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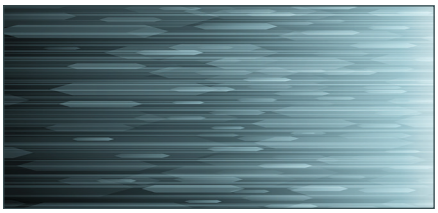

Depression in Heart Failure: A Systematic Review

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ABSTRACT

Objective: This paper sought to identify the instruments used to measure depression in heart failure (HF) and elucidate the impact of treatment interventions on depression in HF. **Methods:** The Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines were followed. Studies published from 1988 to 2018 covering depression and HF were identified through the review of the PubMed and PsycINFO databases using the keywords: "depres*" AND "heart failure." Two authors independently conducted a focused analysis, identifying 27 studies that met the specific selection criteria and passed the study quality checks. **Results:** Patient-reported questionnaires were more commonly adopted than clinician-rated questionnaires, including the Beck Depression Inventory, the Patient Health Questionnaire (PHQ-9), and the Hospital Anxiety and Depression Scale. Six common interventions were observed: antidepressant medications, collaborative care, psychotherapy, exercise, education, and other nonpharmacological interventions. Except for paroxetine, selective serotonin reuptake inhibitors failed to show a significant difference from placebo. However, the collaborative care model including the use of antidepressants showed a significant decrease in PHQ-9 score after one year. All of the psychotherapy studies included a variation of cognitive behavioral therapy and patients showed significant improvements. The evidence was mixed for exercise, education, and other nonpharmacological interventions. **Conclusion:** This study suggests which types of interventions are more effective in addressing depression in heart failure patients.

KEYWORDS: Adult attention-deficit/hyperactivity disorder, comorbid disorders, externalizing disorder, internalizing disorder, nosology

Heart failure (HF) and depression, considered separately, are both highly prevalent illnesses. HF is a chronic syndrome affecting more than 5.7 million adults in the United States and 26 million adults worldwide.[1,2] Depression is a leading cause of disability and premature mortality, affecting roughly 350 million people worldwide.[3]

Additionally, the two diagnoses often go hand in hand. Depressive symptoms in patients with HF are common; a Cochrane review detected depressive symptoms in up to 85 percent of patients with HF.[4] Other systematic reviews place the prevalence of depressive symptoms in patients with HF in the range of 10 to 60 percent.[5] Due to the heightened prevalence of depression in patients with cardiovascular disease (CVD), the American Heart Association has recommended screening for depression among patients with CVD with the Patient Health Questionnaire-2 (PHQ-2) and the Patient Health Questionnaire-9 (PHQ-9).[6]

Beyond commonly coexisting, the two diagnoses magnify one another. Depressive symptoms are associated with negative outcomes in HF.[7] Depression and HF have bidirectional effects through both biological and psychosocial mechanisms.[8–11] In general, functioning impairments are closely correlated with depression severity.[12–14] Also, HF symptoms greatly restrict patients in their ability to partake in daily physical activities.[15–17] Among cardiac patients, those with HF have reported more depressive symptoms and significant mood disruption in comparison with patients with other cardiac illnesses.[18] In the context of chronic illnesses, patients with HF have reported the lowest physical and social functioning.[19] Health-related quality of life (HRQoL) is significantly lower among patients with HF compared to the general population.[20,21]

Surprisingly, a weak predictor of poor HRQoL is HF severity, while one of the largest predictors of poor HRQoL is the severity of depression.[22] Patients with depression and HF experience a worsening in both cardiac functioning and performance on physical exams, such as the six-minute walk test.[23] Studies have reported that patients with HF and more severe physical symptoms experience greater depression severity.[19,24] After adjusting for relevant variables, patients with depression and HF have reported lower mental and physical health scores.[25]

Other studies have concluded a negative impact on the psychosocial and physical health

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of caregivers, due to their feelings of being unprepared for their caregiving responsibilities in addition to being inadequately supported by their given healthcare team.[26] Spouses of patients with HF have reported feeling a significant reduction in well-being and feeling burdened in the caregiving role. In 2004, Dracup et al[27] found that the spouses of patients with HF were at greater risk for low levels of emotional well-being and tended to feel a lack of control over the health outcomes of their loved ones. Caregiver burden is also correlated with caregiver depression. Hooley et al[28] found that depressed caregivers [Beck Depression Inventory (BDI) II score ≥10 points] have greater burden scores.

Studies have consistently shown that emergency department visits are increased in patients with HF and depression.[29,30] Moreover, patients with depression and HF are 4.1 times more likely to be at risk of hospitalization than patients without depression on antidepressants (95% confidence interval: 1.2–13.9; p=0.022.[31] A history of depression in patients with HF might also be a predictor of key quality outcome measures, such as prolonged hospital stays. A study performed in the United Kingdom found that more than 986,000 bed-days were distributed among 54,000 male patients diagnosed with HF and more than 1.37 million bed-days were distributed among 59,000 women diagnosed with HF. The increased severity of depressive symptoms was found to increase the risk for functional decline or death at six months among patients with HF.[32] After adjusting for confounders, a study of 1,017 outpatient patients with HF concluded that depression was an independent risk factor for mortality.[33]

The present systematic review of published literature relating to depression in HF was performed to identify areas where future studies could elaborate further by addressing the following questions: 1) what are the instruments used to measure depression in HF, and 2) what is the impact of treatment interventions on depression in HF?

METHODS

Search strategy. We performed this systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement.[34] A systematic literature search was conducted on articles in the PubMed and PsycINFO databases published within the past 30 years, from January 1988 to July 2018, after setting exclusion and inclusion criteria. The keywords used for the search were "depres*" AND "heart failure." We also conducted a manual search of reference lists for identified papers and previous reviews of HF and depression.

