End-stage Renal Disease and Depression: A Systematic Review

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PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The program is comprised of four ESP Centers across the US and a Coordinating Center located in Portland, Oregon. Center Directors are VA clinicians and recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Center Program and Cochrane Collaboration. The Coordinating Center was created to manage program operations, ensure methodological consistency and quality of products, and interface with stakeholders. To ensure responsiveness to the needs of decision-makers, the program is governed by a Steering Committee comprised of health system leadership and researchers. The program solicits nominations for review topics several times a year via the program website.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, Deputy Director, ESP Coordinating Center at Nicole.Floyd@va.gov.

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ACKNOWLEDGMENTS

This topic was developed in response to a nomination by the VHA Kidney Disease and Dialysis Program office and the VHA Dialysis Dashboard committee for an evidence review on screening and treatment of depression in end-stage renal disease (ESRD) patients. The scope was further developed with input from the topic nominators (*ie*, Operational Partners), the ESP Coordinating Center, the review team, and the technical expert panel (TEP).

In designing the study questions and methodology at the outset of this report, the ESP consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

The authors gratefully acknowledge Robin Paynter, MLIS, and the following individuals for their contributions to this project:

Operational Partners

Operational partners are system-level stakeholders who have requested the report to inform decision-making. They recommend Technical Expert Panel (TEP) participants; assure VA relevance; help develop and approve final project scope and timeframe for completion; provide feedback on draft report; and provide consultation on strategies for dissemination of the report to field and relevant groups.

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Technical Expert Panel (TEP)

To ensure robust, scientifically relevant work, the TEP guides topic refinement; provides input on key questions and eligibility criteria, advising on substantive issues or possibly overlooked areas of research; assures VA relevance; and provides feedback on work in progress. TEP members are listed below:

Michael Fischer, MD, MSPH
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Suzanne Watnick, MD
Northwest Kidney Centers
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Peer Reviewers

The Coordinating Center sought input from external peer reviewers to review the draft report and provide feedback on the objectives, scope, methods used, perception of bias, and omitted evidence. Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The Coordinating Center and the ESP Center work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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ABSTRACT

Aim: We conducted a systematic review to evaluate the performance characteristics of screening tools for depression in Veterans with end-stage renal disease (ESRD), and to better understand the impact, benefits, and harms of depression screening and subsequent treatment for depression.

Methods: We searched electronic databases, clinical trial registries, and reference lists through April 2019 for diagnostic accuracy studies of depression tools for patients with ESRD and for trials examining the effectiveness of interventions for the treatment of depression in patients with ESRD. We abstracted data on study design, interventions, and outcomes. Dual assessment of a study's full text, quality, and strength of evidence (SOE) was agreed upon by consensus using pre-specified criteria.

Results: We included 20 treatment RCTs and 16 diagnostic accuracy studies. The best-studied tool was the Beck Depression Inventory-II (BDI-II). Across 4 BDI-II studies, a cutoff of ≥16 provides the best balance between sensitivity and specificity. The BDI-II performed reasonably well when compared to a gold standard clinical interview.

SSRIs were the most studied type of drug and the evidence was largely insufficient. We found moderate SOE that long-term, high-dose Vitamin D3 is ineffective for reducing depression severity. Cognitive behavioral therapy (CBT) is more effective than (undefined) psychotherapy and placebo for depression improvement and quality of life (low SOE), and acupressure is more effective than treatment as usual (TAU) or sham to reduce depression severity (low SOE).

Conclusion: There is limited research evaluating the diagnostic accuracy of most screening tools for depression in patients with ESRD. The BDI-II with a cutoff of ≥16 provides a good balance of sensitivity and specificity. More research is needed to support the use of other tools. We found low SOE that CBT, sertraline, and acupressure may be beneficial. There is moderate SOE that high-dose Vitamin D3 is ineffective. More research is needed.

EVIDENCE REPORT

INTRODUCTION

The incidence and prevalence of end-stage renal disease (ESRD) in the United States (US) have increased steadily over the past 4 decades.[1] Veterans experience a higher burden of chronic kidney disease (CKD) and ESRD than the population at large.[2] Roughly 13,000 Veterans initiate dialysis annually, making up nearly 11% of all cases in the US.[2]

Patients with ESRD experience major depressive disorder (MDD) at 3 to more than 6 times that of the general US population, depending on the method of assessment.[3,4] Comorbid depression is associated with treatment noncompliance, poorer quality of life, worse sleep, increased emergency department (ED) visits, hospitalizations, suicide, and all-cause mortality.[5-8]

Veterans experience MDD at more than twice the rate of the general US population (7.1% vs 13.5%).[3,9] According to United States Renal Data System (USRDS) data, rates of depression in Veterans with ESRD increased steadily between 2007 and 2015, with recent data indicating prevalence rates of 33%.[10]

In the Veterans Health Administration (VHA), some Veterans with ESRD receive kidney care entirely within the VHA. However, due to space limitations and variation in dialysis care available across VHA settings (inpatient, outpatient, or none), a large percentage of Veterans are referred to dialysis units in the community.

The Centers for Medicare and Medicaid Services' (CMS) inclusion of depression screening for ESRD patients as part of their pay-for-performance (P4P) Quality Incentive Program (QIP) requires routine depression screening for patients with ESRD.[11] However, due to the lack of system-wide screening tool requirements, there is wide variation in the tools used to initially screen for depression, as well as for follow-up after a positive initial screen (ranging from the Patient Health Questionnaire 2 [PHQ-2] to the Center for Epidemiologic Studies Depression Scale [CES-D], and the Beck Depression Inventory [BDI-II], to a clinical interview). In addition, the implementation of depression screening likely varies widely by site, potentially ranging from the PHQ-2 included on written intake forms or verbal assessment in a waiting room, to a confidential interview with a licensed clinician. Follow-up to a positive screen also varies widely, and Veterans with ESRD and comorbid depression may be referred to mental health providers within the VHA, or to community hospitals and mental health settings.

Currently, there are no established guidelines for the treatment of depression in patients with ESRD. Roughly 30% of Veterans receive an antidepressant during the ESRD post-transition phase.[10] Efficacy studies are limited, however, and the evidence is unclear.[12] Psychosocial treatments and Cognitive Behavioral Therapy (CBT) are also commonly used; however, interventions vary widely, and the evidence is limited.[13]

Given the wide variation in depression screening and treatment options for Veterans with ESRD, an understanding of the validity of screening tools used in both VHA and community settings, and the subsequent depression treatment-related outcomes for Veterans in all US healthcare settings, is vital.

The purpose of this review is to identify depression screening tools (and/or thresholds) appropriate for Veterans with ESRD, and to better understand the impact, benefits, and harms of depression screening and subsequent treatment for depression in Veterans (and Veteran subpopulations) with ESRD.

METHODS

TOPIC DEVELOPMENT

This topic was nominated by Dr. Susan Crowley, VHA National Program Director for Kidney Disease and Dialysis. The scope was refined through a process that included a preliminary review of published peer-reviewed literature and consultations with our operational partners and a technical expert panel (TEP). Our approach was guided by a conceptual framework developed in consultation with our operational partners and TEP (Figure 1).

The Key Questions (KQs) for this systematic review were:

KQ1. What are the performance characteristics of screening tools for depression in patients with ESRD?

KQ2. What is the impact of screening for depression in patients with ESRD on intermediate and/or patient outcomes?

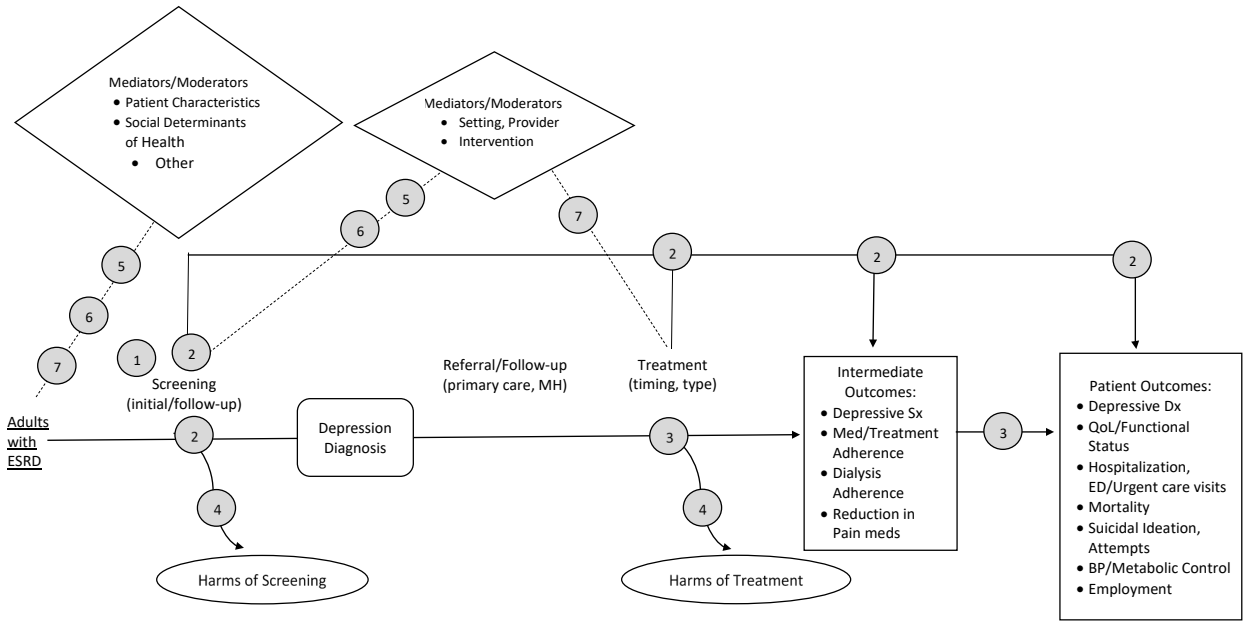
KQ3. What is the effectiveness of depression treatment in patients with ESRD and depression?
- a. pharmacological treatment
- b. non-pharmacological treatment
- c. pharmacological and non-pharmacological treatments combined

KQ4. In patients with ESRD and depression, what are the potential harms of:
- a. screening?
- b. treatment?
  - i. pharmacological
  - ii. non-pharmacological

KQ5. Do the benefits or harms of screening differ by:
- a. patient characteristics or other social determinants of health?
- b. setting?
- c. screening characteristics/process?
- d. other (*eg*, patient engagement/receptivity to treatment, social support)?
- e. timing and type of follow up?

KQ6. Do the benefits or harms of treatment differ by:
- a. patient characteristics or other social determinants of health?
- b. setting?
- c. provider characteristics (*eg*, mental health, primary care provider [PCP], other)?
- d. other (*eg*, patient engagement/receptivity to treatment, social support)?
- e. timing and type of follow up?

Figure 1. Analytic Framework



Note. Associated key questions are noted in the shaded circles.

SEARCH STRATEGY

Search strategies were developed in consultation with a research librarian and were peer reviewed by a second research librarian using the instrument for Peer Review of Search Strategies (PRESS).[14] We conducted a review of the literature by systematically searching, reviewing, and analyzing the scientific evidence as it pertains to the research questions. To identify relevant trials, we searched Ovid MEDLINE, PsycINFO, Elsevier EMBASE, and Ovid EBM Reviews Cochrane Database of Systematic Reviews (CDSR, DARE, HTA, Cochrane CENTRAL, *etc*). We searched all available years of publication from database inception (1946 for Ovid MEDLINE®) through April 2019. We reviewed the bibliographies of relevant articles and contacted experts to identify additional studies. To identify in-progress or unpublished studies, we searched the VHA HSR&D website, ClinicalTrials.gov, and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP).

STUDY SELECTION

Criteria for population, interventions, comparators, outcomes, timing, and setting (PICOTS) were developed in collaboration with our operational partners and TEP (see Table 1). Based on pre-specified criteria, 80% of titles and abstracts were reviewed manually by 2 reviewers, and the remaining 20% were reviewed by at least 2 reviewers using Abstrackr, a web-based abstract screening tool.[15] Two reviewers then independently assessed the full text of included citations for final inclusion. All discordant results were resolved through consensus or consultation with a third reviewer. Articles meeting eligibility criteria were included for data abstraction.

We included diagnostic accuracy studies of depression tools for patients with ESRD. We also included randomized and non-randomized controlled trials, and observational studies of patients with ESRD and comorbid depression (defined by established thresholds for chronically ill

populations)[16-20] that directly compared pharmacological and non-pharmacological interventions to each other, placebo, or waitlist control. We excluded studies examining patients with acute kidney injury (AKI), or with CKD stages 1-4. To examine the impact of screening and effectiveness of treatment for depression in patients with ESRD (KQs 2 and 3) we included only randomized and non-randomized controlled trials. Citation lists of included systematic reviews were reviewed for relevant studies. For each key question of interest, we used a "best evidence" approach to guide additional study design criteria depending on the question under consideration and the literature available (see Table 1 and Appendix B).[21]

Table 1. PICOTS by Key Question

Key Question:	KQ1: What are the performance characteristics of screening tools for depression in patients with ESRD?	KQ2: What is the impact of screening for depression in patients with ESRD on intermediate and/or patient outcomes?	KQ3: What is the effectiveness of depression treatment in patients with ESRD and depression: a. pharmacological? b. non-pharmacological? c. pharmacological and non-pharmacological treatments combined	KQ4: In patients with ESRD, what are the potential harms of: a. screening? b. treatment for depressed patients? i. Pharmacological? ii. non-pharmacological?	KQ5: Do the benefits or harms of screening differ by: a. patient characteristics or other social determinants of health? b. setting? c. screening characteristics/ process? d. other (*eg*, patient engagement/ receptivity to treatment, social support)? e. timing and type of follow up?	KQ6: Do the benefits or harms of treatment differ by: a. patient characteristics or other social determinants of health? b. setting? c. provider characteristics (*eg*, mental health, PCP)? d. other (*eg*, patient engagement/ receptivity to treatment, social support)? e. timing and type of follow up?
Population	Adults with ESRD	Adults with ESRD	Adults with ESRD and depression (Cutoffs: PHQ-9 ≥ 10;[16] CES-D ≥ 18;[17] HAM-D ≥ 12;[18] BDI-II ≥ 16;[17,18] BDI ≥ 13;[18] HADS ≥ 8[19,20])		a. Adults with ESRD b. Adults with ESRD and depression (Cutoffs: PHQ-9 ≥ 10;[16] CES-D ≥ 18;[17] HAM-D ≥ 12;[18] BDI-II ≥ 16;[17,18] BDI ≥ 13;[18] HADS ≥ 8[19,20])	Adults with ESRD
Intervention	Depression screening		Pharmacological and non-pharmacological treatments for depression	Depression screening, and pharmacological and non-pharmacological treatments for depression	Depression screening	Pharmacological and non-pharmacological treatments for depression
Comparators	Clinical evaluation, Other screening tools. Exclude DSM-III and earlier	No screening, other screening tool	Placebo, waitlist control, other intervention	a. No screening, other screening tool b. Placebo, waitlist control, other intervention	No screening, other screening tool	Placebo, waitlist control, other intervention

Key Question:	KQ1: What are the performance characteristics of screening tools for depression in patients with ESRD?	KQ2: What is the impact of screening for depression in patients with ESRD on intermediate and/or patient outcomes?	KQ3: What is the effectiveness of depression treatment in patients with ESRD and depression: a. pharmaco-logical? b. non-pharmaco-logical? c. pharmacological and non-pharmacological treatments combined	KQ4: In patients with ESRD, what are the potential harms of: a. screening? b. treatment for depressed patients? i. Pharmaco-logical? ii. non-pharmaco-logical?	KQ5: Do the benefits or harms of screening differ by: a. patient characteristics or other social determinants of health? b. setting? c. screening characteristics/ process? d. other (*eg*, patient engagement/ receptivity to treatment, social support)? e. timing and type of follow up?	KQ6: Do the benefits or harms of treatment differ by: a. patient characteristics or other social determinants of health? b. setting? c. provider characteristics (*eg*, mental health, PCP)? d. other (*eg*, patient engagement/ receptivity to treatment, social support)? e. timing and type of follow up?
Outcomes	Diagnostic test performance: sensitivity, specificity, positive predictive value, and negative predictive value	Therapeutic impact: timing, setting, or type of treatment. Intermediate and Patient outcomes: depressive symptoms, mortality, suicide attempts or completion, hospitalization, ED/urgent care utilization, patient satisfaction, adherence to dialysis, medication, or treatment, pain medication reduction, BP/metabolic control, quality of life, other outcomes (*eg*, employment)	Intermediate and Patient outcomes: depressive symptoms, mortality, suicide attempts or completion, hospitalization, ED/urgent care utilization, patient satisfaction, adherence to dialysis, medication, or treatment, pain medication reduction, BP/metabolic control, quality of life, other outcomes (*eg*, employment)	Adverse effects or unintended consequences	Intermediate and Patient outcomes: depressive symptoms, mortality, suicide attempts or completion, hospitalization, ED/urgent care utilization, patient satisfaction, adherence to dialysis, medication, or treatment, pain medication reduction, BP/metabolic control, quality of life, other outcomes (*eg*, employment)	
Timing	Any					
Settings	All settings in US or international (VHA, hospital community, community mental health, ED, urgent care, other community)					

Key Question:	**KQ1: What are the performance characteristics of screening tools for depression in patients with ESRD?**	**KQ2: What is the impact of screening for depression in patients with ESRD on intermediate and/or patient outcomes?**	**KQ3: What is the effectiveness of depression treatment in patients with ESRD and depression:** **a. pharmaco-logical?** **b. non-pharmaco-logical?** **c. pharmacological and non-pharmacological treatments combined**	**KQ4: In patients with ESRD, what are the potential harms of:** **a. screening?** **b. treatment for depressed patients?** **i. Pharmaco-logical?** **ii. non-pharmaco-logical?**	**KQ5: Do the benefits or harms of screening differ by:** **a. patient characteristics or other social determinants of health?** **b. setting?** **c. screening characteristics/ process?** **d. other (*eg*, patient engagement/ receptivity to treatment, social support)?** **e. timing and type of follow up?**	**KQ6: Do the benefits or harms of treatment differ by:** **a. patient characteristics or other social determinants of health?** **b. setting?** **c. provider characteristics (*eg*, mental health, PCP)?** **d. other (*eg*, patient engagement/ receptivity to treatment, social support)?** **e. timing and type of follow up?**
Study design	Systematic reviews, RCTs, NRCTs, Observational studies	Systematic reviews, RCTs, NRCTs		Systematic reviews, RCTs, NRCTs, Observational studies		

Note. Subpopulations may include: Patient demographic characteristics or social determinants of health; ESRD subgroup (w/o treatment; treated by kidney transplant; treated by HD (home or clinic); treated by PD (home or clinic); clinical severity (ESRD or depression); setting (*eg* VHA, community hospitals, community mental health, ED, urgent care visits for mental health, home vs clinic-based dialysis); other.

