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Effects of 6-Times-Weekly Versus 3-Times-Weekly Hemodialysis on Depressive Symptoms and Self-reported Mental Health: Frequent Hemodialysis Network (FHN) Trials

Mark L. Unruh, MD MS, Brett Larive, MS, Glenn M Chertow, MD MPH, Paul W. Eggers, PhD, Amit X. Garg, MD PhD, Jennifer Gassman, PhD, Maria Tarallo, Fredric O. Finkelstein, MD, and Paul L. Kimmel, MD* on behalf of the FHN Trials Group

Abstract

Background—Patients undergoing maintenance hemodialysis frequently exhibit poor mental health. We studied the effects of frequent in-center and nocturnal hemodialysis on depressive symptoms and self-reported mental health.

Study Design—1-year randomized-controlled clinical trials.

Setting & Participants—Hemodialysis centers in the United States and Canada. A total of 332 patients were randomized to frequent (six times per week) as compared with conventional (three times per week) hemodialysis in the Frequent Hemodialysis Network (FHN) Daily (n=245) and Nocturnal (n=87) Trials.

Intervention—Daily Trial was a trial of frequent (six times per week), as compared with conventional (three times per week) in-center hemodialysis. The Nocturnal Trial assigned patients to either frequent nocturnal hemodialysis (six times per week) or conventional hemodialysis (three times per week).

Outcomes—Self-reported depressive symptoms and mental health.

Measurements—Beck Depression Inventory (BDI) and the mental health composite (MHC) score and emotional subscale of the RAND 36-Item Health Survey at baseline, 4 and 12 months. The MHC score is derived by summarizing these domains of the RAND 36-Item Health Survey: emotional, role emotional, energy/fatigue, and social functioning scales.

Results—In the Daily Trial, subjects randomized to frequent as compared with conventional in-center hemodialysis demonstrated no significant change over 12 months in adjusted mean BDI (-1.9 ± 0.7 vs. -0.6 ± 0.7 ; $p=0.2$), but experienced clinically significant improvements in adjusted

Corresponding Author: Mark Unruh MD MS, University of New Mexico School of Medicine, MSC 10-5550, 1 University of New Mexico, Albuquerque NM 87131-0001, mlunruh@salud.unm.edu.

*A list of Frequent Hemodialysis Network (FHN) Trial Group investigators appears in the Acknowledgements.

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mean MHC (3.7 ± 0.9 vs. 0.2 ± 1.0 ; $P < 0.01$) and the emotional subscale (5.2 ± 1.6 vs. -0.3 ± 1.7 ; $p = 0.01$). In the Nocturnal Trial, there were no significant changes among subjects randomized to nocturnal as compared with conventional hemodialysis on the same metrics.

Limitations—The trial interventions were not blinded.

Conclusions—Frequent in-center hemodialysis, as compared with conventional in-center hemodialysis, improved self-reported general mental health. Changes in self-reported depressive symptoms were not statistically significant. We were unable to conclude whether nocturnal hemodialysis yielded similar effects.

Keywords

hemodialysis; daily hemodialysis; nocturnal hemodialysis; depression; health-related quality of life; clinical trial

The prevalence of end-stage renal disease (ESRD) in the United States is more than a half million persons (nearly 400,000 on maintenance dialysis). The latter figure is expected to reach 750,000 persons in 2020.(1, 2) Despite substantial resources devoted to ESRD treatment, these patients have marked decrements in health-related quality of life (HRQoL) compared to the general population.(3) Unfortunately, advances in dialysis technology and the availability of therapies for ESRD-related complications such as anemia, hyperphosphatemia and secondary hyperparathyroidism over the last decade have yielded no significant improvements in self-reported physical or mental health in patients on maintenance dialysis.(4)

The poor mental health of patients undergoing maintenance hemodialysis may be due in part to a significant burden of depression in this population.(5, 6) The prevalence of depression in the maintenance hemodialysis population has been reported to be between 20% and 30%, and depression in ESRD has been linked to decrements in HRQoL, more frequent hospitalization and premature death.(7–10)

We designed the Frequent Hemodialysis Network (FHN) clinical trials to test whether more frequent hemodialysis would yield clinically important effects on an array of intermediate outcomes, separated into nine domains, including one focused on mood/affect and mental health. We hypothesized that frequent hemodialysis would improve depressive symptoms and self-reported mental health. We also wished to explore whether the effects of more frequent hemodialysis on self-reported depressive symptoms differed according to age, sex, race and level of education.

Methods

Study Design

As described in previous studies from the FHN Trials,^{37, 38} the FHN Daily Trial was a multicenter, prospective, randomized, parallel-group trial of frequent (six times per week), as compared with conventional (three times per week) in-center hemodialysis. The FHN Nocturnal Trial was a similarly designed trial comparing the effects of frequent nocturnal home hemodialysis (six times per week) with conventional (three times per week)

hemodialysis delivered largely at home. Detailed descriptions of the trial designs including randomization, specific inclusion and exclusion criteria, and data collection procedures are described elsewhere.(12) The protocols are accessible at <https://clinicalresearch.ccf.org/fhn/index.html>.

