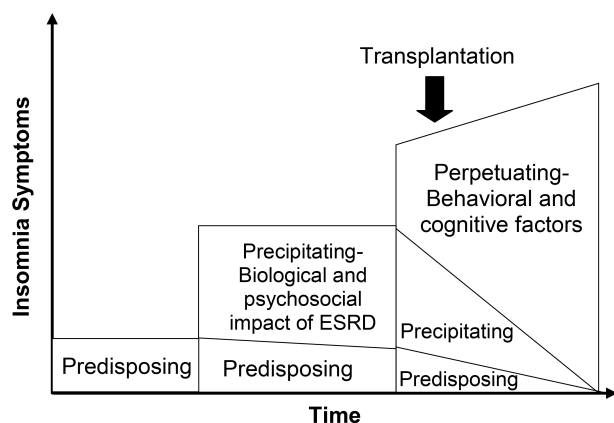
Study Impact: This study confirms the high rates of sleep problems found in prior research and identifies biopsychosocial factors which may contribute to sleep disturbance, particularly insomnia. These results provide evidence for specific factors which may be useful targets in the treatment of insomnia in these populations.

biopsychosocial relationships that may be relevant in the context of ESRD and KTX.

Biopsychosocial Correlates of Sleep and End-Stage Renal Disease

There are several biopsychosocial factors which have been found to be associated with ESRD including age, sex, medical comorbidity, psychological distress, quality of life, and fatigue. These factors have also been found to be highly related to insomnia and other sleep disturbances. Specifically, older age and medical comorbidities are associated with poorer sleep and poorer outcomes in ESRD patients.⁹ Also, in the general population, men are more likely to develop sleep

Figure 1—The 3Ps Model of the development of disturbed sleep in end-stage renal disease.



Predisposing factors include age, gender, and medical comorbidity. Precipitating factors include fatigue, mood, and quality of life. Perpetuating factors include napping and caffeine consumption.

apnea and RLS than are women, while the reverse is true for insomnia.^{7,10,11} Comorbidity rates between poor sleep, ESRD and psychological distress, particularly anxiety and depression (~60% of dialysis patients), are also high.^{12,13} ESRD patients who have elevated depressive symptoms report increased difficulty falling asleep, staying asleep, waking too early in the morning, and increased fatigue in the morning.¹⁴ Quality of life is often compromised among individuals suffering from chronic health conditions such as insomnia and ESRD.^{15,16} Fatigue, which can generally be defined as a perceived lack of physical and/or mental energy that interferes with usual or desired activities, is also associated with insomnia and ESRD.^{17,18}

The Development of Insomnia

Research on insomnia in the context of ESRD and KTX has been largely atheoretical, focusing instead on identifying rates of sleep disorders and a limited number of biopsychosocial correlates. While etiological models have aided the development of treatments for RLS and sleep apnea, research has yet to explore theoretically driven models of the process by which insomnia develops and is maintained over time in these patients. Such theory driven research is important for identifying the mechanisms underlying insomnia and understanding how to effectively treat insomnia in the context of ESRD and KTX.

According to Spielman's 3Ps model, the course of chronic insomnia includes predisposing conditions, precipitating circumstances, and perpetuating factors,¹⁹ which can be seen in **Figure 1**.

Predisposing conditions alone are not sufficient to produce chronic insomnia but precede the onset of insomnia and increase the likelihood for its occurrence and could include age, sex, or comorbid medical conditions.⁷ For example, predispositions to conditions known to reduce renal functioning may serve as predisposing factors in the subsequent development of sleep problems. Additionally, previous

research has found increased rates of insomnia among older adults, women, and individuals with comorbid conditions suggesting that these variables are likely to act as predisposing factors.⁷

Precipitating circumstances co-occur with the onset of acute insomnia and might include stressful personal events or rapid shifts in health which are likely related to increased fatigue, changes in mood resulting in emotional arousal, and decreased quality of life.^{20,21} Fatigue, common among ESRD patients, often accompanies a reduction of daytime activity and a perceived decline in quality of life. The combination of reduced activity and increased fatigue can lead to increased idle time in bed and is likely related to mood disturbance.^{20,22}

Insomnia is maintained by perpetuating factors, which may include changes individuals make in their sleep/wake schedules or daytime behaviors (e.g., stimulant use and napping) as they attempt to compensate for sleeping poorly.²⁰ Specifically, daytime naps may disrupt the sleep homeostat (drive for sleep that increases the longer one is awake) by meeting some of the sleep drive that typically builds during the day. Based on qualitative reports, as dialysis patients experience increasingly altered sleep patterns, including night time awakenings, daytime naps often develop as a compensatory strategy.²⁰ Individuals experiencing significant fatigue and sleep problems may utilize stimulant substances (caffeine or nicotine) as a compensatory daytime strategy, which has adverse effects on nighttime sleep.²³

The development of chronic insomnia (lasting ≥ 6 months) is often related to a combination of predisposing, precipitating, and perpetuating factors that manifest themselves across biopsychosocial domains. The current study explores the role of these three sets of factors among individuals at different stages in the development of insomnia.

