Directly Observed Weekly Fluoxetine for Major Depressive Disorder Among Hemodialysis Patients: A Single-Arm Feasibility Trial

Kelley M. Kauffman, Jacqueline Dolata, Maria Figueroa, Douglas Gunzler, Anne Huml, Julie Pencak, Martha Sajatovic, and Ashwini R. Sehgal

Rationale & Objective: Major depressive disorder (MDD) is common among hemodialysis patients, but treatment can add to their pill burden and may be limited by nonadherence. We sought to investigate the value of directly observed, once-weekly fluoxetine dosing in MDD.

Study Design: Feasibility trial of adult hemodialysis patients with untreated MDD. The diagnosis of MDD was determined using the Mini International Neuropsychiatric Interview.

Setting & Participants: 16 patients at 15 hemodialysis facilities in Northeast Ohio.

Intervention: Patients were initially prescribed 20 mg of fluoxetine once daily for 2 weeks to assess their tolerance. The patients took this fluoxetine unobserved at home. They were then transitioned to 90 mg of fluoxetine once weekly for 10 weeks. The patients took this weekly fluoxetine during hemodialysis treatment and were observed by the study staff. The dose was increased to 180 mg once weekly among patients with an inadequate response based on the judgment of the prescribing clinician.

Outcomes: Mini International Neuropsychiatric Interview diagnosis of MDD at the end of the trial and changes in the Patient Health Questionnaire (PHQ-9) scores over 12 weeks.

Results: One patient withdrew from active treatment after 2 daily doses of 20 mg of fluoxetine because of side effects of stomach cramping, vomiting, dizziness, and lightheadedness but completed the baseline and final assessments. The remaining 15 patients received all scheduled weekly fluoxetine doses during the trial. At 12 weeks, 14 of 16 patients (87.5%) no longer met the criteria for MDD ($P < 0.001$). Among all participants, the mean PHQ-9 scores decreased from 11.3 to 6.6 ($P = 0.002$).

Limitations: Small sample size, modestly elevated baseline PHQ-9 scores, no comparison group, and short treatment duration.

Conclusions: Directly observed, once-weekly fluoxetine may be an effective and well-tolerated treatment option for hemodialysis patients. Future research should investigate longer-term health outcomes of weekly fluoxetine in this population and explore the feasibility of implementing this depression treatment model in routine clinical practice.

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There is substantial evidence that directly observed treatment of tuberculosis and HIV increases adherence, reduces patient burden, and improves outcomes.$^{14,21}$ Directly observed treatment generally involves a standardized treatment regimen that is observed by a health care worker or trained layperson over time. Directly observed therapy has been particularly effective for hard-to-reach, marginalized, and incarcerated populations.$^{21}$

Fluoxetine is the only selective serotonin reuptake inhibitor with a long-acting formulation. Research in the general population has found that the once-weekly formulation of the antidepressant fluoxetine at a dose of 90-180 mg is as effective and safe as the standard formulation fluoxetine at a daily dose of 20 mg for the management of MDD.$^{22,24}$ Additionally, the weekly formulation may be more acceptable by patients who already have a high pill burden, is associated with higher rates of adherence, and does not require kidney- or hemodialysis-related dose adjustments.$^{13,23,25,29}$ This feasibility trial investigates the use of directly observed...
Major depressive disorder (MDD) is a common disorder among patients receiving hemodialysis. However, patients may perceive treatment for MDD to be too burdensome when added to an already taxing hemodialysis regimen. This feasibility trial was designed to examine the efficacy and tolerability of a once-weekly, directly observed fluoxetine treatment protocol for MDD management in this population. Hemodialysis patients with untreated MDD were enrolled for 12 weeks of directly observed fluoxetine treatment. Their safety and progress was monitored by a psychiatric nurse practitioner. Following the completion of the study, only 2 of the 16 patients still met the criteria for MDD. Overall, once-weekly, directly observed fluoxetine for MDD in this population appears to be a safe, effective, and well-tolerated treatment modality.