Study Population

Patients on maintenance hemodialysis who achieved mean equilibrated $Kt/V_{urea} > 1.0$ for the last two baseline hemodialysis sessions and weighed > 30 kg were eligible for inclusion. Major exclusion criteria included age < 13 (Daily) or < 18 (Nocturnal) years, residual kidney function > 3 mL/min/35 L (Daily) or mean of creatinine and urea clearance > 10 mL/min/1.73m² (Nocturnal), life expectancy < 6 months, medical need for hemodialysis > 3 times per week, history of poor adherence to hemodialysis, medical conditions preventing cardiac magnetic resonance imaging, inability to communicate in English or Spanish, and anticipated kidney transplantation or relocation within 14 months. Informed consent was obtained from each subject. The study was approved by the Institutional Review Board at each participating study site.(13)

Intervention, control and adherence

After randomization in the Daily Trial, subjects who were assigned to hemodialysis six times per week ($n=125$) had a target equilibrated Kt/V_n (where $V_n = 3.271 \times V^{2/3}$) of 0.9 provided that the length of the session was between 1.5 and 2.75 hours. Subjects who were assigned to thrice-weekly hemodialysis ($n=120$) continued their usual hemodialysis prescriptions, which included a minimum target equilibrated Kt/V_{urea} (the ratio of the equilibrated urea clearance during each dialysis session [Kt] to the patient's volume of urea distribution [V]) of 1.1 and a session length of 2.5 to 4.0 hours.

After randomization in the Nocturnal Trial, subjects were assigned to either three times per week ($n=42$) hemodialysis to a prescribed standard Kt/V_{urea} of > 2.0 and a session length of 2.5 hours or six times per week nocturnal ($n=45$) hemodialysis to a standard Kt/V_{urea} of 4.0 for 6 hours per session. For both Trials, we calculated adherence as the ratio of dialysis sessions attended to dialysis sessions prescribed, by month.

Primary outcomes

The co-primary composite outcomes of the FHN Trials were death or change in self-reported physical health (RAND 36-Item Health Survey [RAND-36] physical health composite) and death or change in left ventricular mass. The pre-specified main secondary outcome for the mental health domain was change (baseline to month 12) in the Beck Depression Inventory (BDI), a 21-question well-validated survey presented in multiple choice format, which measures the presence and degree of depressive symptoms in adults. Each of the answers is scored on a 0 to 3 scale, and inventory items correspond to a specific category of depressive symptom and/or attitude. A higher score reflects a higher likelihood of depression. It is frequently used to assess depression in patients with ESRD(6, 9, 10, 14, 15), and is associated with mortality in this patient population.(10) The BDI has also been used in patients on frequent hemodialysis.(16) We defined clinically important depressive symptoms as $BDI > 15$, in accordance with other studies in the ESRD population. (14, 17,

18) We examined the cognitive component of the BDI to determine whether the observed differences were due to changes in somatic symptoms.(19)

We measured self-reported mental health using the mental-health composite (MHC) score and several domains of mental health and functioning using the subscales from the RAND-36 by means of computer-assisted telephone interview as previously described.(20) The RAND-36 has been validated across diverse populations and healthcare settings and includes eight scales of self-reported health status: physical functioning, role functioning/physical, bodily pain, general health, energy/fatigue, social functioning, role functioning/emotional, and mental health.(20) These scales are scored from 0 to 100, with higher scores indicating better functioning. The mental health composite (MHC) score is a weighted average normalized to a mean score of 50 and standard deviation of 10, using the RAND Corporation method. The MHC score is derived from summarizing the domains of emotional, role emotional, energy/fatigue, and social functioning. These four scales are those most highly correlated with overall mental well-being. The MHC was dichotomized using a cut-off of <43 in order to classify poor mental health in this population.(21)

For both the main-secondary physical health composite outcome and for other outcomes, the primary assessment of treatment effect was based on the change from baseline to 12 months. The 4-month assessment was considered in secondary analyses to assess short-term response to treatment.

Descriptive variables

We collected data on demographic characteristics at baseline and obtained clinical data and laboratory test results at baseline and serially over the course of the study. We performed standardized assessments of coexisting conditions using a modified version of the Charlson Comorbidity Index(22) supplemented with additional items from the Index of Coexistent Diseases.(23)

Covariates included demographics (age, sex, race/ethnicity), clinical characteristics (ESRD vintage, comorbidities including diabetes mellitus and cerebrovascular disease), laboratory parameters (serum creatinine, hemoglobin, and phosphorus), and medications (opioids, antidepressants, benzodiazepines). Laboratory variables were measured pre-dialysis at laboratories affiliated with each clinical center and, if more than one baseline value was collected, the first value was used.