Application of the 3Ps Model in End Stage Renal Disease

In a hypothesized patient scenario an individual with ESRD has progressively declining kidney function which necessitates dialysis to maintain adequate blood filtration. Prior to this time, the individual experienced health problems causing increased worry and predisposing them to nighttime sleeping difficulties. Over time, emotional distress about their health increases. While on dialysis, the individual experiences anemia and a buildup of waste products in the blood resulting in significant daytime fatigue. In response, they begin to engage in increased napping and caffeine consumption to compensate for their fatigue. The individual now develops acute insomnia due to biological factors, changes in sleep related compensatory behaviors, and continued worry and emotional distress concerning their health. Over time, perpetuating maladaptive compensatory behaviors become increasingly influential and eventually supersede the impact of the predisposing and precipitating factors. The individual's insomnia progresses to a chronic stage. The individual is maintained on dialysis until being matched for KTX. Following successful transplantation, their kidney functioning returns to a level that does not require dialysis. However, the individual

continues to experience insomnia due to their compensatory perpetuating behaviors.

Much of the existing research on sleep disturbance in the context of ESRD and KTX has utilized a single method of measurement involving participants' retrospective recall of their sleep over a designated period of 30 or more days. Given the highly variable nature of sleep and the potential for bias in retrospective recall, more accurate characterization of sleep disorders in these patients calls for research using prospective assessment. As a result, this study is the first to allow for true differential diagnosis of sleep disorders in pre- and post-KTX patients. Second, it is the first to take a theoretical approach to studying the impact of biopsychosocial factors (age, sex, medical comorbidity, fatigue, mood, quality of life (QOL), stimulant consumption, napping) on sleep in pre- and post-KTX patients. These factors were chosen for inclusion, because: (1) previous research has shown they share observable relationships with sleep, ESRD, and KTX; and (2) according to Spielman's model of insomnia,¹⁹ these factors represent the predisposing, precipitating, and perpetuating factors that may contribute to the development and maintenance of chronic insomnia. It is hypothesized that these factors will have a differential impact with predisposing and precipitating factors having a greater impact on the sleep of pre-KTX patients and perpetuating factors having greater impact for post-KTX patients.

METHODS

Participants

The current study included a sample of adults who were on the waiting list for a KTX (N = 25) and those that had received a KTX (N = 30) at the University of Florida (UF) Transplant Center and Nephrology Clinic. Of the 314 participants initially approached about the study, 17.5% of the participants agreed to participate. The most frequent reasons for declining participation were research site being too far (11%), insufficient time to participate (14%), not interested in volunteering (48%), and poor health (4%). For the pre-KTX group, participants were (1) referred for kidney or kidney/pancreas transplant and (2) had chronic kidney disease stages 3, 4, or 5. Among post-KTX, participants had (1) received a kidney or kidney/pancreas transplant, (2) were more than 3 months post-KTX, (3) had a stable allograft with glomerular filtration rate (GFR) \geq 40 mL/min, and (4) were > 12 weeks after the treatment of any acute rejection of the graft.

Procedures

Recruitment occurred during routine visits to the UF Transplant Clinic. Patients were approached first by a member of the Transplant Clinic staff. If individuals were interested in participating, they were given additional information by a trained research assistant. Potential participants were asked to provide consent in a private examination room in the UF Sleep Research Lab. Potential participants were given the opportunity to read and sign the consent form during scheduled visits, or to take the informed consent form home to consult with family

and friends before providing consent. The study protocol was evaluated and approved by the UF Health Science Center Institutional Review Board.

Once informed consent was obtained, a graduate research assistant or trained research assistant conducted a semi-structured clinical interview. Criteria were employed to rule out severe, uncontrolled psychopathology (i.e., suicidal ideation/intent, bipolar disorder, psychotic disorders, and dementia). In addition, measures of depression (Beck Depression Inventory-2) and anxiety (State Trait Anxiety Inventory) were administered.^{24,25} The Mini-Mental State Examination (MMSE) was used to screen for severe global impairment with exclusion criteria including scores < 23 for individuals with a 9th grade education level or higher or < 17 for those with less than a 9th grade level education.²⁶ Participants were administered the Kidney Disease Quality of Life Short Form to measure participants' perspective on their current functional health and well-being.²⁷

Participants who qualified completed multiple sleep measures over a 2-week period. Ambulatory polysomnographic monitoring (PSG; Grass Technologies) was conducted in each participant's home for one night during the 2-week assessment period to screen for physiological sleep disorders (e.g., apnea). In addition, participants completed two weeks of sleep diaries in order to confirm the diagnosis of insomnia. These sleep measures have been recommended as standard assessments in sleep research.²⁸ Appropriate clinical referrals were provided to participants with clinically significant sleep problems. Participants were compensated \$50 for participation.

