

MENTAL ILL-HEALTH AND HEART FAILURE COMORBIDITY

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ABSTRACT

This review aims to understand the co-existence of mental ill-health and heart failure and if this comorbidity affects patient self-care motivation and overall health outcomes. Databases searched were; PubMed®, Google® scholar and Science Direct® for studies related to heart failure, heart failure and mental health, depression and anxiety. Eleven articles were identified and reviewed. There were two studies disagreed with the theory that the mental ill-health and heart failure has disease modification and worsen patient health outcomes, three studies concluded that only anxiety has effect, five studies concluded that both anxiety and depression have effect, six studies concluded that depression only has effect but all eleven stated that more research is required. Recent theories on depression and cardiovascular disease comorbidity and the effect mental ill-health have on medication adherence in heart failure patients was discussed. People with long-term physical illnesses may suffer further complications to their health if they develop mental illness; increasing the cost of their care by an average of 45%, however, in the majority of these cases, the mental issues neither diagnosed nor treated. This review explored the link between cardiovascular disease (CVD) and mental ill health; and how comorbidity of the two conditions affects patients' adherence to therapy behaviour. It was concluded that while the link between mental ill health and heart failure (HF) is recognized, studies that may be used as a basis of evidence to confirm this link are scarce.

Keywords: Neuroplasticity, Heart Failure, Depression, Anxiety, Primary Care

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INTRODUCTION

Heart failure (HF) is a global pandemic reported to affect at least 26 million people worldwide and is increasing in prevalence. In the UK, HF is a significant and increasing public health problem, affecting approximately 920,000 people. It accounts for approximately 2% of the total NHS annual budget—an estimated £2 billion [1]. The incidence and prevalence of HF increase sharply with age, with the average age at diagnosis about 77 y old. HF accounts for 5% of all emergency admissions [2]. Management of HF requires long-term treatment with multiple medications, demonstrated with robust evidence to reduce morbidity and mortality and to improve signs and symptoms. However, even with advances in treatment, the regimens can only be beneficial if patients adhere to their prescribed therapy. Non-adherence to prescribed medications results in a multitude of issues which in 2013 was reported to cost the NHS more than £500 million each year [3].

Heart failure

HF contrary to widespread belief is defined as a clinical syndrome, not a disease. The syndrome results from structural or functional cardio-vascular (CV) disorders leading to a cardiac output that is insufficient to meet metabolic demands, or adequate cardiac output secondary to compensatory neurohormonal activation, which usually presents as an increased left ventricular filling pressure [4]. HF is the end-stage of all heart disease and the pathophysiology behind the syndrome involves multiple physiological changes and ongoing deterioration in CV health.

The net effect of the changes that occur in HF are initially favorable, serving to increase blood volume which in turn, increases heart rate, total peripheral resistance and venous return, which maintains high cardiac output. However, over time these secondary mechanisms contribute to worsening of the condition of the failing heart. The mechanisms activated, cause salt and water retention leading to fluid overload, ultimately precipitating the condition they are trying to improve [5].

Overall, the pathophysiological changes that occur in HF are; myocyte hypertrophy, ventricular dilatation, increased collagen synthesis, increased atrial natriuretic peptide (ANP) secretion,

sympathetic stimulation, peripheral vasoconstriction, salt and water retention, altered myosin gene expression and altered sarcoplasmic Ca^{2+} -ATPase density.

Heart failure clinical presentation

Owing to the multitude of pathophysiological changes that occur in HF, the presentation can be varied. The clinical presentation of HF may be divided into symptoms and signs. Symptoms may include; wheezing, weight loss, peripheral swelling due to edema formation, dyspnoea, fatigue, exercise intolerance and lethargy. The latter three symptoms occur due to the inability of the heart to increase the cardiac output during exercise; as a result, the heart uses the cardiac reserve by fluid retention [6].