Abbreviations: CES-D = Center for Epidemiologic Studies Depression Scale; BDI = Beck Depression Inventory; BP = blood pressure; ED = emergency department; ESRD = End-stage Renal Disease; HADS = Hospital Anxiety and Depression Scale; HAM-D = Hamilton Depression Rating Scale; NRCT = Non-randomized controlled trial; PHQ-9 = Patient Health Questionnaire-9; RCT = Randomized controlled trial; VHA = Veterans Health Administration

DATA ABSTRACTION

Data from studies meeting inclusion criteria were abstracted by 1 investigator and confirmed by at least 1 additional reviewer. From each study, we abstracted the following where available: study design, sample size, setting, population characteristics, subject inclusion and exclusion criteria, the study and comparator interventions including details related to the dosage, setting, timing, and administration of screening and interventions, duration of treatment, duration of follow-up, intermediate and health outcomes, and relevant harms.

QUALITY ASSESSMENT

Two reviewers independently assessed the methodological quality of each study using established methods for each study design. For trials, we used criteria established by the US Preventive Services Taskforce and adapted for depression interventions.[22-24] We supplemented this with the Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies QUADAS-2[25] and the Newcastle-Ottawa Scale[26] for diagnostic accuracy and observational studies respectively (see Appendices C and D). Disagreements were resolved by consensus or a third reviewer.

DATA SYNTHESIS

We qualitatively synthesized the evidence for all key questions and presented the findings in tables. For Key Question 1, we categorized assessment tools as a) screening for MDD, and b) screening for a wider range, from subclinical depressive symptoms to MDD. In addition, we present detailed findings for studies comparing a screening tool to a gold standard clinical interview, and provide a summary of studies that use another tool as a reference standard (*eg*, BDI-II).[27] We were unable to quantitatively synthesize the evidence because studies were not clinically heterogenous and/or of the same intervention and outcome measure.[28]

RATING THE BODY OF EVIDENCE

We assessed the overall strength of evidence (SOE) for outcomes using a method developed for the Agency for Healthcare Research and Quality's (AHRQ) Evidence-based Practice Centers (EPCs).[29] The AHRQ EPC method considers study limitations, directness, consistency, precision, and reporting bias to classify the strength of evidence for individual outcomes independently for randomized controlled trials (RCTs) and observational studies, with supplemental domains of dose-response association, plausible confounding that would decrease the observed effect, and strength of association, as well as separate guidance for applicability.[30] Ratings will be based on the following criteria:

- High: Very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies, the findings are stable, and another study would not change the conclusions.

- Moderate: Moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies and the findings are likely to be stable, but some doubt remains.

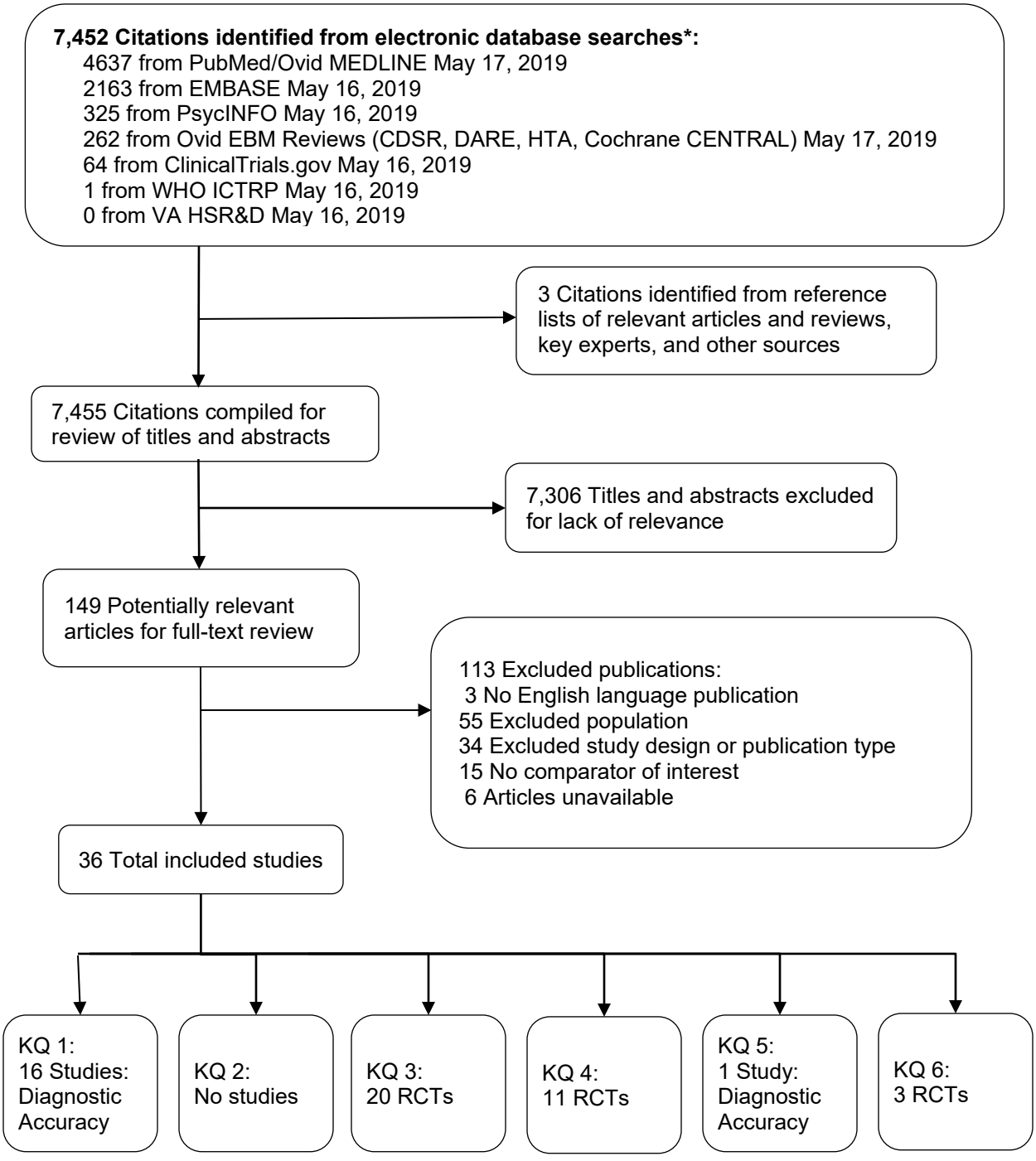
- Low: Limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). Additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.

- Insufficient: No evidence, unable to estimate an effect, or no confidence in the estimate of effect for this outcome. No evidence is available, or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

RESULTS

We reviewed a total of 7,452 studies. After title and abstract review, 149 met inclusion criteria. Upon full-text review, we included a total of 20 RCTs and 16 diagnostic accuracy studies. RCTs examined in Key Questions 4 and 6 were also included in Key Question 3, and the single study included for Key Question 5 was also included in Key Question 1 (see Figure 2; quality assessment is presented in Appendices C and D).

Figure 2. Literature Flow Chart



*after deduplication
Note: studies in KQs 4 & 6 are also included in the KQ3 total, and the KQ5 study is included in KQ1 total

KEY QUESTION 1: What are the performance characteristics of screening tools for depression in patients with ESRD?

Sixteen studies examined the performance characteristics for depression screening in patients with ESRD. Nine studies examined the performance of the Beck Depression Inventory-II (BDI-II).[27] Other tools include the Cognitive Depression Index (CDI[31]; 4 studies), the Center for Epidemiologic Studies – Depression Scale (CES-D[32]; 1 study[33]), the Hospital Anxiety and Depression Scale - Depressive Subscale (HADS-D[34]; 2 studies[35,36]), the Geriatric Depression Scale-15 (GDS-15[37,38]; 2 studies[39,40]), the Hamilton Depression Rating Scale (Ham-D[41]; 1 study[42]), the Patient Health Questionnaire 9 (PHQ-9[43]; 1 study[44]), and others. Of note, we identified only 1 development and validation study of a depression screening tool targeting patients on maintenance dialysis (Depression Inventory – Maintenance Hemodialysis [DI-MHD]).[45] Table 2 provides study characteristics.

Five studies[33,39,44,46,47] were of US populations, with 2 studies including participants at Veterans Health Administration (VHA) facilities.[33,44] Other studies were located in Australia,[48] Canada,[49] China,[45] Italy,[40] the Netherlands,[50,51] Norway,[36] Saudi Arabia,[52] Turkey,[42] and the United Kingdom (UK; see Table 2).[50,53]

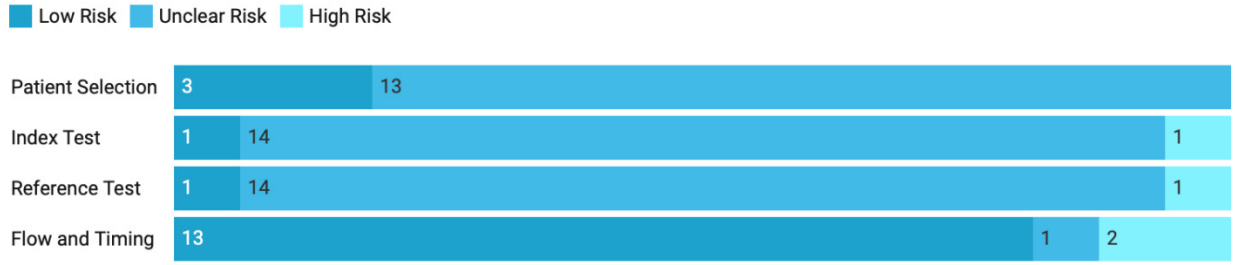
Most studies included only patients undergoing hemodialysis (HD). Only 4 studies also included participants undergoing peritoneal dialysis (PD).[35,36,44,47] Across studies reporting time on dialysis, the minimum number of (mean) months was 8.5[36] and the maximum was 72.2 (see Table 2).[42]

Of the 16, 11 studies compared screening tools (index test) to a gold standard clinical interview (*eg*, Structured Clinical Interview for DSM-IV [SCID-I][54], Mini-International Neuropsychiatric Interview [MINI][55]), and 5 compared tools to other established, validated assessment measures (*eg*, Beck Depression Inventory [BDI-II][27], Hospital Anxiety and Depression Scale [HADS][34]). One study compared the BDI-II to a clinical interview, and another tool to the BDI-II.[45] For the purpose of this review, we focus primarily on the studies using a clinical interview as a reference standard, and summarize the findings of those comparing screening tools to other established tools.

Only 5 studies screened participants for MDD specifically.[39,44,46,48,52,53] Nine studies screened for less severe depressive disorders (*eg*, dysthymia, pervasive depressive disorder) and/or subclinical depressive symptoms in addition to MDD,[35,36,40,42,45,47,49,51,56] and 1 study examined performance characteristics and thresholds for both MDD and less severe depression (see Table 2).[50]

The 16 studies were relatively similar in quality, with the risk of bias largely unclear for patient selection, the index test, and the reference standard. For patient selection, unclear ratings were primarily due to the lack of detail related to the sequence of sample enrollment. For the index test, few studies reported whether study staff were trained in administration or interpretation of the test, and for the reference standard, very few studies reported information related to fidelity. Risk of bias ratings for timing and flow were low for all but 3 studies, with 1 unclear ROB,[52] and 2 high ROB (see Figure 3 and Appendix C for more detail).[39,40]

Figure 3. Risk of Bias of Diagnostic Accuracy Studies



Note. See Appendix C for a description of categories and item list.

Table 2. Characteristics of studies examining the diagnostic accuracy of depression screening tools in patients with ESRD (KQ1)

Author, Year N enrolled Country/ US region, years of enrollment	Study setting Sample characteristics and demographics	Inclusion Criteria/ Exclusion Criteria	Index Test(s); Administration	Reference Standard; Administration	% MDD Positive per Index Test; Reference Standard
Alsuwaida, 2006[52] N = 26 Saudi Arabia	Single Site: hospital-based outpatient HD unit 42% Female Age: 48.1(15.1) Education: NR HD: 100% Dialysis duration: NR History of depression: NR	Inclusion: 18+ years of age, ESRD and on maintenance HD for 3+ months Exclusion: Inability to participate in psychiatric interview, acute kidney failure, and delirium. Diagnosed with psychiatric disorders other than MDD	SRQ (Arabic Version): Self-report. Timing: within a week of clinical interview	Clinical Interview: All participants interviewed by the same psychiatrist (blinded to index test). Timing: up to a week before the index test.	SRQ=NR; 15.4%
Balogun, 2011[39] N = 96 US	Multisite: dialysis units Of 89 participants: 56% Female Age: 73.5(6.2) White: 56.2% Black: 43.8% Education: NR HD: NR Dialysis duration: NR History of depression: NR	Inclusion: 65+ with ESRD treated with chronic hemodialysis and able to give their informed consent Exclusion: acute or other chronic illness [*ie*, metabolic (organic) brain syndrome, known malignancy, dementia], currently using antidepressants, and active alcohol or recreational drug abuse, did not speak English	BDI, GDS-15: NR	Clinical Interview: Geriatric Psychiatrist	Of 62: BDI≥10= 37.1%, GDS-15 ≥5 = 32.3%; 30.6%
Bautovich, 2018[48] N = 45 Sydney, Australia	Single site: outpatient dialysis unit 42% Female Age: primarily 65+ Education: NR HD: 100% Days on dialysis: M= 1241(1098)	Included: 18+ years of age, receiving HD, adequate English language skills Excluded: evidence of psychosis, drug or alcohol dependence, or cognitive dysfunction	BDI, CDI: Self-report. Timing: before clinical interview.	Clinical Interview: Interviewed by a senior psychiatry registrar or psychiatrist, both of whom were experienced in diagnosing depression amongst those with chronic medical illness; Timing: completed immediately after index tests	BDI, CDI = NR; 13.3%

Author, Year N enrolled Country/ US region, years of enrollment	Study setting Sample characteristics and demographics	Inclusion Criteria/ Exclusion Criteria	Index Test(s); Administration	Reference Standard; Administration	% MDD Positive per Index Test; Reference Standard
	History of depression: NR				
Chilcot, 2008[53] N = 40 UK	Multisite: outpatient renal service 40% Female Age: 53.2(14.2) White: 87.5% Black Caribbean: 10% Asian: 2.5% Education: NR HD: 100% (high-flux or on-line) 3x/week Months on dialysis M=51.2 History of depression: NR	Included: Adult ESRD receiving HD for >3 months. Excluded: Psychiatric illnesses other than MDD, <23 MMSE	BDI, CDI: Self-report. Completed on and off dialysis. On-dialysis commenced 30 minutes after the start of a stable session. Off-dialysis conducted at the same as the MINI, M=10.7(4.2) days before/after.	MINI (ref for BDI): Administration by a research psychologist who was trained by a consultant psychiatrist. Timing: 10.7(4.2) days before/after the on-dialysis BDI, and on the same day as the off-dialysis BDI. BDI-II (ref for CDI): Self-report. Same day as the CDI.	BDI≥16 on dialysis = 32.5%, off dialysis = 30%, CDI≥10 on and off dialysis = 32.5%; 22.5%
[1]Collister, 2019[49] N = 50 Canada	Multisite: outpatient HD units 48% Female Age: 64(12.4) Education: NR HD: 100% 3+x/week: 96% Hours of HD M= 3.6(0.4) Dialysis duration: NR History of depression: NR Antidepressants: 16%	Included: 18+ years of age, receiving in-center hemodialysis ≥2x weekly for at least the last 90 days Excluded: unable to complete the study instruments due to a cognitive impairment or an English language barrier	Single question from the ESAS: Self-report scale (0-10) re: feeling blue or sad. Timing: taken during dialysis during the same session as the reference test.	HADS: Self-report. Timing: taken during dialysis during the same session as the reference test.	ESAS = NR; HADS≥7=54%

Author, Year N enrolled Country/ US region, years of enrollment	Study setting Sample characteristics and demographics	Inclusion Criteria/ Exclusion Criteria	Index Test(s); Administration	Reference Standard; Administration	% MDD Positive per Index Test; Reference Standard
[1]Gencoz, 2007[42] N = 45 Turkey	Single site: hospital-based outpatient HD unit 42.2% Female Age: 41.64(11.7) ≤ Middle school: 37.9% HD: 100% Months on HD M=72.24(48.48) History of depression: NR	Included: medically stable with no hospital admission for any reason within the last 3 months, and maintained on dialysis for at least 12 months Excluded: presence of cognitive impairment indicated by MMSE score lower than 24, presence of a history of a psychiatric diagnosis or treatment in the last 6 months, and presence of some practical difficulties like probability of moving to another city, blindness or low educational level, which may decrease the patients' ability to comprehend and/or follow the study protocol. Patients who did not complete all baseline assessments were also excluded from the study.	Ham-D: Administered at baseline and the following month by a clinical psychologist that was blind to the reference standard. Timing re: reference standard: NR	SCID-I (Turkish Translation): Administered at baseline and the following month by a clinical psychologist that was blind to the reference standard. Timing re: index test: NR	Ham-D NR; 4% MDD, 18% other depressive disorders
[1]Giordano, 2007[40] N = 31 Italy	Single site: hospital-based HD unit 35.5% Female Age: 70.3(1) Race: NR Education: NR HD: 100% Dialysis duration: NR History of depression: NR	Inclusion: 3+ HD/wk, 65+ years old, maintaining functional independence or loss of it in only 1 of the 6 basic ADL, no evidence of significant cognitive impairment per MMSE >24, no evidence of severe diseases that might highly influence mood state (*eg*, cancer, symptomatic cerebrovascular disease with residual deficit, schizophrenia and other psychoses), and disease severity as evaluated by the CIRS for overall illness severity for which >3 is moderate Exclusion: Taking antidepressants	GDS-15: Self-report. Administered by a trained interviewer. Timing: same session as reference standard.	BDI: Self-report. Administered by a trained interviewer. Timing: same session as index test.	GDS-15 ≥6 = 32%; BDI-II ≥14= 29%

