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The Effectiveness of Depression Treatment for Adults with ESKD: A Systematic Review

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Abstract

Adults with dialysis-dependent ESKD experience higher rates of depression than the general population, yet efficacy of depression treatments in this population is not well understood. We conducted a systematic review of the benefits and harms of depression treatment in adults with ESKD. We searched multiple data sources through June 2020 for English-language, controlled trials that compared interventions for depression in adults with ESKD to another intervention, placebo, or usual care, and reported depression treatment–related outcomes. Observational studies were included for harms. Two investigators independently screened all studies using prespecified criteria. One reviewer abstracted data on study design, interventions, implementation characteristics, and outcomes, and a second reviewer provided confirmation. Two reviewers independently assessed study quality and resolved any discords through discussion or a third reviewer. Strength of evidence (SOE) was assessed and agreed upon by review-team consensus. We qualitatively analyzed the data and present syntheses in text and tables. We included 26 RCTs and three observational studies. 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 is more effective than (undefined) psychotherapy and placebo for depression improvement and quality of life (low SOE), and acupressure is more effective than usual care or sham acupressure in reducing depression severity (low SOE). There is limited research evaluating treatment for depression in adults with ESKD, and existing studies may not be generalizable to adults in the United States. Studies suffer from limitations related to methodologic quality or reporting. More research replicating studies of promising interventions in US populations, with larger samples, is needed.

Systematic Review registry name and registration number: PROSPERO, CRD42020140227

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Introduction

The incidence and prevalence of ESKD in the United States have increased steadily over the past four decades (1). Psychiatric and mental-health disorders are more common in adults with ESKD, and include issues such as depression, dementia, delirium, substance abuse, psychoses, anxiety, and personality disorders (2–4). Adults with ESKD experience major depressive disorder at anywhere from three to over six times that of the general US population, depending on the method of assessment, and depression is the most common mental-health issue in this population (5,6).

The effect of depression can be extremely detrimental for a wide range of patient outcomes for those with ESKD. For instance, adults with ESKD who have depressive symptoms have a 12% higher rate of hospitalization than those without (7), and those with ESKD and psychiatric issues have a 40%–50% increased risk of all-cause mortality (8). Comorbid depression is associated with increased emergency-department visits, hospitalizations, hospital length of stay, suicide, and treatment nonadherence, along with decreased quality of life (QoL) and sleep (8–13).

There are no established guidelines for treating depression in adults with ESKD. Less than 25% of those on dialysis who are diagnosed with moderate or severe depression actually undergo treatment (12,14,15). There are few studies of treatment efficacy in this population and, while some studies include only participants with clinical depression, others include any adults with ESKD. Psychosocial treatments and cognitive behavioral therapy (CBT) are commonly used; however, interventions vary widely, the evidence is limited, and findings may vary on the basis of the presence and severity of depression.

Given the wide variation in depression treatment options for adults with ESKD, it is vital to understand the depression treatment–related outcomes for those in this population suffering from clinical depression. The purpose of this review is to better understand the benefits and harms of treatment for depression in these adults.

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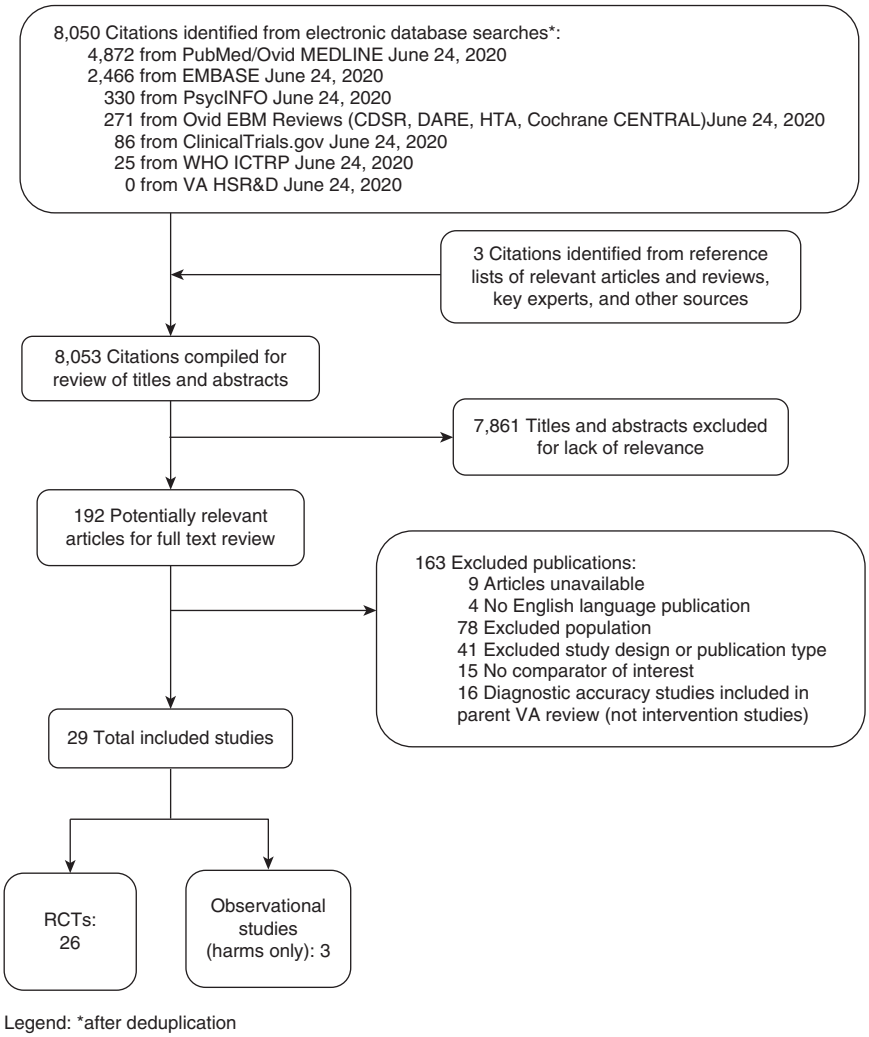

Figure 1. | The f**low diagram of the literature-review process shows 26 RCTs and 3 observational studies.** *After deduplication. CDSR, Cochrane Database of Systematic Reviews; DARE, Database of Abstracts of Reviews of Effects; EBM, Evidence-Based Medicine; HSR&D, Health Services Research and Development Service; HTA, Health Technology Assessment; RCTs, randomized controlled trials; VA, Veterans Affairs; WHO ICTRP, World Health Organization International Clinical Trials Registry Platform.

Materials and Methods

Topic Development

This systematic review was part of a larger review commissioned by the Veterans Health Administration (VHA) (16). A protocol describing the review plan was posted to PROSPERO, a systematic review registry, before study initiation (CRD42020140227). Our methods and reporting follow Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (17). See Supplemental Table 1 for the scope and parameters of the systematic review.

Data Sources and Searches

To identify trials examining the treatment of depression in adults with ESKD, we searched Ovid MEDLINE, PsycINFO, Elsevier EMBASE, and the Ovid Evidence-Based Medicine Reviews (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment, Cochrane CENTRAL, *etc.*) from database inception through June 2020. We reviewed the bibliographies of systematic reviews and other relevant articles, and contacted experts to identify additional studies. To identify unpublished literature, we searched the VHA Health Services Research and Development website, ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry Platform. Search strategies were developed in consultation with a research librarian and peer reviewed by another research librarian using the instrument for Peer Review of Search Strategies (see Supplemental Appendix 1) (18).

Study Selection

Studies were eligible if they (*1*) included adults with dialysis-dependent ESKD not slated for transplant and depression, defined by established thresholds for chronically ill populations (19–23); (*2*) directly compared any pharmacologic or nonpharmacologic treatments for depression to placebo, wait-list control, or other intervention; (*3*) were randomized controlled trials (RCTs) or nonrandomized

Table 1. Characteristics of randomized controlled trials of interventions for depression and studies examining harms of depression treatment in adults with ESKD

Author (Reference); *N* Randomized; Years of Enrollment	Intervention/ Comparator	*N* Sites; Study Setting; Country/US Region	Clinical Characteristics/ Demographics of Study Population	Inclusion Criteria	Depression Screening Tool(s)	Baseline Depression Score, Mean (SD), T versus C
Pharmacologic						
Blumenfield *et al.* (30); *N*=14; Yr NR	Fluoxetine versus placebo	2 sites; hospital dialysis centers; New York, NY	NR	Cutoff for inclusion: HAM-D score ≥16 Other inclusion criteria: age 18–70, normal liver function	HAM-D; BDI-II; MADRS; BSI; VAS	NR
Friedli *et al.* (33); *N*=30; April 2013–May 2015[a]	Sertraline versus placebo	Multisite (5); renal units; England	12% Female; age (SD), 61.7 (13.2) yr; race, 67% White, 13% Black, 13% Asian, 7% mixed	Cutoff for inclusion: BDI-II score ≥16, MINI mild to moderate MDD, MADRS score ≥18 Other inclusion criteria: excluded if already on SSRIs (56)	BDI-II; MINI; MADRS	MADRS: 24.5 (4.5) versus 25.3 (4.2)
Gharekhani *et al.* (35); *N*=54; Yr NR	Ω-3 Fatty acid versus placebo	2 sites; HD centers; Tehran, Iran	HD duration (SD), 70.7 (45.1) mo, 4 h, 2–3× per wk; 48% female; age (SD), 56.8 (13.09) yr	Cutoff for inclusion: BDI-II score ≥16 Other inclusion criteria: adults, HD ≥3 mo and all had same HD Rx	BDI-II	23.52 (7.49) versus 21 (4.72); median (IQR): 22 (17–28) versus 21 (16.50–22.75)
Haghighat *et al.* (36); *N*=49; Yr NR	Synbiotic supplement versus probiotic; supplement versus placebo	1 site; hospital HD center; Iran	52% Female; age (SD), 46.64 (10.69) yr	Cutoff for inclusion: ≥8 Other inclusion criteria: stable patient on HD with arteriovenous fistula, age 30–65, HD 3× per wk for ≥3 mo	HADS	9.16 (1.11) versus 9.77 (1.77) versus 9.20 (1.30); *P*=0.63
Hosseini *et al.* (38); *N*=44; Yr NR	Citalopram versus psychologic training	Single site; hospital HD center; Iran	55% Female; age (SD), 52.3 (15.6) yr	Cutoff for inclusion: HADS ≥8 Other inclusion criteria: NA	HADS	9.42 (3.11) versus 9.58 (3.47)
Mehrotra *et al.* (44); *N*=120; 2017	Sertraline versus CBT	Multisite (3 states); 41 dialysis facilities; United States, NM, TX, WA	Median time on dialysis, 31 mo; mean HD session length (SD), 3.9 (0.4) h; history of major depression, 42%; 43% female; age (SD), 51 (13) yr; race/ethnicity, 43% White, 28% Black, 28% Hispanic, 8% Native American, 12% other; education, 40% ≤high school	Cutoff for inclusion: BDI-II ≥15, then confirmed by MINI Other inclusion criteria: age ≥21, ESKD, on HD for ≥3 mo	BDI-II; MINI; QIDS-SR; QIDS-C	QIDS-C mean (range): SERT 10.9 (9.6–12.1) versus CBT 12.2 (11.0–13.5) BDI-II mean (range): SERT 25.8 (23.3–28.4) versus CBT 26.2 (23.6–28.8)

