Kidney Medicine

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 daily 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.

Trial Registration: This trial was registered at clinicaltrials.gov as NCT03390933.

Visual Abstract included

Complete author and article information provided before references.

Correspondence to K.M. Kauffman (kkauffman729@gmail.com)

Kidney Med. 4(3):100413 Published online January 17, 2022.

doi: 10.1016/j.xkme.2022.100413

Major depressive disorder (MDD) is the most common psychiatric disorder among maintenance dialysis patients, affecting approximately 20%-30% of hemodialysis patients.[1-4] MDD is associated with many adverse outcomes, including poor adherence to treatment, inadequate nutrition, increased hospitalization, and premature death.[4-8] However, treating depression can add to the patient's pill burden and may be limited by nonadherence. Previous studies have reported a self-perception of not being depressed enough for an antidepressant medication, reluctance to add to current pill burdens, and concerns about becoming reliant on antidepressants as possible reasons for nonadherence to depression medication regimens.[9] A previous study estimated that hemodialysis patients already take a median of 19 pills per day.[10] The use of antidepressants for the treatment of depression in the hemodialysis population has been established in previous studies.[9,11-13] However, neither the use of directly observed antidepressant therapy nor weekly fluoxetine has been studied in this population.

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

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. 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.

weekly fluoxetine to treat MDD in patients receiving hemodialysis.

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.[30] 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

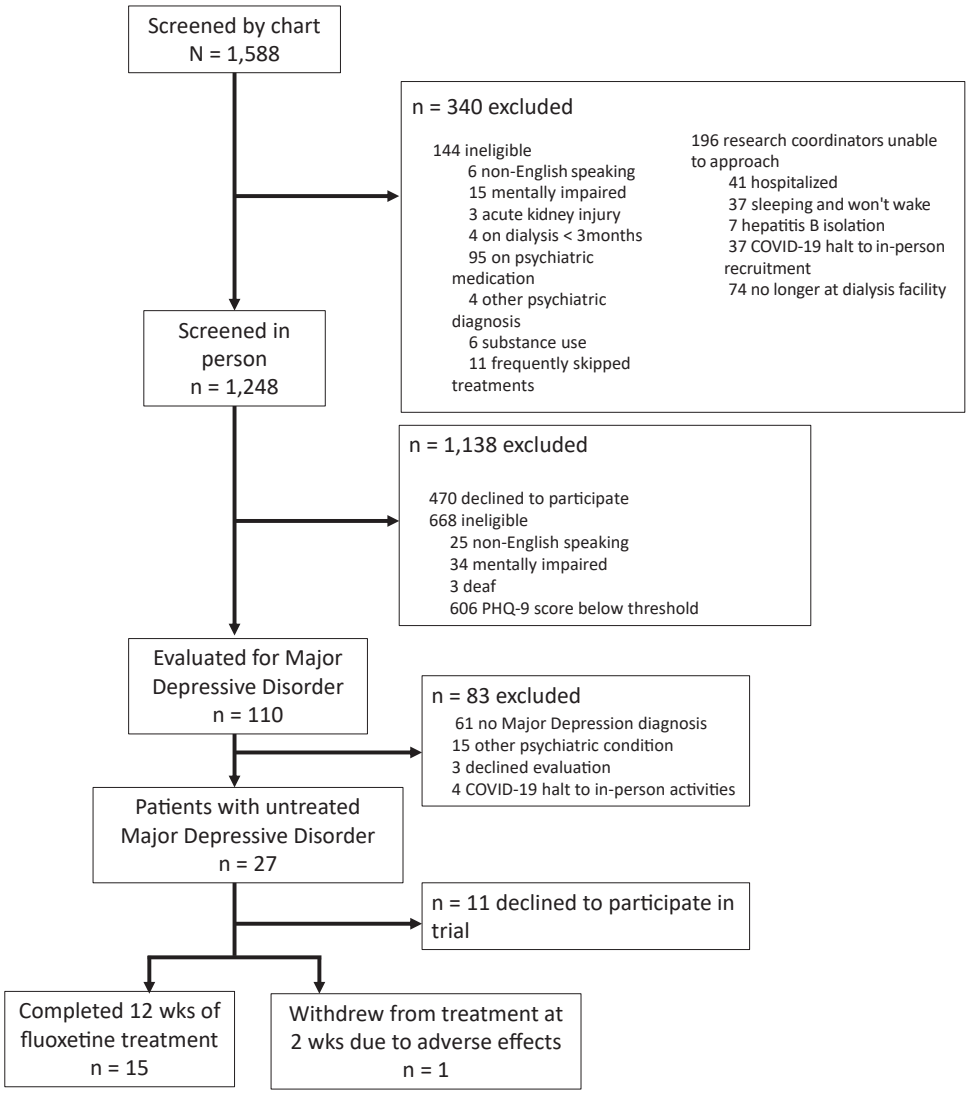


Figure 1. Consolidated Standards of Reporting Trials flowchart. Abbreviation: COVID-19, coronavirus disease 2019.