Author, Year N enrolled Country/ US region, years of enrollment	Study setting Sample characteristics and demographics	Inclusion Criteria/ Exclusion Criteria	Index Test(s); Administration	Reference Standard; Administration	% MDD Positive per Index Test; Reference Standard
[2]Grant, 2008[50] N = 57 UK	Single site: outpatient HD unit 29.8% Female Age: 62.5(15.8) Non-White 7% Education: NR HD: 100% Dialysis duration: NR History of depression: NR	Included: 18 and 90 years of age, ESRD for 3+ months, receiving HD 3x/week. Excluded: Current psychiatric care, on medication for a psychiatric illness or had seen a psychiatrist for follow-up within the last 2 years, severe co-morbid illness requiring hospitalization.	BDI: Self-report. Distributed by a healthcare assistant during a HD session.	Clinical Interview (based on ICD-10 diagnosis): Interviewed by a trained psychologist. Included a full psychiatric history and MMSE. Timing: within 1 week of index test	BDI-II ≥10 = 56.1%; 12.3% BDI-II ≥15 = 31.6%;
[1]Hedayati, 2006[56] N = 98 US Durham, NC March 2003-April 2004	Multi-site: outpatient dialysis units (VA, 2 non-VA) 44.9% Female Age: 57.2(13.8) Veterans: 26.5% AA/Black: 80.6% White: 14.3% Other: 5.1% ≤High school: ≈ 44.5% HD: 100% Years on dialysis: M=4.1(3.8) History of depression: NR	Included: English-speaking with health-care power of attorney and could sign consent. Excluded: NR	BDI, CDI, CESD, Feinstein Scale; RA administered BDI/CESD/Feinstein Scale at enrollment.	SCID-I: Administered by a nephrologist. Timing: within 1 week of index tests	BDI≥14 = 30.6%, CESD ≥18 = 30.6%; 26.5% 17.3% MDD
[1]Loosman, 2010[35] N = 62 Amsterdam Feb-June 2008	Single site: hospital-based HD and outpatient PD 46.8% Female Age: 63.5(14.9) 64.5% Dutch ethnicity Education: NR HD: 82%; PD 18%	Included: Patients with ESRD treated with HD or PD Excluded: Patients who were unable to read or understand Dutch	BDI, HADS: Self-report. Completed while receiving treatment.	MINI: Performed by a medical resident who was extensively trained on the MINI by a psychiatrist. For 1:7 patients, MINI interviews were performed by both the medical resident and the psychiatrist (100% Inter-rater reliability). Timing: NR	BDI, HADS = NR; 33.9%

Author, Year N enrolled Country/ US region, years of enrollment	Study setting Sample characteristics and demographics	Inclusion Criteria/ Exclusion Criteria	Index Test(s); Administration	Reference Standard; Administration	% MDD Positive per Index Test; Reference Standard
	Months on dialysis: 46(65) Previous depression: 9.7% Antidepressants: 3.2%				
Neitzer, 2012[46] N = 134 US CA, TX 2009	Multisite: outpatient HD units 48% Female Age: 59.1(14.7) AA/Black: 22% Asian: 13% White: 60% Other: 4% Education: NR HD: 100% Months on dialysis: Median = 27.5 (2.9-252.2) History of depression: NR	Included: English or Spanish speaking, 18+ years old, due in April to June 2009 for their KDQOL-SF36 assessment. Excluded: Questionnaires with 50% or more of the questions left blank were considered incomplete and excluded.	BDI-FS: Self-report. Completed during HD treatment.	BDI-II: Completed during HD session. Order of completion was not specified.	BDI-FS≥ 4 = 30.1%; BDI II ≥ 16: 28.7%
[1]Preljevic, 2012[36] N = 109 Norway	Multisite: hospital-based HD and PD centers 30.3% Female Age 57.8(15.7) Race: NR 69.4% HS or less HD: 76.6%; PD: 23.3% Months on dialysis: M=8.5 (3.75–22) History of depression: NR	Included: 18+ years receiving either HD or PD for more than 2 months, were in a stable clinical condition and had adequate Norwegian language skills. Excluded: Cognitive dysfunction, psychosis or drug/alcohol abuse; hospitalization during the investigation period; however, they could be enrolled 4 weeks or more after discharge from hospital if they were in a stable clinical condition.	BDI, CDI, HADS-D: Self-report. Completed in a standardized sequence during the dialysis treatment for HD patients and during the routine outpatient control for PD patients.	SCID-I: Administered by an experienced psychiatrist who was blinded to each participant's medical history and scores on all self-report questionnaires. Assessments were conducted during dialysis sessions to standardize the assessment procedure and the time point relative to dialysis treatment. Interviews were audiotaped and 25 randomly selected tapes were scored independently by another psychiatrist to establish inter-rater	BDI≥16 = 20.8%, CDI≥11 = NR, HADS-D≥8 = 20.1%; 22% 14.7% MDD

Author, Year N enrolled Country/ US region, years of enrollment	Study setting Sample characteristics and demographics	Inclusion Criteria/ Exclusion Criteria	Index Test(s); Administration	Reference Standard; Administration	% MDD Positive per Index Test; Reference Standard
				reliability. The interrater reliability for depressive disorder was excellent (κ=1). Timing: NR	
[1]Troidle, 2003[47] N = 97 US June 2000 – January 2002	Multisite: CPD and HD units CP: 46% Female; HD: 40% Female Age: CPD 55.4(11.3); HD 56(8.6) White: CPD 75%; HD 87% CPD: 83%; HD 17% Education: NR Dialysis duration: NR History of depression: NR	NR	2 items from the KDQOL SF-36: Self-report. Likert 1-6. Scored by a social worker. Timing: consecutive	BDI: Self-report. Recorded by a social worker. Timing: consecutive	KDQOL SF-36 = NR; BDI-II ≥11 NR
[1]Van den Beukel,[51] 2012 N = 133 Netherlands	Multisite: outpatient hospital-based dialysis units 39% Female Age: 62(16) Native Dutch: 66% Education: NR HD: 72% Dialysis duration: NR Previous Depression: 9% Antidepressant: 6% Months on dialysis: M=54(65)	Inclusion: 18+ years of age, ESRD for at least 30 days, able to read the Dutch language and had no significant visual, physical, or cognitive impairment that would prevent completion of the questionnaires Exclusion: NR	MHI5 of the SF-36: Self-report. Completed during dialysis. Timing: NR	BDI/CDI (Dutch Translation): Self-report. Completed during dialysis. Timing: NR	MHI5≤70 = 39%; BDI-II ≥16 = 23%, CDI≥10 = 23%

Author, Year N enrolled Country/ US region, years of enrollment	Study setting Sample characteristics and demographics	Inclusion Criteria/ Exclusion Criteria	Index Test(s); Administration	Reference Standard; Administration	% MDD Positive per Index Test; Reference Standard
	History of depression: NR				
Watnick, 2005[44] N = 62 US Portland, OR July 2003-May 2004	Multisite: public and private outpatient HD and PD units (including VA) Female: 32% Age: 63(15) AA/Black: 15% Hispanic: 5% Asian: 5% White: 76% Education: NR HD: 95%, PD: 5% Dialysis duration: NR History of depression: NR	Inclusion: 18+ years old and had started dialysis therapy more than 90 days before enrollment. Exclusion: Did not speak English, MMSE ≤17, medical record documentation of a psychiatric diagnosis other than depression, were deemed unable to participate by the dialysis staff, or were scheduled for kidney transplant within the next month.	BDI, PHQ-9: Self-report.	SCID-I: Interviewed by a mental health professional (completed psychology internship), blinded to BDI/PHQ-9 results. Timing: within 2 weeks of index tests.	BDI, PHQ-9 = NR; 19.4%
[1]Wang, 2019[45] N = 319 China	Multisite: hospital-based HD units 31.4% Female depressed; 43.78% Female non-depressed Age: 49.4 (6.04) depressed; 50.92(6.46) non-depressed Race: NR HS or less: 51.44% depressed; 57.78% non-depressed HD:100%	Inclusion: 18+ years of age; history of maintenance HD >3 months; ability to understand written Chinese, complete the interview and the questionnaire, and provide informed consent Excluded: documented cognitive impairment, had another primary diagnosis (*eg* chronic heart failure, cancer, hyperthyroidism), or had been previously diagnosed with depression and other psychiatric disorders	BDI, DI-MHD: Self-report. Timing: 2 weeks after clinical interview	SCID-I (ref for BDI): Administered by a psychologist and a nephrologist. Timing: 2 weeks before index tests. BDI-II (ref for DI-MHD): Same time as index test.	BDI≥19 = 20.7%, DI-MHD≥25 = 20%; 21.9%

Author, Year N enrolled Country/ US region, years of enrollment	Study setting Sample characteristics and demographics	Inclusion Criteria/ Exclusion Criteria	Index Test(s); Administration	Reference Standard; Administration	% MDD Positive per Index Test; Reference Standard
	Dialysis duration: NR History of depression: NR				

[1] Screened for depressive symptoms or milder forms of depression in addition to Major Depressive Disorder. [2] Included cutoff values for both Major Depressive Disorder as well as for milder forms of depression and subclinical symptoms.

Abbreviations: BDI-II = Beck Depression Inventory – II; BDI-FS = Beck Depression Inventory - Fast Screen; CA = California; CDI = Cognitive Depression Index; CES-D = Center for Epidemiologic Studies – Depression Scale; CVD = cardiovascular disease; DI-MHD = Depression Inventory – Maintenance Hemodialysis; ESAS = Edmonton Symptom Assessment System; ESRD = end-stage renal disease; GDS-15= Geriatric Depression Scale-15 ; HADS-D = Hospital Anxiety and Depression Scale - Depressive Subscale; Ham-D= Hamilton Depression Rating Scale; HD = hemodialysis; HS = high school; ICD-10 = 10th revision of the International Statistical Classification of Diseases and Related Health Problems; KDQOL SF-36 = Kidney Disease Quality of Life Short Form - 36; MDD = major depressive disorder; MHI5 = Mental Health Inventory 5; NR = not reported; MINI = Mini International Neuropsychiatric Interview; MMSE = Mini-Mental Status Examination; NR = Not reported; NC = North Carolina; OR = Oregon; PD = peritoneal dialysis; PHQ-9= Patient Health Questionnaire 9; SCID-I= Structured Clinical Interview for DSM-IV; SF-36 = Kidney Disease Quality of Life Short Form - 36; SRQ = Self-Reporting Questionnaire; TX = Texas; UK = United Kingdom; US = United States; VA = Veterans Affairs

Table 3. Findings of studies examining the diagnostic accuracy of depression screening tools in patients with ESRD

Author, Year N enrolled	Cutoff	Sens (%)	Spec (%)	PPV (%)	NPV (%)	AUC	Summary of Findings
Beck Depression Inventory-II (BDI-II)							
Balogun, 2011[39] N = 96	≥10	68	77	57	85	0.73	Compared to diagnostic interview, the BDI-II cutoff with the best diagnostic accuracy was ≥10.
Bautovich, 2018[48] N = 45	≥18	100	90	60	100	0.99	Compared to diagnostic interview, the BDI-II is an acceptable screening tool, with a cutoff of ≥18.
Chilcot, 2008[53] N = 40	≥16	88.9	87.1	88.8	87	0.961	Consistent with previous research, (off dialysis) BDI-II with a cutoff of ≥16 has good diagnostic accuracy.
[2]Grant, 2008[50] N = 57	≥10	100	50	21.9	100	0.93	Using the general population cut-off score (≥10), the BDI-II significantly over-diagnosed depression in this HD population. A cutoff of ≥15 is more reliable.
	≥15	100	78	NR	NR	0.93	
	≥20	71.4	92	NR	NR	0.93	
[1]Hedayati, 2006[33] N = 98	≥14	62	81	53	85	0.77	When used for screening, the threshold for depression should be higher for ESRD compared with non-ESRD patients (*ie*, ≥14).
[1]Loosman, 2010[35] N = 62	≥13	75	90.2	75	90.2	0.90	At a cutoff of ≥13, the BDI-II is an effective screening tool for depression in depression in ESRD patients.
[1]Preljevic, 2012[36] N = 109	≥12	91	63	39	96	0.92	The BDI-II demonstrated acceptable performance as a screening tool for depression. At a threshold of ≥16 (general population) the BDI-II performed better than the HADS and the CDI; however, a cutoff of ≥17 is more reliable for this population.
	≥13	91	68	43	97	0.92	
	≥14	86	71	44	95	0.92	
	≥15	82	75	46	94	0.92	
	≥16	82	87	62	95	0.92	
	≥17	82	89	67	95	0.92	
	≥18	77	92	71	94	0.92	
[1]Wang, 2019[45] N = 319	≥15	87	49	34	93	0.84	A cutoff of ≥19 indicated depression in this population.
	≥16	87	58	39	94	0.84	
	≥17	87	65	43	94	0.84	
	≥18	87	71	47	95	0.84	
	≥19	83	86	63	94	0.84	
	≥20	74	94	77	92	0.84	
Watnick, 2005[44] N = 62	≥16	91	86	59	98	0.937	The BDI-II ≥16 is a valid measure for depressive disorders in the dialysis population.
Cognitive Depression Index (CDI)							
Bautovich, 2018[48] N = 45	≥11	100	92	67	10	0.98	Compared to diagnostic interview, the CDI ≥11 is an acceptable screening tool.

Author, Year N enrolled	Cutoff	Sens (%)	Spec (%)	PPV (%)	NPV (%)	AUC	Summary of Findings
[1]Hedayati, 2006[33] N = 98	≥8	50	83	52	82	0.76	When used for screening, the threshold for depression should be higher for ESRD compared with non-ESRD patients. The BDI-II or the CESD have better sensitivity and better agreement (kappa) than the CDI (cutoff ≥8).
[1]Preljevic, 2012[36] N = 109	≥9	82	79	50	94	0.89	The CDI (cutoff ≥11) demonstrated acceptable performance as a screening tool for depression. The BDI-II performed better than the CDI.
	≥10	82	86	60	95	0.89	
	≥11	82	93	75	95	0.89	
	≥12	77	95	81	94	0.89	
	≥13	50	98	85	88	0.89	
	≥14	41	98	82	86	0.89	
Center for Epidemiologic Studies – Depression Scale (CES-D)							
[1]Hedayati, 2006[33] N = 98	≥18	69	83	60	88	0.86	When used for screening, the CESD threshold for depression should be higher (≥18) for ESRD compared with non-ESRD patients.
Geriatric Depression Scale-15 (GDS-15)							
Balogun, 2011[39] N = 96	≥5	63	82	60	83	0.81	The GDS-15 ≥5 is a valid tool compared to the gold standard.
Hamilton Depression Rating Scale (Ham-D)							
[1]Gencoz, 2007[42] N = 45	≥10	100	80	59	100	85	The HDRS ≥10 is a reliable and valid instrument that can be used among ESRD patients undergoing HD
Hospital Anxiety and Depression Scale - Depressive Subscale (HADS-D)							
[1]Loosman, 2010[35] N = 62	≥6	90.5	75.6	85.7	75.6	0.89	The HADS-D ≥6 is an effective screening tool for depression in depression in ESRD patients.
[1]Preljevic, 2012[36] N = 109	≥4	100	48	33	100	0.91	At a HADS-D threshold of ≥8 the BDI-II performed better.
	≥5	95	60	38	98	0.91	
	≥6	95	73	48	98	0.91	
	≥7	86	84	58	96	0.91	
	≥8	73	87	59	93	0.91	
	≥9	59	92	65	90	0.91	
	≥10	59	94	72	90	0.91	
	≥11	50	96	79	88	0.91	
Patient Health Questionnaire 9 (PHQ-9)							
Watnick, 2005[44] N = 62	≥10	92	92	71	98	0.94	The PHQ-9 ≥10 is a valid measure for depressive disorders in the dialysis population.
Self-Reporting Questionnaire (SRQ)							
	≥8	100	50	26	NR	0.96	

Author, Year N enrolled	Cutoff	Sens (%)	Spec (%)	PPV (%)	NPV (%)	AUC	Summary of Findings
Alsuwaida, 2006[52] N = 26	≥9/10	100	68	36	NR	0.96	The SRQ has high sensitivity the PPV is poor due to the somatic symptoms in non-depressed patients with ESRD. A cutoff of ≥13 results in an acceptable specificity level without compromising sensitivity.
	≥11/12	100	72	40	NR	0.96	
	≥13	100	82	50	NR	0.96	
	≥14/15	75	91	60	NR	0.96	
	≥16/17	75	95.5	75	NR	0.96	
	≥18	75	100	100	NR	0.96	

[1] Screened for depressive symptoms or milder forms of depression in addition to Major Depressive Disorder.
[2] Included cutoff values for both Major Depressive Disorder as well as for milder forms of depression and subclinical symptoms.