Study selection criteria and methodology. The following inclusion criteria were used: 1) articles published in English or that had a published English translation; 2) articles published in a peer-reviewed journal (with all articles in PubMed being published); 3) original studies in human adults (no reviews, no animal studies, age ≥18 years); 4) original studies of any design that focused on describing or treating depression in HF; and 5) studies that used at least one depression assessment measure. Exclusion criteria included editorials, opinion pieces, and case reports. Two authors independently conducted a focused analysis, then together reached a consensus on 27 studies that were able to meet the specific selection criteria. An independent additional reviewer examined the quality of each study by identifying its strengths and limitations using criteria adapted from Lohr and Carey by the Agency for Healthcare Research and Quality.[35,36] The reviewer assessed sample size, patient selection methods, bias, study group comparisons, blinding, intervention details, outcome measures, and statistical analysis plans. The findings from this study quality check method eventually led to the exclusion of studies that had significant limitations. The search method is displayed in a flow diagram in Figure 1.

Data extraction and yield. Key findings were derived from the full text and tables of the selected 27 studies. The study designs and findings were analyzed for quality and are detailed in Table 1.

RESULTS

Our search strategy identified 3,052 articles. After the elimination of the duplicates, the abstracts of 2,783 studies were reviewed. The studies that did not meet the selection criteria were excluded, leaving 51 studies. Two authors independently conducted a focused analysis using the gathered 51 full-text articles. The two authors then reached a consensus about what studies to include in this review, which yielded 31 studies. The quality check method led to the exclusion of four studies due to the inadequate reporting of results, where depression scores were not explicitly reported pre- and postintervention, and this resulted in a final 27 studies.

The findings from the reviewed studies are displayed in Table 1.

Instruments used to measure depression in HF. The studies in this review employed both patient-reported and clinician-administered depression symptom inventories. For the studies included in this review, the following instruments were used: nine studies used the BDI and BDI II;[37,38] seven studies used the Patient Health Questionnaire (PHQ) exclusively;[39] six studies used the Hospital Anxiety and Depression Scale (HADS) exclusively;[40] six studies used a version of the BDI;[37,38] two studies used the Hamilton Rating Scale for Depression (HAM-D) exclusively,[41] and one of those two studies used two versions of the assessment, the HAM–D–17 and HAM–D-21;[42] one study each used the Montgomery–Åsberg Depression Rating Scale (MADRS) and the Zung Depression Rating Scale (ZDRS) exclusively;[43,44] a single study used the Center for Epidemiologic Studies Depression Scale (CES-D) exclusively.[45] The remaining four studies used more than one instrument to measure depression in patients with HF.

Impact of treatment interventions on depression in HF. Treatment for depression in HF encompasses a wide range of psychopharmacological interventions, cognitive behavioral therapy (CBT), physical exercise programs, psychoeducation, case management, telehealth interventions, palliative care, home-based services, mindfulness, and biofeedback. We classified the study findings into the following seven intervention categories: antidepressant medications,[42,47–49] collaborative care,[50–53] psychotherapy,[54–57] exercise,[57–64] education,[46 65,72] in-home care,[66] and other nonpharmacological interventions.[67–71] One study included in this review combined the exercise and psychotherapy categories.[57] Below, we summarize the results of the included studies broken down by intervention.

Antidepressant medications. The pharmacological agents and the range of doses used include: escitalopram 10 to 20mg,[47] citalopram 20 to 40mg,[42] paroxetine CR 12.5 to 25mg,[49] and sertraline 50 to 200mg.[48] All the interventions in this category were compared to placebos, and the duration of treatment

in the studies ranged from eight weeks to 24 months.

The study in which paroxetine was used as the intervention showed significantly more remission of depressive symptoms relative to the placebo and lower BDI II scores during intervention (69.2% rate of remission, defined as BDI score <10 points) vs. 23.1 percent for controls (p=0.018).[49]

In the other three medication studies, however, the antidepressant medication failed to outperform the placebo. In research by O'Connor,[48] patients taking sertraline had a reduction in the mean delta HADS score of 0.4 (p=0.89). Citalopram numerically outperformed placebo in terms of observed Montgomery-Asberg Depression Rating Scale (MADRS) scores but not on HAM-D scores, while the overall performance did not rise to the level of statistical significance for any of the assessment scores (between-group p-values on depression screens ranged from 0.198 on MADRS to 0.351 on HAM-D-17).[42] For escitalopram, the between-group difference in MADRS score (−0.9 for the intervention group) was not statistically significant (p=0.26).[47]

Collaborative care. Out of the four studies in this category, two looked at a palliative care intervention delivered alongside standard HF care.[52,53] The third study in this category employed and focused upon a specific collaborative care intervention called Collaborative Care to Alleviate Symptoms and Adjust to Illness (CASA),[50] while the fourth employed and focused upon a Patient-centered Disease Management (PCDM) intervention involving three components: multidisciplinary collaborative care for managing HF, screening for the treatment of depression, and telemonitoring with patient self-care support.[51] The range of the treatment duration ranged from a single consult to one year; however, the duration of one of the palliative care interventions was not explicitly stated.[51] Similarly, the duration of the CASA intervention was estimated based on the number of visits reported because its duration was also not explicitly stated in the study.[50]

All four studies reported statistically significant reductions in depression severity. For Rogers et al,[52] the HADS-depression scores for the intervention group decreased by 1.94 points more than in the usual care group (p=0.020). Sidebottom et al[53] reported a PHQ-9 score reduction at three months of 2.90 for the intervention group versus 2.18 for the control group (p=0.00). The CASA intervention study saw significant differences in between-group reductions in PHQ-9 score in the intervention group compared to control (reduction in score of 2.2 points for intervention group versus only 0.8 points for the control group; p=0.02)).[50] The paper looking at the PCDM intervention found a greater reduction in depressive symptoms for the subset of patients initially screened as positive for depression receiving the intervention compared to controls screening positive for depression as measured by the PHQ-9. The between-group difference in score reduction was 2.1 points (p=0.01).[51]

