Title	The effect of antidepressant medications in the management of heart failure on outcomes: mortality, cardiovascular function and depression - a systematic review
Author(s)	Rajeswaran, Thurkka; Plymen, Carla M.; Doherty, Anne M.
Publication Date	2017-11-26
Publication Information	Rajeswaran, Thurkka, Plymen, Carla M., & Doherty, Anne M. (2018). The effect of antidepressant medications in the management of heart failure on outcomes: mortality, cardiovascular function and depression – a systematic review. International Journal of Psychiatry in Clinical Practice, 22(3), 164-169. doi: 10.1080/13651501.2017.1401085
Publisher	Taylor & Francis
Link to publisher's version	https://doi.org/10.1080/13651501.2017.1401085
Item record	http://hdl.handle.net/10379/15410
DOI	http://dx.doi.org/10.1080/13651501.2017.1401085

The effect of antidepressant medications in the management of heart failure on outcomes: mortality, cardiovascular function and depression

- a systematic review

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Article data

Tables: 3

Figure: 1

Word length: 3597

Word length (abstract): 199

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Abstract

Objective: Depression is associated with increased morbidity, mortality and hospital readmission in patients with heart failure (HF).This systematic review aimed to compile studies examining whether the use of antidepressants could improve outcome in patients with HF and concomitant depression.

Methods: The electronic libraries Embase, OVID MEDLINE(R) and PsychInfo were used to search the following terms “heart failure” AND “anti-depressants”; “heart failure” AND “TCA” OR “SSRI” OR “SNRI”. The result of this database search was analysed to select papers that satisfied our inclusion criteria.

Results: Of the 180 papers found in the original database search, only 3 met the inclusion criteria. A further two papers were added from hand-searching through the references. Three of these papers are randomised controlled trials (RCT); the other two, cohort studies.

All studies show that antidepressants are well tolerated in this group. There was no significant difference in depressive symptoms between the test and placebo. The cardiac outcomes of patients with HF are not improved by the use of antidepressants relative to placebo.

Conclusions: Antidepressants are not associated with increased mortality rate as established in previous papers. However, there is inadequate evidence that the use of antidepressants effects significant improvement in depression or cardiac outcomes.

Keywords: Cardiac failure, depression, depressive episode, antidepressive agents, mortality.

Objective

Heart Failure (HF) is a clinical syndrome that results when the hearts' ability to function is impaired such that the demands of the physiological circulation are not met. In the UK, there is an overall age-adjusted incidence of about 1-2%. Although it is a treatable disease, mortality rates are about 30-40% at one year following diagnosis (Cowie et al, 2000). Symptoms of HF include exertional dysponea, orthopnoea, paroxysmal nocturnal dyspnoea and fatigue. The New York Heart Association (NYHA) classification is often used to describe the symptoms of HF and its limitation of exercise capacity, and is prognostic (table 1) (NYHA, 1994).

Depressive disorder is characterised by disturbance of mood, speech, energy and cognition. Symptoms should last for at least 2 weeks. The point prevalence of depressive illness is 5% in the community and is more common in the presence of physical disease, particularly if chronic, stigmatising or painful. Depressed individuals with another physical disorder may view themselves as more sick and disabled. This group also have an increased mortality rate (Faris et al, 2002).

Depression is common in patients with chronic HF, with a reported prevalence between 24 and >40% [3]. Depression has been associated with increased mortality in some studies (Freedland et al, 1991; Jiang et al, 2001; Jiang et al, 2002); one study states that risk of death tripled in those with clinical depression (Faris et al, 2002). However, this finding has not been consistent in all studies (Vaccarino et al, 2001). Depression may lead to increased rates of morbidity and rehospitalisation (Koenig, 1998). Faris et al conducted a retrospective cohort study of 396 patients and were one of the first groups to report increased rates of depression among congestive HF patients (Faris et al, 2002). They found that HF patients with clinical depression had significantly higher mortality (36% vs. 16%) and higher hospital readmission rate (87% vs. 74%) compared to non-depressed patients at 5 year follow up.