Table 1. (Continued)

Author (Reference); *N* Randomized; Years of Enrollment	Intervention/ Comparator	*N* Sites; Study Setting; Country/US Region	Clinical Characteristics/ Demographics of Study Population	Inclusion Criteria	Depression Screening Tool(s)	Baseline Depression Score, Mean (SD), T versus C
Taraz *et al.* (46); *N*=50; Yr NR	Sertraline versus placebo	Single site; outpatient HD clinic; Tehran, Iran	HD for 4 h 3× per wk, 43%; time on HD, 42 mo; 59% female; age (SD), 60 (22) yr; all others NR	Cutoff for inclusion: BDI-II ≥16 Other inclusion criteria: age 18–80, HD ≥3 mo using arteriovenous fistula	BDI-II	29 (13) versus 23 (11); *P*=0.24
Wang *et al.* (49); *N*=160; 2013	*Radix Bupleuri* herbal supplement versus placebo	Single site; Dalian, Northeast China	HD duration (SD), 26 (13) versus 29 (15) mo; 75% female; education, approximately 86% <9 yr; concurrent antidepressant medication use, 51% versus 46%	Cutoff for inclusion: NR Other inclusion criteria: aged 30–55 yr; no history of repeated suicidal behavior, severe substance abuse, severe depression impairing verbal abilities, family history of depression, or brain injury/ disease	MADRS	23.9 (7.8) versus 24.6 (7.4)
Wang *et al.*(50); *N*=746; Yr NR	Vitamin D3 versus placebo	3 sites; dialysis centers, HD and PD, outpatient; Southeast China	39% Female; age, 54% 18–64 yr; 46% ≥65 yr; other demographics, NR	Cutoff for inclusion: BDI-II ≥16 Other inclusion criteria: ESKD, current conventional maintenance PD (three exchanges per day) or HD (3× per wk, 4–4.5 h per session) for ≥3 mo, age ≥18 yr, 15–30 ng/ ml plasma 25(OH)D	BDI-II	22.7 (4.3) versus 21.9 (5.4); *P*=0.31
Nonpharmacologic						
Al Saraireh *et al.* (27); *N*=130; 2017	CBT versus PSE	Multisite; 5 hospital dialysis units; Jordan	Dialysis duration, NR; approximately 50% female; age (SD), 52 (10.7) yr; education, 71% ≤high school; employment, 82% unemployed; race/ insurance, NR	Cutoff for inclusion: NR Other inclusion criteria: diagnosis of chronic kidney failure, chronic dialysis ≥1 yr, verbal comprehension/ communication	HAM-D	PSE 19.6 (5.4) versus CBT 19.5 (5.4); no difference, $t_{(103)}=-0.13$; *P*=0.89

Table 1. (Continued)

Author (Reference); *N* Randomized; Years of Enrollment	Intervention/ Comparator	*N* Sites; Study Setting; Country/US Region	Clinical Characteristics/ Demographics of Study Population	Inclusion Criteria	Depression Screening Tool(s)	Baseline Depression Score, Mean (SD), T versus C
Babamohamadi *et al.* (28); *N*=60; Yr NR	Quran versus TAU	Single site; hospital dialysis ward; Iran	43% Female; age (SD), 53.3 (11.4) yr; race, NR; education, 75% less than diploma; employment, NR (56% "poor"); insurance, NR	Cutoff for inclusion: BDI-II score ≥20 Other inclusion criteria: age 18–65, command of Arabic, HD for ≥6 mo, hemodynamically stable	BDI-II	33.6 (6.7) versus 29.3 (9.0); mean difference, -4.3 (95% CI, −8.7 to 0.0); *P*=0.05
Beizaee *et al.* (29); *N*=80; 2015–2016	Guided imagery versus TAU	Single site; HD center; Iran	41% Female; age (SD), 47.21 (8.34) yr; education, 46% secondary school; employment, 25% unemployed	Cutoff for inclusion: NR Other inclusion criteria: HD 3× per wk for ≥6 mo, age 35–65 yr, read/write in Farsi, intact cognitive functions on the basis of AMT	HADS	10.82 (2.70) versus 11.55 (2.29)
Cukor *et al.* (31); *N*=65; Yr NR	CBT versus wait list	2 sites; dialysis units; Brooklyn, NY	73% Female; age, NR; race, 94% Black; education (SD), 11.2 (3.4) yr; employment, 83% unemployed; insurance, NR	Cutoff for inclusion: BDI-II score ≥10 Other inclusion criteria: ESKD with HD for ≥6 mo	SCID-I; BDI-II; HAM-D	SCID-I with major depression: 55% versus 42% BDI-II: 25.3 (9.3) versus 21.4 (8.9) HAM-D: 15.0 (6.2) versus 13.5 (5.0)
Duarte *et al.* (32); *N*=90; Yr NR	CBT versus psychotherapy	2 sites; dialysis units; Brazil	HD, 3× per wk for 4 h average; 63% female; age (SD), 52.4 (15.9) yr; race, 78% White; education, 83% ≤primary school; employment/insurance, NR	Cutoff for inclusion: MDD with MINI Other inclusion criteria: ESKD with HD for ≥3 mo	BDI-II; MINI	BDI-II: 24.2 (9.7) versus 27.3 (10.7); *P*=0.15 MINI: 6.4 (1.3) versus 6.4 (1.2); *P*=0.96
Frih *et al.* (34); *N*=41; 2012–2013[a]	Exercise (endurance-resistance training) versus TAU	Single site; hospital; Tunisia	HD, 4 h 3×/wk; HD duration, 72.7 (12.7) mo; age (SD), 64.2 (3.4) yr; 0% female; other demographics, NR	Cutoff for inclusion: NR Other inclusion criteria: excluded chronic lung disease, ischemic heart disease, uncontrolled arrhythmias or hypertension, hemodynamically unstable, or musculoskeletal disorders, those regularly exercising	HADS	Approximately 12 versus approximately 13 (exact scores NR)

Table 1. (Continued)

Author (Reference); *N* Randomized; Years of Enrollment	Intervention/ Comparator	*N* Sites; Study Setting; Country/US Region	Clinical Characteristics/ Demographics of Study Population	Inclusion Criteria	Depression Screening Tool(s)	Baseline Depression Score, Mean (SD), T versus C
Heshmatifar *et al.* (37); *N*=70; 2013	Benson relaxation technique versus TAU	Single site; hospital HD unit; Iran	HD, 3× per wk; 18% female; age, 9% 18–35, 33% 35–45, 45% 45–55, 15% 55–65 yr; race, NR; education, 94% ≤high school; employment, 42% unemployed; insurance, NR	Cutoff for inclusion: NR Other inclusion criteria: aged 18–65 yr, HD 3× per wk for ≥6 mo, regular patient of the center	BDI-II	32.46 (9.86) versus 30.58 (9.24)
Kargar Jahromi *et al.* (55); *N*=60; 2014	Telenursing versus TAU	Single site; hospital HD unit; Iran	T versus C:56% versus 40% female; education, 4% >high school; unemployed, 60% versus 44%; other demographics, NR	Cutoff for inclusion: NR Other inclusion criteria: aged 18–65 yr; HD 3–4 h 3× per wk for ≥6 mo; no transplants, hospitalizations, or antidepressant Rx	DASS-21	16.60 (1.50) versus 16.72 (1.83); *P*=0.40
Kalani *et al.* (39); *N*=96; 2011	Acupressure versus sham versus TAU	3 sites; HD centers; Iran	44% female; age (SD), 53.4 (13.9); race, NR; education, 31% nonliterate; employment, 50% unemployed, 41% retired; insurance, NR	Cutoff for inclusion: BDI-II score ≥10 Other inclusion criteria: ESKD diagnosis, age ≥18, HD for ≥3 mo, mental and psychologic ability to participate	BDI-II	T 27.5 (9.1) versus sham 25.7 (7.7) versus C 24.6 (8.6)
Kouidi *et al.* (40); *N*=50; Yr NR	Exercise training versus sedentary control	Single site; hospital renal unit; Greece	HD, 3× per wk for 4 h; 42% female; age (SD), 46.3 (11.2) yr; education, 10.2 (3.4) yr; employment, 17% unemployed; race/ insurance, NR	Cutoff for inclusion: NR Other inclusion criteria: ESKD, 4 h HD 3× per wk for ≥6 mo	BDI-II; HADS	BDI-II: 22.29 (6.71) versus 22.30 (6.81) HADS: 10.63 (2.60) versus 10.40 (2.50)
Lerma *et al.* (41); *N*=60; Yr NR	CBT versus waiting list	2 sites; HD units; Mexico City, Mexico	HD, 3× per wk for 3–4 h; 52% female; age (SD), 41.8 (14.7) yr; education, 36% elementary; employment, 26% unemployed; race/ insurance, NR	Cutoff for inclusion: BDI-II score of 10–29 points Other inclusion criteria: ESKD, literate, no psychiatric illness, regular attendance of HD sessions 3–4 h HD 3× per wk for ≥6 mo	BDI-II	13.6 (7.6) versus 15.8 (10.0)
Li *et al.* (42); *N*=72; 2018–2019	Home nursing visits versus telephone follow-up	Single site; hospital; Hainan, China	Dialysis duration (SD), 22.68 (10.25) mo; 44% female; age (SD), 55.8 (6.2) yr; education, 56% ≤middle school	Cutoff for inclusion: NR Other inclusion criteria: age 30–80, on home PD ≥3 mo, kidney failure	Zung SDS	63.34 (6.28) versus 64.27 (6.11); *P*=0.53

Table 1. (Continued)