Statistical Analysis

For each trial, we estimated that a sample size of 250 subjects would provide 90% power to detect a difference between adjusted mean changes in BDI score between treatment groups of 0.46 of one standard deviation of the baseline BDI.(13, 24, 25) The Daily Trial nearly reached its recruitment target, while the Nocturnal Trial did not.(13, 24, 25) Owing to difficulties in recruitment, the sample size target for the Nocturnal Trial was ultimately reduced to 90 subjects. We estimated that a sample size of 90 would provide 80% power to detect a larger effect in the BDI score of 0.77 of one standard deviation. We performed parallel analyses separately by Trial (Daily and Nocturnal). Baseline characteristics of the

two analytic cohorts were stratified according to intervention status (frequent *versus* conventional), and characterized using mean ($\pm$ standard deviation), median (10th percentile, 90th percentile) or frequency (%), as appropriate.

We compared between-group mean changes in scores from baseline to month 12 for the BDI and the RAND-36 MHC and subscales using linear mixed effects models with unstructured covariance matrix incorporating baseline, 4-month and 12-month scores for each metric. In accordance with the pre-specified analysis plans, we adjusted for baseline score in both trials, and for clinical center in the Daily Trial.(26) To illustrate effects in more clinically interpretable terms, we calculated the relative changes in dichotomized values (BDI: >15 for clinically important depressive symptoms *versus* ≤ 15 for no depression; MHC: <43 for impaired mental health *versus* ≥ 43 for non-impaired mental health). Because BDI was positively skewed, we performed secondary analyses using log transformed BDI. Results from these analyses were expressed as percentage change from baseline.

We pre-specified subgroup analyses according to age, sex, race, and education level. The primary assessment of treatment interactions with quantitative subgroup factors was based on a test for linear interaction which treated the subgroup factor as a continuous variable. Estimated treatment effects are also provided for the subgroups defined by the above indicated cutoffs for descriptive purposes. In the Daily Trial, we present p-values for the interactions without adjustment for multiple comparisons. Due to its limited sample size, we considered subgroup analyses in the Nocturnal Trial in an exploratory fashion without significance testing.

To determine whether the effects of frequent hemodialysis on self-reported mental health were dependent on depressive affect, we conducted one additional *post-hoc* analysis of change in MHC additionally adjusting for baseline BDI. We also compared the proportion of patients with clinically important depressive symptoms and poor mental health as defined above at baseline and 12 months. We examined the subscales of the SF-36 summarized in the MHC. We performed all analyses according to the intention-to-treat principle and interpreted 2-tailed p-values <0.05 as statistically significant. We used SAS software, version 9.2 (SAS Institute Inc, Cary, NC, USA).

Results

Study Subjects

Figures 1A and 1B show the number of subjects enrolled and randomized into the Daily and Nocturnal Trials, respectively. The number with measurements of depressive symptoms and self-reported mental health are presented as well as reasons for missing data (such as death or transplantation).

Daily Trial

As shown in Figure 1A, change in scores of the BDI and the RAND-36 MHC from baseline and 12-month scores were ascertained in 200 and 194 subjects, respectively. Among individuals randomized to frequent hemodialysis, five died and 11 underwent kidney

transplantation; in the conventional hemodialysis group, nine died and 13 underwent kidney transplantation.

Nocturnal Trial

As shown in Figure 1B, change in scores of the BDI and RAND-36 MHC from baseline and 12-month scores were ascertained in 76 and 77 subjects, respectively. Among individuals randomized to frequent hemodialysis, two died and three underwent kidney transplantation; in the conventional hemodialysis group, one died and none had kidney transplantation.

Demographic Characteristics

The baseline characteristics of subjects in the two trials stratified by treatment status (frequent *versus* conventional hemodialysis) are shown in Table 1. In terms of age, sex, race/ethnicity, primary cause of kidney disease, coexisting conditions, and median ESRD vintage, the study population was diverse. There were no statistically or clinically significant differences in baseline characteristics between frequent and conventional groups in either trial.

Selected treatment parameters, including dialysis metrics and medications known to affect the central nervous system are shown in Table 2 for the Daily and Nocturnal Trials. In the Daily Trial, there were no between group differences in the proportion of subjects using benzodiazepines, antidepressants, or opioids at baseline or at 12-months. In the Nocturnal Trial, there were no differences in the use of antidepressants or opioids, but benzodiazepines were more widely used at 12 month follow-up in the group randomized to frequent nocturnal hemodialysis.

Depressive Symptoms and Mental Health

Daily Trial

Main-Secondary Analysis—The mean BDI exhibited a 1.4-U greater decline (95% confidence interval [CI], −3.5 to 0.5 U) at 12 months in the frequent hemodialysis group compared to the conventional in-center hemodialysis group, but the difference between treatment groups was not statistically significant ($p = 0.2$) (Table 3).

Other analyses—The estimated treatment difference in the mean BDI score was slightly larger at the 4-month assessment (1.9 U; 95% CI, −3.5 to −0.3 U; $P = 0.02$). (Table 3). The analyses of the log-transformed BDI values, which assess relative rather than absolute change, followed a similar longitudinal pattern but demonstrated weaker trends in support of a treatment effect. The distribution of dichotomized BDI values presented in Figure 2A illustrate that rates of clinically important depressive symptoms ($BDI > 15$) declined by 14.7% over the 12 months of follow-up in the frequent arm but remained largely unchanged in the control arm (0.9% increase).

