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Authors

Hedrick, Rebecca
Korouri, Samuel
Tadros, Emile
et al.

Publication Date

2020

DOI

10.7573/dic.2020-5-4

Peer reviewed

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ORIGINAL RESEARCH

The impact of antidepressants on depressive symptom severity, quality of life, morbidity, and mortality in heart failure: a systematic review

Rebecca Hedrick MD[1], Samuel Korouri BA[1], Emile Tadros BS[1], Tarneem Darwish MD[1], Veronica Cortez RN, OD[1], Desiree Triay RN[1], Mia Pasini RN, MSN[1], Linda Olanisa LCSW[1], Nathalie Herrera MD[1], Sophia Hanna BA, MA[1], Asher Kimchi MD[2], Michele Hamilton MD[2], Itai Danovitch MD, MBA[1], Waguih William IsHak MD, FAPA[1,3]

[1]Department of Psychiatry and Behavioral Neurosciences, Cedars-Sinai Medical Center, Los Angeles, CA, USA;
[2]Department of Cardiology, Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA;
[3]Department of Psychiatry, David Geffen School of Medicine, Los Angeles, CA, USA

Abstract

Objective: The purpose of this paper is to review the literature on the impact of antidepressants on depressive symptom severity, quality of life (QoL), morbidity, and mortality in patients with heart failure (HF).

Methods: Following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Reporting Items for Systematic Reviews and Meta-Analyses guidelines, studies published from December 1969 to December 2019 that pertain to depression and HF were identified through the use of the PubMed and PsycINFO databases, using the keywords: 'antidepressant*' and 'heart failure.' Two authors independently conducted a focused analysis and reached a final consensus on 17 studies that met the specific selection criteria and passed the study quality checks.

Results: Studies varied in types of antidepressants used as well as in study designs. Ten studies were analyzed for the impact of antidepressant medications on depressive symptom severity. Five of these were randomized controlled trials (RCTs), out of which sertraline and paroxetine showed a significant reduction in depressive symptoms despite the small samples utilized. Four of the 17 studies addressed QoL as part of their outcomes showing no difference for escitalopram (RCT), significantly greater improvements for paroxetine controlled release (RCT), statistical significance for sertraline compared to control (pilot study), and showing significant improvement before and after treatment (open-label trial) for nefazodone. Thirteen of the 17 studies included measures of morbidity and mortality. Although early analyses have pointed to an association of antidepressant use and mortality particularly with fluoxetine, the reviewed studies showed no increase in mortality for antidepressants, and secondary analyses showed improved mortality in patients who achieved remission of depressive symptoms.

Conclusion: Out of the various antidepressants studied, which included sertraline, paroxetine, escitalopram, citalopram, bupropion, nefazodone, and nortriptyline, selective serotonin reuptake inhibitors seem to be a safe treatment option for patients with depression and HF. However, due to the variety of study designs as well as the mixed results for each antidepressant, more information for reducing depression severity, morbidity, and mortality and improving quality of life in patients with HF should be examined using robust large sample RCTs.

Keywords: antidepressants, depression, heart failure, interventions, treatment.

Citation

Hedrick R, Korouri S, Tadros E, Darwish T, Cortez V, Triay D, Pasini M, Olanisa L, Herrera N, Hanna S, Kimchi A, Hamilton M, Danovitch I, IsHak WW. The impact of antidepressants on depressive symptom severity, quality of life, morbidity, and mortality in heart failure: a systematic review. Drugs in Context 2020; 9: 2020-5-4. DOI: 10.7573/dic.2020-5-4

Introduction

Depression is the leading cause of disability affecting 350 million people worldwide.[1,2] Heart Failure (HF) affects 26 million adults worldwide and 5.7 million adults in the USA.[3] Robust studies showed that the prevalence of depression in HF is nearly 48%.[4] Depression and HF have negative bidirectional effects leading to worsening physical and functioning impairments.[5] Patients with HF experiencing depressive symptoms are more likely to have poor self-care and treatment non-adherence.[6] These patients also experience lower health-related quality of life (HRQoL),[7] with the largest predictor of poor HRQoL being severity of depression rather than severity of HF.[8] Moreover, compared to people without depression, patients

with HF and with depression are more likely to have frequent ambulatory care and emergency department visits,[6,9] nearly four times the risk of hospital admissions,[10] a lower threshold for adverse cardiac events,[11] longer hospital stays,[12] and more readmissions.[6] Research studies have shown that depression is an independent risk factor for both cardiac-related and all-cause mortality in HF patients.[9,12,13]

Antidepressant medications are the main intervention for depression in patients with HF. In addition to their potential impact on depression and anxiety, the serotonergic antidepressants, in particular, have other pharmacological properties that may potentially benefit HF patients, including anti-inflammatory action, inhibition of platelet aggregation, and promotion of endothelial stabilization.[13] However, it is not clear which antidepressants are specifically used in HF, and their efficacy has been questioned in light of placebo-controlled trials.[14–16] Furthermore, there remains conflicting evidence whether the use of antidepressants leads to improved or worsened health outcomes and mortality in HF.[13]

This systematic review aims at examining the impact of antidepressant medications on depression in HF by addressing the following questions:

(1) What is the impact of antidepressant medications on depressive symptom severity?
(2) What is the impact of antidepressant medications on HRQoL?
(3) What is the impact of antidepressant medications on morbidity and mortality?

Methods

Search strategy

We performed this systematic review in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[17] A systematic literature search was conducted on articles in the PubMed and PsycINFO databases that were published within the past 50 years, from December 1969 to December 2019, after setting exclusion and inclusion criteria. The keywords used for the search were 'heart failure' AND 'antidepressant*'. We also conducted a manual search of reference lists for identified papers and previous reviews of HF and depression. The current study was not registered with PROSPERO.

Study selection criteria and methodology

The following inclusion criteria were used: (a) articles published in English or had a published English translation; (b) articles published in a peer-reviewed journal (with all articles being published in PubMed); (c) original studies in human adults (aged ≥18, no reviews, no animal studies); (d) original studies of any design that focused on treating depression in HF; and (e) 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 23 studies that were able to meet the specific selection criteria. We also examined the quality of each study by identifying its strengths and limitations using the criteria adapted from Lohr and Carey by the Agency for Healthcare Research and Quality.[18,19] We assessed sample size, patient selection methods, bias, study groups comparison, blinding, intervention details, outcome measures, and statistical analysis plans.

Search results

Our search strategy identified 251 articles, the abstracts of which were reviewed. Studies that did not meet the selection criteria were excluded, resulting in 39 studies. Two authors independently conducted a focused analysis using the full-text articles. The two authors then reached a consensus on which studies to include in this review, which yielded 16 studies. Seven additional studies were identified through other sources including article references leading to a total of 23 studies. The quality check method[18,19] led to the exclusion of 6 studies[20–25] due to inadequate measurement of depression. This process led to a final selection of 17 studies. The search method is displayed in a flow diagram in Figure 1.

A summary of the quality check of each of the remaining 17 studies included for review may be found in Table 1.

Data extraction and yield

Key findings were derived from the full-text and table of the selected 17 studies. A summary of the study designs and findings are detailed in Table 2.