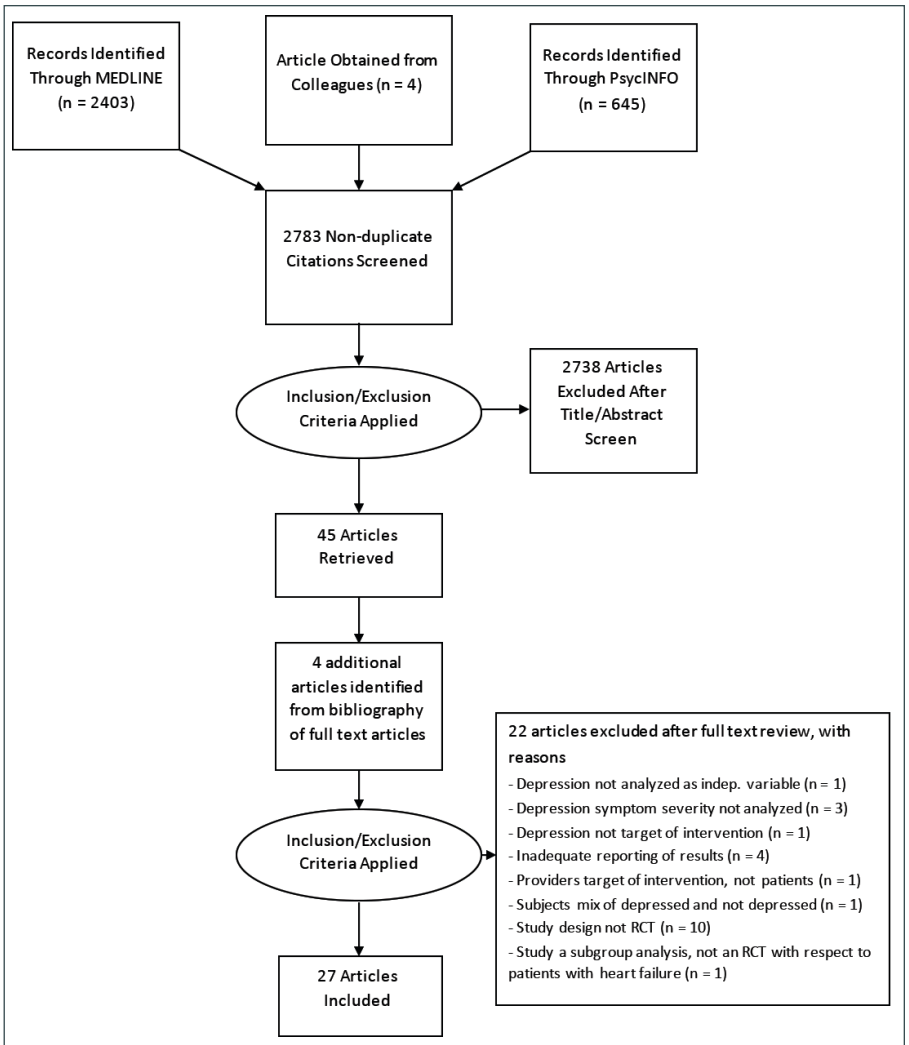

FIGURE 1. PRISMA Flow Diagram.

Psychotherapy. Three papers exclusively studying psychotherapy were included. Two studies compared psychotherapy to usual care.[55,56] One study compared psychotherapy to an online-moderated discussion instead.[54] The duration of the treatment for these studies varied between nine weeks and six months.

One study found significantly lower BDI II scores at 12 months with CBT intervention than in the usual care arm (p=0.005) and significantly lower HAM-D scores at six months (p<0.001).[55] A second study found no significant difference in improvement in BDI II between the two groups (p=0.24), with scores improving over time in both.[56] The third study, which used the online-moderated discussion forum as a comparison group and had the shortest treatment duration (nine weeks), found no significant difference in depressive symptoms between the groups at follow-up according analysis of covariance analysis (p=0.21). However, secondary within-group analysis of depressive symptoms showed that such symptoms decreased significantly in