The frequent in-center hemodialysis intervention led to larger increases in the MHC score compared to the conventional hemodialysis group at both 4 and 12 months of follow-up (mean differences of 3.4 [95% CI, 1.3 to 5.6; $P = 0.002$] and 3.5 [95% CI, 0.9 to 6.0; $P =$

0.007], respectively). The dichotomized values illustrated in Figure 2B show that the proportion of subjects with poor mental health (MHC<43) increased by 1.2% over follow-up in the conventional arm but decreased by 12.0% in the frequent arm. Frequent in-center hemodialysis also resulted in improved emotional and energy subscale scores (Table 3). Changes in the remaining subscales for MHC also favored the frequent in-center group but the trends were not statistically significant: for 12 month changes, mean Emotional Problem scores increased by 3.8 U more (95% CI, -5.1 to 12.5 U; P= 0.1) and mean Social Functioning scores increased by 7.2 U more (95% CI, -2.4 to 10.6 U; P= 0.2)(Table 3).

The effects of frequent hemodialysis on depressive symptoms and self-reported mental health did not significantly differ according to age, sex, race/ethnicity, and level of education. In a *post hoc* analysis, the estimated treatment effect on the change in the MHC was essentially unchanged after adjustment for baseline depression score (1.7 ± 1.3 vs. -1.8 ± 1.4 ; $p < 0.01$).

Nocturnal Trial

Main Secondary Analysis—The mean BDI exhibited a 1.6-U greater decline (95% CI, -4.9 to 1.7 U) at 12 months in the frequent nocturnal group compared to the conventional home or in-center hemodialysis group, but this difference was not statistically significance ($p = 0.3$) (Table 3).

Other Analyses—There were no statistically significant differences between the frequent nocturnal and the conventional home or in-center hemodialysis groups for any of the other assessments of depressive symptoms or self-reported mental health (Table 3, Figures 2A & 2B) at month 12. At month 4, there was a 38% (95% CI, -3.0% to -60.4%) greater decline in the geometric mean BDI in the frequent hemodialysis group compared to the conventional hemodialysis group in the analysis of log transformed BDI. While none of the remaining treatment comparisons were statistically significant at either month 4 or month 12, the signs of all comparisons were in the direction favoring the frequent nocturnal hemodialysis intervention, with trends generally exhibiting similar magnitudes to those observed in the larger Daily Hemodialysis trial.

Discussion

Frequent in-center hemodialysis, as compared with conventional in-center hemodialysis, did not produce a statistically significant reduction in depressive affect symptoms as assessed by the pre-specified main secondary outcome (the BDI) after 12 months of treatment. However, the frequent in-center intervention did lead to improved self-reported general mental health (MHC). Frequent in-center treatment also improved the energy and emotional components of the MHC while the remaining two subscales trended toward the same benefit.

Due in part to the small sample size in the Nocturnal Trial, we were unable to conclude whether frequent nocturnal hemodialysis yielded a benefit for self-reported Mental Health similar to that observed in the Daily Trial, nor whether it led to a moderate benefit on the BDI. The directions of all outcome comparisons for the BDI, physical health composite and their subscales favored the frequent hemodialysis intervention at both the month 4 and

month 12 assessments in both trials. The magnitudes of the favorable trends were generally similar in the two trials, with criteria for statistical significance reached more often in the Daily Trial due to the greater precision associated with the larger sample size of that study. This pattern might be interpreted as consistent with a moderate benefit of frequent dialysis (whether in-center daily or at-home nocturnal) across the depressive symptom-mental health domain, which, due in part to random variation, yielded treatment effect estimates that met the criteria for statistical significance in some cases but not others. It is also important to note that self-reported depressive symptoms differ from the mental well-being as assessed by the MHC, and that these differences be reflected in the different responses to the study intervention. However, it is important to caution that the treatment comparisons of the pre-specified main secondary BDI outcome did not approach statistical significance in either trial, and that the consistent direction of the trends in favor of frequent dialysis may in part reflect correlated results across related outcome measures.

More frequent hemodialysis was associated with gains in self-reported mental health in an observational study of 239 subjects undergoing frequent hemodialysis; a significant within-patient decline in the Beck Depression Inventory (BDI) score of 11.2 to 7.8 ($p < 0.001$) (27) was also described. This change observed in the FREEDOM (Following Rehabilitation, Economics and Everyday-Dialysis Outcome Measurements) Study was larger in magnitude than the change observed in the FHN Trials. The place of short frequent dialysis, time of dialysis, and dose of dialysis in FREEDOM differed from that delivered in the FHN Trials. There are also a number of biases found in observational trials such as FREEDOM which can lead to inflated estimates of effects (28). For example, there were differences in retention between FREEDOM and FHN which may have led to the differences observed between the trials, given that the FREEDOM Study had 46% attrition and FHN had 19%. A randomized trial of nocturnal hemodialysis conducted in Alberta, Canada, demonstrated no significant effect on mental health (29), but this study had limited power to detect clinically important differences between groups.