Author (Reference); *N* Randomized; Years of Enrollment	Intervention/ Comparator	*N* Sites; Study Setting; Country/US Region	Clinical Characteristics/ Demographics of Study Population	Inclusion Criteria	Depression Screening Tool(s)	Baseline Depression Score, Mean (SD), T versus C
Liao *et al.* (43); *N*=128; 2017	Comprehensive nursing versus conventional care	Single site; hospital; Hainan, China	HD duration (SD), 43.56 (13.95) mo; 44% female; age (SD), 52.87 (10.46) yr; education, 57% <high school	Cutoff for inclusion: NR Other inclusion criteria: age ≥18, on HD ≥3 mo for CRF/ESKD	Zung SDS	60.83 (22.67) versus 64.02 (28.58); *P*=0.49
Rahimipour *et al.* (45); *N*=50; Yr NR	Hope therapy versus control	Multisite; hospitals; Iran	HD, 2–3× per wk for 4 h; 48% female; age (SD), 47.82 (15.12) yr; race/ education/ employment/insurance, NR	Cutoff for inclusion: NR Other inclusion criteria: aged 18–65 yr; HD 2–3× per wk for ≥3 mo; not taken medication for depression, anxiety, or stress	DASS-21	13.36 (3) versus 13.64 (3.5); *P*=0.76
Thomas *et al.* (47); *N*=41; 2016	MBSR versus TAU	Single site; hospital HD unit; Montreal, Canada	33% Female; age (SD), 65 (13) yr; race, 49% White, 51% non-White; education, 63% ≤ high school; employment/ insurance, NR	Cutoff for inclusion: PHQ-9 score ≥6 and/ or GAD-7 score ≥6 Other inclusion criteria: on maintenance HD, spoke English or French	PHQ-9	12.7 (4.2) versus 11.9 (5.8)
Tsay *et al.* (48); *N*=108; Yr NR	Acupressure versus TEAS versus control	4 sites; hospital dialysis centers; Northern Taiwan	Duration HD (SD), 50.06 (44.15) mo; 66% female; age (SD), 58.16 (12.19) yr; employment, 76% retired or unemployed; race/education, NR	Cutoff for inclusion: BDI-II score ≥10 Other inclusion criteria: ESKD diagnosis, age ≥18, HD for ≥3 mo, fatigue, PSQI score ≥5	BDI-II	Acupressure 20.37 (10.65) versus TEAS 18.20 (11.11) versus C 21.61 (11.69)
Widyaningrum and Djarwoto (51); *N*=36; 2012	Latihan Pasrah Diri versus control	Single site; hospital HD unit; Java, Indonesia	HD 2× per wk; 61% female; age (SD), 50.06 (7.39) yr; education, 78% ≤ high school; insurance, 6% uninsured; employment/race, NR	Cutoff for inclusion: BDI-II ≥16 Other inclusion criteria: aged 18–60 yr, CKD adults on 2× per wk HD for ≥3 mo	BDI-II	23 (5.34) versus 23.39 (5.02)

Table 1. (Continued)

Author (Reference); *N* Randomized; Years of Enrollment	Intervention/ Comparator	*N* Sites; Study Setting; Country/US Region	Clinical Characteristics/ Demographics of Study Population	Inclusion Criteria	Depression Screening Tool(s)	Baseline Depression Score, Mean (SD), T versus C
Harms-only studies						
Assimon *et al.* (57); *N*=65,654; 2007–2014	SSRIs with higher QT-prolonging potential[b] versus SSRIs with lower QT-prolonging potential[c]	US Renal Data System Database	53% Female; age (SD), 67.0 (17.2) yr; race, 36% Black; ethnicity, 19% Hispanic	Inclusion: new SSRI users who received HD during the 180 d before SSRI initiation and had continuous Medicare Part A, B, and D coverage. Excluded: <18 yr at start of baseline, dialysis vintage ≤90 d at the start of baseline, presence of an implantable automatic cardiac defibrillator, receipt of hospice care during the baseline period, and missing demographic data	NA	NA
Guirguis *et al.* (56); *N*=41; 2013–2015[a]	SSRI observational	Multisite; NR; England	37% Female; age (SD), 62 (16) yr; race, 27% non-White	ASSertID study participants who were excluded from the RCT (33) phase because they were already on SSRIs	BDI-II, PHQ-9	BDI-II: 26 PHQ-9: 12
Vangala *et al.* (58); *N*=54,032; 2009–2015	SSRI versus no SSRI	US Renal Data System Database	Patients versus controls: female, 58% versus 52%; age (SD), 71 (12) versus 61 (14) yr; 29% versus 49% Black; 22% versus 19% Hispanic; 39% versus 25% non-Hispanic White	Inclusion: Medicare Part D, receipt of a low-income subsidy, RRT start date, demographic data, a Medical Evidence Report from 1995 or later, >90 d HD	NA	NA

T, treatment group; C, control group; NR, not reported; NY, New York; HAM-D, Hamilton Depression Rating Scale; BDI-II, Beck Depression Inventory-II; MADRS, Montgomery–Åsberg Depression Rating Scale; BSI, Brief Symptom Inventory; VAS, Visual Analogue Scale; MINI, Mini International Neuropsychiatric Interview; MDD, major depressive disorder; SSRIs, selective serotonin reuptake inhibitors; HD, hemodialysis; Rx, prescription; IQR, interquartile range; HADS, Hospital Anxiety and Depression Scale; NA, not available; CBT, cognitive behavioral therapy; NM, New Mexico; TX, Texas; WA, Washington; QIDS-SR, Quick Inventory of Depressive Symptomatology–Self-Report; QIDS-C, QIDS-Clinician; SERT, sertraline; PD, peritoneal dialysis; 25(OH)D, 25-hydroxyvitamin D; PSE, psychoeducation; TAU, treatment as usual; AMT, Abbreviated Mental Test; SCID-I, Structured Clinical Interview for Diagnostic and Statistical Manual-IV Axis I Disorders; DASS-21, 21-Item Depression, Anxiety, and Stress Scale; SDS, Self-Rating Depression Scale; CRF, chronic renal failure; MBSR, mindfulness-based stress reduction; PHQ-9, Patient Health Questionnaire-9; GAD, Generalized Anxiety Disorder; TEAS, transcutaneous electrical acupoint stimulation; PSQI, Pittsburgh Sleep Quality Index; ASSertID, A Study of Sertraline in Dialysis; RCT, randomized controlled trial.

[a]Part of the larger ASSertID study.

[b]Citalopram and escitalopram.

[c]Fluoxetine, fluvoxamine, paroxetine, and sertraline.

controlled trials in any setting (for harms outcomes, we also included observational studies); (4) assessed patient outcomes of interest (*e.g.*, depression symptom severity, suicidal ideation, QoL); and (5) were published in English. We excluded studies examining adults with AKI or those with CKD stages 1–4. See Supplemental Appendix 2 and Supplemental Table 1 for complete selection criteria. All studies were reviewed for inclusion by two independent reviewers at the title/abstract and full-text levels. Discords were resolved through consensus or consultation with a third reviewer.

Data Abstraction and Quality Assessment

From included studies, we abstracted details on study design, sample size, setting, population characteristics, participant selection criteria, and intervention details (including the dosage, timing, and administration methods; duration of treatment and follow-up; outcomes; and relevant harms). Data from studies meeting inclusion criteria were abstracted by one reviewer and confirmed by an additional reviewer.

Two reviewers independently assessed the methodologic quality of each study using criteria established by the US Preventive Services Taskforce and adapted for depression interventions (24–26). Disagreements were resolved by consensus or a third reviewer.

Data Synthesis and Analysis

We qualitatively synthesized the evidence for each treatment category and outcome of interest. We were unable to quantitatively synthesize the evidence because there were too few studies examining the same intervention and reporting the same outcome measure (52).

Using an established method by Berkman *et al.* (53), for each intervention, we assessed the overall strength of evidence (SOE) that considers study limitations, directness, consistency, precision, and reporting bias to classify the SOE for each outcome independently as high, moderate, low, or insufficient; we used separate guidance for the applicability (external validity) of the evidence to the clinical question (54). Supplemental Table 2 describes SOE domains and grading in more detail.

Results

We reviewed 8050 titles and abstracts, 192 of which qualified for full-text review. Of those, we included a total of 26 RCTs; nine examined pharmacologic interventions and 17 examined nonpharmacologic interventions for the treatment of depression in adults with ESKD. We also included three observational studies reporting harms of selective serotonin reuptake inhibitors (SSRIs; see Figure 1 for literature flow, and Table 1 for study characteristics).

Pharmacologic Treatments

SSRIs

SSRIs versus Placebo. Three studies comparing SSRIs with placebo report conflicting findings and provide insufficient evidence to draw conclusions about their effectiveness in treating depression in adults with ESKD (see Table 2 for study results and Table 3 for SOE ratings). Two small US RCTs (one 8-week, poor-quality trial of fluoxetine [$N=14$] [30], and one recent, fair-quality, 6-month trial of sertraline [A Study of Sertraline in Dialysis; ASSertID; $N=30$] [33]) found no difference in depressive-symptom reduction between those assigned to SSRIs or placebo. One fair-quality, 12-week, Iranian RCT ($N=50$) (46) found that participants who received sertraline reported a significant reduction in depressive symptoms compared with placebo. Small sample sizes and differences in depression assessment tools and statistical analyses detracted from the quality of these studies (see Table 4 for quality ratings).

SSRIs versus Active Comparators.SSRIs versus CBT A recent, fair-quality, multisite, head-to-head RCT ($N=120$) in the United States (A Trial of Sertraline versus Cognitive Behavioral Therapy for ESKD Adults with Depression; ASCEND [44]) provides low-strength evidence that sertraline and CBT are similar when used for the reduction of depressive symptoms (Tables 3 and 4). Over the 12-week study period, both groups improved significantly. Participants who received sertraline experienced significantly greater improvement (effect estimate, −1.85; 95% CI, −3.55 to −0.16; Table 2) when assessed by a clinician (Quick Inventory of Depressive Symptomatology). There was no difference between groups in self-reported symptoms (*i.e.*, Beck Depression Inventory-II; effect estimate, −2.9; 95% CI, −6.7 to 0.8; Table 2).SSRIs versus Psychologic Training

A small ($N=44$), 3-month, poor-quality RCT (38), conducted in Iran, provides insufficient evidence for the comparison of citalopram to "psychologic training" in participants with ESKD and depression (Tables 3 and 4). Although both arms reported a reduction in depressive symptoms, there was no difference between groups (Table 2).

Harms of SSRIs. Adverse events (AEs) reported in the included trials of SSRIs in adults with depression and ESKD were similar in type and frequency to those reported by the general population on SSRIs (59). One trial reported a higher rate of dropout due to AEs associated with sertraline (33% versus 0%; $P=0.04$) (33). Across all four trials (30,33,44,46), a wide range of AEs (*e.g.*, nausea, headaches, dizziness) were reported by participants in both treatment and control groups, but they were not consistently nor uniformly reported (Table 5).