Signs of HF include [7]

- Hypotension
- Orthopnoea
- Paroxysmal nocturnal dyspnoea
- Tachycardia
- Cardiac heaves on palpation of the chest
- Third and fourth heart sounds (S3–gallop rhythm and S4) heard on cardiac auscultation
- Displaced apex beat from the 5th intercostal space; this is usually a lateral displacement and is a sign of cardiomegaly
- Bilateral crepitations noted on lung auscultation
- Elevated jugular venous pressure (JVP) secondary to the venous congestion.
- Hepatomegaly or hepatic tenderness on palpation of the abdomen due to systemic pooling of blood.
- Pulsus alternans—a cardiovascular phenomenon which displays alternating strong and weak pulse pressures during sinus rhythm. It is usually indicative of left ventricular systolic impairment.

Table 1 shows the most basic classification system, which assesses the presentation of signs and symptoms. The New York Heart

Association system is the most widely utilised system [2].

Table 1: New york heart association for the classification of HF

New york heart association (NYHA) functional classification	
NYHA class	Level of limitation
Class I	No limitation of life activities–no fatigue, palpitations or dyspnoea on normal physical exercise
Class II	Slight limitation; normal physical activity causes fatigue, palpitations or dyspnoea. Comfortable at rest
Class III	Considerable limitation; less gentle physical activity causes marked symptoms of HF. Only comfortable at rest
Class IV	Breathlessness and fatigue during rest and any activity increases discomfort

Management of heart failure

Due to the infrastructural changes and remodeling of the myocardium; there are recommended treatment plans to be implemented to improve the outcome of HF. The main aim according to Tamargo and López-Sendón, (2011) are;

- Prevent organ system damage
- Manage the co-morbidities that may contribute to poor prognosis.
- To improve prognosis and reduce mortality
- To reduce symptoms and reduce morbidity by reversing or reducing the cardiac and peripheral dysfunction.
- Reduce the length of stay and subsequent readmission for in-hospital patients

Management for HF should be handled by a multidisciplinary team (MDT), aiming for an integrated approach across the sectors. Good communication is paramount, between healthcare professionals and between the patient and the healthcare professional. The MDT should involve specialist healthcare professionals, including doctors, pharmacists, specialist HF nurses, occupational therapists, physiotherapists and palliative care advisers [9].

Mental ill-health and other chronic diseases comorbidity

Comorbidities need to be effectively addressed as soon as they arise. Not only do they act as independent factors for the outcome; they also have the ability to impede the treatment plan for HF [10]. The burden of an illness can manifest in many ways; depression and anxiety being the most common. The link between the continuing development of heart disease and the onset of depression; supports the theory that suffering from chronic stress due to living with illness, is a risk factor for the depression-anxiety disorder [10].

Patients with chronic disease suffer emotional stress over the years from the point of diagnosis or the initial acute presentation. Many find it difficult to cope with their illness and cannot manage to effectively adapt to their ever-changing psychosocial and physical situation, which eventually leads to a continuing loss of independence.

Mental illness and disorders

Depression belongs to a group of disorders known as the affective mood disorders [11]. Depression can occur as a single episode or as an ongoing condition with periods of remission and relapse [12]. It is one of the most common diagnoses in general practice (GP) and is associated with increased mortality and morbidity [13]. The Diagnostic and Statistical Manual of Mental Disorders (DSM-V), requires five or more symptoms to be present within a 2 w period to make a diagnosis of depression. One of the symptoms must be from the main criteria; which is either a depressed mood or anhedonia [14].

The secondary symptoms are

- Low energy levels/fatigue
- Appetite/weight changes
 - o Comfort eating
 - o Nausea causing reduced appetite
 - o Intentional/non-intentional weight change

- o >5% is significant
- Suicide ideation
 - o Have any plans been made to end their life
 - o Have they acted on any plans
 - o Has there been any self-harm
- Sleep disturbances
 - o Insomnia
 - o Hypersomnia
 - o Repetitive waking during the night
 - o Early morning waking
- Feelings of worthlessness or excessive guilt
 - o Low self-worth, feeling useless and/or excessively guilty and helpless
- Reduced concentration/mentation
 - o Issues with information processing
- Psychomotor agitation or retardation