TABLE 1. Reviewed studies in depression and heart failure

AUTHOR, YEAR, LOCATION	POPULATION AND SETTING	SAMPLE SIZE	CATEGORY	INTERVENTION	COMPARATOR
Angermann, et al, 2016, Germany	Adult patients (NYHA II–IV) at heart failure outpatient clinics	372	Medication	Escitalopram 10–20mg	Placebo
Bekelman et al, 2018, United States	Patients with chronic heart failure at 3 settings (urban safety net, VA, and academically affiliated health systems) (no NYHA data report)	314	Collaborative care	CASA intervention (RN addressed symptoms, social worker provided structured psychosocial care, and a care team reviewed patient's care)	Usual care
Bekelman et al, 2015, United States	Patients from 4 VA centers (NYHA I–IV)	392	Collaborative care	Collaborative care team consisting of a nurse coordinator, cardiologist, psychiatrist, PCP, home telemonitoring, and patient self-management support	Usual care
Blumenthal et al, 2012, United States, Canada, France	Multicenter in the U.S., Canada, France (NYHA I–IV)	2,331	Exercise	Aerobic exercise, first supervised, then independent at home	Usual care
Chang et al, 2016, Taiwan	Outpatients with heart failure in a single center in Tapei (NYHA I–IV)	84	Education	12-week tailored educational support program and accompanying sleep health care manual and video provided by a researcher with clinical experience in cardiovascular nursing	Usual care
Chrysohoou et al, 2013, Greece	Patients (NYHA II–IV) visiting the Heart Failure Unit of the clinic with CHF due to LV systolic dysfunction	72	Exercise	Exercise intervention	Usual activity
Dekker, et al, 2012, United States	Patients age 21 years and older (NYHA III–IV) who were hospitalized with a primary or secondary diagnosis of HF at 2 regional hospitals in Lexington, Kentucky; preserved or nonpreserved systolic function HF	41	Psychotherapy	Cognitive therapy delivered during hospitalization and a 1-week booster phone call	Usual care
Fraguas, et al, 2009, Brazil	72 older outpatients (no NYHA specified) with EF <50% recruited from a geriatric cardiology outpatient clinic at a Brazilian academic medical center	37	Medication	Citalopram (20–40mg)	Placebo
Freedland et al, 2015, United States	Outpatients with HF (NYHA I–III) at Washington University Medical Center	158	Psychotherapy	CBT	Usual care
Gary et al, 2010, United States	Outpatients (NYHA II–III) from a HF clinic in NE Georgia	74	Exercise, psychotherapy	CBT/exercise or CBT or Exercise	Usual care
Gottlieb et al, 2007, United States	Outpatients (NYHA II–III) from a VA clinic in Baltimore, MD	28	Medication	Paroxetine CR 12.5–25mg	Placebo
Jolly, et al, 2009, United Kingdom	Patients (NYHA II–III) recruited from two acute hospital trusts and one primary care trust in the West-Midlands health region, UK	84	Exercise	Home-based exercise plus specialist nurse care	Specialist nurse care alone
Karavidas et al, 2008, Greece	Patients (NYHA II–III), details about setting and whether they are inpatients or outpatients not given	30	Nonpharmacological therapy	Functional electrical stimulation	Placebo
Koukouvou, 2004, Greece	Patients (NYHA II–III) referred from a cardiology clinic in Greece	26	Exercise	Exercise training (ET)	Control group
Kulcu et al, 2007, Turkey	Ambulatory patients (NYHA II–III) at an academic hospital in Ankara	44	Exercise	Cardiac rehabilitation	Control group
Lundgren et al, 2016, Sweden	Both inpatients and outpatients (NYHA I–IV) from 4 hospitals in southeast Sweden	50	Psychotherapy	Web-guided CBT	Online moderated discussion forum (DF)

TABLE 2. Reviewed studies in depression and heart failure

AUTHOR, YEAR, LOCATION	DURATION OF TREATMENT	DEPRESSION INSTRUMENT USED	OUTCOME (DEPRESSION)	DEPRESSION PRIMARY OUTCOME? (IF NOT, WHAT IS)	EFFECT SIZE AND/OR SIGNIFICANCE	QUALITY CHECK
Angermann, et al, 2016, Germany	Up to 24 months	MADRS	No significant improvement in depression	All-cause mortality or hospitalization not reduced	Between-group difference on MADRS = −0.9 (−2.6 to 0.7); p=0.26	RCT, depression rating scale measured pre- and postintervention, confidence intervals reported in results
Bekelman et al, 2018, United States	5–6 months (estimated based on number of visits reported - see notes)	PHQ9	CASA group saw their PHQ9 scores go down more than the usual care group but not clear that this is clinically significant based on effect size	Intervention did not demonstrate improved heart failure-specific health status as measured by KCCQ	Difference between groups at 3 months: −1.6 on PHQ9 (p=0.01); 6 months: −1.4 on PHQ9 (−2.6 to −0.2; p=0.02)	RCT, data from all participants included (intent to treat approach), PHQ9 measured pre- and postintervention, intent to treat analysis used
Bekelman et al, 2015, United States	Unclear—possibly up to one year	PHQ9	Greater improvement in the PHQ-9 score after 1 year in the intervention arm than the usual care arm	Intervention did not demonstrate improved patient health status compared to usual care, as measured by KCCQ	Difference in improvement between groups is 2.1 on the PHQ9 in favor of the intervention group; p=0.01	RCT, PHQ9 measured pre- and postintervention, significance levels reported
Blumenthal et al, 2012, United States, Canada, France	3 months	BDI-II	Difference between the exercise and control groups is modest and the clinical significance is not known	Depression was primary outcome	Aerobic exercise resulted in lower mean BDI-II scores at 3 months (aerobic exercise, 8.95; 95% CI: 8.61–9.29 vs. usual care, 9.70; 95% CI: 9.34–10.06; difference, −0.76; 95% CI: −1.22 to −0.29; p=0.002) and at 12 months (aerobic exercise, 8.86; 95% CI: 8.67–9.24 vs. usual care, 9.54; 95% CI: 9.15–9.92; difference, −0.68; 95% CI: −1.20 to −0.16; p= 0.01).	RCT, BDI-II measured pre- and postintervention, confidence intervals reported
Chang et al, 2016, Taiwan	12 weeks	HADS	Intervention group HADS score did not change by week 12 (control group score went up significantly)	Sleep quality primary outcome: intervention group exhibited significant improvement in the level of sleep quality whereas the control group exhibited no significant differences	Intervention group HADS scores = 7.12 (SD: 2.94) at baseline, 7.19 (4.99) at Week 12; p=0.493 and control HADS scores = 6.39 (2.98) at baseline, 9.51 (3.70) at Week 12; p<0.001	RCT, HADS measured pre and throughout intervention, scores reported with appropriate statistical analysis
Chrysohoou et al, 2013, Greece	12 weeks	ZDRS	Reduction in ZDRS group for intervention statistically significant, but the difference between the intervention group and control group was not, apparently	Quality of life measured by MLHFQ primary outcome	ZDRS for intervention group went from 37 (SD: 8) to 30 (6), ZDRS for control group went from 37 (8) to 41 (10); p=0.54	RCT, ZDRS measured pre- and postintervention, scores reported with appropriate statistical analysis
Dekker et al, 2012, United States	3 months	BDI-II	No significant difference in improvement in BDI-II between the two groups (scores improved over time in both)	Depression one of the primary outcomes	Within-group differences p=0.24	RCT, BDI-II measured pre- and postintervention, scores reported with appropriate statistical analysis
Fraguas, et al, 2009, Brazil	8 weeks (following a 2-week wash-out period on placebo)	HAM-D-17, HAM-D-31, MADRS	Citalopram group showed a "numerical superiority," the difference wasn't statistically significant (there was a "trend towards significance for the MADRS scores")	Depression the primary outcome	Between-group difference of 2.01 for Ham-D-17 (p=0.351); 2.71 for Ham-D-31 (p=0.306); 3.82 for MADRS (p=0.198)	RCT, depression scales measured pre- and postintervention, scores reported with appropriate statistical analysis
Freedland et al, 2015, United States	Up to 6 months	BDI-II, HAM-D	Scores were significantly lower in the CBT than UC arm	Depression the primary outcome	Both arms comparable at baseline; BDI scores at 12 months were usual care 16 (SD: 10.8) vs. CBT 11.2 (10.7); p=0.005 and HAM-D at 6 months usual care 12.1 (6.0) vs. 8.2 (5.9); p<0.001	RCT, depression scales measured pre- and postintervention, scores reported with appropriate statistical analysis