Several studies have examined traditional, non-dialytic interventions aimed at improving depressive symptoms in ESRD. In a pilot trial, Koudi et al. showed that aerobic exercise improved symptoms of depression (30), while a randomized trial of 96 patients on hemodialysis showed no significant benefit of exercise training on depression scores at one year (31). Treatments for depression in ESRD include antidepressants (32–35) and cognitive behavioral therapy (CBT) (36). Recently, Duarte *et al.* (36) performed a 12-week randomized trial using group CBT for major depression in patients on hemodialysis. Patients receiving CBT had significant improvements of BDI and Sleep, Burden of Kidney Disease and overall health scores as measured by the Kidney Disease Quality of Life–Short Form compared with the controls. However, Wuerth et al. performed a quality improvement project among patients undergoing peritoneal dialysis and found that while these patients may be screened and diagnosed for depression, a large proportion (48%) refuse further pharmacotherapy (35). Thus, a trial of more frequent hemodialysis might be an alternative means of attenuating depressive symptoms among patients refusing anti-depressants, exercise, or CBT. Frequent hemodialysis may be particularly beneficial to those with depressive symptoms and other

health conditions, such as refractory hypertension, increased left-ventricular mass or hyperphosphatemia (37–39).

While depression is a major concern in the care of patients with ESRD, there are also major decrements in HRQoL and mental health which in turn are associated with higher rates of cardiovascular disease.(40) The marked burden in HRQoL of patients undergoing ESRD may be in part due to comorbid psychosocial factors, depression, or inadequate clearance of uremic solutes (“toxins”). The HEMO (Hemodialysis) Study showed no significant effect of higher urea clearance (expressed as equilibrated Kt/V) when delivered thrice weekly or differences in membrane flux on HRQoL(41). In the FHN Daily Trial, there were significant improvements in self-reported mental health composite score in the frequent compared to the thrice weekly hemodialysis. The MHC score is derived from summarizing the domains of emotional, role emotional, energy/fatigue, and social functioning. Both emotion and fatigue were significantly improved and there were non-significant positive effects on role-emotional and social functioning from the frequent in-center hemodialysis intervention. The effects of nocturnal hemodialysis on MHC and the subscales were similar in magnitude, but with larger confidence limits due to the smaller sample size.

There are two widely used approaches to understanding whether significant changes observed in HRQoL are clinically important. One method of evaluation is to use a distribution based approach, most commonly relating the mean change to the standard deviation for the score at baseline. In the case of the MHC for the Daily trial, a change in MHC score of 3.5 points in a sample with a standard deviation of 19.1 reflects an effect size of 0.30, which is larger than the effect size of 0.2 proposed as a rule of thumb threshold for a clinically relevant but small effect(42). The changes from Daily Dialysis observed in emotional well-being (effect size, 0.28) and energy/fatigue (effect size, 0.36) are also larger than this rough rule of thumb. The second approach is to relate the study findings to clinical anchors which serve to convey clinical relevance. As a more anchor-based approach presented in Figure 2, we demonstrate that a significantly smaller proportion of those receiving daily dialysis have declines in the MHC score <43. When compared to the effects on emotional well-being and energy/fatigue of correcting anemia from 11.0–12.5 g/dl to 12.0–15.0 g/dl among patients with CKD with erythropoietin, the effects of Daily Dialysis were slightly larger in magnitude for emotional well-being (5.5 vs. 5.0) and fatigue (8.3 vs. 5.2)(43).

Fatigue is a highly prevalent symptom among patients undergoing hemodialysis and improvement in fatigue is highly valued by ESRD patients in decision making for dialysis. (44–46) Ramkumar et al. reported that improvements in fatigue were among the most important reasons for patients to consider undergoing more frequent dialysis.(47) In their study, 57% would agree to undergo more frequent treatments to improve fatigue compared whereas only 19% would do so for up to a 3-year survival benefit. While daily hemodialysis was associated with a significant reduction in post-dialysis fatigue in the FREEDOM Study(27) and in other observational studies (48), this is the first randomized trial of frequent hemodialysis demonstrating a benefit for overall fatigue. The precise mechanism for improvement in fatigue in this trial is difficult to ascertain since more frequent dialysis may impact multiple co-existing contributing factors such as small-molecule clearance,

volume, inflammation, timing of dialysis and health behaviors. We did not observe a significant benefit on fatigue with frequent nocturnal hemodialysis, consistent with findings from the Alberta Study.⁽²⁹⁾ While the lack of significant benefit may be related to the smaller sample size, adverse effects of nocturnal hemodialysis on sleep hygiene, and/or adverse effects of soporific drugs could also play a role.