Results

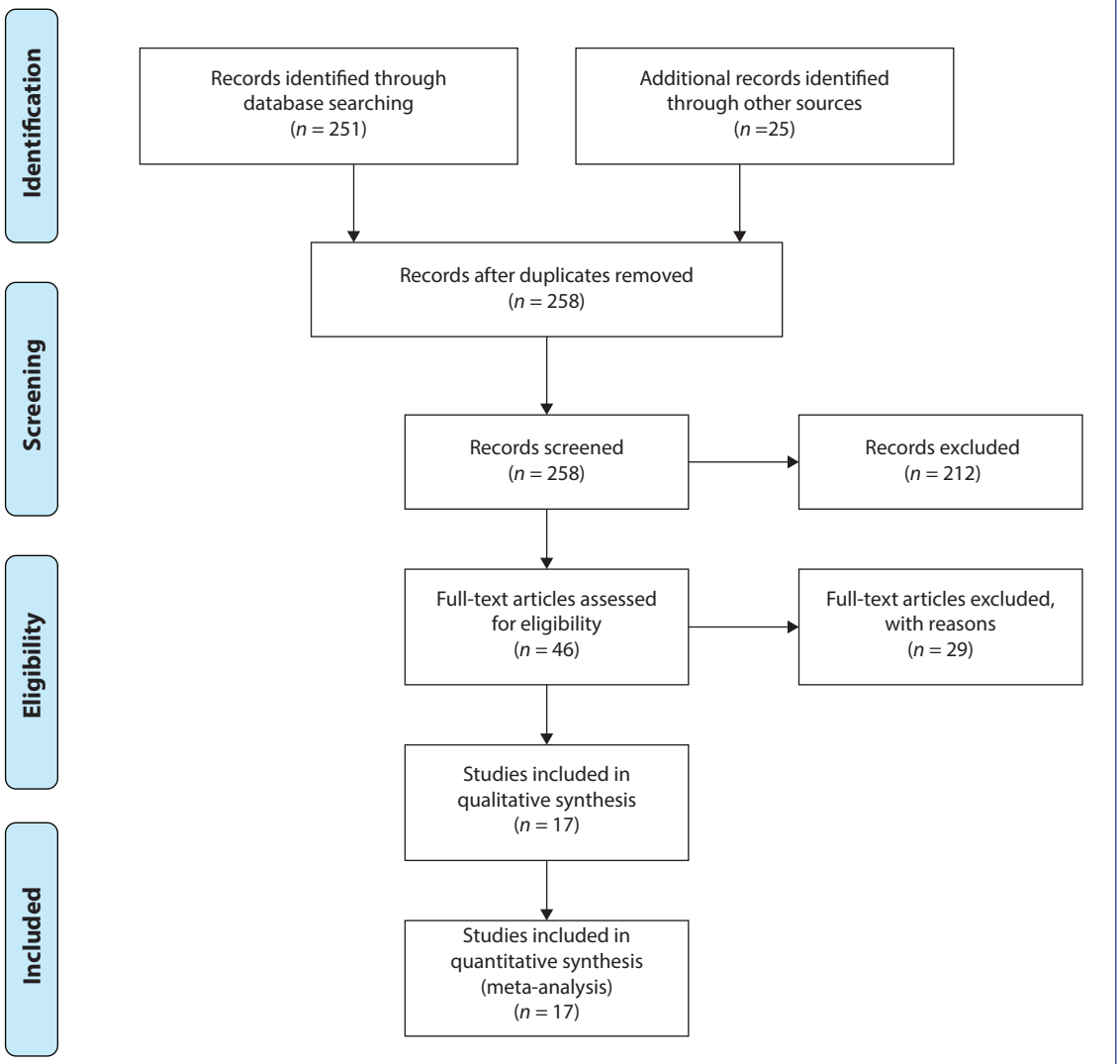
Overview

The findings from the 17 reviewed studies are displayed in Table 2. The study designs included 6 randomized controlled trials (RCTs), 6 prospective studies, 2 cross-sectional studies, 2 pilot studies, 1 open-label study, and 1 secondary analysis study (number is greater than 17 as one article included data from 2 different types of studies – one of them being a RCT and the other a pilot study). Antidepressant studies included 3 sertraline studies, 2 studies on escitalopram and nortriptyline, 1 study for each of the following medications: bupropion, citalopram, fluoxetine, nefazodone, and paroxetine, in addition to 6 studies on a variety of antidepressants. Study samples sizes ranged from 21 to 1017 patients with duration of treatment/follow-up spanning from 3 weeks to 5 years.

What is the impact of antidepressant medications on depressive symptom severity?

Ten of the 17 final studies had outcomes that included the impact of antidepressants on depressive symptom severity.

Figure 1. PRISMA flow diagram.[17]



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The study designs included five RCTs, two prospective studies, one cross-sectional study, one pilot study, and one open-label study. Pharmacological agents and the range of doses that were used in studies assessing depressive symptom severity include sertraline (50 mg),[26,27] sertraline (50–200 mg),[28] citalopram (20-40 mg),[15] nefazodone (50–600 mg),[29] paroxetine controlled release (12.5–25 mg),[30] escitalopram (10-20 mg),[16,31] nortriptyline titrated to therapeutic level of 50 to 150 ng/mL,[32] and one study that used multiple classes of antidepressants (selective serotonin reuptake inhibitors [SSRIs], tricyclic antidepressants [TCAs], norepinephrine and dopamine reuptake inhibitors [NDRIs], serotonin and norepinephrine reuptake inhibitors [SNRIs]) of unknown dosage.[33]

All five RCTs were double-blind placebo-controlled studies. Three showed no difference in depressive severity between antidepressant and placebo, and two showed a significant difference. One small study (n=27) on 8-week citalopram treatment found no significant difference in depression severity across three depression instruments between the citalopram and placebo groups (all p>0.5), although both citalopram and placebo groups showed significant reductions in depressive symptoms on all three depression instruments. However, there was a trend toward significance on depression severity assessed on the Montgomery–Åsberg Depression Rating Scale (MADRS) (p=0.082), with the citalopram group showing a bigger reduction in MADRS.[15] O'Connor et al., who conducted a larger study (n=469) on 12-week sertraline treatment also found no difference compared to placebo in depression severity (p=0.89), although this study also demonstrated significant reductions in depressive symptoms in sertraline and placebo groups (p<0.001 for both).[28] A study on escitalopram treatment (n=372) for a maximum of 24 months found no difference in depression severity as compared to placebo

Table 1. Quality check for reviewed studies on antidepressants in heart failure.

Study	Quality check
Fraguas et al., 2009, Brazil[15]	Double-blind RCT, HAM-D, and MADRS measured pre and post intervention, significance levels reported, intention-to-treat analysis, scores reported with appropriate statistical analysis
O'Connor et al., 2010, United States[28]	Double-blind RCT, HAM-D measured at baseline and at 2-week intervals up to 12 weeks, scores reported with appropriate statistical analysis, intention-to-treat
Gottlieb et al., 2007 United States[4]	Double-blind RCT, BDI measured pre and post intervention, no early termination of treatment in either the paroxetine or placebo groups, scores reported with appropriate statistical analysis
Angermann et al., 2016, Germany[16]	Double-blind RCT, depression scales measured pre and post intervention, scores reported with appropriate statistical analysis, intention-to-treat, no patients lost to follow-up
Lekakis et al., 2010, Greece[26]	Double-blind RCT, depression scales, VCAM-1 levels, and ICAM-1 levels measured pre and post intervention, scores reported with appropriate statistical analysis
Diez-Quevedo et al., 2013, Spain[13]	Prospective correlational study with a large sample size, appropriate statistical analyses used and controlled for all confounding variables, confidence intervals reported, scores reported with appropriate statistical analysis
Tousoulis et al., 2008, Greece[38]	Observational correlational study with a large sample size, used cox regression model to adjust for age, gender, all other medications, cardiovascular risk factors, type of heart failure, individual characteristics of patient groups similar at baseline, scores reported with appropriate statistical analysis
O'Connor et al., 2008, United States[14]	Large sample prospective cohort study, depression status collected prospectively, scores reported with appropriate statistical analysis (multivariate analysis of cox proportional model adjusting for multiple confounds, HR and CI reported)
Podolecki et al., 2017, Poland[31]	Large sample prospective non-randomized interventional study, depression scales measured prospectively, scores reported with appropriate statistical analysis
Roose et al., 1991, United States[35]	Within-subjects nature of study eliminates confounds and reduces need for large sample size, all cardiovascular outcomes measured pre and post intervention, scores reported with appropriate statistical analysis
Roose et al., 1986, United States[32]	Within-subjects nature of study eliminates confounds and reduces need for large sample size, depression rating and cardiovascular outcomes measured pre and post intervention, scores reported with appropriate statistical analysis
Jimenez et al., 2012, United States[33]	Correlational cross-sectional study, appropriate statistical analysis used, multivariate linear regression used to analyze BDI data adjusting for age, sex, LVEF, and NYHA functional class
Tousoulis et al., 2008, Greece[38]	Scores reported with appropriate statistical analysis, analysis adjusted for all potential confounders
Michalakeas et. al., 2011, Greece[27]	BDI scores measured pre- and post-intervention, left ventricular ejection fraction measured pre- and post-intervention, no significant differences between the two groups at baseline, scores reported with appropriate statistical analysis
Lespérance et al., 2003, Canada	Within-subjects design, all three depression instruments measured pre- and post-intervention, scores reported with appropriate statistical analysis
Chung et al., 2013, United States[37]	Used data from 3 previous studies in the HF quality-of-life registry (one longitudinal study, one associational study, another study of unspecified design). The primary outcome variable in this study was collected in the previous studies by 3 co-authors each blinded to the baseline assessments, scores reported with appropriate statistical analysis
Roose et al., 1998, United States[34]	3:1 randomization to fluoxetine: nortriptyline, justifies small sample size since compared randomized fluoxetine patients to a previous study with a comparable group of patients randomized to nortriptyline. Previous nortriptyline studies were done by the same research group and used the same equipment, exclusion and inclusion criteria, methods, and criteria for protocol discontinuation. Total fluoxetine group (27 patients) and total nortriptyline group (60 patients) were comparable on cardiovascular parameters at baseline, all cardiac tests done at baseline and at each follow-up point, scores reported with appropriate statistical analysis

BDI, Beck Depression Inventory; CI, confidence interval; HAM-D, Hamilton Depression Rating Scale; HR, hazard ratio; ICAM-1, intercellular adhesion molecule 1; LVEF, left ventricular ejection fraction; MADRS, Montgomery–Asberg Depression Rating Scale; NYHA, New York Heart Association; RCT, randomized controlled trial; VCAM-1, vascular cell adhesion molecule 1.