Symptoms may be grouped as somatic or non-somatic. The somatic items/symptoms include; appetite or weight changes, sleeping difficulties, fatigue, poor concentration and psychomotor agitation/retardation. The non-somatic symptoms include depressed mood, anhedonia, feelings of worthlessness/excessive guilt, and suicide ideation. Severe depression is more associated with the non-somatic group of symptoms, where moderate depression is associated with the somatic cluster of symptoms [14]. Theories of the pathology of depression have been explored and the most widely accepted hypothesis has been that depression results from an underactivity of monoamine neurotransmitters in the synaptic cleft. However, when patients take antidepressant medication, the levels of noradrenaline and 5-HT increase within hours, but clinical improvement typically occurs only after 2-4 w. This suggests that secondary adaptive changes are occurring in the brain. These are thought to include desensitisation or down-regulation of the somatodendritic monoamine auto receptors rather than the simple increase in monoamine concentration alone. This would explain the delayed onset [15]. Recently research in this area has focussed on the glutamate and neuroplasticity theory, which is thought to provide a more complete explanatory structure for depression [16]. Neuroplasticity refers to the ability of the neural system to adapt to internal and external stimuli and to respond adaptively to future stimuli [17]. Neuroplasticity is a fundamental component of the brain's adaptation to stress; any issues in adaptation may result in psychiatric disorders *e.g.* depression and other stress-related disorders [18]. Neuroplasticity occurs at different levels; from cellular changes to complete organisational changes. These changes will vary between individuals and are influenced by a person's environment and life experiences, which is supported by observed increased RNA and protein synthesis [19] suggesting there are genetic aspects; genetic variation in humans can influence the expression and degree of neuroplasticity. The human genome has numerous gene polymorphisms known to influence neuroplasticity, the two most involved genes appear to be for brain derived neurotrophic factor (BDNF) and apolipoprotein-E

[20]. BDNF is present throughout the brain with higher concentrations found in the hippocampus. This area is responsible for cognitive functions, such as learning, behaviour, memorisation, stress, emotions, and mood [21]. It is directly involved in neuroplasticity through regulation of cellular processes; growth, maintenance and survival of the neuronal circuits involved in cognitive and emotional functions, as well as indirectly through its regulation of other processes that can influence neuroplasticity such as depression [22]. Studies reveal that depressive behaviour and suicide risk is associated with altered BDNF functioning. Direct involvement of BDNF in brain neuroplasticity is linked to short and long-term impacts; immediate effects involve the initiation of rapid depolarization of postsynaptic neurons by stimulating presynaptic neurotransmitter release causing effects on calcium ion channels and glutamate receptors [23]. In the long term, BDNF causes permanent changes in synaptic plasticity, neurotransmitter and neuropeptide production and excitability. These changes serve to aid long-term potentiation and neuroplasticity [24].

The mixed anxiety-depressive disorder is also common in primary care; where the patient exhibits broadly equal amounts of anxiety and depressive symptoms [25]. Stressful life events precipitate the symptoms of anxiety, so anxiety is the emotional response to a threat of loss, whilst depression is the response to the loss itself.

Anxiety disorder includes a variety of subgroups sharing features of disproportionate fear, anxiety and related behavioral problems [26]. They arise from a combination of biopsychosocial factors including genetic vulnerability, biochemical changes, personality type, mood and general behaviors, cultural, socioeconomic status and medical status that interact life experiences leading to anxious feelings [27]. Once these situations are encountered, various anatomical changes happen; the region of the brain thought to be most associated with anxiety is the amygdala [28]. Patients exhibiting anxiety symptoms have a 'hyper-responsive' amygdala generating feelings of anxiety and fear [29]. All nervous system functions; sleeping, memory, reflexes and higher cognitive tasks, result from neural activity. The mediators released are able to modify the neural circuit output to cause adaptation in different behaviors [30]. These neuromodulators change the characteristics of the circuit's fundamental neurons, by controlling the input to these neurones and their synaptic connections.