Nolte et al, 2015, Germany	Multicenter study of HFpEF patients (NYHA II–III)	64	Exercise	Exercise training	Usual care
O'Connor et al, 2010, United States	Patients (NYHA II–IV) at 3 centers in the US	469	Medication	Sertraline 50–200mg	Placebo
Piotrowicz et al, 2016, Poland	Hospitalized patients (NYHA II-III) recruited from the Dept. of Cardiac Rehabilitation, Institute of Cardiology, Warsaw.	69	Exercise	Telemonitored cardiac rehabilitation	Usual care
Ramaekers et al, 2009, the Netherlands	Patients recruited from 3 hospitals in the Netherlands (no NYHA reported)	101	Nonpharmacological therapy	Telemonitoring	Standard care
Redwine et al, 2012, United States	Patients (NYHA II) recruited from the VA San Diego Medical Center and the University of California, San Diego	24	Nonpharmacological therapy	T'ai chi	Usual care
Riegel et al, 2006, United States	Self-identified Hispanics at 2 participating community hospitals near the US–Mexico border	134	Nonpharmacological therapy	Telephone case management	Usual care
Rogers et al, 2017, United States	Hospitalized and recently discharged patients (NYHA III–IV) at high risk of hospitalization	150	Collaborative care	Palliative care intervention	Usual care
Sidebottom et al, 2015, United States	Adult inpatients with a diagnosis of acute HF in a tertiary-care facility in Minneapolis, MN (no NYHA class data)	232	Collaborative care	Palliative care consult with follow-up as determined by provider or standard of care	Control
Swanson et al, 2009, United States	Patients (NYHA I–III) recruited from a HF clinic at Loma Linda University	29	Nonpharmacological therapy	Breathing retraining and biofeedback	Sham biofeedback
Tsuchihashi et al, 2013, Japan	Patients (NYHA I–III) enrolled from 3 cardiology hospitals in Hokkaido, Japan	161	In-home care	Home-based disease management	Usual care
Wang et al, 2017, China	Patients (NYHA II–IV) from the Department of Geriatrics and Cardiology from one hospital	62	Education	Health education (PRECEDE)	Control

ANCOVA: analysis of covariance; BDI: Beck Depression Inventory; CASA: Collaborative Care to Alleviate Symptoms and Adjust to Illness; CBT: cognitive behavioral therapy; CES-D: Center for Epidemiological Studies Depression Scale; CI: confidence interval; CR: controlled release; GEE: generalized estimating equation; HADS: Hospital Anxiety and Depression Scale; HAM-D: Hamilton Depression Rating Scale; HF: heart failure; KCCQ: Kansas City Cardiomyopathy Questionnaire; MADRS: Montgomery–Asberg Depression Rating Scale; MLHFQ: Minnesota Living with Heart Failure Questionnaire; NYHA: New York Heart Association; PCP: Primary Care Physician; PHQ: Patient Health Questionnaire; PRECEDE: Predisposing, Reinforcing, and Enabling Constructs in Educational/Environmental Diagnosis and Evaluation; RCT: randomized controlled trial; RN: registered nurse; UC: usual care; VA: Veteran's Administration; VO2: volume of oxygen; ZDRS: Zung Depression Rating Scale

the CBT group from baseline to follow-up relative to in the discussion forum group (p=0.02).[54]

Exercise. Exercise was the most frequent studied intervention, with eight different studies testing it. The duration of the exercise intervention varied from eight weeks to six months. Only three of the studies found a significant improvement in the intervention group compared to the control.[62–64] One of the studies reported p-values of less than 0.05 for the results of both depression screening measures used (BDI, HADS) for the intervention group relative to the control group.[64] A second study reported p-values of 0.02 for the within-group changes for the intervention (a treadmill walking program) and 0.245 for the within-group changes for the control group.[63] A third study using a home-based walking and resistance exercise program found the between-group difference in HADS score reductions was not statistically significant at six months (p=0.2) but was statistically significant at 12 months (p=0.02).[62] An additional study found that aerobic exercise resulted in a lower mean BDI II score at three, six, and 12 months (p=0.02). Though the between-group difference was significant (0.68-point reduction on the BDI II scale; p=0.01), the clinical significance was characterized by the authors as unknown.[61]

The remaining four studies all reported reductions in depressive symptom severity for the intervention group, but the magnitude did not differ significantly from the control groups.[57–60]

Education. One study using an education intervention showed that anxiety and depression scores significantly increased at 12 weeks in the control group (p<0.001), while individuals in the intervention group did not exhibit significant change at 12 weeks in the supportive nursing care program (p>0.05).[46] Another study in this category reported that, after the intervention, the mean PHQ-9 score decreased significantly in the intervention group (p=0.000).[72] A randomized controlled trial of a 12-week supportive educational nursing care program showed that, relative to in the control group, patients in the intervention group experienced significantly greater decreases in fatigue and significantly greater improvements in quality of life after 12 weeks of intervention.[65]