Hedrick R, Korouri S, Tadros E, Darwish T, et al. Drugs in Context 2020; 9: 2020-5-4. DOI: 10.7573/dic.2020-5-4
ISSN: 1740-4398

Table 2. Reviewed studies on antidepressants in depression and heart failure.

Author, year, location	Population and Setting	Sample size	Antidepressant medication/ category	Type of study	Intervention / study group 1	Comparator/ study group 2	Duration of treatment/ follow-up	Depression instrument used	Outcome (depression)	Depression primary outcome? (if not, what is)	Statistical significance
Fraguas et al., 2009, Brazil.[15]	Patients in the Geriatric Cardiology Outpatient Clinic of the University of Sao Paulo with LVEF ≤ 50% and HAM-D-31 ≥ 18.	37	Citalopram	Double-blind placebo RCT	Citalopram, 20 mg/day and increased to 40 mg/day after 3 weeks, if treatment was tolerated	Placebo	8 weeks	HAM-D-17, HAM-D-31, and MADRS	Both citalopram and placebo groups showed reductions in depressive symptoms on all 3 depression instruments	Depression was primary outcome	No significant difference in depressive symptoms across all three instruments (**all *p*-values >0.5**) between the citalopram and placebo groups
O'Connor et al., 2010, United States[28]	Patients (NYHA II-IV) with left ventricular ejection fraction ≤ 45% and MDD recruited from 3 centers in the United States	469	Sertraline	Double-blind placebo RCT	Sertraline, 50–200 mg	Placebo	12 weeks	HAM-D	Reduction of HAM-D total score for sertraline group was statistically significant, but difference between intervention group and placebo group was not	Primary outcomes were changed across time in depression severity and composite cardiovascular status	HAM-D was significantly decreased from baseline to 12 weeks in both sertraline and placebo groups (*p*-value<0.001), while the difference between both groups at 12-weeks was not significant (**p-value=0.089**). No significant difference was reported between groups in all composite CVS status (All-cause mortality, CVS death, Non-fatal CVS events, HF hospitalization, NYHA functional Class)
Gottlieb et al., 2007 United States[30]	Patients with chronic stabilized heart failure and depression (BDI ≥ 10) were enrolled from University of Maryland Heart Failure Program and the Heart Failure Clinic of the Baltimore VA Medical Center	28	Paroxetine CR	Double-blind placebo RCT	Paroxetine, 12.5 mg/day and then increased to 25 mg/day after 2 weeks	Placebo	12 weeks	BDI	Significantly lower levels of depression on BDI in paroxetine-treated patients compared to placebo-treated patients throughout the intervention. Paroxetine CR also resulted in significantly more remission of depression compared to placebo	Depression and quality of life were the primary outcomes (quality of life assessed by SF-36 and MLWHFQ).	Significantly lower depression scores throughout weeks 4, 8, and 12 in the paroxetine group (**p=0.024),** in paroxetine compared to placebo group, greater improvements observed in SF-36 social function (**p=0.001**), mental health (**p=0.010**), and emotional function (**p=0.029**). Intervention group: 69.2% remission of depression as defined by a BDI<10 *versus* 23.1% for placebo group. Between group difference significance **(p=0.018)**

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Table 2. (Continued)

Author, year, location	Population and Setting	Sample size	Antidepressant medication/ category	Type of study	Intervention / study group 1	Comparator/ study group 2	Duration of treatment/ follow-up	Depression instrument used	Outcome (depression)	Depression primary outcome? (if not, what is)	Statistical significance
Angermann et al., 2016, Germany[16]	Patients with depression and HF (NYHA II-IV) with LVEF ≤ 45% recruited from heart failure outpatient clinics in Germany.	372	Escitalopram	Double-blind placebo RCT	Escitalopram, 10–20 mg, once daily	Placebo	24 months (Median 18.4 months participation in escitalopram and median 18.7 months participation in placebo)	PHQ9 and MADRS	Differences between groups not statistically significant.	Depression severity measure with MADRS at 12 weeks, time to first event of a composite all-cause mortality or hospitalization score, health-related quality of life assessed by KCCQ	Mean MADRS sum score was significantly decreased from baseline to week-12 in both Escitalopram and placebo groups, while no significant difference noticed between both groups. No significant difference noted at the end of 12 months regarding KCCQ scores except for KCCQ symptoms scale, which was significantly lower in treatment patients **(*p*=0.01).** No statistically significant difference reported between both groups regarding hospitalization or all-cause mortality events nor safety parameters or serious adverse event rates expect for worsening depression, which occurred more often in patients in the placebo group (11%) *versus* treatment group (5%), ***p*-value=0.03**
Lekakis et al., 2010, Greece[26]	Patients with depression (Zung Self-rating Depression Scale Score > 50) with HF (NYHA II) and LVEF ≤ 40%	25	Sertraline	Double-blind placebo RCT	Sertraline, 50 mg, once daily	Placebo	3 months	ZungSDS	Depression symptoms were substantially reduced in sertraline group but not in placebo group at 3 months	Depression one of the primary outcomes, as well as plasma levels of monocyte adhesion molecules, VCAM-1 and ICAM-1	After 3 months, significant reduction in Zung SDS, VCAM-1, and ICAM-1 was noted to be greater in the Sertraline group compared to the placebo group with ***p*-values<0.01, 0.04 and 0.028,** respectively

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Author, year, location	Population and Setting	Sample size	Antidepressant medication/ category	Type of study	Intervention / study group 1	Comparator/ study group 2	Duration of treatment/ follow-up	Depression instrument used	Outcome (depression)	Depression primary outcome? (if not, what is)	Statistical significance
Diez-Quevedo et al., 2013, Spain[13]	Patients diagnosed with HF (NYHA I-IV) according to the European Society of Cardiology Criteria admitted to a specialized HF unit of a University Hospital in Barcelona	1017	SSRIs, SNRIs, mirtazapine, TCA	Prospective cohort study	Patients taking SSRIs, SNRIs, mirtazapine, and TCA	Unclear	Up to 23 months with a median 5.4-year follow-up	GDS-4	Prescription of antidepressants was associated with presence of depressive symptoms	Mortality (all-cause and cardiovascular) was the primary outcome	Use of antidepressants (SSRIs and SNRIs) was not independently associated with any type of mortality (***p*>0.05**), fluoxetine prescription was associated with increased all-cause mortality (**HR: 1.55, 95% CI: 1.10–2.19; *p*=0.01**), specifically increased cardiovascular mortality (**HR: 1.83, 95% CI: 1.21–2.76; *p*=0.004**), escitalopram prescription associated with lower all-cause mortality risk (**HR: 0.49, 95% CI: 0.31–0.79; *p*=0.003**), and specifically because of lower cardiovascular mortality (**HR: 0.41, 95% CI: 0.21–0.79; *p*=0.008**)
Tousoulis et al., 2008, Greece[38]	Patients (NYHA IV) with left ventricular ejection fraction ≤ 40% recruited from a clinic in Greece	250	SSRIs, SNRIs, TCA	Prospective cohort study	SSRIs + beta-blocker	SNRIs/TCA + beta-blocker	18 months	DSS	Patients with depression and HF had lower quality of life, more anorexia and more stress compared to patients with HF without depression	Primary outcome was cardiovascular death	Among patients with depression and HF, those receiving SSRIs without beta-blockers had significantly worse 18-month survival compared to those receiving SSRIs with beta-blockers (**HR: 2.201, 95% CI: 1.255–3.860; *p*=0.006**). Those receiving SNRIs/TCA without beta-blockers had significantly increased 18-month survival than those receiving SNRIs/TCA with beta-blockers (**HR: 0.190, 95% CI: 0.044–0.814; *p*=0.025**)