This review focuses on the impact of antidepressant medication in the outcomes of patients with HF. No past reviews focus specifically on HF: most take a wider approach looking at cardiovascular diseases (Zigmond and Snaith 1983). If depression is associated with poorer outcomes in cardiovascular disease, then treating this condition should reduce its negative prognostic impact.

Our objective was to assess the effects on antidepressant medication on the outcome of patients with HF, using three outcome measures: mortality, cardiovascular status and depression status. In addition to antidepressant treatment, studies included in this review also applied the appropriate HF therapy for all HF patients.

Methods

Criteria for considering studies in this review

The inclusion criteria for this review are that the study design must be a RCT ~~or~~, case-control study or cohort study. The sample population needed to be at least 18 years of age and all participants

must have been diagnosed with HF. Studies examining a more broad spectrum of cardiovascular diseases were excluded unless it was possible to separate out patients with HF. Additionally, at least the intervention group must have had depressive symptoms and must be on antidepressants (predominantly selective serotonin reuptake inhibitors (SSRI), serotonin and norepinephrine reuptake inhibitors (SNRI) or tricyclic antidepressants (TCA)). Studies that included participants with psychiatric co-morbidity in addition to depression were excluded.

To be included in this review, the study must include at least one of the following outcome factors: mortality, cardiovascular status and depression status. All studies looking into these factors were included, regardless of what measurement they used to do so.

Furthermore, the article must be published in the English language. Ongoing and unpublished studies were not included in this review.

Search method for identification of studies

The electronic libraries Embase (1974 to 2016), OVID MEDLINE(R) (1946 to November week 3 2016) and PsychInfo (1806 to December 2016) were used to search the following terms “heart failure” AND “anti-depressants”; “heart failure” AND “TCA” OR “SSRI” OR “SNRI”. We applied the restriction of being published in the English Language only.

This search produced 180 articles. After removing duplications, 139 articles remained. The two authors independently assessed the papers and excluded irrelevant papers based on the abstract (n=130). This left 9 papers which were reviewed and assessed according to the inclusion and exclusion criteria. In the case of papers where the full text was not accessible, the authors were contacted on at least two occasions.

At the end of the search, 3 relevant papers remained. Two further papers were found through hand-searching references listed in articles. Of the final 4 papers, 2 were RCTs and the other 2 were cohort studies. Figure 1 demonstrates as a flowchart the process followed by the authors in order to select relevant papers for this review.

Results

Data extraction

The details of the included studies are reported in Table 1. O’Connor et al described a prospective cohort study following 1005 patients aged 18 and above admitted to the Duke University Medical Centre with clinical HF and an ejection fraction of 35% or less (O’Connor et al, 2008). 30% of the total patient population had a BDI score of 10 or more and were considered. Of these patients, only 24.5% were taking antidepressants. The two groups of patients (those on antidepressants, and those not) were matched apart from the fact that patients taking antidepressants were more likely to be white and married. Their main outcome measure was mortality: they reported an increased mortality rate in those on antidepressants compared to those not in their univariate analysis (hazard ratio [HR], 1.32; 95% confidence interval [CI], 1.03-1.69; $P = 0.03$). Following adjustment for

depression on multivariate analysis, antidepressants were no longer associated with reduced survival (HR, 1.19; 95% CI, 0.84-1.71; *P* = 0.33). Furthermore, their multivariate analysis examining the association of survival with the use antidepressants, with adjustments for variables associated with antidepressant use and/or mortality, found that anti-depressants were not associated with poor survival. This provides evidence against earlier papers that argued that antidepressants are associated with poorer prognosis in this group. One of the first papers to discuss this is Fosbol et al, in a cohort study over a time period of 1.9 years (Fosbol et al, 2009). This study did not satisfy all of our inclusion criteria including the fact that the sample population consisted of participants of age 10 and above. Further faults of the paper include: little details are given on cardiovascular confounding factors; we are told that patients were on numerous medication but we are not told why; we are not told of the depression level in patients; we are not told whether the medications were prescribed at a therapeutic dose. The authors state that this group of patients with both HF and depression are associated with poorer prognosis. However, the authors were unable to differentiate whether the use of antidepressants or depression itself was associated with increased mortality.