In-home care. A single study looked at a home-based nursing intervention in comparison with usual care.[66] Overall, the HADS score for the intervention group actually went up by 12 months after a slight reduction at six months (from eight points at baseline to seven points

Gary et al, 2010, United States	12 weeks for exercise, up to 24 weeks of CBT	HAM-D	Decline in all four groups, but none statistically significant overall unless stratified by minor vs. moderate/major depression	Depression one of the primary outcomes	Group 1 (CBT + exercise) d=1.01; group 2 (CBT only) d=0.41; Group 3 (exercise only) d=0.03	RCT, depression scales measured pre- and postintervention, scores reported with appropriate statistical analysis
Gottlieb et al, 2007, United States	12 weeks	BDI-II	Paroxetine CR resulted in significantly more remission of depression compared to placebo and lower BDI scores during intervention	Depression one of the primary outcomes	Intervention group: 69.2% remission of depression as defined by BDI<10 vs. 23.1% for placebo group; between group showed difference significance at p=0.018	RCT, depression scales measured pre- and postintervention, scores reported with appropriate statistical analysis
Jolly, et al, 2009, United Kingdom	24 weeks	HADS	Some evidence of improvement in HADS for exercise at 12 months; no change at 6 months	Quality of Life measured by MLHFQ the primary outcome	Adjusted mean difference on HADS depression score between exercise and usual care group at 6 months: −0.68 (p=0.2); at 12 months: −1.07 (p=0.02)	RCT, depression scales measured pre- and postintervention, scores reported with appropriate statistical analysis
Karavidas et al, 2008, Greece	6 weeks	ZDRS, BDI	Significant improvement in BDI and Zung for intervention group compared to placebo group	Depression one of the primary outcomes	Zung: F statistic = 27.098 (p<0.001); BDI: F statistic = 17.768 (p<0.001)	RCT, depression scales measured pre- and postintervention, scores reported with appropriate statistical analysis
Koukouvou, 2004, Greece	6 months	BDI, HADS	Significant improvement in depression scores in ET group	VO_2 and exercise time primary outcomes	ET Group: BDI 18.6 to 13.1, HADS 13.1 to 8.6; control group: BDI 18.5 to 18.8, HADS 11.6 to 12.2; both p-values <0.05	RCT, depression scales measured pre- and postintervention, scores reported with appropriate statistical analysis
Kulcu et al, 2007, Turkey	8 weeks	BDI	Significant improvement in BDI score in the ET group	Depression one of the primary outcomes	ET Group: BDI 18.4 to 13.5 at 8 weeks (within-group p=0.020); control group: BDI 20.02 to 22.25 (within-group p=0.245)	RCT, depression scales measured pre- and postintervention, scores reported with appropriate statistical analysis
Lundgren et al, 2016, Sweden	9 weeks	PHQ9	No significant difference in depressive symptoms between the groups at follow-up was found in primary ANCOVA analysis; secondary within group analysis of depressive symptoms showed that such symptoms decreased significantly in the CBT group from baseline to follow-up, whereas, in the DF group, there was no significant change	Depression one of the primary outcomes	p=0.21 (primary ANCOVA), p=0.02 (secondary within-group analysis)	RCT, depression scales measured pre- and postintervention, scores reported with appropriate statistical analysis
Nolte et al, 2015, Germany	3 months	PHQ9	Differences between groups not statistically significant	Depression one of the primary outcomes	PHQ9 changes by group: ET −2 (−3 to −1); UC −1 (−2 to 0) difference between groups; p=0.735	RCT, depression scales measured pre- and postintervention, scores reported with appropriate statistical analysis
O'Connor et al, 2010, United States	12 weeks	HADS	Sertraline didn't outperform placebo	Depression the primary outcome	Change in mean delta between groups −0.4 (95% CI −1.7 to 0.9; p=0.89)	RCT, depression scales measured pre- and postintervention, scores reported with appropriate statistical analysis
Piotrowicz et al, 2016, Poland	8 weeks	BDI	Depression symptoms substantially reduced in both groups	Depression one of the primary outcomes	BDI for training group 8.76 to 6.70, vs. 11.57 to 9.09 for control group (both p<0.0001)	RCT, depression scales measured pre- and postintervention, scores reported with appropriate statistical analysis

at six months, then back over eight points by 12 months). These results were expressed in graphical form, without reporting the results numerically.

Other nonpharmacological interventions. Five studies total were included in this category.[67–71]

T'ai chi. T'ai chi for 12 weeks was compared to usual care. Relative to controls, patients with HF in the T'ai chi group experienced reduced BDI symptom scores from pre- to postintervention ($p<0.05$) and a significant group-by-time interaction ($p<0.05$).[67]

Biofeedback. A study comparing biofeedback to sham was unable to show that breathing retraining and biofeedback intervention had a significant effect on the CES-D score ($p=0.097$).[68]

Functional electrical stimulation (FES). Comparing pre and post scores, FES led to the improvement of depressive symptoms as measured by the Zung Self-rating Depression Scale ($p<0.001$) and the BDI ($p<0.001$) as well as quality of life measured by the KCCQ ($p<0.001$).[69]

Telemonitoring. Compared to usual care, telemonitoring was unable to show substantial differences ($p=0.118$).[70]

Telephone case management. Compared to standard care groups, telephone case management did not show a significant difference (p-values not reported).[71]

DISCUSSION

Summary of the review findings. The studies used in this systematic review included a variety of depression assessment tools, protocol lengths, and sample sizes while also employing different intervention modalities to measure the effects of depression in patients with HF. Patient-reported questionnaires were more commonly used than clinician-rated questionnaires, with the BDI, the PHQ, and the HADS being those most frequently used with regard to measuring depression in HF. The interventions mentioned encompassed a broad range of categories that included antidepressant medications, collaborative care, psychotherapy, exercise, education, and other nonpharmacological interventions. The impact of the six treatment interventions were used to address and analyze how depression varied across the included studies.