(Continued)

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Tousoulis et al., 2008, Greece[38] (continued)											Any antidepressant + beta-blocker is associated with better 18-month survival than antidepressant alone (***p*=0.032**), no significant difference in 18-month survival for those not receiving any antidepressant medication (beta-blocker *versus* no beta-blocker) (***p*>0.05**)
O'Connor et al., 2008, United States[14]	Patients (NYHA II-IV) with LVEF 35% or more from the cardiology service at Duke University Medical Center	1005	SSRIs, TCAs, other	Prospective cohort study	Antidepressants or only SSRI use	No antidepressant use	Mean follow-up of 971 days (SD=730 days)	BDI	Depression (BDI ≥ 10) was associated with reduced survival in both univariate and multivariate models	Primary outcome was mortality; compared mortality of HF patients who were taking antidepressants *versus* those who were not taking antidepressants	Long-term mortality was primary outcome. After controlling for depression and other confounders, antidepressant use was not found to be associated with reduced survival (**HR: 1.19, 95% CI: 0.84–1.71; *p*=0.33**), SSRI use was not found to be associated with reduced survival (**HR: 1.06, 95% CI: 0.69–1.62; *p*=0.78**). Depression was associated with reduced survival (**HR: 1.39; 95% CI, 1.12–1.74; *p*=0.003** for both models). No interaction between depression and antidepressant use (**HR: 1.39, 95% CI: 0.65–1.78; *p*=0.77**) or between depression and SSRI use (**HR: 1.08, 95% CI: 0.65–1.78; *p*=0.31**)

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Podolecki et al., 2017, Poland[31]	HF patients with a first-time CRT-D (cardiac resynchronization pacemaker with a defibrillator) admitted to cardiology department in a Heart Disease center in Poland	285	Escitalopram	Prospective interventional study	Treatment group (patients with depression and who agreed to take escitalopram) 10 mg dose once daily, gradually increased to 20 mg/day	2 comparison groups: Observational Group (patients with depression but who did not agree to take antidepressants); Control Group (patients without depression)	Median follow-up: 29.3 months (range: 3.2–47.9)	BDI	Remission rates of depression after both 6 and 12-month follow-ups were higher in treated group *versus* the observational group	Depression remission one of the primary outcomes, MACE (major adverse cardiac events) was considered a composite of hospitalization for decompensated HF or all-cause mortality. MACE: lower LVEF, higher NYHA class, and more often depressive and burdened with atrial fibrillation	Depression Remission Rates after 6 months: **72.1%** in the treatment group, **22.4%** in the observational group (***p*<0.001**). Depression remission rates after 12 months: **75%** in the treatment group, **25.4%** in the observational group (***p*<0.001**). Patients in the treatment group who achieved remission had significantly improved clinical outcomes (as indexed by MACE) compared to untreated patients at long-term follow-up (***p*<0.05**)
Roose et al., 1991, United States[35]	Inpatients from the Affective Disorders Research Unit of the New York Psychiatric Institute who had a DSM-III major depressive disorder and one or more of the following: history of congestive heart failure and/ or enlarged heart (cardiac thoracic ratio > 0.5 in the frontal view, QRS interval > 0.10 seconds, or > 10 ventricular premature depolarizations per hour	36	Bupropion	Prospective within-subjects study	Bupropion, 150 mg/day, increased to 450 mg/day by day 7	Same patients at 3-week endpoint	3 weeks	DSM-III criteria	Did not assess	Primary outcomes were bupropion effects on cardiovascular functioning, as measured by pulse, heart rate, left ventricular ejection fraction, conduction disease (PR and QRS intervals), and number of premature ventricular depolarizations per hour	For patients with impaired LVEF, mean change in ejection fraction from baseline to follow-up period was 2% +/- 6% (***p*>0.05**). For patients with preexisting conduction disease, the mean change in the PR interval was 0.005 +/- 0.01 seconds (***p*=0.06**). Mean QRS interval change was 0.002 +/- 0.01 seconds (***p*>0.05**). For patients with premature ventricular depolarizations, bupropion resulted in an 82% decrease in the number of premature depolarizations (***p*<0.005**)

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Roose et al., 1991, United States[35] (continued)											For 34 of the 36 patients in the study, the mean 24-hour pulse rate increased after bupropion treatment, but this increase was not significant (mean change: 1.8 +/- 10.2 bpm, ***p*>0.05**). Bupropion significantly raised both systolic and diastolic supine blood pressure (systolic: 140 +/– 16 mm Hg to 145 +/– 20 mm Hg, ***p*<0.01**; diastolic: 76 +/– 7 mm Hg to 79 +/– mm Hg**, *p*<0.005**). However, neither of these changes was clinically significant. Orthostatic drop increased from 4 +/– 9 mm Hg to 7 +/– 12 mm Hg. Although this increase was statistically significant (***p*<0.02**) it did not reach clinical significance
Roose et al., 1986, United States[32]	Patients with depression (NYHA-IV) in an affective disorder unit with left ventricular impairment	21	Nortriptyline	Prospective within-subjects study	Nortriptyline patients were started at 1.4 mg/kg with 1/3 or dose given on day 1, dosage was raised to full amount within 5 days to reach therapeutic level of 50 to 150 ng/mL after 10 days	Same nortriptyline patients at follow-up	Not specified	HAM-D	Depressive symptoms improved after treatment	Primary outcomes were depression severity, ejection fraction, orthostatic hypotension, and blood pressure	Mean HAM-D score was 24.9 +/– 8.0 before treatment and after treatment significantly decreased to 11.5 +/– 9.7 (***p* <0.001**). Before treatment, mean ejection fraction was 33.5 +/– 12.3%, and was 32.3 +/– 12.5% after treatment (***p*>0.05)**

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Roose et al., 1986, United States[32] (continued)											Neither mean lying systolic blood pressure nor the mean standing systolic pressure changed significantly as a result of treatment (***p*>0.05**), although both did decrease (133 +/– 17 mm Hg to 132 +/1 mm Hg for lying systolic pressure, 130 +/– 15 mm Hg to 122 +/– 19 mm Hg for standing systolic pressure). Mean orthostatic drop was 3 mm Hg before treatment and 10 mm Hg while receiving nortriptyline, this difference was statistically significant (***p*<0.01**). Orthostatic hypotension developed in only one (5%) of 21 patients
Jimenez et al., 2012, United States[33]	Outpatients (NYHA I-IV) from UCSD HF program and VA San Diego Healthcare System Coronary Care Program	218	SSRIs, TCA, NDRIs, SNRIs	Cross-Sectional study	Self-reported antidepressant usage	Self-reported not using antidepressants	N/A, cross-sectional study	BDI-IA	Antidepressant usage was associated with higher BDI than non-antidepressant usage	Depression was the primary outcome	Antidepressant treatment group had significantly higher BDI (***M*=16.44**) than non-treatment group (***M*=8.69**) at baseline (***p*<.05**)
Tousoulis et al., 2008, Greece[38]	HF patients (NYHA IV) with LVEF ≤ 30% recruited from outpatient clinics	250	SSRIs, SNRIs, TCA	Cross-sectional study	HF patients with depression (154 total) (2 groups: SNRIs/TCA and SSRIs)	HF patients without depression (96 total)	None	DSS	Did not assess	Primary outcome was circulating levels of proinflammatory cytokines and acute phase response proteins (TNF-α, and CRP)	Patients treated with SNRIs/TCA had significantly lower levels of both TNF-α and CRP compared to patients treated with SSRIs (***p*<0.001**) as well as compared to patients who did not have depression (***p*<0.001**)

(Continued)

Table 2. (Continued)

