End-stage Renal Disease and Depression: A Systematic Review

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Prepared by:
Evidence Synthesis Program (ESP) Center
Portland VA Health Care System
Portland, OR
Devan Kansagara, MD, MCR, Director

Authors:
Principal Investigator:
Karli Kondo, PhD

Co-Investigators:
Chelsea Ayers, MPH
Pavan Chopra, MD
Jennifer Antick, PhD
Devan Kansagara, MD, MCR

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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.

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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.

Susan Crowley, MD, FASN
National Program Director for Kidney Disease and Dialysis
Chief, Renal Section
VA Connecticut Healthcare System

Andrew S. Pomerantz, MD
National Mental Health Director, Integrated Services Office of Mental Health and Suicide Prevention
Veterans Health Administration, Washington, DC

Edward P. Post, MD, PhD
National Primary Care Director, Primary Care-Mental Health Integration with the Office of Primary Care
Veterans Health Administration, Washington, DC

Laura D. Taylor, LSCSW
National Director, Social Work, Veterans Health Administration; Care Management, Chaplain, and Social Work.
Veterans Health Administration, Washington, DC

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
Jesse Brown VA Medical Center
Chicago, IL

Steven Weisbord, MD, MSc
VA Pittsburgh Healthcare System
Pittsburgh, PA

Suzanne Watnick, MD
Northwest Kidney Centers
Seattle, WA

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.

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.

EXECUTIVE SUMMARY

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 conducted a systematic review by searching electronic databases, clinical trial registries, and reference lists from database inception through April 2019 for diagnostic accuracy studies of depression tools for patients with ESRD and for randomized and non-randomized controlled trials directly comparing pharmacological and non-pharmacological interventions for depression in ESRD patients to each other, placebo, or waitlist control. We abstracted data on study design, interventions, and outcomes. Dual assessment of studies' full text, quality, and strength of evidence (SOE) was agreed upon by consensus using pre-specified criteria.

RESULTS

We included 20 treatment randomized controlled trials (RCT)s and 16 diagnostic accuracy studies.

Key Question 1. What are the performance characteristics of screening tools for depression in patients with ESRD?

For diagnostic accuracy, the best studied tool was the Beck Depression Inventory-II (BDI-II). Table i uses data from the 2 United States (US) and 2 United Kingdom (UK) studies that screened for major depressive disorder (MDD) to compare positive and negative predictive values across reported MDD prevalence rates for a) the general US population (7.1%); b) Veterans receiving care in Veterans Health Administration (VHA) patient-centered medical homes (13.5%); c) patients with ESRD, diagnosed using a gold standard clinical interview (22.8%); d) Veterans with ESRD (method of diagnosis not-reported; 33%), and e) patients with ESRD, diagnosed using a screening tool (39.3%). Studies evaluate both the BDI-II and the Patient Health Questionnaire-9 (PHQ-9) and highlight the impact of the population-specific prevalence rate on positive and negative predictive values for a specific threshold. It is important to note that at the higher prevalence rates seen in patients with ESRD, negative predictive value is generally high. However, positive predictive value is often less than ideal (due to the higher rate of false positives), and 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 caveats, however, are that very few studies included participants that resemble US Veterans, there was heterogeneity across studies in the way the tools were administered, and very few studies contributed data for the same thresholds.

Table i. 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 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 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 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 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 Quality Incentive Program (QIP) requires a follow-up assessment after an initial positive screen, these short tools may be good options for this purpose. The BDI-Fast Screen (FS) in particular performed well when compared to the BDI-II.

Key Question 2. What is the impact of screening for depression in patients with ESRD on intermediate and/or patient outcomes?

We identified no studies examining the impact of screening on intermediate or health outcomes.

Key Question 3. What is the effectiveness of depression treatment in patients with ESRD and depression?

Among pharmacological interventions SSRIs were the most-studied drug class, and the evidence was largely insufficient, except for low-strength evidence from 1 trial of sertraline that it improves clinician-rated depression more than cognitive behavioral therapy (CBT). We found moderate SOE that long-term, high-dose Vitamin D3 is ineffective for reducing depression severity. For non-pharmacological treatments we found low SOE that CBT is more effective than other forms of psychotherapy and placebo for depression improvement and quality of life. There was also low SOE for acupressure reducing depression severity when compared with usual treatment or sham acupressure (see Table ii). Evidence on all other treatments was insufficient to draw conclusions.

Table ii. 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: Gray = Insufficient evidence; 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; TEAS = transcutaneous electrical acupoint stimulation.

Key Question 4. In patients with ESRD and depression, what are the potential harms of screening and treatment?

Five pharmacological trials reported adverse events. In trials of sertraline, withdrawal due to AEs and nausea were more frequently in participants who received sertraline versus placebo. However, frequency and severity were similar to the general population. Withdrawals due to AEs were also reported in a study of high-dose Vitamin D3.