Measures

Demographics and Health Survey

This survey consists of 13 items collecting information on demographics (age, sex, race, education, work status, height, and weight), sleep disorder symptoms, symptoms due to kidney disease, current medications, and other health information. Body mass index (BMI) was calculated using the following formula: (weight in pounds / [height in inches \times height in inches]) \times 703. Participants were asked to report comorbid medical conditions including heart attack, other heart problems, cancer, AIDS, hypertension, neurological disorder (seizures, Parkinson disease), breathing disorders (asthma, emphysema, allergies), urinary problems (prostate problems), diabetes, pains (arthritis, back pain, migraines), gastrointestinal disorders (stomach, irritable bowels, ulcers, gastric reflux), and other medical conditions. From these endorsements, a total number of comorbid conditions reported was calculated.

Subjective Sleep Measure

Sleep diaries were completed each morning for 14 days and provided subjective estimates of commonly reported sleep-wake variables: (1) sleep onset latency (time from initial lights out until sleep onset; SOL); (2) wake time after sleep onset (time spent awake after initial sleep onset until last awakening; WASO); and (3) total sleep time (computed by subtracting total wake time from the time spent in bed; TST). In the current study, SOL and WASO were combined to create a composite

measure of total wake time (TWT). Sleep diaries have been found to provide a reliable and valid index of insomnia symptoms and are essential in insomnia assessment.²⁸

Sleep Related Compensatory Behaviors

Daily dairies were used to measure daily behavior known to be disruptive to night time sleep including napping (total number of minutes per day), and caffeine consumption (ounces of caffeinated beverages consumed per day). Average values of napping and caffeine consumption were used in the present study.

Physiological Sleep Measure (PSG)

The 25 Channel AURA Recording System (Grass Technologies) was used to conduct in-home overnight sleep monitoring, consisting of 6 electroencephalography (EEG) measures, 2 electrooculography, and chin electromyography (EMG) according to standard placements.²⁹ Other channels included oxygen saturation level, bilateral anterior tibialis EMG, heart rate, thoracic strain gauge, and a nasal/oral thermistor. A single night of PSG was collected during the 2 weeks of assessment. Procedures for PSG training, data management, and scoring were based on the published procedures of the Sleep Heart Health Study.²⁹ All studies were scored by a graduate research assistant trained in PSG scoring up to a 0.8 concordance rate with PSG technicians based on recommended scoring criteria for staging sleep and identifying sleep disorders.³⁰

Criteria for Diagnosing Sleep Disorders

Chronic Insomnia

Individuals were identified as having chronic insomnia based on self-reported sleep over two weeks based on a SOL or WASO > 30 min, a frequency ≥ 6 times over the two weeks, and lasting > 6 months.²⁸ In addition, individuals must report significant distress and daytime impairments related to their sleep problem. These criteria are consistent with research³¹ and DSM-IV criteria for the diagnosis of insomnia.³²

Obstructive Sleep Apnea

Obstructive sleep apnea was diagnosed according to research and clinical recommendations.^{29,33} A diagnosis of obstructive sleep apnea consists of both apneic (a complete cessation of airflow) and hypopneic (a decrease in airflow volume) events. Cessations of breathing occur with EEG-measured arousals and decreases in oxygen saturation $\geq 3\%$. In order for hypopneic events to be considered clinically meaningful, EEG-measured arousals must be associated with $\geq 30\%$ reduction in airflow and 4% oxygen desaturation or 50% reduction in airflow and 3% oxygen desaturation. The number of these events per hour was calculated, and individuals having an apnea-hypopnea index (AHI) > 10 events per hour were considered positive for sleep apnea.

Restless Legs Syndrome

In accordance with NIH and research recommended diagnostic criteria, RLS was identified through report of (1) feelings of creeping, crawling sensations that result in the urge to move the limbs and (2) occur before bed or when at rest.¹⁰

Additionally, the participant had to report (3) relief of these sensations with movement and (4) a greater intensity of these sensations before bedtime and improvement in the morning. Individuals needed to report all 4 symptoms in order to establish the presence of RLS.

Quality of Life

Kidney Disease Quality of Life Short Form (KDQOL) was used to collect data on domains of QOL. The KDQOL is a brief measure of physical and psychosocial functioning, both generally and specific to kidney disease,²⁷ with higher values reflecting better QOL. This measure also includes the items on the Short Form Health Survey (SF-36).³⁴ The KDQOL and SF-36 show good psychometric properties, and overall, the scale have been found to be significantly related to other questions about perceived health status, number of days in the hospital, disability days, and overall health.²⁷

Fatigue

Multidimensional Fatigue Symptom Inventory-Short Form is an empirically developed measure of clinical fatigue which includes 30 items that load onto 5 fatigue factors (general, physical, mental, emotional, and vigor), with higher scores indicating greater fatigue and has been found to be valid and reliable (> 0.85).³⁵ A single total fatigue score provided by the measure was used as an estimate of fatigue.

