Sound mind *vs* sound heart

Depressive and anxiety disorders have both have been associated with an increased risk of cardiovascular disease. This article highlights the multifactorial and bidirectional interaction between cardiovascular diseases, depression and anxiety, and the need for early assessment, diagnosis and intervention.

A figurative interdependence between the heart and sadness has long existed in language and in literature. In 1628, English physician William Harvey noted: 'every affection of the mind that is attended either with pain or pleasure, hope or fear, is the cause of an agitation whose influence extends to the heart' (Goldstein, 2004). It is becoming clear that the comorbidities of depression and cardiovascular disease do not occur by chance but rather are an inevitable consequence of the relationship between the two conditions. Carney and Freedland (2003) reported that major depressive disorder is an independent risk factor for the occurrence of a major cardiac event, and that depressed patients have a higher than expected rate of sudden cardiovascular accidents. Owing to this concomitant occurrence of the two conditions, it is imperative that they are managed in tandem.

Psychiatric illnesses in cardiac patients are frequently undiagnosed and untreated as a result of health-care, patient and societal factors. When mental and physical illnesses co-exist, it is likely that they mimic each other and thus contribute to underdiagnosis of depression and anxiety (Glasser and Gravdal, 1997).

Prevalence

As reported by a national comorbidity study of depression, the prevalence of depression in patients with acute myocardial infarction is higher (19.8%) than in the general population (4.9%) (Thombs et al, 2006). Anxiety has been associated with more than twice the risk of coronary heart disease than non-anxious counterparts in a prospective study of 49 321 Swedish men, aged 18–20 years (Janszky et al, 2010) as well as an increased rate of cardiac death (Roest et al, 2010).

Symptoms pertaining to mental health and cardiovascular diseases may have common aetiopathological pathways. There may also be a cause–effect interrelationship between the two pathologies, thereby confounding the clinician.

Cardiovascular diseases causing depression or anxiety

Free-floating anxiety (persistent or recurrent worry) that does not meet diagnostic criteria is seen in 20–25% of post-myocardial infarction patients (Crowe et al, 1996). Following a major cardiac event patients can feel anxious, low and may become concerned about the impact of their physical health on their future (Crowe et al, 1996).

This general fear or reaction can transform into continuous negative thoughts: 'Am I going to die?', 'My life will never be the same!', 'What if it happens when I'm alone?', and so on. If these negative cognitions become prolonged and overwhelming ruminations which adversely affect daily functioning, the patient needs to be assessed by professionals. Anxiety disorders can range from a brief adjustment disorder to chronic generalized anxiety disorder, panic disorder, phobias, obsessive compulsive disorder or lifelong post-traumatic stress disorder (Crowe et al, 1996).

In a prospective cohort study, the prevalence of post-traumatic stress disorder in cardiac arrest survivors is 27% more than 2 years after the incident (Gamper et al, 2004). Serious cardiac events can be traumatic and some patients develop symptoms of post-traumatic stress disorder including flashbacks, intrusive thoughts, avoidance behaviour (avoiding anything reminding them of the event) and increased arousal (insomnia and irritability) (Mayou et al, 1976).

The symptoms of panic attack are frequently confused with those of a heart attack, especially by individuals who have recently experienced a myocardial infarction. This misinterpretation occurs as a result of high overlap of symptoms like chest pain, dizziness, shortness of breath, stomach discomfort and nausea which leads to repeated

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presentations in hospitals and admissions. However, it may be that cardiac activity and function reach conscious awareness and are experienced as symptoms.

Depression and anxiety leading to cardiovascular diseases

In a prospective study on participants from north west London, high levels of phobic anxiety were associated with a fourfold increase in relative risk of ischaemic heart disease (Haines et al, 1987). A larger study showed similar results and a dose–response relationship (relative risk = 2.5, 95% confidence interval = 1.00–5.96), noting that this association led to an increased risk of sudden death (Kawachi et al, 1994). There is also evidence that patients with panic disorder have reduced heart rate variability which can cause sudden death as a result of cardiac arrhythmias (Lombardi et al, 2001).