The study findings should be judged in light of several limitations. First, difficulty in recruitment reduced the sample size of the Nocturnal Trial, which precluded detection of smaller but possibly important effects of frequent nocturnal hemodialysis on mental health and depression. Second, the trials were not blinded, given the stark differences in the interventions. Third, we used patient-reported metrics to assess depressive symptoms and mental health in the FHN trials. More formal assessment by psychiatrists, clinical psychologists, or other mental health professionals might have provided additional insight into the effects of the intervention on the mental health domain.

In summary, frequent in-center hemodialysis, as compared with conventional in-center hemodialysis, improved self-reported general mental health. While mean changes in self-reported depressive symptoms were not significantly different, the effects were nominally positive and the proportion of subjects with high BDI scores was reduced. Frequent nocturnal hemodialysis had no significant effects on depressive symptoms or mental health, however, the magnitude of the treatment effects were consistent with those observed in frequent in-center hemodialysis. These findings support the contention that frequent hemodialysis may improve mental health and well-being in patients with ESRD.

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Figure 1.

Flow diagrams for (1) Daily Trial and (B) Nocturnal Trial showing the number of subjects enrolled, assigned to each study arm, and with baseline and 12-month ascertainment of each metric. *Two patients received kidney transplants late during follow-up and were included in the 12-month change in MHC and BDI analyses

A

B **Figure 2.****A.** Fraction of subjects who had a BDI Score >15 (Daily and Nocturnal Trials).**B.** Fraction of subjects who had a score <43 on the RAND-36 Mental Health Composite (Daily and Nocturnal Trials).

Table 1**Baseline Characteristics of FHN Participants**

Variables	Daily Trial				Nocturnal Trial			
	n	All (N=245)	3x/wk HD (n=120)	6x/wk HD (n=125) n	n	AI (N=87)	3x/wk HD (n=42)	6x/wk HD (n=45)
Age (y)	245	50.4 ± 13.9	52.0 ± 14.1	48.9 ± 13.6	87	52.8 ± 13.6	54.0 ± 12.9	51.7 ± 14.4
Male sex	245	151 (61.6%)	73 (60.8%)	78 (62.4)	87	57 (65.5)	28 (66.7)	29 (64.4)
Race /Ethnicity	245				87			
Black/ African-American/ African		102 (41.6%)	53 (44.2%)	49 (39.2%)		23 (26.4%)	11 (26.2%)	12 (26.7%)
White/ Caucasian, non-Hispanic		89 (36.3%)	46 (38.3%)	43 (34.4%)		48 (55.2%)	21 (50.0%)	27 (60.0%)
Other/Mixed		54 (22.1%)	21 (17.5%)	33 (27.4%)		16 (18.3%)	10 (23.8%)	6 (13.3%)
Primary language English	245	196 (80.0%)	101 (84.2%)	95 (76%)	87	77 (88.5%)	36 (85.7%)	41 (91.1%)
ESRD vintage (y)	245	3.64 (0.63; 14.26)	3.40 (0.58; 12.94)	3.85 (0.69; 17.31)	87	0.91 (0.09; 11.48)	0.53 (0.10; 6.00)	1.32 (0.09; 12.55)
Education	242				86			
< High school graduate		51 (21.1%)	21 (17.6%)	30 (24.4%)		13 (15.1%)	5 (11.9%)	8 (18.2%)
High school graduate		58 (24.0%)	32 (26.9%)	26 (21.1%)		21 (24.4%)	9 (21.4%)	12 (27.3%)
> high school		133 (55.0%)	66 (55.5%)	67 (54.5%)		52 (60.5%)	28 (66.7%)	24 (54.5%)
Diabetes	245	100 (40.8%)	50 (41.7%)	50 (40.0%)	87	37 (42.5%)	18 (42.9%)	19 (42.2%)
Stroke	245	18 (7.3%)	9 (7.5%)	9 (7.2%)	87	2 (2.3%)	1 (2.4%)	1 (2.2%)
Charlson Comorbidity Index	245	1.82 ± 1.95	1.88 ± 2.03	1.76 ± 1.89	87	1.72 ± 1.75	1.88 ± 1.93	1.58 ± 1.57
Beck Depression Index	240	10 (3; 24)	10 (3; 24)	11 (3; 26)	87	10 (3; 26)	10 (4; 26)	10 (3; 19)
Benzodiazepines	245	31 (12.6%)	13 (10.8%)	18 (14.4%)	87	15 (17.2%)	7 (16.7%)	8 (17.8%)
Antidepressants	245	35 (14.3%)	15 (12.5%)	20 (16.0%)	87	22 (25.3%)	10 (23.8%)	12 (26.7%)
Opioids	245	42 (17.1%)	19 (15.8%)	23 (18.4%)	87	18 (20.7%)	7 (16.7%)	11 (24.4%)
Predialysis SBP (mmHg)	245	146 ± 18	146 ± 18	147 ± 18	87	149 ± 18	153 ± 22	145 ± 13
Predialysis DBP (mmHg)	245	80 ± 12	78 ± 12	81 ± 11	87	81 ± 12	83 ± 13	80 ± 11
Weekly standard Kt/V	245	2.52 ± 0.35	2.53 ± 0.39	2.50 ± 0.31	84	2.34 ± 0.31	2.34 ± 0.34	2.35 ± 0.28
Hemoglobin (g/dL)	244	11.9 ± 1.3	12.0 ± 1.2	11.9 ± 1.3	87	11.8 ± 1.1	11.9 ± 1.1	11.6 ± 1.1
Phosphate (mg/dL)	245	5.78 ± 1.64	5.64 ± 1.53	5.91 ± 1.73	87	5.80 ± 1.61	5.77 ± 1.65	5.82 ± 1.59
Albumin (g/dL)	245	3.94 ± 0.42	3.94 ± 0.46	3.94 ± 0.37	87	3.91 ± 0.49	3.92 ± 0.51	3.90 ± 0.48