Author, year, location	Population and Setting	Sample size	Antidepressant medication/ category	Type of study	Intervention / study group 1	Comparator/ study group 2	Duration of treatment/ follow-up	Depression instrument used	Outcome (depression)	Depression primary outcome? (if not, what is)	Statistical significance
Michalakeas et. al., 2011, Greece[27]	Hospitalized patients with CHF screened for depression (BDI > 10 and/or Zung SDS > 40)	52	Sertraline	Pilot Study	Sertraline, 50 mg, once daily for 3 months	Control Group: patients who refused to receive antidepressant treatment	3 months	BDI and Zung SDS	Sertraline group had a decrease in BDI score, control group had no change in BDI score, between-group changes were not significant	Primary outcomes were levels of markers of oxidative stress (e.g., MDA), depression severity and QOL measured by 6-minute walking distance	Significant improvement in BDI score pre–post intervention in the sertraline group (***p*=0.015**), no significant difference in control group (***p*>0.05**). Significant reduction in MDA levels in Sertraline group (**2.68 ± 0.97** *versus* **2.14 ± 0.79 µmol/L; *F*=4.657; *p*=0.037**) compared to no change in control group, and had an increase in 6-minute walking distance in Sertraline group (**291 ± 110** *versus* **361 ± 87 m; *p*=0.02**), compared to no difference in control (***p*=0.15**)
Lespérance et al., 2003, Canada[29]	Outpatient clinic patients and patients hospitalized in the Montreal Heart Institute, a tertiary care cardiology hospital. Patients had NYHA II or III, LVEF ≤ 40%, and score of 15 or more on the 17-item HAM-D	28	Nefazodone	Open-label trial	Nefazodone, 50 mg, daily, dosage increased to 100 mg after 4 days, then increased to 400 mg daily by the 4-week visit. Then gradually titrated to dosages up to 600 mg over 12 weeks if response was insufficient	Same subjects receiving nefazodone treatment at follow-up	12 weeks	17-Item HAM-D, BDI, CGI	Reduced depression scores post-intervention compared to pre-intervention across all 3 depression instruments	Primary outcomes were depression and quality of life	Nefazodone resulted in reduced HAM-D, BDI, CGI from pre to post-intervention (***p*<0.0001**). Nefazodone also improved quality of life measured by the Minnesota Living with Heart Failure Scale pre- to post-intervention (***p*=0.006**)

(Continued)

Table 2. (Continued)

Author, year, location	Population and Setting	Sample size	Antidepressant medication/ category	Type of study	Intervention / study group 1	Comparator/ study group 2	Duration of treatment/ follow-up	Depression instrument used	Outcome (depression)	Depression primary outcome? (if not, what is)	Statistical significance
Chung et al., 2013, United States[37]	HF Outpatients from a Kentucky Clinic who were in 3 prior studies conducted at the University of Kentucky. Data from these patients were taken from HF Quality-of-Life Registry, patients had not received any intervention and had data on depressive symptoms, antidepressant use, and hospitalization/ death outcomes	209	SSRIs, TCA, SNRIs, other	Secondary analysis study	Patients on antidepressant	Patients not on antidepressants	1-year follow-up period	PHQ-9	Patients with depression (PHQ-9 score > 9) were more likely to have severe functional decline (NYHA III or IV) compared to patients who did not have depression	Primary outcome was cardiac-event free survival, defined in this study as time to combined end point of hospital admission for cardiovascular reasons or all-cause death during the 1 year follow-up	Patients with depression had >2x the risk of cardiac hospitalization or death compared to patients who did not have depression (**HR: 2.401, 95% CI: 1.247–4.623; *p*=0.009**). There was no difference in event-free survival between patients (with and without depression) taking antidepressants and those not taking antidepressants (***p*=0.49**)
Roose et al., 1998, United States[34]	Patients with depression (HAM-D ≥ 16) with one or more of the following: LVEF ≤ 50%, ventricular arrhythmia defined as ≥ 10 ventricular premature depolarizations per hour, intraventricular conduction disease defined as QRS interval ≥ 0.10 seconds	27 fluoxetine patients (14 had HF), 60 nortriptyline patients (31 had HF)	Fluoxetine and Nortriptyline	Pilot study (5 fluoxetine patients) and open label randomized controlled study (22 fluoxetine patients and 7 nortriptyline patients), and data obtained from previous randomized nortriptyline studies (53 nortriptyline patients)	Fluoxetine, 20 mg/day, for the first 2 weeks, 40 mg/day during week 3, 60 mg/ day for 4 more weeks if the patient had not recovered by the end of week 3	Nortriptyline, calculated for 1 mg/kg of body weight, 1/3rd dose given on days 1 and 2, 2/3rd dose given on days 3 and 4, full dose on day 5. Dose was adjusted 1 week later, if needed to, reach plasma level of 50–150 ng/mL	2 and 7-week follow-up for fluoxetine treated patients and 3-week follow-up for nortriptyline patients	HAM-D	Did not assess depressive symptoms at follow-up	Main outcome was adverse cardiovascular effects of fluoxetine, (ejection fraction, ventricular premature depolarizations, QRS duration) and comparison of effects to those of nortriptyline	In patients with LVEF ≤ 50% at baseline, fluoxetine induced significant increase of 7% in ejection fraction at 2-week follow-up (***p*=0.05**). In patients with QRS interval ≥ 0.10 seconds at baseline, fluoxetine had no effect on QRS (***p*=0.93**) interval at 2 weeks. In patients with ≥ 10 ventricular premature depolarizations per hour at baseline, fluoxetine had no frequency effect (***p*=0.39**) at 2 weeks. Results at 7-week follow-up were similar

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Hedrick R, Korouri S, Tadros E, Darwish T, et al. Drugs in Context 2020; 9: 2020-5-4. DOI: 10.7573/dic.2020-5-4
ISSN: 1740-4398

Table 2. (Continued)

Author, year, location	Population and Setting	Sample size	Antidepressant medication/ category	Type of study	Intervention / study group 1	Comparator/ study group 2	Duration of treatment/ follow-up	Depression instrument used	Outcome (depression)	Depression primary outcome? (if not, what is)	Statistical significance
											In patients with LVEF ≤ 50% at baseline, nortriptyline induced significant 7% decrease in ejection fraction at 3-week follow-up (***p*=0.04**), In patients with QRS interval ≥ 0.10 seconds at baseline, nortriptyline had no significant effect on QRS interval (***p*=0.11**) at 3 weeks. In patients with ≥ 10 ventricular premature depolarizations per hour at baseline, nortriptyline induced a significant 47% decrease in frequency (***p*=0.01**) at 3 weeks. ANOVA comparison of fluoxetine and nortriptyline effects showed significant between-group differences in ejection fraction (***p*=0.01**) and ventricular premature depolarizations per hour (***p*=0.03**)

Note: statistically significant *p*-values are shown in bold.
ANOVA, analysis of variance; BDI, Beck Depression Inventory; CGI, Clinical Global Impression Scale; CI, confidence interval; CR, controlled release; CVD, cardiovascular disease; DSM, Diagnostic and Statistical Manual of Mental Disorders; DSS, Depression Severity Score; GDS, Geriatric Depression Scale; HAM-D, Hamilton Depression Rating Scale; HF, heart failure; ICD, International Classification of Diseases; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, Left Ventricular Ejection Fraction; MADRS, Montgomery-Asberg Depression Rating Scale; MDD, Major Depressive Disorder, MI, myocardial infarction; MLHFQ, Minnesota Living with Heart Failure Questionnaire; NYHA, New York Heart Association; PHQ, Patient Health Questionnaire; RCT, randomized controlled trial; SF-36, 36-Item Short Form; SHF, systolic heart failure; SSRIs, selective serotonin reuptake inhibitors; VA, Veteran's Administration; Zung SDS, Zung Self-Rating Depression Scale.

(p=0.26).[16] A small study (n=25) on sertraline treatment for 3 months found that compared to baseline, the reduction of Zung self-rating Depression Scale Score was greater after 3 months of sertraline treatment than after placebo [58 ± 6 *versus* 44±4 postsertraline (change=–24%) and 60 ± 5 *versus* 58 ± 8 post-placebo (change=–2%), F=20.1; p<0.01].[26] One study with a small sample size (n=27) on paroxetine controlled release found significantly lower depression scores compared to placebo at 4, 8, and 12-week treatment time points (p=0.024), and significantly more remission of depression compared to placebo (p=0.018).[30]

Of the two prospective studies, one focused on escitalopram and the other on nortriptyline. The escitalopram study (n=285) followed patients for a median of 29.3 months who either agreed to take escitalopram or did not agree to do so. Depression remission rates were significantly higher at 6-month and 12-month follow-up time points in the treatment *versus* no treatment group (p<0.001).[31] In a small study (n=21) by Roose et al. on one group of nortriptyline patients followed prospectively, depression severity decreased significantly pre- to post-intervention (p<0.001).[32]

One cross-sectional study (n=218) analyzed how self-reported antidepressant usage was associated with depression severity as compared to no self-reported antidepressant usage. The results showed that those who used antidepressants had significantly higher depression scores compared to non-users (p<0.05)[33]; however, due to the cross-sectional design of this study we cannot ascertain whether antidepressant use is followed by increased depression severity or if increased depression severity is followed by antidepressant use.