Mood

Beck Depression Inventory-Second Edition (BDI-II) and State-Trait Anxiety Inventory-State Form (STAI-Y) were used to assess current mood status at the end of the assessment period.^{24,25} The BDI-II has been found to have adequate psychometric properties among young and older adults and discriminate validity in separating depressed and non-depressed individuals.³⁶ The STAI-Y has been found to be correlated with other measures of anxiety and good internal consistency.²⁵ In the interest of parsimony and based on prior research, in the current study, the 2 measures (BDI-II and STAI) were treated as measures of negative mood and were combined into one variable in final analyses by converting measure scores into Z scores and combining them.³⁷

Statistical Analyses

Collected data were entered into IBM SPSS v20.0 statistical analysis software and standard screening procedures were used to identify missing or incomplete data. Data were assessed for normality to ensure that statistical assumptions were met within limits that allow for testing of the specified hypotheses.

In order to test the impact of group (pre- versus post-KTX) on continuous variables, including demographic and medical factors, TWT, TST, comorbidity, fatigue, mood, QOL, napping, and caffeine consumption, multiple ANOVAs were run. Categorical demographic variables were analyzed using χ^2 tests. Demographic and medical variables of interest included age, sex, race, education, BMI, comorbidities, and number of current medications. To test the fit for the Spielman 3P Model of chronic insomnia separate hierarchical regressions for pre-KTX and for post-KTX were used to estimate the mean relationship between TWT and TST as predicted by age, sex, comorbidity, QOL,

Table 1—Mean demographic and health variables by kidney transplant group.

	Pre-Kidney Transplant (n = 25)	Post-Kidney Transplant (n = 30)	df	Test Statistic	p
Age, mean (SD)	51.75 (13.73)	55.37 (12.51)	54	F = 1.02	0.39
Education, years, mean (SD)	13.63 (2.16)	14.47 (2.99)	54	F = 1.08	0.30
BMI, mean (SD)	29.36 (6.21)	30.69 (5.82)	54	F = 0.67	0.42
Race and ethnicity, %			3	$\chi^2 = 3.15$	0.37
Caucasian	48%	63.3%			
African American	36%	23.3%			
Hispanic or Latino	16%	10.1%			
Asian American	0%	3.3%			
Sex, %	64% Female	50% Female	1	$\chi^2 = 1.09$	0.41
Number of comorbid medical conditions, mean (SD)	3.28 (1.28)	3.83 (1.76)	54	F = 1.71	0.20
Number of current medications, mean (SD)	10.04 (4.92)	11.87 (5.35)	54	F = 1.66	0.20

Numbers represent mean values or percentages. SD, standard deviation; BMI, body mass index, calculated using the formula: (weight in pounds / [height in inches × height in inches]) × 703.

Table 2—Mean outcome variables by kidney transplant group.

	Pre-Kidney Transplant (n = 25)	Post-Kidney Transplant (n = 30)	df	Test Statistic	p
TST, minutes, mean (SD)	469.65 (75.36)	444.91 (66.66)	53	F = 1.64	0.21
Male	462.72 (82.13)	432.16 (57.06)			
Female	473.56 (73.79)	458.57 (75.02)			
TWT, minutes, mean (SD)	64.28 (38.98)	47.36 (34.19)	53	F = 2.51	0.09
Male	29.21 (16.92)	44.90 (34.94)			
Female	84.02 (33.54)	50.01 (34.49)			
Total fatigue, score, mean (SD)	16.65 (18.14)	16.14 (22.33)	52	F = 0.01	0.96
Negative mood, z-score, mean (SD)	-0.08 (0.72)	-0.01 (.95)	51	F = 0.41	0.52
QOL, score, mean (SD)	34.03 (10.63)	39.89 (11.65)	53	F = 3.41	0.07
Caffeine, servings, mean (SD)	1.07 (1.40)	1.78 (1.79)	53	F = 2.53	0.12
Napping, minutes, mean (SD)	30.15 (21.82)	26.42 (27.18)	53	F = 0.30	0.59
Sleep apnea, %	32.00%	33.33%	1	$\chi^2 = 0.01$	0.92
RLS, %	32.00%	13.30%	1	$\chi^2 = 2.79$	0.09
Insomnia, %	68.00%	48.30%	1	$\chi^2 = 2.14$	0.14

Numbers represent mean values or percentages. SD, standard deviation; TST, total sleep time; TWT, total wake time; QOL, quality of life; RLS, restless legs syndrome.

fatigue, mood, napping, and caffeine consumption. In the first block of these models, age, sex, and comorbidity were loaded. In the second block, the QOL, fatigue, and mood were included. In the third block, napping, and caffeine consumption were included. Significant factors from the models computed for pre-KTX and post-KTX were directly compared to determine the relative importance of predictors in estimating TST and TWT for the 2 groups. This comparison was completed by converting the derived β -weights for each predictor into semi-partial correlations, which were then converted into z-scores and were compared using a Fischer Z score transformation.