All psychopharmacological agents in this review were tested against placebos and included the following medications: escitalopram, citalopram, paroxetine, and sertraline.[42,47–49] The duration of the treatment regimens ranged from two to 24 months and were unable to show any significant preference to antidepressant medication over placebos, with the exception of one treatment: the use of paroxetine CR 12.5 to 25mg was able to provoke a significant reduction in depressive symptoms and BDI II score.[49] Five studies included in this review tested the effect of collaborative care intervention on depression in patients with HF. The two studies that included palliative care interventions were both able to demonstrate an improvement in depressive symptoms.[52,53] Meanwhile, the study that included the CASA group demonstrated improvements in PHQ-9 scores.[50] In addition, another study by the same first author (Bekelman) reported a decrease in PHQ-9 scores after one year.[51] Three studies in this review employed psychotherapy techniques by comparing the effects of the intervention groups to usual care and an online-moderated discussion forum.[54–56] All the psychotherapy studies included a variation of CBT as the intervention. The Freedland study exhibited the best results due to its weekly one-hour CBT sessions, occurring for a duration of up to six months, that resulted in significantly lower BDI II scores reported at 12 months and significantly lower HAM-D scores reported at six months.[55]

Although exercise was the most frequently used intervention, there appeared to be many limitations in determining the overall effect on depression in patients with HF. One exercise intervention study failed to include statements regarding the clinical significance of its outcomes.[61] Another study had varying results at different time points, with no proven statistical significance when considering within-group analysis.[62] Although a different study reported clinical significance, it lacked proper calculations between the groups for BDI.[58] The remaining exercise intervention studies were unable to show any statistical clinical significance.[57,59]

Two studies included in the education intervention category reported significant improvements in depression scores within their intervention groups.[46,72] One education intervention study showed significant improvements in sleep quality outcomes within the intervention group receiving a 12-week educational support program and additional education on sleep; in contrast, the control group receiving usual care experienced significant increases in depression. However, the intervention group did not show significant results in terms of decreasing depression scores.[46] The second study reported that, after receiving nine weeks of education intervention, PHQ-9 scores decreased significantly.[72]

Three studies included in the other nonpharmacological intervention category compared interventions to usual and/or standard care.[67,70,71] One study compared interventions to sham biofeedback.[68] A study that included T'ai chi as the intervention showed significant improvements in depressive symptoms but it should be noted that the study had a small sample size.[67] All other studies mentioned in this category that involved telemonitoring, telephone case management, breathing retraining, and biofeedback were unable to yield significant results in terms of reducing depressive symptoms.[68,70,71]

Interpretation of the review findings. Through the analysis of the 27 studies that met the specific selection criteria and passed the study quality checks of this review, it can be interpreted that treatment interventions might greatly impact depression in HF; in particular, psychotherapy intervention had the most significant influence. A study using psychotherapy as the intervention was able to result not only in significantly lower BDI II scores but also significantly lower HAM-D scores; notably, both outcomes correspond to improvements in depressive symptoms.[55] Collaborative care also proved to be an impactful form of intervention with its ability to improve depressive symptoms.[50–53] Collaborative care follows psychotherapy in terms of the extent of impact on depression in HF due to its results being supported by the use of only one instrument (PHQ-9) and the results of psychotherapy intervention being supported by the use of two instruments (BDI II and HAM-D). Education was the third-most impactful form of intervention: it resulted in significant improvements in depression scores within the intervention groups.[46,65,72] However, the intervention group in one study was unable to show significant effects on decreasing depression scores.[46]

Antidepressant medications serve as the fourth-most impactful form of intervention for depression in HF because paroxetine CR 12.5 to 25mg was the only medication out of the

Ramaekers et al, 2009, the Netherlands	3 months	HADS	No substantial difference between groups	Adherence to HF recommendations primary outcome	Delta for 2 groups: for intervention, −1.1±2.6; for control group 0.0±3.0; overall difference between groups −1.1; p=0.118	RCT, depression scales measured pre and post (during) intervention, scores reported with appropriate statistical analysis
Redwine et al, 2012, United States	12 weeks	BDI	Compared to controls, patients with HF in the t'ai chi group experienced reduced BDI symptom scores from pre- to post-intervention, with a significant group-by-time interaction	Depression the primary outcome	(F [4,19] = 4.5; p<0.05 and partialg2 = 0.28) after controlling for age, gender, EF and category of HF	RCT, depression scales measured pre- and postintervention, scores reported with appropriate statistical analysis
Riegel et al, 2006, United States	6 months	PHQ9	No significant between group differences for change in PHQ9 scores at 3 or 6 months	Health-related quality of life and depression primary outcomes	Usual care group PHQ9 scores: 8.6±5.4 at baseline, 2.3±2.3 at 3 months, and 2.0±2.1 at 6 months; intervention group 8.8±5.8 at baseline, 1.9±2.1 at 3 months, and 1.5±2.0 at 6 months; no p-values reported.	RCT, depression scales measured pre- and postintervention, scores reported with appropriate statistical analysis
Rogers et al, 2017, United States	6 months	HADS	Depression symptoms improved more in the patients receiving the intervention than the UC alone patients	General, heart failure, and palliative care-specific quality of life primary outcomes	Between group differences on HADS-depression scale at 6 months vs. 2 weeks PAL: −1.94 (95% CI: −3.57 to −0.31; p=0.020)	RCT, depression scales measured pre- and postintervention, scores reported with appropriate statistical analysis
Sidebottom et al, 2015, United States	Single consult plus up to 3 or more visits	PHQ9	Improvement in depression at 3 months was significantly greater in the intervention group vs. the control group, but the magnitude was extremely small	Depression one of the primary objectives	Mean difference in PHQ9 change between two groups: 0.72 (0.41–1.03), p=0.000	RCT, depression scales measured pre- and postintervention, scores reported with appropriate statistical analysis
Swanson et al, 2009, United States	6 training sessions	CES-D	No significant effect on CES-D score	Depression one of the primary outcomes	Overall significance within-group difference (treatment vs. controls) on CES-D, based on three-way interactions: p=0.097	RCT, depression scales measured pre- and postintervention, scores reported with appropriate statistical analysis
Tsuchihashi et al, 2013, Japan	2 months	HADS	Depression score didn't change significantly at each time point from baseline in either group (went down by 6 months, back up by 12 months)	Depression one of the primary outcomes	The HADS-depression scores did not change significantly at each time point from baseline in either group (no p-values given for this finding)	RCT, depression scales measured pre- and postintervention, scores reported with appropriate statistical analysis
Wang et al, 2017, China	9 weeks	PHQ9	Intervention group's PHQ scores went down much more than control group	Depression one of the primary outcomes	Intervention group means on PHQ9 scores: 7.23 to 2.71; control group means: 7.03 to 6.94; p=0.000	RCT, depression scales measured pre- and postintervention, scores reported with appropriate statistical analysis