### METHODS

#### Setting and Participants

The study was conducted at 15 in-center hemodialysis facilities that are part of the Centers for Dialysis Care system in Northeast Ohio. All adult, English-speaking, cognitively intact patients who had been on maintenance hemodialysis for at least 3 months were invited to participate in an ongoing project investigating the psychometric properties of a depression screening instrument, the Patient Health Questionnaire (PHQ-9), among hemodialysis patients. A PHQ-9 score of ≥10 is an established threshold for clinically relevant depressive symptoms. However, we found in our preliminary work that some patients with scores of <10 still met the diagnostic criteria for MDD. As a result, patients who scored ≥10 on the PHQ-9 or scored 5-9 while also reporting anhedonia or a depressed mood were further evaluated by the study psychiatric nurse practitioner (KMK) using the Mini International Neuropsychiatric Interview. Anhedonia and depressed mood are the first 2 questions in the PHQ-9 and correspond to the 2 key MDD diagnostic criteria. Patients with MDD based on the Mini International Neuropsychiatric Interview were invited to participate in a trial of weekly, directly observed fluoxetine treatment. To focus on untreated depression, we excluded patients who were already taking a psychiatric medication or had other psychiatric diagnoses. To ensure that patients would be present for directly observed treatment, we excluded patients who skipped more than 3 treatments in the previous 4 weeks or had a substance use disorder. Current and previous medication histories were established with chart abstraction and verbal reports from patients. Any current or past use of psychiatric medications was confirmed before enrollment. However, only current use of a psychiatric medication and a known or documented fluoxetine allergy were considered exclusion criteria. Despite having an initial patient recruitment goal of 96 participants, only 16 were enrolled in this feasibility study. This resulted primarily from more patients than expected scoring below our thresholds on the PHQ-9 and/or being on a psychiatric medication before enrollment (Fig 1). All participants provided written informed consent, and the study was approved by the institutional review board of the MetroHealth System, Cleveland, Ohio (IRB17-00768).

#### Intervention

Eligible participants were initially prescribed 20 mg of fluoxetine once daily for 2 weeks to assess tolerance. The patients took this daily fluoxetine unobserved at home. Clinical evaluations were performed on days 3, 7, and 14 and involved repeating the PHQ-9; asking about fluoxetine adherence; and assessing side effects, such as nausea, headache, and trouble sleeping.

The patients were then transitioned to 90 mg of fluoxetine once weekly for 10 weeks. The patients took this weekly fluoxetine during hemodialysis treatment while observed by study staff. Clinical evaluations were performed every 2 weeks and involved a clinical interview and a repeat PHQ-9 to assess the response to fluoxetine and any side effects. The dose was increased to 180 mg once weekly among patients with an inadequate response as determined by the prescribing clinician’s evaluation of PHQ-9 results and patient reports of symptom response to treatment.

#### Outcomes

The primary study outcomes were a Mini International Neuropsychiatric Interview diagnosis of MDD at the end of the trial and a change in PHQ-9 scores over 12 weeks.

#### Analysis

We used descriptive statistics (percentage, mean, and standard deviation) to analyze the demographic and medical characteristics of participants. To compare final and baseline outcomes, we used the paired t test for continuous variables (PHQ-9 score) and McNemar test for dichotomous variables (MDD diagnosis). The exact binomial confidence intervals were calculated using the online calculator from the University of California San Francisco (sample-size.net/confidence-interval-proportion/). Of note, 95% confidence intervals are not necessarily symmetric around midpoint estimates, especially when the percentages are close to 0% or 100%. An intention-to-treat approach was used, and all 16 participants were analyzed as an outcome.