One pilot study (n=52) by Michalakeas et al. compared a treatment group of patients, who agreed to take recommended sertraline, to a control group of patients, who did not agree to take recommended sertraline. The sertraline treatment group had a significant reduction in depressive symptoms (p=0.015), whereas the control group did not show a significant reduction at 3 months follow-up (p>0.05).[27]

One open-label trial (n=28) followed one group of patients receiving nefazodone for 12 weeks. Nefazodone treatment resulted in significantly decreased depression scores pre to post treatment across three depression instruments (p<0.0001).[29]

In summary, small RCT studies found paroxetine (p=0.024) and sertraline (p<0.01) showed significant reduction in depression scores.[30,26] However, other studies regarding sertraline showed mixed results.[28,27] Escitalopram showed no difference in severity but showed higher remission over time (p<0.001).[16] Citalopram showed no difference in severity but showed a trend toward reduction on MADRS (p=0.082).[15] Nortriptyline (p<0.001) and nefazodone (p<0.001) were also found to reduce depression scores.[32,29] Studies looking at the use of other antidepressants (SSRIs, TCA, NDRIs, SNRIs, buproprion, and fluoxetine) were not able to draw conclusions about causation in relation to depression severity.[33–35]

What is the impact of antidepressant medications on health-related quality of life?

Four of the seventeen final studies had quality of life (QoL) as an outcome measure. The study designs included two RCTs, one pilot study, and one open-label design. Pharmacological agents and the range of doses used in these studies include paroxetine controlled release (CR) (12.5–25 mg),[30] escitalopram (10–20 mg),[16] sertraline (50 mg),[27] and nefazodone (50–600 mg).[29]

Both RCTs were placebo-controlled studies. One study (n=28) compared paroxetine CR to placebo for 12 weeks and assessed QoL by the 36-item short form health survey (SF-36). The results showed that significantly greater improvements were observed in the paroxetine CR group on the SF-36 domains of social functioning (p<0.001), mental health (p=0.01), and emotional function (p=0.029).[30] A much larger trial (n=372) on escitalopram treatment found that quality-of-life measures assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ) showed no difference between the escitalopram and placebo groups (p=0.26), except for the KCCQ symptom scale, which was significantly lower in the treatment group (p=0.01).[16]

One pilot study (n=52) comparing a treatment group of patients, who agreed to take recommended sertraline, to a control group of patients, who did not agree to sertraline, examined the 6-minute walking distance as a measure of QoL. The study found that the sertraline treatment group had a statistically significant improvement in this parameter (p=0.02), while the control group experienced no difference (p=0.15).[27]

An open-label trial of nefazodone (n=28) assessed the same patients before and after treatment and assessed HRQoL with the MLHFQ. The results showed that QoL was significantly improved pre to post treatment in this group of patients (p=0.006).[29]

In short, paroxetine, sertraline, and nefazodone treatment led to significant improvements in QOL metrics (p<0.001, p=0.01, p=0.29), (p=0.02), (p=0.006), respectively.[30,27,29] Escitalopram showed no significant difference except in the KCCQ Symptom Domain in an RCT (p=0.01).[16]

What is the impact of antidepressant medications on morbidity and mortality?

Thirteen out of the 17 final studies included measures of morbidity and mortality. The study designs included three RCTs, six prospective studies, one pilot study, one cross-sectional study, a secondary analysis study, and one study which combined data from a pilot study, an RCT, and prior

studies by the same author. Pharmacological agents and the range of doses used in these studies include a wide variety of antidepressants and dosage ranges.

Two pilot studies were assessed that focused on morbidity. The first was the study by Michalakeas et al. described above. The study found no significant changes in ejection fraction either for the sertraline group pre to post intervention ($p>0.05$) or for the control group pre to post intervention ($p>0.05$).[27] The second study combined results from a pilot study, a, RCT, and data from previous studies by the same author. Roose et al. compared adverse cardiovascular measures between patients given fluoxetine ($n=27$) at daily dosages between 20 and 60 mg and patients given nortriptyline ($n=60$) at dosages titrated to reach plasma level of 50–150 ng/mL. They found that fluoxetine, at 2- and 7-week follow-up periods, led to a 7% increase in ejection fraction pre to post intervention ($p=0.05$) and had no effect on the number of premature ventricular depolarizations per hour ($p=0.39$). At a 3-week follow-up period, nortriptyline led to a 7% decrease in ejection fraction pre to post treatment ($p=0.04$) and led to a significant 47% decrease in the number of premature ventricular depolarizations per hour ($p=0.01$). Between-group differences in ejection fraction ($p=0.01$) and ventricular premature depolarizations per hour ($p=0.03$) were significant.[34]

Two of the prospective studies described earlier were also focused on morbidity. Podolecki et al. found that for those patients who achieved remission from depression in the escitalopram treatment group, they had significantly less major adverse cardiac events at long-term follow-up as compared to untreated patients ($p<0.05$).[31] The Roose et al. ($n=21$) study found that nortriptyline treatment (titrated to 50–150 ng/mL) did not significantly change ejection fraction pre to post treatment ($p>0.05$).[32] In another small study ($n=36$), Roose et al. followed a group of patients prospectively who received treatment with bupropion (150–450 mg). Bupropion was shown to increase supine blood pressure, had a low rate of orthostatic hypotension, and had no effect on pulse rate.[35] The results showed that for patients who had impaired left ventricular ejection fraction at baseline, no change in ejection fraction occurred at the 3-week follow-up ($p>0.05$). For patients with a preexisting conduction disease, they found no significant changes in the timing of the PR or the QRS interval ($p>0.05$ for both). However, for patients with premature ventricular depolarizations at baseline, treatment resulted in an 82% decrease in the number of premature depolarizations at 3-week follow-up ($p<0.005$).[35]

One cross-sectional study looked at pro-inflammatory markers tumor necrotic factor (TNF)-alpha and C-reactive protein (CRP) in 154 patients with depression and HF. Patients were split into 3 groups: those who had been taking SNRIs/TCA for at least the past 6 months, those who had been taking SSRIs for at least the past 6 months, and HF patients who did not have depression. The study showed that patients treated with SNRIs/TCA had significantly lower levels of both TNF-alpha and CRP compared to patients treated with SSRIs ($p<0.001$) and compared to patients who did not have depression ($p<0.001$).[36]

A secondary analysis study was conducted from the three previous studies in the HF QoL registry. A total of 209 patients either on or not on antidepressants were assessed for cardiac-event free survival, defined as time to a hospitalization due to cardiovascular reasons or all-cause death, during a 1-year period. The analysis found that there was no significant difference in event-free survival between patients who were taking antidepressants and those who were not ($p=0.49$).[37]

Another prospective study ($n=250$) showed a difference in mortality depending on type of antidepressant taken with beta-blockers. Specifically, Tousoulis et al. found that patients who took SSRIs alone had significantly decreased 18-month survival compared to patients who took SSRIs with beta-blockers (hazard ratio [HR]: 2.201, 95% confidence interval [CI]: 1.255–3.860; $p=0.006$). Conversely, patients who took SNRIs/TCA alone had significantly increased 18-month survival compared to patients who took SNRIs/TCA with beta-blockers (HR: 0.190, 95% CI: 0.044–0.814; $p=0.025$), thus suggesting that it is safer to take SSRIs rather than SNRIs/TCA in conjunction with beta-blockers for HF.[38] Another prospective study ($n=1005$) focused also on various antidepressant classes (SSRIs, TCA, and other) as well as only SSRIs and their impact on long-term mortality for HF. This study by O'Connor et al. found that, after controlling for adjustment for depression and other confounders, antidepressant use was not associated with reduced survival (HR: 1.19, 95% CI: 0.84–1.71; $p=0.33$), and, similarly, SSRI use alone was not associated with reduced survival (HR: 1.06; 95% CI: 0.69–1.62, $p=0.78$).[14]

A large study ($n=1107$) by Diez-Quevedo et al. followed patients over time (median follow-up of 5.4 years) and looked for associations between antidepressant usage and mortality risk. Their results showed that use of antidepressants, in general, is not associated with any type of mortality ($p>0.05$); however, fluoxetine prescriptions, but not duration of fluoxetine treatment, were associated with increased all-cause mortality (HR: 1.55, 95% CI: 1.10–2.19; $p=0.01$) and increased cardiovascular mortality (HR: 1.83, 95% CI: 1.21–2.76; $p=0.004$). They also found that escitalopram was associated with decreased all-cause mortality (HR: 0.49, 95% CI: 0.31–0.79; $p=0.003$) as well as decreased cardiovascular mortality (HR: 0.41, 95% CI: 0.21–0.79; $p=0.008$).[13]