O'Connor et al then undertook an RCT with an initial sample size of 469. Their outcome measures were mortality, depression status in terms of the Hamilton Rating Scale for Depression: 31 item (HAM-D-31) and composite cardiovascular status in terms of various factors (NYHA, left ventricular ejection fraction, and cardiovascular event) (O'Connor et al, 2010). All patients had depression and scored similarly at entry into the study in terms of depression score. 234 participants were randomised to sertraline. Both the test and the placebo group did exhibit a significant reduction in the HDRS total score. In the sertraline the composite cardiovascular status worsened in 29.9%, improved in 40.6%, remained unchanged in 29.5%. In the placebo group, 31.1% worsened, 43.8% improved, and 25.1% remained unchanged. But, they found no statistically significant difference between the test and the placebo in all three outcome measures. In their long term follow-up phase (sertraline group, 788±480 days and placebo group, 808±506 days), they found no difference in the mortality rate between the two groups. In their study plan they state that 80% power is needed in order to detect true differences at the end of the 12 week treatment phase. This required a sample of 440. Although they enrolled 469, after a large number of drop outs, 290 participants remained. In an attempt to overcome the issue, they conducted two forms of analysis. The first was an intention-to-treat (allowed patients who were present at least one time point to be included and took away the issue of dealing with missing data) and second as per-protocol analysis (including just those who completed the study). The two analyses found the same result, but the final analysis did not mirror that set by their protocol.

Fraguas et al conducted an RCT on 72 older (over 65 years) outpatients with ejection fraction greater than 50 and diagnosed with major depressive disorder by DSM-IV (Fraguas et al, 2009). Here the main outcome measures were depressive status and cardiovascular status. Depressive status was measured using three tools: HAM-D-17, HAM-D-31 and Montgomery-As berg Depression Rating Scale (MADRS). 37 patients, 19 randomised to the citalopram arm and 18 to the placebo arm took part in an 8 week double-blind treatment phase. No significant difference was seen between the test and placebo group on the HAM-D-17 and HAM-D-31 score. However, a statistically significant difference was seen in the MADRS scoring system. The authors raise the question if this scoring

system is more sensitive in this population. Cardiovascular status was assessed using a cardiopulmonary exercise test (looking into length of expiratory efforts, heart rate, blood pressure and oxygen consumption). They found no significant difference in the pre and post-treatment parameters in any of the groups. Overall, this paper shows that there is no difference in the cardiovascular status between the test and placebo group, and very little difference in depression status. The trial was interrupted due to high placebo rate. Yet the authors argue that a longer period may have been needed to observe the full effect of the antidepressant.

Tousoulis et al demonstrated that treatment with SNRI and/or TCA is associated with lower levels of TNF-alpha and CRP in patients with severe congestive HF and major depression, compared to those receiving SSRIs or no treatment (Tousoulis et al, 2009). They report that those on SNRI/TCA had a higher depressive score at the end of the study. However, they note that these antidepressants were given to patients with higher initial depressive scores compared to those placed on SSRI or non-treatment. Without adjustment for the initial depression scores, it is difficult to conclude that participants on SNRI/TCA had more severe depression at the end of the study. They state that there were initially 250 consecutive patients present in the outpatient clinic. Of this they prospectively investigated 154 patients, but did not explain why the remaining 96 were excluded. This paper used non-validated measures of both depression and cardiovascular status: they evaluated depressive symptoms using the chronic disease self-management programme (CDSMP), which is not a validated measure of depressive symptoms. Cardiovascular status was measured using left ventricular ejection fraction and inflammatory markers, rather than NYHA criteria.

We noted that none of these studies reported significant side-effects from anti-depressant medications, and that anti-depressant medications are well tolerated in this population.

Angermann at al, in the MOOD-HF study published in 2016 reported the findings of an RCT of escitalopram, an SSRI (n=185) and placebo (n=187) [16]. Their outcome measures were mortality, depression status (MADRS) and cardiovascular status by hospitalisation and Kansas City Cardiomyopathy Questionnaire (KCCQ), a cardiac quality of life measure. All participating patients had a diagnosis of depression on SCID and scored similarly at entry into the study in terms of depression score. The primary outcome was death or hospitalisation, with rates of 63% (n=116) in the escitalopram arm and 64% (n=119) in the placebo arm. Specifically the mortality rates were 10% (n=18) and 7% (n=14) respectively. Both the arms of the trial showed similar reductions in MADRS score. The authors concluded that 18 months of treatment with escitalopram made no difference to depression or cardiovascular status and had no effect on mortality rates.