### Plain-Language Summary

Major depressive disorder (MDD) is a common disorder among patients receiving hemodialysis. However, patients may perceive treatment for MDD to be too burdensome when added to an already taxing hemodialysis regimen. This feasibility trial was designed to examine the efficacy and tolerability of a once-weekly, directly observed fluoxetine treatment protocol for MDD management in this population. Hemodialysis patients with untreated MDD were enrolled for 12 weeks of directly observed fluoxetine treatment. Their safety and progress was monitored by a psychiatric nurse practitioner. The study was conducted at 15 in-center hemodialysis facilities in Northeast Ohio. All adult, English-speaking, cognitively intact patients who had been on maintenance hemodialysis for at least 3 months were invited to participate in an ongoing project investigating the psychometric properties of a depression screening instrument, the Patient Health Questionnaire (PHQ-9), among hemodialysis patients. A PHQ-9 score of ≥10 is an established threshold for clinically relevant depressive symptoms. However, we found in our preliminary work that some patients with scores of <10 still met the diagnostic criteria for MDD. The primary study outcomes were a Mini International Neuropsychiatric Interview diagnosis of MDD at the end of the trial and a change in PHQ-9 scores over 12 weeks. The study was approved by the institutional review board of the MetroHealth System, Cleveland, Ohio (IRB17-00768).
participants are reported in the results. Analyses were performed using JMP Pro 15 statistical software (SAS).

RESULTS

Of 1,588 Centers for Dialysis Care hemodialysis patients screened by chart abstraction, 1,248 were screened in person and 110 were evaluated for MDD. Reasons for exclusion are shown in the Consolidated Standards of Reporting Trials flowchart (Fig 1). A total of 27 patients with untreated MDD were identified, and 16 of them agreed to participate in the clinical trial. These 16 participants were predominantly women, African American, and non-Hispanic. Their mean age was 56.7 years, and the most common cause of kidney failure was diabetes (Table 1). The 11 eligible patients who declined to participate did not differ from the 16 enrolled participants with respect to age, sex, race, ethnicity, cause of kidney failure, years on dialysis, or PHQ-9 score (Table S1).

One patient withdrew from active treatment because of side effects from daily fluoxetine. The patient reported stomach cramping, vomiting, dizziness, and lightheadedness after the first dose of 20 mg of fluoxetine on an empty stomach. A second dose the next day with dinner also led to similar side effects. As a result, the patient withdrew from further treatment but completed the 12-week final study assessment. Several other patients reported milder side effects when taking daily doses of fluoxetine. Four patients reported nausea after taking their first daily fluoxetine doses on an empty stomach. This resolved when subsequent daily fluoxetine doses were taken with food. One patient reported a headache after the first daily dose that resolved with the use of a pain reliever and did not recur. Four patients reported daytime drowsiness when taking daily fluoxetine, which resolved by changing dosing to bedtime. One patient reported nervousness and restlessness when the weekly fluoxetine dose was increased from 90-180 mg. These side effects resolved and remission
of depression symptoms was maintained when the weekly dose was decreased to 90 mg.

Of the 16 participants who began the trial, 15 received all scheduled weekly fluoxetine doses. At 12 weeks, 14 of 16 patients (87.5%) no longer met the criteria for MDD (P < 0.001). One of the 2 participants who had MDD at 12 weeks was the patient who withdrew. Among all 16 participants, the mean PHQ-9 scores decreased from 11.3 to 6.6 (P = 0.002; Table 2). Individual-level changes in PHQ-9 scores are illustrated in the graph in Fig 2.

**DISCUSSION**

We found that directly observed, once-weekly fluoxetine may be an effective and well-tolerated treatment option for hemodialysis patients. Because hemodialysis patients typically receive treatment at dialysis facilities 3 times a week, it may be feasible for this approach to be implemented in routine clinical practice. Specifically, a member of the dialysis treatment team could be responsible for directly observing patients when they take fluoxetine. The strengths of this study include a focus on patients with untreated MDD, the use of validated instruments to screen for and diagnose MDD, and management of patients by an experienced psychiatric nurse practitioner.