Given the conflicting data, it is important to examine randomized placebo-controlled trials in order to clarify this issue. All three RCTs examining morbidity and mortality were placebo-controlled and were described earlier. The O'Connor et al. study found that sertraline treatment did

not significantly impact all-cause mortality, death for cardiovascular reasons, non-fatal cardiovascular events, HF hospitalization, or the New York Heart Association (NYHA) functional class, as compared to placebo (all *p*-values >0.05) in the SADHART-CHF trial.[28] However, a secondary analysis of remission in the same study by Jian et al. showed that patients in the remission group (44.3% of the sample) had significantly lower fatal and non-fatal cardiovascular events than those in the non-remission group (41.4% of the sample) (1.34 ± 1.86 *versus* 1.93 ± 2.71, adjusted p=0.01).[39] The Angermann et al. study found that the number of patients with a hospitalization or all-cause mortality event during treatment did not statistically differ between the escitalopram and placebo groups (p=0.92).[16] The Lekakis et al. study examined plasma levels of two monocyte adhesion molecules, vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1). Increased levels of both these molecules can have adverse cardiovascular effects, thus rendering them an index of morbidity. The study found greater reductions in both VCAM-1 and ICAM-1 in the sertraline-treated patients compared to placebo (p=0.04 and p=0.028, respectively).[26]

In summary, the results of these studies are varied and some are even contradictory. Escitalopram treatment was found to have no effect on all-cause mortality in one study and decreased in another (p=0.003), and yet another study found a decrease in cardiac events (p<0.05).[16,13,31] Treatment with buproprion showed significant reduction in premature depolarizations (p<0.005).[35] Inflammatory markers were less in patients taking SNRI/TCA than those using SSRIs (p<0.001) or no depression (p=0.001).[36] SNRI/TCA treatment showed a greater 18-month survival than the same treatment with beta-blockers, but SSRI treatment with beta-blockers showed a higher 18-month survival than without beta-blockers.[36] Many of the other studies showed no connection between the use of antidepressants and morbidity/mortality.[13,14,28]

Discussion

Summary of the review findings

In this systematic review, 17 studies were used to assess the impact of antidepressants on depressive symptom severity, HRQoL, and morbidity/mortality.

Sertraline was found to have mixed results in relation to depression severity. One placebo-controlled RCT showed a significant reduction in depression scores (p<0.01])[26], while another placebo-controlled RCT with sertraline failed to separate from placebo.[28] However, one pilot study showed that sertraline-compliant patients experienced a significant reduction in depressive symptoms (p=0.015), compared to no significant reduction in the control group (p>0.05).[27] Sertraline was found to not have a significant impact on all-cause mortality, death from cardiovascular reasons, non-fatal cardiovascular events, or NYHA functional class.[28]

Paroxetine CR was also found to significantly reduce depression symptom severity in a placebo-controlled RCT with a size of 28 participants (p=0.024).[30] An RCT study using the SF-36 to assess QOL showed that paroxetine treatment led to significant improvements in social functioning (p<0.001), mental health (p=0.01), and emotional function (p=0.029) compared to placebo.[30]

RCT studies on escitalopram showed no difference from the placebo group in depression severity[16]; however, it had significantly higher depression remission rates at 6- and 12-month follow-ups compared to no treatment (p<0.001). When QOL was assessed using the KCCQ in an RCT, escitalopram showed no difference from the placebo group, except for the KCCQ Symptom Domain, which was significantly lower in the treatment group (p=0.01).[16] Escitalopram was found to have no significant impact on hospitalization or all-cause mortality compared to placebo.[16] Patients who achieved depression remission on escitalopram had significantly less major cardiac events at follow-up (p<0.05). Escitalopram was found to decrease all-cause (p=0.003) and cardiovascular (p=0.008) mortality.[13] A large RCT specifically designed with all-cause mortality as a primary outcome failed to show a significant improvement of escitalopram treatment compared to placebo.[16]

Citalopram treatment showed no statistically significant difference from placebo on depressive symptom severity but did show a trend toward a reduction in depression severity on the MADRS (p=0.082).[15]

Nortriptyline treatment did show a significant decrease in depression severity pre to post treatment (p<0.001).[32] Similarly, nefazodone significantly improved post-treatment depression scores in an open-label trial (p<0.001).[29] Nefazodone treatment also showed that QoL significantly improved when comparing pre to post treatment as assessed using the MLHFQ (p=0.006).[29]

A cross-sectional study looking at the use of several antidepressants (SSRIs, TCA, NDRIs, SNRIs) showed that those who used anti-depressants had higher depression scores; yet due to the cross-sectional nature of the study, it was not possible to draw any conclusions about causation.[33] Inflammatory markers CRP and TNF-alpha were lower in HF patients treated with SNRI/TCA than HF patients treated with SSRIs (p<0.001) and patients with no depression and HF (p=0.001).[36] Treatment with SSRIs alone showed decreased 18-month survival compared to SSRIs with beta-blockers. Interestingly, SNRI/TCA treatment showed an increase in 18-month survival compared to the same treatment with beta-blockers.[36]

The bupropion and fluoxetine trials were focused on impact on ejection fraction and conduction and did not unfortunately examine the impact on depressive symptoms severity.[34,35] In another study conducted, fluoxetine prescriptions were found to show an increase in all-cause (p=0.01) and cardiovascular (p=0.004) mortality.[13]

Three other studies conducted looked to see if there was any connection between antidepressant use and mortality. All three studies showed no significant association between antidepressant usage and mortality, event-free survival, or reduced survival.[13,14,37]

Interpretation of the review findings and comparing this review findings to previous reviews

Through the analysis of the 17 studies able to meet the specific selection criteria and pass the quality checks of this review, it can be interpreted that the impact of antidepressants on depressive symptom severity, QoL, morbidity, and mortality in patients with depression and HF is mixed. This is partly due to the heterogeneity of the studies analyzed, and thus a push for more rigorous RCTs to establish antidepressant efficacy is needed. Positive results on morbidity outcomes have been seen with non-SSRI antidepressants, such as bupropion[35] and nortriptyline[32]; however, unlike many of the SSRI studies, these results were not obtained in randomized control studies and thus it is difficult to interpret these types of antidepressants as more safe than the SSRIs.

Sertraline seems to have a positive effect on depression severity and QoL, with two studies showing decreased depression severity via improvement in the Beck Depression Inventory score[27] and the Zung Self-Rating Depression Scale.[26] One study, however, found no difference between sertraline and placebo in the Hamilton Depression Rating Scale score, and also found no difference in mortality, cardiovascular death, HF hospitalization, and NYHA functional class.[28] Sertraline also improves QoL via increases in 6-minute walking distance.[27] Thus, sertraline might be the SSRI treatment of choice for reducing depressive symptoms and improving QoL. With respect to QoL, however, the most impactful antidepressant was paroxetine CR, which improved SF-36 domains of mental health, social functioning, and emotional function, notwithstanding the small sample size of the study.[30]

The results of the current review can be compared to those of previous reviews. A recent meta-analysis showed that, in eight selected studies, antidepressants (SSRIs, TCAs, SNRIs) were associated with mortality, and with a relatively weaker but still notable risk of cardiovascular death.[40] When analyzed separately, however, the use of SSRIs, TCAs, or SNRIs was not associated with an increased rate of cardiovascular death.[40] This meta-analysis focused on the impact of antidepressants on patients with HF, and not necessarily on patients who also had depression. Thus, our findings add to the literature by looking specifically at the impact of antidepressants in patients with depression and HF as well as outcomes of depressive symptoms, QoL, and morbidity, which, to our knowledge, have not been looked at simultaneously in this specific patient population in previous reviews and meta-analyses. A review by Rajeswaran et al. looked at five studies and found that antidepressants are not associated with increased mortality rate.[41] A review by Parissis et al. focused solely on studies that looked at sertraline, and, similar to our findings, found the antidepressant sertraline to benefit QoL for cardiac patients but stated that there needs to be more evidence for sertraline's effect on morbidity and mortality.[42] Other reviews establish SSRIs as the safest treatment option for patients with depression and HF,[43,44] and this statement is consistent with our findings as well. Large study, randomized comparisons of SSRIs with antidepressants in other classes should be conducted to further define their safety in cardiac morbidity and mortality and to further identify the most efficacious treatments for reducing depressive symptom severity and improving QoL in this patient population.