Assessment of Quality

In order to assess the quality of the t~~w~~hree~~o~~ RCTs we used the 5-point Oxford Rating Scale (Walsh et al, 2002). The three RCTs were given a score of 5, as both had appropriate randomisation and double-blinding and both trials reported the reasons for patient withdrawals and dropouts. According to this, one would assume that both these trials were of high quality. However, Fraguas et al stopped their trial well in advance of the original planned period, due to high placebo rate, but suggested in their discussion that a longer period may have been required for observation of full antidepressant effect (Fraguas et al, 2009).

To further assess the quality of the two RCTs and also the three~~wo~~ cohort studies, a self-devised assessment scheme was used. The assessment criteria include:

For subject selection:

1) Were the eligibility criteria specified?
2) Were sufficient attempt made to avoid selection bias?
3) Did they have a large sample size?
4) Did they provide an adequate description of participants who withdrew from participation or those who declined to take part?

For outcome measurement and reporting:

5) Are the demographics of the study group clearly described?
6) Are valid tools used to measure outcome?
7) Was an appropriate method used to report the data?
8) Are the measurement and reporting independent of bias from the study designers?

For satisfying each of these criteria, the study receives a point. A total of 7-8 indicates high quality papers. A score of 4-6 indicates medium quality. A score of 0-3 indicates low quality. Table 2 shows the scores given to each of the four papers. Four of the five papers were of high quality whereas Tousoulis et al was of medium quality (Tousoulis et al, 2009).

Conclusions

These studies show that antidepressants are well tolerated in this group, and are not associated with poorer outcomes. O'Connor et al showed that once adjusting for depression, antidepressants are no longer associated with increased mortality (O'Connor et al, 2008). One of the first papers to discuss this is Fosbol et al, a cohort study over a time period of 1.9 years, which concluded that the use of antidepressants is associated with poorer prognosis, but were unable to differentiate whether the use of antidepressants or depression itself was associated with increased mortality (Fosbol et al, 2009). Limitations include little detail are given on cardiovascular confounding factors, indications and dose of prescribed medications, depression and status of same. O'Connor et al showed that once adjusting for depression, antidepressants are no longer associated with increased mortality (O'Connor et al, 2008).

The three RCTs compared depressive status of participants at the start and the end of the trial (Fraguas et al, 2009; O'Connor et al, 2010; Angerman et al, 2016). All found little difference in the depression status between those placed on antidepressants and those not. There may have been many reasons as to why this pattern appeared. First, placebo effects are common in antidepressant trials. ~~30%~~ A placebo response rate of 30% was found in one study of 75 antidepressant trials (Walsh et al, 2002). This was defined as the number of placebo-treated patients who had 50% or more

reduction in the HAM-D-31 score (Walsh et al, 2002). Other factors in the trials may have contributed to the high rates of placebo effects, for example in the O'Connor trial the extra nursing support provided to all participants, may have had a role (O'Connor et al, 2010). Fraguas et al also suggests that the interpersonal relationship of the psychiatrist with the patients may have contributed to the placebo effect (Fraguas et al, 2009). A design contrasting this approach with low or usual level of support could verify this hypothesis.

These studies raised the question of whether a more sensitive test with more comprehensive scales is required in order to assess depression status. Fragaus et al found that MADRS made it possible to discriminate between placebo and active drug affect more so than compared to HAM-D-31 [12]. Moreover, in O'Connor et al depression status may not have improved on sertraline as the level of depression was sub-clinical (O'Connor et al, 2010). A recent meta-analysis suggested that antidepressants may have little effect in patients with HAM-D-31 scores of less than 23 (Fournier et al, 2010). The baseline HAM-D-31 scores in O'Connor were 19.9 and 18.4 in the sertraline and placebo groups respectively (O'Connor et al, 2010). Furthermore, a possible source of bias might be the similarities of cardiac symptoms with those of depression. This could influence diagnosis and depression severity score.