Neuromodulation *via* these mechanisms produces various symptoms, including, apprehension motor tension, muscle stiffness, inability to relax, becoming easily fatigued, muscle aches, irritability, hypervigilance (*e.g.* poor concentration, insomnia and irritability); and increased sympathetic activity [31]. In extreme cases, patients develop panic disorder, which is described by the DSM-V as 'a discrete period of intense fear or discomfort in which four (or more) of the symptoms developed abruptly and reached a peak within 10 min [32].

Approximately one-third of patients with depression will present with panic disorder. Over a lifetime, around half of patients who have panic disorder will develop depression and about half of depressed patients will develop panic disorder [33].

The link between heart failure, depression and anxiety

The link between mental health and heart failure has been previously noted, but studies informing the best interventions to improve prognosis in both areas are limited. Chronic anxiety is an independent risk factor for CVD; [34] and depression alone, predicts a significantly worse prognosis in chronic HF [35].

A meta-analysis (2006) discussed the prevalence, intervention effects and associations of depression with clinical outcome in HF [36]. Rutledge *et al.*, (2006) assessed three main areas; the prevalence of depression among patients with HF, the magnitude of the relationship between depression and clinical outcomes in the HF population and the evidence for treatment effectiveness in reducing depression in HF patients. They used clinical interview methods and diagnostic criteria from the DSM-V plus depression symptom inventories (*e.g.* Beck Depression Inventory and the Hospital Anxiety and Depression Scale) to diagnose depression in HF patients. This was compared to that documented into the patient's medical record and the current use of antidepressant medication.

The use of the diagnostic tools questionnaires resulted in a larger proportion of patients being diagnosed with clinically significant depression (33.6%); compared to 19.3% [36]. This suggests 'under' diagnosis of clinically significant depression. Conversely, the difference may reflect patients answering 'yes' to a question and perhaps over-exaggerating on their emotions at a certain time. This study concluded that overall, 21.5% of HF patients exhibited clinically significant depression. The combined diagnosis was explored further, suggesting higher rates of death and secondary events (risk ratio (RR) = 2.1 and 95% confidence interval (CI) 1.7 to 2.6) in the co-morbid group. Increased health care use and rates of hospitalization and emergency room visits were also noted.

The relative risk for onset of coronary artery disease (CAD) in depressed individuals was calculated to lie between 1.5 and 2.0; while the diagnosis of depression in patients who have a diagnosis of CAD was calculated to be between 1.5 and 2.5 [37]. Although no firm conclusions were drawn from this study; they based their theory on the underlying pathophysiological changes that occur in a depressed patient. Additionally, it is also thought that the altered natriuretic peptide levels in areas of the brain which regulate blood pressure and fluid control may contribute [38].

Plasma levels of natriuretic peptides are elevated in congestive heart failure. One study reported these have an antagonistic effect on blood pressure and fluid neurotransmitters in HF and are associated with the emotional and mental changes seen in HF [39]. Further investigating this concept, Herrmann-Lingen, *et al.*, (2003) reported that anxiety tends to reduction with high atrial natriuretic peptide levels [40]. They suggested the reason may be a negative feedback loop, which limits the psychological distress a patient may experience and in turn, reduces the adverse autonomic implications seen in severe HF; volume or pressure overload leads to ventricular wall stress and subsequent BNP release. This causes peripheral vasodilatation, increase in natriuresis and diuresis and inhibition of the sympathetic nervous system and the RAAS [41]. Depression is thought to affect the regulation of the autonomic system; by reducing the parasympathetic tone and increasing the sympathetic tone; which ultimately leads to an increased heart rate, exaggerated response to physical stressors, higher variability in ventricular repolarization, reduced baroreceptor sensitivity and lowered tolerability for adverse cardiac events *e.g.*, myocardial ischaemia [42]. Increased sympathetic output increases cortisol, serotonin, renin, aldosterone, angiotensin and free radicals [43].

High levels of circulating catecholamines increase blood pressure and coronary vasoconstriction. They also induce platelet activation, predisposing this population group to an increased risk of thromboembolism through an inhibitory effect on the synthesis of the protective eicosanoids [44].