We are not aware of any previous trials on the efficacy of directly observed weekly fluoxetine in hemodialysis patients. Furthermore, weekly fluoxetine is not widely used in other clinical settings, and this study identifies a population where this drug formulation could optimize care engagement and health outcomes. In this study, an experienced psychiatric nurse practitioner prescribed fluoxetine to participants, managed their treatment, and observed treatment adherence. Future studies may examine the feasibility of dialysis nurse practitioners completing these activities. To overcome obstacles to direct observation, the use of telehealth technologies (ie, video conferencing) may be useful in monitoring adherence and assessing responses to treatment. Future research may also investigate the feasibility of using telehealth in this population.

Previous studies of daily antidepressant use found that only 33%-55% of patients reach remission from their first treatment regimen. Remission rates decrease with subsequent antidepressant regimens. In hemodialysis populations, although studies have been limited, remission rates from antidepressant treatment have shown mixed efficacy. In 2 studies, sertraline showed either no significant improvement over placebo or a modest improvement compared to cognitive behavioral therapy. Two other studies showed significant improvements in depressive symptom scores with sertraline or fluoxetine treatment versus placebo. As a result, the 87.5% remission rate in this trial is potentially important, as it continues to add to the data supporting the efficacy and safety of antidepressants for the treatment of depression in hemodialysis patients. We hypothesized that high fluoxetine adherence because of direct observation resulted in better remission rates than those noted in previous antidepressant studies.

However, it should be noted that the presence of nonpharmacologic treatments, such as cognitive behavioral therapy, could be a confounding variable in our remission rates. Cognitive behavioral therapy may be difficult for hemodialysis patients to engage in regularly because of their high burden of disease and treatment maintenance. This potential confounder was addressed by the psychiatric nurse practitioner meeting with patients weekly to speak with patients about their current functioning, health, response to treatment, and

| Table 1. Characteristics of Fluoxetine Trial Participants (n = 16) |
|---------------------------------|-----------------|
| Characteristics                  | Results         |
| Age, y                          | 56.7 (16.2)     |
| Female                          | 13 (81%)        |
| Race                            |                 |
| African American                | 13 (81%)        |
| White                           | 3 (19%)         |
| Ethnicity                       |                 |
| Hispanic                        | 1 (6%)          |
| Non-Hispanic                    | 15 (94%)        |
| Cause of kidney failure         |                 |
| Diabetes                        | 9 (56%)         |
| Hypertension                    | 1 (6%)          |
| Glomerulonephritis              | 3 (19%)         |
| Other                           | 3 (19%)         |
| Time on dialysis, y             | 6.6 (5.1)       |
| Baseline PHQ-9 score            | 11.3 (4.9)      |
| PHQ-9 score                     |                 |
| >10                             | 9 (56%)         |
| 5-9, with anhedonia or depressed mood | 7 (44%) |

*Note: Results are n (%) for categorical variables and mean (standard deviation) for continuous variables.
Abbreviation: PHQ-9, Patient Health Questionnaire.

| Table 2. Outcomes of Fluoxetine Treatment (n = 16) |
|---------------------------------|-----------------|
|                                 | Baseline       | 12 Weeks      | Change         | P Value |
| PHQ-9 score, mean (SD) [95% CI] | 11.3 (4.9) [8.7 to 13.9] | 6.6 (4.1) [4.5 to 8.8] | -4.7 (5.3) [-7.3 to -2.1] | 0.002 |
| Depression diagnosis, n (%) [95% CI] | 16 (100%) [79% to 100%] | 2 (12.5%) [1.6% to 38%] | -14 (-87.5%) [-98% to -62%] | <0.001 |

*Note: One patient stopped treatment because of medication side effects but still completed the final assessment.
Abbreviations: CI, confidence interval; PHQ-9, Patient Health Questionnaire; SD, standard deviation.
*Based on the Mini International Neuropsychiatric Interview.
nervousness, headache, asthenia, and diarrhea. Despite the daily formulation, with the most common being in a general MDD sample also appear to be similar to that psychiatric medications before enrollment (Fig 1). Additionally, the baseline PHQ-9 scores were modestly elevated and a lower threshold for inclusion was established. Thus, the findings may not apply to patients with higher PHQ-9 scores or to patients we excluded, such as those taking psychiatric medications or those with psychiatric comorbid conditions. However, in clinical settings, it is not uncommon for patients to score 5-9 on the PHQ-9, which corresponds to mild depressive symptoms, while also meeting the Diagnostic and Statistical Manual of Mental Disorders diagnostic criteria for MDD (5 or more symptoms, 1 of which is anhedonia or depressed mood, occurring most of the day, nearly every day for at least 2 consecutive weeks and causing clinically significant distress or impairment) and reporting distress from symptoms. 36