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

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.

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.[31-33] 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.[9,11] Two other studies showed significant improvements in depressive symptom scores with sertraline or fluoxetine treatment versus placebo.[12,13] 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 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,[a] 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.
[a]Based on the Mini International Neuropsychiatric Interview.

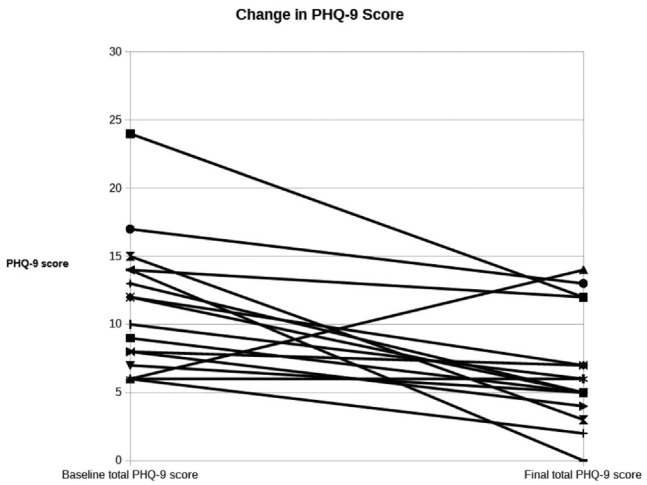


Figure 2. Individual-level changes in PHQ-9 scores. Abbreviation: PHQ-9, Patient Health Questionnaire.

nonpharmacologic treatments for depression symptoms. Through these clinical interviews, it was noted that 1 of the 16 participants did begin receiving psychotherapy, but it was intermittent. The remaining participants did not report receiving nonpharmacologic treatments.

Weekly fluoxetine was approved by the US Food and Drug Administration for the treatment of MDD nearly 2 decades ago.[34] Studies in the general population indicate that relapse rates are similar in individuals with MDD continued on daily dosing versus those who are switched to weekly fluoxetine.[24,35] Side effects of weekly fluoxetine in a general MDD sample also appear to be similar to that of the daily formulation, with the most common being nervousness, headache, asthenia, and diarrhea.[35] Despite the withdrawal of 1 patient in this trial because of side effects, all side effects reported during the study were described by patients and assessed by the prescribing clinician to be mild to moderate, suggesting that weekly fluoxetine may be a safe and well-tolerated treatment option for hemodialysis patients with MDD. Patients may also find the dosing regimen less burdensome than daily antidepressant treatment.

Several limitations must be considered in interpreting our results. The study sample size is small for multiple reasons, including more patients than anticipated scoring below the threshold on the PHQ-9 or already being on 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,

OH (KMK, JD, MF, AH, JP, ARS); Population Health Research Institute, Center for Health Care Research & Policy, Center for Reducing Health Disparities, The MetroHealth System, Case Western Reserve University, Cleveland, OH (DG, ARS); Division of Nephrology, Institute for Health, Opportunity, Partnership, and Empowerment, Center for Reducing Health Disparities, The MetroHealth System, Case Western Reserve University, Cleveland, OH (ARS); Department of Psychiatry and of Neurology, Case Western Reserve University School of Medicine, Cleveland, OH (MS); and Neurological and Behavioral Outcomes Center, University Hospitals Cleveland Medical Center, Cleveland, OH (MS).

Address for Correspondence: Kelley M. Kauffman, MSN, APRN-CNP, PMHNP-BC, Center for Reducing Health Disparities, The MetroHealth System, 2500 MetroHealth Drive R206A, Cleveland, OH 44109. Email: kkauffman729@gmail.com

Authors' Contributions: Study design: KMK, JD, MF, DG, AH, JP, MS, ARS; data collection: MF, JP, KMK; data analysis: KMK, ARS; interpretation: KMK, JD, MF, DG, AH, JP, MS, ARS; supervision and mentorship: JD, DG, AH, MS, ARS. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Support: This research was supported by National Institutes of Health grant DK112905.