Key Question 5. Do the benefits or harms of screening differ by subpopulations?

One study compared the BDI-II administered on- versus off-dialysis. Agreement was generally high, particularly among depressed participants. However, among non-depressed participants, somatic symptom scores and overall BDI-II scores were higher when assessed on dialysis.

Key Question 6. Do the benefits or harms of treatment differ by subpopulations?

Three trials examined differences in the benefits or harms of interventions for the treatment of depression in patients with ESRD by subpopulation. Findings suggest no difference in the effect of high-dose Vitamin D3 or omega-3 fatty acids by demographic characteristics. Participants with vascular depression receiving high-dose Vitamin D3 reported significantly greater symptom reduction than those with MDD. Finally, among participants receiving CBT, symptom reduction was greater for those who received the intervention immediately versus the waitlist control.

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 and 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, and do not differ significantly from each other. 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.

ABBREVIATIONS TABLE

Abbreviation	Term
AE	Adverse event
AKI	Acute kidney injury
BDI	Beck Depression Inventory
BDI-II	Beck Depression Inventory-II
BDI-FS	Beck Depression Inventory-Fast Screen
BP	Blood pressure
BRT	Benson Relaxation Technique
CA	California
CBT	Cognitive Behavioral Therapy
CDI	Cognitive Depression Index
CDSR	Cochrane Database of Systematic Reviews
CES-D	Center for Epidemiologic Studies Depression Scale
CI	Confidence interval
CKD	Chronic Kidney Disease
CMS	Centers for Medicare and Medicaid Services
COPD	Chronic Obstructive Pulmonary Disease
CVD	Cardiovascular disease
DASS	Depression, Anxiety, and Stress Scale
DBP	Diastolic blood pressure
DI-MHD	Depression Inventory – Maintenance Hemodialysis
DM	Diabetes Mellitus
EBM	Evidence-based Medicine
ED	Emergency department
EPC	Evidence-based Practice Center
ESAS	Edmonton Symptom Assessment Scale
ESP	Evidence Synthesis Program
ESRD	End-stage Renal Disease
ET	Exercise training
FLU	Fluoxetine
GDS-15	Geriatric Depression Scale-15
HADS	Hospital Anxiety and Depression Scale
Ham-D	Hamilton Depression Rating Scale
HD	Hemodialysis
HR	Heartrate
HRV	Heartrate variability
HS	High school
ICD-10	International Statistical Classification of Diseases and Related Health Problems-10
KDQOL-SF 36	Kidney Disease Quality of Life-Short Form 36
KQ	Key Question
LPD	Latihan Pasrah Diri

MA	Meta-analysis
MADRS	Montgomery–Åsberg Depression Rating Scale
MAOI	Monoamine oxidase inhibitor
MBSR	Mindfulness-based Stress Reduction
MD	Mean difference
MDD	Major depressive disorder
MHI5	Mental Health Inventory 5
MINI	Mini International Neuropsychiatric Interview
MMSE	Mini-Mental Status Examination
MX	Mexico
NM	New Mexico
NR	Not reported
NRCT	Non-randomized controlled trial
NS	Not significant
NY	New York
OPCC&CT	Office of Patient Centered Care and Cultural Transformation
OR	Oregon
P	P-value
P4P	Pay-for-performance
PBO	Placebo
PCP	Primary care provider
PD	Peritoneal dialysis
PFS	Piper Fatigue Scale
PHQ-9	Patient Health Questionnaire-9
PICOTS	Population, interventions, comparators, outcomes, timing, setting, and study design
PLC	Profile of Quality of Life in the Chronically Ill
PSE	Psychoeducation
PSQI	Pittsburgh Sleep Quality Index
pts	Participants
QIDS-C	Quick Inventory of Depressive Symptomatology - Clinician
QIP	Quality Incentive Program
QOL	Quality of Life
QUADAS	Tool for the Quality Assessment of Diagnostic Accuracy Studies
RCT	Randomized controlled trial
RR	Relative risk
SAE	Serious adverse event
SBP	Systolic blood pressure
SCID-I	The Structured Clinical Interview for DSM-IV Axis I Disorders
SE	Standard error
SERT	Sertraline
SMD	Standard mean difference
SOE	Strength of evidence
SR	Systematic review

SRQ	Self-Reporting Questionnaire
SSRI	Selective serotonin reuptake inhibitor
TAU	Treatment as usual
TEAS	Transcutaneous Electrical Acupoint Stimulation
TEP	Technical expert panel
TX	Texas
UK	United Kingdom
US	United States
VA	Veterans Affairs
VHA	Veterans Health Administration
WA	Washington