RESULTS

The total sample consisted of 25 pre-KTX and 30 post-KTX patients. **Table 1** provides a summary of demographic and

health characteristics of the 2 groups. The total sample was 56% female and had a mean age of 53.7 years (SD = 13.1). The median time since kidney transplant for the post-KTX group was 74 months (ranging from 6 to 322 months). In this sample, 5 pre-KTX and 6 post-KTX participants reported currently using sleeping medication with no significant difference between groups is use of this medication. Seven pre-KTX participants and 28 post-KTX participants reported currently using immunosuppressant medication. Pre-KTX and post-KTX participants were compared on demographic and medical variables and no significant group differences were found (**Table 1**). There were trends toward greater TWT and lower QOL among pre-KTX patients (**Table 2**). There were no significant group differences on the other sleep related continuous variables. Comparing rates of apnea, RLS, and insomnia between the two groups found that pre-KTX patients had a trend toward higher prevalence of RLS symptoms compared

Table 3—Hierarchical regression predicting total wake time and total sleep time for pre-kidney transplant patients.

	Total Wake Time						Total Sleep Time					
	B	SE	β	t	r	p	B	SE	β	t	r	p
Block 1 Predisposing												
Constant	-75.25	46.47		-1.62		0.14	492.75	158.72		3.11		0.01
Age	0.73	0.42	0.30	1.72	0.28	0.11	-0.19	1.44	-0.04	0.13	-0.03	0.90
Sex	50.48	13.98	0.74	3.61	0.58	0.00	35.16	47.73	0.24	0.73	0.18	0.48
Comorbidity	-3.76	5.86	-0.15	-0.64	-0.10	0.53	-14.08	20.04	-0.26	-0.70	-0.18	0.50
Block 2 Precipitating												
QOL	0.51	0.70	0.16	0.73	0.12	0.48	-1.16	2.4	-0.17	-0.48	-0.12	0.64
Fatigue	0.16	0.63	0.07	0.26	0.04	0.79	-0.24	2.15	-0.05	-0.11	-0.03	0.91
Mood	19.82	10.40	0.35	1.9	0.31	0.07	-30.56	35.55	-0.25	-0.86	-0.22	0.69
Block 3 Perpetuating												
Caffeine	-0.08	4.35	-0.01	-0.02	0.00	0.99	9.45	14.86	0.19	0.64	0.16	0.54
Napping	0.31	0.36	0.21	0.86	0.14	0.40	0.31	1.21	0.10	0.25	0.06	0.81

For the final total wake time model $R^2 = 0.67$, $p < 0.05$. For the final total sleep time model $R^2 = 0.15$, $p = 0.95$. QOL, quality of life.

Table 4—Hierarchical regression predicting total wake time and total sleep time for post-kidney transplant patients.

	Total Wake Time						Total Sleep Time					
	B	SE	β	t	r	p	B	SE	β	t	r	p
Block 1 Predisposing												
Constant	65.12	51.73		1.26		0.16	214.55	114.14		1.88		0.16
Age	0.26	0.49	0.09	0.53	0.09	0.60	-0.19	1.09	-0.04	-0.18	-0.03	0.86
Sex	6.06	12.31	0.09	0.49	0.08	0.63	45.94	27.17	0.35	1.69	0.31	0.11
Comorbidity	-1.04	3.79	-0.05	-0.28	-0.05	0.79	0.87	8.37	0.02	0.10	0.02	0.92
Block 2 Precipitating												
QOL	-1.06	0.71	-0.36	-1.49	-0.24	0.15	3.63	1.58	0.64	2.31	0.43	0.03
Fatigue	-0.96	0.58	-0.35	-1.65	-0.27	0.12	2.17	1.29	0.40	1.68	0.31	0.11
Mood	12.66	7.64	0.35	1.66	0.27	0.02	22.88	16.86	0.32	1.36	0.25	0.45
Block 3 Perpetuating												
Caffeine	-3.08	3.19	-0.16	-0.96	-0.16	0.35	11.64	7.06	0.31	1.65	0.31	0.12
Napping	0.44	0.24	0.35	1.8	0.30	0.09	0.15	0.53	0.06	0.07	0.05	0.78

For the final total wake time model, $R^2 = 0.49$, $p = 0.07$. For the final total sleep time model, $R^2 = 0.35$, $p = 0.31$. QOL, quality of life.

to post-KTX patients (**Table 2**). Average sleep onset latency (pre-KTX = 33.1 min and post-KTX = 28.5 min) and wake after sleep onset (pre-KTX = 20.9 min and post-KTX = 20.1 min) did not differ significantly between the 2 groups. There were no significant group differences in the prevalence of insomnia or obstructive sleep apnea.

Regression Analysis of the 3P Model

A summary of the final models calculated for pre-KTX participants can be seen in **Table 3**, and a summary of the final models calculated for post-KTX can be seen in **Table 4**.