ANCOVA: analysis of covariance; BDI: Beck Depression Inventory; CASA: Collaborative Care to Alleviate Symptoms and Adjust to Illness; CBT: cognitive behavioral therapy; CES-D: Center for Epidemiological Studies Depression Scale; CI: confidence interval; CR: controlled release; GEE: generalized estimating equation; HADS: Hospital Anxiety and Depression Scale; HAM-D: Hamilton Depression Rating Scale; HF: heart failure; KCCQ: Kansas City Cardiomyopathy Questionnaire; MADRS: Montgomery–Asberg Depression Rating Scale; MLHFQ: Minnesota Living with Heart Failure Questionnaire; NYHA: New York Heart Association; PCP: Primary Care Physician; PHQ: Patient Health Questionnaire; PRECEDE: Predisposing, Reinforcing, and Enabling Constructs in Educational/Environmental Diagnosis and Evaluation; RCT: randomized controlled trial; RN: registered nurse; UC: usual care; VA: Veteran's Administration; VO2: volume of oxygen; ZDRS: Zung Depression Rating Scale

four mentioned that resulted in a significant reduction of depressive symptoms and BDI II scores; escitalopram, citalopram, and sertraline were all unable to demonstrate any significant preference over the placebos.[49] While a study using nonpharmacological intervention resulted in significant improvements in depressive symptoms, this fifth form of intervention cannot be interpreted as greatly impacting depression in HF due to the study's small sample size.[67] This could possibly lead to bias in addition to other studies in this category failing to yield significant results in reducing depressive symptoms.[68,70,71] The sixth intervention category of exercise was determined to be the least significant in

impacting depression in HF because of its lack of clinical significance statistical significance, or proper calculations for BDI within the studies included in this category.[58,61,62]

Comparing this review's findings to previous reviews. Prior research has explored the impact of different types of intervention for depression in patients with HF—mainly antidepressant medication, psychotherapy, exercise, and collaborative care—to establish the most impactful form of intervention for this population.[7,73–76] However, the academic community has found this task challenging because of the substantial heterogeneity in the type, quality, and/or appropriateness of the interventions for target patient groups.[75]

Likewise, this paper corroborates that studies describing the instruments used to measure depression in HF and the adopted interventions are heterogeneous; notwithstanding, to date, to our knowledge, this is the only systematic review that has identified and classified six different modalities of intervention, assessing their quality and impact in the target population.

Notably, this study confirms that psychotherapy is the most impactful intervention regarding the improvement of depressive symptoms in patients with HF as underlined by prior reviews and recommended as first-line treatment for patients with CVD.[7,74,77]

This review positions psychopharmacological therapy as the fourth most impactful modality of treatment, supporting existing literature that questions its superiority over other interventions.[48,77,78,79]

Similarly, exercise has been highlighted by prior research as an effective therapy with an important impact in the reduction of depressive symptoms.[61,77] However, this paper calls in to question these assertions, having found a lack of clinical and statistical significance.

Strengths and limitations. The strengths in this review are that this is a systematic review of articles published in the last 30 years. All analyzed studies are randomized, controlled trials that report measurements pre- and postintervention, with only one study reporting measurements pre- and throughout intervention.[46]

The limitations of this paper include a possible decrease in the statistical power of some of the evaluated studies due to small sample size. The substantial heterogeneity in the sensitivity and specificity of the instruments used to measure depressive symptoms could also be interpreted as a weakness since the studies analyzed take as a target population for intervention those patients with HF that screen positive using these instruments.[74] This method could fail to include patients with subsyndromal depression; higher mortality rates have been observed in patients after acute myocardial infarction who have lower levels of depressive symptoms, which is not generally considered clinically significant.[80] In general, it is important to distinguish between statistical significance and clinical significance when looking at the numerical decrease of depression assessment scores, which not every included paper did.

CONCLUSIONS AND FUTURE DIRECTIONS

Depression is widely accepted as a major cause of morbidity and poor quality of life among patients with CVD, especially those with HF, and leads to staggering social, economic, and psychological costs worldwide.[74,81] This situation has critically influenced the academic dialogue regarding the tools used to measure depressive symptoms in patients with HF and the impact of different modalities of treatment in this population. Despite its prevalence, current studies describing evaluation instruments and interventions among patients with HF and depression are too heterogeneous to permit definitive conclusions.

The review of articles included in this paper show that interventions exist that possess a demonstrated benefit for patients suffering from depression in the setting of HF, while some types of intervention (psychotherapy) tend to yield superior results relative to others (e.g., exercise). Future research is needed to create evidence-based evaluation and treatment algorithms tailored to the specific needs of the target population.

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