Additionally, three observational studies focused specifically on potential harms related to SSRIs in adults with ESKD and depression (Table 6). Two examined Medicare beneficiaries who received SSRIs that were included in the US Renal Data System registry. A case-control study ($N=54,032$) found that SSRIs increased the risk of hip fracture regardless of dose or duration (58), and the second (57), a retrospective cohort study ($N=65,654$), found that adults, especially older adults and women, taking SSRIs with higher QT-prolonging potential (*i.e.*, citalopram and escitalopram) were at higher risk for sudden cardiac death (adjusted hazard ratio, 1.18; 95% CI, 1.05 to 1.31). The final study was a follow-up to the ASSertID RCT (33) that examined SSRI practice patterns in adults with ESKD, and included participants who were already on SSRIs at baseline ($N=41$). Findings suggest poor medication management and both under- and overtreatment (56).

Table 2. Efficacy of interventions from randomized controlled trials for depression in adults with ESKD

Author (Reference); Year; *N* Randomized (T versus C); Duration of Treatment and Follow-Up	Treatment	Comparator	Findings, Treatment versus Comparator		Quality
			Depression	Other outcomes	
Pharmacologic					
SSRIs versus control					
Blumenfield et al. (30); 1997; 7 versus 7; Tx=8 wk, F/U=8 wk	Fluoxetine: 20 mg/d for 8 wk	Matched placebo	Mean change from baseline (at 4 wk; at 8 wk): BDI-II: −12 versus −4.17 (P=0.05); −9.57 versus −8.8 (P=0.91) BSI: −6.29 versus 0.2 (P=0.04); −4.43 versus −3.2 (P=0.88) HAM-D: no 4 wk assessment; −9.00 versus −7.5 (P=0.72) MADRS: −7.20 versus −6.75 (P=0.93); −11.14 versus −6.67 (P=0.45) VAS: −210.0 versus −58.3 (P=0.37); −303.0 versus −140 (P=0.45) Electronic VAS: −262.4 versus 5.6 (P=0.05); −389.0 versus −87.8 (P=0.13)	NA	Poor
Friedli et al. (33); 2017; 15 versus 15; Tx=6 mo, F/U=6 mo[a]	Sertraline: 100 mg/d (50 mg/d to start; dose could be increased to maximum at 2 and 4 mo)	Matched placebo	MADRS between-group difference at 6 mo: −0.67 (95% CI, −5.7 to 4.4) Within-groups decrease significant for both groups Mean change at study end: MADRS: −14.5 (95% CI, −20.2 to −8.8) versus −14.9 (95% CI, −18.4 to −11.5) BDI-II: −15.7 (95% CI, −24.3 to −7.1) versus −13.0 (95% CI, 19.6 to −6.4)	NA	Fair
Taraz et al. (46); 2013; 25 versus 25; Tx=12 wk, F/U=12 wk	Sertraline: 100 mg/d (50 mg/d for first 2 wk)	Matched placebo	BDI-II scores (SD) for baseline, 6 wk, 12 wk, Δ baseline to 12 wk: sertraline, 29 (13), 21 (11.5), 15 (5.5), −11.3 (5.8) versus placebo, 23 (11), 22.5 (8.5), 22.5 (9), −0.5 (5); comparison Δ baseline to 12 wk between groups, P=0.001	NA	Fair

Table 2. (Continued)

Author (Reference); Year; *N* Randomized (T versus C); Duration of Treatment and Follow-Up	Treatment	Comparator	Findings, Treatment versus Comparator		Quality
			Depression	Other outcomes	
SSRIs versus active comparator					
Hosseini et al. (38); 2012; 22 versus 22; Tx=3 mo, F/U=3 mo	Citalopram: 20 mg/d	Psychologic training: six 1-h sessions on kidney-disease education, problem solving, stress management, and muscle-relaxation techniques	Postintervention HADS (SD): 6.26 (4.18) (P=0.001) versus 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
Mehrotra et al. (44); 2019; 60 versus 60; Tx=12 wk, F/U=12 wk	Sertraline: 200 mg/d unless limited by AEs (titration began at 25 mg/d and adjusted each visit)	CBT: ten 60-min sessions during HD for 12 wk, adapted for maintenance HD population	QIDS-C scores (SD): 5.9 (4.5) versus 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) versus 18.7 (95% CI, 15.2 to 22.2) Effect estimate: −2.9 (95% CI, −6.7 to 0.8)	NA	Fair
Supplements versus placebo					
Gharekhani et al. (35); 2014; 27 versus 27; Tx=4 mo, F/U=4 mo	Ω-3 Fatty acids: 1800 mg/d for 4 mo	Matched placebo: paraffin oil capsules	Mean end of study BDI-II (SD): 13.44 (5.66) versus 20.33 (7.56) Difference (SD): −10.08 (8.07) versus −0.88 (8.41); P=0.001 Within groups: Significant decrease (P<0.001) versus no significant change	NA	Poor
Haghighat et al. (36); 2019; 16 versus 18 versus 15; Tx=12 wk, F/U=12 wk	Synbiotic supplement: *L. acidophilus* strain T16, *B. bifidum* strain BIA-6, *B. lactis* strain BIA-7, *B. longum* strain BIA-8 (2.7×107 CFU/g each) per 5 g sachet + prebiotic (5 g FOS + 5 g GOS + 5 g inulin per three 5 g sachets); probiotic supplement same as above, except prebiotics replaced with placebo	Matched placebo	End-of-treatment HADS-D scores (SD): synbiotic 6.92 (1.27) versus placebo 9.40 (1.5); P<0.001; Synbiotic (SD) 6.92 (1.27) versus probiotic 8.48 (1.61); P=0.011 Mean difference in HADS-D scores from baseline: symbiotic, −2.24 (95% CI, −3.29 to −1.38); probiotic, −1.28 (95% CI, −2.05 to −0.53); placebo, 0.20 (95% CI, −0.43 to0.76); P=0.001 Synbiotic versus placebo (*post hoc*): P<0.001	NA	Good

Table 2. (Continued)

Author (Reference); Year; *N* Randomized (T versus C); Duration of Treatment and Follow-Up	Treatment	Comparator	Findings, Treatment versus Comparator		Quality
			Depression	Other outcomes	
Wang et al. (49); 2015; 80 versus 80; Tx and F/U=3 mo	*Radix Bupleuri* herbal supplement: 1 g root powder in capsule daily	Placebo	Mean (SD) MADRS scores at 3 mo: 13.32 (8.25) versus 16.73 (9.46) Change from baseline MADRS: −11.36 versus −2.24; Mean difference, 4.72 (95% CI, 0.69 to 9.12); $P=0.02$	QoL (RAND-36): change from baseline 14.21 versus −1.12; MD, −4.61 (95% CI, −11.32 and 2.75); $P=0.04$	Poor
Wang et al. (50); 2019; 373 versus 373; Tx and F/U=52 wk	High-dose oral vitamin D3: 52-wk treatment of 50,000 IU/wk	Matched placebo	No between-groups difference in Δ values Within-group BDI-II scores (SD), baseline to end of study: 22.7 (4.3) to 19.6 (3.7) ($P=0.02$) versus 21.9 (5.4) to 20.8 (5.1) ($P=0.03$)	NA	Fair
Nonpharmacologic					
Cognitive behavioral therapy					
Al Saraireh et al. (27); 2018; 65 versus 65; Tx=12 wk, F/U=12 wk	CBT: seven individual 1-h sessions following the traditional CBT sessions protocol	PSE: 7 individual 1-h sessions	Post-test HAM-D scores (SD): 15.0 (5.5) versus 11.1 (2.3) Between-groups depression scores favored PSE ($t=4.68$; $P<0.01$) over CBT	NA	Poor
Cukor et al. (31) (crossover); 2014; 38 versus 27; Tx=3 mo, F/U=6 mo	CBT: individual 60-min CBT chairside during dialysis; modified for population; 10 sessions over 3 mo	Wait-list control	BDI-II: mean change score (SD) during treatment:−11.7 (1.5) points ($P<0.001$) versus −4.8 (1.4) points ($P<0.001$) Raw mean (SD) change: 24.7 (9.8) to 11.7 (9.8) versus 14.5 (8.5) to 9.1 (6.5) Mean (SD) change in BDI-II score in untreated group during wait-list period: −6.7 (1.7) points; $P<0.001$ (raw mean change, 21.9 [8.9] to 14.5 [8.5]). Magnitude of improvement greater in the intervention-first group versus wait-list 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	QoL: treatment effect, +12.0 (SD, 3.4; $P=0.003$) points versus +11.3 points (SD, 3.7; $P=0.01$) Raw mean (SD) score change: 99.5 (27.9) to 115.3 (25.5) versus 110.6 (25.1) to 119.7 (24.7); $P=0.04$ Fluid adherence: model-estimated mean change score (SD) during treatment −1.3% (0.3) Δkg/d ($P=0.001$) versus −1.1% (0.3) Δkg/d ($P=0.001$) Raw mean (SD) change: 4.0 (2.0) to 2.8 (1.6) versus 3.6 (2.0) to 2.5 (2.0); $P=0.002$	Fair

Table 2. (Continued)

Author (Reference); Year; *N* Randomized (T versus C); Duration of Treatment and Follow-Up	Treatment	Comparator	Findings, Treatment versus Comparator		Quality
			Depression	Other outcomes	
Duarte et al. (32); 2009; 46 versus 44; Tx=12 wk, F/U=9 mo	CBT: group CBT sessions, 90 min 1× per wk for 12 wk, followed by 6 mo maintenance with monthly meetings	Individualized psychotherapy (routinely available in dialysis unit) 30–50 min 1× per wk for 12 wk; followed by as-needed psychologic care for 6 mo	BDI-II: after 3 mo, 14.1 (SD, 8.7) versus 21.2 (SD, 9.1); $P=0.001$; after 9 mo, 10.8 (SD, 8.8) versus 17.6 (SD, 11.2); $P=0.002$	Suicide Risk Module (MINI): baseline 2.2 (SD, 5.1) versus 1.4 (SD, 3.5); $P=0.23$; after 3 mo, 1.2 (SD, 4.2) versus 0.7 (SD, 1.9); $P=0.43$; after 9 mo, 0.6 (SD, 1.2) versus 0.6 (SD, 2.0); $P=0.95$	Fair
			MINI: the mean change from baseline (SE) favored intervention	Overall reduction, within-group comparison: significant reduction within T group ($P=0.007$) versus C ($P=0.13$)	
			After 3 mo: 4.5 (SE, 0.4) versus 2.1 (SE, 0.6); $P<0.001$ After 9 mo: 4.4 (SE, 0.4) versus 2.9 (SE, 0.5); $P=0.03$	QoL: CBT group significantly improved several dimensions of KDQOL. Between-groups significant improvement in burden of kidney disease, quality of social interaction, sleep, overall health, and mental component summary dimensions	
Lerma et al. (41); 2017; 38 versus 22; Tx=5 wk, F/U=9 wk	CBT: 5 group sessions (2 h), 1× per wk after HD session	Waiting list	End-of-treatment BDI-II, 10.2 (SD, 8.2) versus 15.0 (SD, 10.9); $P=0.08$ Follow-up BDI-II: 7.1 (SD, 7.2) versus 14.7 (SD, 9.7); $P=0.003$ Within-group reduction in scores: $P<0.001$ versus $P=0.87$ RR of reducing depressive symptoms (between groups), 1.7 Adjusted RR between groups for depression, 0.33 (95% CI, 0.05 to 0.55; 33% clinical utility)	Overall QoL (PLC): baseline, 99.4 (SD, 21.3) versus 91.5 (SD, 19.5); $P=0.20$ After 5 wk, 109.6 (SD, 21.1) versus 94.0 (SD, 21.0); $P=0.02$ After 9 wk, 112.5 (SD, 23.8) versus 91.3 (SD, 22.5); $P=0.004$ Overall within-group $P=0.001$ versus $P=0.663$; Cohen d=0.93 (large)	Fair
Nursing interventions					
Kargar Jahromi et al. (55); 2016; 30 versus 30; Tx=unclear, F/U=30 d	Telenursing: 30-min telephone follow-up sessions 30 d after dialysis shift	TAU	DASS-21 depression subscale after intervention (mean [SD]): 8.96 (1.17) versus 16.20 (1.60); $P=0.05$	NA	Poor
Li et al. (42); 2020; 36 versus 36; Tx=6 mo, F/U=6 mo	Home nursing visits: care, guidance for patient and family, counseling, and dietary guidance	Telephone follow-up at 1, 3, and 6 mo after discharge	After intervention SDS: 36.48 (SD, 5.06) versus 48.80 (SD, 5.27); $P<0.001$ Both groups experienced significant decline in scores ($P<0.001$)	QoL (KDQOL-36): both groups experienced significant improvement ($P<0.001$); scores in Tx group higher than C ($P<0.001$)	Poor