The final model predicting TWT among pre-KTX participants was significant, with female sex shown to be a significant individual predictor and greater negative mood trending towards significant prediction of increased TWT, $R^2 = 0.67$, $F_{8,17} = 3.23$, $p < 0.05$. **Table 3** summarizes the regression predicting TWT among pre-KTX participants and **Table 5** shows the model building steps. The final model for TWT among post-transplant participants was trending towards significance,

$R^2 = 0.49$, $F_{8,20} = 2.29$, $p = 0.07$. Inspection of the individual predictors showed that greater mean napping was trending towards prediction of greater TWT. The next largest predictors of increased TWT were greater negative mood and less fatigue. **Table 4** shows the regression results among post-KTX participants and **Table 6** shows the model building steps. The effects of sex from the pre- and post-KTX models were directly compared using the Fisher r-to-z transformation which revealed that sex was a significantly different predictor of TWT ($z = 2.01$, $p < 0.05$) among pre-KTX participants ($r = 0.58$) as compared to post-KTX participants ($r = 0.08$). Female sex was moderately related to increased TWT among pre-KTX participants and had very small positive relationship with TWT among post-KTX.

Among pre-KTX patients, the final model for TST was not statistically significant (**Table 3**), and there were no significant individual predictors of TST. The largest relative relationships were less TST being related to more medical problems, male sex, and more negative mood. The results for this model can be seen in **Table 3** and model building steps can be seen in **Table 5**.

Table 5—Model steps in hierarchical regression predicting total wake time and total sleep time for pre-kidney transplant patients.

	Total Wake Time						
	R ²	df 1	df 2	F for model	p for model	F for change in R ²	p for change in R ²
Model 1: Predisposing	0.52	3	22	6.48	0.00		
Model 2: Predisposing and Precipitating	0.65	6	19	4.56	0.00	1.78	0.19
Model 3: Predisposing, Precipitating, and Perpetuating	0.67	8	17	3.23	0.03	0.38	0.69

	Total Sleep Time						
	R ²	df 1	df 2	F for model	p for model	F for change in R ²	p for change in R ²
Model 1: Predisposing	0.07	3	22	0.46	0.72		
Model 2: Predisposing and Precipitating	0.12	6	19	0.34	0.91	0.28	0.84
Model 3: Predisposing, Precipitating, and Perpetuating	0.15	8	17	0.30	0.95	0.27	0.77

Predisposing factors include age, sex, and medical comorbidity; precipitating factors include quality of life, fatigue and mood; perpetuating factors include caffeine consumption and napping.

Table 6—Model steps in hierarchical regression predicting total wake time and total sleep time for post-kidney transplant patients.

	Total Wake Time						
	R ²	df 1	df 2	F for model	p for model	F for change in R ²	p for change in R ²
Model 1: Predisposing	0.07	3	25	0.57	0.64		
Model 2: Predisposing and Precipitating	0.37	6	22	2.05	0.10	3.36	0.04
Model 3: Predisposing, Precipitating, and Perpetuating	0.49	8	20	2.29	0.07	2.29	0.13

	Total Sleep Time						
	R ²	df 1	df 2	F for model	p for model	F for change in R ²	p for change in R ²
Model 1: Predisposing	0.06	3	25	0.48	0.70		
Model 2: Predisposing and Precipitating	0.26	6	22	1.21	0.34	1.89	0.16
Model 3: Predisposing, Precipitating, and Perpetuating	0.35	8	20	1.28	0.31	1.37	0.28

Predisposing factors include age, sex, and medical comorbidity; precipitating factors include quality of life, fatigue and mood; perpetuating factors include caffeine consumption and napping.

Among post-KTX patients, the final model for TST was not statistically significant (**Table 4**), but there was a significant positive relationship between QOL and TST such that lower QOL was related to less TST. The next largest predictors of less TST were male sex, less general fatigue, less average amount of caffeine consumed, and less negative mood. The model building steps for TST among post-KTX can be seen in **Table 6**.

DISCUSSION

Review of Findings

These results support the findings of previous research, that rates of RLS are lower among patients after receiving kidney transplantation, while the rates of sleep apnea and insomnia appear to be the same among the pre and post transplant groups.²⁻⁶ The occurrence of insomnia and RLS among post-KTX patients remain considerably higher than rates observed in individuals of the same age in the general population.⁷ Furthermore, while not statistically significant, pre-KTX participants were reporting longer total wake time on average, suggesting that the disturbance to pre-transplant patients' sleep may be larger in magnitude relative to post-KTX. Although nonsignificant

in the current study, the results none the less support previous findings that pre-KTX individuals experience lower quality of life as compared to post-KTX individuals. The results did not show an overall difference between the groups on the amount of fatigue or mood disturbance. The lack of a finding of increased fatigue among pre-KTX patients is somewhat surprising when compared to previous research but may be partially explained by pre-transplant participants in this study sleeping more on average.²³ Alternatively, it is possible that a secondary factor, such as reduced social or occupational demands due to compromised health, reduced the amount of fatigue reported.