In depression, macrophage activation *via* the cholinergic anti-inflammatory pathway is no longer inhibited and therefore contributes to the elevation of pro-inflammatory markers such as C-reactive protein and cytokines (interleukin-1beta, interleukin-6 and tumour necrosis factor-alpha (TNF-alpha)). The TNF-alpha is known to reduce serotonin levels and produce an overall depressed mood, fatigue, loss of appetite, sleep disturbances, malaise and decreased libido [45]. The increased levels of inflammatory cytokines have been reported to be independent predictors of HF-related exacerbations and deaths [46]. The study also concluded that increased serum IL-6 is a powerful independent predictor of the combined-point; death, new heart failure episodes and the need for heart transplantation.

More complex mechanisms also exist; immune activation of leucocytes and natural killer cells; and the activation of the HPA axis ('stress axis') result in hypercortisolaemia, an increase in adrenocorticotrophic hormone (ACTH) and ACTH-releasing factor; along with an increase in endogenous steroid hormone production [47]. The foremost constituent components of the stress axis are the paraventricular nucleus (PVN) of the hypothalamus, the anterior pituitary and the cortex of the adrenal glands [48]. Cells in the PVN release corticotrophin-releasing hormone (CRH) in response to the natural circadian drive and also to stressors; trauma, psychosocial agitations or pharmacological agents *etc.* The CRH travels through

the portal vascular system and binds to corticotrophs in the anterior pituitary; resulting in synthesis and release of ACTH [49]. This circulating ACTH binds to receptors on adrenocortical cells; causing the synthesis and release of cortisol into the bloodstream. The characteristic circadian pattern of cortisol secretion shows an increase in the early morning, peaking just before the time of waking. An abundance of physiological stressors will have a contributing effect on the cortisol levels, which may result in raised afternoon and evening cortisol levels, far above the predicted circadian peak in the morning [49]. Cortisol elevation from chronic stress response would produce neurotoxic effects on the hippocampal neurons through the glucocorticoid and mineralocorticoid receptors resulting in a decrease in neurogenesis, synaptogenesis and dendritic spines and increased apoptosis of neurons. The cortisol will ultimately exercise its effects throughout the brain and the periphery [50]. The morphological loss of neurones leads to functional deficits, a long term depression (reduction in the efficacy of neuronal synapses) or long term potentiation (persistent increase in synaptic strength) of the hippocampus; which in turn, causes a reduction in GABA neurotransmitter control of the HPA axis [51]. Interestingly, this links in with the neuroplasticity theory of depression, as previously discussed. It has been reported that cortisol inhibits neuroplasticity in the CNS [52].

GABA reduces the HPA axis output in response to stress and the resulting reduction exacerbates the HPA axis stress axis output, causing a further morphological and functional loss in the hippocampus. A malicious cycle is thus formed; eventually causing structural atrophy and the functional deficit of the hippocampus. Atrophy levels usually range from 8%-19%; something that is frequently seen in depression [53]. Chronic/long-term stress and therefore prolonged glucocorticoid secretion also cause a reduction in BDNF in the brain [54]. Interestingly, the biological activation of the HPA axis system seems to have a prognostic value, with evidence of an increased risk of depression relapse and even suicide [49].

Depression manifests clinically through autonomic, metabolic, immune-inflammatory and HPA axis dysfunction; all of which affect the incidence of CVD by initially causing thickening of the tunica

intima and tunica media (the two innermost layers of the arterial wall), precipitating atherosclerosis [55]. Depression also decreases vagal tone and can also increase sympathetic tone, further raising CV risk [32]. The nervous system also regulates internal organ function so it has been suggested that neuroplasticity is also associated with the pathophysiology of other diseases including neuropsychiatric disorders [56].