Table 2. (Continued)

Author (Reference); Year; *N* Randomized (T versus C); Duration of Treatment and Follow-Up	Treatment	Comparator	Findings, Treatment versus Comparator		Quality
			Depression	Other outcomes	
Liao et al. (43); 2020; 64 versus 64; Tx=unclear, during inpatient stay, F/U=3 mo	Comprehensive nursing: health education 1–2× per wk; CBT; progressive relaxation, extended f/u care	Conventional care	After intervention SDS: 51.02 (SD, 20.59) versus 60.06 (SD, 28.91); $P=0.05$ Improvement in scores from baseline: 9.81 (SD, 19.32) versus 3.96 (SD, 10.79); $P=0.04$	QoL (KDQOL-36) at 3-mo f/u: greater improvements from baseline for physical activity, mental state, burden of kidney disease, symptoms of kidney disease, and effects of kidney disease in T compared with C (all $P<0.05$)	Poor
Acupressure					
Kalani et al. (39); 2019; 32 versus 32 versus 32; Tx=4 wk, F/U=4 wk	Acupressure: applied during first 2 h of HD; 3× per wk for 4 wk; each session lasted 20 min	Sham: same as acupressure group except pressure applied 1 cm from acupressure pointsControl: TAU	Post-test BDI-II: T 20.6 versus sham 25.5 versus C 24.9; significant difference T versus sham and C ($P=0.001$ for both); no difference between sham and C ($P=0.22$)	NA	Fair
Tsay et al. (48); 2014; 36 versus 36 versus 36; Tx=4 wk, F/U=4 wk	Acupressure: applied for 15 min 3× per wk for 4 wkTEAS: applied for 15 min 3× per wk for 4 wk	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 between acupressure and TEAS ($P=0.95$)	Fatigue (PFS): baseline T 5.92 (SD, 1.39) versus TEAS 5.60 (SD, 1.30) versus C 6.01 (SD, 1.60); follow-up T 4.61 (SD, 1.72) versus TEAS 4.70 (SD, 1.50) versus C 5.70 (SD, 1.80); *post-hoc* analysis found significantly lower levels in T ($P=0.006$) and TEAS ($P=0.02$) versus C. No difference between T and TEAS Sleep quality (PSQI): baseline T 8.85 (SD, 4.50) versus TEAS 7.12 (SD, 4.51) versus C 9.35 (SD, 3.48); follow-up T 7.80 (SD, 4.00) versus TEAS 6.32 (SD, 4.55) versus C 9.75 (SD, 4.65); compared with controls, significantly better with T ($P=0.05$) and TEAS ($P=0.016$); no difference between T and TEAS	Poor

Table 2. (Continued)

Author (Reference); Year; *N* Randomized (T versus C); Duration of Treatment and Follow-Up	Treatment	Comparator	Findings, Treatment versus Comparator		Quality
			Depression	Other outcomes	
Exercise					
Frih et al. (34); 2017; 28 versus 22; Tx=4 mo, F/U=4 mo	Exercise (endurance-resistance) training: 60 min, 4× per wk on nondialysis days	Sedentary controls; no intervention	Favors exercise: T HADS depression scores were not different than C before intervention, but significantly lower than C after intervention ($P<0.01$). Within-group decrease also significant for T, but not C Significant group × period interaction effect for HADS depression scores: $F_{(1, 39)}=43.91$, $P<0.001$	SF-36 PCS: T significantly improved ($P<0.01$) from baseline; no difference for C; no difference between groups at either time point SF-36 MCS: T improved significantly, but not C; no difference before, but T significantly better than C after ($P<0.01$)	Poor
Kouidi et al. (40); 2010; 25 versus 25; Tx=1 yr, F/U=1 yr	ET program (intradialytic): warm-up, cycling, strengthening, cooldown, 3× per wk, 60–90 min during first 2 h of HD session	Sedentary control	Favors ET in both BDI-II and HADS scores ($P<0.001$)	Heart rate variability indices: Standard deviation of all RR intervals, mean square successive differences, percentage of RR intervals differing by more than 50 ms from the preceding RR,low freqency (LF), high frequency (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
Other interventions					
Babamohamadi et al. (28); 2017; 30 versus 30; Tx=1 mo, F/U=1 mo	Quran: listen to audio of Quran recitation on headphones for 20 min, beginning 5 min before dialysis	TAU	Post-test BDI-II scores: 14.5 (SD, 4.8) versus 31.6 (SD, 9.2); $P<0.001$ Significant between-subjects treatment effect, independent of age ($F=9.3$, $P=0.004$, Cohen $d=0.85$).	NA	Poor

Table 2. (Continued)

Author (Reference); Year; *N* Randomized (T versus C); Duration of Treatment and Follow-Up	Treatment	Comparator	Findings, Treatment versus Comparator		Quality
			Depression	Other outcomes	
Beizaee et al. (29); 2018; 40 versus 40; Tx=4 wk, F/U=4 wk	Guided imagery: 3× per wk for 4 wk, in-person with psychologist; 30 mins before HD session; includes audio recording of nature sounds	TAU, nearly silent environment	Post-test HADS scores: 10.02 (SD, 2.58) versus 11.65 (SD, 2.33)	SBP: mean (SD) before, 129.22 (12.70) versus 132.85 (13.22); mean (SD) after, 121.75 (12.73) versus 134.87 (12.68) DBP: mean (SD) before, 82.50 (11.32) versus 81.75 (8.51); mean (SD) after, 81.00 (10.32) versus 81.87 (8.14) HR (SD): before, 77.95 (6.97) versus 75.42 (8.56); after, 73.75 (6.25) versus 77.22 (7.92)	Fair
Heshmatifar et al. (37); 2015; 35 versus 34; Tx=1 mo, F/U=1 mo	Benson relaxation technique: performed 20 min 2× per d for 1 mo	TAU	Only T group scores decreased; the difference between groups was significant ($P=0.01$)	NA	Poor
Rahimipour et al. (45); 2015; 25 versus 25; Tx=8 wk, F/U=12 wk	Hope therapy: sessions using Schneider hope therapy theory, 1× per wk for 8 wk, 1–1.5 h during first 2 h of dialysis	Control: listening session in which patients could talk about their disease and problems, 1× per wk for 8 wk	Immediately after 8-wk intervention ($t=12.75$; $P<0.001$), and at 1-mo follow-up (t=13.83; $P<0.001$)	NA	Poor
Thomas et al. (47); 2017; 21 versus 20; Tx=8 wk, F/U=8 wk	MBSR[a]: guided, chairside meditative practices, 10–15 min, 3× per wk during hemodialysis sessions	TAU[a]	Change in PHQ-9: −3.0 (SD, 3.9) versus 2.0 (SD, 4.7); $P=0.45$	NA	Fair
Widyaningrum and Djarwoto (51); 2013; 18 versus 18; Tx=3 wk, F/U=3 wk	LPD relaxation technique and repetitive prayer practice, 2× per d for 21 d	Control group (not described)	Significantly decreased BDI-II scores within both groups, and greater in LPD, but between group difference NS ($P=0.20$)	QoL (KDQOL-SF36): significantly greater change in sleep and overall health associated with LPD versus control; no other differences were significant	Poor

T, treatment group; C, control group; SSRIs, selective serotonin reuptake inhibitors; Tx, treatment; F/U, follow-up; BDI-II, Beck Depression Inventory-II; BSI, Brief Symptom Inventory; HAM-D, Hamilton Depression Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; VAS, Visual Analogue Scale; NA, not applicable; Δ, change; HADS, Hospital Anxiety and Depression Scale; AE, adverse event; CBT, cognitive behavioral therapy; HD, hemodialysis; QIDS-C, Quick Inventory of Depressive Symptomatology–Clinician; *L. acidophilus*, *Lactobacillus acidophilus*; *B. bifidum*, *Bifidobacterium bifidum*; FOS, fructo-oligosaccharides; GOS, galacto-oligosaccharides; HADS-D, Hospital Anxiety and Depression Scale–Depression; QoL, quality of life; PSE, psychoeducation; MINI, Mini International Neuropsychiatric Interview; KDQOL, Kidney Disease Quality of Life; RR, relative risk; PLC, Profile of Quality of Life in the Chronically Ill; DASS-21, 21-Item Depression, Anxiety, and Stress Scale; SDS, Self-Rating Depression Scale; SE.standard error; TEAS, transcutaneous electrical acupoint stimulation; PFS, Piper Fatigue Scale; PSQI, Pittsburgh Sleep Quality Index; SF-36, 36-Item Short Form Health Survey; PCS, Physical Component Scale; MCS, Mental Component Scale; ET, exercise training; MSSD, mean squared successive difference; SBP, systolic BP; DBP, diastolic BP; HR, heart rate; MBSR, mindfulness-based stress reduction; PHQ-9, Patient Health Questionnaire-9; LPD, Latihan Pasrah Diri.
[a]Both treatment and control groups also received psychoeducational literature on anxiety and depression.