Mechanisms

A combination of pathophysiological, behavioural mechanisms and medication factors seems to link depression and anxiety to cardiovascular diseases.

Physiological mechanisms

Cardiovascular autonomic dysregulation

Depression is associated with elevated heart rate and reduced heart rate variability. These are well-known risk factors for cardiac morbidity and mortality, and may explain the increased risk associated with depression. Patients with depression have excessive sympathetic tone and reduced parasympathetic tone, further reducing heart rate variability. This increases the risk of myocardial ischaemia, arrhythmias and sudden cardiac death (Glasser and Gravdal, 1997; Carney and Freedland, 2003; Goldstein, 2004).

Neuroendocrine mechanisms

Mental stress results in hypothalamic-adrenocortical and sympatho-adrenal hyperactivity. This causes heightened autonomic activity, increased catecholamines and increased corticosteroids leading to an acute rise in blood pressure and increased levels of glucose, cholesterol and free fatty acids. These changes may precipitate plaque rupture and coronary thrombosis, resulting in myocardial infarction and sudden cardiac death (Rosmond and Bjorntorp, 2000).

Inflammatory mechanisms

Inflammation is a key element in the development of atherosclerotic cardiovascular disease. C-reactive protein, an inflammatory marker, plays an important role in cardiovascular disease (Ford and Erlinger, 2004). It has been suggested in the National Health and Nutrition Examination Survey (NHANES) III that a history of major depressive disorder is strongly associated with elevated levels of C-reactive protein (Ford and Erlinger, 2004). Psychosocial factors including early life diversity, hostility, social isolation, low socioeconomic status and chronic work stress have been associated with elevated levels of other inflammatory markers (IL-6, IL-1β, tumour necrosis factor-α and C-reactive protein) (Steptoe et al, 2007).

Serotonin and platelet aggregation

Baseline elevation in platelet reactivity is seen in depressed patients both with and without ischaemic heart disease. This is the result of abnormalities in serotonin metabolism which enhance platelet aggregation in coronary arteries, increasing cardiovascular risks and the likelihood of thrombus formation (Markowitz and Mathews, 1991). These abnormalities include increased plasma concentrations of serotonin and catecholamines, increased serotonin binding density and reduced density of serotonin transporter sites (Biegon et al, 1987; Pandy et al, 1990; Markowitz and Mathews, 1991). Increased levels of platelet factor 4 and beta-thromboglobulin are also seen in patients with depression, which are directly proportional to platelet aggregation (Pollock et al, 2000; Serebruany et al, 2003a). Treatment of depression with selective serotonin-reuptake inhibitors or psychotherapy reduces platelet activity (Morel-Kopp et al, 2009). Higher platelet levels have also been associated with anxiety and mental stress (Brydon et al, 2006). Alterations in serotonergic neuronal function also occur in the CNS in patients with major depression (Owens and Nemoerof, 1994).

Behavioural mechanisms

Individuals with depression and anxiety are more likely to engage in unhealthy lifestyle behaviours such as smoking, alcohol misuse, lack of exercise, sedentary lifestyles, poor diet, lack of motivation and energy, and non-adherence to medications. More depressed patients report not taking their medications as prescribed (14% *vs* 9% of controls) while twice as many report forgetting to take their medications. Skipping medications was also more common among the depressed population (9% *vs* 4%) (Gehi et al, 2005). Depression is also associated with poorer compliance with cardiac treatment regimens, cardiac rehabilitation and exercise programmes, and greater cardiac risk factors in lifestyle (Carney et al, 1995; Ziegelstein et al, 2000). Unsurprisingly, individuals with cardiac disease have poorer cardiac outcomes when associated with depression (Carney and Freedland, 2003). They are more likely to have a poorer quality of life, more health complaints and higher disability rates (Carney and Freedland, 2003; Fauerbach et al, 2005; De Jonge et al, 2006). Individuals with mental illness have poorer insight and are generally less likely to seek help (Blumenthal et al, 1982).