If stress can influence the HPA axis, increasing glucocorticoid levels, this will reduce BDNF concentration and decrease neuroplasticity, leading to depression. If neuroplasticity is the ability of the nervous system to respond to stimuli by reorganizing its structure, function and connections [17], a decrease will impact the autonomic nervous system, both directly and through the HPA axis and the hippocampus; causing autonomic dysfunction, which could possibly lead to CVD [57]. This raises the question; are certain patients 'predisposed' to developing a mental illness with CVD? Patients with reduced neuroplasticity will be at risk of developing depression and also CVD. A recent study (n=10,341) provides evidence to support these links. They reported an association between depression and the future risk of developing CVD, which was reported to be similar across the sub-groups of CVD [58]. They also reported that moderately depressed patients were at a higher risk of developing CVD, compared to mildly and severely depressed patients. The reason for this is that moderately depressed patients exhibit somatic symptoms whilst severely depressed patients are at higher risk of suicide due to predominant non-somatic/cognitive-affective symptoms. Furthermore, the study reported a higher risk of CVD amid depressed patients who also suffered from anxiety symptoms.

RESULTS

Out of eleven studies compared, two disagreed with the theory that co-morbidity with mental ill-health and heart failure is associated with disease modification and worsening patient health outcomes. Three studies concluded that only anxiety has an effect, five studies concluded that both anxiety and depression produce an effect, whilst six concluded that only depression demonstrates an effect. However, all eleven state that more research is required (table 2).

Table 2: Analysis of studies conclusions in relation to the agreement or disagreement with the theory of mental ill-health and heart failure has disease modification and worsen patient health outcomes

Paper	Citation	Sample	Type of study	Results (Direct quotation)	Agree with the theory of anxiety and HF comorbidity and disease modification	Agree with the theory of depression and HF comorbidity and disease modification	Disagree with the comorbidity diseases modification theory	More research required
1	Almas A, Forsell Y, Iqbal R, Janszky I, Moller J. Severity of Depression, Anxious Distress and the Risk of Cardiovascular Disease in a Swedish Population-Based Cohort. PLoS One. 2015. 10: available at 10.1371/journal.pone.0140742	10,443 patients	longitudinal cohort study	This study found that severity level of depression seems to be of significance for increased risk of CVD among depressed persons, a higher risk of CVD among depressed individuals with symptoms of anxious distress.	√	√	X	√
2	Carney R, Freedland K, Veith R. Depression, the autonomic nervous system, and coronary heart disease. Psychosomatic Medicine. 2005. 67: 29-33.	N/A	Review	Studies of medically well, depressed psychiatric patients have found elevated levels of plasma catecholamines and other markers of altered ANS function compared with controls. Studies of depressed patients with CHD have also uncovered evidence of ANS dysfunction, including elevated heart rate, low heart rate variability, exaggerated heart	X	√	X	√

				rate responses to physical stressors, high variability in ventricular repolarization, and low baroreceptor sensitivity. All of these indicators of ANS dysfunction have been associated with increased risks of mortality and cardiac morbidity in patients with CHD				
3	Herrmann-Lingen C, Binder L, Klinge M, Sander J, Schenker W, Beyermann B, Von Lewinski D, et al. High plasma levels of N-terminal pro-atrial natriuretic peptide associated with low anxiety in severe heart failure. <i>Psychosomatic Medicine</i> . 2003. 65: 517-522.	119 patients	Cross sectional study	Pro-ANP plasma levels are independently and inversely related to anxiety. This might be part of a negative feedback loop limiting psychological distress and its adverse autonomic consequences in severe heart failure.	√	X	X	√
4	Jiang W, Kuchibhatla M, Cuffe M, Christopher E, Alexander J, Clary G, Blazing M, et al., Prognostic Value of Anxiety and Depression in Patients With Chronic Heart Failure. <i>Circulation</i> . 2004. 110: 3452-3456.	374 patients	Cross sectional study	Although anxiety and depression are highly correlated in CHF patients, depression alone predicts a significantly worse prognosis for these patients.	X	√	X	√
5	Lett H, Blumethal J, Babyak M, Sherwood A, Strauman T, Robins C, Newman F. Depression as a risk factor for coronary artery disease: evidence, mechanisms, and treatment. <i>Psychosomatic Medicine</i> . 2004. 66: 305-315	N/A	Review	There is substantial evidence for a relationship between depression and adverse clinical outcomes. However, despite the availability of effective therapies for depression, there is a paucity of data to support the efficacy of these interventions to improve clinical outcomes for depressed CAD patients. Randomized clinical trials are needed to further evaluate the value of treating depression in CAD patients to improve survival and reduce morbidity	X	X	√	√
6	Mbakwem A, Aina F and Amadi C. Expert Opinion-Depression in Patients with Heart Failure: Is Enough Being Done? <i>Cardiac Failure Review</i> . 2016. 2: 110-112.	N/A	Expert opinion, metaanalysis	Results from metaanalysis suggest a twofold increase in mortality in HF patients with compared to those without depression. Pharmacological management of depression in HF has not been shown to improve major outcomes. No demonstrable benefits over cognitive behavioural therapy and psychotherapy have been demonstrated.	X	√	X	√
7	Öhlin B, Nilsson P, Nilsson L, Berglund G. Chronic psychosocial stress predicts long-term cardiovascular morbidity and mortality in middle-aged men. <i>European heart journal</i> . 2004. 10: 867-873.	13,609 patients	population-based screening and intervention programme	Self-reported chronic stress is an independent risk factor for CVD. The adjustment itself might reflect mechanisms whereby psychosocial stress directly or indirectly exerts its effects on the body, indicating a possible over-adjustment.	√	√	√	√
8	Parissis J, Fountoulaki K, Paraskedavidis I, Kremastinos D. Depression in chronic heart failure: novel pathophysiological mechanisms and therapeutic approaches. Expert opinion on		Review	Depression is four to five times as common in chronic heart failure (CHF) patients as in the general population, may confer a higher risk of developing CHF in susceptible populations, and is significantly related to higher hospital readmission rates and increased mortality in	X	√	X	√