Table 3. Summary of the evidence on interventions for depression in adults with ESKD

Outcome	Conclusion	Strength of Evidence (Justification)[a]
Pharmacologic		
SSRIs versus controls (k=3, n=94)		
Depression severity	Fluoxetine (30) No benefit (k=1, n=14) Sertraline (33,46) Mixed findings (k=2; n=80)	Insufficient (NC, SLM)
SSRIs versus active comparator (k=2; n=164)		
Depression severity	Sertraline versus CBT (44) Benefit for both; no difference between groups (k=1, n=120)	Low (SLM, UC)
	Citalopram versus psychologic training (38) Benefit for both; no difference between groups (k=1, n=44)	Insufficient (SLH, UC)
Supplements versus placebo (k=4; n=986)		
Depression severity	Ω-3 Fatty acids (35) Increased benefit (k=1, n=54)	Insufficient (NP, SLH, UC)
	High-dose vitamin D3 (50) No benefit (k=1, n=746)	Moderate (SLM, UC)
	Synbiotic or probiotic (36) Increased benefit (k=1, n=49)	Insufficient (UC)
	Radix Bupleuri (49)[b] Increased benefit (k=1, n=137)	Insufficient (UC, SLH)
QoL	*Radix Bupleuri* (49)[b] Increased benefit (k=1, n=137)	Insufficient (UC, SLH)
Nonpharmacologic		
CBT versus active comparator (k=2; n=220)		
Depression severity	CBT versus psychoeducation (27) Benefit for both, but favored psychoeducation (k=1, n=130)	Insufficient (SLH, UC)
	CBT versus psychotherapy (32) Benefit for both, but favored CBT (k=1, n=90)	Low (SLM, UC)
Suicide risk	CBT versus psychotherapy (32) Benefit in intervention but not control group; no difference between groups (k=1, n=90)	Low (SLM, UC)
QoL	CBT versus psychotherapy (32) Increased benefit for some domains of KDQOL (k=1, n=90)	Low (SLM, UC)
CBT versus control (k=2; n=125)		
Depression severity	Increased benefit (k=2; n=125) (31,41)	Low (SLM)
QoL	Increased benefit (k=2; n=125) (31,41)	Low (SLM)
Fluid adherence	Increased benefit (k=1; n=65) (31)	Insufficient (SLM, UC)
Acupressure versus control (k=2; n=204)		
Depression severity[c]	Acupressure versus TAU (39,48) Increased benefit (k=2; n=204) Acupressure versus sham (39) Increased benefit (k=1; n=96)	Low (SLM)
Fatigue	Acupressure versus TAU (48) Increased benefit (k=1, n=108)	Insufficient (SLH, UC)
Sleep quality	Acupressure versus TAU (48) Increased benefit (k=1, n=108)	Insufficient (SLH, UC)
Acupressure versus active comparator (k=1, n=108) (48)		
Depression severity	Acupressure versus TEAS Benefit for both; no difference between groups	Insufficient (SLH, UC)
Fatigue	Acupressure versus TEAS Benefit for both; no difference between groups	Insufficient (SLH, UC)
Sleep quality	Acupressure versus TEAS Benefit for both; no difference between groups	Insufficient (SLH, UC)
Nursing interventions: intensive versus less-intensive nursing (k=3; n=260)		
Depression severity	Increased benefit (k=3; n=260) (42,43,55)	Insufficient (SLH, NP)
QoL	Increased benefit (k=2; n=200) (42,43)	Insufficient (SLH, NP)
Benson relaxation technique versus control (k=1; n=70) (37)		
Depression severity	Increased benefit	Insufficient (SLH, UC)

Table 3. (Continued)

Outcome	Conclusion	Strength of Evidence (Justification)[a]
Exercise training versus control (k=2 n=100)		
Depression severity	Increased benefit (k=2; n=100) (34,40)	Insufficient (SLH, UP)
HRV	Increased benefit (k=1; n=50) (40)	Insufficient (SLH, UC, UP)
Guided imagery versus TAU (k=1; n=80) (29)		
Depression severity	Unclear effect	Insufficient (SLM, UC)
Vital signs	Unclear effect	Insufficient (SLM, UC)
Hope therapy versus active control (k=1; n=50) (45)		
Depression severity	Increased benefit	Insufficient (SLH, UC, UP)
LPD versus control (k=1; n=36) (51)		
Depression severity	No benefit	Insufficient (SLH, UP, UC)
QoL	No benefit	Insufficient (SLH, UP, UC)
MBSR versus TAU (k=1; n=41) (47)		
Depression severity	No benefits	Insufficient (SLM, UP, UC)
Quran versus TAU (k=1; n=60) (28)		
Depression severity	Increased benefit	Insufficient (SLH, UC, UP)

SSRIs, selective serotonin reuptake inhibitors; k, number of studies; n, sample size; NC, not consistent; SLM, study limitations medium; CBT, cognitive behavioral therapy; UC, unknown consistency; SLH, study limitations high; NP, not precise; QoL, quality of life; KDQOL, Kidney Disease Quality of Life; TAU, treatment as usual; TEAS, transcutaneous electrical acupoint stimulation; UP, unclear precision; HRV, heartrate variability; LPD, Latihan Pasrah Diri; MBSR, mindfulness-based stress reduction.
[a]The overall strength of evidence for each outcome is determined on the basis of the consistency, coherence, and applicability of the body of evidence, and the internal validity of individual studies. The strength of evidence is classified as follows (53): high, further research is very unlikely to change our confidence on the estimate of effect; moderate, further research is likely to have an important effect on our confidence in the estimate of effect and may change the estimate; low, further research is very likely to have an important effect on our confidence in the estimate of effect and is likely to change the estimate; and insufficient, any estimate of effect is very uncertain.
[b]Some participants were concurrently using antidepressant medications.
[c]Some participants are represented more than once.

Supplements versus Placebo

High-dose Vitamin D3. A large (N=746), fair-quality, 52-week RCT (50) provides moderate-strength evidence that long-term, high-dose vitamin D3 does not reduce depression severity in adults with ESKD (Tables 3 and 4). In addition, no differences were reported by age, sex, body mass index, or plasma albumin level. Although overall differences in depressive-symptom reduction between groups were NS, a subgroup of participants with vascular depression (but not those with major depressive disorder) receiving vitamin D3 did report significantly greater reduction in depressive symptoms at 1 year (Table 2).

Harms of Vitamin D3. AEs associated with high-dose vitamin D3, including joint pain, diarrhea, nausea, and vomiting, resulted in study withdrawal of five participants. No statistical analyses of AEs or withdrawals due to AEs were reported (50).

Ω-3 Fatty Acids. A single, poor-quality RCT (N=54) (35), conducted in Iran, provides insufficient evidence to form conclusions about the effect of Ω-3 fatty acids versus placebo on depression severity in adults with ESKD (Tables 3 and 4). At 16 weeks, the Ω-3 fatty acids group reported a significantly greater reduction in depressive symptoms compared with both placebo and their own baseline. No differences were identified by age, sex, baseline depression severity, or length of time on hemodialysis (Table 2). No serious AEs (SAEs) were reported in this trial.

Synbiotic and Probiotic Supplements. One good-quality, 12-week RCT (N=49) (36) provides insufficient evidence for the use of synbiotic or probiotic supplements versus placebo on depression severity in Iranian adults with ESKD and Hospital Anxiety and Depression Scale–Depression (HADS-D) scores of eight or higher (Tables 3 and 4). HADS-D scores at the end of treatment were significantly lower in adults receiving synbiotics than those receiving placebo (P<0.001) and probiotics (P=0.01). HADS-D scores were also significantly reduced from baseline in the symbiotic compared with placebo (P<0.001) groups, but not in the other comparisons (Table 2). The reported AEs were few and mild (Table 5).

Radix Bupleuri Herbal Supplement. A poor-quality, 3-month RCT (N=160) (49) of *Radix Bupleuri* root powder supplements compared with placebo provides insufficient evidence for its use for depression in adults with ESKD (Tables 3 and 4). Participants who were being treated with antidepressant medications (about half of each group) continued on those treatments concurrently during this trial. Participants taking *Radix Bupleuri* experienced significantly more reduction in Montgomery–Åsberg Depression Rating Scale scores compared with the placebo group (P=0.02; Table 2). They also experienced improvement in QoL (measured by RAND-36) compared with the placebo group (P=0.04). The trial did not report on AEs.

Nonpharmacologic Treatments

CBT

CBT versus Psychotherapy. One fair-quality RCT (N=90) (32) provides low-strength evidence that small-group CBT is more effective than brief, individualized psychotherapy for reducing depression severity in participants with ESKD (Tables 3 and 4). Depressive symptoms improved significantly in both groups. Participants receiving CBT also experienced a significant within-group decrease in suicide risk and improved on several QoL domains (*i.e.*, burden of