Abbreviations: AUC = Area under (receiver operating characteristic [ROC]) curve; BDI-II = Beck Depression Inventory – II; CDI = Cognitive Depression Index; CES-D = Center for Epidemiologic Studies – Depression Scale; GDS-15 = Geriatric Depression Scale-15; HADS-D = Hospital Anxiety and Depression Scale - Depressive Subscale; Ham-D = Hamilton Depression Rating Scale; NPV = Negative predictive value; NR = Not reported; PHQ-9 = Patient Health Questionnaire 9; PPV = Positive predictive value; Sens = sensitivity; Spec = specificity; SRQ = Self-Reporting Questionnaire

Diagnostic Accuracy Studies: A Primer

The performance of a diagnostic test is described by its sensitivity and specificity, along with the positive and negative predictive values. Depression assessment tools generate outcomes along a continuous scale, much like a lab test such as the thyroid stimulating hormone. Usually, there is a trade-off between sensitivity and specificity: at lower diagnostic thresholds (*ie*, lower scores on a depression instrument in which higher scores indicate more symptoms) one is more likely to capture all patients that have depression (*ie*, higher sensitivity) but there are also likely to be more false positive tests (*ie*, lower specificity). The area under the receiver operating curve (AUC) describes a test's overall performance and its ability to correctly distinguish patients with and without disease across a range of diagnostic thresholds. Generally, tests with higher AUC are better able to discriminate patients with and without disease, though tests with similar AUC can still perform differently at different diagnostic thresholds. The choice of diagnostic instrument and diagnostic threshold depends in part on how important it is to detect all patients with disease (which might be very important for treatable and potentially fatal conditions), how important it is to minimize the risk of false positives (*ie*, because treatment of the condition is potentially harmful, burdensome, or costly), and to what extent the diagnostic test has been evaluated in the population of interest (Veterans in the United States with ESRD, in this case).

Summary of Findings

Diagnostic Accuracy by Screening Tool

Beck Depression Inventory-II (BDI-II)

The BDI-II is a widely used, validated 21-item self-report tool designed to assess depression severity in adolescents and adults, and was by far the most widely studied instrument in the ESRD population. It closely mirrors DSM-IV criteria for major depressive disorder, and includes questions related to cognitive, affective, and somatic symptoms.[27]

Table 4 lists the performance characteristics of 5 studies examining the accuracy of the BDI-II in diagnosing Major Depressive Disorder compared to a gold standard clinical interview (*eg*, SCID-I).[39,44,48,50,53] Sample sizes ranged from N = 40[53] to N = 96.[39] Two of the 5 studies were conducted in the United States.[39,44] One was a small, multicenter study that included 1 VHA site (N = 62), and reported an optimal BDI-II cutoff of ≥16. Sensitivity was 0.91 and specificity was 0.86, with an AUC of 0.94.[44] The second was a multicenter study of adults 65 and older (N = 96). At a cutoff of ≥10, sensitivity was 0.68, specificity was 0.77, and reported AUC was 0.73 (see Table 2 for study details).[39]

One study in Table 4 reported BDI-II performance across a range of thresholds.[50] The threshold that optimized the sensitivity and specificity of the BDI-II for MDD was ≥15, with a reported area under the receiver operating curve (AUC) of 0.93. One study reported an AUC that was much lower than the others.[39] This study's population was limited to older adults, and it is possible that age differences may have contributed to the difference in performance characteristics (see Table 2 for study details).[39]

Table 4. Beck Depression Inventory-II (BDI-II) characteristics by threshold among studies screening for Major Depressive Disorder (MDD)

Threshold	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC
≥10[39,50]	68	77	57	85	0.73
	100	50	21.9	100	0.93
≥15[50]	100	78	NR	NR	0.93
≥16[44,53]	88.9	87.1	88.8	87	0.961
	91	86	59	98	0.937
≥18[48]	100	90	60	100	0.99
≥20[50]	71.4	92	NR	NR	0.93

Abbreviations: AUC = Area under (receiver operating characteristic [ROC]) curve; BDI-II = Beck Depression Inventory-II; NPV = Negative predictive value; NR = Not reported; PPV = Positive predictive value

Table 5 also lists performance characteristics for the BDI-II, but unlike the studies in Table 4, these 4 studies screened for depressive symptoms and disorders ranging from subclinical to MDD.[35,36,45,56] Sample sizes ranged from N = 43[53] to N = 319.[45] Only 1 study (N = 98) was conducted in the United States, with 1 of the 3 sites at a VHA.[56] At a threshold of ≥14, sensitivity was 0.62, specificity was 0.81, and reported AUC was 0.77. The largest study (N = 319), conducted in China, compared the BDI-II (≥19) to the SCID-I as part of a development and validation study for a depression tool designed specifically for patients undergoing maintenance hemodialysis.[45] Sensitivity, specificity, PPV, NPV, and AUC were 0.83, 0.86, 63%, 94%, and 0.84 respectively (see Table 2 for study details).

Table 5. Beck Depression Inventory-II (BDI-II) characteristics by threshold among studies screening for Major Depressive Disorder (MDD) and less severe depression

Threshold	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC
≥12[36]	91	63	39	96	0.92
≥13[35,36]	75	90.2	75	90.2	0.90
	91	68	43	97	0.92
≥14[56,36]	62	81	53	85	0.77
	86	71	44	95	0.92
≥15[36,45]	82	75	46	94	0.92
	87	49	34	93	0.84
≥16[36,45]	82	87	62	95	0.92
	87	58	39	94	0.84
≥17[36,45]	82	89	67	95	0.92
	87	65	43	94	0.84
≥18[36,45]	77	92	71	94	0.92
	87	71	47	95	0.84
≥19[45]	83	86	63	94	0.84
≥20[45]	74	94	77	92	0.84

Abbreviations: AUC = Area under (receiver operating characteristic [ROC]) curve; BDI-II = Beck Depression Inventory-II; NPV = Negative predictive value; NR = Not reported; PPV = Positive predictive value

Cognitive Depression Index (CDI)

The CGI is a subset of the BDI and includes the first 15 of the 21-items included in the BDI, eliminating items related to somatic symptoms. It was developed for use in patients with Chronic Kidney Disease, with the goal of reducing the likelihood of the overdiagnosis of depression.[57]

Three studies compared the performance characteristics of the CGI to a gold standard clinical interview,[36,48,56] of which only 1 screened for major depressive disorder (N = 45; cutoff ≥10).[48] Sensitivity and specificity values, and AUC were 0.79, 0.81, and 0.94 respectively (see Tables 2 and 3).[48]

The 2 studies screening for the range of depressive symptoms and diagnoses examined cutoff values of ≥8 (N = 98)[56] and ≥11 (N = 109).[36] Sensitivity values were 0.50[56] and 0.82,[36] specificity was 0.83[56] and 0.93,[36] and AUC was 0.76[56] and 0.89 (see Tables 2 and 3).[36] Of note, 1 study[36] examined both the BDI at a threshold of ≥16 and CDI (≥11) and found that the BDI performed better.

Hospital Anxiety and Depression Scale – Depression Subscale (HADS-D)

The Hospital Anxiety and Depression Scale – Depression Subscale (HADS-D) is a widely-used 21-item scale that includes ratings of physical, cognitive, and affective symptoms of depression.[34]

Two studies examined the performance characteristics of the HADS-D in patients with ESRD.[35,36] Both studies also screened for less severe depression diagnoses and/or subclinical symptoms. One study (N = 62) examined a cutoff value of ≥6 and found sensitivity, specificity, and AUC values of 0.91, 0.76, and 0.89 respectively. [35] The other (N = 109), examined a cutoff value of ≥8 and reported sensitivity, specificity, and AUC values of 0.73, 0.87, and 0.91 respectively. Of note, this study also examined the BDI and found that it performed better (≥16; see Tables 2 and 3).[36]

Center for Epidemiologic Studies – Depression Scale (CES-D)

The CES-D is a widely used 20-item tool that was revised in 2004 and evaluates depressive symptoms across 4 factors: depressive affect, well-being, somatic symptoms, and interpersonal relations.[32]

A 3-center multisite study (1 VHA; N = 98)[56] compared the CES-D (≥18) to the SCID-I for MDD and other less severe forms of depression and subclinical symptoms. Sensitivity, specificity, and AUC were 0.69, 0.83, and 0.89 respectively (see Tables 2 and 3).

Hamilton Depression Rating Scale (Ham-D)

The Ham-D is a 17-item rating scale that assesses the frequency and intensity of depressive symptoms. It was developed in 1960, and last revised in 1967.[41]

A single small study (N = 45) conducted in Turkey compared the HAM-D (≥10) to the SCID-I in patients with ESRD undergoing hemodialysis and screened for the range of depressive symptoms

and disorders. Reported sensitivity was 1.00, specificity, 0.80, and AUC was 0.85 (see Tables 2 and 3).[42]

Geriatric Depression Scale-15 (GDS-15)

The GDS-15 is a shortened version of the original 30-item GDS, which assesses depressive symptoms in older adults and was developed in 1982.[37,38]

One study (N = 96) compared the GDS-15 (≥5) in older adults with ESRD to a gold standard clinical interview for MDD. Sensitivity was 0.62, specificity was 0.82, and AUC was 0.81 (see Tables 2 and 3).[39]

Patient Health Questionnaire-9 (PHQ-9)

The PHQ-9 was developed in 2001 to be a short form assessment of depression and severity. It is widely used in the US and internationally.[43]

One small multisite study (N = 62) that included a VHA center examined the PHQ-9 (≥10) compared to the gold standard SCID for MDD. Sensitivity and specificity were both 0.92, and AUC was 0.94 (see Tables 2 and 3).[44]

Self-Reporting Questionnaire (SRQ)

The SRQ was developed by the World Health Organization (WHO) to screen for a range of mental health disorders.[58]

A single very small study (N = 26) conducted in Saudi Arabia compared the SRQ (≥13) to the gold standard SCID-I in patients with ESRD for MDD. Sensitivity, specificity, and AUC were 1.00, 0.82, and 0.96 respectively (see Tables 2 and 3).[52]

Screening Tools Compared to Other Tools

Seven studies used other established tools (*ie*, BDI-II, HADS) as reference standards.[40,45-47,49,51,53] Table 6 lists their performance characteristics. Only 2 studies screened for MDD specifically, both evaluating shortened versions of the BDI-II (BDI-II Fast Screen [BDI-FS], CDI).[46,53] Of the 2, the BDI-FS,[59] a 7-item version of the BDI-II that excludes somatic symptoms and was designed to screen for MDD in medical patients, had high sensitivity and specificity as compared to the BDI-II ≥16.[46] Among those screening for the range of depressive symptoms and disorders, the GDS-15 (≥6)[46] and the Depression Inventory – Maintenance Hemodialysis (DI-MHD; ≥25), a scale developed specifically for patients with ESRD,[45] appear to perform well in this population (see Table 2 for study details).

Table 6. Studies comparing a depression tool to another validated depression tool

Author, Year N enrolled	Cutoff	Sens (%)	Spec (%)	PPV (%)	NPV (%)	AUC	Summary of Findings
Beck Depression Inventory – Fast Screen (BDI-FS)							
Neitzer, 2012[46] N = 134	≥4	97.2	91.8	81.4	98.9	0.98	Reference standard: BDI-II ≥16
Cognitive Depression Index (CDI)							
Chilcot, 2008[53] N = 40	≥10	77.8	80.6	77.7	80.6	0.94	Reference standard: BDI-II ≥16
Depression Inventory – Maintenance Hemodialysis (DI-MHD)							
[1]Wang, 2019[45] N = 319	≥23	97	55	84	89	0.94	Reference standard: BDI-II ≥19
	≥24	97	72	90	91	0.94	
	≥25	97	86	95	93	0.94	
	≥26	93	90	96	84	0.94	
	≥27	85	90	95	70	0.94	
Edmonton Symptom Assessment System (ESAS) – single question							
[1]Collister, 2019[49] N = 50	≥2	81	74	NR	NR	0.81	Reference standard: HADS ≥6.
Geriatric Depression Scale-15 (GDS-15)							
[1]Giordano, 2007[40] N = 31	≥6	94	85	89	92	0.95	Reference standard: BDI-II ≥14.
Kidney Disease Quality of Life Short Form - 36 (KDQOL SF-36) “Have you felt downhearted and blue?”							
[1]Troidle, 2003[47] N = 97	≤3	82	69	NR	NR	NR	Reference standard: BDI-II ≥11.
Kidney Disease Quality of Life Short Form - 36 (KDQOL SF-36) “Have you felt so down in the dumps so that nothing could cheer you?”							
[1]Troidle, 2003[47] N = 97	≤3	65	67	NR	NR	NR	Reference standard: BDI-II ≥11.
Mental Health Inventory 5 (MHI5)							
[1]Van den Beukel, 2012[51] N = 133	≥66	67	78	NR	NR	0.82	Reference standard: BDI-II ≥16 (≥66+) and CDI≥10 (≥74+)
	≥70	77	72	44	91	0.82	
	≥74	83 81 CDI	65 65 CDI	NR	NR	0.82 0.81 CDI	
	≥78	90	54	NR	NR	0.82	
	≥82	93	45	NR	NR	0.82	

[1] Screened for depressive symptoms or milder forms of depression in addition to Major Depressive Disorder.

Abbreviations: AUC = Area under (receiver operating characteristic[ROC]) curve; BDI-II = Beck Depression Inventory – II; BDI -FS = Beck Depression Inventory - Fast Screen; CDI = Cognitive Depression Index; DI-MHD = Depression Inventory – Maintenance Hemodialysis; ESAS = Edmonton Symptom Assessment System; GDS-15 = Geriatric Depression Scale-15; HADS-D = Hospital Anxiety and Depression Scale - Depressive Subscale; KDQOL-36 = Kidney Disease Quality of Life Short Form - 36; MHI5 = Mental Health Inventory 5; NPV = Negative predictive value; NR = Not reported; PHQ-9 = Patient Health Questionnaire 9; PPV = Positive predictive value; Sens = sensitivity; Spec = specificity; SRQ = Self-Reporting Questionnaire

Ongoing studies

No ongoing studies were identified.

KEY QUESTION 2: What is the impact of screening for depression in patients with ESRD on intermediate and/or patient outcomes?

No studies were identified to provide evidence for Key Question 2.

KEY QUESTION 3. What is the effectiveness of depression treatment in patients with ESRD and depression?

We identified 20 RCTs examining pharmacological or nonpharmacologic interventions for the treatment of depression in patients with ESRD. Five trials examined selective serotonin reuptake inhibitors (SSRIs), including 3 of sertraline and 1 each of fluoxetine and citalopram; 2 trials examined nutritional supplements including omega-3 fatty acids and high-dose, oral vitamin D3. Thirteen trials examined nonpharmacologic interventions including 5 trials of CBT, 2 acupressure trials, and 1 each of Benson Relaxation Technique, exercise training, guided imagery, hope therapy, Latihan Pasrah Diri, Mindfulness-based Stress Reduction (MBSR), and Quran readings. All studies were of participants receiving HD. A single study included both patients receiving HD and PD (see Table 7).

Summary of findings

A. *Pharmacological treatment*

We identified 7 RCTs examining pharmacological interventions for depression in participants with ESRD. There was low SOE that there is no difference in depression severity reduction between sertraline and CBT, though both are beneficial. Regarding dietary supplements, there was moderate SOE that long-term, high-dose Vitamin D3 is not effective for reducing depression severity in ESRD patients. Findings for all other pharmacotherapies were insufficient to draw conclusions.

SSRIs

The data to guide the treatment of depression in patients with ESRD with SSRIs is limited. We identified 5 RCTs investigating the effects of SSRIs on depression – 3 comparing SSRIs to placebo and 2 comparing SSRIs to an active comparator.

SSRIs versus placebo

Studies comparing SSRIs to placebo report conflicting findings and provide insufficient evidence for the use of SSRIs to treat depression in patients with ESRD. A small (N = 14), poor-quality RCT[60] conducted in 1997 compared fluoxetine to placebo. At 4 weeks, participants receiving fluoxetine reported a significantly larger reduction in depressive symptoms from baseline, compared to placebo. However, by 8 weeks the differences were no longer significant. A more recent, fair-quality RCT (N = 30)[61] in England compared sertraline to placebo and found that although both groups reported a reduction in depressive symptoms, there was no difference between groups at the end of treatment (6 months) or 6-month follow up. A second, larger fair-

quality RCT (N = 50)[62] conducted in Iran also compared sertraline to placebo. Participants who received sertraline reported a significant reduction in depressive symptoms at 12 weeks (see Tables 7 and 8). Overall, these fair- to poor-quality studies provide insufficient evidence for the use of SSRIs to treat depression in patients with ESRD (see Table 10). Studies were hampered by small sample sizes, and differences in depression assessment tools and statistical analyses (see Table 9).

SSRIs versus active comparators

A recent fair-quality multi-site US study by Mehrotra et al (N = 120)[63] compared sertraline to CBT. The primary outcome was clinician-rated depression measured with the QIDS-C, and both groups improved over 12 weeks. However, the sertraline group experienced significantly greater improvement (effect estimate: −1.85; 95% CI: −3.55 to −0.16]). For the secondary endpoint of self-rated depression (BDI-II) the difference between the groups was not significant (effect estimate: −2.9 [95% CI: −6.7 to 0.8]). The strength of evidence for this comparison was low (see Tables 7, 8, and 9).

A poor-quality RCT (N = 44)[64] conducted in Iran provides insufficient evidence for the comparison of citalopram to "psychological training" in depressed patients with ESRD. Although both arms experienced a reduction in depressive symptoms, there was no difference between citalopram and the comparator (see Tables 7, 8, and 9).

Supplements

Two RCTs compared supplements to placebo for the treatment of depression in ESRD patients. A large (N = 746), fair-quality, 52-week RCT[65] conducted in Southeast China compared ESRD patients (treated with either HD or PD) receiving either high-dose vitamin D3 or placebo. Both arms reported a reduction in depression symptoms at 52 weeks with no significant difference between groups (see Tables 7 and 8). Given the size and quality of the study, the strength of evidence is moderate that long-term, high-dose vitamin D3 is an ineffective treatment for depression in patients with ESRD (see Table 9).