This is what we found to be the case in our hemodialysis population. Adding qualitative data from clinical interviews between the psychiatric nurse practitioner and the participants may have added clarity and richness to our understanding of the participants’ experiences with and acceptance of the directly observed fluoxetine treatment. There was no comparison group. As a result, we are unable to compare efficacy and safety with other treatments or to evaluate the potentially confounding effect of frequent interactions with the psychiatric nurse practitioner. The side effects were assessed only by clinical interview and assessment by the psychiatric nurse practitioner. Having a standardized measurement tool to assess side effects would improve the ability to compare results to other antidepressant feasibility studies. Our sample predominantly included women and African Americans, which is not representative of the general US hemodialysis population. Our sample may have been skewed toward female participation because of MDD being twice as common in women as in men. 37-40 Although study results have been inconsistent, both sex and racial differences in pharmacokinetics have been reported, with some showing selective serotonin reuptake inhibitors to be more effective in women, especially before menopause, compared with men. 38-40 Additionally, 1 study suggests that African Americans may have poorer response and remission rates to pharmacotherapy than non-Hispanic Whites, even after controlling for other clinical, social, and economic factors. 41 Lastly, the short time frame of the trial limits our ability to assess the long-term efficacy and safety or to determine how this approach would perform in maintenance treatment of MDD.

In conclusion, directly observed, once-weekly fluoxetine at doses of 90-180 mg may be an efficacious and well-tolerated treatment option for hemodialysis patients. Future research should investigate long-term outcomes of weekly fluoxetine in this population and explore the feasibility of implementing this depression treatment model in routine clinical practice.

**SUPPLEMENTARY MATERIAL**

**Supplementary File (PDF)**

Table S1: Characteristics of patients who refused fluoxetine trial participation (n=11).

**ARTICLE INFORMATION**

**Authors’ Full Names and Academic Degrees:** Kelley M. Kauffman, MSN, APRN-CNP, PMHNP-BC, Jacqueline Dolata, MBA, Maria Figueroa, Douglas Gunzler, PhD, Anne Huml, MD, MS, Julie Pencak, Martha Sajatovic, MD, and Ashwini R. Sehgal, MD

**Authors’ Affiliations:** Center for Reducing Health Disparities, The MetroHealth System, Case Western Reserve University, Cleveland,
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Is once weekly Fluoxetine a potentially safe and effective treatment for major depressive disorder in adults receiving dialysis?

Feasibility study
Ohio, USA

N = 16 adults receiving dialysis diagnosed with major depressive disorder (MDD)

Women 81%
Black 81%
Mean age 57 years

Study design

| 2 weeks | 10 weeks | Inadequate response |
|---------|----------|---------------------|
| Tolerance testing at home | Supervised in dialysis unit | Fluoxetine 180 mg weekly |
| Fluoxetine 20 mg once daily | Fluoxetine 90 mg weekly |

Findings* at 12 weeks

- Evaluation for MDD by Mini International Neuropsychiatric Interview

- 87.5% No longer met criteria for MDD (p<0.001)
- Mean PHQ-9 Score Decreased from 11.3 to 6.6 (p = 0.002)

One patient withdrew from the trial

Conclusion: Directly-observed, once weekly fluoxetine may be an effective and well-tolerated treatment option for hemodialysis patients.

Reference: Kauffman KM, Dolata J, Figueroa M et al. Directly-observed weekly Fluoxetine for major depressive disorder among hemodialysis patients: a single-arm feasibility trial. Kidney Medicine, 2022.

Visual Abstract by Anju Yadav MD FASN @docanjuyadav