Table 4. Quality and applicability assessment of randomized controlled trials

Author (Reference)	Rating Criteria[a]																	Funding source	Overall Quality Rating	Applicability
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17			
Al Saraireh *et al.* (27)	Y	NR	N	NA	Y	U	U	N	Y	N	Y	N	Y	U	Y	NA	N	Investigator	Poor	Fair
Babamohamadi *et al.* (28)	NR	NR	N	U	Y	U	U	N	Y	N	U	N	Y	Y	U	U	N	NR	Poor	Poor
Beizaee *et al.* (29)	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	N	N	U	Y	NA	Y	University	Fair	Fair
Blumenfield *et al.* (30)	NR	Y	U	U	N	U	Y	Y	Y	N	N	N	Y	U	Y	N	N	Industry grant	Poor	Fair
Cukor *et al.* (31)	NR	NR	Y	U	Y	Y	Y	Y	Y	N	N	Y	Y	U	Y	N	N	NIDDK	Fair	Fair
Duarte *et al.* (32)	Y	Y	N	U	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	N	Government	Fair	Fair
Friedli *et al.* (33)	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	N	Y	U	Y	N	N	NIH grant	Fair	Good
Frih *et al.* (34)	Y	NR	U	Y	Y	Y	N	N	Y	Y	N	Y	Y	U	Y	N	N	NR	Poor	Fair
Gharekhani *et al.* (35)	Y	U	Y	N	Y	N	N	Y	Y	Y	N	N	Y	Y	Y	N	N	University	Poor	Good
Haghighat *et al.* (36)	Y	Y	Y	U	Y	Y	Y	Y	Y	U	Y	N	Y	Y	Y	Y	N	Ahvaz Jundishapur Univ Med Sci	Good	Fair
Heshmatifar *et al.* (37)	NR	NR	Y	U	Y	U	U	N	Y	N	N	Y	Y	U	U	N	U	NR	Poor	Fair
Hosseini *et al.* (38)	U	NR	Y	Y	Y	U	U	N	Y	N	N	Y	Y	U	Y	N	N	Government	Poor	Fair
Jahromi *et al.*	NR	NR	Y	Y	Y	Y	N	Y	Y	N	U	N	Y	Y	N	U	N	NR	Poor	Fair
Kalani *et al.* (39)	N	U	Y	U	Y	U	U	U	Y	U	Y	N	Y	Y	Y	U	N	University	Poor	Fair
Kouidi *et al.* (40)	NR	NR	Y	U	Y	U	U	N	Y	N	N	Y	Y	U	Y	N	N	NR	Poor	Fair
Lerma *et al.* (41)	Y	NR	Y	U	Y	Y	Y	N	Y	N	N	N	Y	Y	Y	N	N	Government	Fair	Fair
Li *et al.* (42)	Y	N	Y	Y	Y	N	N	N	N	U	U	N	Y	U	Y	U	N	NR	Poor	Fair
Liao *et al.* (43)	Y	NR	Y	Y	Y	U	U	U	Y	N	N	N	Y	U	Y	N	N	NR	Poor	Fair
Mehrotra *et al.* (44)	Y	Y	U	Y	Y	Y	N	N	Y	N	Y	N	Y	Y	Y	Y	N	Government, University, NIDDK, DCI	Fair	Fair
Rahimipour *et al.* (45)	U	NR	U	U	Y	U	U	U	N	U	U	U	Y	U	Y	U	N	NR	Poor	Fair
Taraz *et al.* (46)	Y	U	Y	Y	Y	U	U	Y	Y	N	N	N	Y	Y	Y	N	N	University grant	Fair	Good
Thomas *et al.* (47)	Y	NR	N	U	Y	Y	U	N	Y	N	Y	N	Y	Y	Y	N	N	University grant	Fair	Fair
Tsay *et al.* (48)	NR	NR	Y	U	Y	U	U	N	Y	N	N	Y	Y	U	Y	N	N	Government	Poor	Fair
Wang *et al.* (49)	NR	NR	Y	N	Y	U	U	Y	Y	Y	Y	N	Y	U	Y	N	N	NR	Poor	Fair
Wang *et al.* (50)	Y	Y	Y	Y	Y	U	Y	Y	Y	N	N	U	Y	Y	Y	N	N	NR	Fair	Poor
Widyaningrum *et al.* (51)	NR	NR	Y	U	Y	U	U	U	N	U	U	U	Y	U	Y	U	N	NR	Poor	Poor

Y, yes; NR, not reported; N, no; NA, not applicable; U, unclear; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; NIH, National Institutes of Health; Univ Med Sci, University of Medical Sciences; DCI, Dialysis Clinic Inc.

[a]The quality rating criteria (adapted from the US Preventive Services Task Force criteria [26]) involved evaluating the following questions:(*1*) randomization adequate?(*2*) allocation concealment adequate?(*3*) groups similar at baseline?(*4*) maintain comparable groups?(*5*) eligibility criteria specified?(*6*) outcome assessors masked?(*7*) care provider masked?(*8*) patient masked?(*9*) reporting of attrition, crossovers, adherence, and contamination?(*10*) important differential loss to follow-up or overall high loss to follow-up?(*11*) intention-to-treat analysis?(*12*) postrandomization exclusions?(*13*) were outcomes prespecified and defined, and ascertained using accurate methods?(*14*) intervention fidelity?(*15*) follow-up long enough for outcomes to occur? (minimum 4 wk for drugs)(*16*) appropriate handling of missing data?(*17*) evidence of selective outcome reporting?

Table 5. Adverse events reported in depression treatment trials in patients with ESKD

Severity	System	Adverse Event	Blumenfield *et al.* (30)		Friedli *et al.* (33)[a]		Haghighat *et al.* (36)		Mehrotra *et al.* (44)		Taraz *et al.* (46)[b]	
			FLU (*N*=6)	PBO (*N*=7)	SERT (*N*=15)	PBO (*N*=15)	Probiotic (*N*=25)	PBO (*N*=25)	CBT (*N*=60)	SERT (*N*=60)	SERT (*N*=21)	PBO (*N*=22)
Nonserious	Autonomic	Dry mouth	0	1	—	—	—	—	—	—	—	—
	Cardiovascular	Cardiac unspecified	—	—	—	—	—	—	3	9	—	—
		Hypotension	4	1	—	—	—	—	—	—	—	—
		Palpitations	—	—	1	0[a]	—	—	—	—	—	—
	Gastrointestinal	Abdominal pain	1	2	—	—	—	—	—	—	—	—
		Constipation	0	1	—	—	—	—	—	—	—	—
		Diarrhea	1	1	—	—	—	—	—	—	—	—
		Dyspepsia	1	0	—	—	—	—	—	—	6	4
		Gastroenteritis	0	2	—	—	—	—	—	—	—	—
		Gastrointestinal unspecified	—	—	—	—	—	—	11	22	—	—
		Nausea	5	2	1	0[a]	—	—	—	—	7	3
		Vomiting	3	3	—	—	—	—	—	—	—	—
	Musculoskeletal	Myalgia	1	1	—	—	—	—	—	—	—	—
	Neurologic	Dizziness	1	0	1	0[a]	—	—	—	—	5	3
		Headache	3	0	1	0[a]	1	1	—	—	4	2
		Insomnia	2	1	1	0[a]	—	—	—	—	—	—
		Nervous system unspecified	—	—	—	—	—	—	0	8	—	—
		Sensation disturbance	1	0	—	—	—	—	—	—	—	—
		Tremors	1	0	—	—	—	—	—	—	—	—
	Psychiatric	Abnormal thought	1	0	—	—	—	—	—	—	—	—
		Anorexia	—	—	—	—	—	—	—	—	2	4
		Anxiety	0	1	—	—	—	—	—	—	—	—
		Nervousness	1	1	—	—	—	—	—	—	—	—
	Respiratory	Bronchitis	1	0	—	—	—	—	—	—	—	—
		Cough	0	2	—	—	—	—	—	—	—	—
		Dyspnea	1	0	—	—	—	1	—	—	—	—
		Pharyngitis	1	0	—	—	—	—	—	—	—	—
		Rhinitis	1	0	—	—	—	—	—	—	—	—
		Upper respiratory tract infection	1	0	—	—	—	—	—	—	—	—
	Skin	Furunculosis	1	0	—	—	—	—	—	—	—	—
		Pruritus	1	0	—	—	—	—	—	—	—	—
		Skin ulcer	0	1	—	—	—	—	—	—	—	—
		Sweating	—	—	1	0[a]	—	—	—	—	—	—
	Other	Dehydration	0	1	—	—	—	—	—	—	—	—
		Edema	0	1	—	—	—	—	—	—	—	—
		Fatigue	—	—	—	—	—	1	—	—	—	—
		Flu syndrome	1	0	—	—	—	—	—	—	—	—
		Hair loss	—	—	—	—	—	—	—	—	1	1
		Other unspecified	—	—	—	—	—	—	3	17	—	—
		Sexual dysfunction	—	—	—	—	—	—	—	—	2	1
		Tooth infection	1	0	—	—	—	—	—	—	—	—

Table 5. (Continued)

Severity	System	Adverse Event	Blumenfield *et al.* (30)		Friedli *et al.* (33)[a]		Haghighat *et al.* (36)		Mehrotra *et al.* (44)		Taraz *et al.* (46)[b]	
			FLU (*N*=6)	PBO (*N*=7)	SERT (*N*=15)	PBO (*N*=15)	Probiotic (*N*=25)	PBO (*N*=25)	CBT (*N*=60)	SERT (*N*=60)	SERT (*N*=21)	PBO (*N*=22)
Severe	Gastrointestinal	Gastrointestinal unspecified	—	—	—	—	—	—	1	1	—	—
	Cardiovascular	Cardiac unspecified	—	—	—	—	—	—	4	4	—	—
	Other	Death	—	—	1	0	—	—	2	0	—	—
		Major bleeding	—	—	—	—	—	—	1	2	—	—
		Other unspecified	—	—	—	—	—	—	2	9	—	—

FLU, fluoxetine; PBO, placebo; SERT, sertraline; CBT, cognitive behavioral therapy.
[a]The events reported in this table are only those that resulted in study dropout. There were other adverse events reported narratively, but it was not clear from the text in which category or study arm they occurred, so they are not recorded in this table.
[b]It is unclear whether the events of study dropouts were included in these totals. There was one death in each group and some attrition due to adverse events, but the dropouts were not analyzed in this per-protocol study.

Table 6. Adverse events reported in observational studies of adults with ESKD and depression

Author (Reference); *N*; Years; Source	Treatment versus Comparator	Outcomes of Interest	Findings
Assimon *et al.* (57); *N*=65,654; 2007–2014; Medicare Recipients in the US Renal Data System Database	SSRIs with higher QT-prolonging potential[a] versus SSRIs with lower QT-prolonging potential[b]	1-yr sudden cardiac death	Compared to SSRIs with lower QT-prolonging potential, those with higher QT-prolonging potential were associated with higher risk of sudden cardiac death (AHR, 1.18; 95% CI, 1.05 to 1.31); this association was more pronounced among older adults (AHR, 1.19; 95% CI, 1.05 to 1.35), women (AHR, 1.23; 95% CI, 1.06 to 1.44), patients with conduction disorders (AHR, 1.47; 95% CI, 1.05 to 2.06), and those treated with other non-SSRI QT-prolonging medications (AHR, 1.29; 95% CI, 1.10 to 1.50)
Guirguis *et al.* (56); *N*=41; 2013–2015; ASSertID Study	Antidepressants (no comparator)	Antidepressant-management practices related to NICE guidelines	At baseline, 30 patients had BDI-II scores ≥16, and 22 remained high at follow-up; At baseline, 11 patients had BDI-II scores <16; five of 11 were ≥16 on follow-up; 27 of the 41 patients (66%) either deteriorated or failed to improve; 16 patients (39%) had no review of antidepressant medication; a significant proportion of patients were taking agents cautioned against, or with no available prescribing information in, for patients on HD, or they were taking doses that might be considered subtherapeutic; 15% had no evidence of ever having had MDD over their lifetime according to the MINI, in spite of their being on antidepressants

Table 6. (Continued)

Author (Reference); *N*; Years; Source	Treatment versus Comparator	Outcomes of Interest	Findings
Vangala *et al.* (58); *N*=54,032; 2009–2015; Medicare Recipients in the US Renal Data System Database	SSRI versus no SSRI	Hip fracture	Any SSRI use was associated with increased hip fracture risk (AOR, 1.25; 95% CI, 1.17 to 1.35); risk for fracture was estimated for low (AOR, 1.20; 95% CI, 1.08 to 1.32), moderate (AOR, 1.31; 95% CI, 1.18 to 1.43), and high SSRI use (AOR, 1.26; 95% CI, 1.12 to 1.41); the relationship between hip fracture events and SSRI use was also seen in the examination of new short-term use (AOR, 1.43; 95% CI, 1.23 to 1.67); no significant interaction with age, sex, BMI, race, or ethnicity was discovered in the short-term analysis

SSRIs, selective serotonin reuptake inhibitors; AHR, adjusted hazard ratio; ASSertID, A Study of Sertraline in Dialysis; NICE, National Institute for Health and Care Excellence; BDI-II, Beck Depression Inventory-II; HD, hemodialysis; MDD, major depressive disorder; MINI, Mini International Neuropsychiatric Interview; AOR, adjusted odds ratio; BMI, body mass index.
[a]Citalopram and escitalopram.
[b]Fluoxetine, fluvoxamine, paroxetine, and sertraline.

kidney disease, quality of social interaction, sleep, overall health, and mental health) over the study period (Table 2). No study dropouts from serious AEs were reported.