A single, poor-quality RCT (N = 54),[66] conducted in Iran, examined the effect of omega-3 fatty acids versus placebo. Findings indicate a significant reduction in depression symptoms in the treatment arm at 4 months, and no change was associated with placebo. The evidence is insufficient to form conclusions (see Tables 7, 8, and 9).

B. Non-pharmacological treatment

We identified 13 RCTs examining non-pharmacological interventions for depression in participants with ESRD. There was low SOE that CBT is more effective than other psychotherapy for depression severity and QOL, but not for suicide risk. CBT was also more effective than placebo for depression severity and QOL (low SOE). There was also low SOE for acupressure reducing depression severity when compared with usual treatment or sham acupressure. Findings for all other non-pharmacological interventions were insufficient to draw conclusions.

Cognitive Behavioral Therapy

Five RCTs investigated CBT for the treatment of depression in patients with ESRD.

CBT versus active comparator

We identified 3 RCTs that compared CBT to an active comparator for the treatment of depression in patients with ESRD. A fair-quality RCT (N = 90)[67] conducted in Brazil compared group CBT to individualized psychotherapy for participants with MDD, and found a greater reduction in depression symptoms (both clinician and self-reported) associated with CBT (BDI-II: P = 0.001 after 3 months of treatment, P = 0.002 at 9 months follow-up; MINI: P < 0.001 after 3 months of treatment. P = 0.031 at 9 months follow-up; low SOE). In addition, participants receiving CBT also experienced a significant within group decrease in suicide risk and improved on several quality-of-life domains over the study period, while the those assigned to psychotherapy did not. However, the between-group difference in suicide risk reduction was nonsignificant (low SOE). At the end of the study period, there was a significant difference favoring CBT in several quality of life domains (*ie*, burden of kidney disease, quality of social interaction, sleep, overall health, and the mental health; low SOE; see Tables 7, 8, and 9).

Two other trials compared CBT to an active comparator. A poor-quality Jordanian RCT (N = 130)[68] compared CBT to psychoeducation, and while both groups reported a reduction in depression symptoms, the psychoeducation group experienced greater improvement. The strength of evidence for this comparison is insufficient. The third study by Mehrotra and colleagues[63] was also included in the pharmacotherapy section because it examined CBT versus sertraline for treatment-seeking participants with ESRD and depression. For the primary outcome of clinician-rated depression severity, both groups experienced improvement, but sertraline was more effective than CBT. However, there was no difference between the CBT and sertraline groups in self-reported depression severity, and the strength of evidence was low (see Tables 7, 8, and 9).

CBT versus control

Two fair-quality RCTs[69,70] provide low-strength evidence of CBT's benefit when compared with waitlist control. A fair-quality, New York-based RCT (N = 65) examined individual CBT during dialysis and found a greater magnitude of reduction in depression symptoms (P = 0.03) and a significant improvement in quality of life (P = 0.04) among those receiving CBT compared with those on the waitlist.[69] The study also found that fluid adherence was improved for the CBT group at all timepoints, but the strength of evidence for that comparison is insufficient. The second study was a fair-quality RCT (N = 60) examining once-weekly group CBT sessions following dialysis in those with mild-moderate depression in a Mexican ESRD population. Findings also indicate a significant reduction in depression and increased quality of life (low SOE; see Tables 7, 8, and 9).[70]

Acupressure

Two RCTs contribute to low-strength evidence that acupressure is more effective than control for reducing depression severity in ESRD patients. Both studies used similar acupressure procedures. A fair-quality, 3-arm, Iranian RCT (N = 96)[71] compared acupressure to sham acupressure (*ie*, pressure applied 1 cm from the acupressure point), and usual care. Participants

receiving acupressure reported a significantly greater reduction in depression symptoms compared to both sham and usual care (no difference between sham and usual care). A second 3-arm poor quality RCT (N = 108)[72] compared acupressure to transcutaneous Electrical Acupoints Stimulation (TEAS) and usual care in participants in Northern Taiwan. TEAS was applied to the same acupressure points and is theorized to have a similar effect to acupressure and acupuncture.[72] Findings indicate a greater reduction in depressive symptoms and fatigue, and an improvement in sleep quality associated with both acupressure and TEAS than usual care (no significant difference between acupressure and TEAS). The evidence examining acupressure for fatigue and sleep quality is insufficient to draw conclusions (see Tables 7, 8, and 9).

Other treatments

We included RCTs of 7 other therapies: Benson Relaxation Technique,[73] exercise training,[74] guided imagery,[75] hope therapy,[76] Latihan Pasrah Diri (LPD),[77] MBSR,[78] and Quran readings for Muslim patients (see Tables 7, 8, and 9).[79] All were small, single trials with methodological issues, and the evidence was insufficient for all of these treatments.

C. Pharmacological and non-pharmacological treatments combined

No trials addressing the combination of pharmacological and non-pharmacological treatments were identified.

Ongoing studies

We identified 3 relevant trials of depression treatments for patients with ESRD, all of which have not yet reported results or been published (see Table 10 for details).

Table 7. Characteristics of randomized controlled trials of interventions for depression in ESRD outpatients

Author, Year Intervention, N enrolled Country/US region, years of enrollment	Study setting, clinical characteristics, demographics	Inclusion Criteria/ Depression Diagnosis	Depression Screening Tool(s) and their application	Baseline Depression Score Mean ± SD, T vs C
Pharmacological				
Blumenfield, 1997[60] Fluoxetine N = 14 New York, NY Years: NR	2 sites: Hospital dialysis centers Demographics: NR	Included: 18-70 yrs old, normal liver function, score of at least 16 for MDD by Hamilton scale. Excluded: chronic illness other than ESRD and DM, suicidal risk, Axis 1 dx except MDD, psychotropic meds other than Lorazepam, pregnant or not on contraception if child bearing age, MAOI in the past 2 weeks or participation in any drug trial within 4 weeks Depression diagnosis: MDD	Psychiatrist administered HAM-D for dx; BDI; MADRS; Depression Scale of Brief Symptom Inventory; self-report VAS for severity of depression	NR
Friedli, 2017[61] Sertraline N = 30 England April 2013 - May 2015	Multisite (5): Renal units 12% Female Age: 61.7 (13.2) Race: 67% white, 13% AA, 13% Asian, 7% mixed	Included: BDI-II score ≥16, diagnosed with mild to moderate MDD with MINI, and MADRS score ≥18 Excluded: current or past 3 months tx for depression (antidepressants or psychologic therapies), planned living donor kidney transplant within trial period, prognosis of <1 year, several associated medical conditions (Hepatic impairment, Hepatitis B and C, HIV/AIDS, Creutzfeldt–Jakob disease, pregnancy or childbearing potential and not using adequate birth control, substance dependency, psychosis, personality disorder, dementia, or panic disorder with the exception of other anxiety disorders), and contraindicated medications (Monoamine oxidase inhibitors, Pimozide, Triptans, Antipsychotics, Dopamine antagonists, Tramadol, Linezolid, Warfarin), those with severe depression or suicidal ideation, and cognitive impairment on the Folstein MMSE (cut point of 23). Depression diagnosis: MDD	BDI-II; MINI; MADRS patient completed BDI-II, then interviewed by psychiatrist for MINI	MADRS: 24.5 (4.5) vs 25.3 (4.2)

Author, Year Intervention, N enrolled Country/US region, years of enrollment	**Study setting, clinical characteristics, demographics**	**Inclusion Criteria/ Depression Diagnosis**	**Depression Screening Tool(s) and their application**	**Baseline Depression Score** Mean ± SD, T vs C
Gharekhani, 2014[66] Omega-3 fatty acid N = 54 Tehran, Iran Year: NR	2 sites: HD Centers Duration: 70.7 +/- 45.1 mos 4 hrs, 2-3x/wk 48% Female Age: 56.8 ± 13.09 yrs	Included: Adults, TIW HD for at least 3 months and all had same HD rx Excluded: BDI-II<16; pregnancy; current inflammatory or infectious diseases; malignancy; prognosis of <4 months; asthma or COPD; other known psychiatric disorders; hypothyroidism; hemoglobinopathies; concurrent involvement in other research studies; history of medical or surgical illness in past 3 months; previous medication or HD noncompliance; malabsorption syndrome; coagulopathies or increased risk of bleeding; need to take anticoagulant medications including warfarin; intake of omega-3 fatty acids supplement in recent 3 months; hypersensitivity to fish or fish-derived products; concurrent use of corticosteroid, immunosuppressive, immunomodulator, anti-depressant, antiepileptic (except gabapentin), anti-psychotic, or nonsteroidal anti-inflammatory medications Depression diagnosis: Any	BDI-II; application details NR	BDI-II: 23.52 ± 7.49 (Median/IQR: 22 (17, 28)) vs 21±4.72 (Median/IQR: 21 (16.50, 22.75)).
Hosseini, 2012[64] Citalopram N = 44 Iran Years NR	Single-site: hospital HD center 55% female Age: 52.3 ± 15.6	Included: HADS≥8 Excluded: history of psychiatric disorders, stressors other than ESRD in past 6 months, new anxiety episode during study, based on the stress events table by Holmz-Rahe, any change occurred in the hemodialysis schedule, starting other psychiatric therapies during the study, those not completing all training sessions. Depression diagnosis: Any	HADS: completed twice by the patients under the supervision of a psychiatrist, once before the random allocation of the patients and once months after the start of interventions	HADS: 9.42 ± 3.11 vs 9.58 ± 3.47

Author, Year Intervention, N enrolled Country/US region, years of enrollment	**Study setting, clinical characteristics, demographics**	**Inclusion Criteria/ Depression Diagnosis**	**Depression Screening Tool(s) and their application**	**Baseline Depression Score** Mean ± SD, T vs C
Mehrotra, 2019[63] Sertraline vs CBT N = 120 US: NM, TX, WA 2017	Multisite (3 states): 41 dialysis facilities Median time since starting dialysis (IQR), mo: 31 (44) Mean hemodialysis treatment time per session (±SD), h: 3.9 ± 0.4 43% Female Age: 51 ± 13 Race: 43% white; 28% Black; 28% Hispanic; 8% Native Amer; 12% other Education: 40% ≤ high school History of major depression: 42%	Included: 21 ≥ y/o, ESRD, On HD ≥3 months, MDD or dysthymia (BDI-II ≥15, then confirmed by MINI) Excluded: suicidal, receiving intensive psychotherapy for depression, or using medications with potential antidepressant effects at effective therapeutic doses, and those with cognitive impairment, present or past psychosis, or alcohol or substance use disorder Depression diagnosis: MDD or dysthymia	BDI-II and MINI for screening. QIDS-SR during trial, and QIDS-C and BDI-II at 12 weeks. Final QIDS-C and BDI-II by computer-assisted telephone interviewing	QIDS-C mean (range): SERT 10.9 (9.6 to 12.1) vs CBT 12.2 (11.0 to 13.5) BDI-II mean (range): SERT 25.8 (23.3 to 28.4) vs CBT 26.2 (23.6 to 28.8)
Taraz, 2013[62] Sertraline N = 50 Tehran, Iran Years NR	Single site: outpatient HD clinic HD for 4 hrs 3x/wk 43% Time on HD (months): 42 (59) Female Age: 60 (22) all others NR	Included: 18 - 80 y/o, HD ≥3 months using arteriovenous fistula, depression diagnosis: BDI-II ≥16 Excluded: inflammatory cause of ESRD, autoimmune diseases, active infections, malignancy, severe mental illness, cognitive dysfunction, hemorrhage/clotting disorders, hypersensitivity to sertraline, treatment with antibiotics, non-steroidal anti-inflammatory drugs, steroids, immunosuppressives, or antidepressant medications within 1 month before the study. Depression diagnosis: Any	BDI-II; application details NR	BDI-II: 29 (13) vs 23 (11); P = 0.243

Author, Year Intervention, N enrolled Country/US region, years of enrollment	**Study setting, clinical characteristics, demographics**	**Inclusion Criteria/ Depression Diagnosis**	**Depression Screening Tool(s) and their application**	**Baseline Depression Score** Mean ± SD, T vs C
Wang, 2016[65] Vitamin D3 N = 746 Southeast China Years NR	3 sites: Dialysis centers HD and PD Outpatient 39% Female Age: 54% 18-64; 46% 65+ Other demographics: NR	Included: ESRD, current conventional maintenance PD (3 exchanges a day) or HD (3x/wk, 4–4.5 hrs/session) ≥3 months, age ≥18 years, 15 to 30 ng/mL plasma 25(OH)D BDI-II cutoff: 16 Excluded: cognitive deficits such as considerable memory loss, confusion/ dementia, and intellectual disability; illiteracy or inability to answer the questionnaire; antidepressants in 2 years before study; presence of severe depressive symptoms before dialysis Depression diagnosis: MDD, vascular depression	BDI-II-II: Structured interviews were conducted by 2 experienced psychiatrists independently to determine diagnoses and severity of depression for each patient.	BDI-II: 22.7 ± 4.3 vs 21.9 ± 5.4 (P = 0.31)
Non-pharmacological				
Al Saraireh, 2018[68] CBT vs PSE N = 130 Jordan, 2017	Multisite: 5 hospital dialysis units Dialysis duration: NR ~50% Female Age: 52 ± 10.7 Education: 71% ≤ high school Employment: 82% unemployed Race/Insurance NR	Included: diagnosis of chronic kidney failure; chronic dialysis ≥1 year; verbal comprehension/communication Excluded: on antidepressants Depression diagnosis: NR	HAM-D: Data collectors with previous experience on psychiatric research read the items of the instrument for the participants and documented their response.	HAM-D: PSE 19.6 ± 5.4 vs CBT 19.5 ± 5.4 No difference: t(103) = −0.13; P = 0.89
Babamohamadi, 2017[79] Quran N = 60 Iran, year NR	Single site: hospital dialysis ward 42.6% Female Age: 53.3 (11.4) Race: NR Education: 75% less than diploma Employment: NR (55.6% "poor") Insurance: NR	Included: 18-65 y/o; BDI-II score ≥20; command of Arabic; HD for ≥6 months; hemodynamic stable Excluded: using antidepressants, acute mental problems, history of mental illness, impaired consciousness, hearing impairment Depression diagnosis: moderate	BDI-II-II: self-completed before start of dialysis/first session, and again after the last one	BDI-II-II: 33.6 (6.7) vs 29.3 (9.0); mean difference: -4.3 (95% CI: -8.7 to 0.0) P = 0.05

Author, Year Intervention, N enrolled Country/US region, years of enrollment	**Study setting, clinical characteristics, demographics**	**Inclusion Criteria/ Depression Diagnosis**	**Depression Screening Tool(s) and their application**	**Baseline Depression Score** Mean ± SD, T vs C
Beizaee, 2018[75] Guided Imagery N = 80 Iran, 2015-2016	Single-site: HD center Sex: 41.25% Female Age: 47.21(8.34) Education: 46.25% Secondary Employment: 25% unemployed	Included: HD 3x/wk for ≥6 months; 35-65 y/o; read/write in Farsi, intact cognitive functions based on Abbreviated Mental Test (AMT) Excluded: hearing impairment, history of psychiatric disorders, taking tranquillizer or sedative drugs 4h before the intervention, and hemodialysis instability. Depression diagnosis: Any	HADS: completed before and after intervention	HADS: 10.82 ± 2.70 vs 11.55 ± 2.29
Cukor, 2014[69] N = 65 CBT Brooklyn, NY, year NR	2 sites: dialysis units 72.7% Female Age: NR Race: 93.9% Black Education: 11.2 (3.4) yrs Employment: 83.4% Unemployed Insurance: NR	Included: ESRD with HD for ≥6 months; BDI-II score ≥10 Excluded: current hospitalization, altered mental status (MMSE <23), psychosis, current substance abuse, current ongoing psychotherapy, change in psychotropic medication in last 6 months, lack of English proficiency to participate in talk therapy Depression diagnosis: Moderate	BDI-II-II (self-reported), HAM-D (clinician assessed), and SCID-I (major depression): Applied before randomization and after 3 and 6 months	SCID-I % w/ major depression: 54.5 vs 42.2 BDI-II: 25.3 (9.3) vs 21.4 (8.9) HAM-D: 15.0 (6.2) vs 13.5 (5.0)
Duarte, 2009[67] CBT N = 90 Brazil, year NR	2 sites: dialysis units HD: 3x/wk for 4 hrs avg. 63.4% Female Age: 52.4±15.9 Race: 78.1% white Education: 83% ≤ primary school Employment/Insurance: NR	Included: ESRD with HD for ≥3 months; MINI MDD diagnosis Excluded: transplant scheduled, current hospitalization, psychiatric comorbidity (Axis I DSM-IV), cognitive or mental retardation, current substance abuse, or unstable clinical condition Depression diagnosis: MDD	BDI-II and MINI: questionnaires administered and rated by trained psychologist immediately before the start of the intervention, after 3 months, and at the end of 9 months	BDI-II: 24.2±9.7 vs 27.3±10.7 (P = 0.149) MINI: 6.4±1.3 vs 6.4±1.2 (P = 0.955)