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Medication factors

Safe and effective treatment of depression and anxiety disorders is an essential component in reducing the mortality and morbidity of heart diseases. Tricyclic antidepressants, venlafaxine and monoamine oxidase inhibitors are not considered first-line agents in the treatment of depression in cardiac events.

Tricyclic antidepressants are cardiotoxic because they inhibit potassium channels in myocardial cells and cause a resultant delay in cardiac conduction. They have also been linked to decreased heart rate variability and QT prolongation, both of which can precipitate arrhythmias and sudden death (Cohen et al, 2000). Tricyclic antidepressants increase heart rate by 10% and have been implicated in orthostatic hypotension. The effect is dose dependent and can occur at both therapeutic and toxic doses (Cohen et al, 2000).

Venlafaxine (a serotonin-noradrenaline reuptake inhibitor) has been associated with dose-dependent increases in blood pressure and is contraindicated in conditions with a high risk of cardiac arrhythmias or uncontrolled hypertension (Joint Formulary Committee, 2013).

Monoamine oxidase inhibitors have been implicated in the development of orthostatic hypotension at therapeutic doses and severe hypertensive reactions to sympathomimetic medications or with amine-containing foods (including cheese and wine).

In 2011, the US Food and Drug Administration issued a warning that higher doses of citalopram were associated with prolongation of QT interval and that 40 mg per day should be the maximum permissible safe dose. In March 2012, the safe permissible dose was reduced to 20 mg/day for patients older than 60 years and for those taking P450 2C19 inhibitors, such as moclobemide, chloramphenicol, fluoxetine or omeprazole.

Clinical trials for treatment of depression in cardiovascular diseases

Several clinical trials have been conducted to determine the safety and efficacy of treatments for depression in patients with cardiovascular diseases. The SADHART study (Sertraline Antidepressant Heart Attack Trial) was a randomized double-blind, placebo-controlled trial involving seven countries from 1997–2001, enrolling 369 post-myocardial infarction patients with major depressive disorder. This was the first trial to study the safety and efficacy of sertraline. The incidence of severe cardiovascular adverse events was 14.5% with sertraline compared to 22.4% with placebo (Glassman et al, 2002).

The ENRICHD study (Enhancing Recovery in Coronary Heart Disease) was a multicentre randomized controlled clinical trial of cognitive behavioural therapy for depression and low social support in post-myocardial infarction patients. A total of 2481 patients were recruited (26% with low social support, 39% with depression, 34% with low social support and depression). Pharmacological intervention was offered only if patients failed to demonstrate symptom reduction after 5 weeks of therapy. The intervention did not increase event-free survival. It did improve depression and social isolation, although the relative improvement was less than expected because a substantial improvement was seen in usual care patients (Berkman et al, 2003). The cumulative use of antidepressant in both arms increased from 4.8% to 20.6% in the usual group and from 9.1% to 28% in the intervention group.

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The Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE trial) was a 2 × 2 factorial, parallel-group, 12-week trial conducted among 284 outpatients with coronary artery disease and depression. The objective was to document the short-term efficacy of a selective serotonin-reuptake inhibitor (citalopram) and interpersonal psychotherapy (a short-term, manual-based psychotherapy focusing on the social context of depression) in reducing depressive symptoms in patients with coronary artery disease and major depression. The trial concluded that citalopram was superior to placebo in reducing the score on the 12-week Hamilton Depression rating scale. There was no evidence of a benefit of interpersonal psychotherapy over clinical management. Similar to the results of SADHART, response to selective serotonin-reuptake inhibitors was more pronounced in patients with a history of recurrent depression (Lesperance et al, 2007).