Alternatively perhaps the correct dose of antidepressant was not used. O'Connor points out that the pharmacokinetics of many drugs are altered in acute decompensation of HF (O'Connor et al, 2010). Therefore perhaps a higher dose of the drug is required. It is possible that mechanism of depression and mood disorders differs between the HF population and the general population. This would make usual antidepressant medication regimens inadequate. Angerman measured serum escitalopram levels in order to ensure adequate dosing (Angerman et al, 2016).

Tousoulis et al state that treatment with SNRI and/or TCA is associated with lower levels of CRP and TNF-alpha in this population compared to those receiving SSRIs or non-treatment (Tousoulis et al, 2009). Proinflammatory factors can play a key role in the pathophysiology of HF. In animal models, these agents have been shown to have a negative inotropic effect on the myocardium (Blum and Miller, 2001). They have also been shown to promote left ventricular remodelling and to cause myocardial beta-adrenergic receptors to uncouple (Fournier et al, 2010). The evidence suggests that cytokines appear to form an important link between depression and morbidity/mortality in patients diagnosed with HF (Pasic et al, 2003; Ferketich et al, 2005). Proinflammatory cytokines, in particular TNF-alpha, are elevated in patients with HF and major depression, compared to HF patients without depression (Miller et al, 2002; Ferketich et al, 2005). There is increasing evidence to show that all categories of antidepressant (SSRI, TCA and SNRI) may exert some immunosuppressive effect (Maes et al, 1997; Xia et al, 2006). Tousoulis demonstrated that treatment with TCAs/SNRI were associated with lower levels of TNA-alpha and CRP in HF patients (Tousoulis et al, 2009). This would form an interesting basis for future studies, to see if controlling the levels of inflammatory factors using antidepressants could improve cardiovascular status.

The strengths of this review are that it focuses on an important topic examining clinically meaningful outcomes: mortality, HF symptoms and depressive symptoms. There have been a small number of

quality papers examining the question of whether antidepressants could improve outcome in HF patients.

The weaknesses of this paper to some extent reflect the weaknesses of the literature. Due to a paucity of robust literature in this area, this review comprises only three RCTs. The other two papers are cohort/ studies. Although the cohort studies provide valuable information, they do carry an inherent bias. Furthermore, the heterogeneous nature of the studies meant that it was difficult to conduct a meaningful comparison of the papers. First, HF is a complex clinical syndrome; different studies focus on different type of HFs. The studies all use different type of antidepressants. The studies look at different outcome measures. Even those that compare cardiovascular status, for example, use different measurements e.g. NYHA vs. performance in cardiopulmonary exercise test. The studies also have vastly varying follow up period; this is especially of importance when looking at remission of depressive symptoms and mortality rate. These variations meant that the studies were difficult to compare, and in particular it meant that it was not possible to extend to a meta-analysis.

This systematic review acknowledges that depression is prevalent among those diagnosed with HF. It has been shown that antidepressants are well tolerated by this population. However, these studies do not provide convincing evidence that antidepressants cause significant improvement in depression or cardiovascular status, although this finding may be related to important limitations in the included studies. It is unclear why antidepressants do not improve depression status compared to placebo in this patient group: this would inform choice of routine medication for depression in this population. Secondly, there is preliminary evidence that TCA/SNRIs may reduce inflammatory factors in this group~~. This could in turn improve~~ , which may have implications for cardiovascular status. Further research is required to establish the clinical significance of this finding, especially considering the potential effects of SSRIs and TCAs on blood pressure and QTc interval prolongation. Finally, with no evidence of efficacy of antidepressant medications in this population, it is important to consider other modalities of treatment of depression in heart failure, such as ~~psychotherapies including~~ cognitive behavioural therapy, which may be effective in this population (Jevanantham et al, 2017).

Acknowledgements

None

Disclosure of interests

None to declare.

Key points:

- Antidepressants are well tolerated in patients with heart failure.
- Once depression is adjusted for, antidepressants are no longer associated with increased mortality.

- We were unable to find convincing evidence that antidepressants cause significant improvement in depression.
- We were unable to find convincing evidence that antidepressants cause significant improvement in cardiovascular status.
- There is evidence that TCA/SNRI reduce inflammatory factors in this group: this ~~may have implications for improving cardiovascular status~~warrants further research .