Although the following five studies were not included in the systematic review because they did not contain a particular depression measure, they are worth discussing because of their relevance to the mortality data. Bangalore et al. conducted a large retrospective cohort study (n=1568) comparing patients receiving adequate antidepressant treatment (fluoxetine-equivalent dose of ≥20 mg/day for non-elderly or >10 mg/day for elderly, and >80% of days are covered by antidepressant use) and those receiving inadequate antidepressant treatment for 3 months.[20] The results showed that patients receiving inadequate antidepressant treatment experienced significantly higher risk of adverse cardiovascular disease events (HR: 1.20, 95% CI: 1.04–1.39; p=0.02) relative to patients who received adequate antidepressant treatment; as well as higher risks of myocardial infarction (HR: 1.37, 95% CI: 0.80–2.33; p=0.25) and congestive HF (HR: 1.14, 95% CI: 0.91–1.42; p=0.25), although neither of these increases reached statistical significance.[20] Brouwers et al. assessed antidepressant use and risk for mortality in 121,252 HF patients with or without a diagnosis of clinical depression. The results showed that antidepressant use in patients with HF is associated with an increased risk for all-cause and cardiovascular mortality, irrespective of having clinical depression. Analyses of individual antidepressants showed that prescriptions of citalopram (most commonly prescribed antidepressant in this sample), escitalopram, venlafaxine, and mirtazapine at baseline were associated with increased all-cause and cardiovascular mortality risk, whereas fluoxetine, sertraline, nortriptyline, amitriptyline, and duloxetine were only significantly associated with increased all-cause mortality.[21] Although they were among the least commonly prescribed medications, paroxetine and imipramine were not significantly associated with mortality.[21] Analyses by Veien et al. suggested that pharmacologically treated depression is associated with a 49% increased mortality risk, and that patients taking SSRIs with beta-blockers had increased risk for all-cause mortality (p<0.0001) and cardiovascular mortality (p<0.0001).[24] However, these high-risk patients received lower doses of beta-blockers

than patients with no antidepressant therapy, which might explain the increased mortality risk.[24] Furthermore, one retrospective cohort study looked at 99,335 patients in the Danish Civil Registration System who had HF and were taking a combination of TCA and beta-blocker or SSRI and beta-blocker. The results showed that patients who had taken SSRIs with beta-blockers showed increased risk for all-cause mortality (HR: 1.36, 95% CI: 1.29–1.44; $p<0.0001$) and increased risk of cardiovascular mortality (HR: 1.30, 95% CI: 1.23–1.36; $p<0.0001$). Patients who had taken TCA with beta-blockers also showed increased risk (but a lower risk than was shown with SSRIs and beta-blockers) of all-cause mortality (HR: 1.33, 95% CI: 1.18–1.51; $p<0.0001$) and cardiovascular mortality (HR: 1.10, 95% CI: 1.05–1.15; $p=0.0006$).[23] However, a study by Faris et al. ($n=396$) found that self-reported use of antidepressants did not significantly affect long-term (48 +/- 35 months) mortality as compared to patients who did not report use of antidepressants ($p=0.16$).[22]

Strengths and limitations

The strengths of this review lie in its analysis of all studies published in the last 50 years including RCTs, not only focusing on depressive symptoms severity but also on the QoL, morbidity, and mortality. The limitations of this paper include a substantial heterogeneity in study designs, sample sizes, and measurement instruments used in patients with depression and HF. Moreover, the reviewed studies did not adequately detail participants' severity of HF as well as comorbid conditions, which could have significant impact on QoL, morbidity, and mortality, or limit the safe/effective use of antidepressant medications. The inconclusive evidence in downstream indicators, such as morbidity and mortality, remains a significant issue, prompting the need to design and conduct large placebo-controlled randomized trials that should include the antidepressants with the most favorable profile of efficacy and safety for the treatment of depression in patients with HF.

Conclusions and future directions

The purpose of this systematic review is to understand the impact of antidepressants on patients with HF. The American Heart Association recommends screening for depression, yet there are no official guidelines on depressive symptom management in HF and there is a lack of consensus on how to best manage them. It is well understood that depression is an independent risk factor for worse outcomes in HF, [5] and that undertreated depression in HF is associated with higher morbidity and mortality.[20] Yet there is conflicting evidence on the efficacy and safety of antidepressants in patients with depression and HF. Out of the various antidepressants studied, which included sertraline, paroxetine, escitalopram, citalopram, bupropion, nefazodone, and nortriptyline, SSRIs seem to be a safe treatment option for patients with depression and HF.

Despite the small sample studies, sertraline and paroxetine CR showed favorable efficacy of, safety, efficacy, and likelihood of improving QoL. Although early analyses have pointed to an association of antidepressant use and mortality [21,23] particularly with fluoxetine, our systematic review generally found no increase in mortality for antidepressants and secondary analyses showed improved mortality in patients who achieved remission of depressive symptoms. However, due to the variety of study designs, as well as mixed results for each antidepressant, more information for reducing depression severity, morbidity, and mortality and improving QoL in patients with HF should be examined using robust large-sample RCTs.

Research is needed into ways of simultaneously maximizing the safety and efficacy of antidepressant medications in patients with HF, tailoring treatment to depression severity and patient preference, and improving adherence to both depression and HF treatments. More research is warranted on the potential benefits and hazards of coadministration of antidepressants with these other medications utilized in patients with HF. Secondary analyses have pointed to the fact that patients who achieved remission had significantly lower fatal and non-fatal cardiovascular events. Further research is needed with remission from depression as the primary outcome.[39]

In terms of implementation, research has shown that patients respond better to antidepressants as evidenced by lower depression severity, less functional impairment, and greater HRQoL, when patients with depression are treated using the Collaborative Care model (CCM).[45–47] Although CCM has been successfully implemented among inpatients with cardiac disease and depression,[48,49] more research is needed to compare CCM to antidepressant administration as usual in cardiac patients.

An important dimension in the treatment of depression in HF is psychotherapy, such as cognitive behavioral therapy, which has shown efficacy for depression in HF.[50] Behavioral activation psychotherapy is a patient-centered and personalized psychotherapy treatment that is evidence-based as shown in more than 25 randomized clinical trials and has been established as a feasible and effective treatment for depression with effects comparable to cognitive behavioral therapy and antidepressant medication with positive impact on cardiac patients and caregivers.[51–53] There are no trials comparing psychotherapy to antidepressants or to their combination for patients with depression and HF.

Further research with robust large–sample, double–blind, placebo-controlled randomized trials comparing antidepressants as well as psychotherapy and their impact on depressive symptoms, QoL, morbidity, and mortality for patients with HF would allow for a clear analysis and recommendations of their effects and more importantly help match patients with the best treatment on which they would most likely experience remission in order to minimize morbidity and mortality.

Contributions: Rebecca Hedrick, Samuel Korouri, and Waguih William IsHak contributed to writing the main body of the text. All other authors contributed equally to editing and finalizing the manuscript. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosure and potential conflicts of interest: The authors declare that they have no conflicts of interest.
The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at: https://www.drugsincontext.com/wp-content/uploads/2020/06/dic.2020-5-4-COI.pdf

Acknowledgements: None.

Funding declaration: Research reported in this article was partially funded through a Patient-Centered Outcomes Research Institute® (PCORI®) Award (2017C2-7716 - IsHak). Disclaimer: The statements presented in this article are solely the responsibility of the authors and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute (PCORI), its Board of Governors or Methodology Committee.

Article URL: https://www.drugsincontext.com/the-impact-of-antidepressants-on-depressive-symptom-severity,-quality-of-life,-morbidity,-and-mortality-in-heart-failure:-a-systematic-review

Correspondence: Waguih William IsHak, Department of Psychiatry & Behavioral Neurosciences, Cedars-Sinai Medical Center, 8730 Alden Drive, Thalians, Suite E-132, Los Angeles, CA 90048, USA. Waguih.IsHak@cshs.org

Provenance: invited; externally peer reviewed.

Submitted: 8 May 2020; **Peer review comments to author:** 21 May 2020; **Revised manuscript received:** 5 June 2020; **Accepted:** 12 June 2020; **Publication date:** 29 July 2020.

Drugs in Context is published by BioExcel Publishing Ltd. Registered office: Plaza Building, Lee High Road, London, England, SE13 5PT.

BioExcel Publishing Limited is registered in England Number 10038393. VAT GB 252 7720 07.

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