	investigational drugs. 2005. 14: 567-577.		established CHF.				
9	Rutledge T, Reis V and Link S. Depression in heart failure: a meta-analytic review of prevalence, intervention effects and associations with clinical outcomes. Journal of the American College of Cardiology. 2006. 48:1527-37.		Clinical depression is a common problem among patients with heart failure (HF) and may significantly impair patient prognosis. Patients with depression were also more than twice as likely to experience premature death or secondary events over time. Because of their high rate of symptoms, progressive course, and frequent hospitalizations, HF patients may be particularly vulnerable to depression	X	√	X	√
10	Zheng Z, Wu J, Wang R, Zeng Y. Diabetes mellitus may induce cardiovascular disease by decreasing neuroplasticity. Functional Neurology. 2014. 29: 7-13	Review	Neuroplasticity may be associated with the pathogenesis of other diseases besides neuropsychiatric diseases. Decreased neuroplasticity is associated with cardiovascular disease (CVD) and a disease related to decreased neuroplasticity may confer a greater CVD risk.	√	√	X	√
11	Zheng Z, Zeng Y and Wu J. Increased neuroplasticity may protect against cardiovascular disease. The international journal of neuroscience. 2013. 123: 599-608.		The nervous system monitors and coordinates internal organ function. Thus, neuroplasticity may also be associated with the pathogenesis and the treatment of some other diseases besides neuropsychiatric diseases. The cardiovascular system is controlled by the nervous system, mainly by the autonomic nervous system. Stress may lead to depression and cardiovascular disease (CVD). CVD is associated with depression, which is a disorder of decreased neuroplasticity. And the mechanisms of depression and CVD are related	√	√	X	√

CONCLUSION

HF and mental health co-morbidity burden both the patient and the healthcare provider. Clinicians have an opportunity to intervene in such cases. The symptomatic perspective and the psychosocial aspects for an individual, need to be carefully considered from the presentation. Gauging the level of acceptance and adherence to therapy, will facilitate timely intervention and provide the opportunity to develop a comprehensive and tailored management plan for the patient. By addressing this issue, other facets of the symptomatic cube could also be simultaneously improved. The overall aim would be to promote improved quality of life for the patient. Non-adherence to a medical treatment plan can be detrimental to a patient's health. This review of recent literature revealed no new information or consensus on the assessment or treatment of depression in patients with HF. Also, there is no routine use of any diagnostic tool to assess medication adherence when reviewing a patient.

AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

Declare none

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