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Table 1: New York Heart Association Classification of Heart Failure		
NYHA Class	**Exercise Tolerance**	**Symptoms**
I	No limitation	No symptoms during usual activity
II	Mild Limitation	Comfortable with rest. Symptoms during normal physical activity.
III	Moderate Limitation	Comfortable only at rest. Symptoms during gentle physical activity.
IV	Severe Limitation	Symptoms at rest. Exacerbated by any physical activity.

Table 2: Extracted data from the papers included in this review

Title	Design	No of Patients: Control	Study Duration	Intervention	Baseline EF, mean (SD) %	Outcome – Test: Placebo		
						Mortality	Depression Status	Cardiovascular status
Fraguas et al, 2009 [11]	RCT	19:18	8 weeks	Citalopram (SSRI)	EF <50%	NA	Change in score: HAM-D-17 – 9.74:9.19 HAM-D-31 – 16.47:14.13 MADRS – 15.05:9.44 *	Performance in cardiopulmonary exercise test: No statistical significant difference.
O'Connor et al, 2010 [12]	RCT	138:96	12 weeks	Sertaline (SSRI)	Sertraline 31.3 (9.5) Placebo 29.5 (10.1)	18%:10%	Mean change in HAM-D-31: -6.2:-5	Composite Cardiovascular Status - Worsened: 29.9%:43.8% Improved: 40.6%:43.8% Unchanged: 29.5%:25.1%
O'Connor et al, 2008 [13]	Cohort	129:12:12 :843 (SSRI:TCA: Others:No treatment)	971 days (mean)	SSRI TCA Others	SSRI 31.6 (11.9); TCA 41.5 (13.1) Nil 30.5 (11.6)	46.9%:41. 9% *	NA	NA
Tousoulis et al, 2009 [14]	Cohort	120:34:96 (SSRI: SNRI/TCA: No treatment)	6 months	TCA SSRI SNRI	SSRI 31.9 (0.8) TCA/SNRI 33.8 (1.4) Nil 32.4 (0.96)	NA	CDSMP SNRI/TCA> SSRI>No treatment	Inflammatory markers: TNF-alpha levels: SNRI/TCA<SSRI/ No depression CRP: SNRI/TCA <SSRI/No depression (actual values are not given, only figures)
Angermann et al, 2016 [16]	RCT	185:187	18months	Escitalopram (SSRI)	Escitalopram 34.9 (8.3) Placebo 34.7 (8.2)	10%:7%	Change in score: MADRS 9:8.9	Cardiovascular hospitalisation (HF) – 22%:22% NYHA class- 10:15% worsened, 66:59% were unchanged, 24:27% improved.

*RCT=Randomised Controlled Trial, NA= Not Applicable, * = statistically significant difference, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, HAM-D-31 = 31-item Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale, CDSMP = Chronic disease self-management programme, KCCQ = Kansas City Cardiomyopathy Questionnaire*

Table 3: Application of the self-designed scoring system to grade the quality of the papers.										
Paper	1	2	3	4	5	6	7	8	Total	Quality
O'Connor et al, 2010 [12]	Y	Y	Y	Y	Y	Y	Y	N	7	High
Tousoulis et al, 2009 [14]	Y	N	Y	N	Y	N	Y	Y	4	Medium
O'Connor et al, 2008 [13]	Y	Y	7	Y	Y	Y	Y	Y	8	High
Fraguas et al, 2009 [11]	Y	Y	Y	Y	Y	Y	Y	N	7	High
Angermann et al, 2016 [16]	Y	Y	Y	Y	Y	Y	Y	Y	8	High

Y = Yes, N= No.

For subject selection: 1) Were the eligibility criteria specified? 2) Was there sufficient attempt made to remove bias? 3) Did they have a large sample size? 4) Did they provide an adequate description of participants who withdrew from participation or those who declined to take part?

For outcome measurement and reporting: 5) Are the demographics of the study group clearly described? 6) Are valid tools used to measure outcome? 7) Was an appropriate method used to report the data? 8) Are the measurement and reporting independent of bias from the study designers?