The observed rates of ongoing sleep disorders indicate that such disorders may be undertreated among both pre- and post-KTX patients. Given the serious medical symptoms these patients manage on a daily basis, including high blood pressure, cardiovascular disease, diabetes, anemia, and electrolyte imbalances, the impact of disturbed sleep may be overlooked by medical providers. However, sleep symptoms do cause significant distress.¹ Patients with an extensive list of daily medications would be understandably reluctant to add additional medication for the treatment of sleep symptoms. Cognitive behavioral treatments for sleep disorders, particularly cognitive behavioral therapy for insomnia (CBTi), may be a safe and

effective treatment for these symptoms (while not adding significantly to the patient's medication regimen). CBTi has been found to be efficacious among numerous groups of medically ill individuals, including cancer and chronic pain patients, who have comparably intensive medical regimen and complications. Additionally, there are a small number of studies which have investigated CBTi among kidney dialysis patients and found significant improvements.^{21,38-41} However, one of the primary limitations of CBTi is the relatively limited number of providers who are trained to provide this intervention and the resulting limited accessibility of this treatment for many patients.

Unique patterns of biopsychosocial factors in sleep disturbance were observed among pre- and post-KTX patients. The prediction of total wake time using biopsychosocial factors was significant among pre-KTX participants and was approaching significance among post-KTX. This suggests that the biopsychosocial factors observed in this study are meaningful predictors of the amount of time spent awake in the night. The attempt to predict total sleep time was not successful for either group. Despite this, some observations can be made regarding the individual factors and the implications of these factors within the Spielman 3Ps model of insomnia.

Among pre-KTX patients, the best predictors of sleep disturbance were those classified as predisposing factors (i.e., sex) and precipitating (i.e., mood) factors of insomnia. If interpreted within the context of the 3Ps model, this would suggest that more of these individuals are earlier in the process of the development of insomnia and perpetuating factors have not yet assumed a maintenance role. The relationship between female sex and increased time awake in the night is consistent with prior research indicating that women are more likely to report insomnia symptoms.⁷ However, the relative strength of this relationship among pre-KTX patients suggests that end-stage renal disease may have a particularly deleterious effect on the sleep of women. Alternatively, it may be that men have a response bias to under-report sleep problems. There are documented sex differences in the selection of dialysis type, with men more often using in-clinic hemodialysis and women more often using in-home peritoneal dialysis.⁴² However, neither form of dialysis has been found to be consistently associated with greater insomnia symptoms.⁴³ The positive relationship between mood and total wake time suggests that pre-KTX participants experienced greater insomnia symptoms concurrent with worse mood and is consistent with previous research.^{13,14,23} This relationship may be the result of worse sleep resulting in greater mood disturbance, worse mood impairing sleep or a third factor impacting both mood and sleep. While the relationship between these two factors was clearly present, further research is needed to determine the causal relationship.¹²⁻¹⁴ Interestingly, the factors explored in this study had relatively little relationship with total sleep time and it remains uncertain which factors are related to time spent sleeping. Other areas for exploration may be more biologically/medically based factors such as dialysis frequency, creatinine levels, and hormones such as cortisol, all of which may impact the timing of the circadian rhythm system. In addition, social factors such as work and family responsibilities may change during a patient's illness resulting in reduced social pressure to adhere to traditional sleep patterns and further disrupting sleep.

Among post-KTX participants, there was evidence that precipitating and perpetuating factors affected sleep. The largest predictor of time awake in the night among post-KTX participants was worse mood. As with the pre-KTX participants, it is not possible to determine the direction of this relationship, but these results emphasize the importance of further research into the interactions between mood and sleep among kidney disease patients. The trending relationship between increased napping and increased total wake time suggests that patients' daytime behaviors may be related to insomnia among post-KTX patients. If conceptualized within the 3-P model, this result would suggest that increased napping would maintain difficulty falling asleep and staying sleep as a result of disruption of the natural sleep need that builds across a day. Indeed, there is evidence that napping increases while patients are receiving dialysis.²⁰ This behavior change may continue after transplantation, becoming a perpetuating factor of insomnia and may be a fruitful area for intervention in the treatment of insomnia. The relationship between perceived reduced quality of life and decreased total sleep time suggests that perceptions of impaired physical health are interrelated with reduced amounts of sleep. This relationship may be mediated through a psychological factor such as rumination about health and sleep or a physiological variable, such as increased pain, and warrants further investigation. Also of note, among post-KTX participants, precipitating factors explored all had small to moderate effects sizes for total wake time and total sleep time. With a larger sample it is possible these factors would have been significant. When taken collectively, the results among post-KTX patients offer evidence of numerous psychological factors related to insomnia, and these factors have been previously identified as predisposing and perpetuating factors of insomnia.¹⁹ Intervention on these psychological factors may be critical for improvement of insomnia symptoms in this population. The evidence-based treatment, CBTi, specifically addresses perpetuating psychological factors through systematic strategies for changing napping habits, caffeine consumption, managing nighttime rumination, and creating a more structured sleep schedule.

It should be noted that while the attempts to explain total wake time for each group were successful, the attempts to explain total sleep time for each group were not. It appears that the biopsychosocial factors chosen in this study are better predictors of wake time in the night. Despite a number of the biopsychosocial factors used to predict total wake time and total sleep time not being significant for the pre- and post-KTX groups, a few observations can be made regarding the relative strength and direction of these relationships. These results suggest that women were more likely to report spending time awake during the night prior to transplantation as compared to women who were assessed after transplantation. This difference may be related to the relatively early stage of insomnia among these patients. Consistent with past research and the hypotheses of this paper, it appears that pre-transplant patients are still experiencing greater impact from predisposing factors such as female sex.