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Note: Values for categorical variables are given as number (percentage); values for continuous variables, as mean $\pm$ standard deviation or median (10th; 90th percentile).
FHN, Frequent Hemodialysis Network; HD, hemodialysis; ESRD, end-stage renal disease; SBP, systolic blood pressure; DBP, diastolic blood pressure

Table 2

Selected Baseline and End-of-Study Characteristics

Characteristic	Daily Trial				Nocturnal Trial			
	Baseline		Month 12		Baseline		Month 12	
	3×/wk HD (n=120)	6×/wk HD (n=125)	3×/wk HD (n=120)	6×/wk HD (n=125)	3×/wk HD (n=42)	6×/wk HD (n=45)	3×/wk HD (n=42)	6×/wk HD (n=45)
Weekly standard Kt/V _{urea}	2.49 ± 0.38	2.49 ± 0.27	2.47 ± 0.27	3.49 ± 0.63	2.35 ± 0.35	2.33 ± 0.30	2.61 ± 0.44	4.47 ± 1.60
Ultrafiltration rate (ml/min)	14.8 ± 4.0	15.0 ± 5.5	14.5 ± 4.3	13.9 ± 4.7	10.9 ± 6.2	10.1 ± 6.4	10.4 ± 3.8	6.0 ± 3.6
Benzodiazepine use	10 (13%)	14 (14%)	13 (14%)	16 (16%)	7 (18%)	5 (14%)	6 (15%)	10 (27%)
Antidepressant use	11 (12%)	15 (15%)	14 (15%)	15 (15%)	9 (23%)	10 (26%)	10 (27%)	9 (24%)
Opioid use	15 (16%)	17 (17%)	21 (23%)	22 (21%)	7 (18%)	11 (30%)	14 (36%)	14 (38%)

Note: Values for categorical variables are given as number (percentage); values for continuous variables, as mean ± standard deviation.

HD, hemodialysis.

* End-of-study sample sizes range from 92 to 104 in the daily study and 37 to 40 in the nocturnal study.

Table 3

Comparison of changes for frequent (6-times-weekly) vs. conventional (3-times-weekly) in-center HD