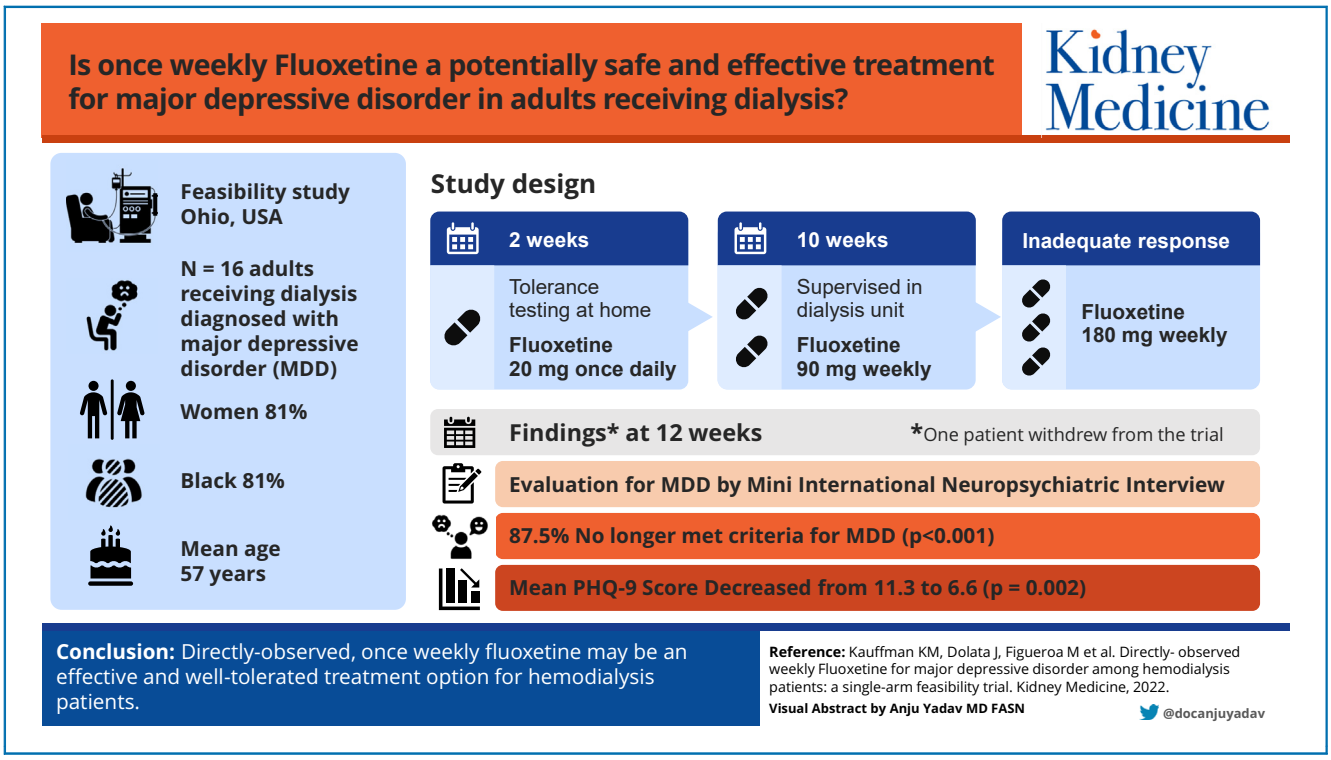
Financial Disclosure: Dr Gunzler has a book royalty agreement with Taylor & Francis Publishing. Dr Sajatovic has received grant support from Nuromate, Otsuka, Alkermes, the International Society for Bipolar Disorders, the National Institutes of Health, the Centers for Disease Control and Prevention, and the Patient-Centered Outcomes Research Institute; has served as a consultant to Otsuka, Janssen, Alkermes, Myriad, Frontline Medical Communications, and Health Analytics; receives royalties from Springer Press, Johns Hopkins University Press, Oxford Press, and UpToDate; and receives compensation for the preparation of continuing medical education activities from the American Physician's Institute, MCM Education, CMEology, Potomac Center for Medical Education, Global Medical Education, Creative Educational Concepts, and the Psychopharmacology Institute. The remaining authors declare that they have no relevant financial interests.

Peer Review: Received June 28, 2021. Evaluated by 2 external peer reviewers, with direct editorial input by a Statistical Editor and the Editor-in-Chief. Accepted in revised form November 28, 2021.