Author, Year Intervention, N enrolled Country/US region, years of enrollment	**Study setting, clinical characteristics, demographics**	**Inclusion Criteria/ Depression Diagnosis**	**Depression Screening Tool(s) and their application**	**Baseline Depression Score** Mean ± SD, T vs C
Heshmatifar, 2015[73] Benson Relaxation Technique N = 70 Iran, 2013	Single site: hospital HD unit HD: 3x/wk 18% Female Age: 9% 18-35; 33% 35-45; 45% 45-55; 15% 55-65 Race: NR Education: 94% ≤ high school Employment: 42% Unemployed Insurance: NR	Included: 18-65 y/o; HD 3x/wk for ≥6 months; regular patient of the center Excluded: mental/muscular disorders or severe physical disabilities; mental health medication use; history of depression or hospitalization due to mental disorders before CHD and hemodialysis; history of accidents or unpleasant events over the past 6 months; kidney transplant or PD; death Depression diagnosis: Any	BDI-II-II: no description of application, but did say that patients' depression had to be confirmed by a neurologist	BDI-II: 32.46±9.86 vs 30.58±9.24
Kalani, 2019[71] Acupressure N = 96 Iran, 2011	3 sites: HD centers 44% Female Age: 53.4±13.9 Race: NR Education: 31% non-literate Employment: 50% Unemployed; 41% retired Insurance: NR	Included: ESRD diagnosis; Age 18+; HD for ≥3 months; BDI-II score ≥10; mental and psychological ability to participate Excluded: wounds or fractures at acupressure points; used complementary medicine in last 3 months; lower extremity amputation; unstable physiological symptoms; high creatinine and high urea; acute mental and psychological problems for the past 6 months Depression diagnosis: Any	BDI-II: pts fill before and after intervention	BDI-II: Tx 27.5 ± 9.1 vs PBO 25.7 ± 7.7 vs C 24.6 ± 8.6 (not sig diff)
Kouidi, 2010[74] Exercise training N = 50 Greece, year NR	Single site: hospital renal unit HD: 3x/wk for 4 hrs 41.6% Female Age: 46.3 ± 11.2 Education: 10.2 ± 3.4 yrs Employment: 16.6% Unemployed Race/Insurance: NR	Included: ESRD; 4 hrs HD 3x/wk for ≥6 months Excluded: history, clinical signs, or symptoms of psychiatric, neurological, cardiologic, or pulmonary disorders; diabetes mellitus; significant electrolytic instability or undisciplined patients; musculoskeletal limitation or other medical problems contraindicating participation in an ET program Depression diagnosis: NR (mild-severe)	BDI-II and HADS: administered to all patients at the beginning and at the end of the study by the same physician, who was not familiar with the patients	BDI-II: 22.29 ± 6.71 vs 22.30 ± 6.81 HADS: 10.63 ± 2.60 vs 10.40 ± 2.50

Author, Year Intervention, N enrolled Country/US region, years of enrollment	**Study setting, clinical characteristics, demographics**	**Inclusion Criteria/ Depression Diagnosis**	**Depression Screening Tool(s) and their application**	**Baseline Depression Score** Mean ± SD, T vs C
Lerma, 2017[70] CBT N = 60 Mexico City, MX Year NR	2 sites: HD units HD: 3x/wk for 3-4hrs 51.6% Female Age: 41.8 ± 14.7 Education: 35.5% elementary Employment: 25.8% Unemployed Race/Insurance: NR	Included: ESRD; mild-moderate depression; literate; no psychiatric illness; regular attendance of HD sessions 3-4 hrs HD 3x/wk for ≥6 months Excluded: BDI-II > 29 points were referred for appropriate psychiatric evaluation and care. Depression diagnosis: mild-moderate (BDI-II score of 10–29 points)	BDI-II: questionnaires completed in privacy with supervision of a trained technician	BDI-II: 13.6 ± 7.6 vs 15.8 ± 10.0
Rahimipour, 2015[76] Hope therapy N = 50 Iran, year NR	Multi-site: hospitals HD: 2-3x/wk for 4 hrs 48% Female Age: 47.82 (15.12) Race/Education/Employment/ Insurance: NR	Included: 18–65 y/o; HD 2-3x/wk for ≥3 months; not taken medication for depression, anxiety, or stress Excluded: NR Depression diagnosis: NR	DASS-21 questionnaire; application details NR	DASS-21:13.36 ± 3 vs 13.64 ± 3.5; No difference (t = 0.3; P = 0.76)
Thomas, 2017[78] MBSR N = 41 Montreal, Canada, 2016	Single site: hospital HD unit 33% Female Age: 65 ± 13 Race: 49% white, 51% nonwhite Education: 63% ≤ high school Employment/Insurance: NR	Included: On maintenance HD; spoke English or French; had depression (PHQ-9 score ≥6) and/or anxiety symptoms (GAD-7 score ≥6) Excluded: sig cog impairment; psychosis; suicidal ideation/intent Depression diagnosis: Any	PHQ-9: Participants completed questionnaires with an independent assessor	PHQ-9: 12.7 ± 4.2 vs 11.9 ± 5.8

Author, Year Intervention, N enrolled Country/US region, years of enrollment	**Study setting, clinical characteristics, demographics**	**Inclusion Criteria/ Depression Diagnosis**	**Depression Screening Tool(s) and their application**	**Baseline Depression Score** Mean ± SD, T vs C
Tsay, 2004[72] Acupressure N = 108 Northern Taiwan, Year NR	4 sites: hospital dialysis centers Duration HD: 50.06 (44.15) months 66% Female Age: 58.16 (12.19) Employment: 76.1% Retired or Unemployed Race/Education: NR	Included: ESRD diagnosis; Age 18+; HD for ≥3 months; fatigue; PSQI score ≥5; BDI-II score ≥10 Excluded: lower-extremity amputations, comorbid psychiatric disorders, congestive heart failure, COPD, insulin-dependent diabetes, neuromuscular disease, systemic lupus erythematosus, rheumatoid arthritis, cancer, regular steroid therapy, or use of anti-hypertension medications. Depression diagnosis: Any	BDI-II; application details NR	BDI-II: Acupressure 20.37±10.65 vs TEAS 18.20 ± 11.11 vs C 21.61 ± 11.69
Widyaningrum, 2013[77] Latihan Pasrah Diri N = 36 Java, Indonesia, 2012	Single site: hospital HD unit HD: 2x/wk 61.1 % Female Age: 50.06 (7.39) Education: 77.8% ≤ high school Insurance: 5.6% uninsured Employment/Race: NR	Included: CKD patients on 2x/wk HD for ≥3 months; BDI-II ≥16, 18-60 y/o Excluded: taking antidepressant or psychotropic meds, undergoing psychotherapy, or unable to do relaxation exercises Depression diagnosis: Any	BDI-II; application details NR	BDI-II: 23 ± 5.34 vs 23.39 ± 5.02

Abbreviations: BDI-II = Beck Depression Inventory-II; CKD = chronic kidney disease; COPD = Chronic Obstructive Pulmonary Disease; DASS = Depression, Anxiety, and Stress Scale; DM = diabetes mellitus; DSM-IV = Diagnostic and Statistical Manual-IV; ESRD = end-stage renal disease; ET = Exercise training; GAD = Generalized Anxiety Disorder; HADS = Hospital Anxiety and Depression Scale; Ham-D =Hamilton Depression Rating Scale; HD = hemodialysis; MADRS = Montgomery–Åsberg Depression Rating Scale; MAOI = Monoamine oxidase inhibitors; MDD = Major Depressive Disorder; MINI = Mini International Neuropsychiatric Interview; MMSE = Mini-Mental Status Examination; MX = Mexico; NM = New Mexico; NR = not reported; NY = New York; P = p-value; PD = peritoneal dialysis; PHQ-9 = Patient Health Questionnaire-9; PSE = psychoeducation; PSQI = Pittsburgh Sleep Quality Index; QIDS-C = Quick Inventory of Depressive Symptomatology - Clinician; SD = standard deviation; SERT = Sertraline RCT = randomized controlled trial; TEAS = Transcutaneous Electrical Acupoint Stimulation; TX = Texas; US = United States; WA = Washington; wk = week

Table 8. Efficacy of interventions for depression in ESRD patients from randomized controlled trials

Author, Year N randomized (T vs C), Duration of treatment and follow-up	Intervention description	Comparator description	Findings, Treatment vs Comparator Depression	Other outcomes	Quality
PHARMACOLOGICAL					
SSRIs vs control					
Blumenfield, 1997[60] N = 14 Fluoxetine vs placebo 7 vs 7 Tx = 8 weeks F/U = 8 weeks	Fluoxetine: 20mg/day for 8 weeks	Matched placebo	No difference between groups at 8 wks. FLU sig better than PBO at 4 weeks on BDI, BSI, and electronic VAS, but not other scales. HAM-D only reported end of study difference: not significant. Mean change from baseline (at 4 wks; at 8 wks): BDI: -12 vs -4.17 (P = 0.05); -9.57 vs -8.8 (P = 0.91). BSI: -6.29 vs 0.2 (P = 0.04); -4.43 vs -3.2 P = 0.88 HAM-D: no 4 wk assessment; -9.00 vs -7.5 (P = 0.72) MADRS: -7.20 vs -6.75 (P = 0.93); -11.14 vs -6.67 (P = 0.45) VAS: -210.0 vs -58.3 (P = 0.37); -303.0 vs -140 (P = 0.45) Electronic VAS: -262.4 vs 5.6 (P = .05); -389.0 vs -87.8 (P = 0.13)	NA	Poor
Friedli, 2017[61] Sertraline vs placebo	Sertraline: 100mg/day (50mg/day to start. Dose could be	Matched placebo	No treatment effect MADRS between group difference at 6 months:	NA	Fair

Author, Year N randomized (T vs C), Duration of treatment and follow-up	Intervention description	Comparator description	Findings, Treatment vs Comparator: Depression	Findings, Treatment vs Comparator: Other outcomes	Quality
15 vs 15 Tx = 6months F/U = 6months	increased to max at 2 and 4 months)		-0.67 (-5.7 to 4.4); NS Within groups decrease significant for both groups Mean change at study end MADRS: -14.5 (95% CI: -20.2 to -8.8) vs -14.9 (95% CI: -18.4 to -11.5) BDI-II: -15.7 (95% CI: -24.3 to -7.1) vs -13.0 (95% CI: 19.6 to -6.4); between groups diff NS		
Taraz, 2013[62] Sertraline vs placebo 25 vs 25 Tx = 12 weeks F/U = 12 weeks	Sertraline: 100mg/day (50mg/day for 1st 2 weeks)	Matched placebo	Favors SERT BDI-II scores (Baseline, 6 weeks, 12 weeks, Baseline to 12 weeks): Sertraline: 29 (13); 21 (11.5); 15 (5.5); −11.3±5.8 vs Placebo: 23 (11); 22.5 (8.5); 22.5 (9); −0.5±5, Comparison baseline to 12 weeks between groups (P = 0.001).	NA	Fair
SSRIs vs active comparator					
Hosseini, 2012[64] Head-to-head Citalopram vs psychological training 22 vs 22 Tx = 3 months F/U = 3 months	Citalopram: 20mg/day	Psychological training: 6 1-hr sessions explaining kidney anatomy; physiopathology and causes of kidney failure; treatment modalities with their dis/advantages; HD mechanisms; required care for HD patients; stages of adaptive reaction; problem solving, stress	Post-intervention HADS: 6.26 ± 4.18 (P = 0.001) vs 7.33 ± 4.80 after training (P = 0.04). No difference between groups (P = 0.16). Between groups mean differences also NS (P = 0.65)	NA	Poor

Author, Year N randomized (T vs C), Duration of treatment and follow-up	Intervention description	Comparator description	Findings, Treatment vs Comparator Depression	Other outcomes	Quality
		management, and muscle relaxation techniques.			
Mehrotra, 2019[63] Head-to-head Sertraline vs CBT 60 vs 60 Tx = 12 weeks F/U = 12 weeks	Sertraline: 200mg/day unless limited by AEs (titration began at 25 mg/d and adjusted each visit)	CBT: 10 60-minute sessions during HD for 12 weeks. Therapy included standard components of the intervention (psychoeducation, behavioral intervention, cognitive intervention, and health behavior modification) adapted for maintenance hemodialysis (adherence to dialysis and challenging disease-specific cognitive distortions and maladaptive thought patterns)	Sertraline more effective than CBT for physician reported, but not self-reported, depression after sensitivity analyses with multiple imputation. QIDS-C scores: 5.9 ± 4.5 vs 8.1 ±5.1 *Effect estimate*: −1.85 (95% CI: −3.55 to −0.16) BDI-II scores: 14.1 (95% CI: 11.2 to 17.0) vs 18.7 (95% CI: 15.2 to 22.2. *Effect estimate*: −2.9 (95% CI: −6.7 to 0.8)	NA	Fair
Supplements					
Gharekhani, 2014[66] Omega-3 fatty acid vs placebo 27 vs 27 Tx = 4 months F/U = 4 months	Omega-3 fatty acids: 1,800 mg/day (as 6 soft-gel capsules, each containing 180 mg EPA and 120 mg DHA, 2 capsules taken 3x/day) for 4 months	Matched placebo: Paraffin oil capsules	Favors Omega-3 Mean end of study BDI-II: 13.44 ± 5.66 vs 20.33 ± 7.56. Diff: −10.08 ± 8.07 vs −0.88 ± 8.41; P = 0.001 Within groups: Sig decrease (P < 0.001) vs ND	NA	Poor
Wang, 2016[65] Vitamin D3 vs placebo 373 vs 373	High-dose Oral Vitamin D3: 52-week treatment of 50,000 IU/wk. Treatment time 7-9:00 PM.	Matched placebo	No between groups difference in delta values. Within group BDI-II scores baseline to end of study: 22.7 ± 4.3 to 19.6 ± 3.7; P = 0.021	NA	Fair

Author, Year N randomized (T vs C), Duration of treatment and follow-up	Intervention description	Comparator description	Findings, Treatment vs Comparator: Depression	Findings, Treatment vs Comparator: Other outcomes	Quality
Tx = 52 weeks F/U = 52 weeks			vs 21.9 ± 5.4 to 20.8 ± 5.1; P = 0.033		
NON-PHARMACOLOGICAL					
Al Saraireh, 2018[68] CBT vs PSE (head-to-head) 65 vs 65 Tx = 12 weeks F/U = 12 weeks	CBT: 7 individual 1-hr sessions following the traditional CBT sessions protocol	Psychoeducation (PSE): 7 individual 1-hr sessions. The intention of psychoeducation is to educate people about their disease, its treatment, and rehabilitation. Moreover, this technique should promote acceptance of the disease, active participation of the patient in the treatment process, and learning different strategies to deal with the problems caused by the disease.	Both groups experienced significant decrease in depression scores. Post-test HAM-D scores: 15.0 (5.5) vs 11.1 (2.3). Between groups depression scores favored PSE (t = 4.68; P < 0.01) over CBT.	NA	Poor
Babamohamadi, 2017[79] Quran vs TAU 30 vs 30 Tx = 1 mo F/U = 1 mo	Quran: Listen to audio of Quran recitation on headphones for 20 minutes, beginning 5 minutes before dialysis	TAU	Favors Quran. Post-test BDI-II scores: 14.5 ± 4.8 vs 31.6 ± 9.2; P < 0.0001. Significant between-subjects treatment effect, independent of age (F = 9.3, P = 0.004, Cohen's d = 0.85).	NA	Poor

Author, Year N randomized (T vs C), Duration of treatment and follow-up	Intervention description	Comparator description	Findings, Treatment vs Comparator: Depression	Findings, Treatment vs Comparator: Other outcomes	Quality
Beizaee, 2018[75] GI vs TAU 40 vs 40 Tx = 4 weeks F/U = 4 weeks	Guided Imagery: 3x/wk for 4 weeks administered by certified psychologist 30 mins prior to HD session Audio recording of nature sounds. Told to breathe, relax, and imagine they are in the place with the sounds (*ie,* waterfall, sea waves, jungle, *etc*)	TAU, nearly silent environment	Post-test HADS scores: 10.02 ± 2.58 vs 11.65 ± 2.33	SBP: Mean Before 129.22 ± 12.70 vs 132.85 ± 13.22; After 121.75 ± 12.73 vs 134.87 ± 12.68 DBP: Before 82.50 ± 11.32 vs 81.75 ± 8.51; After 81.00 ± 10.32 vs 81.87 ± 8. 14 HR: Before 77. 95 ± 6. 97 vs 75. 42 ± 8.56; After 73.75 ± 6.25 vs 77.22 ± 7.92	Fair
Cukor, 2014[69] CBT vs waitlist (crossover) 38 vs 27 Tx = 3 months F/U = 6 months	CBT: Individual 60min CBT chairside during dialysis CBT modified for pop. 10 sessions over 3 months	Wait-list control	Favors tx first compared to wait list. Mean change score during treatment was -11.7 points (SD 1.5; P,0.001) (raw mean change from 24.7 [SD 9.8] to 11.7 [SD 9.8]) among those receiving treatment first, and -4.8 points (SD 1.4; P < 0.001) for those receiving treatment after completing the waitlist (raw mean change from 14.5 [SD 8.5] to 9.1 [SD 6.5]) There was also significant mean change in BDI-II score in the untreated group during the waitlist period (-6.7 points [SD 1.7]; P < 0.001) (raw mean change from 21.9 [SD 8.9] to	QOL: favors tx, irrespective of when it occurs. Treatment effect = +12.0 points (SD 3.4; P = 0.003) (raw mean score change from 99.5 [SD 27.9] to 115.3 [SD 25.5]) for tx first vs +11.3 points (SD 3.7; P = 0.01) (raw mean change from 110.6 [SD 25.1] to 119.7 [SD 24.7]) for those treated after waitlist. Between group difference in mean change score sig P = 0.04 Significant increase in QOL associated with treatment, but not waitlist. P = 0.04.	Fair