Variable	n/ HD	Observed Data			Adjusted Means and Treatment Effects ²				
		Baseline	Month 4	Month 12	Month 4		Month 12		
					Change from Baseline	6x vs 3x	Change from Baseline	6x vs 3x	
Daily Trial									
BDI Score	86	3x	12.4 ± 9.5	12.5 ± 10.1	12.1 ± 9.9	+0.1 ± 0.6	-1.9* (-3.5, -0.3)	-0.6 ± 0.7	-1.4 (-3.2, 0.5)
	95	6x	12.6 ± 8.6	11.0 ± 8.6	10.7 ± 8.8	-1.8 ± 0.6		-1.9 ± 0.7	
Cognitive Subscale of BDI Score [^]	86	3x	7.0±7.4	7.2±7.6	6.9±7.4	+0.1 ± 0.4	-1.1(-2.3,0.0)	+0.4±0.6	-0.6 (-2.0, 0.9)
	95	6x	7.1± 6.3	6.3 ± 6.3	6.3± 6.5	-1.1 ± 0.4		-1.0 ± 0.5	
Mental Health Composite (RAND-36)	89	3x	46.0 ± 10.3	45.1 ± 10.4	45.7 ± 11.8	-0.4 ± 0.8	3.4** (1.3, 5.6)	+0.2 ± 1.0	3.5** (1.0, 6.0)
	100	6x	44.3 ± 13.0	47.7 ± 11.8	48.8 ± 11.4	+3.0 ± 0.8		+3.7 ± 0.9	
Emotional Well-Being (RAND-36) [^]	90	3x	77.6 ± 16.3	76.2 ± 19.2	75.6 ± 20.9	-0.3 ± 1.5	4.1* (0.2, 7.9)	-0.3 ± 1.7	5.5* (1.3, 9.8)
	102	6x	73.1 ± 22.5	77.9 ± 19.3	80.3 ± 17.5	+3.8 ± 1.4		+5.2 ± 1.6	
Role Limitation due to Emotional Problems (RAND-36) [^]	90	3x	78.4 ± 35.2	75.4 ± 39.3	77.1 ± 38.4	-1.7 ± 3.3	6.1 (-2.4, 14.5)	-0.1 ± 3.5	3.8 (-5.1, 12.7)
	102	6x	73.6 ± 38.1	78.3 ± 36.1	80.2 ± 36.1	+4.4 ± 3.1		+3.6± 3.3	
Energy/Fatigue (RAND-36) [^]	90	3x	51.2 ± 20.8	51.1 ± 19.2	51.6 ± 20.5	+0.6 ± 1.8	7.1** (2.4, 11.8)	+1.6 ± 2.0	8.3** (3.2, 13.5)
	102	6x	47.1 ± 25.2	55.8 ± 24.7	58.6 ± 23.4	+7.7 ± 1.8		+10.0 ± 1.9	
Social Functioning (RAND-36) [^]	90	3x	72.3 ± 25.5	70.6 ± 24.8	72.8 ± 29.5	-1.5 ± 2.3	4.7 (-1.0, 10.4)	+0.9 ± 2.5	4.1(-2.4, 10.6)
	102	6x	70.4 ± 28.0	73.5 ± 25.8	76.8 ± 25.5	+3.2 ± 2.2		+5.0 ± 2.4	
Nocturnal Trial									
BDI Score	38	3x	12.2 ± 9.2	11.8 ± 8.2	11.1 ± 10.2	0.0 ± 1.0	-1.7(-4.4, 0.9)	-0.4 ± 1.2	-1.6 (-4.9, 1.7)
	35	6x	11.2 ± 8.1	10.0 ± 8.0	9.7 ± 8.6	-1.8 ± 1.0		-2.0 ± 1.2	
Cognitive Subscale of BDI Score [^]	38	3x	6.5 ± 6.9	6.7± 6.0	6.6 ± 7.8	+0.5 ± 0.7	-1.3 (-3.1, 0.5)	+0.6 ± 0.9	-1.6 (-4.1, 0.8)
	35	6x	6.2 ± 6.1	5.6 ± 5.5	5.3 ± 5.9	-0.8 ± 0.7		-1.1 ± 0.9	
Mental Health Composite (RAND-36)	38	3x	45.9 ± 12.6	46.4 ± 10.3	45.6 ± 12.2	+0.1 ± 1.5	2.1(-1.7, 5.9)	-0.7 ± 1.6	3.7 (-0.5, 8.3)
	35	6x	45.6 ± 10.5	48.0 ± 10.2	48.2 ± 11.7	+2.3 ± 1.5		+3.0 ± 1.6	
Emotional Well-Being (RAND-36) [^]	39	3x	77.1 ± 21.7	77.8 ± 18.4	75.6 ± 21.4	+0.3 ± 2.4	3.0(-3.0, 9.1)	-2.0 ± 2.7	5.3 (-1.8, 12.5)
	36	6x	75.7 ± 18.1	79.7 ± 15.5	78.4 ± 18.0	+3.4 ± 2.4		+3.3 ± 2.7	

Variable	n ¹	HD	Observed Data ^{***}			Adjusted Means and Treatment Effects ²			
			Baseline	Month 4	Month 12	Month 4		Month 12	
						Change from Baseline	6× vs 3×	Change from Baseline	6× vs 3×
Role Limitation due to Emotional Problems (RAND-36) [^]	39	3×	77.0 ± 39.3	81.3 ± 34.2	82.9 ± 33.2	+0.5 ± 4.7	3.4(−8.4, 15.3)	+1.7 ± 5.5	4.9(−8.2, 18.2)
	36	6×	87.4 ± 24.9	88.6 ± 26.5	89.7 ± 26.7	+3.9 ± 4.7		+6.6 ± 5.4	
Energy/Fatigue (RAND-36) [^]	39	3×	48.4 ± 19.5	51.2 ± 18.3	49.6 ± 22.6	+2.5 ± 3.2	1.6(−6.5, 9.7)	+0.1 ± 3.3	3.0(−5.9, 11.9)
	36	6×	48.6 ± 22.9	52.4 ± 21.3	51.4 ± 25.0	+4.1 ± 3.2		+3.1 ± 3.3	
Social Functioning (RAND-36) [^]	39	3×	75.6 ± 25.6	74.7 ± 21.7	76.0 ± 26.2	−0.6 ± 3.7	3.2(−6.1, 12.5)	+0.3 ± 3.9	7.2(−3.1, 17.5)
	36	6×	73.1 ± 25.3	76.0 ± 24.8	80.4 ± 26.1	+2.6 ± 3.7		+7.5 ± 3.9	

Abbreviations: BDI, Beck Depression Inventory; RAND-36, RAND 36-Item Health Survey; 3×, three times weekly; 6×, six times weekly; HD, hemodialysis

* p 0.05

** p 0.01

*** Mean ± standard deviation

[^] Subscale score

¹ For observed data, numbers are the randomized patients providing baseline, 4-month and 12-month measurements. For adjusted results all available data are used.

² Results of mixed effects analyses controlling for the baseline level of the factor analyzed; ±SE or with 95%CI