REFERENCES

1. Cohen SD, Norris L, Acquaviva K, Peterson RA, Kimmel PL. Screening, diagnosis, and treatment of depression in patients with end-stage renal disease. *Clin J Am Soc Nephrol*. 2007;2(6):1332-1342.
2. Hedayati SS, Bosworth HB, Kuchibhatla M, Kimmel PL, Szczech LA. The predictive value of self-report scales compared with physician diagnosis of depression in hemodialysis patients. *Kidney Int*. 2006;69(9):1662-1668.
3. Watnick S, Wang PL, Demadura T, Ganzini L. Validation of 2 depression screening tools in dialysis patients. *Am J Kidney Dis*. 2005;46(5):919-924.
4. Kimmel PL, Peterson RA, Weihs KL, et al. Behavioral compliance with dialysis prescription in hemodialysis patients. *J Am Soc Nephrol*. 1995;5(10):1826-1834.
5. Boulware LE, Liu Y, Fink NE, et al. Temporal relation among depression symptoms, cardiovascular disease events, and mortality in end-stage renal disease: contribution of reverse causality. *Clin J Am Soc Nephrol*. 2006;1(3):496-504.
6. Cohen SD, Kimmel PL. Nutritional status, psychological issues and survival in hemodialysis patients. *Contrib Nephrol*. 2007;155:1-17.
7. Kimmel PL, Peterson RA, Weihs KL, et al. Multiple measurements of depression predict mortality in a longitudinal study of chronic hemodialysis outpatients. *Kidney Int*. 2000;57(5):2093-2098.
8. Lacson E Jr, Bruce L, Li NC, Mooney A, Maddux FW. Depressive affect and hospitalization risk in incident hemodialysis patients. *Clin J Am Soc Nephrol*. 2014;9(10):1713-1719.
9. Friedli K, Guirguis A, Almond M, et al. Sertraline versus placebo in patients with major depressive disorder undergoing hemodialysis: a randomized, controlled feasibility trial. *Clin J Am Soc Nephrol*. 2017;12(2):280-286.
10. Chiu YW, Teitelbaum I, Misra M, de Leon EM, Adzize T, Mehrotra R. Pill burden, adherence, hyperphosphatemia, and quality of life in maintenance dialysis patients. *Clin J Am Soc Nephrol*. 2009;4(6):1089-1096.
11. Mehrotra R, Cukor D, Unruh M, et al. Comparative efficacy of therapies for treatment of depression for patients undergoing maintenance hemodialysis: a randomized clinical trial. *Ann Intern Med*. 2019;170(6):369-379.
12. Taraz M, Khatami MR, Dashti-Khavidaki S, et al. Sertraline decreases serum level of interleukin-6 (IL-6) in hemodialysis patients with depression: results of a randomized double-blind, placebo-controlled clinical trial. *Int Immunopharmacol*. 2013;17(3):917-923.
13. Blumenfield M, Levy NB, Spinowitz B, et al. Fluoxetine in depressed patients on dialysis. *Int J Psychiatry Med*. 1997;27(1):71-80.
14. Ilievska-Poposka B, Zakoska M, Mitreski V. Evaluation of the directly observed treatment's acceptance by tuberculosis patients in the Republic of Macedonia. *Open Access Maced J Med Sci*. 2018;6(5):896-900.
15. Belknap R, Holland D, Feng PJ, et al. Self-administered versus directly observed once-weekly isoniazid and rifapentine treatment of latent tuberculosis infection: a randomized trial. *Ann Intern Med*. 2017;167(10):689-697.
16. Karumbi J, Garner P. Directly observed therapy for treating tuberculosis. *Cochrane Database Syst Rev*. 2015;2015(5):CD003343.
17. Ford N, Nachega JB, Engel ME, Mills EJ. Directly observed antiretroviral therapy: a systematic review and meta-analysis of randomised clinical trials. *Lancet*. 2009;374(9707):2064-2071.
18. Machouf N, Lalonde RG. Directly observed therapy (DOT): from tuberculosis to HIV. *Rev Epidemiol Sante Publique*. 2006;54(1):73-89.
19. Wohl AR, Garland WH, Valencia R, et al. A randomized trial of directly administered antiretroviral therapy and adherence case management intervention. *Clin Infect Dis*. 2006;42(11):1619-1627.
20. Volmink J, Garner P. Directly observed therapy for treating tuberculosis. *Cochrane Database Syst Rev*. 2003;1(1):CD003343.
21. Mitty JA, Stone VE, Sands M, Macalino G, Flanigan T. Directly observed therapy for the treatment of people with human immunodeficiency virus infection: a work in progress. *Clin Infect Dis*. 2002;34(7):984-990.
22. Miner CM, Brown EB, Gonzales JS, Munir R. Switching patients from daily citalopram, paroxetine, or sertraline to once-weekly fluoxetine in the maintenance of