In the Myocardial Infarction and Depression – Intervention Trial (MIND–IT), investigators tested antidepressant use *vs* usual care in a randomized controlled design to determine whether antidepressant treatment for depression post-myocardial infarction improves long-term depression status and cardiovascular prognosis (Van den Brink et al, 2002). It was an effectiveness study rather than an efficacy study. Mirtazapine (a non-tricyclic antidepressant that promotes noradrenergic and serotonergic neurotransmission) was used in the treatment group. Results showed that an active treatment strategy for depression post-myocardial infarction did not improve the long-term depression status or cardiac prognosis compared with usual care. At 18 months post-myocardial infarction, about one-third of the intervention and control patients continued to have ICD-10 depression. These findings were consistent with the results of the ENRICHD study, which showed no overall effect of cognitive behavioural therapy on the risk of all-cause mortality and re-infarction in myocardial infarction patients with depression and/or a low level of social support. However, it did show small differences in depression between the intervention and care as usual groups (Van den Brink et al, 2002; Berkman et al, 2003).

KEY POINTS

- Depression or anxiety and cardiovascular illness have a bidirectional interaction.
- A combination of pathophysiological, behavioural mechanisms and medication factors link depression and anxiety to cardiovascular diseases.
- Patients should be screened and diagnosed at both primary and secondary settings (both by cardiologists and psychiatrists) for timely intervention.
- A biopsychosocial approach to treatment by closely liaising with mental health professionals improves outcomes.

Assessment and biopsychosocial approach to treatment

The American Heart Association recommendations include using PHQ-2 (Personal Health Questionnaire), and PHQ-9 if there is a positive response to one or both questions of PHQ-2 (Lichtman et al, 2008). Treatment of depression and anxiety disorders with antidepressants (selective serotonin-reuptake inhibitors), psychotherapy or both appears to be effective in reducing depressive symptoms and reducing further risk for heart diseases. Selective serotonin-reuptake inhibitors may restore reduced heart rate variability and attenuate platelet activation in depression, thereby having a cardioprotective effect (Serebruany et al, 2003b). However, selective serotonin-reuptake inhibitors have been associated with increased risk of bleeding, thus requiring caution in patients taking anticoagulants or with a history of bleeds (Serebruany et al, 2003b).

Cognitive behavioural therapy can be beneficial for depression in cardiac patients and it may be an alternative for those who cannot tolerate antidepressants. Psychological therapies could also be proposed for insight orientation in general (Milani and Lavie, 2007).

Cardiac rehabilitation can reduce depressive symptoms and improve cardiovascular fitness (Milani and Lavie, 2007). It may reduce levels of hostility as well as anxiety and depression symptoms. It can be difficult for depressed patients to engage with rehabilitation programmes, but cardiology teams should encourage them by regular support in the community.

Simple measures such as relaxation techniques, progressive muscle relaxation, breathing techniques, good understanding of the illness, and involving families in the management and decision-making process can be highly useful.

Relevance to health-care professionals

Depression, anxiety and cardiovascular illnesses can co-exist and complicate each other. According to the Global Burden of Disease study, by 2030 unipolar depression and ischaemic heart disease will be the two leading causes of disability-adjusted life-years (World Health Organization, 2008). Active management of comorbid psychiatric conditions can potentially reduce the morbidity and mortality associated with cardiovascular diseases. GPs have a key role in identifying pathology at earlier stages at the primary care level. The American Heart Association recommends that if patients score 10 or higher on PHQ-9, they should be referred for a more comprehensive clinical evaluation by secondary services. Cardiologists should consciously aim to screen and identify depression and anxiety among their patients. Only half of cardiovascular physicians report that they treat depression in their patients and not all patients who are recognized as depressed are treated for it (Feinstein et al, 2006).

Conclusions

In spite of the fact that gaps in our knowledge still exist, there is likely a bidirectional interaction between depression or anxiety and cardiovascular diseases affecting patient morbidity and mortality. Assessment with appropriate screening tools at an early stage, and safe and effective interventions improve outcomes. Interventions should encompass a holistic approach including antidepressants, psychological therapies and social support with cardiac rehabilitation programmes. These not only improve quality of life, but evidence suggests that they may improve cardiac outcomes. However, there are a number of methodological complexities associated with research regarding depression and cardiovascular disease. In future more trials on a larger scale might improve specific pharmacotherapy. Challenges lie ahead for frontline clinicians but close liaison with mental health professionals is encouraged to provide the most effective management for these patients. **BJHM**

Conflict of interest: none.

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