CBT versus Psychoeducation. A poor-quality RCT (27), conducted in Jordan, provides insufficient evidence to form conclusions about the comparison of CBT with psychoeducation (Tables 3 and 4). Participants receiving CBT reported a significantly greater reduction in depressive symptoms (both groups reported significant improvement; Table 2).

CBT versus Sertraline. A head-to-head RCT (44) provides low-strength evidence that sertraline and CBT are similar when used for the reduction of depressive symptoms in participants with depression and ESKD. See the section *SSRIs versus CBT* above and Tables 2–4 for more detail.

CBT versus Control. Two fair-quality RCTs (31,41) provide low-strength evidence that CBT is more effective than wait-list control for reducing depression severity and improving QoL in participants with ESKD (Tables 3 and 4). There is insufficient evidence to form conclusions about the benefit of CBT on fluid adherence (31).

One study compared outcomes (depressive symptoms, QoL, and fluid adherence) on the basis of the timing of the intervention (treatment first or after 90-day wait listing). Results indicated that participants receiving CBT experienced significantly greater benefit across all outcomes in both phases. However, findings suggest a sequence effect for depressive-symptom reduction (the treatment-first group experienced greater benefit than the wait-list group), but none for QoL or fluid compliance (Table 2) (31).

Acupressure

We found low-strength evidence that acupressure is more effective than both usual care and sham acupressure for reducing depression severity in participants with ESKD (Table 3). There is insufficient evidence to form conclusions about the comparison of acupressure to transcutaneous electrical acupoint stimulation (TEAS) for the reduction of depressive-symptom severity, fatigue, or sleep-quality improvement. A fair-quality, three-arm RCT ($N=96$) (39) compared acupressure with sham acupressure (*i.e.*, pressure applied 1 cm from the acupressure point) and usual care. Participants receiving acupressure reported a significantly greater reduction in depression symptoms than those receiving sham acupressure or usual care (there was no difference between sham and usual care). A second three-arm RCT (poor quality; $N=108$) (48) compared acupressure with both TEAS and usual care. Participants in both the acupressure and the TEAS groups reported greater reductions in depressive symptoms and fatigue, and better-quality sleep than those who received usual care (Tables 2 and 4).

Intensive Nursing

Three poor-quality RCTs (42,43,55) provide insufficient evidence for the effect of intensive nursing interventions, compared with less-intensive nursing, for improving depressive symptoms in adults with ESKD (Tables 3 and 4). One study in China ($N=72$) compared home-nursing visits with telephone follow-up for adults on peritoneal dialysis (42). Although both groups' Zung Self-Rating Depression Scale scores were improved from baseline ($P<0.001$), the home-nursing group's depression scores were significantly lower than the control group after intervention ($P<0.001$). Another Chinese study of a comprehensive nursing intervention compared with usual care ($N=128$) (43) in adults on hemodialysis found that the intervention group had significantly greater reduction in Self-Rating Depression Scale scores from baseline ($P=0.04$), and those scores were significantly better after intervention compared with the control group ($P=0.05$). An Iranian RCT ($N=60$) using the Depression, Anxiety, and Stress Scale found that telenursing follow-ups compared with usual care (no telephone follow-ups) resulted in significantly lower depression scores (Table 2) (55). These studies did not report on AEs.

Exercise

There was insufficient evidence from two poor-quality studies (34,40) on exercise training for depression in adults with ESKD (Tables 3 and 4). One study ($N=50$) (34) examined the effect of 4 months of endurance and resistance training four times weekly in Tunisian male participants. Training sessions were on off-dialysis days and the exercise group significantly improved on HADS-D scores compared with sedentary controls. The other, a Greek RCT ($N=50$) (40), examined intradialytic exercise (during hemodialysis cycling and strength training) three times per week for a year and found significant improvement on both the Beck Depression Inventory-II and HADS-D with exercise compared with sedentary controls (Table 2). AEs were not reported.

Other Treatments

We included RCTs of six other therapies: Benson relaxation technique (37), guided imagery (29), hope therapy (45), Latihan Pasrah Diri (51), mindfulness-based stress reduction (47), and Quran readings for Muslim participants (28). All were small, single trials with methodologic challenges, and the evidence is insufficient for all interventions (Tables 2–4). Two of these studies (Latihan Pasrah Diri [51] and mindfulness-based stress reduction [47]) reported no AEs, whereas the others did not report on AEs.

Discussion

In this systematic review, we examined nine RCTs of pharmacologic interventions and 17 of nonpharmacologic interventions for comorbid depression in adults with ESKD. We also found three observational studies that contributed to the evidence on harms of SSRIs. We found moderate-strength evidence that long-term, high-dose vitamin D3 is ineffective for reducing depressive symptoms, and low-strength evidence that both sertraline and CBT were similar for improving depressive symptoms. We also found low-strength evidence that CBT is more effective than both standard psychotherapy and wait-list controls, and that acupressure is more effective than usual care. We found insufficient evidence to draw conclusions about all other interventions. Overall, we found limited evidence for each intervention, sample sizes were small, and nearly all studies were hampered by methodologic flaws.

SSRIs, compared either with placebo or an active comparator, were the best-studied pharmacologic intervention. No other antidepressant categories were identified. Findings from placebo-controlled trials of SSRIs were mixed, but sertraline at least warrants further study. Among the three trials examining sertraline, one reported benefit over placebo, and another found no difference between sertraline and CBT (44). Harms related to SSRIs were not uniformly reported. The type and rate of harms reported and/or evaluated in included RCTs suggest little to no increase in risk for adults with ESKD compared with otherwise healthy adults using SSRIs. Primary side effects were minor (*e.g.*, nausea, fatigue). However, observational studies suggest that clinicians should consider known risks (*e.g.*, QT prolongation) when making prescribing decisions, and to coordinate care to avoid over- or undertreatment.

Vitamin D3 is an interesting intervention for adults with ESKD, due to the associated risks of hypercalcemia and hyperphosphatemia (60). Five adults withdrew from the study due to treatment-related AEs. Although not attributed to hyperphosphatemia, the reported AEs (*i.e.*, joint pain, diarrhea, nausea, and vomiting) may be related. The negative finding regarding vitamin D3, along with its risks, suggests that clinicians should not recommend its use as a depression treatment in this population. Given the large size and length of the trial, the SOE for this finding is moderate, and future studies are unlikely to change conclusions.

Very few nonpharmacologic studies reported harms; however, most interventions presented minimal risk. Differences by subpopulation (*i.e.*, demographic, clinical) were also reported in very few studies, and reported differences were insufficient to form conclusions. Future research should uniformly report harms and examine these subgroups.

Many of the studies were hampered by small sample sizes, posing challenges related to group comparability and statistical power. The duration of treatment and follow-up varied widely across studies, making it more challenging to compare results. For instance, between two studies of sertraline, one was twice as long as the other (3 versus 6 months). The methods used to screen for and diagnose depression were heterogeneous, as was the implementation of interventions (*e.g.*, timing, doses, comparators, modes of delivery). For example, among CBT studies, although all of them met in person, half of the studies used private sessions, and sessions were conducted in groups in the other studies. Session lengths varied and, in one study, CBT was delivered while the participants were receiving hemodialysis. Given the association with hemodialysis and somatic complaints, hemodynamic changes, and alterations in mental acuity, treatments (particularly psychologic ones) that are administered during hemodialysis may be confronted with these challenges; although treating adults outside of hemodialysis sessions has its own challenges, including the increased time burden and physical and mental fatigue. Among other psychologic treatments, some were applied in person, whereas others were practices expected to be followed at home. In addition to these issues, the lack of methodologic detail reported in many of the studies resulted in poor-quality ratings and uncertainty about study processes.

Another important limitation to the current evidence base is that most of the studies were conducted outside of the United States and examined participants and health systems that differ greatly from the general US population. These differences may be reflected in both the patient demographics and medical disease burden, and in how care is delivered, particularly because the majority of US adults on dialysis receive their care from large dialysis organizations in coordination with their nephrology provider.

This is the only systematic review to date that examines both pharmacologic and nonpharmacologic treatment of depression in adults with ESKD. This review confirms and adds to a 2016 Cochrane review of antidepressants in adults with ESKD, which included meta-analyses of harms reported in trials included in our report (59). Although we also included more recent trials, outcomes were not reported in a way that allowed for a quantitative synthesis of harms. Our review adds to the pharmacologic evidence by including studies of dietary supplements. A Cochrane review examining psychosocial interventions for adults with ESKD was recently published (61); however, it includes studies of participants with and without clinical depression. How a participant with ESKD responds to an intervention may vary widely depending on the severity of their baseline depressive symptoms. To reduce clinical heterogeneity, we included only studies with participants meeting established depression-screening thresholds for chronically ill populations (19–23). Finally, additional trials included in our review, particularly the ASCEND (44) and ASSertID trials (33,44), add to both the pharmacologic and nonpharmacologic evidence.

Future research, particularly in the United States, is needed to better evaluate both pharmacologic and nonpharmacologic interventions for this population. In particular, larger replication studies of CBT, acupressure, and SSRIs (such as sertraline), and examination of their effects in different subgroups of adults with ESKD and depression (such as severity of depression, duration of ESKD diagnosis, peritoneal versus hemodialysis, and presence of comorbidities), will help decision makers to implement depression treatments that are not only evidence based, but are also the best fit for their patient population.

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Author Contributions

J.R. Antick, D. Kansagara, and K. Kondo provided supervision; C.K. Ayers was responsible for project administration; C.K. Ayers, P. Chopra, D. Kansagara, and K. Kondo reviewed and edited the manuscript; C.K. Ayers, P. Chopra, and K. Kondo were responsible for investigation; C.K. Ayers and K. Kondo were responsible for data curation and methodology; and all authors conceptualized the study, were responsible for formal analysis, and wrote the original draft.

Supplemental Material

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Supplemental Appendix 1. Search strategies (parent VA review).

Supplemental Appendix 2. Study selection criteria (parent VA review).

Supplemental Table 1. PICOTS by key question.

Supplemental Table 2. Strength of evidence domains and grading.

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