response for depression. *J Clin Psychiatry*. 2002;63(3):232-240.
23. Norman TR, Olver JS. New formulations of existing antidepressants: advantages in the management of depression. *CNS Drugs*. 2004;18(8):505-520.
24. Schmidt ME, Fava M, Robinson JM, Judge R. The efficacy and safety of a new enteric-coated formulation of fluoxetine given once weekly during the continuation treatment of major depressive disorder. *J Clin Psychiatry*. 2000;61(11):851-857.
25. Claxton A, de Klerk E, Parry M, Robinson JM, Schmidt ME. Patient compliance to a new enteric-coated weekly formulation of fluoxetine during continuation treatment of major depressive disorder. *J Clin Psychiatry*. 2000;61(12):928-932.
26. Hedayati SS, Yalamanchili V, Finkelstein FO. A practical approach to the treatment of depression in patients with chronic kidney disease and end-stage renal disease. *Kidney Int*. 2012;81(3):247-255.
27. Judge R. Patient perspectives on once-weekly fluoxetine. *J Clin Psychiatry*. 2001;62(suppl 22):53-57.
28. Nagler EV, Webster AC, Vanholder R, Zoccali C. Antidepressants for depression in stage 3-5 chronic kidney disease: a systematic review of pharmacokinetics, efficacy and safety with recommendations by European Renal Best Practice (ERBP). *Nephrol Dial Transplant*. 2012;27(10):3736-3745.
29. Prescriber's Digital Reference. LLC. Fluoxetine hydrochloride-drug summary. Accessed March 15, 2021. http://www.pdr.net/drug-summary/Fluoxetine-Tablets-fluoxetine-hydrochloride-1416.5847
30. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry*. 1998;59(suppl 20):22-57.
31. Iovieno N, van Nieuwenhuizen A, Clain A, Baer L, Nierenberg AA. Residual symptoms after remission of major depressive disorder with fluoxetine and risk of relapse. *Depress Anxiety*. 2011;28(2):137-144.
32. Gaynes BN, Warden D, Trivedi MH, Wisniewski SR, Fava M, Rush AJ. What did STAR*D teach us? Results from a large-scale, practical, clinical trial for patients with depression. *Psychol Serv*. 2009;60(11):1439-1445.
33. Warden D, Rush AJ, Trivedi MH, Fava M, Wisniewski SR. The STAR*D project results: a comprehensive review of findings. *Curr Psychiatr Rep*. 2007;9(6):449-459.
34. Center Watch. Prozac weekly (fluoxetine HCL). Accessed February 13, 2019. www.centerwatch.com/drug-information/fda-approved-drugs/drug/685/prozac-weekly-fluoxetine-hcl
35. Wagstaff AJ, Goa KL. Once-weekly fluoxetine. *Drugs*. 2001;61(15):2221-2228. discussion 2229.
36. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Publishing; 2013.
37. Keers R, Aitchison KJ. Gender differences in antidepressant drug response. *Int Rev Psychiatry*. 2010;22(5):485-500.
38. Grigoriadis S, Robinson GE. Gender issues in depression. *Ann Clin Psychiatry*. 2007;19(4):247-255.
39. Sagud M, Hotujac L, Mihaljević-Peles A, Jakovljević M. Gender differences in depression. *Coll Antropol*. 2002;26(1):149-157.
40. Kornstein SG. Gender differences in depression: implications for treatment. *J Clin Psychiatry*. 1997;58(suppl 15):12-18.
41. Shao Z, Richie WD, Bailey RK. Racial and ethnic disparity in major depressive disorder. *J Racial Ethn Health Disparities*. 2016;3(4):692-705.


Is once weekly Fluoxetine a potentially safe and effective treatment for major depressive disorder in adults receiving dialysis?
Kidney Medicine
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
Tolerance testing at home
Fluoxetine 20 mg once daily
10 weeks
Supervised in dialysis unit
Fluoxetine 90 mg weekly
Inadequate response
Fluoxetine 180 mg weekly
Findings* at 12 weeks
*One patient withdrew from the trial
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)
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