Author, Year N randomized (T vs C), Duration of treatment and follow-up	Intervention description	Comparator description	Findings, Treatment vs Comparator: Depression	Findings, Treatment vs Comparator: Other outcomes	Quality
			14.5 [SD 8.5]). BDI-II: The magnitude of BDI-II improvement was significantly greater in the intervention group than it was in patients in the intervention waitlist condition (P = 0.03) HAM-D: The difference in mean change score between treated and untreated groups was highly significant (P < 0.001). SCID-I: Between groups not reported	Fluid Adherence: favors tx irrespective of when it occurs: model-estimated mean change score during treatment -1.3%Δkg/d (SD 0.3; P = 0.001) (raw mean change from 4.0 [SD 2.0] to 2.8 [SD 1.6]) for tx first and -1.1%Δkg/d (SD 0.3; P = 0.001) (raw mean change from 3.6 [SD 2.0] to 2.5 [SD 2.0]) among waitlist first. difference between tx groups and control sig P = 0.002	
Duarte, 2009[67] CBT vs psychotherapy 46 vs 44 Tx= 12 weeks F/U = 9 months	CBT: Group CBT sessions (with psychologist specialized in CBT) 90 minutes 1x/wk for 12 weeks; Pts not on HD during sessions; Structured, manualized methodology; Followed by 6 months maintenance w/ monthly mtgs	Individualized psychotherapy with psychologist (routinely available in dialysis unit) 30-50 min 1x/wk for 12 weeks; Followed by as-needed psychological care for 6 months	Both groups experienced improvement on BDI-II and MINI (P < 0.001), but T's improvement was greater. BDI-II: After 3 months 14.1 ± 8.7 vs 21.2 ± 9.1 (P = 0.001); After 9 months 10.8 ± 8.8 vs 17.6 ± 11.2 (P = 0.002) MINI: the mean change from baseline ± SE favored intervention. After 3 months: 4.5 ± 0.4 vs 2.1 ± 0.6; P < 0.001 After 9 months: 4.4 ± 0.4 vs 2.9 ± 0.5; P = 0.031	Suicide Risk Module (MINI): No between groups difference. Baseline 2.2 ± 5.1 vs 1.4 ± 3.5, P = 0.287; After 3 months 1.2 ± 4.2 vs 0.7 ± 1.9, P = 0.433 After 9 months 0.6 ± 1.2 vs 0.6 ± 2.0, P = 0.947 Overall reduction, within group comparison: Significant reduction within T group (P = 0.007) vs C (P = 0.130) QOL: CBT group significantly improved several dimensions of	Fair

Author, Year N randomized (T vs C), Duration of treatment and follow-up	Intervention description	Comparator description	Findings, Treatment vs Comparator: Depression	Findings, Treatment vs Comparator: Other outcomes	Quality
				KDQOL. Between groups sig improvement in burden of kidney disease, quality of social interaction, sleep, overall health, and mental component summary dimensions.	
Heshmatifar, 2015[73] BRT vs TAU 35 vs 34 Tx = 1 month F/U = 1 month	Benson relaxation technique (BRT): Pts attend training sessions, then demonstrate technique to researcher during each of their HD sessions. The rest of the practices were done without supervision using a pamphlet and CD. Performed 20 minutes 2x/day for 1 month.	TAU	Only T group's scores decreased. The difference between groups was significant (P = 0.01).	NA	Poor
Kalani, 2019[71] Acupressure vs Sham vs TAU 32 vs 32 vs 32 Tx = 4 weeks F/U = 4 weeks	Acupressure: Applied during 1st 2hrs of HD. 3x/wk for 4 weeks. to both the legs, both the arms, and the back. the main acupressure points included SP6, ST36 GB34, K1, BL23 and HT7. Each session lasted 20 minutes; 2 minutes for the primary surface stroke to relax	Sham: Same as acupressure group except pressure applied 1cm from actual acupressure points. Control: TAU	Post-test: Tx 20.6 vs PBO 25.5 vs C 24.9 significant difference between T and other groups (P = 0.001 for both); No difference between PBO and C (P = 0.220).	NA	Fair

Author, Year N randomized (T vs C), Duration of treatment and follow-up	Intervention description	Comparator description	Findings, Treatment vs Comparator Depression	 Other outcomes	Quality
	the solidity and the remaining 18 minutes for pressing the 6 points (3 minutes for each point). average of 3–4 kg pressure				
Kouidi, 2010[74] ET vs control 25 vs 25 Tx = 1 year F/U = 1 year	Exercise Training (ET) program: 3x/wk 60-90 min. during 1st 2 hrs of HD session physician and trainer supervised sessions: warm-up, cycling, strengthening, and cool-down	Sedentary control	Favors ET in both BDI-II and HADS scores (P < 0.001)	Heart rate variability (HRV) Indices: SDNN, MSSD, pNN50, LF, HF, and LF/HF all significantly increased in exercise group, but not controls. After intervention exercise group was significantly better in all variables P < 0.001	Poor
Lerma, 2017[70] CBT vs waitlist 38 vs 22 Tx = 5 wks F/U = 9 wks	CBT: 5, group Cognitive Behavioral Intervention sessions (2hrs) 1x/wk after HD session 3 techniques: 1. Behavioral activation; 2. Deep breathing and muscle relaxation; 3. Cognitive restructuring	Wait list	BDI-II after 5 weeks (end of intervention): 10.2 ± 8.2 vs 15.0 ± 10.9; P = 0.084 BDI-II after 9 weeks (follow-up): 7.1 ± 7.2 vs 14.7 ± 9.7; P = 0.003. Significant overall within group reduction in scores for tx (<0.001), but not controls (0.866). Between groups RR of reducing depressive symptoms = 1.7 Adjusted RR between groups for depression = 0.33 (33% clinical utility, 95% CI: 0.05 to 0.55)	Overall QOL (by PLC) favors treatment: Baseline: 99.4 ± 21.3 vs 91.5 ± 19.5; P = 0.203; After 5 weeks:109.6 ± 21.1† vs 94.0 ± 21.0; P = 0.016 After 9 weeks: 112.5 ± 23.8 vs 91.3 ± 22.5; P = 0.004 Overall within group P = 0.001 vs P = 0.663. Cohen's d = 0.93 (large)	Fair

Author, Year N randomized (T vs C), Duration of treatment and follow-up	Intervention description	Comparator description	Findings, Treatment vs Comparator: Depression	Findings, Treatment vs Comparator: Other outcomes	Quality
Rahimipour, 2015[76] Hope therapy vs control 25 vs 25 Tx = 8 weeks F/U =12 weeks	Hope therapy: Sessions utilizing Schneider's hope therapy theory 1x/wk for 8 weeks 1-1.5 hr during 1st 2hrs of dialysis administered by researcher	Control: Listening session with researcher's coworker in which pts could talk about their disease and problems 1x/wk for 8 weeks	Immediately after 8wk-intervention (t = 12.75; P < 0.001), and at 1-month follow-up (t = 13.83; P < 0.001)	NA	Poor
Thomas, 2017[78] MBSR + psychoed vs TAU + psychoed 21 vs 20 Tx = 8 weeks F/U = 8 weeks	MBSR: guided, chairside meditative practices 10–15 minutes 3x/wk during hemodialysis sessions 4 meditation techniques drawn from mindfulness-based cognitive therapy (body scan, guided meditation, silent meditation, and gentle arm movements) Both control and intervention groups received psychoeducational literature on anxiety and depression.	TAU. Both control and intervention groups received psychoeducational literature on anxiety and depression.	No significant change in PHQ-9: -3.0±3.9 vs 2.0±4.7; P = 0.45	NA	Fair
Tsay, 2004[72] Acupressure vs TEAS vs control 36 vs 36 vs 36 Tx = 4 weeks F/U = 4 weeks	Acupressure: applied for 15min 3x/wk for 4 weeks 3 min massage, then 4 acupoints (specific points in paper) treated	Control group (not described)	Acupressure and TEAS are similarly effective, and significantly more effective than no intervention (P = 0.009 and P = 0.008 respectively). No difference	Fatigue (by PFS): Baseline Acu 5.92 ± 1.39 vs TEAS 5.60 ± 1.30 vs C 6.01 ± 1.60; Follow-up Acu 4.61 ± 1.72 vs TEAS 4.70 ± 1.50 vs C 5.70 ±	Poor

Author, Year N randomized (T vs C), Duration of treatment and follow-up	Intervention description	Comparator description	Findings, Treatment vs Comparator: Depression	Findings, Treatment vs Comparator: Other outcomes	Quality
	for 3 min each with finger force 3-4kg by investigators and RAs who had received training from Chinese medicine physician vs Transcutaneous Electrical Acupoint Stimulation (TEAS): applied for 15min 3x/wk for 4 weeks 3 min massage, then 4 acupoints (specific points in paper) treated for 3 min each with 2hz/100hz alternating every 3 seconds applied with paired skin electrodes on acupoints		between acupressure and TEAS (P = 0.95)	1.80. Post-hoc analysis found significantly lower levels in Acu (P = 0.006) and TEAS (P = 0.02) when compared with controls. No difference between Acu and TEAS Sleep quality (by PSQI): Baseline Acu 8.85 ± 4.50 vs TEAS 7.12 ± 4.51 vs C 9.35 ± 3.48; Follow-up Acu 7.80 ± 4.00 vs TEAS 6.32 ± 4.55 vs C 9.75 ± 4.65. Compared to controls significantly better with Acu (P = 0.05) and TEAS (P = 0.016). No difference between Acu and TEAS	
Widyaningrum, 2013[77] LPD vs control 18 vs 18 Tx= 3 weeks F/U= 3 weeks	Latihan pasrah diri (LPD): method combining relaxation and remembrance by focusing practice on breathing and words in the dhikr (relaxation and repetitive prayer) for evoking relaxation response. 2x/ day for 21 days	Control group (not described)	Significantly decreased BDI-II scores within both groups, and greater in LPD, but between group difference not significant (P = 0.201)	QOL (by KDQOL-SF36): significantly greater pre-post change associated with LPD vs control in sleep and overall health. No other differences were significant.	Poor

Note. See Appendix D for details regarding quality assessment.

Abbreviations: AE = adverse event; BDI-II = Beck Depression Inventory; BRT = Benson relaxation technique; BSI = ; CBT = Cognitive Behavioral Therapy; CKD = chronic kidney disease; DASS = Depression, Anxiety, and Stress Scale; DBP = diastolic blood pressure; DSM = Diagnostic and Statistical Manual of Mental Disorders; ESRD = end-stage renal disease; ET = exercise training; FLU = fluoxetine; HADS = Hospital Anxiety and Depression Scale; HAM-D = Hamilton Depression Rating Scale; HD = hemodialysis; HR = heart rate; HRV = heart rate variability; KDQOL-SF = Kidney Disease Quality of Life Short Form; LPD = Latihan Pasrah Diri; MBSR = mindfulness-based stress reduction; MINI = Mini International Neuropsychiatric Interview; NR = not reported; NS = not significant; P = p-value; PBO = placebo; PD = peritoneal dialysis; PFS = Piper Fatigue Scale; PSE = psychoeducation; PHQ = Patient Health Questionnaire; PLC = Profile of Quality of Life in the Chronically Ill; PSQI = Pittsburgh Sleep Quality Index; QIDS-C = Quick Inventory of Depressive Symptomatology - Clinician; QOL = quality of life; RR = relative risk; RCT = randomized controlled trial; SCID-I = The Structured Clinical Interview for DSM-IV Axis I Disorders; SERT = sertraline; SPB = systolic blood pressure; SSRI = Selective serotonin reuptake inhibitor; TAU = treatment as usual; TEAS = Transcutaneous Electrical Acupoint Stimulation

Table 9. Summary of the evidence on interventions for depression in patients with ESRD

Outcome	Conclusion	Strength of Evidence (Justification)*
SSRIs vs controls (k = 3, n = 94)		
Depression severity	Fluoxetine[60] No benefit (k = 1, n = 14) Sertraline[61,62] Mixed findings (k = 2; n = 80)	Insufficient (NC, SLM)
SSRIs vs active comparator (k = 2; n = 164)		
Depression severity	Sertraline vs CBT[63] Benefit for both; no difference between groups (k = 1, n = 120)	Low (SLM, UC)
	Citalopram vs psychological training[64] Benefit for both; no difference between groups (k = 1, n = 44)	Insufficient (SLH, UC)
Supplements vs placebo (k = 2; n = 800)		
Depression severity	Omega-3 Fatty Acids[66] Increased benefit (k = 1, n = 54)	Insufficient (NP, SLH, UC)
	High-dose Vitamin D3[65] No benefit (k = 1, n = 746)	Moderate (SLM, UD, UC)
CBT vs active comparator (k = 2; n = 220)		
Depression severity	CBT vs psychoeducation[68] Benefit for both, but favored psychoeducation (k = 1, n = 130)	Insufficient (SLH, UC)
	CBT vs psychotherapy[67] Benefit for both, but favored CBT (k = 1, n = 90)	Low (SLM, UC)
Suicide risk	CBT vs psychotherapy[67] Benefit in intervention but not control group; no difference between groups (k = 1, n = 90)	Low (SLM, UC)
QOL	CBT vs psychotherapy[67] Increased benefit for some domains of KDQOL (k = 1, n = 90)	Low (SLM, UC)
CBT vs control (k = 2; n = 125)[69,70]		
Depression severity	Increased benefit (k = 2; n = 125)	Low (SLM)
QOL	Increased benefit (k = 2; n = 125)	Low (SLM)
Fluid Adherence	Increased benefit (k = 1; n = 65)[69]	Insufficient (SLM, UC)

Outcome	Conclusion	Strength of Evidence (Justification)*
Acupressure vs control (k = 2; n = 204)		
Depression severity[a]	Acupressure vs TAU[71,72] Increased benefit (k = 2; n = 204) Acupressure vs sham[71] Increased benefit (k = 1; n = 96)	Low (SLM)
Fatigue	Acupressure vs TAU[72] Increased benefit (k = 1, n = 108)	Insufficient (SLH, UC)
Sleep quality	Acupressure vs TAU[72] Increased benefit (k = 1, n = 108)	Insufficient (SLH, UC)
Acupressure vs active comparator (k = 1, n = 108)		
Depression severity	Acupressure vs TEAS[72] Benefit for both; no difference between groups	Insufficient (SLH, UC)
Fatigue	Acupressure vs TEAS[72] Benefit for both; no difference between groups	Insufficient (SLH, UC)
Sleep quality	Acupressure vs TEAS[72] Benefit for both; no difference between groups	Insufficient (SLH, UC)
Benson Relaxation Technique vs control (k = 1; n = 70)[73]		
Depression severity	Increased benefit	Insufficient (SLH, UC)
Exercise training vs control (k = 1; n = 50)[74]		
Depression severity	Increased benefit	Insufficient (SLH, UC, UP)
HRV	Increased benefit	Insufficient (SLH, UC, UP)
Guided Imagery vs TAU (k = 1; n = 80)[75]		
Depression severity	Unclear effect	Insufficient (SLM, UC)
Vital signs	Unclear effect	Insufficient (SLM, UC)
Hope therapy vs active control (k = 1; n = 50)[76]		
Depression severity	Increased benefit	Insufficient (SLH, UC, UP)
LPD vs control (k = 1; n = 36)[77]		
Depression severity	No benefit	Insufficient (SLH, UP, UC)
QOL	No benefit	Insufficient (SLH, UP, UC)
MBSR vs TAU (k = 1; n = 41)[78]		
Depression severity	No benefits	Insufficient (SLM, UP, UC)

Outcome	Conclusion	Strength of Evidence (Justification)*
Quran vs TAU (k = 1; n = 60)[79]		
Depression severity	Increased benefit	Insufficient (SLH, UC, UP)

[a]Some participants are represented more than once

*The overall quality of evidence for each outcome is based on the consistency, coherence, and applicability of the body of evidence, as well as the internal validity of individual studies. The strength of evidence is classified as follows:[29]
High = Further research is very unlikely to change our confidence on the estimate of effect.
Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Insufficient = Any estimate of effect is very uncertain.

Abbreviations: CBT = cognitive behavioral therapy; HRV = heartrate variability; k = number of studies; LPD = Latihan Pasrah Diri; MBSR = mindfulness-based stress reduction; n = sample size; NC = not consistent; ND = not direct; NP = not precise; SLH = study limitations high; SLM = study limitations medium; SSRI = Selective Serotonin Reuptake Inhibitor; TAU = treatment as usual; UC = unknown consistency; TEAS = Transcutaneous Electrical Acupoint Stimulation; UD = unclear directness; UP = unclear precision

Table 10. Ongoing randomized controlled trials of depression treatments in patients with ESRD

PI/Study Director (Registration); Study Design; Sponsors; Estimated Study Completion	Study Title	Purpose of Study	Participants; Intervention(s)/ Comparator	Outcomes and Timing
Looper, K (NCT02686333) • RCT • Sponsored by the Lady Davis Institute, Jewish General Hospital, Montreal, Canada • June 2019	Meditation Intervention for the Treatment of Depression and Anxiety Symptoms in Patients Undergoing Dialysis: A Randomized Control Trial	Examine the use of brief meditation interventions for patients with symptoms of anxiety and depression who are undergoing dialysis	50 Patients on maintenance hemodialysis with anxiety and depression 10-15 minutes of individually conducted medication practices (silent meditations, guided meditations, body scans, gentle arm movement exercises) vs mental health lit. and TAU	Secondary: Change in PHQ-9 after 8 weeks
Rej, S (NCT03406845) • Head-to-head RCT • Sponsored by the Lady Davis Institute, Jewish General Hospital, Montreal, Canada • June, 2019	Brief Chair-Side Mindfulness Intervention for Depression and Anxiety Symptoms in Patients Undergoing Dialysis: A Pilot Randomized Control Trial with an Active Control Group	Examine the acceptability of meditation Examine techniques versus health promotion in people receiving dialysis who have anxiety or depression	60 adult patients on maintenance HD with depression and/or anxiety Tailored, chair-side mindfulness intervention based on Mindfulness-based Cognitive Therapy (MBCT) vs group health promotion based on the Health Enhancement Program (HEP) as active control for 8 weeks	PHQ-9 depression scores at 8 weeks and 6 months follow-up Other outcomes: sleep, QOL, perceived stress and improvement, social difficulties, HRV, ESAS
Khatami, SMR (IRCT201201175113N2) • Single-blind RCT • Nephrology Research Center, Tehran University of Medical Sciences, Iran • Started 2012, end NR	A Clinical Trial Comparing the Effect of Omega-3 with Sertraline and Placebo on Depression General Health Conditions Among Dialysis Patients	Compare the efficacy of Omega-3 and Sertraline for depression in ESRD patients	75 adult HD patients with depression Omega-3 1500mg vs Sertraline 50-150mg vs placebo for 3 months	HADS at 4, 8, and 12 weeks

Abbreviations: ESAS = Edmonton Symptom Assessment Scale; ESRD = end-stage renal disease; HADS = Hospital Anxiety and Depression scale; HD = hemodialysis; HRV = heartrate variability; NR = not reported; PHQ = Patient Health Questionnaire; QOL = quality of life; RCT = randomized controlled trial; TAU = treatment as usual

KEY QUESTION 4: In patients with ESRD and depression, what are the potential harms of screening and treatment?