Implications for Clinical Practice

This study specifically investigated the relative impact of various factors in disturbed sleep. Behavior such as napping has

been suggested as a factor in the maintenance of sleep disturbance in this population.²⁰ These sleep related behaviors are specifically targeted when using CBTi and the current results, along with previous studies investigating cognitive behavioral therapy for insomnia among dialysis patients, suggest that such treatment may be a viable treatment option for both dialysis and transplant patients.^{21,41} However, it is also important to note that within the current study there were group-specific differences in the impact of quality of life, and sex.

Among pre-KTX patients, women and patients with more depression or anxiety were found to have more disrupted sleep. By comparison, among post-KTX patients, patients with lower quality of life and increased napping were found to have the most disrupted sleep. These results suggest that a nuanced approach to the treatment of sleep disorders is warranted when treating unique populations. In the treatment of sleep disturbance among pre- and post-KTX patients, clinicians should use measurement tools and history-taking to assess if other factors such as depression and anxiety, compromised health, or napping are relevant contributing factors to the patient's sleep disturbance and treatment plans should be developed which specifically target these relationships.

Limitations

There are limitations to the current study which should be noted. The current study relied on voluntary participation, with a relatively low proportion of the approached patients agreeing to participate (17.5%), and consequently this study may not be representative of pre- and post-KTX patients more generally. However, demographic factors and rates of sleep disorders, including insomnia are consistent with those observed in previous research and do not suggest an oversampling of a particular group of patients.²³ In addition, the limited sample size of this study limits generalizability of these findings to other samples. While these results suggest links among female sex, napping, quality of life, and negative mood to disturbed sleep, these relationships are correlational, and causal conclusions cannot be drawn from this study. However, these results do provide a rationale to further explore these relationships. While many of the factors explored in this study were not statistically significant, the patterns observed may provide direction for future research focusing on the impact of behavioral and other psychological factors on insomnia and these results illustrate the importance of a nuanced understanding of the biopsychosocial factors involved in insomnia development and maintenance. While biological markers of kidney functioning were not included in the estimates of sleep disturbance, implicit in the groupings of pre- and post-transplant status are physiological differences in kidney functioning. Thus, not including this type of factor is not seen a major limitation of the current study.

Future Directions

More research and resources focusing on the impact of sleep disturbance and fatigue among chronic kidney disease patients are needed. These patients experience significant impairments in various domains of life related to their disease, including quality of life, fatigue, and particularly sleep. For sleep treatments to become more available, it is important for additional advocacy

and research to be conducted to increase awareness of patients' sleep problems among health care providers and encourage patients to voice concerns regarding these symptoms. The similar rates of sleep apnea observed in the two groups demonstrate the importance of continuing to assess for and treat these symptoms across the course of kidney disease. The assessment and treatment of apnea and insomnia symptoms among chronic kidney disease patients has the potential to improve overall patient outcomes by reducing the overlap of symptoms and resulting improved diagnosis and treatment. Untreated sleep symptoms among chronic kidney disease patients may increase the difficulty in determining the cause of other symptoms. For example, fatigue could be an indication of a change in kidney functioning and necessitate medical intervention or fatigue may be related to poor nighttime sleep or a dysregulation of the circadian rhythm. By addressing the factors involved in the patient's sleep disturbance and fatigue, the medical professional can more accurately determine if the cause of the fatigue is due to the effects of kidney disease and can provide more effective treatment.

In order to gain greater insight into the psychological factors involved in sleep disturbances among kidney disease patients, there is a critical need for true experimental manipulation of these factors. The use of evidence-based treatments such as CBTi in an experimental study with intervention and control conditions allows for direct testing of the implications of the current study and examination of treatment mechanisms. By using an experimental intervention study which specifically intervenes on precipitating and perpetuating factors of insomnia, it would be possible to determine whether these factors drive insomnia among chronic kidney disease patients.

ABBREVIATIONS

AHI, apnea-hypopnea index
 BDI-II, Beck Depression Inventory-Second Edition
 BMI, body mass index
 CBTi, cognitive behavioral therapy for insomnia
 EEG, electroencephalography
 EMG, electromyography
 ESRD, end-stage renal disease
 KDQOL, Kidney Disease Quality of Life Short Form
 KTX, kidney transplantation
 MMSE, Mini-Mental State Examination
 PSG, polysomnography
 QOL, quality of life
 RLS, restless legs syndrome
 SOL, sleep onset latency
 STAI-Y, State-Trait Anxiety Inventory-State Form
 TST, total sleep time
 TWT, total wake time
 WASO, wake time after sleep onset

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Address correspondence to: Jacob M. Williams, TIRR Memorial Hermann, 1333 Moursund, Houston, TX 77030; Tel: (713) 797-7576; Email: jacob.williams@memorialhermann.org

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