Five pharmacological trials reported adverse events. Sertraline trials most commonly reported AEs. Some harm outcomes were more common with Sertraline than placebo including study dropouts due to AEs, nausea, and other nonserious AEs, but none of these were more severe than for the general population. There were also some dropouts due to AEs in the trial of high-dose Vitamin D3. There were no serious AEs in the non-pharmacological trials.

A. Screening

No included studies reported on harms of screening.

B. Treatment

Summary of Findings

Five pharmacological trials reported adverse events (AEs). Sertraline trials most commonly reported AEs. Some harm outcomes were more common with Sertraline than placebo including study dropouts due to AEs, nausea, and other nonserious AEs, but none of these were more severe than for the general population. There were also some dropouts due to AEs in the trial of high-dose Vitamin D3. There were no serious AEs in the non-pharmacological trials.

Pharmacological

SSRIs

A wide range of AEs were reported by participants in both the treatment and control groups in 4 trials examining SSRIs. Across trials, AEs were not consistently reported. The following AEs were reported in 2 or more trials: nausea, infections, headaches, dizziness or hypotension, gastrointestinal issues, sexual dysfunction, and insomnia. Three of 4 trials reported nausea as a common AE.[60-62] Other reported AEs included major bleeding, cardiac and nervous system conditions.[63] Three sertraline trials performed analyses of adverse events between groups. One trial reported significantly more study dropouts due to adverse or serious adverse events associated with sertraline (33% vs 0%; P = 0.04).[61] A second trial reported no difference in the frequency of adverse events, with the exception of more frequent reports of nausea associated with sertraline (P = 0.033).[62] In the third trial, there were no significant differences between SAEs associated with sertraline and CBT (RD = 0.08; 95% CI: −0.11 to 0.28). However, there were more nonserious AEs associated with sertraline (RD = 0.65: 95% CI: 0.25 to 1.05).[63] Only the trial of citalopram included no reported SAEs.[64] Overall, AEs for SSRIs in ESRD patients with depression were no more severe than reported by the general population treated with SSRIs. There is no evidence that SSRIs are more harmful for this population.

Supplements

No serious AEs associated with omega-3 fatty acids were reported.[66] Adverse events associated with high dose vitamin D3, including joint pain, diarrhea, nausea, and vomiting resulted in study withdrawal of 5 participants.[65] No statistical analyses were performed, and the evidence is insufficient to form conclusions.

Non-pharmacological

Four trials of non-pharmacological interventions reported on adverse events. No adverse events were reported in trials of Latihan Pasrah Diri,[77] MBSR,[78] and exercise training.[74] One CBT trial reported no discontinuations due to serious adverse events.[67] With the exception of exercise training, due to the nature of the interventions the potential for serious adverse events is unlikely; however, the evidence is insufficient to draw any conclusions.

KEY QUESTION 5: Do the benefits or harms of screening differ by subpopulation?

We identified 1 study that examined differences in the benefits or harms of depression screening in patients with ESRD. A small (N = 43) multisite diagnostic accuracy study conducted in UK outpatient hemodialysis units compared depression screening (BDI, CDI) completed on and off dialysis.[53] Findings indicated that there was generally a high level of agreement, particularly among depressed patients. However, non-depressed patients had higher mean overall BDI-II (9.6[6.2] versus 7.3[5.7], P = 0.007) and somatic symptom item scores (4.4[2.5] versus 3.3[2.1], P = 0.01) on assessments completed while undergoing dialysis.

KEY QUESTION 6: Do the benefits or harms of treatment differ by subpopulation?

Three trials examined differences in the benefits or harms of interventions for the treatment depression in patients with ESRD by subpopulation. Interventions examined were omega-3 fatty acids,[66] high-dose vitamin D3,[65] and CBT.[69]

Patient Characteristics

Two trials explored differences in effect by patient clinical and demographic characteristics. A large, multisite fair-quality trial (N = 746) of high-dose vitamin D3 found no differences in effect by age or gender, body mass index (BMI), or plasma albumin level. However, findings did indicate that among participants with vascular depression, and not major depressive disorder, those who received Vitamin K reported a significantly greater reduction in depressive symptoms at one year than those receiving placebo.[65] The second was a small (N = 54), poor-quality trial examining the use of omega-3 fatty acids. It found no significant difference in benefits or harms by age, gender, baseline depression severity, nor length of time on hemodialysis (see Table 8 and 9, and Appendix E for more detail).[66]

Timing and Type of Follow-up

A small, fair-quality trial (N = 65)[69] comparing CBT to waitlist control examined differences in depressive symptoms, quality of life, and fluid compliance based on the timing of the intervention (first or after 90-day waitlist). In both phases, participants who received CBT experienced significantly greater benefits across outcomes. Findings suggest a sequence effect for depressive symptom reduction (greater benefit for first group versus waitlist), but none for quality of life or fluid compliance (see Table 7 and 8, and Appendix E for more detail).[69]

DISCUSSION

We identified 16 studies evaluating the diagnostic accuracy of a variety of depression screening tools, and 20 RCTs examining the effectiveness of pharmacological and non-pharmacological interventions for adults with ESRD and depression. Overall, samples included in studies evaluating screening tools bear little resemblance to Veterans seeking care in VHA settings. In addition, except for the BDI-II, the evidence base is quite limited due to the small number of studies examining each tool and small samples. Similarly, for intervention studies, we identified limited research for each intervention, sample sizes were small, and nearly all studies were hampered by methodological flaws.

The BDI-II was by far the best-studied screening tool. However, there was heterogeneity in the way depression was operationalized. Half of the studies evaluated the performance characteristics associated with thresholds intended to screen for MDD, while the other half defined depression more loosely, with some including subclinical depressive symptoms. Among the studies evaluating the BDI-II as a tool to identify MDD, the threshold that best optimized the balance between sensitivity and specificity for patients with ESRD was ≥16. Interestingly, this finding was reported in the single study that screened for MDD specifically and included a VHA population. Of note, the PHQ-9 tool is commonly used in VHA primary care settings, but we identified only a single, 15-year-old study evaluating it in this patient population.[44]

Table 11 uses data from the 2 US[39,44] and 2 UK studies[50,53] that screened specifically for MDD to compare positive and negative predictive values across reported MDD prevalence rates for a) the general US population (7.1%)[3]; b) Veterans receiving care in VHA patient-centered medical homes (Patient Aligned Care Teams [PACT]; 13.5%)[9]; c) patients with ESRD, diagnosed using a gold standard clinical interview (22.8%)[4]; d) Veterans with ESRD (method of diagnosis NR; 33%)[10]; and e) patients with ESRD, diagnosed using a screening tool (39.3%).[4] Although these rates are representative of US populations, we included the 2 UK studies because the population and health system is similar to the VHA. Studies evaluate both the BDI-II and the PHQ-9 and highlight the impact of the population specific prevalence rate on positive and negative predictive values for a specific threshold. Across studies, the negative predictive values, or accuracy of eliminating depression as a diagnosis are generally high, and false negative findings are unlikely. However, the positive predictive values, or accuracy of correctly diagnosing depression, range from 0.26 to 0.88, and depending on the population, potential of a false positive may be high. Providers should keep this in mind if using the results of depression screening tools to guide treatment decisions.

Across the 4 BDI-II studies, a cutoff of ≥16 provides the best balance between sensitivity and specificity. In fact, we found that in some studies, the BDI-II performed reasonably well when compared to a gold standard clinical interview. The caveat however, is that there was heterogeneity across studies in the way the tools were administered, and very few studies contributed data for the same thresholds. Most of the diagnostic accuracy studies were conducted outside of the US, and/or in health systems that differ from the VHA. Studies of non-Veterans with ESRD may also be less applicable due to both demographic (*eg*, gender, socioeconomic and housing status) and clinical differences (*eg*, multiple comorbidities, substance use, mental health).

Table 11. Positive and negative predictive values associated with depression rates in 4 US populations

Author, Year N, % MDD (Ref), % MDD Tool, Cutoff	Sensitivity (%)	Specificity (%)	Prevalence Assumption (%)	Positive Predictive Value	Negative Predictive Value
Beck Depression Inventory-II (BDI-II)					
Balogun, 2011[39] N = 96 30.6%, 37.1% BDI ≥10	68	77	7.1[a]	0.88	0.50
			13.5[b]	0.32	0.94
			22.8[c]	0.47	0.89
			33.0[d]	0.59	0.83
			39.3[e]	0.66	0.79
Watnick, 2005[44] N = 62 19.4%, NR BDI ≥16	91	86	7.1[a]	0.33	0.99
			13.5[b]	0.50	0.98
			22.8[c]	0.66	0.97
			33.0[d]	0.76	0.95
			39.3[e]	0.81	0.94
Chilcot, 2008[53] N = 40 22.5%; 30-32.5% BDI ≥16	88.9	87.1	7.1[a]	0.35	0.99
			13.5[b]	0.52	0.98
			22.8[c]	0.67	0.96
			33.0[d]	0.77	0.94
			39.3[e]	0.82	0.92
Grant, 2008 N = 57 12.3%; 31.6% BD I≥15	100	78	7.1[a]	0.26	1.0
			13.5[b]	0.42	1.0
			22.8[c]	0.57	1.0
			33.0[d]	0.69	1.0
			39.3[e]	0.74	1.0
Patient Health Questionnaire 9 (PHQ-9)					
Watnick, 2005[44] N = 62 19.4%, NR PHQ-9≥10	92	92	7.1[a]	0.47	0.99
			13.5[b]	0.64	0.99
			22.8[c]	0.77	0.97
			33.0[d]	0.85	0.96
			39.3[e]	0.88	0.95

[a] General US population, [b] Veterans receiving care in VHA patient-centered medical homes, [c] Patients with ESRD, diagnosed using a gold standard clinical interview, [d] Veterans with ESRD (diagnosis method NR), [e] Patients with ESRD, diagnosed using a screening tool.

Abbreviations: BDI-II = Beck Depression Inventory-II; MDD = Major Depressive Disorder

Studies evaluating a (typically short) screening tool against an established validated tool performed well overall. Since the QIP requires a follow-up assessment after an initial positive screen, these short tools may be good options for this purpose. In particular, the BDI-FS performed well when compared to the BDI-II.

We identified no studies examining the impact of screening on intermediate or health outcomes. Only 1 study examined subgroup differences in screening, and it found that non-depressed participants reported significantly more somatic symptoms when depression screening was administered during dialysis sessions versus off dialysis. Not only were scores on somatic items significantly higher, but BDI-II scores were significantly higher as well. This has implications for dialysis units working to streamline processes, as it illustrates the potential for over-diagnosis and over-treatment.

SSRIs, compared either to placebo or an active comparator, were the best-studied pharmacological intervention. Findings from placebo-controlled trials were mixed, and the evidence is insufficient due to lack of consistent findings, small samples, and other methodologic flaws. We found low-strength evidence that despite improvement in both treatment groups, there is no difference between sertraline and CBT. We found moderate-strength evidence that high dose vitamin D3 is ineffective for reducing depressive symptoms. Vitamin D3 is an interesting intervention for patients with ESRD, due to the risk of hyperphosphatemia in this population, which can be exacerbated by vitamin D. Five patients withdrew from the study due to treatment-related AEs. Though not attributed to hyperphosphatemia, the reported AEs (*ie*, joint pain, diarrhea, nausea and vomiting) may be related.

Across non-pharmacological interventions, we found low-strength evidence that CBT is more effective than psychotherapy or placebo for reducing depression severity and increasing quality of life. We also found low-strength evidence that acupressure is more effective for reducing depression severity than sham or usual care. Findings for all other non-pharmacological interventions were insufficient to draw conclusions.

Table 12. Strength of evidence of intervention effectiveness

Intervention	N	Depression Severity	Quality of Life	Fatigue	Sleep Quality
SSRI vs control	94	Insufficient	--	--	--
Citalopram vs psychological training	44	Insufficient	--	--	--
Sertraline vs CBT	120	No Difference	--	--	--
CBT vs psychotherapy	90	Benefit	Benefit	--	--
CBT vs psychoeducation	130	Insufficient	--	--	--
CBT vs control	125	Benefit	Benefit	--	--
MBSR vs TAU	41	Insufficient	--	--	--
Guided Imagery vs control	80	Insufficient	--	--	--
Benson Relaxation Technique vs. control	70	Insufficient	--	--	--
Latihan Pasrah Diri vs control	36	Insufficient	Insufficient	--	--
Hope Therapy vs active control	50	Insufficient	--	--	--
Quran vs TAU	60	Insufficient	--	--	--
Exercise training vs. control	50	Insufficient	--	--	--
Acupressure vs TAU	204	Benefit	--	Insufficient	Insufficient
Acupressure vs sham	96	Benefit	--	--	--
Acupressure vs TEAS	108	Insufficient	--	Insufficient	Insufficient
High dose Vitamin C vs placebo	746	No Difference	--	--	--
Omega 3 Fatty Acids vs placebo	54	Insufficient	--	--	--

Note. Colors represent the Strength of Evidence (SOE). Gray = Insufficient, yellow = low SOE, blue = moderate SOE.

Abbreviations: CBT = cognitive behavioral therapy, MBSR = mindfulness-based stress reduction, SSRI = selective serotonin reuptake inhibitor, TAU = treatment as usual.

Very few intervention studies reported harms; however, most interventions presented minimal risk. Harms related to SSRIs were not uniformly reported. That said, the type and rate of harms reported and or evaluated in multiple studies suggest little to no increase in risk compared to otherwise healthy individuals using SSRIs.

Differences by subpopulation were reported in very few studies, and no reported differences were insufficient to form conclusions.

LIMITATIONS

There are several important limitations to this evidence base, in addition to small samples sizes and a limited number of studies examining specific tool thresholds and specific interventions. Across studies of both screening and treatment, a good number of studies were conducted outside of the United States, many of which examined participants and health systems that differ from general US and Veteran populations. In addition, the lack of methodological detail reported in many of the studies resulted in poor quality ratings, and uncertainty about study processes. For screening studies, the definition of depression varied widely, which hampered our ability to synthesize the body of research for each tool. Future studies should use standardized language (*eg*, DSM-5[80]).

For intervention studies, there was significant heterogeneity in outcome measures used to assess depressive symptoms, and it is possible that the small sample sizes in many of the studies resulted in a lack of power to detect differences.

This is the only systematic review to date that examines the breadth of both screening and treatment of depression in adults with ESRD. This review confirms and adds to a 2016 Cochrane review of antidepressants in adults with ESRD that included meta-analyses of harms reported in trials included in our report.[81] Although we also included more recent trials, outcomes were not reported in a way that allowed for a quantitative synthesis of harms. Newer trials included in our review, particularly the ASCEND (A Trial of Sertraline vs. Cognitive Behavioral Therapy for End-stage Renal Disease Patients with Depression) trial,[63] add to both the pharmacological and non-pharmacological evidence.

RESEARCH GAPS/FUTURE RESEARCH

There are many areas ripe for further research in this field. As described above, diagnostic accuracy studies of depression tools conducted in US and Veteran ESRD populations are needed. In addition, the PHQ-9 is a commonly used tool in VHA and community settings. Additional research evaluating its performance characteristics is warranted. There are a handful of studies supporting the use of the BDI-II as a screening tool for MDD in this population. Larger studies with representative samples evaluating a range of thresholds would help to guide decision-making and implementation. Relatedly, there were several high-performing tools that used the BDI-II as a reference standard. Short, population-targeted tools (*eg*, BDI-FS, GDS-15) may be appropriate as an initial screen for depression in dialysis settings. However, more research is needed to validate existing findings. Finally, the DI-MHD was the only screening tool we identified developed specifically for this population. It performed well as compared to the BDI in a large sample in China; however, to date it has not been compared to a gold standard clinical

interview. Additional research validating the DI-MHD has the potential to impact screening practices in this population.

We identified no studies examining the impact of screening on outcomes, and only 1 study that examined subgroup differences. This study compared differences in overall and somatic BDI-II scores when completed on versus off dialysis and touches on only 1 of many important implementation issues (*eg*, timing, location, administration). Also important but missing is evidence of potential demographic and clinical differences. Research in these areas will help decisionmakers to implement screening processes that are not only evidence-based, but also the best fit for their patient population.

Future research is also needed to better evaluate both pharmacological and non-pharmacological interventions for this population.

IMPLICATIONS FOR THE VHA

Our findings have several implications for the VHA. They will be used to help guide the selection and implementation of screening for Veterans with ESRD, and the interventions for those with comorbid depressive disorders. They will also help to guide future Health Services Research and Development (HSR&D) priorities. Currently in VHA settings, Veterans with ESRD are screened for depression using a variety of tools, including the PHQ-9. Our findings highlight the moderate positive predictive values in this population. Clinicians should be prepared to validate positive screens prior to making treatment decisions that may be burdensome or introduce the possibility of harm.

CONCLUSION

There is limited research evaluating the diagnostic accuracy of most screening tools for depression in patients with ESRD, and the existing studies may not be generalizable to patients in the US, or Veterans receiving care in VHA settings. Screening and intervention studies suffer from limitations related to methodological quality or reporting. In adults with ESRD, the BDI-II with a cutoff of ≥16 provides a good balance of sensitivity and specificity. More research is needed to support the use of other tools. We found low-strength evidence that sertraline and CBT provide benefit for depressive symptoms. There is low-strength evidence that CBT is more effective than psychotherapy or placebo for depressive symptoms and quality of life, low-strength evidence that acupressure is more effective for reducing depression than sham or usual care, and moderate-strength evidence that high-dose vitamin D3 is ineffective. Although our ability to form conclusions about the effectiveness of interventions for depression in patients with ESRD is limited, it is important to note that across studies within group improvements were common, despite insignificant differences between groups, suggesting that treatment generally may be better than no treatment in this population. More research is needed.

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